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АНАЛИЗ ВНЕШНИХ ФЕНОТИПИЧЕСКИХ ПРИЗНАКОВ НЕДИФФЕРЕНЦИРОВАННОЙ ДИСПЛАЗИИ СОЕДИНИТЕЛЬНОЙ ТКАНИ В АСПЕКТЕ ПАТОГЕНЕЗА И ВОЗРАСТНОЙ ДИНАМИКИ ТЕЧЕНИЯ ДИСПЛАСТИЧЕСКОГО ПРОЦЕССА

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Analysis of External Phenotypic Signs of Undifferentiated Connective Tissue Dysplasia in Aspect of Pathogenesis and Age Dynamics of The Course of The Dysplastic Process

Резюме

В статье представлено текущее состояние и проблемы клинической диагностики недифференцированной дисплазии соединительной ткани, основанной на определении внешних фенотипических признаков, при этом постулируется примат клинической диагностики данного состояния. Рассмотрены ассоциированные с данной проблемой термины — фенотипический признак, стигма, малая аномалия развития, врождённый порок развития. Вводится оригинальная концепция диспластического процесса для описания глобальной в популяции и индивидуальной для конкретного пациента динамики состояния изменённого обмена соединительной ткани, которая определяется взаимодействием наследственных и поведенческих факторов, условиями среды и естественным процессом роста и старения организма. Приводится оригинальная классификация внешних фенотипических признаков по категориям принадлежности к системе органов, методике определения, влиянию на клиническую картину, потенциальной динамике признака, частоте встречаемости, отношению к онтогенезу, диспластическому процессу и поражённому элементу соединительной ткани как основа патогенетического анализа их диагностической значимости. В качестве примера применения данного подхода анализируются малые аномалии развития, анамнестические (нарушение гемостаза, травматические эпизоды), субъективные (варианты болевого синдрома), костные (долихостеномелия, костно-хрящевые дисплазии, ограничение разгибания локтевого сустава) и кожные внешние фенотипические признаки, для каждого из которых уточнены методики определения и обозначены возможные ограничения в реальной клинической практике. Для кожных признаков проведена группировка по отношению к основным свойствам кожи, определяемым конкретным структурным элементом соединительной ткани. Для признака повышенной растяжимости предложена альтернативная методика определения манёвром растягивания на плоскости между двумя стандартными штрихами.

Ключевые слова: *соединительная ткань, дисплазия, фенотипический признак, диспластический процесс*

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Abstract

The article presents the current state and problems of clinical diagnostics of undifferentiated connective tissue dysplasia based on the determination of external phenotypic features, while postulating the primacy of clinical diagnostics of this condition. The terms applied to this problem are considered — phenotypic feature, stigma, minor developmental anomaly, congenital malformation. An original concept of the dysplastic process is introduced to describe the global in the population and private for a specific patient dynamic of the course of the state of altered metabolism of connective tissue, which is determined by the interaction of hereditary and behavioral factors, environmental conditions and the natural process of growth and aging of the organism. An original classification of external phenotypic features by categories of belonging to the organ system, determination method, influence on the clinical picture, potential dynamics of the feature, frequency of occurrence, relation to ontogenesis, dysplastic process and the affected element of connective tissue is given as the basis for pathogenetic analysis of their diagnostic significance. As an example of the application of this approach, minor developmental anomalies are analyzed, anamnestic (impaired hemostasis, traumatic episodes), subjective (variants of pain syndrome), bone (dolichostenomelia, osteochondral dysplasia, limitation of elbow joint extension) and skin external phenotypic signs, for each of which the methods of determination are specified and possible limitations in real clinical practice are indicated. For skin signs, a grouping is carried out in relation to the main properties of the skin determined by a specific structural element of connective tissue. For the sign of increased extensibility, an alternative method of determination by a stretching maneuver on a plane between two standard strokes is proposed.

Key words: *connective tissue, dysplasia, phenotypic trait, dysplastic process*

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CD — congenital defect, EPC — external phenotypic character(s), MDA — minor development abnormality, UCTD — undifferentiated connective tissue disease

Currently, diagnosing undifferentiated connective tissue disease (UCTD) is rather an art than an algorithm of actions. A direct consequence of the absence of clear objective diagnostic criteria is the lack of a separate ICD code for this condition, which prevents global medical data comparison and systematic development of unified methodological approach [1]. Code M35.8 (Other specified systemic involvement of connective tissue) recommended by the Russian professional community does not specify UCTD etiopathogenesis and describes a wider group of medical conditions; second, it differs from the global best practices of assigning this patient group code M35.7 (Joint hypermobility syndrome), since joint hypermobility is one of the most specific and well-studied symptoms of UCTD in Western countries. It is widely known that experienced clinicians can visually recognise UCTD patients [2, p. 38]. An additional or alternative approach is an analysis of a full comprehensive examination and a final decision taken by a clinician for each patient individually [3, p. 34]. However, a detailed analysis of all UCTD signs using clinical, genealogic and imaging methods is very time-consuming and expensive, or even impossible if talking about molecular genetic testing. The situation is aggravated by the high incidence of this condition (minimum 20 %) [4], necessitating the wide practical use of diagnostic tools. Therefore, a method with the highest diagnostic value and available for primary care providers in routine settings should be prioritised, i.e. clinical examination of external phenotypic characters (EPC), which is possible due to the biomechanical (shape-generating) function of connective tissue. Minor heart abnormalities show that the number of internal phenotypic characters closely correlates with the number of diagnosed EPCs, and it can be used in clinical diagnostics [5]. This is phenotypic character identification which lays the foundation for all existing diagnostic scales and criteria [6, 7]. However, these diagnostic scales and criteria have not been analysed for their clinical significance; at best, its formal mathematical equivalent was used. Clinical significance of any fact associated with a patient character can be described only in terms of its practical application, which can be either diagnostic or prognostic. For diagnostic purposes, of importance is the association between this fact and implementation of certain links of a pathological process, underlying the condition on question, which cause frequent clinical manifestations, which make it possible to identify them. For prognostic reasons, of importance are the effects of this fact for

the course (quality of life) or outcome of the disease, including the risk of complications.

Currently, phenotypic characteristics and, thus, diagnosis cannot be treated as the key, unlike genetic and biochemical diagnostics [8]. This is related both to genetic heterogenity of disease entities and varied penetration of mutant allels, impact of external factors on gene expression, which creates ambigous connections between genotype and phenotype: different damages to one and the same gene can clinically present as different phenotypes; damages to different genes can have a similar phenotype. However, taking into consideration the multitude of various causes of EPC and their combinations in clinical manifestations in the form of established syndromes can theoretically boost the accuracy of phenotypical diagnosis.

The objective of this article is to identify a group of UCTD-associated EPCs and determine their clinical importance in terms of the course of dysplastic process, as exemplified by several groups of EPCs.

The meaning and justified use of some terms should be discussed in advance. A phenotypic character is a conventional and unique clinical fact (phenomenon, symptom) related to the patient's morphofunctional characteristic. A phenotypic character should be distinguished from the biological term "phene", which means an individual variant of a certain character and not the presence of the character itself. Also, we won't use the term "stigma", firstly because of its relation to the diagnosed disease, and secondly because of its historical negative accent. Minor development abnormalities (MDA, synonyms: minor malformations or developmental defects, micro anomalies, congenital morphogenetic variants, dysembryogenic stigma, dysgenic or dysplastic characteristics) are minor morphological defects (anatomic abnormality), which are not associated with functional defects of organs and systems. This definition should be supplemented with the presence of the association with the ontogenesis process, persistence [9] and absence of any correlation with age-related features (involution is rare) [10]. A congenital defect (CD) is a congenital abnormality in the organ structure as compared to the anatomic norm, causing clinically significant impairment of its functions [10]. Therefore, a criterion to differentiate between MDA and CD is impaired function. A dysplastic process means a dynamic condition of altered connective tissue exchange, resulting from the interaction between inherited and behavioural factors, environmental conditions and the natural process of growth and ageing of the body. This concept is needed because of the presence of age-related dynamics in connective tissue exchange, which should be taken into account in interpretation of certain EPCs, also when assessing the probability of their natural alternation over time.

The semiotic status of EPC requires clarification; it is definitely symptomatic, i.e. it has a descriptive function. Establishing its association with UCTD as a medical condition or grouping by symptoms requires an additional pathogenetic study with confirmation of laboratory and imaging correlations or statistical associations, grouping these EPCs, which is a partial analysis of the clinical importance of each EPC. Thus, EPC is any unique character irrespective of its nature, inclusion in the organ system or other characteristics, but its clinical interpretation always requires a proof in order to avoid a risk of an accidental mistake.

A study map of phenotypic characters can be diagnostically valuable only with the clear understanding of the methods to establish such characters and strict adherence to such methods by all specialists; otherwise comparability would become challenging. T.I. Kadurina was the first researcher to stress this issue; she established objective criteria for some EPCs directly in the diagnostic chart [6]. For the same reason, phenotypic characters should be analysed in terms of their possible objective definition in the real-time clinical settings.

Each EPC should be analysed together with other clinical presentations because, formally, one phenotypic character can be a part of various clinical conditions — from normal condition or minor abnormality up to a character of a serious inherited pathology (for instance, abnormal ear shape in Beals syndrome patients). Almost all EPCs can be an isolated connective tissue defect in one case and a symptom of a systemic inherited pathology and pleiotropic action of mutant genes in other cases [3, p. 38].

Genetic origin of dysplastic process is out of question; however, we are unable to exhaustively describe pathogenesis of initial elements of EPC, as it can vary due to genetic heterogenity of connective tissue dysplasia, even within a family in inherited disorders [11]. However, we can describe them during or after character formation, because its course corresponds to the anatomical and functional nature of EPC. Therefore, there are two main stages of pathogenesis: before and after EPC formation, including a vicious circle, where this EPC affects dysplastic process.

Nevertheless, some elements of pathogenesis can be assumed on the basis of differential CTDs with known etiopathogenesis, for which this EPC is specific. Thus, a differential CTD is the best model to study pathogenesis of a specific EPC. An affected element in connective tissue can be roughly assumed by the elemental structure of extracellular matrix in affected tissue.

We will use the following plan to study and describe EPC:

1) Classification of a number of various EPCs in order to systematise them and identify groups similar in comparative characteristics.
2) Analysis of each EPC in terms of resulting classification.
3) Description of existing methods to identify these characters; if necessary and possible, proposed adaptation for unification and improvement of diagnostic method significance.
4) Presentation of assumed pathogenesis of these characters based on publications, including with due account to the defective element in connective tissue metabolism and alternative clinical state causes.
5) Assessment of age-related changes in these characters.

Below is a proprietary EPC classification with comments:

1) Association with the organ system [6] — depends on the affected connective tissue location. This comparative character is the most clinically significant, as it defines patient's routing in the clinical network. Besides, understanding of the organ system embryogenesis makes it possible to assume patterns in formation and distribution of subclinical connective tissue defects. Due to its integrative function, connective tissue is present in each and every organ system, including nervous system, and mental disorders are EPC.
2) Method of identification:
   - Objective — can be clearly defined upon subjective examination by a medical professional:
     – Examination (majority of EPCs) — morphological EPCs;
     – Functional test (joint hypermobility, skin hyperextensibility of skin) — functional EPCs;
     + Some EPCs require identification and diagnosis clarification by a medical professional, e.g., scoliosis, flat foot, eye pathology, nasal septum deviation;
   - Subjective — identified as specific senses and feelings by the patient or active complaints;
   - Anamnestic — identified when taking patient's history.

It is also important to differentiate objective characters related to anamnestic data, which can be observed only in specific events, for instance, keloid scars or tissue paper syndrom after a skin damage.

3) Effects on clinical presentation:
   - Clinically significant — affect quality of life and disease outcome;
   - Clinically insignificant — minor development abnormalities.

It is worth nothing that this classification is often relative, because further investigations can bring about actual data on the clinical significance of formed MDAs.

4) Possible character changes:
   - Reversible — can resolve spontaneously over time;
   - Irreversible — can be corrected only with surgery.

This comparative character is a result of morphogenesis, particularly of the rate of connective tissue exchange involved in the formation of this EPC.

5) Incidence:
   - Primary — are common in impaired connective tissue exchange and are highly specific for dysplastic process;
   - Secondary — are less common in impaired connective tissue exchange and are less specific for dysplastic process.
6) Association with ontogenesis:
   - Inherited — the fact and nature of inheritance can be established only following a genealogic analysis (preceding and succeeding generations);
   - Acquired:
     – Congenital;
     – Postnatal.
7) Association with dysplastic process:
   - Cause markers — are a direct cause of impaired connective tissue metabolism, always irreversible;
   - Consequence markers — are a direct consequence of impaired connective tissue metabolism, always reversible;
   - Cause-effect markers — are a direct consequence of impaired connective tissue metabolism, in some way or another they aggravate the process;
   - Associated marker — does not have any direct pathogenetic association with dysplastic process or has unspecified pathogenetic status.

Each of these variants can be of diagnostic importance; however, cause markers are a stronger evidence of CTD, while consequence markers are an evidence of severity.

8) Relation to an effected element of connective tissue:
   - Collagens;
   - Elastin;
   - Glycosaminoglycans (GAGs).

This comparative character is the most pathogenetic, as it describes the mechanism of connective tissue damage in a specific EPC.

Classification based on the relation to the germinal layer has no high diagnostic value, because all connective tissue structures have common mesenchimal origin from the mesodermic layer. Mesenchimal cells form in mesodermal palisades as a result of separation. Further differentiation of the majority of cells in embryogenesis depends on inductive

interaction between epithelial and mesenchimal tissues [12, p. 210]. An alternative understanding is that all germinal layers participate in mesenchyme formation [2, p. 11, 13, p. 16]. Mesenchyme is the totality of loose reticular dendritic cells located bewteen compact cell rudiments (fetal organs). Mesenchyme forms the internal environment for the fetus prior to formation of special integrative systems, and ensures the processes of fetal cell migration, then gives rise to stromal cells (especially for connective tissue, smooth muscle cells), skeletal tissue, vascular system and blood [13, p. 16]. Mesenchyme itself forms during Carnegie stage 6 (week 3): extraembryonic mesenchyme as exoderm thickening in the caudal pole of archiblast, with follow-up lateral cell migration; and intraembryonic mesenchyme resulting from exoderm cell introversion in the germ band area [12, pp. 84–88]. Therefore, the cause of dysplastic process is involvement of a specific cell pool during ontogenesis, specifically in individual or multiple, inherited or newly acquired genetic defects, which can occur at any stage during ontogenesis. It is worth mentioning that other layers are a source of specific epithelia and cells of parenchymatous organs. Skin, teeth, breasts, and nervous system are mostly ectodermic in their origin, while digestive and respiratory systems are mostly enderonic [12, pp. 208, 220, 222, 336]. Knowledge of formation periods of external body parts (face, limbs, etc.) and corresponding internal organs allows suspecting an internal pathology in the presence of EPCs [14].

We will discuss EPCs according to their classifications. Each section contains a common group characteristic, including involved connective tissue elements, and description of individual EPCs; ICD-10 and ICD-11 codes will be provided where available. Groups of craniofacial, wrist and feet characters are grouped on the basis of their anatomical similarity, which is useful for practical diagnostic use. This article discusses only EPCs, which can be identified by GPs. Specialised orthopedic, ophthalmologic and dental EPCs will be discussed in specialised articles. Clinical evaluations were conducted on the basis of a quantitative estimate vs. other EPCs using point-based systems (I.A. Viktorova, L.N. Abbakumova, T.I. Kadurina) or in accordance with the author's interpretation of these characters into primary and secondary (T. Milkovska-Dmitrova and A. Karkashov).

MDAs

This is a separate group; it is the most general and unspecified group, which is a result both of heterogeneity of these EPCs and low awareness of the medical community of this problem [9], thus, the lack of studies and full understanding of the clinical significance MDAs, where several aspects can be distinguished:

1) Isolated MDAs can be observed in healthy individuals [9, 15].
2) Multiple MDAs are clinically significant, quantification of which in publications varies between 3 and 7 [15]:
   - Accumulation of MDAs in several generations as a sign of dysplastic stigmatization [10];
   - Risk stratification for the inherited pathology for detailed diagnosis and family planning [9];
   - Risk stratification for hidden CDs for detailed diagnosis [15];
   - Indications for common preventive measures [9].
3) Clinically significant is a combination of MDA and CD, which indicates unconditionally abnormal nature of MDA [9].
4) Clinically significant is a combination of specific MDAs, for instance, transverse palmar crease, upslanting palpebral fissures, epicanthal fold, brachydactylia, clinodactyly, sandal gap in Down syndrome [14].
5) Clinically significant are specific MDAs, for instance alar neck folds (Turner syndrome and Noonan's syndrome), postaxial polydactyly (Bardet-Biedl syndrome), breast nipple hypoplasia or aplasia on one side (Poland's syndrome), vertical notches on the ear lobe (Beckwith-Wiedemann syndrome) [14].

Therefore, MDAs are just a sign of antenatal ill-being irrespective of the causative factor, including inheritance. There is a proven correlation between MDA incidence and anthropometric characteristics within the population and the ecological conditions in the location of early development [16], aggravated obstetric and gynecological history (number of pregnancies, mother's age, mother's drug addiction, premature birth) [17, 18]. In a clinical and genealogic analysis, inherited nature of feet and hand MDAs are observed only in one quarter of all cases [19]. Over 50 % of all MDAs have a composite origin [20].

The terms "norm", "MDA", "CD", and "EPC" should be defined here. The most close concepts are MDA and CD, which have common morphological nature and are associated with impaired ontogenesis. They are caused by similar factors; however, the causative factor differs in intensity, exposure duration and period of fetal exposure (critical or non-critical development stages) [9]. Abnormality is a condition beyond variations or borderline changes in the normal condition [15]. The correlation between MDA and EPC is more complicated. In general, MDAs are associated with dysplastic process, that is why a direct pathogenetic correlation with it is doubtful, but possible, it being proven by the traditional use of MDA in diagnosting connective tissue

dysplasia [10, Table 1] due to a high incidence of MDAs in UCTD, but this topic requires additional studies for each specific MDA. The association is a result of the shared causative factors of MDA and connective tissue displasia. In this regard, it is not a surprise that articles by Russian authors on MDAs were in the area of neurology [9] and orthopedics [21], i.e. fields of medicine, which study pathologies of the systems, where connective tissue prevails. Of note, all MDAs are EPCs, and just some morphological EPCs are MDAs. The majority of MDAs tend to progress before puberty ends, then the process stops together with growth of the body.

Anamnestic and subjective EPCs

This EPC group is the most polygenic one, therefore, in order to establish its association with dysplastic process, other causes should be ruled out (idiopathic nature of disorders), and very often it is a very time-consuming process, which requires additional diagnostic and medical resources.

The group of anamnestic characters (Table 1) can be classified as follows:

- No signs upon examination; however, they can be retrospectively recovered by the patient (e.g., easy bruising).
- Diagnoses made by a medical professional (eye specialist, trauma orthopaedist, dentist), also on the basis of additional examination techniques (laboratory tests, imaging).
- Prior diagnoses, which were not observed upon examination as they were corrected (e.g., hernias in any location).

This group of characters includes mostly symptoms of hemostasis pathology, impaired sexual maturation, and a history of traumas.

In terms of diagnostic informative value, this group is inferior to objective characters, because diagnosis depends on the possibility to compare with normal values under similar conditions. Connective tissue dysplasia has a huge impact on the quality of patient's life, so that they are in completely different settings, where internal differences can be left hidden. The patient will be living with impaired functionality and anamnestic EPCs will emerge only under a stress as dysplastic process decompensation or in a specific life style, e.g., in sportsmen. Besides, these characters are somehow subjective, which is a result of both the patient's psychological constitution, where existing EPCs can be disregarded or left out altogether, and unclear incidence and intensity (lack of clear criteria). Also, this group of characters is greatly impacted by the healthcare service availability, because in the absence of comprehensive examinations and consultations by medical professionals, which is the case with minor changes, these EPCs will be disregarded, while their identification by a non-competent GP will lead to diagnosis subjectification and possible overdiagnosis. Therefore, this group of EPCs reflects not only internal features of the patient's health, but also external factors of the patient's life style, quality of healthcare services and patient's psychological constitution.

Out of a wide group of subjective characters observed in UCTD, only a few complaints, which are specific to dysplastic process and related to joint disorders, are used in the diagnosis (Table 2).

Table 1. *Anamnestic EPF*

EPF	Clinical assessment	ICD-10 and ICD-11 codes
Petechiae/ecchymosis/nosebleeds	Kadurina T.I. — medium	Other specified hemorrhagic conditions D69.8, 3B6Y
Easy occurrence of hematomas	Abbakumova L.N. — medium	Other specified coagulation disorders D68.8, 3B6Y
Juvenile uterine bleeding	Kadurina T.I. — small	Heavy menstruation during puberty N92.2, other specified abnormal bleeding from the uterus and vagina N93.8, GA2Y
Delayed puberty	Kadurina T.I. — small	Delayed puberty E30.0, 5A91
Dislocations and subluxations in joints or only dislocations	Milkovska-Dmitrova T. and Karkashov A. — secondary Viktorova I.A. — medium	Recurrent dislocations and subluxations of the joint M24.4, bone dysplasia with multiple dislocations of the joints LD24.E, the specified code depends on the location and is assigned by an orthopedic traumatologist
Varicose veins of the lower extremities, vulva, and pelvis in young adults	Not defined	varicose veins of lower extremities without ulcer or inflammation I83.9, Chronic venous Insufficiency of lower extremities BD74, Varicose veins of vulva BD75.2, Varicose veins of pelvis BD75.3
Hernias and prolapses of pelvic organs and/or postoperative hernias, diaphragmatic hernia	Not defined	Prolapse of female genital organs N81, hernia of the anterior abdominal wall K43, DD55, diaphragmatic hernia K44, DD50.0
Bone fragility — more than 2 fractures in history from falls	Not defined	Osteogenesis imperfecta Q78.0, congenital bone fragility LD24.K0
Hearing loss, deafness	Not defined	Unspecified hearing loss H91.9, deafness AB5Z

Table 2. *Subjective EPF*

EPF	Clinical assessment	ICD-10 and ICD-11 codes
Pain in the spine	Kadurina T.I. — medium	Back pain — M54, ME84
Arthralgia/microtraumatic transient synovitis or transient joint pain	Kadurina T.I. — medium or Milkovska-Dmitrova T. and Karkashov A. — secondary	Joint effusion — M25.4, Transitional synovitis — FA27.3 Joint pain — M25.5, ME92

However, these symptoms can be a consequence of other pathologies — rheumatological, traumatological, orthopaedical, infectious or metabolic pathologies. The specificity of these complaints can be boosted due to clarification of the clinical presentation and history; however, the specificity is unclear. UCTD patients are known to have numerous complaints, resulting from a low pain threshold and specific psychological profile.

Bone EPCs

The majority of bone EPCs are specific orthopaedical characters (deformed chest, spine and limbs, bone and cartilage dysplasias) and dental characters (high archlike palate, impaired tooth growth and density). GPs can use a measuring tape for measurements and calculate bone indices in order to identify constitution and individual disproportions. Given limitations of a measuring tape, it is essential to use values, which minimise the impact of muscles on measurement results; a sliding caliper will help in eliminating these limitations.

Bone characters have the highest sensitivity and specificity for clinical diagnosis of UCTD, since they are the least age-related (save for spine and foot deformities).

The connective part of a (demineralised) bone contains 90 % of type I collagen, 1–2 % of type V collagen, 2–3 % of osteonectin, and 1 % of proteoglycans, sialoproteins, osteocalcin, and α2-glucoprotein each.

Differential CTDs associated with the most pronounced changes in bones are Marfan's syndrome and brittle bone disease.

Dolichostenomelia (Q74.8 "Other specified congenital malformations of limb(s)", I.A. Viktorova — minor, T.I. Kadurina — moderate). According to the meaning of the components of this term: "dolichos" is long, "stenos" is narrow, and "melos" is a part of the body, limb, the term means elongation and thinning of limbs. This condition has clear clinical global signs for estimated indices; both must be present [22]:

- The ratio between the upper body (from the top of the head to upper symphysis) and the lower body (from upper symphysis to the floor) is < 0.86.
- The ratio between arm span and height is ≥ 1.05.

There are also additional characters [2, p. 45]:

- The ratio between feet length and height is > 15 %.
- The ratio between hand length and height is > 11 %.
- The difference between arm span and height is > 7 cm.

Bone and cartilage dysplasiae (same code) are bone structure abnormalities caused by impaired histogenesis; the clinical evaluation is unspecified [2, p. 48]:

- Acromelia is associated with shortening of distal limb sections (hands, feet);
- Mesomelia manifests as shortening of central limb sections (forearm, shin);
- Rhizomelia is shortening of proximal limb sections (shoulder, hip).

Identification is based on the measurements of limb section length and calculation of the ratios between section length and limb length; the resulting values are also compared to the normal values.

Restricted elbow extension of ≤ 170 degrees (ICD is not available) — the clinical evaluation is unspecified [22]. It is measured as part of goniometry.

Elbow extension is controlled by three factors: flexor muscle resistance (biceps, brachialis, brachioradial muscle), anterior joint capsule tension, and crazy bone contact with cubital fossa [23, p. 98]. Therefore, restricted extension is caused by disproportional crazy bone enlargement as compared to cubital fossa.

Skin EPCs

In its composition, the connective tissue part of the skin, comprising mostly the proper dermal layer, is similar to ligaments and tendons. Since skin is able to renew tissues faster, first, skin EPCs are most susceptible to age-related changes; second, they are very sensitive to changes in the current connective tissue metabolism.

All EPCs, participating in the diagnostic process, should be identified on a specific, pre-defined standard skin area, which is hardly exposed to external factors (native skin), primarily to mechanical load and solar irradiation, and which shows innate characteristics of the individual and not the features of their environment. The interscapular region is optimal, because it is covered with clothes most of the time.

It is worth noting that this group has a large number and some analogy-based metaphoricity in EPC terminology; however, the majority of them can be grouped together based on the affinity of the described skin characteristics.

We believe that the key characteristics are skin stretchability, surface condition, consistence, and elasticity; however, the main characteristic is consistency, as it affects the majority of the all other qualities. Soft skin is most likely stretchable and velvety (T.I. Kadurina — minor), while dense skin would be poorly stretchable and smooth. In terms of the connective tissue element, this characteristic is based on the collagenous matrix quality, in particular its architectonics parameters: in case of a poor structure, even de-fragmentation, more space would be required to line up individual fibres along the mechanical power application line during stretching; clinically, it means high stretchability. The surface section of this matrix will be also altered, it will have fine irregularities, showing as velvety skin. A characteristic, which is close to consistence, is tissue tension (the ability of soft tissue, particularly skin, to mechanically resist external exposure), which also depends on the rate of hydration [24].

Skin elasticity is the ability of skin to recover its shape after removal of deforming load. This quality depends on the elastic component of connective tissue. To sum up, skin is streched due to mechanical properties of the collagenous matrix, and skin shape is recovered due to the elastic matrix. Each of the discussed clinical properties of skin is self-sufficient and, to a great extent, depends on a specific element of connective tissue.

Some skin EPCs are palpable (tactile characteristics and functional tests) and some can be seen upon examination (visual properties). Tactile characteristics are surface condition (stroking), consistence (pinching with tissue compression), elasticity (pinching, but removal of compression), and stretchability (pulling).

Consistence can be soft (loose) or dense. Skin surface can be velvety or smooth; these are alternative, mutually exclusive characteristics. Velvet has thick fluff, giving the fabric specific tactile properties. Velvety skin means the degree of skin humidity, which, in turn, depends on the degree of hyaluronic acid and water in skin matrix. Two different connective tissue elements impact one skin property, because both collagenic fibrils and GAG take part in derma frame formation [25, p. 31]. In children, velvety skin can be a result of abundance of lanugo hairs; however, this mechanism is possible in adult patients with UCTD (lanugo hairs of various length). The synonym of this characteristic is chamois-like skin (L.N. Abbakumova — minor), because one of the stages in chamois preparation is fluffing, similar to teaseling, giving it similar tactile properties; and delicate skin (T.I. Kadurina — minor).

In terms of elasticity, skin can have decreased elasticity (synonyms: fragile, loose skin (I.A. Viktorova — moderate), which swags by gravity) and normal elasticity (synonyms: elastic, resilient, firm skin). In terms of stretchability, skin can have decreased (rigid skin), normal and increased (ropy skin) stretchability ; however, this characteristic should be assessed quantitatively.

Increased stretchability (hyperextensibility, not hyperlaxity) (other specified disorders of skin and subcutaneous tissue in diseases classified elsewhere (Ehlers-Danlos syndrome), L99.8, M.J. Glesby, T. Milkovska-Dmitrova and A. Karkashov + “flappy” — primary, L.N. Abbakumova — moderate, I.A. Viktorova — major, T.I. Kadurina — moderate to major).

There are several methods to determine skin stretchability, but they are based on pulling, which can be criticised because of the challenges with this procedure standartisation, which requires clarification of the following questions: Which skin area? (potential impact from peculiar interface between skin and subcutaneous tissue) What skin area to be gripped? How to grip skin relatively to skin strain lines? What pulling force to apply to the skin fold? What point and what side of the skin fold to use for fold length measurements? None of the methods answers these questions. In Russia, we mostly use measurements of hyperextensibility of skin on the dorsum of hand, halfway through the projection of the 3rd metacarpal bone; the fold is formed in parallel with this bone. Alternatively, skin of the forehead or above outer ends of the clavicle can be used [26]. Assessment criteria also differ: increased skin stretchability means skin fold length of 2–3 cm and above. Degree of stretchability can be measured: minor — up to 2 cm, moderate — up to 3 cm, and severe — 4 cm and over [6]. The binary version of this characteristic can be assessed as well, where hyperextensibility means the possibility of forming a skin fold at the nose tip or external ear. The force applied should not cause any pain. Foreign publications recommend studying a skin fold at the upper third of the palmar surface of forearm laterally [27, 28].

An adequate alternative is stretching on a surface between two standard lines (2 cm apart) at the upper third of the palmar surface of forearm laterally, as it allows preventing all mentioned limitations of the methods, which are based on the use of a skin fold. The force applied is limited by a sudden rise in skin resistance to stretching; this is a moment, when collagenous matrix lies along mechanical strain lines.

Another group of affinity is thin skin (T.I. Kadurina — moderate, I.A. Viktorova + “translucent skin” — minor), which is sometimes called fragile (strength characteristic). This EPC also includes visible venous or vascular pattern of skin (synonym: vascularity) (L.N. Abbakumova — moderate, T. Milkovska-Dmitrova and A. Karkashov — primary), because this visual

feature is used to clinically identify skin thinning. Examinations are conducted on skin of chest and back, limbs are used less often. It is also suggested to identify dilated capillaries of skin on face and back (L.N. Abbakumova — minor). Tool-based methods can be used, e.g., anthropologic invasive skin thickness gage and ultrasound cutometry. There are specialised combined diagnostic equipment used in dermatology, which is the golden standard in the measurements of the majority of skin parameters [29], and dermatological ultrasound examination [30].

A separate group is skin changes associated with traumas and/or active growth (teenagers, pregnant women, sportsmen, obese people). After a trauma, when skin heals, there can be skin areas resembling tissue paper (I.A. Viktorova — moderate, T.I. Kadurina — minor to moderate, depending on the size), which look like wide atrophic (below skin level, shiny) scars with multiple folds, resembling crumpled up paper. Usually, it is possible to retrospectively identify the fact of a non-linear trauma (abrasion, impact injury) or past infections with skin involvement (streptoderma, chicken pox, etc.). We believe that a higher clinical value lies not with the size or number of these EPCs, which, to a greater extent, are related to the nature of trauma and its probability, but the very fact of this type of skin regeneration. A similar mechanism underlies formation of stretch marks (L90.6, EE40.1) in rapid growth areas (breast, buttocks, shoulders during puberty, abdomen in pregnant women or obese people), which are also atrophic scars, but are numerous and linear (I.A. Viktorova — minor, T.I. Kadurina — major). It is recommended to evaluate them in posterolateral areas of chest, at the level of inferior thoracic segment and lumbar spine section [6]. The colour of strech marks does not have any clinical significance and only shows their age (discoloration over time). A synonym of this EPC is skin scarring (L.N. Abbakumova — minor).

Another type of pathological skin healing is keloid scars, when the poor fibril quality is compensated with their amount, and a hypertrophic scar with impaired structure is formed (L91.0, EE60.0), T.I. Kadurina — minor to moderate, depending on the number. Such scars can appear in the area of any trauma, including surgery and vaccination sites, and require targeted history taking in order to know where to look for them.

Consistence is directly associated with EPC multiple pigment spots, skin hyperpigmentation (unspecified disorder of pigmentation L81.9, abnormal skin pigmentation ED64), M.J. Glesby, L.N. Abbakumova — minor, T.I. Kadurina — moderate. Since soft skin is well-stretchable near natural bony prominences, for instance, above spinous processes of thoracolumbar vertebrae, there are conditions for mechanical stimulation of melanine deposits in these areas. Over 20 such deposits means they are multiple.

Skin colour depends on microcirculation condition, which is impacted by its vegetative regulation and overall pigmentation, which in clinical settings can be assessed using phototypes in Fitzpatrick scale. UCTD patients are pale (L.N. Abbakumova — minor), which is a sign of sympathicotonia.

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МИКРОСОСУДИСТАЯ СТЕНОКАРДИЯ: ПАТОФИЗИОЛОГИЯ СНИЖЕНИЯ КОРОНАРНОГО РЕЗЕРВА

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Microvascular Angina Pectoris: The Pathophysiology of Decreased Coronary Reserve

Резюме

Проведен обзор современной российской и зарубежной литературы, посвященной проблеме нарушенного коронарного резерва кровотока как проявление микрососудистой дисфункции. При поиске информации по этому вопросу использованы материалы следующих баз данных: РИНЦ, Best Evidence, Scopus, Elsevier, PubMed, Clinical Evidence, Cochrane Library. Нарушение коронарного резерва кровотока — важное проявление микрососудистой дисфункции и ключевой диагностический критерий микроваскулярной стенокардии. Оценка этого показателя имеет высокую прогностическую и терапевтическую значимость. Учитывая гетерогенность патогенеза, дальнейшие исследования необходимы для персонализированного подхода к лечению пациентов с микроваскулярной стенокардией.

Ключевые слова: *микрососудистая дисфункция, коронарный резерв кровотока, ишемия, эндотелиальная дисфункция, гиперреактивность гладкомышечных клеток, ПЭТ, ОКТ, МРТ, CFR*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересовф

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Abstract

A review of modern Russian and foreign literature on the problem of impaired coronary blood flow reserve as a manifestation of microvascular dysfunction has been conducted. When searching for information on this issue, materials from the following databases were used: RSCI, Best Evidence, Scopus, Elsevier, PubMed, Clinical Evidence, Cochrane Library. Violation of the coronary blood flow reserve is an important manifestation of microvascular dysfunction and a key diagnostic criterion for microvascular angina. The evaluation of this indicator has high prognostic and therapeutic significance. Given the heterogeneity of pathogenesis, further research is needed for a personalized approach to the treatment of patients with microvascular angina.

Key words: *microvascular dysfunction, coronary blood flow reserve, ischemia, endothelial dysfunction, smooth muscle cell hyperreactivity, PET, OCT, MRI, CFR*

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MVA — microvascular angina, IHD — ischemic heart disease, CFR — coronary flow reserve, NO — nitrogen oxide, ED — endothelial dysfunction, CBF — coronary blood flow, ROS — reactive oxygen species, SOD — superoxide dismutase, IL-1, IL-6, IL-18 — interleukins 1, 6, 18, TNF-α — tumor necrosis factor alpha, CRP — C-reactive protein, NKcells — natural killer cells, TMAO — trimethylamine N-oxide, NF-kB — nuclear factor kappa B, NLRP3 — NOD-like receptor family pyrin domain containing 3, CYP2C19 — cytochrome P450 2C19, HDL-C — high-density lipoprotein cholesterol, sST2 — soluble suppression of tumorigenicity 2, IL-33 —interleukin-33, hs-CRP — high-sensitivity C-reactive protein, suPAR — soluble urokinase plasminogen activator receptor, ET —endothelin, VCAM-1 — vascular cell adhesion molecule 1, ICAM-1 — intercellular adhesion molecule 1, PVAT — perivascular adipose tissue, PGI2 —prostacyclin, EDHF — endothelium-derived hyperpolarizing factor, INOCA — ischemia with non-obstructive coronary arteries, CMD — coronary microvascular dysfunction

Introduction

Microvascular angina (MVA) is a specific form of ischemic heart disease (IHD), where clinical representation of angina is combined with the absence of angiographically significant stenosis of large epicardial coronary arteries [1]. Given clinical significance of microvascular angina, it is useful to discuss possible pathogenic mechanisms of its development. In their review, Kaski J-C et al. identify four key types of microvascular dysfunction: endothelial dysfunction, impaired regulation of resistance arteriole tonicity, structural vascular remodelling, and inflammatory and metabolic disorders [2]. These mechanisms can function both individually and in combination, forming a heterogenous clinical pattern of MVA in different groups of patients. One of the key pathophysiological mechanisms underlying MVA is an impaired coronary flow reserve (CFR), an important parameter of the coronary flow ability to increase myocardial perfusion in response to oxygen demand. The article describes contemporary ideas of CFR physiology, mechanisms of its impairment in microvascular dysfunction, diagnostic methods, and clinical significance of this phenomenon. CFR shows the ratio between the highest (hyperemic) and baseline (at rest) coronary flow [3]. Reduced CFR values demonstrate vascular system inability to adequately adapt to increased metabolic demand of the myocardium. Normal CFR value is > 2.5. Any values below this level reflect microvascular dysfunction in the absence of anatomical stenosis of the main arteries.

The coronary blood supply has three functional components:

- Epicardial arteries (> 500 μm)
- Pre-arterioles (100–500 μm)
- Arterioles (< 100 μm), which regulate resistance to blood flow.

Regulation is based on metabolic, myogenic and endothelial mechanisms, with the participation of nitrogen oxide (NO), prostacyclin and endothelin-1.

Mechanisms of Coronary Reserve Impairment

Microvascular angina results from functional and/or structural changes in coronary microvessels, and a combination of both factors is not uncommon. Specifically, functional disorders causing MVA can manifest as impaired vessel dilation (abnormal vasodilation) and/or excessive narrowing of coronary microvessels (microvascular spasm). Impaired vasodilation can be a result both of endothelium-dependent and endothelium-independent mechanisms [9].

Endothelial dysfunction

Endothelial dysfunction (ED) means a pathological condition with imbalance between vasodilators, antimitogenic and antithrombotic substances (endothelium-dependent relaxants) and vasoconstrictors, prothrombotic and proliferative substances (endothelium-dependent constrictors) [11]. Besides, ED is associated with decreased bioavailability of nitrogen oxide (NO): its synthesis decreases and/or its degradation increases, thus restricting the vasodilatative property of vessels. Studies showed that the presence of cardiovascular risk factors contributes to endothelial dysfunction, which causes persistent decrease in coronary blood flow (CBF) or vasoconstriction with evident miocardial perfusion impairment [9, 11]. Endothelial secretion imbalance leads to production of vasoconstrictors, such as endothelin-1, which cause changes in the systolic rhythm of coronary arteries and blood flow disturbances. These processes facilitate

deposition of metabolites in the myocardium, aggravate vascular endothelium dysfunction and can cause MVA [13].

Oxidative stress (ROS) and impaired arteriola autoregulation

Studies show that decreased bioavailability of nitrogen oxide (NO) together with higher production of reactive oxygen species (ROS) relates pro-inflammatory condition to endothelial dysfunction, observed in MVA [8]. Vasodilator-resistant endothelial dysfunction can lead to myocardial ischemia, especially during physical exercises.

MVA patients have vasoactive substance imbalance: higher levels of intercellular adhesion molecule 1, endothelin-1 and superoxide dismutase (SOD) activity, resulting in excessive accumulation of ROS. These vasoconstrictive factors are not compensated by endogenous NO and other vasodilators [3]. Although studies have partially invalidated the theory of endothelial causes of MVA, by showing reduced peripheric vessel response to endothelin in MVA patients, non-invasive methods of pulse-wave velocity evaluation showed similar disorders in vascular reactivity in patients with MVA and IHD [2, 3]. Endothelial dysfunction also stimulates precursor cell mobilisation from bone marrow, but their functional activity is impaired, causing incorrect proliferation [3]. Inflammation and impaired immune response speed up atherosclerosis development by impacting the microvascular system. The key role in the inflammatory cascade is played by interleukins IL-1, IL-6 and tumour necrosis factor alpha (TNF-α) [8].

Higher C-reactive protein (CRP) levels in MVA patients show the connection between disease pathophysiology and chronic inflammation. Immune system disorders, including NK cell activation and higher pro-inflammatory cytokine levels, contribute to vessel constriction and lymphocyte recruiting and increase oxidative stress.

In addition to immune diseases, chronic infections, e.g., Helicobacter pylori, are more often observed in MVA patients and can cause endothelial dysfunction because of incorrect immune regulation [3]. The interest in the role of intestinal microbiota in atherosclerosis has been recently increasing [8]. Metabolites, for instance trimethylamine N-oxide (TMAO), are produced from choline, betaine and L-carnitine in the presence of intestinal bacteria. Higher TMAO levels trigger NF-kB signal path, boosting expression of pro-inflammatory genes, including cytokines, adhesion molecules and chemokines. TMAO also stimulate oxidative stress and activation of NLRP3-inflammasome and release of IL-18 and IL-1β. Therefore, diet has a huge impact on TMAO values and atherosclerosis progression [8]. A recent study in obese IHD patients showed that the use of probiotics, synbiotics and functional probiotic products contributed to control of plasma TMAO and HDL-C levels. Further studies are needed to assess the efficacy of TMAO inhibition in the management of atherosclerosis [8].

Support of the inflammatory component in MVA pathophysiology is evidenced by reduced levels of serum dihydroxyeicosatrienoic acid, one of the key epoxyeicosatrienoic metabolites, possessing antiinflammatory and vasodilatory properties. This metabolite is formed in the presence of cytochrome P450 (CYP) 2C19, and in MVA patients a share of "bad metabolites" of this enzyme is higher, causing impaired vascular tone regulation and unrestricted vasoconstriction of small coronary vessels [3]. Platelet activation, which depends on eicosanoid reaction, is associated with increased expression of their soluble ligand CD40, stimulating further release of pro-inflammatory cytokines and facilitating development of pro-atherogenic processes [3]. At the same time, the serum concentration of soluble suppression of tumorigenicity 2 (sST2) receptor for interleukin-33 (IL-33) rises. Activation of this receptor is associated with development of heart fibrosis and endothelial dysfunction in MVA patients.

Another factor, which aggravates antiinflammatory mechanisms in MVA patients, is vitamin D deficiency. Imbalance between pro- and antiinflammatory agents is worsened even more by lower levels of high density lipoprotein cholesterol, which acts as endogenous inhibitor of vascular inflammation [3]. Studies showed that MVA patients have significantly lower serum vitamin D levels vs. healthy individuals, making it possible to consider vitamin D deficiency as a potential risk factor contributing to intensification of inflammatory processes, endothelial dysfunction and development of MVA [1]. Systemic inflammation is aggravated even more by circulating pro-inflammatory microparticles, which are thought to be responsible for NO modulation and release of cytokines, as well as monocyte recruiting [8]. Although the theory of inflammation is quite convenient, the data on beneficial effects of anti-inflammatory drugs on MVA pathogenesis are insufficient [3, 8]

Smooth muscle cell hyperresponsiveness and abnormal vasoconstriction in acetylcholine provocation tests

Acetylcholine is a vasoactive mediator, which triggers a vasospasm by activation of cholinergic receptors on smooth muscle cells of the vascular wall. In normal endothelium, acetylcholine causes vasodilation due to

stimulation of nitrogen oxide (NO) release. However, in endothelial dysfunction, the ability of endothelium to produce NO decreases significantly, leading to dominancy of muscarine receptors of smooth muscles and development of vasoconstriction. In a microvascular spasm during an acetylcholine provocation test, the patient experiences ischemic changes on the electrocardiogram, and typical clinical symptoms of angina can be observed; at the same time, there are no angiographic signs of epicardial coronary artery stenosis [6].

Catecholamine hypersensitivity

The dominance of the adrenergic system in MVA patients is also evidenced by results of radionuclide scanning, which demonstrated impaired uptake of the tracer, an analogue of adrenalin, competiting with endogenous catecholamines in vegetative nerve terminals of the heart muscle [2]. A similar conclusion is confirmed by disorders in the system of neural regulation of cardiac activity, which were assessed using a spectral analysis of RR segments and metabolic studies. Symptoms of adrenergic activation in MVA patients can partially result from tissue hypersensitivity to an unstable level of endogenous catecholamines. This adrenergic receptor hypersensitivity is likely not to be limited to cardiac and respiratory disorders and reflects the stimulating action of receptors in the bronchial tree and pulmonary blood flow in these patients. During physical exercises, intramuscular pH values and phosphocreatine levels drop rapidly, and it takes time for them to get back to normal values [3]. There are evidences of sympathic dysfunction in vascular remodelling and microvascular complications. Some publications describe data on impaired parasympathetic tone and sympathic dominance in MVA patients [14]

Microvascular inflammation and remodelling: the role of cytokines

Chronic low-level inflammation plays a key role in pathogenesis of microvascular dysfunction (MVD). Endothelium-dependent MVD, assessed via microvascular response to acetylcholine, correlates with higher levels of inflammatory markers, including high-sensitivity C-reactive protein (hs-CRP) and soluble urokinase plasminogen activator receptor (suPAR) [8]. The central mediators of an inflammation process are pro-inflammatory cytokines, such as interleukin-1 (IL-1),interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) [3].

Immune cell activation is associated with release of endothelin (ET) and immunomodulatory activators of ET, causing endothelial dysfunction. During inflammatory activation, higher expression of vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) occur, boosting interaction between monocytes and endothelium. Higher monocyte integrin affinity contributes to their adhesion and migration via vascular wall, causing endothelial cell damage.

The signaling pathway, mediated by NOD-like receptor family pyrin domain containing 3 (NLRP3), has also a role to play in pathogenesis of microvascular damage. In ischemic reperfusion, heart microvessel cells (CMEC) demonstrate increased NLRP3 expression, caspase-1 activation, and significant rise in pro-inflammatory interleukin IL-1β and IL-18 levels, resulting in localised inflammation and facilitating endothelial dysfunction [10]. Besides, damages in the signalling function of perivascular adipose tissue (PVAT) impact localised inflammation, atherosclerotic process and microvascular function regulation. Studies of isolated vessels showed that PVAT inflammation disturbs normal control of the microvascular function of skeletal muscles [7].

Perivascular fibrosis and vascular wall thickening

Structural abnormalities, related to coronary microvascular dysfunction, are mostly represented by narrowing of arteriole and capillary orifice, perivascular fibrosis and capillary depression, often with higher left ventricle weight. These events have been documented in patients with hypertrophic cardiomyopathy and hypertensive heart disease. In both conditions, observed morphological changes are described by unfavourable arteriole remodelling, causing medial wall thickening (mostly because of smooth muscle hypertrophy and increased collagen accumulation), and various degrees of intima muscle thickening, resulting in altered coronary physiology and CBF. An important common feature of these conditions is diffuse microvascular remodelling, involving the entire left ventricle [7].

Coronary microvascular dysfunction is associated with structural and functional remodelling of microcirculation, leading to impaired self-regulation of coronary blood flow. Endothelium is essential for CBF regulation through modulation of vasorelaxants, such as nitrogen oxide (NO), prostacyclin (PGI2) and endothelium-derived hyperpolarizing factors (EDHF). Dysfunctional endothelium is a result of the action of pathological vasoconstrictors (such as endothelin-1, superoxide, hydrogen peroxide andthromboxane), which cause vascular imbalance. Besides, microvascular spasm involves impaired vasomotion (physiological beating) and is closely connected with the presence

of endothelial dysfunction [6]. Decreased CFR is associated with:

- A higher cardiovascular risk

Sixteen studies in 8,446 patients showed 3.7-fold increase in the risk of death in patients with abnormal CFR. This conclusion is important because total mortality is resistant to bias and is a clinically significant result. Also, abnormal CFR causes 3.4-fold increase in cardiovascular risk even with correction of some other prognostic factors in individual studies, such as age, hypertension, diabetes mellitus,dyslipidemia, smoking, and a history of myocardial infarction. On the average, decrease in CFR by 0.1 unit is associated with 16 % increase in the risk of death. This conclusion demonstrates that CFR is a risk continuum, where lower levels predispose patients to more unfavourable clinical results [5].

- Poor prognosis in INOCA patients

INOCA (ischemia with non-obstructive coronary arteries) is a clinical syndrome with ischemic symptoms in the absence of a primary stenosis of the epicardial coronary artery of ≥ 50 %. In the majority of cases, INOCA is caused by CMD (coronary microvascular dysfunction, including microvascular spasm), epicardial coronary spasm or a combined pathology. INOCA patients have worse quality of life and a higher long-term cardiac risk, recurrent hospital admissions and high healthcare costs. Predictive effects of CFR changes were studied in INOCA patients. In patients with abnormal CFR, long-term results, such as primary unfavourable cardiac events and target vessel insufficiency, rise vs. patients with normal CFR [4]. It was demonstrated that INOCA patients have lower quality of life. Moreover, the annual costs for INOCA patient management are very high because of frequent hospitalisations and repeated invasive tests [12].

- Resistivity to conventional antianginal therapy

Other drugs, such as ranolazine, ivabradine, nicorandil, can be used in MVA patients resistant to conventional therapy. Their main mechanism of action in MVA is boosting antianginal effects. Nicorandil can contribute to higher CFR levels. Studies of the use of trimetazidine in MVA patients show various results. All these drugs are considered to be stage 2 and 3 in the management of patients with refractory MVA [2, 12].

Therapeutic Approaches in Abnormal CFR

Despite heterogeneity of pathophysiologic mechanisms of MVA, baseline drug therapy is an important element of treatment. Conventional antianginal drugs, including β-adrenoceptor blocking agents, angiotensin-converting enzyme inhibitors (ACE inhibitors)/angiotensin II receptor blockers (ARB), as well as calcium channel blockers (CCB), are currently the first-line therapy in MVA patients. If monotherapy is not efficient enough, a combination of agents can be used, particularly β-blockers and CCB.

In patients with an unstable angina threshold due to physical excercises, combined drug therapy with individually selected medications may be preferable. In the absence of clinically significant response to conventional therapy, it is recommended to consider alternative drug strategies with the use of nicorandil, ranolazine, ivabradine and estrogens, proton pump inhibitors, taking into account individual clinical and functional characteristics of the patient [16]. RAAS blockers (ACE inhibitors/ARB) facilitate improved endothelial function, increase CFR values in patients with microvascular dysfunction [17], while β-blockers reduce oxygen demand of the myocardium. Ivabradine prolongs diastole and improves coronary perfusion. Nitrates demonstrate limited clinical efficacy in MVA patients, which is the difference between the management of this pathology and conventional angina [16]. Ranolazine and nicorandil are promising drugs for the management of refractory MVA. Nicorandil, which can activate ATP-sensitive potassium channels and nitrate component, has a combined effect: it dilates blood vessels, improves coronary blood flow, reduces pre- andafterload, and decreases platelet aggregation. Protective effects of nicorandil are a result of antioxidative activity, inhibition of apoptosis and inflammatory miocardial response to ischemia, which is confirmed by preclinical and clinical studies [15]. The antianginal effect of ranolazine is possible due to late sodium current (late INa) inhibition in cardiac cells. In ischemia, pathological late sodium current is activated, causing Na^+ accumulation in the cell. It activates Na^+/Ca^{2+} exchange and leads to secondary intracellular accumulation of Ca^{2+} [18].

Therefore, reasonable selection of a drug therapy in microvascular angina should take into account individual characteristics of the disease and variability of clinical response to conventional antianginal agents. If the conventional approach is not efficient, alternative drugs can be used, for instance ranolazine, nicorandil, ivabradine, and RAAS blockers. Special attention should be paid to medications affecting pathological elements of microvascular ischemia, particularly to ranolazine, which treats ion imbalance at the cellular level, and nicorandil, which combines vasodilatory, antioxidant and cytoprotective properties [19, 20]. Combination therapy adjusted for the clinical and functional characteristics of the patient ensures more efficient control of symptoms and contributes to better prognosis in microvascular angina.

Discussion

More recently, MVA has been considered a clinically significant form of IHD, which is associated with dysfunction of coronary microvessels in the absence of epicardial artery obstruction. According to the results of recent randomised studies and large registries, the incidence of MVA in patients with suspected IHD, but without significant coronary artery stenosis is 30 to 50 % [21, 22]. One of the most large-scale studies describing the role of MVA in ACS is ISCHEMIA, where some patients with initially minor damage to large vessels were diagnosed with marked microvascular dysfunction with prognosis worsening and higher cardiovascular risk [23]. Similar data were confimed in study CorMicA (Coronary Microvascular Angina), a randomised controlled study, demonstrating that the use of functional stratification of microvascular tone and an individual approach to therapy improved the quality of life and angina symptoms in this patient group [24]. Moreover, results of a subset analysis of women in WISE (Women's Ischemia Syndrome Evaluation) registry shows that microvascular ischemia in women is associated with a higher risk of cardiovascular death and cardiac insufficiency, underlining the clinical significance of MVA as a predictor of severe outcomes [25, 26]. Therefore, microvascular angina is no longer considered a benign condition. Recent data show its significance in the development of ACS and other unfavourable cardiovascular events and the need in early diagnosis and target therapy.

The main challenge of MVA is the array of clinical presentations and lack of understanding of pathogenesis of this condition. When assessing therapy efficacy, it is essential to consider not only antianginal therapy, which was discussed earlier, but also approaches to prescription of prognosis-modifying drugs [27]. Numerous studies prove that several renin-angiotensin-aldosterone system blockers can improve endothelial function and decrease cardiovascular risks, while statins have modulatory action in regard to cholesterol levels and inflammatory processes [28, 30]. Calcium antagonist therapy also has a tole to play, because it cane relieve symptoms by relaxing vessels and improving coronary blood supply [29, 30]. Antiplatelet drugs can be useful in reduction of the risk of clotting, which is particularly important in patients with comorbidities [30, 31]. The use of antioxidants is also very important, because they can decrease oxidative stress, which contributes to pathophysiology of microvascular angina [33]. Thus, a comprehensive therapy approach taking into account all various drug classes can considerably improve the quality of patients' life and reduce cardiovascular risks.

Conclusion

Chronic low-level inflammation is a key factor in the development and progression of microvascular dysfunction, which is proven by increased levels of proinflammatory cytokines and markers of systemic inflammation. Activation of immune cells and associated signalling paths, such as NLRP3 inflammasome, causes endothelial cell damage and impaired vascular homeostasis. Defective regulation of perivascular adipose tissue aggravates localised inflammation and functional microvascular disorders. These data emphasise the importance of a comprehensive approach to diagnosis and therapy of microvascular dysfunctions with due account of proinflammatory strategies, aiming at endothelial function normalisation and prevention of vascular complications. Further studies are needed for the development of efficient therapeutic interventions to modulate inflammatory processes and facilitate microvascular remodelling.

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ГИПЕРУРИКЕМИЯ И СЕРДЕЧНО-СОСУДИСТЫЙ РИСК: МИКРОБИОТА КИШЕЧНИКА — КЛЮЧЕВОЕ ЗВЕНО ПАТОГЕНЕЗА И НОВАЯ МИШЕНЬ ТЕРАПИИ

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Hyperuricemia and cardiovascular risk: gut microbiota as a key link in pathogenesis and a new target for therapy

Резюме

Гиперурикемия — это значимый и самостоятельный фактор риска сердечно-сосудистых заболеваний. В последние годы внимание ученых привлекает микробиота кишечника и ее влияние на различные процессы в организме человека. На данный момент существуют доказательства важной роли микробиоты в патогенезе гиперурикемии. Увеличение численности патогенной микрофлоры способствует вялотекущему воспалению и повышению уровня мочевой кислоты через механизмы метаболизма пуринов. Цель данного обзора заключается в анализе и систематизации современных данных о влиянии кишечной микробиоты в патогенезе гиперурикемии и сердечно-сосудистого риска. В статье обсуждаются перспективные методы коррекции гиперурикемии, такие как модификация образа жизни, трансплантация фекальной микробиоты, пробиотики и постбиотики. Обзор подчёркивает необходимость дальнейшего изучения микробиоты как ключевого звена патогенеза гиперурикемии и разработки новых, инновационных терапевтических стратегий.

Ключевые слова: *гиперурикемия; сердечно-сосудистые заболевания; микробиота кишечника; пробиотики; постбиотики*

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Abstract

Hyperuricemia is a significant and independent risk factor for cardiovascular diseases. In recent years, scientists have been paying attention to the gut microbiota and its impact on various processes in the human body. Currently, there is evidence of the important role of the microbiota in the pathogenesis of hyperuricemia. An increase in the number of pathogenic microflora contributes to chronic inflammation and an increase in uric

acid levels through the mechanisms of purine metabolism. The purpose of this review is to analyze and systematize current data on the impact of the intestinal microbiota on the pathogenesis of hyperuricemia and cardiovascular risk. The article discusses promising methods for correcting hyperuricemia, such as lifestyle modification, fecal microbiota transplantation, probiotics, and postbiotics. The review highlights the need for further research on the microbiota as a key factor in the pathogenesis of hyperuricemia and the development of new and innovative therapeutic strategies.

Key words: *hyperuricemia; cardiovascular diseases; gut microbiota; uric acid; probiotics; postbiotics*

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HU — hyperuricemia, UA — uric acid, NO — nitrogen oxide, EH — essential hypertension, CVD — cardiovascular disease, SCFA — short-chain fatty acids, BP — blood pressure, XDH — xanthine dehydrogenase, LPS — lipopolysaccharides, L. — Lactobacillus, XO — xanthine oxidase, E — Escherichia, TMAO — trimethylamine N-oxide, FMT — fecal microbiome transplant.

Introduction

Hyperuricemia (HU) presumes the elevation of serum uric acid (UA) levels over 420 μmol/L [1, 2]. In different documents reference UA ranges vary based on the gender, with HU confirmed when UA levels reach ≥ 416.0 μmol/L (7.0 mg/dL) in males or ≥ 357.0 μmol/L (6.0 mg/dL) in females [3]. Asymptomatic HU can be additionally defined as elevated UA levels over 405 μmol/L without clinical manifestations [4].

UA is mainly synthesized in the liver, bowel, and the vascular endothelium as a final metabolic product of exogenous purines (consumed with food) and endogenous purines (formed in damaged, dying, or dead cells) [2, 5, 6].

While extracellular UA acts as an antioxidant, intracellular UA is actually a prooxidant, causing inflammation in endothelial and smooth muscle cells, as well as intracellular oxidative stress, thus leading to endothelial dysfunction [3, 6, 7]. UA affects the renin-angiotensin-aldosterone system via two mechanisms, including the stimulation of renin plasma activity and renal renin expression. Besides, UA was detected in atherosclerotic plaques [3]. It reacts with nitrogen oxide (NO), a very important vasodilator, forming 6-aminouracil and thus depleting NO levels, promoting essential hypertension (EH). UA also prevents NO production by inhibiting endothelial NO synthase and decreases arginine availability, which promotes endothelial dysfunction and EH even more [3, 8]. The PAMELA study has demonstrated that each serum UA level elevation by 1 mg/dL is associated with an approximately 30 % increase in EH risk [8]. It has been confirmed that asymptomatic HU increases the risk of both ischemic and hemorrhagic stroke twice within three years, i.e. asymptomatic HU may be one of the risk factors for strokes and other cardiovascular diseases (CVDs) or complications [7]. UA monitoring is required to support the metabolic health in the population.

Intestinal microbiome specifically contributes to HU. 80 % UA is formed due to the degradation of endogenous purines, while 20 % UA is formed from exogenous purines (i.e. food). A high-purine diet (seafood, animal by-products, alcohol) is a risk factor for HU and an important cause of intestinal microbiome imbalance in patients [3, 9, 10, 11]. Purine nucleotides are hydrolyzed to adenine and guanine, deaminated with the formation of xanthine, and then oxidized to UA [9].

The goal of literature review was to systematize the information about the effects of dysbiosis as an independent CVD risk factor in HU, mediating inflammation and endothelial dysfunction. Studies of microbiome effects on the human health have been active lately, with strategies being developed to affect the microbial composition to treat diseases and achieve active longevity. A microbiome is not a simple concomitant factor, but rather a specific pathogenetic event, acting via purine metabolism mechanisms, neurotransmitter production, stimulation of proinflammatory cytokines, etc. This article discusses the prospective methods of HU correction, including postbiotics, fecal microbiome transplant, and nutrition.

Materials and Methods

The PubMed database was searched for publications devoted to the association of hyperuricemia and cardiovascular diseases, microbiome effects on these conditions published within the prior 5 years (since 2020) using the following search terms: “hyperuricemia and

cardiovascular diseases", "microbiome and hyperuricemia", "microbiome and cardiovascular diseases". A total of 5,397 scientific publications were detected, with 42 (including 5 Russian) articles corresponding to this review topic included into the review.

Results and Discussion

High-performance methods and analytical tools developed within the latest 15 years in the sphere of microbiome studies have changed our views on its importance for the host body. Intestinal microbiome is a complex ecological system, a multicellular metabolically active "organ" consisting of prokaryotic cells, eukaryotic host cells, and bacteriophages, creating a unique intestinal ecosystem.

A sufficient number of studies elucidating the association of HU, CVDs, and intestinal microbiome is currently available. These describe the microbiome effects on UA levels, endothelial dysfunction, participation in atherogenesis; favorable and pathogenic/opportunistic flora has been defined, with alternative treatment methods proposes for different diseases (Table 1).

Compared to patients with normouricemia, patients with HU demonstrated altered microbiome composition characterized by the decreased Coprococcus spp. counts [11]. Coprococcus spp. form the main genera of the Lachnospiraceae Bacillota family which maintain microbial homeostasis and metabolic health, as they promote the production of an important metabolite butyrate [12]. Butyrate is a short-chain fatty acid (SCFD) which plays a key role in maintaining the intestinal health, supplying the colonic cells, improving the barrier function, suppressing inflammation and promoting a balanced microbiome [13]. It also decreases the blood pressure (BP), suppresses the production of proinflammatory cytokines (i.e. tumor necrosis factor α, interleukin 12, interferon γ), and enhances the production of an anti-inflammatory interleukin 10 by monocytes [14], while also suppressing xanthine dehydrogenase (XDH) activity [15]. Thus, decreased Coprococcus counts in patients with HU lead to elevated UA levels, intestinal barrier function worsening, promoting the low-grade inflammation in the body and worsening the CVD prognosis.

The intestinal microbiome in patients with gout was characterized by decreased Faecalibacterium prausnitzii counts [9].

Faecalibacterium prausnitzii is another microbe producing butyrate. Higher microbial counts were reported in patients with normal UA levels [11, 16]. Fecal microbiome sequencing has demonstrated that people with higher Faecalibacterium prausnitzii counts had lower coronary artery disease incidence vs. the control group. In murine studies Faecalibacterium prausnitzii suppressed inflammation and had antiatherosclerotic effects after the oral administration. This effect was caused by the decreased lipopolysaccharide (LPS) synthesis in the bowel along with enhanced mechanical and mucous barriers, thus leading to decreased plasma LPS levels and antiatherosclerotic effects [17].

Collinsella aerofaciens is represented in the colon of a healthy human, producing the formic and lactic acids.

Collinsella spp. modulate serum UA levels via four mechanisms. Firstly, Collinsella spp. directly produce UA. Secondly, Collinsella spp. indirectly inhibit UA degradation by other bacteria. Thirdly, metabolites produced by Collinsella spp. decrease the renal and intestinal UA excretion. Finally, Collinsella spp. contains genes of purine metabolism enzymes, e.g. analogues of hypoxanthine-guanine phosphoribosyl transferase participating in the hypoxanthine reutilization, as well as genes of UA precursor synthesis and XDH transforming xanthine into UA [18]. This bacterium can alter cholesterol absorption in the bowel, decreasing hepatic glycogenesis and enhancing triglyceride synthesis. Collinsella spp. directly correlate with the total cholesterol and low-density lipoprotein levels [19].

Lactobacillus (L.) and Pseudomonas promote UA degradation and excretion in the bowel with SCFA production [9].

L. gasseri PA-3 is a bacterium detected in the yoghurt and other cultured milk products, thus presuming that food habits may affect UA levels [18]. L. gasseri PA-3 may absorb and utilize purines in the bowel, thus decreasing intestinal purine absorption and decreasing serum UA levels [9, 18]. L. brevis DM9218 may efficiently decrease serum UA levels in rats with HU due to the inhibition of xanthine oxidase (XO) activity [9, 20, 21]. L. reuteri TSR332 and L. fermentum TSF331 may control HU via cleaving purines [9].

XDH and XO may be secreted by Escherichia (E.) bacteria in intestinal epithelial cells, accelerate hypoxanthine and xanthine degradation, and transform more purines into UA [9].

The microbial composition also directly affects the cardiovascular system. Some bacteria belonging to Streptococcus and E. coli genera may exhibit proinflammatory effects, producing neurotransmitters in the autonomous nervous system that alter the vascular tone, leading to EH [22], while several L. and Bifidobacterium strains exhibit anti-inflammatory properties and are considered important probiotics [23].

Increased counts of Gram-negative microbes, including Klebsiella, Parabacteroides, Desulfovibrio, Prevotella, correlated with higher BP values. LPS (or endotoxins) form the main component of the outer membrane in Gram-negative bacteria and have proinflammatory properties [14]. Enhanced LPS entering the intestinal

lumen after the cell lysis may promote the production of a large amount of cytokines, enhance the intestinal wall permeability, and cause the low-grade inflammation called "metabolic endotoxemia" [9].

Klebsiella pneumoniae belonging to the Klebsiella genus of the Enterobacteriaceae family, just like other Gram-negative bacteria, may form extracellular vesicles, permeate the intestinal barrier, and migrate to various tissues if the intestinal barrier integrity is impaired due to inflammation, aging, etc. Extracellular vesicles impair the endothelial dysfunction and promote the generation of superoxide anion radicals in endothelial cells, causing endothelial dysfunction [24].

A recent study evaluating the intestinal microbiome alterations in the Chinese population has demonstrated that Desulfovibrio spp. is an obligate anaerobe belonging to sulfate-reducing microbes that breathes anaerobically using sulfate as a final electron acceptor and reducing it to hydrogen sulfide. On the one hand, hydrogen sulfide may become an energy source for mitochondria, while on the other hand it becomes a rather toxic compound in higher concentrations, impairing the intestinal barrier function, elevating the circulating LPS levels, and producing the microbial urease [25, 26].

It has been demonstrated that an atherosclerotic plaque contains a specific microbial medium containing various microbes, e.g. Streptococcus, Pseudomonas, Klebsiella, Veillonella spp., Chlamydia pneumoniae. The comparative intestinal microbiome studies have detected that patients with clinically manifesting atherosclerosis had higher counts of Collinsella spp., Enterobacteriaceae family representatives, Streptococcaceae, along with lower counts of Eubacterium, Roseburia, and Ruminococcaceae producing SCFA compared to healthy persons [14]. Streptococcus may permeate the aortic endothelial cells in humans, stimulating pro-inflammatory cytokines associated with atherosclerosis [19, 27, 28]. Klebsiella and other representatives of the Enterobacteriaceae family are associated with increased tumor necrosis factor α or interleukin-1β levels along with the production of the bacterial metabolite trimethylamine N-oxide (TMAO). In its turn, increased TMAO levels enhance the platelet sensitivity, promoting thrombosis [29].

Veillonella spp. belong to the Bacillota phylum of the Negativicutes class; these affect the formation of atherosclerotic plaques via amino acid fermentation with the production of SCFA [28].

Intestinal Roseburia intestinalis spp., just like Faecalibacterium prausnitzii, are common bacteria producing butyrate due to fiber fermentation.Roseburia intestinalis promotes the metabolic alteration from glycolysis to the use of fatty acids and suppression of systemic inflammation, prevents the formation of atherosclerotic plaques, and slows down atherosclerosis [28, 30].

SCFA effects on CVDs and HU are ambiguous, depending on their type and source. For example, butyrate has cardioprotective properties, while excessive propionate is hazardous in HU. An optimal SCFA balance is important for the body.

Table 1. *The effect of the intestinal microbiota on uric acid levels and cardiovascular risks*

Bacterium	Role in hyperuricemia	Role in cardiovascular diseases
Coprococcus	Butyrate production -> inhibits xanthine dehydrokinase activity -> decreases uric acid levels	Butyrate production -> suppresses low-grade inflammation -> reduces blood pressure
Faecalibacterium prausnitzii	Butyrate production -> inhibits xanthine dehydrokinase activity -> decreases uric acid levels	Decreased synthesis of lipopolysaccharides -> anti-atherosclerotic effect
Collinsella	Produce uric acid, inhibit the degradation of uric acid by other bacteria, and reduce renal and intestinal excretion of uric acid.	Increases triglyceride synthesis, cholesterol and low-density lipoprotein levels
Lactobacillus	Absorbs and utilizes purine in the intestine -> reduces uric acid levels; Inhibits xanthine oxygenase activity	Reduced inflammation -> lower blood pressure
Escherichia	They secrete xanthine dehydrokinase and xanthine oxygenase; they convert purines into uric acid	Neurotransmitter production -> increased blood pressure
Klebsiella	Production of short-chain fatty acids -> breakdown and elimination of uric acid from the body	Impairs endothelial function -> endothelial dysfunction and aging; Found in atherosclerotic plaques; Trimethylamine N-oxide production -> promotes thrombosis
Desulfovibrio	Produces urease	Endotoxin production -> intestinal barrier disruption -> high lipopolysaccharide levels
Veillonella	-	Fermentation of amino acids to form short-chain fatty acids -> formation of atherosclerotic plaques
Roseburia intestinalis	-	Use of fatty acids in metabolism, reduction of systemic inflammation -> prevents the formation of atherosclerotic plaques

Effects of Drug Products on the Microbiome and UA

XO inhibitors are the main pharmacological drugs used in the HU treatment. XO inhibitors decrease UA levels by suppressing the UA synthesis. Allopurinol is a purine XO inhibitor with an active metabolite (oxypurinol) acting as a reversible covalent inhibitor that is excreted with urine. On the contrary, febuxostat is a potent non-purine non-competitive XO inhibitor metabolized in the liver. The recent studies have shown that these drugs not only relieve HU symptoms, but also affect the intestinal microbiome positively. Both drugs could lead to the increased Bifidobacterium counts and decreased pathogenic and/or opportunistic flora counts after decreasing UA levels [9].

SGLT2 inhibitors decrease UA levels due to its enhanced urine excretion and possibly due to the decreased amount of reactive oxygen species that promote UA reabsorption in renal tubules [31].

Alternative Treatment

Thanks to the analyzed mechanisms of microbiome effects on the serum UA levels, the treatment affecting the bacterial count as a specific pathogenetic element is actively searched for (Table 2).

Injecting the Alistipes indistinctus live culture into the body led to the 2.5-fold increase in the UA excretion with feces due to the enhanced production of a hippuric acid metabolite. Hippuric acid may become an alternative treatment of HU and associated metabolic disorders; its biochemical mechanisms are sufficient themselves to restore normal serum urate levels without affecting the renal excretion [11].

Chinese scientists modified the E. coli Nissle 1917 (EcN) probiotic strain for UA cleavage. It demonstrated the ability to cleave UA efficiently both with the oral and intravenous administration. Direct EcN administration into the blood is a new idea for the treatment of metabolic disorders. It has been reported that EcN injections into blood vessels are safe as these do not contain virulence genes and accommodation factors that promote its colonization and survival in the host body [32].

Such microbiome metabolites as polysaccharides beneficially contributed to the UA regulation. During studies, a polysaccharide from Ulva lactuca decreased UA levels, while a polysaccharide from Enteromorpha prolifera significantly decreased serum UA and urea nitrogen levels [9].

Lifestyle modification cannot significantly affect HU, but is a mandatory treatment and metabolic health prerequisite. A Mediterranean diet does not affect the urate level decrease significantly, but is associated with a lower CVD incidence and enhanced life expectancy. With a low-purine diet, serum urate levels decrease approximately by 1 mg/dL. The studies have demonstrated that serum urate levels significantly elevate after the consumption of all alcoholic beverageas, except for wine. Tea and general caffeine consumption were not associated with serum urate levels. An enhanced dairy product consumption was associated with lower serum urate levels [9, 10, 14]. When creating diets for patients with HU, main objective include the limitation of exogenous (food) purines, which somewhat decreased serum UA levels, and the adequate liquid consumption [33].

Sulforaphane, an isothiocyanate obtained from the cabbage family vegetables, has an 80% bioavailability due to its small size and lipophilic origin. In rat experiments it enhanced UA excretion by increasing the renal transporter protein expression and suppressed UA reabsorption decreasing the urate transporter 1 and glucose transporter 9 expression in kidneys. It is also promising that sulforaphane may act as allopurinol, decreasing the XO and adenosine deaminase activity [34].

Table 2. *Comparison of hyperuricemia correction methods*

Method	Mechanism of action	Advantages	Disadvantages
Medicinal products	Direct effect on uric acid metabolism through inhibition of xanthine oxygenase; Increased urinary excretion of uric acid	Fast effect, high efficiency	Side effects
Diet	Reduction of exogenous purines	Security, accessibility, positive impact on other systems	Reduction of uric acid by about 1 mg/dl
Physical exercises	Increased uric acid excretion after exercise	Positive effect on the whole body	During exercise, it temporarily increases uric acid
Fecal microbiota transplantation	Restoring the balance of the microbiota	Long-term effect	Invasiveness, risk of infection, low adherence
Probiotics	Increased excretion of uric acid through the intestine; Breakdown of uric acid	Naturalness, minimum side effects	Survival variability, weak colonization
Postbiotics	Decreased xanthine oxidase activity; decreased uric acid reabsorption, etc.	Stability, dosing, acts immediately	More research is needed

Resveratrol is a flavonoid contained in grapes, wine, and some berries. The mechanism via which resveratrol improves the condition in persons with HU may presume the regulation of the intestinal microbiome composition and function. It is important to note that unlike several animals, humans lack a functional enzyme uricase, i.e. direct uric acid cleavage in the body is impossible. However, the microbiome may affect the intestinal urate excretion, which is one of the methods to decrease UA levels in the body [20].

Physical exercises may lead to the temporary increase in UA levels due to accelerated metabolism, although UA elimination from the serum enhances after training [35].

The effects of probiotics, prebiotics, and fecal microbiome transplant on HU is being currently studied [9].

Probiotics are defined as "viable microbes that are beneficial for the host health when consumed in adequate amounts" [23]. Lactobacillus and Bifidobacterium spp. representatives have been used successfully as probiotics for many years. These bacteria produce lactic acid from carbohydrates, creating an acidic medium that suppresses the growth of several pathogenic bacteria [20].

A single complex large-scale crossover study analyzed the association between the consumption of prebiotics/probiotics and HU in adult US citizens. It has been demonstrated that the consumption of probiotics may decrease serum UA levels. Probiotics upregulate the beneficial flora that has a regulatory role in the metabolism of UA and purines, altering the metabolic balance of amino acids, non-saturated fatty acids, etc., and affects the extrarenal excretion, suppressing the transport of urate transporters in the intestine [2].

Probiotic drugs are considered suitable for modulating the NLRP3 inflammasome signaling pathway to improve HU [9]. Inflammasomes are multimeric protein intracellular platforms that activate in response to infections or tissue injury [36]. HU activates the NLRP3 inflammasome-mediated pyroptosis. Pyroptosis is a form of cellular death characterized by the plasma membrane rupture, cytoplasm swelling, osmotic lysis, DNA cleavage, and a release of a large amount of proinflammatory cytokines [37]. Bifidobacterium spp. may have probiotic effects, suppressing the NLRP3 signaling pathway and NLRP3 mRNA expression. Bifidobacterium spp. are the most important probiotics in the human body, playing a leading role in the prevention of pathogen invasion, mucosal homeostasis, intestinal integrity maintenance, and host immunity regulation [38].

Fecal microbiome transplant (FMT) has recently become a new strategy in HU treatment. FMT presumes transplanting a functional healthy human flora to the patient's gastrointestinal tract in order to form a new intestinal microbiome to treat intestinal and extraintestinal diseases. The mechanism of decreased UA levels in FMT may presume two pathways: accelerated UA decomposition and excretion; effects on UA metabolism with UA transporter regulation in the intestinal epithelium [21].

Treatment Perspectives

The modern medicine is aimed at achieving active longevity of the population. Intestinal microbiome modulation is one of the prospective options to achieve this target, as its composition significantly affects the metabolic health. Thanks to probiotics or other drugs and microbiome effects, it may be possible to decrease the risk of several diseases, decrease polypharmacy, and enhance the treatment efficacy.

A postbiotic (a drug containing non-viable microbes and/or their components that is beneficial for the host health) is one of the promising options. This may be represented by a heterogenous mixture of cellular structures and metabolites, e.g. teichoic acids, exopolysaccharides, peptidoglycans, bacteriocins, etc. [39].

Thus, a G1PB postbiotic was obtained by constant heating of Pediococcus acidilactici GQ01 at 65 °C for 30 minutes. G1PB suppressed the XO activity leading to decreased serum UA, creatinine, and urea nitrogen levels in mice with HU. The drug also regulated the expression of genes and proteins associated with the renal UA reabsorption and excretion [15]. Hippuric acid (see above) is also a postbiotic.

Traditional probiotics demonstrate their potential in decreasing UA levels, although their use is limited due to variable strain survival in the gastrointestinal tract and effects dependent on the colonizing ability [40]. Due to colonization resistance, the majority of probiotics are excreted from the intestine with feces after the oral administration soon after their consumption stops [41]. Postbiotics are a prospective alternative without similar limitations. This can be explained by the larger stability of postbiotics during storage, shipping, consumption, along with a high safety level [42]. Postbiotics may probably form a pathway towards the standardized, safe, and target therapy.

Conclusion

An intestinal microbiome plays a specifically important role in the pathogenesis of HU, which (along with dysbiosis) leads to worse CVD outcomes. Decreased counts of such beneficial bacteria as Coprococcus and Faecalibacterium prausnitzii, as well as the increased counts of pathogenic and/or opportunistic bacteria (e.g., Collinsella, Klebsiella) promote the chronic low-grade inflammation, endothelial dysfunction, and elevated UA levels which worsen cardiometabolic risks.

Prospective correction methods include probiotics modulating purine metabolism and decreasing UA levels; postbiotics that have benefits in stability, efficacy, and suppressed XO activity; FMT restoring the flora balance and thus improving UA excretion; lifestyle modification supplementing the main treatment methods.

Further studies should be aimed at developing innovative personalized therapeutic strategies. The integration of new approaches into clinical practice may promote the improved cardiometabolic health with the decreased polypharmacy rate.

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ТЕРАПЕВТИЧЕСКИЙ И РЕГЕНЕРАТИВНЫЙ ПОТЕНЦИАЛ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК, ПОЛУЧЕННЫХ ИЗ ЖИРОВОЙ ТКАНИ, В ЛЕЧЕНИИ САХАРНОГО ДИАБЕТА 1 И 2 ТИПА (ОБЗОР ЛИТЕРАТУРЫ)

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Regenerative Potential of Adipose-Derived Mesenchymal Stem Cells in The Treatment of Type 1 And Type 2 Diabetes Mellitus (Review)

Резюме

Работа посвящена анализу терапевтического потенциала мезенхимальных стволовых клеток, полученных из жировой ткани, при лечении сахарного диабета 1 и 2 типа и его осложнений. Приведены краткие сведения о распространенности заболевания, рассмотрены основные существующие подходы к лечению сахарного диабета, направленные на поддержание нормального уровня глюкозы и гликированного гемоглобина, обосновано использование мезенхимальных стволовых клеток, полученных из жировой ткани. Основной недостаток инсулинотерапии, заключающийся в неспособности имитировать физиологическую регуляцию гликемического профиля и полностью устранять сосудистые осложнения у пациентов, стал поводом для поиска более совершенных методик, использующих регенеративный потенциал мезенхимальных стволовых клеток, полученных из жировой ткани. Описаны морфологические и иммуногистохимические особенности данных клеток, охарактеризован широкий спектр факторов роста и сигнальных молекул, определяющих их иммуномодулирующие, антиоксидантные и антиапоптические свойства. Паракринное влияние мезенхимальных стволовых клеток, полученных из жировой ткани, может быть использовано при трансплантации островков поджелудочной железы для повышения их выживаемости. Способность сохранять остаточную массу β-клеток пациента, а также восполнять их количество путем дифференцировки в инсулинпродуцирующие клетки обусловливает использование данных клеток при лечении сахарного диабета 1 типа. В то же время положительное влияние на механизмы инсулинорезистентности, стимуляция гликогенеза и регуляция гликемического профиля характеризуют их перспективность для терапии сахарного диабета 2 типа. Полипотентность и пластичность мезенхимальных стволовых клеток, полученных из жировой ткани, позволяют применить их для лечения диабетических осложнений: трофических язв, диабетических ретино- и нефропатии. Обсуждается состояние клинических исследований, направленных на получение доказательных данных об эффективности и безопасности мезенхимальных стволовых клеток, полученных из жировой ткани, при терапии сахарного диабета 1 и 2 типов.

Ключевые слова: *мезенхимальные стволовые клетки, полученные из жировой ткани, сахарный диабет, диабетические осложнения, лечение*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

The article is devoted to the analysis of the therapeutic potential of mesenchymal stem cells obtained from adipose tissue in the treatment of diabetes mellitus types 1 and 2 and their complications. Brief information on the prevalence of the disease is provided, the main existing approaches to the treatment of diabetes mellitus aimed at maintaining normal glucose and glycated hemoglobin levels are considered, the use of mesenchymal stem cells obtained from adipose tissue is based. The main disadvantage of insulin therapy is the impossibility of imitation the physiological regulation of the glycemic profile and completely eliminating vascular complications in patients. This fact became the reason for searching for more advanced techniques using the regenerative potential of mesenchymal stem cells obtained from adipose tissue. The morphological and immunohistochemical features of these cells are described; a wide range of growth factors and signaling molecules determining their immunomodulatory, antioxidant and antiapoptotic properties is characterized. The paracrine effect of mesenchymal stem cells obtained from adipose tissue can be used in transplantation of pancreatic islets to increase their survival. The ability to preserve the residual mass of the patient's β-cells, as well as to supply their number by differentiating into insulin-producing cells determines the use of these cells in the treatment of type 1 diabetes mellitus. At the same time, a positive effect on the mechanisms of insulin resistance, stimulation of glycogenesis and regulation of the glycemic profile characterizes the demand for them in the treatment of type 2 diabetes mellitus. Pluripotency and plasticity of mesenchymal stem cells obtained from adipose tissue allow their use in the treatment of diabetic complications: trophic ulcers, diabetic retinopathy and nephropathy. The state of clinical trials aimed at obtaining evidence-based data on the efficacy and safety of mesenchymal stem cells obtained from adipose tissue in the treatment of types 1 and 2 diabetes mellitus is discussed.

Key words: *mesenchymal stem cells, adipose tissue, diabetes mellitus, diabetic mellitus complications*

Conflict of interests

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DM — diabetes mellitus, HbA1c — glycated hemoglobin, IPC — insulin-producing cells, MSC –mesenchymal stem cells, ASC — adipose-derived stem cells (mesenchymal stem cells derived from adipose tissue)

Introduction

The progressive growth rate of diabetes mellitus (DM) incidence has allowed this disease to be assigned the status of an epidemic [1-3]. According to the Federal Register of Diabetes Mellitus in the Russian Federation as of January 1, 2021, the number of DM patients has doubled compared to the year 2000 and approached 5 million (4,799,522). The majority of patients with Type 1 Diabetes Mellitus (T1DM) are of working age, with a peak prevalence at 30--39 years, whereas the largest number of patients with Type 2 Diabetes Mellitus (T2DM) are aged over 65 years [2, 4]. Such a distribution of patients leads to significant economic costs and social burden, including expenses for medical care, reduced working capacity, and the need for social protection measures.

As is well known, DM refers to a group of diseases characterized by multiple etiologies and heterogeneity of development. According to the 2019 WHO classification, several types of DM are distinguished, the main ones being Type 1 DM (T1DM), Type 2 DM (T2DM), hybrid forms of diabetes, other specific types, unclassified diabetes, and hyperglycemia first detected during pregnancy. Despite the different pathogenetic mechanisms underlying these diseases, it is generally recognized that the primary characteristic common to all forms of DM is hyperglycemia resulting from the destruction or dysfunction of pancreatic β-cells [5]. The necessity of maintaining normal glucose and glycated hemoglobin (HbA1c) levels in T1DM leads to lifelong dependence on insulin therapy. Hypoglycemic agents are primarily used for T2DM therapy; however, about 14–25 % of patients eventually require exogenous insulin injections [2, 6]. For a long time after the discovery of insulin by Frederick Banting and Charles Best in 1921, insulin therapy remained the only treatment for T1DM, and all research efforts were directed toward improving insulin production technology, optimizing delivery methods, and glycemic self-monitoring techniques [7]. However, exogenous insulin cannot mimic the physiological regulation of the glycemic profile and completely prevent the development of vascular complications. Moreover, the development of macro- and microangiopathies is associated with low levels of C-peptide secreted by the islet β-cells, which could potentially be compensated by the use of long-term functioning, hormonally active β-cells [8, 9].

Pancreatic islet transplantation and the introduction of the so-called Edmonton Protocol into practice have allowed for the successful restoration of endogenous insulin production. Adequate glycemic control achieved immediately after transplantation was maintained for one year in 44 % of recipients [10]. However, the cumulative incidence of unsuccessful islet transplantations over a 5-year long-term retrospective period exceeded

70 % [11]. Furthermore, this procedure is limited due to the lack of a sufficient number of donor cells and the necessity of immunosuppressive therapy for their survival [12].

In recent decades, mesenchymal stem cells (MSCs) have been considered a promising source of insulin-producing cells (IPCs) due to their multipotency, sufficient quantity in the human body, and immunomodulatory properties [13, 14]. Current achievements in this field are mainly aimed at optimizing the control of T1DM progression. Additionally, it has been established that MSCs can improve insulin resistance in peripheral tissues through the secretion of paracrine factors via extracellular vesicles — exosomes [15, 16].

Sources and Morphological Features of Adipose-Derived MSCs (ASCs)

The most popular sources of MSCs are adipose tissue, red bone marrow, umbilical cord, and dental pulp [6, 17, 18]. Adipose-derived MSCs (ASCs), compared to other MSCs, possess a similar proliferative potential and differentiation capacity; however, they have advantages due to the accessibility and less invasive nature of their harvesting [19]. Moreover, it has been noted that adipose tissue contains a higher concentration of MSCs than other sources [20, 21]. ASCs include MSCs from brown and white fat, as well as visceral and subcutaneous fat. The latter includes cells of the dermal layer of the skin, particularly the dermal papilla and interfollicular dermis, as well as hypodermal cells [16, 20, 21]. A particularly abundant source of ASCs is subcutaneous fat obtained through liposuction [22]. The extracted tissue samples undergo enzymatic separation and are seeded in Petri dishes with a specific nutrient medium containing glucose and penicillin [18, 23]. Cultured cells are washed with phosphate-buffered saline, after which they are identified based on their ability to differentiate into osteogenic, chondrogenic, and adipogenic lineages [23]. Morphologically, ASCs are fibroblast-like, spindle-shaped cells with light, euchromatic oval nuclei. These cells exhibit adhesiveness to plastic and are characterized by a set of specific surface markers, the main ones being CD73, CD90, and CD105, while CD36 and CD49d are unique to ASCs [19]. At the same time, they must be negative for markers of hematopoietic and endothelial cells, as well as MHCII, c-kit, Lin, and HLA-DR [6, 14, 19, 24]. ASCs from the dermis and hypodermis are capable of differentiating into keratinocytes, dermal fibroblasts, melanocytes, and endothelial cells [16]. There is evidence confirming the ability of ASCs to differentiate into neurons, smooth myocytes, cardiomyocytes, and hepatocytes — i.e., derivatives of ectodermal, mesodermal, and endodermal sources [15, 25]. It has been noted that ASCs obtained from brown fat are characterized by higher proliferative properties and differentiation potential than ASCs from white adipose tissue [20, 25].

ASCs are being extensively studied for the treatment of a wide range of diseases: multiple sclerosis, myocardial infarction, liver cirrhosis, muscular dystrophy, and trophic ulcers. Their ability to replace damaged β-cells and regulate blood glucose levels is considered a means of restoring the insulin-producing function of the pancreas [15]. The implantation of autologous cells significantly reduces the probability of their rejection, eliminating the need for long-term immunosuppressive drug therapy. Furthermore, using one's own ASCs resolves a complex of ethical issues arising from the use of donor or embryonic stem cells and simplifies the legal aspects of the procedure, which are encumbered by numerous regulatory requirements. However, despite the advantages of autologous ASC therapy, its effectiveness may be reduced due to the influence of the diabetic microenvironment [15]. The persistent hyperglycemic environment in DM can reduce the differentiation potential of ASCs, their proliferation rate, and their immunomodulatory effects [18, 26]. Donor age also influences the proliferation intensity of ASCs: cells from donors under 30 years of age exhibit higher proliferative activity and differentiation rates compared to ASCs from older donors [20]. To date, there is no consensus regarding the optimal delivery method for ASCs from the standpoint of therapeutic effect. Existing methods involve the administration of in vitro differentiated IPCs intravenously, into the portal vein, the thymus, or the subcutaneous adipose tissue of the patient [19, 27].

Therapeutic Potential of ASCs for the Treatment of Type 1 Diabetes Mellitus

The ability of ASCs to differentiate into IPCs was first discovered in 2003, and in less than 20 years, their effect on pancreatic β-cell function has become the subject of extensive preclinical and clinical trials, many of which have entered Phase II [14]. The therapeutic effect of ASCs is attributed to a combination of several effects, primarily their property of replacing damaged β-insulocytes and normalizing blood glucose levels. Genes responsible for the embryonic development of the pancreas are involved in the complex process of ASC differentiation into IPCs [18]. In a study conducted by Dai P. et al. on dogs, the reprogramming process of ASCs into IPCs was induced by a combination of genes Pbx1, Rfx3, Pdx1, Ngn3, Pax4, and MafA [28]. The listed genes were synthesized and ligated into the linear shuttle adenoviral vector pAdTrack-CMV (BglII and HindIII restriction sites), after which the construct was recombined with pAdEasy-1 in E. coli to form the adenoviral vector pAdEasy-Pbx1-Pdx1-Ngn3-Pax4,

co-expressing multiple genes [27]. Using the RedTrack-CMV adenoviral shuttle vectors as mediators, the adenoviral vector pAdEasy-Rfx3-MafA was generated using the same method [28]. The resulting vectors were used to transduce ASCs cultured in Petri dishes, leading to their reprogramming into IPCs [25]. PCR analysis of the obtained IPCs established the expression of β-cell marker genes, including Neurogenin-3 (Ngn-3), Homeobox protein Nkx6.1, V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MafA), and Insulin-1 (Ins-1), and a glucose-stimulated insulin secretion (GSIS) test was performed [18]. To enhance insulin synthesis potential, ASCs undergo genetic modification. Specifically, ASCs overexpressing glucagon-like peptide-1 (GLP-1) and FGF21 have been described; these, being metabolically active hormones, stimulate higher insulin secretion and optimize carbohydrate metabolism [15]. The binding of insulin to its tyrosine kinase receptor triggers a cascade of intracellular phosphorylation reactions: insulin receptor substrate (IRS) proteins, activation of phosphatidylinositol 3-kinase (PI3-kinase), and serine-threonine kinase (Akt). The realization of this signaling pathway stimulates multiple biological reactions, including the translocation of glucose transporter type 4 (GLUT4) in the liver, muscles, and adipose tissue, glucose uptake, increased glycogen synthesis in the liver and muscle tissue, and reduced insulin resistance [29]. Similar to the mechanism of glucose uptake by cells via the GLUT4 transporter, insulin stimulates the translocation to the membrane of several long-chain fatty acid transport proteins: CD36 (cluster of differentiation 36), FATP1 and 4 (fatty acid transport protein family members), and FABPpm (plasma membrane-associated fatty acid-binding protein). It is known that free fatty acids activate several serine kinases (IKK and JNK), which subsequently phosphorylate and degrade insulin receptor substrate-1 (IRS-1), a key protein in insulin signal transduction. There is an opinion that this molecular mechanism may be responsible for insulin resistance associated with hyperlipidemia. Thus, the induction of adipogenesis, linked to the capacity for fatty acid uptake, is an important factor in maintaining systemic insulin sensitivity [30]. Alongside this, adipose tissue produces a number of biologically active substances that regulate energy homeostasis, lipid, and glucose metabolism, such as leptin, adiponectin, resistin, and tumor necrosis factor-alpha (TNF-α). An imbalance of these factors can also provoke the development of insulin resistance or impaired insulin secretion [29] **(Figure 1)**.

In addition to differentiation into IPCs, ASCs activate a paracrine signaling system by secreting a wide spectrum of growth factors, including transforming growth factor (TGF-β1, TGF-β3), granulocyte colony-stimulating factor (G-CSF), basic fibroblast growth factor (b-FGF), vascular endothelial growth factor (VEGF), nerve growth factor (NGF), insulin-like growth factor (IGF), hepatocyte growth factor (HGF), von Willebrand factor (VWF), and others. The secretome of ASCs also contains a range of anti-inflammatory, antioxidant, and anti-apoptotic signaling molecules, which promotes the regeneration of endogenous β-cells and the preservation of their functional mass [19, 22, 25]. ASCs demonstrate a significant immunomodulatory effect by inducing M2 macrophage polarization [31]. As is known, macrophage phenotypes M1 and M2 represent two extremes of activation. The M1 phenotype releases a range of cytokines with pro-inflammatory, antimicrobial, and antitumor activity, while M2 macrophages are an alternatively activated type exerting anti-inflammatory, regenerative, angiogenic, and immunomodulatory effects. Macrophages constitute a significant proportion of immune cells in adipose tissue, reaching 40–50 % in obesity.

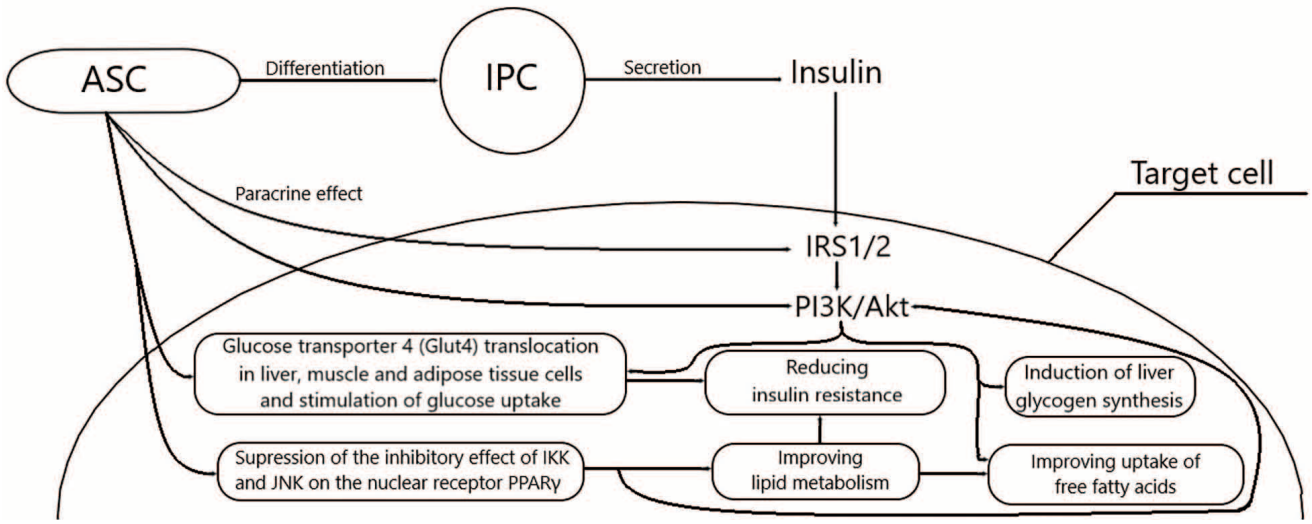

Figure 1. *ASC effect on carbohydrate and lipid metabolism and insuline resistance*

Normally, M2 macrophages predominate, maintaining tissue homeostasis, whereas in obesity, pro-inflammatory M1 macrophages dominate, contributing to the development of chronic inflammation and insulin resistance. The diabetic environment also shifts the balance of macrophages towards M1, exacerbating organopathology [32]. The polarization process of macrophages is regulated by multiple signaling cascades, including the PI3K/AKT, JAK/STAT, NF-κB, Wnt, and Notch signaling pathways. The STAT6 pathway has been established to play a key role in the activation of M2-type macrophages. Experimental studies have revealed the presence of a number of proteins, DNA, mRNA, and microRNAs within ASC exosomes that influence the differentiation and activity of M1/M2 macrophages. For instance, ASC exosomes contain MFGE8 — a glycoprotein that ensures the clearance of apoptotic cells and exhibits anti-inflammatory properties by stimulating M2 macrophage polarization. Cytokines from ASC exosomes exert a similar influence. For example, prostaglandin E2 reduces the expression of M1 markers and increases the expression of M2 markers. Interleukin-6 (IL-6) increases the expression of the IL-4 receptor and STAT6 phosphorylation, stimulating M2 polarization. IGF-2 induces a decrease in inflammatory cytokines and enhances the expression of several genes, such as methyl-CpG-binding protein 2 (Mecp2), an inhibitor of macrophage inflammation. MicroRNAs and long non-coding RNAs from ASC exosomes can activate the transcription of genes that ensure the phenotypic transformation of macrophages from the M1 type to M2. Furthermore, it has been noted that ASC exosomes restore the structure and function of macrophage mitochondria, increase ATP production, and reduce oxidative stress. There is an opinion that the immunomodulatory action of ASCs is based on a mechanism affecting CD4+ T-lymphocytes, involving the induction of apoptosis and cell cycle arrest through the activation of JNK signaling pathways and mitochondrial apoptosis **(Figure 2)**.

In experiments, ASCs inhibited the proliferation of dendritic cells and autoreactive T-lymphocytes. Their interaction with these immunocytes led to a decrease in the level of pro-inflammatory cytokines, e.g., interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and an increase in the level of anti-inflammatory cytokines, such as interleukin-10 (IL-10), prostaglandin E2 (PGE2), and indoleamine 2,3-dioxygenase (IDO). These properties of ASCs have enabled their use as a means of protecting transplants and the patient's own β-cells from inflammatory reactions and autoimmune damage. It is important to emphasize that ASCs positively influenced revascularization processes, which is a critically important factor considering the high risk of cultured islet death due to ischemia [14, 15].

Such effects of ASCs were demonstrated in an experiment on mice: upon co-transplantation of islets with ASCs, significantly less loss of their mass was observed (1.1 ± 0.81 % and 2.7 ± 1.9 % for co-cultured mouse and human pancreatic islets, respectively, versus 22.1 ± 10.5 % using the same technique without ASCs). Despite the fact that the restoration of normoglycemia was temporary, co-transplantation showed higher rates of its restoration with ASC co-transplantation (22.3 ± 4.7 days compared to the control group — 38.5 ± 7.6 days) [33]. Thus, it was noted that the use of ASCs reduces the required mass of transplanted islets and improves their insulin-producing function.

The successful results of experiments obtained in animals prompted investigations into the efficacy and safety of ASC use in humans. In a prospective trial from

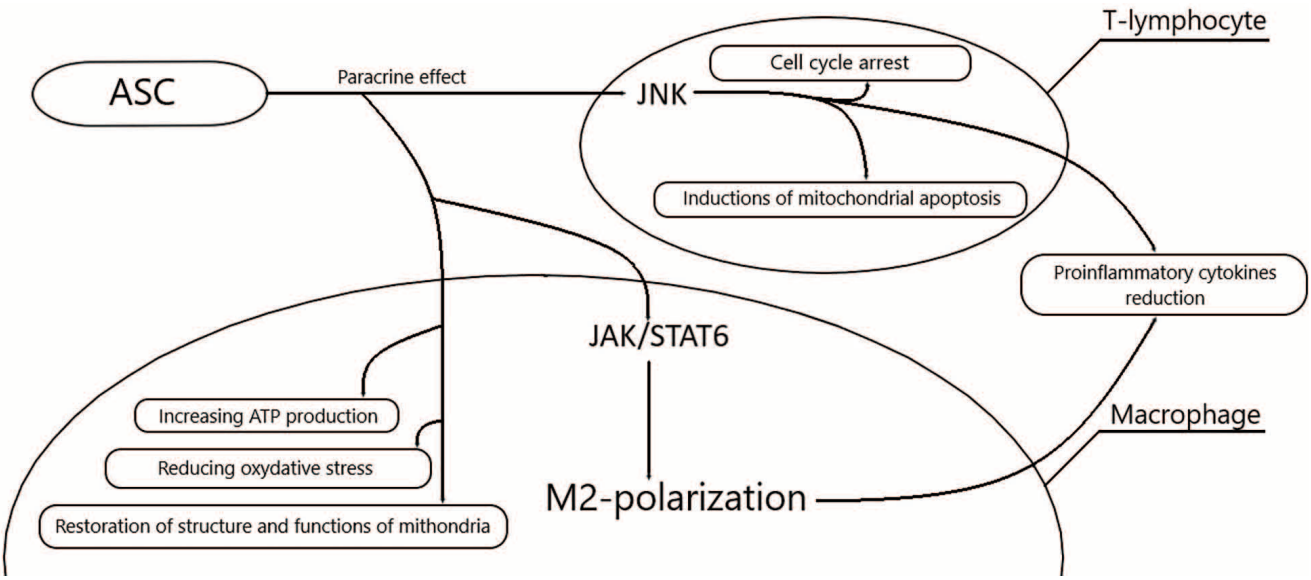

Figure 2. *Immunomodulatoryeffect of ASC*

2015-2021 involving 8 patients with newly diagnosed T1DM, a single intravenous infusion of allogeneic ASCs at a dose of 1 million cells/kg combined with daily vitamin D2 administration resulted in a significant reduction in exogenous insulin requirement almost threefold after 3 months (0.22 ± 0.17 vs. 0.61 ± 0.26 units/kg in the control group) [27]. This positive effect remained stable for 12 months. An increase in basal C-peptide was noted after 6 months; however, subsequently, its levels equalized with those of the control group [34, 35].

Regenerative Potential of ASCs in the Treatment of Type 2 Diabetes Mellitus

Recently, the possibility of using ASCs in the therapy of T2DM, characterized by the development of insulin resistance in insulin-sensitive tissues and pancreatic β-cell dysfunction, has been studied. Several scientific concepts explaining the mechanisms of insulin resistance formation have been proposed: ectopic lipid accumulation in peripheral tissues, a pro-inflammatory environment, endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress. Among the possible mechanisms of the positive influence of ASCs in T2DM are the regeneration of pancreatic β-cells, increased glucose utilization in the liver and optimization of hepatic metabolism, anti-inflammatory effects, and increased insulin sensitivity [15]. The mechanism of reducing insulin resistance upon ASC transplantation is hypothesized to be realized through several key events: phosphorylation of the IRS-1 substrate is activated, ensuring effective signal transduction into the cell; expression of the Akt2 gene, which regulates the phosphoinositide pathway of insulin signal transduction, is increased; and translocation of the GLUT4 glucose transporter to the membranes of muscles and adipose tissue is enhanced, increasing its uptake. Thus, the introduction of ASCs enhances the cascade of reactions in the insulin pathway, restoring normal tissue response to insulin action [15, 19]. The high plasticity of ASCs allows them to differentiate into vascular endothelial cells, improving the blood supply to the pancreas [19, 22, 25]. The anti-inflammatory effect is expressed in a significant decrease in the concentration of tumor necrosis factor α (TNF-α), interleukins 6 and 1β (IL-6, IL-1β) [15, 36]. It is assumed that TNF-α and IL-6 are directly involved in the formation of insulin resistance. One probable mechanism is the ability of TNF-α to inhibit the activity of the nuclear receptor PPARγ (peroxisome proliferator-activated receptor gamma), which controls lipid metabolism and maintains high tissue sensitivity to insulin [37] (Fig.1). Furthermore, it is noted that increased expression of TNF-α is observed in obese humans and rodents, which stimulates lipolysis, raises the level of free fatty acids, and disrupts normal insulin signaling, thereby exacerbating the state of insulin resistance [19, 37]. In an experimental rat model with induced T2DM, the administration of ASCs resulted in a statistically significant reduction in hyperglycemia and HbA1c, which persisted for 6 weeks. Histological analysis revealed an increase in the number of islets β-cells and their VWF content, with a simultaneous decrease in the activity of caspase-3, a crucial pro-apoptotic factor [38]. In another study on rats with induced T2DM, it was shown that ASCs pre-treated with the neuropeptide Orexin A exerted a greater therapeutic effect than ASCs without Orexin A. This phenomenon is presumably explained by the fact that Orexins A and B, being stimulators of white adipogenesis, positively influence lipid homeostasis and insulin sensitivity in rodents [15, 37].

Use of ASCs for the Treatment of Diabetic Complications

Currently, the regenerative potential of autologous and allogeneic ASCs in DM and its complications is being studied in several investigations, which include the treatment of skin wounds and trophic ulcers, diabetic retinopathy, and nephropathy. The safety and tolerability of ASC transplantation are being assessed, along with dose determination, frequency of administration, and the early efficacy of this procedure [39, 40, 43]. ASCs can both differentiate into epithelial cells and paracrinely stimulate their proliferation, inhibit inflammation, promote vascularization, and collagen synthesis [14, 15, 19, 40, 41]. In a study conducted by Woo S.H. et al., for the treatment of skin wounds, ASCs were combined with elastin-like polypeptides containing the arginine-glycine-aspartic acid motif — polymers derived from human elastin, possessing a structure that mimics fibronectin-integrin interactions in the extracellular matrix [39]. The experimental results showed that the combined use of ASCs with these polypeptides positively affects wound healing and enhances angiogenesis [39]. Quiñones E. D. et al. compared the efficacy of 2D and 3D culture methods for ASCs in terms of the functionality of their exosomes. It was established that MSCs cultured in 3D spheroids have a higher level of secretion of trophic factors (IL-11, VEGF, bFGF) and overall therapeutic potential than MSCs in monolayer culture. This is likely due to the fact that MSCs located in the central core of the spheroid are less susceptible to hypoxic and mechanical stress. Furthermore, a phenomenon of cell self-activation with increased PGE2 production is suggested, which enhances the anti-inflammatory immunomodulatory potential [40]. Bour F. et al. proposed another combined approach to treating diabetic wounds using a three-dimensional matrix scaffold derived from dermis together with ASCs. This method demonstrated

increased collagen secretion, expression of TGF-ß, bFGF, VEGF, and other regenerative genes, as well as improved stereological, biomechanical, and tensiometric characteristics overall, alongside decreased expression of TNF-α, IL-1ß, and numerical density of neutrophils and macrophages in the experimental groups [41]. Ma T. et al. created a model of a bilayer cell patch containing epidermal stem cells and angiogenic ASCs for the treatment of diabetic wounds [42]. The use of ASCs for diabetic retinopathy has been proposed: these cells can differentiate into pericytes and endothelial cells and delay the breakdown of the blood-retinal barrier. Intravitreal administration of ASCs in diabetic mice prevented capillary loss by 50 %. Moreover, a reduction in the expression of inflammatory factors characteristic of this disease was observed [20]. Diabetic nephropathy is one of the main causes of death in patients with T1DM and T2DM. Morphologically, it is characterized by glomerular enlargement, damage to podocytes and the glomerular basement membrane, and damage to the renal tubular apparatus. In vivo studies have shown that the application of exosomes produced by ASCs and containing microRNAs (*miR-150, miR-134, miR16-5p, miR-26a-5p*) significantly alleviates the course of the disease. Specifically, the ability of miR-26a-5p to inhibit podocyte apoptosis and counteract oxidative stress in the kidneys has been noted [19, 43]. The combined use of ASCs with antioxidants demonstrated a good therapeutic effect in treating liver and kidney dysfunctions in rats with T1DM and a significant ($p < 0.05$) improvement in urea, uric acid, and creatinine levels compared to control groups [44].

Safety of ASC Application

Federal Law of the Russian Federation No. 180-FZ of June 23, 2016, "On Biomedical Cell Products" legalized the use of cell technologies in medical practice in Russia. The use of adult ASCs resolves the ethical contradictions associated with the inadmissibility of terminating the development of a human embryo when obtaining embryonic stem cells. In accordance with the Order of the Ministry of Health of the Russian Federation dated June 4, 2015, adipose tissue is included in the approved list of transplantable objects (Order of the Ministry of Health of the Russian Federation No. 306n/3 dated June 4, 2015, "On Approval of the List of Transplantable Objects"). Thus, defining the legal status of ASCs expands the boundaries of their use for clinical research. However, despite the high regenerative potential of ASCs and the approved legal documents permitting their use, cell therapy is still far from widespread implementation in practical medicine. Some publications report possible negative effects and technical difficulties associated with this direction. To achieve therapeutic efficacy, a high concentration of MSCs, ranging from 1×10^6 to 1×10^8 cells, is required, which is obtained through prolonged cultivation. The manipulative stress to which ASCs are subjected during passaging leads to the accumulation of chromosomal abnormalities. Research results reveal statistically significant DNA damage in ASCs starting from the fifth cell passage [45]. Consequently, to ensure the maximum possible safety of clinical trials involving ASCs, strict monitoring of cytogenetic anomalies in cell culture is necessary. Experimental data indicate that stem cells share similarities with clonogenic tumor cells. There is an opinion that MSCs may act as the cellular origin of tumors or enhance existing precancerous tendencies due to the generation of growth factors. It is indicated that the probability of malignant transformation of human MSCs can reach 45.8 %. It should be noted that transformed MSCs are capable of participating in the creation of the stroma and the tumor-associated vascular network [46]. However, unlike transformed cancer cells, MSCs demonstrate both pro- and anti-tumor properties. Thus, patient biology is a key factor largely determining the therapeutic effect and the body's response. The structure and frequency of side effects when using autologous MSCs were analyzed in a multicenter study involving 2,372 patients with degenerative joint diseases: a total of 325 adverse events were registered, accounting for about 14 %. The vast majority of these effects were associated with pain syndrome due to the progression of the underlying disease. Cases of neoplasms accounted for 0.3 %, which is somewhat lower than the average rate in the general population [47].

The use of multipotent cells presents researchers with the task of controlling their differentiation pathway to avoid the emergence of undesirable cell lineages. The ability of ASCs, besides the chondrogenic, osteogenic, and adipogenic lineages, to differentiate into myofibroblasts with subsequent development of fibrous tissue is well known. A case of chronic kidney disease progression 5 months after ASC therapy due to massive fibrosis of glomeruli and interstitial tissue has been described [48].

Various cultivation conditions contribute to the heterogeneity of MSCs in terms of morphology, cell membrane receptor profile, and secretome. For instance, it has been found that culturing MSCs under normoxic conditions induces a senescent morphology characterized by increased cell volume. The use of large MSCs for cell therapy leads to their entrapment in non-target organs with capillary diameters smaller than the size of the MSCs (e.g., lungs, brain) and can be complicated by vascular obstructions and stroke [49]. It is evident that to enhance the safety and efficacy of MSC use, the development of a standardized cultivation protocol and the production of a homogeneous cell population with optimal sizes are necessary.

Allogeneic MSCs pose a certain risk associated with the potential presence of viral DNA or mycoplasma contamination, which could negatively affect the recipient's health and reduce the effectiveness of the transplantation [50]. Thus, strict adherence to biosafety rules during cell cultivation is a mandatory condition for the use of ASCs in clinical practice.

Conclusion

In summary, it should be noted that the use of ASCs opens new perspectives in the regenerative therapy of Type 1 and Type 2 Diabetes Mellitus. This method contributes to the improvement of glycated hemoglobin and C-peptide parameters, reducing patient dependence on exogenous insulin. The therapeutic effect of ASCs, confirmed by the results of preclinical and clinical studies, is determined not only by differentiation into insulin-producing cells but also by the paracrine secretion of a broad spectrum of cytokines, immunomodulatory, and angiogenic factors. The regenerative potential of ASCs allows for their use in combating diabetic complications. However, before their application becomes a widely used technique, a larger body of scientific data confirming the safety and efficacy of this therapy must be accumulated.

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РОЛЬ ПЕЧЕНОЧНОЙ ДИСФУНКЦИИ, ПРОЯВЛЯЮЩЕЙСЯ ГИПЕРАММОНИЕМИЕЙ, У ПАЦИЕНТОВ С ТЯЖЕЛОЙ ТЕРМИЧЕСКОЙ ТРАВМОЙ: КЛИНИЧЕСКИЙ ОПЫТ

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The Role of Hepatic Dysfunction Manifested by Hyperammonemia in Patients with Severe Thermal Trauma: Clinical Experience

Резюме

Введение. У пациентов с термической травмой в результате изменения микроциркуляции и дисфункции печени происходит нарушение обезвреживания аммиака, процессов его детоксикации и накопления в организме. Развивается гипераммониемия, которая усугубляет явления энцефалопатии. На сегодняшний день остаются вопросы по применению гипоаммониемической терапии у пациентов с ожогами и её влиянию на исходы заболевания. **Цель:** оценка выраженности печеночной энцефалопатии, уровня аммиака капиллярной крови и его снижения на фоне терапии у пациентов с термической травмой. **Материалы и методы.** В исследование выборочно включена группа из 29 пациентов с тяжёлой ожоговой травмой (Индекс Франка более 145 ед.), находившихся на лечении в реанимационном отделении, и группа с легкой ожоговой травмой (Индекс Франка не более 90 ед.) из 15 пациентов, находившихся в условиях коечного отделения. Выраженность печеночной энцефалопатии определяли по шкале West Haven. Уровень аммиака в сыворотке крови исследовали методом микродиффузии с применением портативного экспресс-анализатора PocketChemTM BA PA-4140. Для коррекции гипераммониемии с помощью инфузомата внутривенно вводился орнитин в дозе 80 г/сут в течение 10 дней. Все статистические расчёты выполнены с использованием программного обеспечения SPSS v27 (Statistical Package for the Social Sciences). **Результаты.** Пациенты с ожоговой травмой, согласно индексу Франка, были разделены на 3 подгруппы (1-3), глубина поражения соответствовала от 31 ед. до 91 ед. и более. Высокий уровень аммиака в крови зарегистрирован во всех трех подгруппах, а при индексе Франка 91 ед. и выше более чем у половины пациентов превышал 285 мкмоль/л. Отмечена прямая связь между индексом Франка и уровнем аммиака у пациентов с ожоговой травмой (p=0,01). Чем выше Индекс Франка, тем выше уровень аммиака в плазме крови. Данная тенденция прослеживается как до начала лечения (rs_1=0,971, rs_2=0,996), так и после начала лечения (rs_1=0,898, rs_2=0,948) по обеим группам пациентов. На 2-3-й день комбинированного лечения с включением орнитина отмечено уменьшение аммиака в крови на 20-30 % от исходного уровня во всех исследуемых группах (p <0,001). Уровень аммиака после лечения статистически

значимо снизился у всех 44 пациентов (p <0,001). **Выводы.** Печеночная дисфункция является одним из проявлений системного ответа на термическую травму. Поэтому нарушение процессов утилизации аммиака может оказывать неблагоприятное воздействие на клиническую картину в целом. Наличие дисфункции печени, высокий уровень аммиака и как следствие развитие печёночной энцефалопатии утяжеляют течение ожоговой болезни, что существенно затрудняет оказание помощи данной категории пациентов.

Ключевые слова: *термическая травма, печеночная дисфункция, гипераммониемия, печеночная энцефалопатия, лечение гипераммониемии*

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Abstract

Introduction. In patients with thermal injury, changes in microcirculation and liver dysfunction lead to impaired detoxification of ammonia, resulting in its accumulation in the body. This develops hyperammonemia, which exacerbates the phenomena of encephalopathy. To date, questions remain regarding the application of hypoammonemic therapy in burn patients and its impact on disease outcomes. **Aim:** To assess the severity of hepatic encephalopathy, the level of ammonia in capillary blood, and its reduction against the backdrop of therapy in patients with thermal injury. **Materials and methods.** The study selectively included a group of 29 patients with severe burn injury (IF more than 145 units) who were treated in the intensive care unit, and a group with mild burn injury (IF no more than 90 units) of 15 patients who were in the hospital ward. The severity of hepatic encephalopathy was determined using the West Haven scale. The level of ammonia in the serum was investigated by microdiffusion method using the portable express analyzer PocketChemTM BA PA-4140. For the correction of hyperammonemia, ornithine was intravenously administered via an infusion pump at a dose of 80 g/day for 10 days. All statistical calculations were performed using the software SPSS v27 (Statistical Package for the Social Sciences). **Results.** According to the Frank index, patients with burn injury were divided into 3 subgroups (1-3), the lesion depth ranged from 31 units to 91 units or more. High levels of ammonia in the blood were recorded in all three subgroups, and with a Franck index of 91 units. and higher than 285 mmol/l in more than half of the patients. There was a direct relationship between the Franck index and the level of ammonia in patients with burn injury (p=0.01). The higher the Franc Index, the higher the level of ammonia in the blood plasma. This trend can be traced both before the start of treatment (rs_1=0.971, rs_2=0.996) and after the start of treatment (rs_1=0.898, rs_2=0.948) in both groups of patients. On the 2-3 day of combined treatment with the inclusion of ornithine, a decrease in ammonia in the blood by 20-30 % of the baseline level was noted in all study groups (p <0.001). The level of ammonia after treatment decreased significantly in all 44 patients (p <0.001). **Conclusions.** Hepatic dysfunction is one of the manifestations of the systemic response to thermal injury. Therefore, disruption of ammonia utilization processes can have an adverse effect on the overall clinical picture. The presence of liver dysfunction, high levels of ammonia and, as a result, the development of hepatic encephalopathy aggravate the course of burn disease, which significantly complicates the provision of care to this category of patients.

Key words: *thermal injury, liver dysfunction, hyperammonemia, hepatic encephalopathy, treatment of hyperammonemia*

Conflict of Interest

Co-author of the article Ilchenko L.Yu. is the editor-in-chief of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. The decision to publish the article was made by the editorial board without the participation of the editor-in-chief. The authors did not declare any other conflicts of interest

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Compliance with the principles of ethics

The study protocol was approved by the local ethics committee (Minutes No 3-25 dated 05.09.2025). Approval and protocol procedure was obtained according to the principles of the Declaration of Helsinki. Written consent was obtained from the patients for publication of relevant medical information and all of accompanying images within the manuscript.

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BAS — biologically active substances, DIC syndrome — disseminated intravascular coagulation syndrome, IL-6 — interleukin-6, FI — Frank's index, VLDL — very low density lipoproteins, HE — hepatic encephalopathy, TG — triglycerides, TBSA — total body surface area.

Background

A thermal injury is one of the most common severe trauma categories in the modern world. Pathophysiology of a thermal damage is a complex mechanism, and it depends on a number of factors: burn area (damaged body surface area), depth of the damage and inflammation intensity, which is quantified by Frank's index (FI), a prognostic index of burn injury severity used to forecast mortality among patients.

Burns covering over 30 % of the total body surface area (TBSA) cause significant fluid depletion in combination with production and release of inflammatory mediators, which results in a systemic effect, namely in a typical cardiovascular dysfunction, known as burn shock. Pathophysiologically, microcirculation is disturbed as a result of a vascular spasm due to pain and stress response of the body. A huge amount of catecholamines is released in the bloodflow. Arteriolovenular and arteriovenous shunts open, and cardiac shunt occurs, bypassing the microcirculatory bloodstream. Effects of high temperatures in a thermal injury lead to red blood cell hemolysis; protein is lost through the wound bed, and moisture is evaporated from the burned surface. Biologically active substances (BAS), kinins, toxic tissue degradation products accumulate in the body and cause increased vascular permeability and cell membrane penetration. Protein and plasma leave the vascular bed and accumulate in soft tissues. Edema develops, and the blood flow to internal organs decreases. Clots are not uncommon. Pain reaction and loss of plasma are the key mechanisms in burn shock development.

In 1932, David Cuthbertson proposed a theory of metabolic response to a severe trauma comprising two phases: "flux" and "reflux" [1]. The reflux phase is associated with hypermetabolism, hematogenic shock and reduced oxygen supply and consumption. The flux phase is the key in body recovery after a thermal trauma. Numerous clinical manifestations, including muscle mass loss resulting from metabolic response during the flux phase, are related to organ dysfunction in patients with severe burns.

In 2011, Wenzhong Xiao et al. [2] published an article describing a shift in human immune cells during the first 12 hours after the injury, which is the worst in burns.

In deep burns covering over 30 %, severe stress response of the body can be observed. Catecholamines are released; they cause hypermetabolism, ischemia of peripheral tissues, slow wound healing, and immunosuppresion. The probability of sepsis, multisystem organ dysfunction and death increases. Hypermetabolic reaction at the cellular and systemic levels is harmful. At the systemic level, the structure and functions of the vital organs (heart, liver, skeletal muscles, skin), immune system and transmembrane transport system are jeopardise [1]. Hypermetabolic processes, inflammatory reaction associated with protein breakdown, aminoacid degradation, insulin resistance, hyperglycaemia, and lipolysis, contribute to the development of organ failure, first of all, of the liver [3–6]. A severe burn triggers proinflammatory processes, hypoperfusion, edema and facilitates hepatic cell apoptosis.

Homeostasis of the most important nitrogen-containing intermediate products, ammonia and glutamine, is a strictly regulated process, where teh central role is played by the intestines/liver axis [7]. Following a thermal trauma, the rate of blood flow to intestines drops by almost 60 % vs. initial values and remains hypoxic for approximately four hours. It can be assumed that the hepatic blood flow rate also drops, causing programmed cell death [5]. All this eventually leads to hepatic dysfunction.

A thermal injury causes homeostasis disturbances, which results in an inflammatory response aimed to restore the initial condition of the body. The liver is one of the vital organs responding to a thermal injury.

Studies showed that, immediately after a burn, liver damage can be associated with massive edema of hepatic parenchyma, as evidenced by hypoalbuminemia. All this is proven by a burn model in rats, where it has been demonstrated that 2–7 days after a thermal trauma, the liver weight increases significantly [8]. Numerous studies emphasise that hepatomegaly persists for three weeks after a burn. As early as one day after a trauma, signs of cholestatic and cytolytic syndromes can be observed [8].

Lower production of protein components of very low density lipoproteins (VLDL), that carry triglycerides (TG) and fatty acids, reduces their release by the liver, which can lead to adipose infiltration of this organ. It further increases the risk of sepsis. Besides, extrahepatic tissue uses less TG as an energy substrate [1, 4].

Adipose infiltration is a common event and is usually reversible. Nevertheless, it has been demonstrated that it is associated with increased bacterial translocation, hepatic failure and endotoxemia, and the liver has the critical role in response to a thermal injury [6, 9].

Following a serious trauma, such as a severe burn, hepatic protein synthesis shifts from hepatic housekeeping proteins (albumin, prealbumin, transferrin and retinol-binding protein) to acute phase proteins, which act as inflammation mediators; they function as transport proteins and participate in burn wound healing [3]. At the same time, interleukin-6 (IL-6), an essential mediator of an acute inflammation phase response, is synthesised in the liver by fibroblasts, Kupffer cells and activated monocytes, macrophages, vascular endothelial cells, microglial cells and astrocytes.

J. Albrecht, M.D. Norenberg (2006) [10] proposed the Troic horse hypothesis, according to which glutamine acts as an ammonia carrier in astrocyte mitochondria after it has been metabolised back to glutamate and

ammonia, thus resulting in oxidative stress and cellular dysfunction.

Recent studies showed that hyperammoniemia facilitates development of sarcopenia. Skeletal muscles become the main organ to metabolise ammonia, substrates of this metabolism get depleted, and muscle mass decreases. Myostatin is a potent inhibitor of autocrine increase in myocyte production, which inhibits growth of skeletal muscles and reduces muscle mass in hyperammoniemia. Hyperammoniemia induces autophagy, and damaged proteins are cleaved or digested in order to maintain cell function. It has been demonstrated that hyperammoniemia reduces skeletal muscle strength and increases muscle fatigue, resulting in marked muscle dysfunction [11].

Clinical Profile of Patients and Study Methods

This study was conducted in 2024–2025 at A.V. Vishnevskiy National Medical Research Center of Surgery of the Ministry of Defense.

The purpose of the study was to assess the intensity of HE, capillary ammonia levels and their reduction in patients with thermal injuries.

The study included two groups of patients. Group 1 included 29 male patients aged 18 to 54 years old (36±18), admitted to ICU with severe burns. The total burn area exceeded 40 % of the body surface; deep burns comprised over 35 %, Frank's index was 145 units and over. All patients were in burn shock: 21 patients had severe shock and 8 patients has extremely severe shock. Group 2 (patients with minor burns) included 15 patients in a general ward aged 20 to 44 years old (32±12). The total burn area was less than 40 % of the body surface; deep burns comprised 5–10 %, Frank's index was 31–90 units.

Blood ammonia levels were measured with the help of a portable rapid-response analyzer PocketChemTM BA PA-4140, which was registered in Russia in 2018. The analyser measures ammonia levels within 180 seconds. The advantage of this method is the use of dry chemicals; the method is based of the microdiffusion method, which ensures high precision of measurements. The measurement range is 8 μmol/L to 285 μmol/L. Normal blood ammonia levels are not more than 60 μmol/L. In this study, capillary blood was sampled in accordance with the study method.

All patients underwent therapy in accordance with the clinical guidelines "Chemical and thermal burns. Sunburns. Airway burns", prepared by the Combustion Association World Without Burns and approved by the Ministry of Health of the Russian Federation in 2024 [12]. Also, ornithine 80 g daily was injected for 10 days using a pump system, in order to reduce blood ammonia levels.

Statistical data processing was performed with the help of SPSS v27 (Statistical Package for the Social Sciences). Sampling characteristics were described using descriptive statistics methods: calculation of mean (M), standard deviation (SD), median value. The relationship between Frank's index and blood ammonia concentrations was assessed using correlation analysis: Pearson's correlation coefficient and Spearman's rank correlation (rs1 — group 1, rs2 — group 2). Correlation was considered significant at 0.01 (bivariate correlation).

Wilcoxon rank sum test was used to analyse blood ammonia levels before and after therapy in both groups of patients. The study continued with comparison of the intensity of each parameter: Frank's index, ammonia concentration before and after therapy using Mann-Whitney U-test. Differences were statistically significant at $p < 0,05$.

Results and Discussion

One of the most important functions of the liver is ammonia detoxication, which is impaired in patients with thermal traumas. Ammonia is a toxic substance, the majority of which is present in blood in its ionised form ($NH4+$). In healthy individuals, fasting blood concentrations are low (8–60 μmol/L) [13].

Ammonia is a waste product of inorganic nitrogen, which is metabolised and produced by all tissues. In healthy individuals, ammonia is produced mainly in intestines as a result of three key mechanisms: urea hydrolysis by bacterial urease, bacterial protein deamination and glutamine metabolism in intestinal mucosa [8]. Stomach, small intestine and colon participate in ammonia exchange; however, the central role in this process belongs to the liver. It is the main sorce and place of its inactivation.

Five urea cycle enzymes (carbamoyl phosphate synthetase, ornithine-carbamoyl-transferase (ornithine transcarbamylase), argininosuccinate synthetase, arginine succinate lyase, and arginase (arginine hydrolase)) participate in convertion of toxic ammonia into non-toxic urea, which is excreted in urine. Unprocessed ammonia is transported with blood to pericentral hepatocytes for efficient ammonia detoxication in the liver due to activity of glutamine synthetase, which converts ammonia into glutamine, thus completing the intrahepatic cycle of glutamine [8]. When these processes are disturbed, a serious manifestation of hepatic dysfunction develops, which presents as higher ammonia levels.

Ammonia affects neurons and astrocytes, star cells, immune cells, myocytes, hepatic cells, etc. Astrocytes are the only cells in the brain, which contain glutamine synthetase, an important enzyme of the glutamatergic system. Therefore, then ammonia concentrations in teh brain rise, these glial cell start removing it by converting

glutamate into glutamine, catalysed byglutamine synthetase. Ammonia has toxic effects on hepatic cells. In the presence of ammonia, gluconeogenesis, lycogenolysis, glycolysis, and ketogenesis are inhibited. The main sources of energy balance are damaged, and brain neurons are de-energised as a result of insufficient amount of substrates. Oxidative stress develops, which causes inflammation, intracellular edema and cell death.

Higher blood ammonia levels are an important factor of hepatic encephalopathy (HE) [14]. HE means neuropsychic disorders developing in patients with damaged liver, resulting from peripheral blood shunt and impaired deintoxication function of the liver [15, 16]. In patients with HE and burns, the rate of ammonia elimination by the liver drops significantly. Higher blood ammonia levels result in ammonia penetration through the hematoencephalic barrier, contributing to neurotoxic effects.

All patients with thermal burns were distributed as follows:

Frank's index: 1) 31 to 60 units — 7 patients; 2) 61 to 90 units — 8 patients; 3) 91 units and over — 29 patients. Quantitative parameters of ammonia in group 1 and group 2 were considerably lower than in sub-group 3 (Fig. 1). An evaluation of the correlation between ammonia concentration and Frank's index showed significant positive correlation (p=0.01) in both groups of patients. There is direct relation between Frank's index and ammonia concentration. The higher Frank's index is, the higher plasma ammonia levels are. This trend is observed both prior to therapy (rs1=0.971, rs2=0.996) and after therapy (rs1=0.898, rs2=0.948) in both groups of patients.

Hepatic encephalopathy grades. HE stages can be assessed using capillary ammonia levels: 1) increase of up to 1.33 times of the upper limit of normal (corresponded to West Haven HE stage 1); 2) increase of 1.33–1.67 times of the upper limit of normal corresponded to West Haven HE stage 2); 3) increase of 1.67–2 times of the upper limit of normal (corresponded to West Haven HE stage 3); 4) over 2 upper limits of normal (corresponded to West Haven HE stage 4).

Out of 15 patients with minor burns, 5 had stage 1 hepatic encephalopathy: errors in calculation (addition), ammonia level was 1.33 times higher than the upper level of normal; number connection test run for 31–50 seconds. 10 patients had stage 2 hepatic encephalopathy: minimal temporal and spatial disorientation, abnormal behaviour, errors in calculation (subtraction), ammonia level was 1.33–1.67 times higher than the upper level of normal; number connection test run for 51–80 seconds.

In patients with severe thermal injuries treated in ambustial ICU, the only method to evaluate HE (West Haven scale) is to measure ammonia concentration. On the basis of ammonia levels, 29 patients had teh following distribution: 1 patient had stage 2 HE, 4 patients — stage 3 HE, and 24 patients — stage 4 HE.

It has been established that all 29 patients with severe burns had higher urea levels (over 8.1 mmol/L). It is most likely a consequence of patients' state of shock and decreased filtration capacity of kidneys, which is supported by high blood creatinine concentrations (150 μmol/L and higher). In patients with minor burns, 8 patients had normal urea levels, while 7 patients had over 8.1 mmol/L.

The purpose was to evaluate the efficacy of the modern drug therapy for correction of hyperammoniemia, used in hepatology, when used in patients with burns. Contemporary therapeutic methods aim to reduce ammoniogenesis, absorb ammonia in the digestive tract, activate ammonia excretion by urogenesis activation after primary disease correction or addition of intermediate products of urea cycle and glutamine synthesis [17]. For the therapy, a hepatotrophic product, possessing hypoammoniemia properties, was used, where the active substance was ornithine.

Ornithine has detoxication properties; it reduces high ammonia levels in the body or liver dysfunction. The mechanism of its action is associated with participation in the Krebs urea cycle (activates the cycle function and restores hepatic cell enzyme activity: ornithine carbamoyltransferase and carbamoyl phosphate synthetase).

All examined patients (44 individuals) with thermal traumas received hypoammoniemia agents. The drug resulted in reduction in ammonia levels by 20–30 % vs. baseline on day 2–3 of therapy ($p < 0.001$). Following therapy, ammonia levels were significantly lower in all 44 patients ($p < 0.001$). Patients with minor burns: 1) before therapy: M = 74.8 (95 % CI 71.15–78.45), SD = 6.59, median = 75 (95 % CI 71–81); 2) after therapy: M = 56.67 (95 % CI 53.42–59.91), SD = 5.86, median = 57 (95 % CI 52–62); 3) FI: M = 55.93 (95 % CI 48.63–63.24), SD = 13.19, median = 62 (95 % CI 51–69). Patients with severe burns: 1) before therapy: M = 227.66 (95 % CI 198.72–256.59), SD = 76.08, median = 268 (95 % CI 241–281); 2) after therapy: M = 169.55 (95 % CI 138.94–200.16), SD = 80.47, median = 175 (95 % CI 110–204); 3) FI: M = 176.41 (95 % CI 163.64–189.19), SD = 33.58, median = 167 (95 % CI 155–191). Significant differences were observed for all variables ($p < 0.001$).

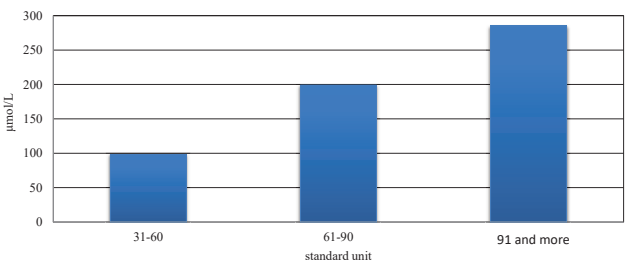

Figure 1. *Relationship between ammonia level (μmol/L) and Frank index (standard unit) in patients with thermal injury*

Evaluation of effects of therapy was possible in 15 controls. 10 days after therapy initiation, all patients had West Haven HE stage 0 to 1; ammonia levels in all patients were below 73 μmol/L.

Conclusion

Hepatic dysfunction is a systemic response to a thermal trauma. Impaired ammonia utilisation results in hyperammoniemia. No doubt that the liver is essential for the organisation and regulation of metabolic processes in patients with burns, therefore hepatic dysfunction can have an unfavourable impact on the clinical presentation in general.

Systemic inflammatory response is a pathogenetic foundation for multiorgan failure in patients with thermal injuries. Progressing dysfunction and resulting organ and system insufficiency are main clinical presentations of burn disease and the key cause of mortality. The main reasons are severe systemic inflammation, including burn shock, progressive disseminated intravascular coagulation syndrome (DIC syndrome), and purulent-septic complications [18, 19].

This study demonstrates that, together with existing multiorgan failure, hepatic dysfunction develops, which leads to high blood ammonia levels in patients with thermal injuries. West Haven scale used in patients with hepatic pathologies can help in assessing the intensity of hepatic encephalopathy in this group of patients.

The study of the ammonia effects on the clinical presentation and mortality, as well as development of the ways to correct hyperammoniemia in patients with severe burn trauma require additional research in this area.

Вклад авторов:

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Павлов А.И.: ресурсы, создание рукописи и её редактирование, руководство исследованием, администрирование проекта

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ПРЕДИКТОРЫ 28-ДНЕВНОЙ ЛЕТАЛЬНОСТИ ПРИ ЦИРРОЗЕ ПЕЧЕНИ

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Clinical and Laboratory Characteristics and Mortality in Patients with Liver Cirrhosis

Резюме

Цель: Определение независимых клинико-лабораторных предикторов 28-дневной летальности у пациентов с циррозом печени (ЦП). **Материалы и методы:** В проспективное когортное исследование включены 137 пациентов с циррозом печени (декомпенсированный цирроз без Acute-on-Chronic Liver Failure (ACLF), n=72; с ACLF, n=65). Для выявления независимых предикторов 28-дневной летальности использовался однофакторный и многофакторный регрессионный анализ Кокса. Были построены и сравнены три модели: комплексная (все значимые переменные), базовая клиническая (CLIF-C OFs, SpO_2/FiO_2, пневмония, стадии ACLF) и расширенная лабораторная (базовая модель + лактат, аммиак, С-реактивный белок (СРБ)). **Результаты:** В однофакторном анализе значимыми предикторами летальности были степень тяжести по шкале CLIF-C OFs, стадии ACLF 2 и 3, наличие пневмонии и инфекции мочевыводящих путей (ИМП), повышенные уровни лактата, аммиака, СРБ и трансаминаз, а также снижение SpO_2/FiO_2. Во всех многофакторных моделях независимыми предикторами неблагоприятного исхода оставались: CLIF-C OFs, стадии ACLF 2 и ACLF 3, наличие пневмонии, ИМП, повышенный уровень лактата, аммиака, СРБ, снижение SpO_2/FiO_2. **Заключение:** Краткосрочный прогноз при ЦП определяется тяжестью органной недостаточности, инфекционными осложнениями и маркерами метаболического стресса и воспаления. Для стратификации риска необходим комплексный подход с использованием шкал CLIF-C OFs и мониторингом лактата, аммиака и СРБ, что позволит оптимизировать ведение пациентов.

Ключевые слова: *цирроз печени, острая печеночная недостаточность на фоне хронической (ACLF), декомпенсация цирроза печени*

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Abstract

Background: To identify independent clinical and laboratory predictors of 28-day mortality in patients with liver cirrhosis. **Materials and Methods:** A prospective cohort study included 137 patients with liver cirrhosis (decompensated cirrhosis without ACLF, n=72; with ACLF, n=65). Univariate and multivariate Cox regression analysis was used to identify independent predictors of 28-day mortality. Three models were built and compared: a comprehensive model (all significant variables), a basic clinical model (CLIF-C OFs, SpO_2/FiO_2, pneumonia, ACLF stages), and an extended laboratory model (basic model + lactate, ammonia, C-reactive protein). **Results:** In the univariate analysis, significant predictors of mortality were the severity according to the CLIF-C OFs score, ACLF grades 2 and 3, the presence of pneumonia and urinary tract infection (UTI), elevated levels of lactate, ammonia, C-reactive protein (CRP) and transaminases, as well as decreased SpO_2/FiO_2. In all multivariate models, the following remained independent predictors of an unfavorable outcome: CLIF-C OFs score, ACLF grades 2 and 3, presence of pneumonia, UTI, elevated levels of lactate, ammonia, CRP, and decreased SpO_2/FiO_2. **Conclusion:** The short-term prognosis in liver cirrhosis is determined by the severity of organ failure, infectious complications, and markers of metabolic stress and inflammation. A comprehensive approach using the CLIF-C OFs score and monitoring lactate, ammonia, and CRP is necessary for risk stratification, which will allow for optimized patient management.

Key words: *liver cirrhosis, acute-on-chronic liver failure (ACLF), decompensation of liver cirrhosis.*

Conflict of interests

Co-author of the article Nikitin I.G. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article has passed the peer-review procedure adopted by the journal. Nikitin I.G. did not participate in the decision to publish this article. The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics

The study protocol was approved by the Local Ethics Committee of N.I. Pirogov Russian national research medical university (Approval No. 235, December 18, 2023). Informed consent was obtained from all patients who participated in the study.

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ALT — alanine aminotransferase, AST — aspartate aminotransferase, DLC — decompensated liver cirrhosis, UTI — urinary tract infection, CRP — C-reactive protein, MBP — mean blood pressure, LC — liver cirrhosis, ACLF — Acute-on-Chronic Liver Failure, CLIF-C OFs — CLIF Consortium Organ Failure score, HBV — Hepatitis B Virus, PAMPs — Pathogen-Associated Molecular Patterns

Introduction

Acute-on-chronic liver failure (ACLF) is one of the most severe complications of liver cirrhosis (LC) characterized by the multi-organ failure and high short-term mortality. Despite predictive models, the structure and significance of clinical and laboratory death predictors in patients with decompensated liver cirrhosis (DLC) without ACLF remain rather indefinite.

The results of the first part of our study demonstrated a significant contribution of infectious and metabolic factors into DLC and ACLF mortality. Due to this, an issue of complex risk stratification and validation of multifactorial predictive models remains important.

LC is one of the leading causes of death globally, while ACLF determines the poor prognosis in this patient category.

According to the "Global, Regional, and National Cirrhosis Burden 2017" International Study, Russia holds a fourth place globally considering the LC mortality increment, in which alcoholic liver injuries play the key role [1].

Risk stratification and prediction of outcomes in such patients are an important, but complex objective for clinical physicians.

Considering the increasing LC mortality, the detection of the corresponding associated factors is of utmost significance.

Study objective: determining independent clinical & laboratory 28-day mortality predictors in patients with LC.

Study Materials and Methods

The study was arranged in the State Budget Healthcare Institution "V.M. Buyanov City Clinical Hospital" (G.I. Storozhakov Department of Hospital Therapy of the Institute of Clinical Medicine). The analysis included 137 patients with LC (76 males and 61 females; mean age 50 [42–58] years) hospitalized within the period from October 2023 till April 2025.

Inclusion criteria: males and females aged 18 to 75 years with LC that signed the informed consent for the study participation and anonymous publication of results.

Non-inclusion criteria: severe decompensated somatic extrahepatic diseases; psychic diseases; a malignancy detected in the patient before or during the hospitalization; patients not signing the informed consent.

The diagnosis was established based on the clinical and laboratory-instrumental data. According to the CLIF-C OF (organ dysfunction) score, patients were divided into two groups — the main group (n=72, mean age 52±11 years, 37 (51.4 %) males)) with ACLF and the reference group (n=65, mean age 49±11 years, 38 (58.5 %) males)) with the DLC without ACLF.

To assess the independent contribution of clinical, laboratory, and infectious factors into the 28-day mortality prognosis, a Cox proportional-hazard regression model was used. The analytical approach included two steps: first, a univariate analysis was arranged for all potentially significant variables (demographic, clinical parameters, laboratory markers, infections present); variables with the significance level of $p < 0.1$ in the univariate analysis together with clinically significant factors determined by experts were selected for the multivariate analysis.

Three models were prepared for the multivariate regression analysis: a complex model (all variables with $p < 0.1$); a basic clinical model (CLIF-C OFs score, SpO_2/FiO_2, presence of pneumonia, ACLF stage); an advanced laboratory model (markers of inflammation and metabolic disorders: lactate, ammonia, C-reactive protein (CRP) added to the clinical model). The model was optimized step-by-step using the Wald's backward method. The entrance and exclusion criteria were $p < 0.1$ and $p > 0.15$, respectively. The hazard ratio (HR) was calculated for all models with 95 % confidence intervals and p values; values of $p < 0.05$ were considered statistically significant.

Results

Baseline clinical and laboratory characteristics of groups compared (DLC without ACLF and ACLF of variable severity) are specifically described in the first part of the publication.

Table 1 describes the results of uni- and multivariate Cox regression analyses arranged to detect factors associated with the risk of poor outcomes in patients. The analysis included demographic, clinical, and laboratory parameters, as well as infectious complications and severity based on the CLIF-C OFs score.

Considering the univariate Cox analysis, statistically significant factors associated with the increased risk included CLIF-C OFs parameters (HR 1.582; 95 % CI 1.291–1.938; $p < 0.001$) and ACLF stages determined based on the CLIF-C OFs score: the risk was significantly elevated in patients with ACLF 2 (HR 4.567; 95 % CI 1.546–13.493; p=0.006) and ACLF 3 (HR 7.382; 95 % CI 2.325–23.439; p=0.001) vs. decompensated patients without ACLF. The following factors also increased the risks of death: presence of pneumonia (HR 5.049; 95 % CI 1.103–23.098; p=0.037), urinary tract infections (UTIs) (HR 3.004; 95 % CI 1.230–7.339; p=0.016), elevated levels of lactate (HR 1.209; 95 % CI 1.031–1.418; p=0.020), ammonia (HR 1.010; 95 % CI 1.003–1.018; p=0.006), CRP (HR 1.012; 95 % CI 1.003–1.020; p=0.006), and transaminases (ALT and AST).

An inverse correlation was detected for SpO_2/FiO_2 (HR 0.994; 95 % CI 0.990–0.998; p=0.009): each index increase by 10 units decreased the risk of death by 6 %. A trend to the increased risk of death was observed for repeated hospitalizations (HR 1.482 [0.508–1.716]; p=0.088) and ascites on admission (HR 0.986 [0.327–2.972]; p=0.091).

The complex multivariate model included all variables with $p < 0.1$ based on the univariate analysis results. In this model, the independent predictors of poor outcomes still included CLIF-C OFs (HR 1.545; 95 % CI 1.260–1.895; $p < 0.001$), ACLF 2 and 3, SpO_2/FiO_2 (HR 0.995; 95 % CI 0.991–0.999; p=0.022), lactate (HR 1.185; 95 % CI 1.015–1.384; p=0.032), ammonia (HR 1.009; 95 % CI 1.002–1.016; p=0.015), CRP (HR 1.010; 95 % CI 1.001–1.019; p=0.028), as well as the presence of pneumonia (HR 4.880; 95 % CI 1.080–22.050; p=0.040), UTIs (HR 2.950; 95 % CI 1.210–7.190; p=0.018).

Regarding the basic multivariate model, all variable parameters (CLIF-C OFs, SpO_2/FiO_2, pneumonia, ACLF stages) retained their statistical significance ($p < 0.05$). With that, the most significant impact on the prognosis was observed in ACLF 3 (HR 7.600; 95 % CI 2.450–23.580; $p < 0.001$) and in patients with pneumonia (HR 5.200; 95 % CI 1.150–23.500; p=0.032), which defines a more than five-fold increased risk of death. Increased CLIF-C OFs score and decreased SpO_2/FiO_2 were also associated with the increased risk of poor outcomes.

The advanced model additionally included laboratory parameters (lactate, ammonia, CRP). All the aforementioned factors retained their statistical significance in the latter model. The inclusion of additional laboratory markers helped to increase the prognostic value of the laboratory tests for lactate (HR 1.172; 95 % CI 1.005–1.367; p=0.042), ammonia (HR 1.008; 95 % CI 1.001–1.015; p=0.022), and CRP (HR 1.009; 95 % CI 1.000–1.018; p=0.050).

The introduction of laboratory markers (lactate, ammonia, CRP) into the advanced (final) model helped to enhance the accuracy of the death risk prognosis compared to a clinical-only assessment. This confirms the required complex approach to the stratification of patients with DLC with or without ACLF.

Thus, based on the multivariate analysis, the main independent predictors of poor outcomes in patients included the severity parameters (CLIF-C OFs), presence of pneumonia, and laboratory markers of systemic inflammation and metabolic disorders.

Table 1. *Association of clinical and laboratory factors with patient survival: results of univariate and multivariate Cox analyses*

Factors	ОР (95% ДИ) однофакторный анализ/ HR (95% CI) Univariate analysis	p value	ОР (95% ДИ) Комплексная модель/ HR (95% CI) Complex model	p value	ОР (95% ДИ) Базовая клиническая модель/ HR (95% CI) Basic clinical model	p value	ОР (95% ДИ) Расширенная лабораторная модель/ HR (95% CI) Extended laboratory model	p value
Age	1,019 [0,984; 1,056]	0,285	Не применимо	NA	Не применимо	NA	Не применимо	NA
Gender (male)	1,036 [0,469; 2,287]	0,930	Не применимо	NA	Не применимо	NA	Не применимо	NA
Readmissions	1,482 [0,508; 1,716]	0,088	1,415 [0,762; 1,762]	0,067	Не применимо	NA	Не применимо	NA
Ascites	0,986 [0,327; 2,972]	0,091	1,549 [0,277; 8,671]	0,062	Не применимо	NA	Не применимо	NA
SpO_2/FiO_2	0,994 [0,990; 0,998]	0,009	0,995 [0,991; 0,999]	0,022	0,992 [0,988; 0,996]	<0,001	0,993 [0,989; 0,997]	0,003
MAP	0,977 [0,941; 1,016]	0,244	Не применимо	NA	Не применимо	NA	Не применимо	NA
CLIF-C OFs	1,582 [1,291; 1,938]	<0,001	1,545 [1,260; 1,895]	<0,001	1,612 [1,320; 1,970]	<0,001	1,580 [1,295; 1,928]	<0,001
Lactate	1,209 [1,031; 1,418]	0,020	1,185 [1,015; 1,384]	0,032	Не применимо	NA	1,172 [1,005; 1,367]	0,042
ALT	1,007 [1,002; 1,011]	0,008	1,006 [1,001; 1,010]	0,018	Не применимо	NA	Не применимо	NA
AST	1,003 [1,001; 1,004]	0,006	1,002 [1,000; 1,004]	0,045	Не применимо	NA	Не применимо	NA
CRP	1,012 [1,003; 1,020]	0,006	1,010 [1,001; 1,019]	0,028	Не применимо	NA	1,009 [1,000; 1,018]	0,050
NLR	1,064 [0,996; 1,136]	0,064	1,055 [0,990; 1,125]	0,098	Не применимо	NA	Не применимо	NA
Ammonia	1,010 [1,003; 1,018]	0,006	1,009 [1,002; 1,016]	0,015	Не применимо	NA	1,008 [1,001; 1,015]	0,022
Total Bilirubin	1,002 [1,000; 1,003]	0,067	1,001 [0,999; 1,003]	0,210	Не применимо	NA	Не применимо	NA
alkaline phosphatase	1,001 [1,000; 1,003]	0,052	Не применимо	NA	Не применимо	NA	Не применимо	NA
UTI	3,004 [1,230; 7,339]	0,016	2,950 [1,210; 7,190]	0,018	Не применимо	NA	Не применимо	NA
Pneumonia	5,049 [1,103; 23,098]	0,037	4,880 [1,080; 22,050]	0,040	5,200 [1,150; 23,500]	0,032	5,100 [1,130; 23,020]	0,035
ACLF 2	4,567 [1,546; 13,493]	0,006	4,320 [1,480; 12,610]	0,008	4,850 [1,680; 14,000]	0,004	4,700 [1,620; 13,650]	0,005
ACLF 3	7,382 [2,325; 23,439]	0,001	7,150 [2,290; 22,340]	0,001	7,600 [2,450; 23,580]	<0,001	7,420 [2,380; 23,150]	<0,001

Note: HR — hazard ratio; CI — confidence interval. Data are presented as HR (95% CI). NA indicates that the variable was not included in the corresponding multivariate model. ACLF 2 and ACLF 3 variables were included as dummy variables using "decompensated cirrhosis without ACLF" as the reference category. The comprehensive model included all variables with p <0.1 from the univariate analysis. The basic clinical model was based on key clinical indicators. The extended laboratory model included variables from the basic clinical model with the addition of laboratory markers. SpO2 — pulse oximetric saturation, FiO2 — fraction of inspired oxygen; MAP — mean arterial pressure; CLIF-C OFs — CLIF Consortium Organ Failure score; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CRP — C-reactive protein; NLR — neutrophil-to-lymphocyte ratio; UTI — urinary tract infection

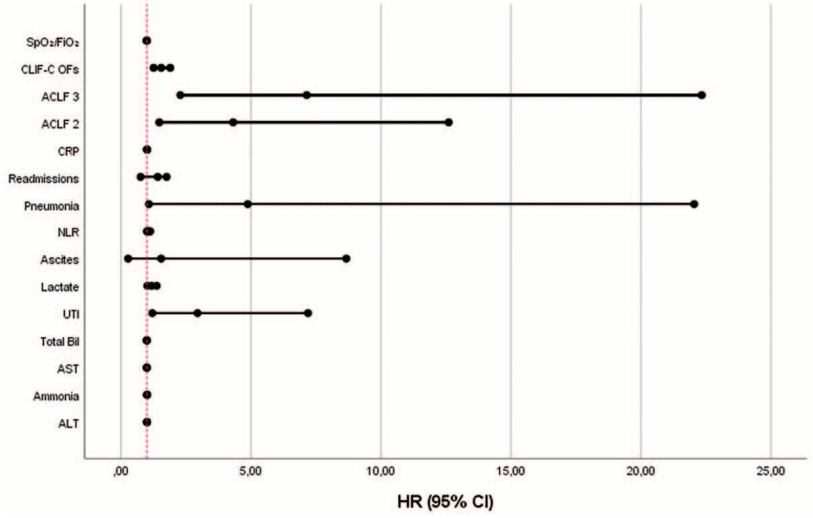

Figure 1. *Forest plot: independent predictors of 28-day mortality in patients with decompensated liver cirrhosis and ACLF according to multivariate Cox regression analysis. Hazard ratios (HR) and 95 % confidence intervals (CI) are displayed; significant factors are highlighted*

Note: SpO2 — pulse oximetric saturation, FiO2 — fraction of inspired oxygen; CLIF-C OFs — CLIF Consortium Organ Failure score; ACLF — Acute-on-Chronic Liver Failure; CRP — C-reactive protein; NLR — neutrophil-to-lymphocyte ratio; UTI — urinary tract infection; Total Bil. — total bilirubin; AST — aspartate aminotransferase; ALT — alanine aminotransferase.

The SpO_2/FiO_2 demonstrated protective effects. As the respiratory index increased, the mortality level decreased (and vice versa). The data obtained confirmed the required complex assessment of the patient's condition accounting for both clinical and laboratory parameters for the risk stratification and optimization of the management tactics.

See Figure 1 for the visual representation of the main independent risk factors for death.

Discussion of Results

Our analysis of factors affecting the 28-day mortality demonstrated that the lactate, CRP, ammonia levels, the CLIF-C OFs score, presence of pneumonia or UTIs demonstrated the highest values.

Thus, decreased SpO_2/FiO_2 index (p=0.001) and mean blood pressure (MBP) levels ($p < 0.001$), as well as elevated lactate levels (p=0.040) in deceased persons reflect the severity of circulatory and metabolic disorders typical for terminal ACLF stages.

Lactate is a product of anaerobic glycolysis, a marker of tissue hypoxia and metabolic alterations emerging in response to hormonal effects (e.g., epinephrine release). Lactate is excreted predominantly via three pathways — gluconeogenesis, tricarboxylic acid cycle in the liver, and renal excretion. The liver is responsible for about 70 % of the total lactate clearance in the body. The liver dysfunction leads to elevated plasma lactate levels, which is due to the impaired mitochondrial oxidation and decreased hepatocyte ability to utilize lactate. Besides, hyperlactatemia may develop due to the impaired microcirculation and tissue hypoxia leading to the enhanced anaerobic glycolysis. LC manifests with the impaired function of visceral microvessels, which is accompanied by hypoperfusion and, thus, hypoxia in the microcirculation of peripheral tissues. Thus, elevated blood lactate levels serves as a biochemical marker of tissue hypoperfusion and metabolic stress.

Multiple experimental and clinical studies in animals and humans have confirmed that the lactate level efficiently reflects the patient's condition severity and may be used to predict their outcomes [2, 3].

A prospective Chinese trial evaluating patients with the Hepatitis B Virus (HBV) and ACLF demonstrated that elevated serum lactate levels were an independent prognostic marker of a 28-day, 3-month, and 6-month mortality. The investigators proposed to include lactate into MELD and MELD-Na models (prognostic models used to assess the liver cirrhosis severity and short-term mortality), which could enhance their prognostic significance when assessing patient survival [4].

Besides its role in the pathogenesis of hepatic encephalopathy, hyperammoniemia is a potential marker in the assessment of severity and outcomes of chronic liver diseases.

In our study, ammonia levels were statistically significantly higher in the ACLF group; the maximum values obtained in the ACLF 3 group confirm the required further analysis of the association between hyperammoniemia and the organ dysfunction severity.

Besides, ammonia levels in the blood of deceased persons were somewhat higher than in the group of survived ones, although the difference was not statistically significant (184 vs. 142 μmol/L; p=0.068). With that, the inclusion of ammonia into predictive models has demonstrated its association with the increased risk of death, which was also shown by Wang X., et al. [5].

The Russian Liver Society experts consider hyperammoniemia as one of the main pathogenetic mechanisms in LC; however, measuring ammonia levels is recommended only for the differential diagnosis of encephalopathy [6].

Increased ammonia levels are a definite prognostic marker of organ dysfunction in ACLF in patients with alcoholic hepatitis and LC. The studies have demonstrated that ammonia levels may serve as an indicator of the condition severity and can predict clinical outcomes.

In the study of Tranah T. H., et al. [7], ammonia was proposed as an independent prognostic criterion for hospitalization due to the emergence of hepatic complications and mortality in LC patients, demonstrating a higher prognostic accuracy compared to the traditional scales analyzing the hepatic dysfunction severity.

Thus, the CANONIC study showed that the CLIF-SOFA organ dysfunction score, white blood cell count, a history of LC decompensation, and ascites on admission were independent factors associated with death.

In our study, repeated patient hospitalizations presumed a 48 % increase in the mortality risk; however, accounting for a wide CI [0.508–1.716] and p=0.088, this association cannot be considered clinically significant. Additionally, no significant associations were detected for the ascites on admittion and death ($p > 0.05$), while wide CIs (especially in the multivariate model) represent indefinite assessments. These trends are worth analyzing in studies with larger sample powers.

Infectious complications play an important role in the pathogenesis of ACLF, leading to poor prognosis. The multivariate analysis in our cohort demonstrated that pneumonia and UTIs were independent predictors of 28-day mortality in patients with DLC and ACLF. Pneumonia increased the risk of death more than 5-fold (HR 5.049–5.200; $p < 0.05$ in all models), while UTIs increased it almost 3 times (HR 2.950–3.004; $p < 0.02$), which confirms their critical role in the development of organ failure, sepsis, and multi-organ dysfunction in patients with LC.

Mechanisms of infectious complications in LC are associated with the significant immune imbalance caused by the hepatic failure itself and systemic metabolic disorders. Bacterial infections act as a trigger for the systemic inflammatory reaction, activating PAMPs (pathogen-associated molecular patterns) and proinflammatory cytokines, which in turn worsens the organ dysfunction and becomes the main event in the pathogenesis of ACLF.

The results obtained define the need for active prevention and quick diagnosis of infections in a high-risk patient group, especially with early ACLF signs. Adequate antibiotic therapy is also critically important to improve outcomes in this population. All together, our data confirm the latest publications, where infectious complications were considered one of the most significant poor prognostic factors in patients with DLC and ACLF [8, 9].

Conclusion

Our data confirm the decisive role of systemic inflammation, infectious complications, and metabolic disorders in the short-term prognosis for patients with DLC and ACLF. The key independent 28-day mortality predictors include the ACLF stages, severity based on the CLIF-C OFs score, elevated lactate, ammonia, and CRP levels, presence of pneumonia and urinary tract infections.

The implementation of the CLIF-C OFs score for routine death risk stratification in patients with DLC and ACLF will help to detect patients with the most probable poor outcomes, timely referring them to the specialized departments and liver transplant centers.

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Тотолян Г.Г.: оформление статьи и сопроводительных материалов

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Contribution of Authors

All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication

Taraki B.M.: data collection and analysis, statistical processing of data, text writing

Adamova I.G.: data collection and analysis, statistical processing of data

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ЧИСТАЯ АДЕНОКАРЦИНОМА С КИШЕЧНОЙ ДИФФЕРЕНЦИРОВКОЙ ЯИЧКА КАК ПЕРВОЕ ПРОЯВЛЕНИЕ ТЕРАТОМЫ ЯИЧКА: КЛИНИЧЕСКИЙ СЛУЧАЙ И ОБЗОР ЛИТЕРАТУРЫ ПО ТАКТИКЕ ВЕДЕНИЯ

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Pure Adenocarcinoma with Intestinal Differentiation of The Testis as The First Presentation of a Testicular Teratoma: A Case Report with Literature Review of Management

Резюме

Чистая аденокарцинома — это соматический тип злокачественного новообразования, возникающего из герминогенной опухоли, встречается крайне редко, но такие случаи описаны. Обычно соматическая малигнизация проявляется как саркома, реже — как карцинома. Этот редкий феномен, как правило, объясняется развитием тератоматозного компонента. В большинстве случаев диагноз не вызывает затруднений благодаря смешению различных компонентов герминогенной опухоли и наличию герминогенной неоплазии in situ (GCNIS). Однако в некоторых редких случаях метастатическая карцинома в яичке может оказаться чем-то иным. В данном клиническом случае описывается 35-летний мужчина с опухолью яичка в виде аденокарциномы с кишечными чертами, напоминающей метастатическую колоректальную карциному. В окружающей ткани яичка была обнаружена GCNIS, а флуоресцентная гибридизация in situ на аномалии хромосомы 12p выявила наличие i(12p) в тестикулярной аденокарциноме, что подтверждает общее герминогенное происхождение. После забрюшинной лимфодиссекции были обнаружены метастатические отложения слизистой аденокарциномы. Обширное клиническое обследование помогло исключить метастазирование из другого первичного очага, в частности из желудочно-кишечного тракта. Наше наблюдение указывает на то, что аденокарцинома кишечного типа в препарате после орхиэктомии, хотя чаще и представляет собой метастаз из первичной опухоли желудочно-кишечного тракта, может быть первичной опухолью яичка герминогенного происхождения. Пациент был пролечен радикальной орхиэктомией с забрюшинной метастазэктомией с последующей химиотерапией, направленной на соматический тип злокачественной гистологии, по схеме для колоректальной аденокарциномы. В течение периода наблюдения 3,5 года у пациента сохранялась полная ремиссия.

Ключевые слова: *Яичко, тератома, соматическая малигнизация, аденокарцинома, слизистая, кишечный фенотип*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Pure adenocarcinoma is a somatic-type malignancy that comes from a germ cell tumor and is extremely rare but has been reported. It is usually seen as sarcoma, and less often as carcinoma. This rare phenomenon is generally attributed to the development of a teratomatous component. In most cases, the diagnosis remains straightforward due to the mixing of different germ cell tumor parts and the existence of germ cell neoplasia in situ (GCNIS). But, there are some rare instances where metastatic carcinoma to the testis could be something more. This case presentation discusses a 35-year-old man who had a testicular tumor of adenocarcinoma with enteric features, which looked like metastatic colorectal carcinoma. GCNIS was found in the background testicular tissue, and fluorescence in situ hybridization for chromosome 12p abnormalities showed the presence of i(12p) in the testicular adenocarcinoma, which supports a shared germ cell origin. After the retroperitoneal lymph node dissection, it was found that there were metastatic deposits made up of mucinous adenocarcinoma. Extensive clinical workup helped exclude metastasis from another primary, particularly the GI tract. Our report indicates that adenocarcinoma of intestinal type in an orchiectomy specimen, although usually strongly suggestive of metastasis from a gastrointestinal tract primary, maybe a primary testicular neoplasm of germ cell tumor origin. The patient was treated with radial orchidectomy with retroperitoneal metastasectomy followed by somatic-type malignant histology-directed chemotherapy for colorectal adenocarcinoma. The patient remained in complete remission for a 3.5-years follow-up period.

Key words: *Testis, teratoma, somatic malignancy, adenocarcinoma, mucinous, intestinal phenotype*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

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Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «Pure Adenocarcinoma with Intestinal Differentiation of The Testis as The First Presentation of a Testicular Teratoma: A Case Report with Literature Review of Management» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

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GCNIS — Germinogenic neoplasia in situ, TGCT — Germinogenic testicular tumor, CT — Computed tomography, SMT — Somatic malignant transformation, GCT — Germinogenic tumor, ADC — Adenocarcinoma, SCC — Squamous cell carcinoma, FOLFOX — Folinic acid, Oxaliplatin, 5-fluorouracil

Introduction

Testicular germ cell tumors are a type of solid neoplasms which account for the greatest incidence (> 90 %) of testicular cancer among young adult men(1). TGCTs are histologically divided into 2 categories: non-seminomas and seminomas(2). Non-seminomas include embryonal carcinomas, choriocarcinomas, teratomas and yolk sac tumours. Testicular teratomas have further been subclassified as either prepubertal type or post-pubertal type. Prepubertal-type teratomas are generally not aggressive and do not have a link to germ cell neoplasia in situ (GCNIS), while post-pubertal-type teratomas can be malignant and are linked to GCNIS(3). Additionally, teratomas that occur after puberty tend to spread to areas outside the gonads, such as the retroperitoneal lymph nodes. It is uncommon for testicular post-pubertal-type teratomas to develop into a somatic-type malignancy. We present our case of a testicular pure adenocarcinoma with background GCNIS. The primary tumor showed enteric differentiation while the retroperitoneal lymph node metastasis showed colloidal mucinous cystadenocarcinoma histomorphology. Although no other teratoma components were identified with the tumor, the presence of GCNIS in the adjacent testicular tubules supported germ cell origin. Molecular characterization of the primary tumor was undertaken supporting germ cell origin. Comprehensive clinical and imaging workup helped

further exclude primary gastrointestinal or pancreaticobiliary tract primaries.

Case Presentation:

A 35-year-old man, married with two children had a history of right orchiopexy for incidentally discovered undescended testis at the age of 7. The patient reported no family history of testicular cancer or other malignancies. Genetic counseling was offered, but no known hereditary cancer syndromes (e.g., Lynch syndrome, BRCA mutations) were identified in preliminary screening. He denied smoking or alcohol intake or recent scrotal trauma. There were no clinical signs of hormonal imbalance (e.g., gynecomastia, changes in libido). Serum testosterone and gonadotropin levels were within normal limits. He had 5 years history of on and off abdominal and lower right back pain accompanied with right testicular swelling, that did not respond to oral analgesics. Testicular ultrasound showed a large solid right testicular mass lesion. He was seen in a private Hospital where computerized tomography (CT) imaging was done in September 2020 and showed multiple bulky retroperitoneal/right para-aortic lymphadenopathy (figure 1) along with a testicular mass with central cavitation. CT scan findings were indicative of nodal metastasis from the clinically detected testicular mass. CT scan (with venous phase) of the chest and upper abdomen was negative for lung and liver metastasis. The analysis of tumor markers indicated that there were no elevated levels of lactate dehydrogenase, beta human chorionic gonadotropin, alpha-fetoprotein.

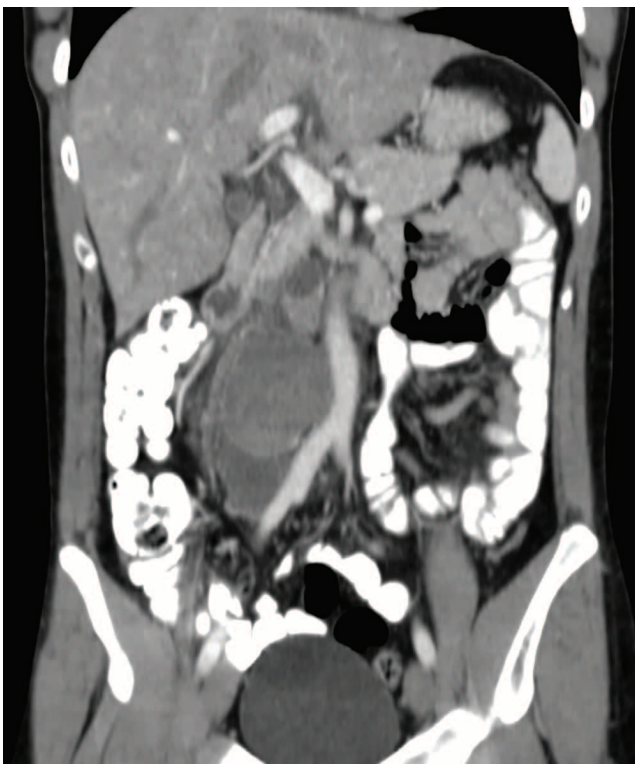


Figure 1. *September 2020 (multiple right para-aortic lymph node mass with the largest lymph node measures 5×5,4 cm compressing the IVC)*

In September 2020 the patient underwent a right inguinal radical orchiectomy. In October 2020 he had retroperitoneal lymph node dissection. His personal medical history was notable for the absence of prior significant injuries. There was no family history suggestive of hereditary cancer syndromes, such as Lynch syndrome or BRCA-related cancers, although genetic counseling was pursued for reassurance. He denied any history of gynecomastia, reduced libido, or other signs suggesting hormonal imbalance, with physical examination showing normal secondary sexual characteristics and stable serum testosterone and gonadotropin levels. During the initial evaluation, no symptoms typically indicative of systemic intoxication—such as persistent fever, generalized weakness, or significant appetite loss—were documented. His blood pressure readings during serial clinic visits remained within normal range. Additionally, his two children underwent clinical examination and were found to be healthy with no detectable abnormalities.

Histology of the right testes showed moderately differentiated adenocarcinoma (with intestinal differentiation) on a background of germ cell neoplasia in situ, indicative of a teratoma with somatic malignancy. Immunoperoxidase stains showed that the tumor was positive for the epithelial glycoprotein BER-EP4, CK20, CDX-2 and negative for the germ cell markers SALL-4, OCT4, AFP, CD30, PLAP. Seminiferous tubules showed germ cell neoplasia insitu (GCNIS) that is positive for PLAP and OCT4. (Fig. panel 1A-1H panel). Lymphovascular invasion was present. Tumor excision was locally complete. However, right para-aortic lymphadenectomy was performed showing metastatic deposits of an adenocarcinoma displaying mucinous differentiation, involving all four excised lymph nodes. (Fig. panel 2A-2D). Full medical and imaging follow-up with a body scan did not show evidence of another primary in the gastrointestinal and pancreaticobiliary tracts or elsewhere in the body.

Testicular tumor tissue was submitted for chromosomal microarray studies. Genomic alterations observed include a complex pattern of discontinuous gains (5 to 7 copies) and amplifications involving chromosome 12p (including CCND2 and KRAS) as well as lower level gain of chromosome 12q (3 copies). The abnormalities identified on chromosome 12p are structurally complex and are not typical of a classic isochromosome 12p, these findings are consistent with over-representation of most of the 12p relative to 12q. Such over-representation of chromosome 12p has been reported in association with a subset of testicular germ cell tumors, although these findings are not diagnostic of GCT.

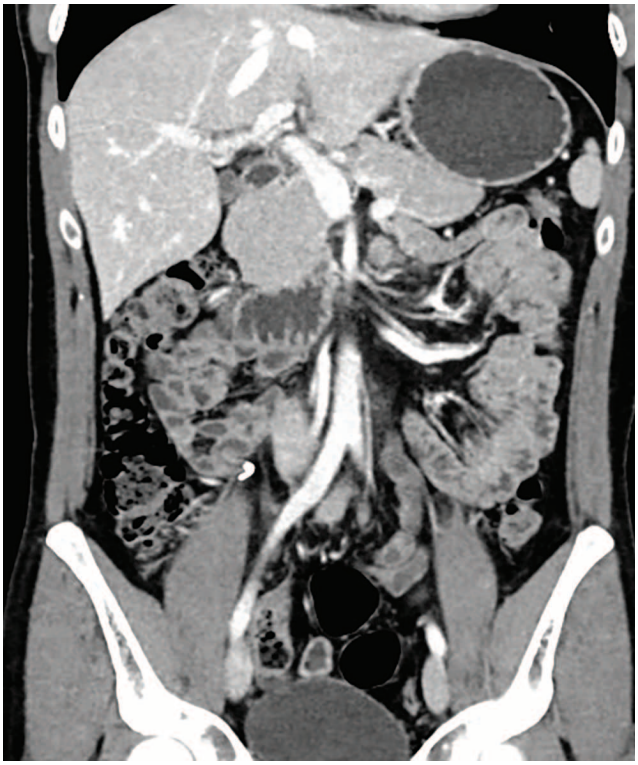


Figure 2. *September 2021 (represent stable findings)*

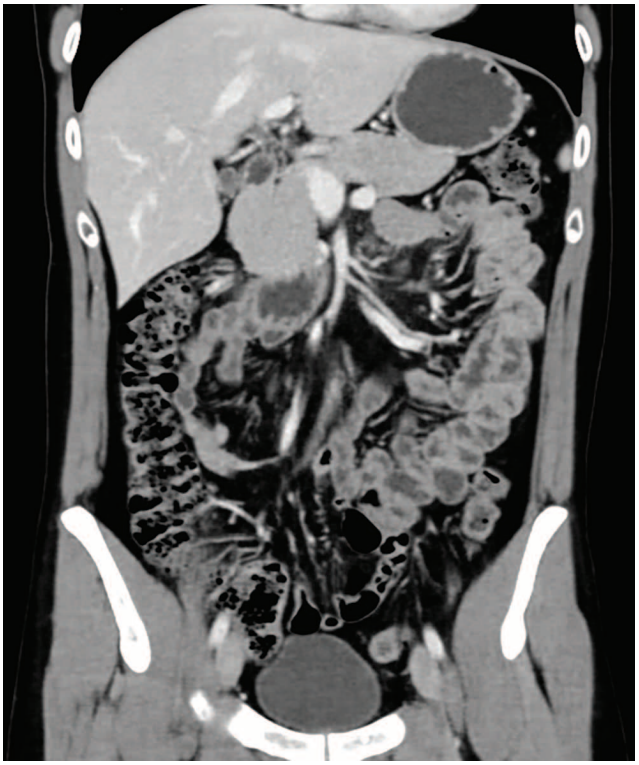
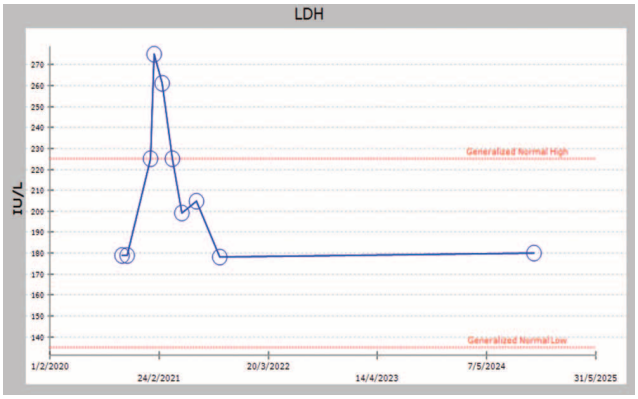


Figure 3. *April 2025 (No metastasis in chest, abdomen and pelvis)*



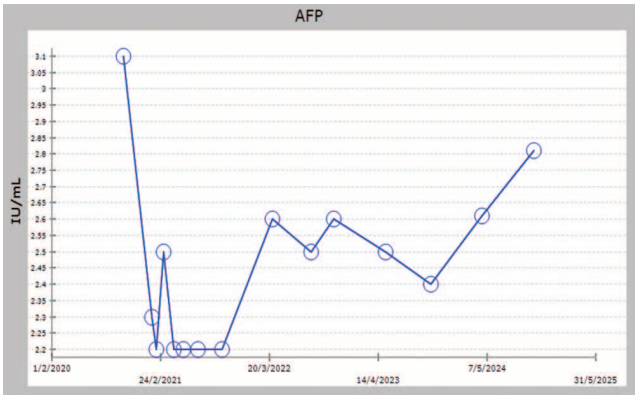


Figure 4. *Tumor markers*

Because of metastatic disease that was surgically debulked, the patient was subjected to somatic-type malignant histology-directed chemotherapy, in this case colorectal carcinoma regime was applied. Surgical resection was immediately followed by 12 cycles of chemo/adjuvant (FOLFOX) completed over 6 months from October 2020 to March 2021. CT scan in April 2021 and laboratory results were normal. The latest clinic follow-up was in April 2025 when he had no clinical, radiologic (Fig. 2,3), or biochemical (fig. 4) evidence of relapse or recurrence. He was planned to continue 3-month follow-ups and to repeat CT scans in 6 months.

Discussion

Our case presents several unique and clinically significant features that distinguish it from typical testicular germ cell tumors. The 35-year-old patient demonstrated pure adenocarcinoma with intestinal differentiation arising from a germ cell tumor, confirmed by the presence of GCNIS in adjacent testicular tissue and characteristic chromosome 12p abnormalities. The absence of elevated tumor markers (LDH, β-hCG, AFP) at presentation was particularly noteworthy, as this combination is unusual in typical testicular germ cell tumors but can occur in somatic-type malignancies.

Histologically, our case showed moderately differentiated adenocarcinoma with enteric features in the primary tumor, while metastatic deposits in retroperitoneal lymph nodes displayed mucinous adenocarcinoma characteristics. The molecular analysis revealed complex chromosome 12p gains (5-7 copies) involving CCND2 and KRAS genes, along with lower-level chromosome 12q gains, supporting the germ cell origin despite the absence of typical i(12p). Importantly, comprehensive clinical workup successfully excluded primary gastrointestinal or pancreaticobiliary sources, confirming the testicular origin.

The clinical presentation was also distinctive, with a 5-year history of intermittent symptoms, absence of systemic intoxication signs, normal hormonal parameters, and notably, a history of cryptorchidism requiring orchiopexy at age 7. The patient's excellent response to histology-directed FOLFOX chemotherapy, resulting in 42 months of complete remission, contrasts sharply with the generally poor prognosis reported in the literature for carcinomatous somatic-type malignancies.

Teratoma is a common type of TGCT that includes components from two or more germ-cell layers, which are endoderm, mesoderm and ectoderm(4).Teratoma with malignant transformation (SMT) is a rare type of teratoma that has somatic-type malignant elements found in different organs and tissues(5).This entity includes a range of tumors such as carcinomas like squamous cell carcinoma, adenocarcinoma and sarcomas such as rhabdomyosarcoma and malignant nerve sheath tumor, hematopoietic malignancies like leukaemia, and other types like nephroblastoma, carcinoid and primitive neuroectodermal tumors(6).

SMT can show up as either primary or metastatic GCT and can also develop in places outside the gonads, like the intracranial cavity retroperitoneum and mediastinum(4). SMT makes up less than 5 % of metastatic testicular tumors and usually impacts younger men(7-9).

Hwang MJ and colleagues examined the clinicopathologic characteristics of 63 GCTs, which included 22 in the testis and 41 with metastases(10). The patients with SMT in the testis had a median age of 26 years, which is younger compared to those with metastatic SMT, who had a median age of 38.5 years. Sarcoma was the most common type of testicular tumors, while carcinoma was the most common type of tumors in metastases, with most carcinomas being adenocarcinomas.

Several theories have been discussed by people in regards to how malignant transformation occurs in a GCT. Malignant transformation may occur either by the differentiation of totipotent germ cell elements into somatic tissues, which then transform into malignancy, or by malignant transformation of already existing teratomatous components(9).According to Oosterhuis et al., mature teratoma of metastases derives from primary tumors with mature components. These authors claim that the observed differentiation in metastases is due to the selective destruction of non-teratomatous elements by chemotherapy, rather than differentiation of totipotent germ cells(11), which allows for the selective growth of the chemo resistant teratomatous elements.

This process allows for the selective growth of the chemo-resistant teratomatous elements. Additionally, the occurrence of chromosome 12p abnormalities in these tumors, particularly the isochromosome 12 seen in most instances, indicates a shared clonality in GCTs(12, 13). Both adenocarcinoma with enteric differentiation and mucinous adenocarcinomas have occurred as variants of SMT. However, in our case, mucinous differentiation was only manifest in the retroperitoneal lymph node metastasis which may argue for Green's theory(13).

The first pathogenetic event of GCT happens during embryonal development, impacting a gonocyte or primordial germ cell. Even though this starts in the uterus, the tumor won't show up clinically until after puberty, with carcinoma in situ (CIS) being the precursor. All invasive TGCT, including both nonseminomas and seminomas , along with CIS cells, are aneuploid. Invasive TGCT primarily shows consistent structural chromosomal abnormalities, particularly gains on the short arm of chromosome 12, which are mostly caused by the formation of isochromosome (i(12p)). This indicates that having more copies of a gene or genes on 12p is linked to the occurrence of a clinically evident TGCT(14, 15).

SMTs are identified histologically by the invasion of nearby germ-cell elements by very atypical somatic cells(16). According to the authors, the key characteristic for diagnosing SMT is the growth of somatic malignant elements. Clinically significant SMT is identified when the somatic-type component occupies a field of view at low magnification, specifically with a 4× lens. Carcinomas like SCC, ADCs, neuroendocrine carcinomas are a rare group among SMT patients (16). Some tumors show staining for carcinoembryonic antigen and cytokeratins but they test negative for GCT markers like human chorionic gonadotropin, alpha-fetoprotein and placental alkaline phosphatase(17).

One of the most challenging aspects of our case was distinguishing primary testicular adenocarcinoma from metastatic colorectal carcinoma to the testis. Our comprehensive approach, including negative gastrointestinal workup, presence of GCNIS, and molecular confirmation of germ cell origin, was crucial for accurate diagnosis.

Metastatic carcinoma to the testes is rare and most commonly incidentally found at autopsy(18). The most common tumor to metastasize to the testes excluding leukemia and lymphomas is kidney (9 %), prostate

(35 %), melanoma (18 %), lung (18) (18) and colorectal less than 8 %(19). From 1950 to 2017, 75 cases of colorectal metastasis in testis have been reported(20). The testicular mass is even rarer as the first sign of a primary tumor(21). Our case adds to the limited literature on primary testicular adenocarcinomas that can mimic metastatic colorectal cancer, emphasizing the importance of thorough molecular and histologic evaluation. Ouellette says that there are fewer than 25 documented cases of colorectal cancer that have metastasized to the testis. The rarity of testicular metastases may be explained by low scrotum temperature limits metastases dissemination to the testes through the blood.

Treatment

There isn't a lot of research out there, so we don't have a set standard for SMT care. Instead, we rely on management advice from centers that handle a lot of these cases. For localized SMT disease, the usual treatment is radical orchiectomy. The importance of adjuvant chemotherapy is still a topic of debate. In the past, TGCTs that have somatic-type malignancy haven't really responded well to radiation and the usual platinum-based chemotherapy treatments(22, 23).

Evidence is in favor of aggressive resection as having negative margins is essential for long term remission and better oncological results(24). A study from 1998 involving 46 SMT patients who underwent complete resection showed that they had better oncological outcomes during follow-up in comparison with those people who had positive margins and incomplete resection (P=0.003) (24). Patients who have clinical stage I disease should definitely be considered for primary retroperitoneal lymph node dissection (RPLND). Conversely, patients with advanced but resectable disease typically undergo post-chemotherapy RPLND. This procedure requires a collaborative surgical effort and the complete removal of any essential vascular and visceral structures.

Several authors have suggested that histology-specific systemic chemotherapy regimens could be a more effective way to manage SMT. Efforts to direct chemotherapy at the transformed histology in metastatic teratomas have produced varied results, with certain studies indicating lasting positive responses while others report no response at all (13, 25). .Atwi and colleagues showed responses in patients who had a specific type of cancer(25).

In a study, seven of the 10 SMT patients with a response to regimens tailored to the histology of the somatic malignancy achieved a partial response and three had a long term response (13, 26). In a similar study in Europe, 8 SMT patients who received chemotherapy directed against the non-GCT component at relapse had a 50 % partial response(12).

The effectiveness of chemotherapy directed at TGCT and somatic-type malignant histology in metastatic cases, especially for patients with various histologic subtypes, is still mostly unknown. Patients with SMT can show systemic progressive disease and have normal serum tumor markers even when they are receiving proper treatment with cisplatin-based regimens because of their chemoresistant characteristics. Patients with SMT do not respond well to standard GCT treatments and tend to experience late systemic failure(27). Therefore, the best approach for managing SMT should include removing all areas affected by the disease along with systemic therapy focused on malignant transformation. Even so, dealing with SMT is still tough, and there aren't really good treatment options available for advanced cases(28, 29). Gene expression profiling is a new way to gain insights into molecular mechanisms and find possible targets that could be acted upon in difficult SMT cases. At the first diagnosis of a testicular tumor, our patient had retroperitoneal lymph node metastasis. Since we used FOLFOX every 3 weeks as adjuvant chemotherapy for colorectal cancer, we selected FOLFOX every 3 weeks as adjuvant chemotherapy. After surgery, the patient has been relapse or recurrence free for 42 months.

Prognosis

The outcomes of carcinomatous SMT depend on the stage and whether the disease can be surgically removed (30). When looking at different SMT histologies, carcinomas tend to have a delayed relapse, often occurring 5 years or more after the initial GCT diagnosis. They also rarely show a response to fluorouracil-based chemotherapy treatments or radiation(24). There isn't much information about the results of SMT, and what we do have mostly comes from small case series, primarily from large cancer centers(24, 30-32). Patients who are in stage I of the disease usually have a favorable prognosis, while those with metastatic disease experience worse outcomes in terms of cancer treatment, even when they undergo aggressive surgery and receive standard cisplatin-based systemic therapy for germ cell tumors, which has historically resulted in cancer-specific survival rates of about 50 %(33).The largest single-institution SMT series included patients with carcinoma, nephroblastoma, and sarcoma, sarcomatoid yolk sac tumor(10).

Approximately 75 percent of the patients had stage II–III disease, and the total estimated 5-year cancer-specific survival rate was 64 %, with a median follow-up of 71 months. No differences were found in outcomes between patients with sarcoma and those with carcinoma, although the patterns of recurrence varied. Patients with carcinomas tended to relapse several years later than those with sarcomas after the initial GCT diagnosis. A study conducted by Hwang MJ and colleagues

involving 63 patients found that those with metastatic SMTs had a suggestively lower overall survival rate compared to patients with SMTs in the testis, with a five-year survival rate of 35 % versus 87 % (P=0.011)(10). Additionally, patients with carcinomatous SMTs showed a significantly poorer prognosis compared to those with sarcomatous or PNET SMs, with 5-year survival rates of seventeen percent, 77 percent, and 73 percent, respectively (P=0.002), when analyzing the entire cohort, which included testicular and metastatic SMTs. The histologic subtype of SMT really impacts the clinical outcome, and it turns out that the carcinomatous SMT has an elevated risk for mortality.

Conclusion

In summary, this case highlights the rare occurrence of pure testicular adenocarcinoma with intestinal differentiation as a primary germ cell tumor, emphasizing the critical role of histopathological and molecular characterization in confirming its origin. The patient's detailed clinical history, imaging workup, and tailored treatment approach—involving radical orchiectomy, retroperitoneal metastasectomy, and histology-specific chemotherapy—led to a durable remission over a follow-up period exceeding 3.5 years. This case underscores the necessity of individualized treatment strategies and long-term surveillance in managing somatic-type malignancies arising from germ cell tumors.

SMT is a rare kind of GCT. Managing SMT patients effectively requires a team-based approach that includes proactive surgery and systemic therapy tailored to the specific histology. Surgery can really help patients with early-stage malignant TSCST, but for those with a lot of metastatic disease, the results aren't great since these tumors don't respond well to chemoradiation. More future studies are really important to help clarify how these rare malignant tumors develop. This will help us find targets we can act on, new ways to predict outcomes, and new treatment methods.

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Ашраф АЛаккад: клиническое ведение пациента, сбор данных, утверждение окончательного варианта рукописи

Наджла С. Бен Гашир: концепция и дизайн исследования, сбор и интерпретация данных, подготовка рукописи

Бабита А. Мохамед: гистопатологический анализ, интерпретация данных, редактирование рукописи

Ареф Чехаль: клиническое ведение пациента, интерпретация данных, критический пересмотр рукописи

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Ashraf ALakkad: made a major contribution to the development of the concept of the article with writing and editing the case report

Najla Saleh Ben Ghashir: contributed to the development of concept and writing up of the manuscript, the collection and interpretation of the clinical data, and critically reviewed the final version of puplication

Babitha Alingal Mohamed: contributed to the interpretation of clinical data and critically reviewed the manuscript

Aref Chehal: contributed to the interpretation of clinical data and critically reviewed the manuscript

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КЛИНИЧЕСКИЙ СЛУЧАЙ ДИАГНОСТИКИ ЭОЗИНОФИЛЬНОГО ЭЗОФАГИТА У ПАЦИЕНТА, ДЛИТЕЛЬНОЕ ВРЕМЯ СТРАДАЮЩЕГО БРОНХИАЛЬНОЙ АСТМОЙ ТЯЖЕЛОГО ТЕЧЕНИЯ И ПОЛУЧАЮЩЕГО ТЕРАПИЮ ГИБП (ДУПИЛУМАБ)

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Clinical Case of Diagnosis of Eosinophilic Esophagitis in A Patient Who Was Suffering for A Long Time with Severe Bronchial Asthma and Receiving Therapy with A Gerd (Dupilumab)

Резюме

Представлен клинический случай диагностики эозинофильного эзофагита (ЭоЭ) у пациента, длительное время страдающего бронхиальной астмой (БА) тяжелого течения и получающего терапию генно-инженерными биологическими препаратами (ГИБП): Дупилумаб. Трудности диагностики связаны с одной стороны, с необходимостью гистологической верификации диагноза, с другой стороны, с гетерогенностью проявлений заболевания. Частое сосуществование ЭоЭ и других аллергических заболеваний подчеркивает единство патогенетических путей, объединенных реакциями мукозального иммунитета. Приведенный нами клинический случай демонстрирует возможность диагностики ЭоЭ в отсутствии характерных жалоб и эндоскопической картины у пациента, имеющего поливалентную аллергию и длительный анамнез тяжелой БА. Своевременное применение эффективной терапии способствует предотвращению ремоделирования стенки пищевода с развитием стриктур, которые могут значительно ухудшать качество жизни пациента.

Ключевые слова: *Бронхиальная астма, гастроэзофагеальная рефлюксная болезнь, мукозальный иммунитет, Т2-воспаление; эозинофильный эзофагит*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

We presented a clinical case of diagnosing eosinophilic esophagitis in a patient suffering from severe asthma for a long time and receiving therapy with genetically engineered biological drugs: Dupilumab. Difficulties in diagnosis are associated, on the one hand, with the need for histological verification of the diagnosis, and on the other hand, with the heterogeneity of the manifestations of the disease. The frequent coexistence of EoE and other allergic diseases emphasizes the unity of pathogenetic pathways united by mucosal immune reactions. Our clinical case demonstrates the possibility of diagnosing EoE in the absence of characteristic complaints and endoscopic picture in a patient with polyvalent allergies and a long history of severe asthma. Timely use of effective therapy helps prevent remodeling of the esophageal wall with the development of strictures, which can significantly worsen the patient's quality of life.

Key words: *Bronchial asthma, gastroesophageal reflux disease, mucosal immunity, T2 inflammation, eosinophilic*

Conflict of interests

The authors declare no conflict of interests

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BA — bronchial asthma, EoE — eosinophilic esophagitis, GEBD — genetically engineered biologic drugs, PPI — proton pump inhibitors, SGCS — systemic glucocorticosteroids, IGCS/LABA — inhaled glucocorticosteroids / long-acting beta2-agonists, LAAC — long-acting anticholinergics, FGS — fibrogastroscopy, GERD — gastroesophageal reflux disease, SPG — spirogram, BAS — biologically active supplement

Introduction

The incidence of eosinophilic esophagitis (EoE) in bronchial asthma (BA) patients varies from 12 % to 68 % [1]; however, the pathogenetic relation between the two conditions has become obvious. The common pathogenic links include susceptibility to atopic disease, development of Th2-immune response, and effects of food and airborne allergens [2]. Being a Th2-associated disease, EoE can also be discussed as part of an atopic march [3]. A separate clinical entity of EoE has appeared relatively recently; and despite availability of a number of regulatory documents, principles of EoE diagnosis and treatment are still being actively developed and improved [2].

EoE can affect patients of any age, mostly men. The number of EoE cases grows from year to year; on the one hand, it follows the tendency towards higher incidence of allergic conditions in general; and on the other hand, it can be a result of better awareness of clinicians about this pathology. This systemic review demonstrates that asthma is more common in EoE patients vs. controls. These patients more often have polyvalent hypersusceptibility and higher IgE levels [1]. The incidence of EoE is as high as 81.7 to 118.4 cases per 100,000 people [2, 4]. It is worth noting that, among inflammatory esophagus conditions, EoE takes the second place in terms of the incidence after peptic esophagitis [4]. There are currently no epidemiological data on the incidence of EoE in Russia.

EoE is an immune-mediated oesophagus disease, which is characterised by marked eosinophilic infiltration of esophageal mucosa. The antigen can contact immune competent cells in mucosa in genetically predisposed individuals with mutated tight junction protein genes, which ensure epithelial integrity. Genetic disorders also affect the immune system factors, the increased activity of which causes polarised immune response (T2 inflammation); and the most important is hyperexpression of the gene, which is responsible for the synthesis of thymic stromal lymphopoietin (TSLP) [2]. Therefore, exposure to food allergens or airborne allergens leads to activation of dendritic or mast cells triggering T2 inflammation [5–6]. Cytokines IL-4, IL-5, and IL-13, synthesised by activated Th2 lymphocites, facilitate

eosinophil involvement in the inflammation site and their activation. Eosinophils release cytotoxic proteins and other inflammatory mediators, which cause tissue damage and, ultimately, esophageal wall remodelling. The consequence of fibroblast and smooth muscle cell involvement in the process is fibrogenesis and hyperplasia, also mediated by IL-4, IL-5, and IL-13 and impairing esophageal wall architectonics. As a result, persistent inflammation can lead to esophageal strictures, which have a great impact on the patients' quality of life and, in some cases, require surgery [2].

Challenges with EoE diagnosis are associated with the fact that eosinophilic infiltration of mucosa is not a pathognomonic sign of a desease. Eosinophilia can be observed in patients with peptic esophagitis, a number of autoimmune conditions, and gluten-sensitive enteropathy. The key role in the disgnosis is played by histologic examinations, for which reason the diagnostic criteria, called EoE-specific histologic scoring system, or EoEHSS, have been developed [7].

EoE is also known to be a heterogenic disease, both in terms of the array of clinical manifestations (from lack of symptoms to dysphagia, which significantly deteriorates the patient's quality of life) and response to therapy. Interestingly, some patients' clinical condition can improve with an elimination diet; other patients achieve remission after proton pump inhibitor (PPI) therapy; and some cases require initiation of target therapy, namely genetically engineered biologic drugs (GEBD) [2].

Here is a clinical case of eosinophilic esophagitis diagnosis in a patient, who had severe bronchial asthma (BA) for a long time and was treated with genetically engineered biologic drugs (GEBD): dupilumab.

Patient G., born in 1952, was admitted to the allergology ward on January 19, 2024, complaining of choking spells (approx. two times at night and 5 to 6 times during the day), triggered by physical exercise, strong smells, cigarette smoke, allergens; shortness of breath after low-intensity activities (climbing stairs to the second floor); attack-like cough with yellow thick discharges; heartburn; nagging pain in the left lumbar region, which gets more intense at night; occasional nasal blockage, especially in the morning and at night; and decreased sense of smell.

He did not have any signs of atopic disease as a child. The patient does not smoke and has never smoked. He is hypersensitive to captopril (in the form of Quincke's edema). Since 1996, the patient has experienced signs of rhinitis, especially in spring and summer; he occasionally took antihistamines. BA was diagnosed in 2001. Severe BA required frequent hospital admissions and 3–4 courses of systemic glucocorticosteroids (SGCS) annually. On the onsent of the condition, the patient was prescribed high doses of inhaled glucocorticosteroids + long-acting beta2-agonists (IGCS+LABA); in 2009, a third controller medication belonging to long-acting anticholinergics (LAAC) was initiated. Also, since asthma symptoms could not be controlled and the patient developed steroid resistance, a baseline therapy with prednisolone 5 mg/day was added. The patient took his medications regularly, demonstrated correct inhalation technique and proper compliance. Since the patient complained of heartburn, he underwent annual fibrogastroscopy (FGS); there were no signs of peptic esophagitis; in 2016, numerous erosions in the antral stomach were found. Because SGCS were required, the patient constantly used PPIs.

In October 2020, when the patient experienced severe BA, steroid resistance, concomitant nasal obstruction, polysensitization to domestic, epidermal and plant allergens, lack of control despite the therapy corresponding to step 5 of the Global Initiative for Asthma (GINA 2020), taking into account patient's compliance and absense of high eosinophil levels, GEBD: dupilumab was added at an initial dose of 600 mg s/c in the shoulder, with subsequent adjustment to 300 mg s/c fortnightly. After two years of therapy, the patient's condition improved: fewer choking spells during the day and at night, fewer hospital admissions, better nasal breathing and sense of smell, as well as better pulmonary function (Table 1). SGCS were discontinued during the first year of GEBD therapy.

In December 2023, the patient had community-acquired pneumonia, after which his BA aggravated for the first time since GEBD initiation, and inpatient treatment was required. The patient was admitted to the allergology ward for baseline therapy correction and develoment of a plan for further therapy with the genetically engineered biologic drug.

Table 1. *Spirogram indicators in dynamics in 2020-2021*

Indicators of respiratory function	At the time of initiation of therapy		After 12 months of therapy	
	before the salbutamol test	after the salbutamol test	before the salbutamol test	after the salbutamol test
FEV_1, %	73,7	110,5	119,4	122,8
FVC, %	88,7	110,5	114,6	118,3
FEV_1/FVC	64,75	77,88	80,07	79,43

Notes: FEV_1 — forced expiratory volume in 1 second, FVC — forced vital capacity

Table 2. Immunogram

Immunogram indicators	Actual values	Units of measurement	Reference values
Determination of total IgA	2.9	мг/мл	(0.8 — 4.0)
Determination of total IgM	0.6	мг/мл	(0.4 — 2.0)
Determination of total IgG	**5.2** <	мг/мл	(5.3 — 16.5)
Circulating immune complexes	14		(0 — 100)
T-lymphocytes (CD3+CD19-)	**56.00** <		(61.00 — 85.00)
B-lymphocytes (CD3-CD19+)	**33.20** >		(7.00 — 17.00)
T- helpers (CD3+CD4+)	48.20		(35.00 — 55.00)
T- cytotoxic (CD3+CD8+)	**7.90** <		(19.00 — 35.00)
NK-cells	8.70		(8.00 — 17.00)
T-NK cells (CD3+CD16+56+)	1.40		(0.50 — 6.00)
T- activated (CD3+HLADR+)	2.50		(0.50 — 6.00)
IRI (immunoregulatory index)	**6.10** >		(1.50 — 2.60)

Upon examination, the patient's condition is moderately severe; average height and weight: 75.0 kg, 172 cm; body mass index 25.4 kg/m2; skin is clear, moderately wet and normally coloured.

Nasal breathing is slightly obstructed on both sides; chest shape is unremarkable; percussion sound is clear and comes from the lungs, in projection of all pulmonary fields; breathing is harsh, with moderate dry rale in all fields, worsening with forced breathing; respiratory rate 19 per minute; oxygen saturation 95 %. The heart rhythm is normal, with muffled heart tones; no murmurs; heart rate: 81 bpm; pulse 81 bpm; blood pressure: 120/80 mm Hg on both arms; abdomen is not dilated and participates in breathing, soft, painless when palpated in all sections; the liver is painless along the costal margin; stool is normal. Urination is normal; no costovertebral angle tenderness on both sides; no edema.

Lab test results: white blood cells 13.96×109/L with neutrophilic shift (72.1 %, 10.07×109/L), Hb 136 g/L, platelets 211x109/L. No signs of lab activity: ESR 4 mm/h, CRP 2.4 mg/L. Total IgE 31 IU/mL (0–150). No high eosinophil levels were observed during the observation period.

The immunogram (Table 2) shows signs of B-cell sequence activation: decreased total T lymphocyte count 56 % (61–85 %), increased B lymphocyte count 33.2 % (7–17 %), T cytotoxic 7.9 % (19–35 %), immunoregulatory index (IRI) 6.1 (1.5–2.6), total IgG 5.2 g/L (5.3–16.5 g/L).

Imaging:

Comparative spirometry with salbutamol: forced expiratory volume during the first second (FEV1) 105.9–111.1 %, forced vital capacity (FVC) 113.7–114.3 %, FEV1/FVC 71.22–74.37. No signs of impaired pulmonary ventilation. Normal FVC. After inhalation of 400 μg of salbutamol, bronchodilation test was negative; FEV1 increased by 5 % (150 mL).

In order to rule out eosinophilic esophagitis, biopsy material was sampled from five sections (upper, middle and lower third of esophagus, stomach and duodenum):

No. 1. The sample contains small fragments of duodenum mucosa with moderately diffuse infiltration with lymphohistiocytic cells and moderate amount of neutrophils. Mucosa absorbs alcian blue in bottle cells.

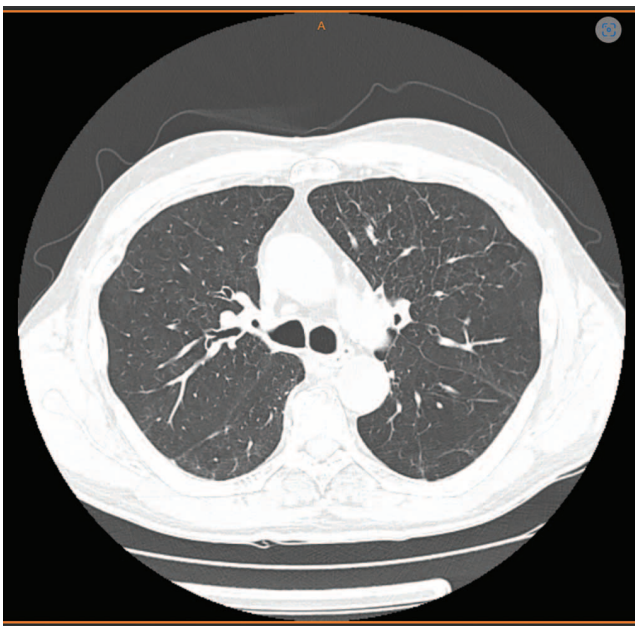
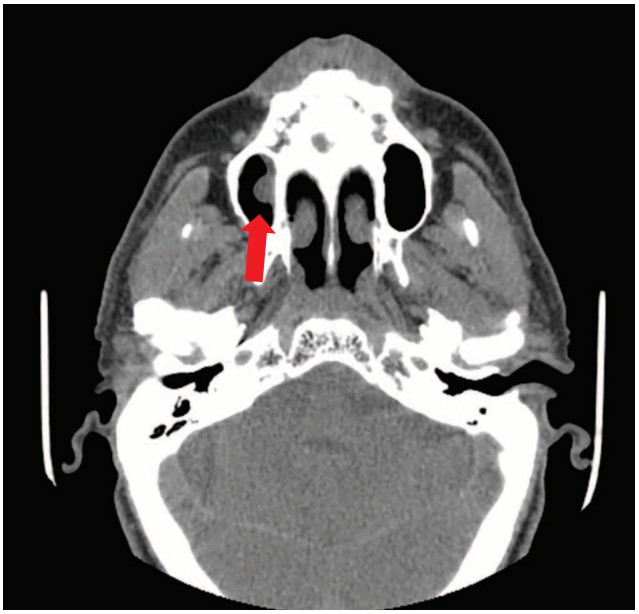


***Figure 1.** Multislice computed tomography of the chest organs (MSCT OC)*

Note. CT scan of the chest: The lungs are straightened. No infiltrative shadows. Unevenly distributed interstitial changes are present on both sides, with pulmonary emphysema, predominantly panlobular. A single discoid atelectasis is present in the right middle lobe. Large bronchi are patent. Single small mediastinal lymph nodes are present. There is no fluid in the pleural cavities.



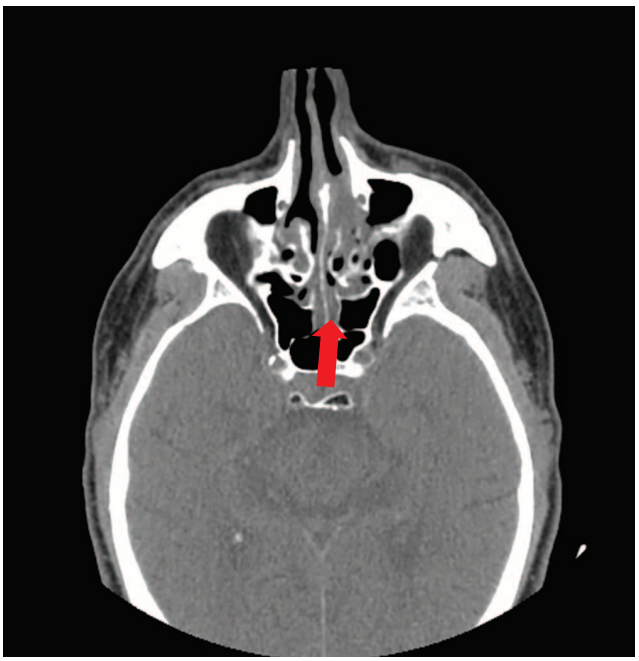


Figure 2. *Multislice computed tomography of the paranasal sinuses*

Note: The right maxillary sinus shows polypoid parietal lesions, and the ethmoidal labyrinth cells also show parietal lesions due to mucosal thickening. The frontal, left maxillary, and main sinuses are unremarkable. The nasal septum is moderately deviated in an S-shape.

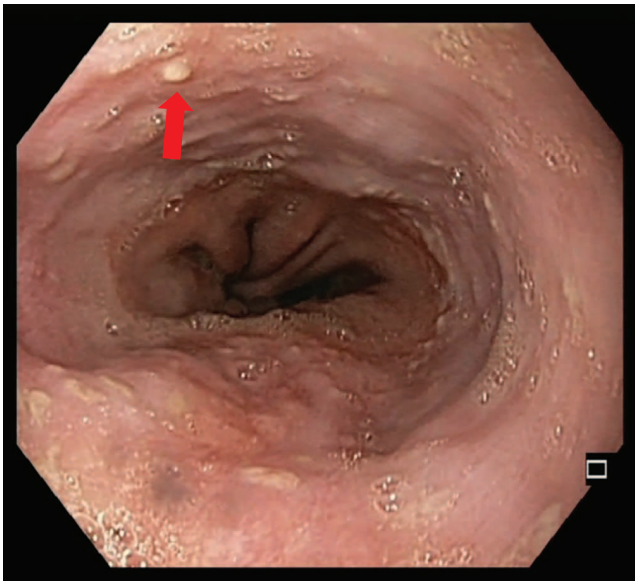


Figure 3a *— notes the presence of areas of whitish plaque in the esophagus*

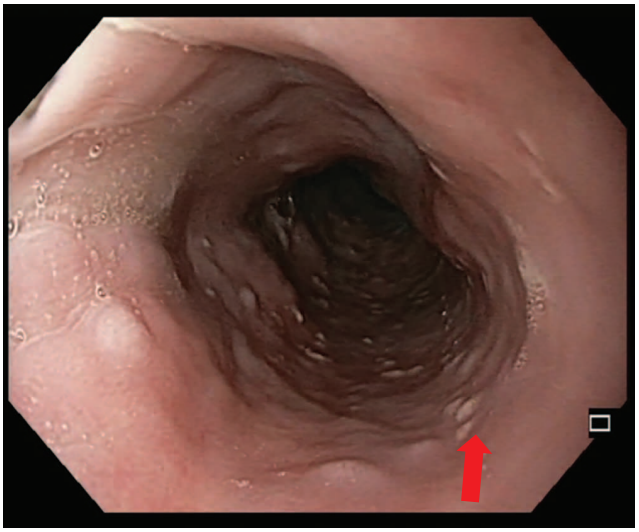


Figure 3b *— notes the presence of areas of whitish plaque in the esophagus*

Figure 3. *Esophagogastroduodenoscopy (EGD)*

No. 2. The sample contains fragments of stomach mucosa (metaplasia?). Lamina propria shows minor infiltration with neutrophils, lymphocytes, histocytes. Mucosa does not absorb alcian blue. H. pylori are not observed.

Nos. 3, 4. The samples contain layers of multilayer squamous epithelium without atypia and underlying tissue. The basal areas of epithelial layers have neutrophilic infiltration foci. Eosinophil count is 0–5 per HPF (x400 magnification). Mucosa does not absorb alcian blue.

No. 5. The samples contain layers of multilayer squamous epithelium without atypia and underlying tissue. The basal areas of epithelial layers have neutrophilic infiltration foci. Two fields of vision in basal areas have eosinophil accumulation of over 15 per HPF (x400 magnification). Mucosa does not absorb alcian blue.

Histology result: The morphological pattern may correspond to that of eosinophilic esophagitis; final diagnosis will be made taking into account clinical data, provided other pathology associated with eosinophil infiltration of esophageal mucosa has been ruled out.

Pursuant to recommendations of the Russian Gastroenterological Association [2], eosinophil infiltration and eosinophil density of ≥ 15 per high-power field (x400) at least in one biopsy sample is a criterion for diagnosing EoE. In this clinical case, a typical histology pattern was observed only in one biopsy sample from the upper third of esophagus, emphasising the importance of correct biopsy procedure (at least six different areas of mucosa).

The examination results were used to make the clinical diagnosis:

Primary disease: severe non-allergic bronchial asthma, moderate exacerbation, partially controlled. External respiration: stage 0. Respiratory insufficiency: stage 0. Firth step therapy: salmeterol/fluticasone 50/500 μg two puffs twice daily + tiotropium bromide respimat 2.5 μg two puffs in the morning + dupilumab 300 mg s/c fortnightly.

Severe persistent allergic rhinitis. Allergic intermittent conjunctivitis. Hypersensitivity to domestic, epidermal and plant allergens.

Concomitant pathology: IHD, postinfarction cardiosclerosis (2012). Exertional angina FC II. Stage III hypertensive disease, target BP value achieved, risk IV. Condition after ACVA in 2012 and 2015. Stage II discirculatory encephalopathy of mixed origin (hypertensive, atherosclerotic) with mild vestibulo-ataxic cognitive disorders. Symptomatic limb polyneuropathy, sensorimotor type.

Chronic pancreatitis, remission. Benign prostatic hypertrophy I. Chronic prostatitis.

Eosinophilic esophagitis.

Given the patient was diagnosed with EoE, a medical panel was summoned and the dose of the medication was corrected. Since 2020 the patient has been treated with GEBD because of the severe BA together with chronic rhinosinusitis polyposa; the dose was 300 mg fortnightly. In February 2024, the frequency was adjusted to once weekly as per the package insert and taking into account patient's weight. Therapy resulted in less intense esophageal symptoms; however, the patient did not come for repeated hospitalisation and no biopsy was performed over time.

Discussion

The majority of EoE cases described in Russian publications were observed in children. This is likely associated with the fact that in children the disease is often symptomatic. N. V. Bakulin at al. [8] describe a case of IgG4-associated esophagitis and EoE in a 17-year-old patient. The time from disease onset until diagnosis was 14 years; histologic samples needed to be re-examined in a specialised facility by several morphologists. The clinical presentation comprised progressing dysphagia and odynophagia; the patient had family history of atopic conditions and as a child he had atopic dermatitis. The peculiarity of this case was challenging interpretation of histology samples: initially, the morphological pattern was interpreted as low-degree intraepithelial neoplasia because of marked eosinophilic infiltration. When the samples were re-examined, typical signs of EoE were reported: more than 50 eosinophils per HPF, with clusters resembling eosinophil microabscesses. At the same time, immunohistochemistry revealed dense IgG4+ plasma cell infiltration in granulation tissue (50–70 IgG4-positive plasma cells per HPF, x400), meeting the criteria of IgG4-associated esophagus damage. A combination of the mentioned histological changes suggests common links between EoE and IgG4-associated conditions. It is assumed that IgG4 activation follows IgE-mediated response and can have a protective functions, blocking effects of IgE, including mast cell activation. There is a correlation between disease intensity and amount of intraepithelial and interepithelial eosinophils and IgG4+ plasmic cells [8].

In this clinical case, eosinophil infiltration was diagnosed only in the upper third of esophagus. It might be related to regular PPI therapy, facilitating reduction in the damaging action of hydrochloric acid on mucosa. One of the predictors of poor response to PPI therapy is the presence of significant IgG4+ infiltration in esophageal mucosa, therefore initial treatment with SGCS and GEBD should be considered these patients.

Unlike the observation in this article, EoE can be asymptomatic, with the typical endoscopic and histological pattern, as demonstrated by A. V. Paraskevova et al. [9]. In that case, EoE was diagnosed in a 52-year-old patient, who regularly took biologically active supplements (BASs) and who was diagnosed with typical signed of EoE during her preparation to surgery: circular mucosal thickening because of whitish papillary projections, longitudinal striation. Also, this case was remarkable because of the absence of a history of atopic conditions. Discontinuation of BASs and a course of PPIs resulted in complete endoscopic and histological remission; the patient did not have continuous recurrances typical of EoE; therefore, the condition was considered drug-induced (BAS) eosinophilic esophagitis. The same article describes a case of simultaneous gastroesophageal reflux disease (GERD) and EoE in one patient and analyses challenges with differential diagnosis of these conditions. It is well-known that gastroesophageal reflux disease can facilitate antigen interaction with immune competent cells and can trigger immune response, through mucosa damage, which causes EoE [10]. In a published clinical case, patient L., 68 years of age, had a long history of heartburn; he suffered from dysphagia and food regurgitation for three

years, and the patient sought medical help. In this case, peripheral blood eosinophilia was observed together with a typical endoscopic presentation (vertical sulci, mobile concentric rings, whitish effusion) and morphological signs of the disease.

Therefore, a histological examination of biopsy material taken from esophagus mucosa is essential for diagnosis of EoE. The diagnosis cannot be ruled out in the absence of typical clinical and endoscopic signs of the disease. This clinical case demonstrates possibilities of EoE diagnosis in the absence of typical complaints and endoscopic presentation in the patient with polyvalent allergy and a long history of severe BA.

EoE is treated with an elimination diet, PPIs, topical GCS and GEBD. The elimination diet means exclusion of products, which are known to cause allergic inflammation, i.e. milk, wheat, eggs, soya, nuts and fish (six-food elimination diet, SFED). SFED is a most well-studied approach, where the histological response is achieved in 67.9 % of patients vs. 13.3 % in placebo controls [11]. In a study by Frandsen L. T. et al. [12], high doses of PPIs completely eliminated symptoms in 68 % of patients and achieved histological remission in 49 % of EoE patients. A systematic review of eight double-blind placebo-controlled clinical studies of topical GCS (TGCS) therapy in 437 patients demonstrated that TGCS were associated with histological remission in 64.9 % of patients vs. 13.3 % of patients treated with placebo [11].

Given similar pathogenesis, GEBD therapy in patients with BA and EoE is justified. In their review Durrani S .R. et al. (2018) [1] conducted an analysis of GEBD efficacy in severe eosinophilic asthma when used to treat EoE: mepolizumab and reslizumab showed their efficacy for histological remission; however, their use did not affect EoE symptoms. Omalizumab did not have any beneficial effect. The most promising EoE therapy is dupilumab, since the drug has demostrated its beneficial effect both on clinical and histological remission. In May 2022, dupilumab was approved by the Food and Drug Administration (FDA) as an EoE therapy for patients over 12 years old weighing over 40 kg [13].

Dupilumab is a fully humanized anti-IL-4Rα antibody (IL-4Rα is a common receptor element for IL-4 and IL-13). IL-4 and IL-13 effects are implemented through signal transducer and activator of transcription (STAT) -6, which ensures signalling transduction to the cell nucleus. The key role in differentiation of naive Th lymphocytes into Th2 cells is played by IL-4. The shared objectives of IL-4 and IL-13 are ensuring eosinophil recruiting in mucous membranes, switching antibody synthesis to isotype IgE, dendritic cell activation, and maturation of M2 macrophages. IL-4 and IL-13 are also known to have the ability to inhibit expression of proteins, which ensure epithelial barrier integrity [14]. IL-13 is distinguished for its effects on tissue remodelling as a result of smooth muscle cell hyperplasia, collagen deposits and angiogenesis [15]. It is obvious that possible blocking of IL-4 and IL-13 effects ensures successful therapy of T2-associated conditions, including EoE. In this clinical case, the therapy resulted in positive clinical changes, improvement in pulmonary function, while dose adjustment contributed to less intense esophageal symptoms.

Conclusion

EoE is a T2-associated disease, which has been allocated a separate clinical entity quite recently and the incidence of which has been rising over the past decades. Challenges with disease diagnosis are associated with the need to verify diagnosis histologically, on the one hand, and with heterogenous disease presentaton, on the other hand. The fact that EoE is often associated with other allergic conditions underlines the existence of common pathogenetic components, unitied by mucosa-associated immunity reactions. This clinical case demonstrates possibilities of EoE diagnosis in the absence of typical complaints and endoscopic presentation in the patient with polyvalent allergy and a long history of severe BA. Timely initiation of efficient therapy facilitates prevention of esophageal wall remodelling and strictures, which can significantly deteriorate the quality of patient's life.

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КЛИНИЧЕСКИЙ СЛУЧАЙ МИОКАРДИТА АБРАМОВА-ФИДЛЕРА У ПАЦИЕНТА СТАРЧЕСКОГО ВОЗРАСТА

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Clinical Case of Idiopathic Abramov-Fiedler Myocarditis in The Elderly

Резюме

Миокардит Абрамова-Фидлера (идиопатический гигантоклеточный миокардит) относится к числу наиболее злокачественных форм неревматических воспалительных поражений миокарда. Заболевание традиционно диагностируется у лиц молодого и среднего возраста и сопровождается развитием быстро прогрессирующей сердечной недостаточности, жизнеугрожающих аритмий и тромбоэмболических осложнений. Представленный клинический случай имеет особое значение в связи с развитием миокардита Абрамова–Фидлера у пациента старческого возраста, что нетипично для данной нозологии. Пациент 80 лет был госпитализирован с клинической картиной острого коронарного синдрома с подъёмом сегмента ST. При поступлении отмечались интенсивные загрудинные боли, гипотензия, одышка и признаки острой левожелудочковой недостаточности. Лабораторные исследования выявили значительное повышение уровня тропонина и ферментов цитолиза. На электрокардиограмме регистрировался подъём сегмента ST по нижнебоковой стенке левого желудочка, а при коронароангиографии стеноз правой коронарной артерии составил лишь 30 % при сохранённом коронарном кровотоке. Несмотря на проводимую терапию, у пациента развился кардиогенный шок, завершившийся летальным исходом на вторые сутки заболевания. Патологоанатомическое исследование выявило очаги обширного воспалительного поражения миокарда с дистрофо-некротическими изменениями кардиомиоцитов, массивной смешанно-клеточной инфильтрацией и наличием гигантских многоядерных клеток. Иммуногистохимическое окрашивание с использованием антител к CD68 подтвердило макрофагальную природу клеточных элементов инфильтрата, что соответствует критериям гигантоклеточного миокардита. Данный клинический случай демонстрирует диагностические сложности, возникающие при атипичном течении миокардита Абрамова-Фидлера в пожилом возрасте, когда ведущую роль в клинической картине играют признаки, имитирующие острый коронарный синдром. Полученные данные указывают на необходимость высокой настороженности врачей в отношении воспалительных заболеваний миокарда у пациентов старших возрастных групп и подчёркивают значение патоморфологического и иммуногистохимического подтверждения диагноза.

Ключевые слова: *идиопатический миокардит Абрамова-Фидлера, гигантоклеточный миокардит, острый коронарный синдром, пожилой возраст, кардиогенный шок, сердечная недостаточность, морфологическая диагностика, иммуногистохимия, аутопсия, патоморфология*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

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Abstract
Abramov-Fiedler myocarditis (idiopathic giant cell myocarditis) represents one of the most malignant forms of non-rheumatic inflammatory heart disease. It is typically diagnosed in young and middle-aged patients and is characterized by rapidly progressive heart failure, life-threatening arrhythmias, and thromboembolic complications. The present clinical observation is of particular interest due to the development of Abramov-Fiedler myocarditis in an elderly patient, which is uncommon for this condition. An 80-year-old male was admitted with a clinical picture of ST-segment elevation acute coronary syndrome. On admission, he presented with severe retrosternal chest pain, hypotension, dyspnea, and signs of acute left ventricular failure. Laboratory tests revealed markedly elevated troponin and cytolytic enzymes. Electrocardiography demonstrated ST-segment elevation in the inferolateral wall of the left ventricle, while coronary angiography showed only a 30 % stenosis of the right coronary artery with preserved coronary flow. Despite intensive therapy, the patient developed cardiogenic shock and died on the second day of illness. Post-mortem examination revealed extensive myocardial inflammatory lesions with dystrophic and necrotic changes of cardiomyocytes, massive mixed-cell infiltration, and the presence of multinucleated giant cells. Immunohistochemical staining using CD68 antibodies confirmed the macrophage origin of the infiltrating elements, consistent with the diagnosis of giant cell myocarditis. This clinical case highlights the diagnostic challenges of atypical Abramov–Fiedler myocarditis in elderly patients, where the presentation may closely mimic acute coronary syndrome. The findings emphasize the importance of maintaining clinical vigilance for inflammatory myocardial diseases in older individuals and underscore the decisive role of morphological and immunohistochemical confirmation in establishing the diagnosis.

Key words: *idiopathic Abramov-Fiedler myocarditis, giant cell myocarditis, acute coronary syndrome, elderly patient, cardiogenic shock, heart failure, morphological diagnosis, immunohistochemistry, autopsy, pathomorphology*

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RVC — Regional Vascular Center, STEACS — ST-elevation acute coronary syndrome, BP — blood pressure, BMI — body mass index, SpO2 — oxygen saturation, RR — respiratory rate, HR — heart rate, CBC — common blood count, ECG — electrocardiogram, CAD — coronary artery disease, CAG — coronary angiography, RCA — right coronary artery

Introduction

The older patients are in the risk group for cardiovascular events, including acute myocardial infarction, acute cerebrovascular accident, pulmonary embolism. With the specific clinical signs, any physician starts working with these patients excluding the typical life-threatening conditions. Besides, several inflammatory diseases (including myocarditis) are mostly diagnosed in middle-aged patients. The post-COVID syndrome often manifested with viral myocarditis and atypical clinical manifestations, although the association with the trigger factor could not always be traced.

The idiopathic Abramov-Fiedler myocarditis is characterized by severe diffuse inflammatory, dystrophic, and degenerative myocardial alterations. Clinical signs of this disease are mainly defined by the rate of dystrophic and necrotic alterations in cardiomyocytes. The viral hypothesis for the Abramov-Fiedler myocarditis is confirmed by statistical data: chronic idiopathic myocarditis develops in 4–9 % patients after the acute viral myocarditis vs. 0.005 % in the general population. Approximately 20 % cases of Abramov-Fiedler myocarditis develop in patients with autoimmune diseases, e.g. Takayasu arteriitis, Hashimoto thyroiditis, Crohn's disease. Antimyocardial antibodies and cellular cytotoxicity are detected, thus confirming the immunopathological inflammation mechanism. The drug therapy of idiopathic myocarditis has low efficacy, and the majority of patients die due to complications.

Typical morphological signs of the Abramov-Fiedler myocarditis include isolated cardiac lesions, a combination of widespread dystrophic, infiltrative-inflammatory

myocardial alterations with diffuse cardiosclerosis, intracardiac thrombi and embolism of systemic arteries [1]. Gross pathology in the Abramov-Fiedler myocarditis reveals floppy walls and distended cardiac chambers with intramural thrombi; the wall section demonstrates mottled myocardial discoloration. The biomaterial microscopy detects muscle fiber hypertrophy, diffuse myolysis fields with the muscle tissue substituted with the fibrous one, and signs of coronariitis (inflammatory infiltrates along the small branches of coronary arteries).

A unique clinical case below describes idiopathic Abramov-Fiedler myocarditis in an older male without an overt history of autoimmune or viral diseases.

Clinical Case Study

The male patient N., 80 years old, was brought by the ambulance to the Regional Vascular Center (RVC) on March 24, 2024 at 7:45 p.m. with the diagnosis of ST-elevation acute coronary syndrome (STEACS).

On admission, the patient complained of sudden-onset substernal burning pain not associated with physical exertion, shortness of breath at rest, cold sweat, blood pressure (BP) drop to 80/40 mm Hg, dull pain in the right subcostal area, nausea and one-time vomiting of food.

Medical history: the patient did not suffer from cardiovascular diseases and did not monitor the BP values. He was not regularly followed up by the cardiologist. A day before the hospitalization, the patient started having the complaints above, but he did not seek medical attention. Due to pain worsening, he called the ambulance team on March 24, 2024. The ambulance staff suspected STEACS. The following medical care was provided for the patient before the hospital: acetylsalicylic acid 250 mg, clopidogrel 300 mg, intravenous heparin 4,000 U, nitroglycerin 0.5 mg, 1 % morphine (1 mL). The patient was hospitalized into the RVC emergency department.

According to the patient, he did not suffer from tuberculosis, venereal or parasitic diseases. In 2004, he was diagnosed with a gastric polyp, but did not receive any treatment. He had a history of frequent common colds, treating himself independently. He had been smoking for many years. The patient denied any allergic reactions to drugs.

Upon the admission to the inpatient department, the patient's condition was moderately severe. The patient's consciousness was clear. The body position was forced (lying on a stretcher). The body temperature was 36.6 °C. The oxygen saturation (SpO2) was 99 %. Physical examination: average constitutional build. The skin color and moisture level were physiological. No edema was detected. The body mass index (BMI) was 24.2 kg/m2. Lung auscultation revealed vesicular breathing with no rales. The respiratory rate (RR) was 16 per minute. Cardiac auscultation revealed a systolic murmur at the apex; cardiac tones were regular, muffled. The BP was 80/40 mm Hg. The heart rate (HR) was 80 beats per minute.

The common blood count (CBC) parameters were within the acceptable limits.

The biochemistry panel revealed increased troponin and CK-MB levels, thus confirming myocardial ischemia. Speaking about other specific biomarkers, elevated AST and LDH levels were also detected, thus indirectly signifying cardiomyocyte injury. In the lipid panel the LDL-C level was over the reference range, confirming a very high risk of adverse cardiovascular events. The detected high CRP level confirmed the active inflammation.

Electrocardiogram (ECG) dated March 24, 2025: sinus rhythm with HR 80 beats per minute, 2 mm ST segment elevation in leads II, III, AVF, V5, V6 (inferolateral wall of the left ventricle).

Chest X-ray was arranged on the same day. Chest X-ray demonstrated signs of hypervolemia in the pulmonary circulation, pulmonary congestion, emphysema, fibrotic alterations, aortic atherosclerosis.

The plain abdominal X-ray was arranged to exclude bowel obstruction — no air-fluid levels were visualized. Pneumatosis of the small and large bowel loops was detected. The abdominal ultrasound revealed hepatomegaly, irregular liver structure, and dilated hepatic veins. Other organs did not demonstrate pathological alterations. A small amount of free fluid was detected in all abdominal cavity regions and over the liver, spleen.

Table 1. *Biochemical blood analysis*

Indicator	Result	Reference values
Th T, (ng/L)	14740	0-200
CK-MB, (U/L)	98,12	0-24
ALT, (U/L)	636	0-35
AST, (U/L)	790,2	0-31
Glucose, (mmol/l)	6,34	3,5-5,5
Total protein (U/L)	62,92	62-83
CRP, (mg/L)	27,06	0-0,3
Chol, (mmol/L)	4,49	2,8-5,5
HDL-C, (mmol/L)	1,26	1,03-1,55
LDL-C, mmol/L	3,19	0-2,6
Triglycercides, (mmol/L)	1,21	0-2,1
LDH, (U/L)	1524,4	135-225

Note: CK-MB — creatine kinase MB fraction, Tn I — troponin I, ALT — alanine aminotransferase, AST — aspartate aminotransferase, CRP — C-reactive protein, HDL-C– high density lipoprotein cholesterol, LDL-C — low density lipoprotein cholesterol, LDH — lactate dehydrogenase

Echocardiography demonstrated a small amount of fluid in the pericardial cavity, 40 % ejection fraction (Simpson's), impaired local contractility (hypokinesis) in the inferolateral wall of the left ventricle.

Based on the clinical manifestations, physical examination and diagnostic investigations, the diagnosis of coronary artery disease (CAD), STEACS of the inferolateral wall of the left ventricle was established. Coronary angiography (CAG) revealed the 30 % stenosis of the right coronary artery (RCA), TIMI III blood flow. Other coronary arteries did not have occlusions. After CAG, the patient was transferred to the intensive care unit according to the current STEACS clinical guidelines.

Upon the admission to the intensive care unit, the patient's condition was stably severe. The patient's consciousness was clear. The body temperature was 36.5 °C. The skin had a normal physiological color. Lung auscultation revealed vesicular, but diffusely weakened breathing; RR was 16 per minute, SpO2 was 97 %. Cardiac auscultation revealed regular rhythm, muffled cardiac tones, and a systolic murmur at the apex. The BP was 110/70 mm Hg, HR was 80 beats per minute.

The patient developed sudden cardiac arrest during the night of 24/25 March, 2025. BP and HR could not be recorded. Asystole was recorded in the ECG. Full-scale resuscitation procedures were arranged within 30 minutes, to no effect. The biological patient's death was confirmed.

The patient's body was referred to the autopsy with the following diagnosis:

Main disease: CAD. Acute ST-elevation myocardial infarction of the inferolateral wall of the left ventricle dated March 24, 2024. CAG (March 24, 2024): 30 % RCA stenosis.

Complications: AHF (Killip IV). Acute left ventricular heart failure. Cardiogenic shock. Asystole.

Concomitant diseases: Chronic kidney disease, stage 3B. Multi-organ failure.

The following diagnosis was established based on the autopsy and pathohistology results:

Main disease: Idiopathic giant-cell (Abramov-Fiedler) myocarditis.

Complications: Diffuse myocardial dystrophy and necrosis. Acute left ventricular heart failure. Acute generalized venous congestion (interstitial-alveolar pulmonary edema, acute nutmeg liver). Cardiogenic shock. Acute prerenal failure.

Concomitant diseases: Essential hypertension (myocardial weight 500 g, thickness of the left ventricular wall 1.8 cm, glomerular hyalinosis, hyalinosis of splenic vessels). COPD (non-specific peribronchial-septal pneumofibrosis, panacinar emphysema). Chronic pancreatitis.

Pathology:

During the autopsy, a yellow-gray circular irregular myocardial focus was detected; it had a transmural (sometimes intramural) localization and a total area of 56 cm2. Signs of severe generalized venous congestion (congestive hyperemia of lungs, kidneys, liver, bowel, and vascular meningeal plexuses) were also found. Pieces for histology were collected and placed into the 10 % buffered neutral formalin during the autopsy. After a 48-hour fixation, the pieces were treated in alcohols with increasing concentrations, after which the specimens were paraffin-embedded, and the 4 μm slices were prepared and stained with hematoxylin-eosin. The immunohistochemistry with anti-CD68 primary antibodies (PG-M1 clone) and the Elabscience 2 Step Plus (Poly-HRp anti-Rabbit/mouse IgG with DAB solution, Cat. No E-IR-R213) were arranged on the Autostainer 360 immunohistostainer (Thermo Fisher Scientific, USA). The prepared glasses were scanned using the Pannoramic 250 (3DHISTECH Ltd., Hungary) with subsequent analysis of histological slices under various magnification using the CaseViewer (3DHISTECH Ltd., Hungary) software.

The heart microscopy revealed widespread involvement of the contractile myocardial parenchyma into the inflammatory process with massive interstitial infiltration with various inflammatory elements (lymphocytes, eosinophils, macrophages, and scattered giant multinucleated cells) (Figure 1). Myocardial fibers underwent significant dystrophic alterations with wavy fibrils, contracted cytoplasm volume, and fibrotic substitution foci. Lungs had signs of acute venous congestion with interstitial-alveolar pulmonary edema, acute centrilobular hepatic congestion, and acute tubular lesions (cytoplasm hydrops, fragmentation of apical epitheliocyte

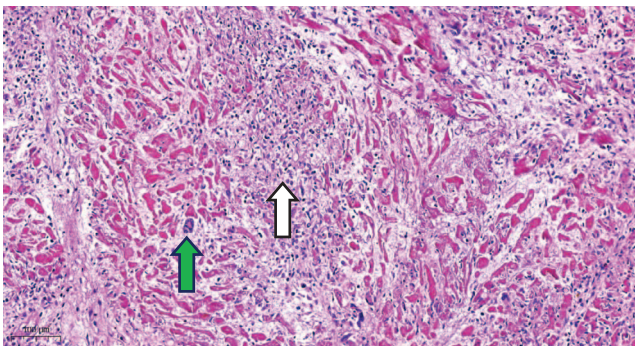

Figure 1. *Micrograph of the intramural myocardium. Pronounced dystrophic-necrotic changes in myofibrils, focal replacement of the parenchyma by connective tissue elements (white arrow) against the background of abundant interstitial mixed cellular infiltration with the appearance of giant multinucleated cells (green arrow). Magnification ×200; hematoxylin and eosin staining*

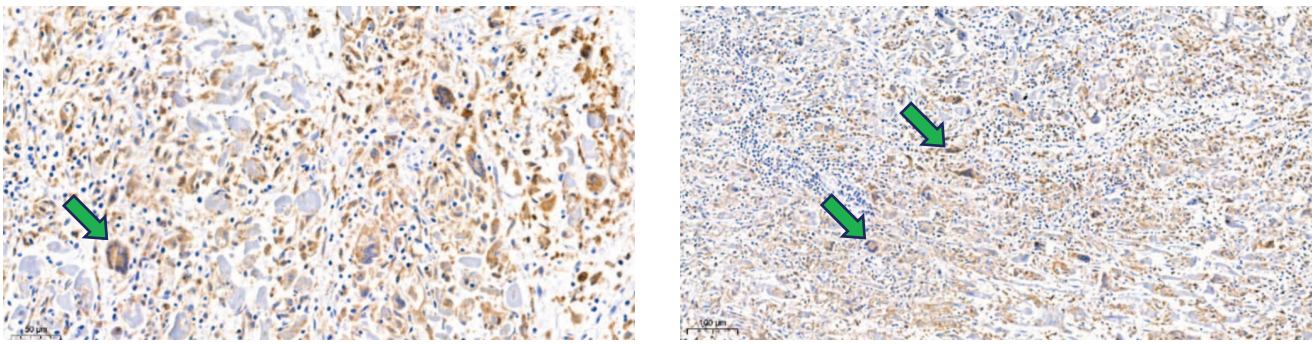

Figure 2. *Photomicrograph of immunohistochemical staining of myocardium for CD68. Persistent cytoplasmic positive staining in multinucleated and mononuclear histiocytic (arrow) inflammatory elements and complete absence of staining in the myogenic component. Immunohistochemical staining for CD68. Magnification ×400, ×200; hematoxylin and eosin staining*

poles in kidneys). To confirm the macrophagal origin of the giant-cell component in the inflammatory infiltrate, immunohistochemistry with anti-CD68 antibodies was arranged, which revealed persistent positive cytoplasmic staining of multinucleated elements, confirming its histiocytic histogenesis (Figure 2).

Based on the autopsy and pathohistology findings, the following diagnosis was established: Idiopathic giant-cell (Abramov-Fiedler) myocarditis complicated with diffuse cardiomyocyte dystrophy and necrosis (dystrophic variant), acute left ventricular heart failure, and acute prerenal failure.

Discussion

The incidence of myocarditis has increased over the past few years, with the current incidence being equal to 10–12 cases per 100,000 population. According to the statistics, myocarditis is more common among young males under 45 years of age, however a more severe disease course is typical for females. The average age of patients with the confirmed diagnosis of idiopathic myocarditis is 42 years [2].

In the case described, the patient belonged to the older age group, which blunted the clinical awareness of physicians concerning inflammatory diseases. The incidence of coronarogenic myocardial diseases of atherosclerotic origin increases with age, displacing other diseases. In our clinical case, the combination of several risk factors (including age, gender, smoking) formed the foundation to suspect the acute coronary syndrome initially.

Abramov-Fiedler myocarditis is considered a very severe form of non-rheumatic myocarditis with high mortality. Young and relatively healthy persons are the typical patients with Abramov-Fiedler myocarditis. Most often patients with the confirmed diagnosis of idiopathic myocarditis had a history of viral or autoimmune diseases, e.g. Coxsackie viral infections, Crohn's disease, Hashimoto thyroiditis, systemic lupus erythematosus, etc. [3].

According to the patient N.'s words, he had frequent common colds which were never verified or treated medically with specific treatment. Due to the atypical or subclinical myocarditis course, the majority of its cases are detected only on autopsy. However, it should be noted that the most typical clinical symptoms for myocarditis include cardiac pain and ventricular arrhythmias or heart blocks. Heart failure quickly progresses in 75 % cases, while 50 % patients develop sustained ventricular tachycardias [4].

A day before the hospitalization and during the short-term hospital stay, our patient had substernal intensive burning pain, but he did not complain of palpitations. No arrhythmias typical for the Abramov-Fiedler myocarditis were diagnosed.

The laboratory and instrumental diagnosis confirming myocarditis is rather difficult and costly. Detected elevated serum levels of cardiospecific enzymes (troponin, CK) may reflect the damaging effects of any factors on cardiomyocytes. The results of instrumental investigations have to be accounted for to confirm the specific diagnosis. Considering our patient, the combination of elevated troponin levels and typical ST segment alterations in the ECG provided the clinical presumption of an acute myocardial infarction; however, CAG demonstrated only 30 % RCA stenosis without its thrombotic occlusion.

The mortality in myocarditis reaches 20–40 % [5]; in the majority of cases, patients die from acute left ventricular failure (ALVF) or ventricular fibrillation. In our case, quick ALVF development (cardiogenic shock) became the cause of death.

The histology of the autopsy material reveals typical dystrophic necrobiotic alterations of cardiomyocytes in the myocardium and the interstitial tissue along with the

widespread inflammatory infiltrate mainly represented by lymphocytes, although giant multinucleated cells are also detected [5]. The microscopy of the patient's biomaterial revealed widespread involvement of the contractile myocardial parenchyma into the inflammatory process with massive interstitial infiltration with various inflammatory elements (lymphocytes, eosinophils, macrophages, and scattered giant multinucleated cells), which coordinates with the general immunohistochemistry results.

In this case myocarditis developed in an elderly patient (80 years old), which is an atypical case. These autopsy data specific for the Abramov-Fiedler myocarditis may be potentially associated with prior viral diseases, including COVID-19. It should be noted that arrhythmias and thromboembolic complications typical for the disease were missing.

Conclusions

The Abramov-Fiedler myocarditis belongs to very severe forms of non-rheumatic myocarditis with high mortality, which usually develops in young patients. The clinical case presented demonstrates a rare disease course in an elderly patient with clinical signs imitating acute coronary syndrome, along with the absence of typical manifestations (significant arrhythmias, intracardiac thrombi). Pathomorphological and immunohistochemistry data helped to verify the diagnosis of giant-cell myocarditis.

The clinical case underscores the need for enhanced awareness of inflammatory diseases in elderly patients, even in the setting of risk factors for the coronary artery disease. Accounting for the possible role of viral infections, including prior COVID-19, in the disease pathogenesis, an advanced-age variant of the Abramov-Fiedler myocarditis should be considered.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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