Научно-практический журнал для работников здравоохранения

Включён в Перечень ведущих рецензируемых периодических изданий ВАК Минобрнауки РФ

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE

www.medarhive.ru

ДЕКАБРЬ 2024 (№ 6(80))

УЧРЕДИТЕЛЬ И ИЗДАТЕЛЬ
Общество с ограниченной ответственностью «Синапс»
107076, Москва, ул. Короленко, д.3А, офис 18Б
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Подписано в печать 19.11.2024 года
Тираж 3000 экземпляров.

Издание зарегистрировано в Федеральной службе по надзору в сфере связи, информационных технологий и массовых коммуникаций (Роскомнадзор).

Свидетельство о регистрации
ПИ № ФС77-45961 от 26 июля 2011 г.

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Отпечатано в типографии «Onebook.ru»
ООО «Сам Полиграфист»
г. Москва, Волгоградский проспект, д. 42, корп. 5
www.onebook.ru

Журнал включен в Российский индекс научного цитирования (РИНЦ)

Статьи журнала представлены в Российской универсальной научной электронной библиотеке www.elibrary.ru

Подписной индекс в каталоге «Урал-Пресс Округ» 87732

DOI: 10.20514/2226-6704-2024-6

Scientific and practical journal for health professionals

Included the List of the Russian reviewed scientific magazines in which the main scientific results of theses on competition of academic degrees of the doctor and candidate of science have to be published.

Архивъ внутренней медицины

THE RUSSIAN ARCHIVES OF INTERNAL MEDICINE
www.medarhive.ru
DECEMBER 2024 (№ 6(80))

FOUNDER AND PUBLISHER
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107076, Moscow, Korolenko str., 3A, of. 18B
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Signed for printing on 19.11.2024
Circulation 3000 exemplars

It is registered by state committee of the Russian Federation on the press

The certificate on registration of mass media ПИ № ФС77-45961, 26 July 2011

ISSN 2226-6704 (Print)
ISSN 2411-6564 (Online)

Printed «Onebook.ru»
«Sam Poligrafist»
Moscow, Volgograd Prospect, 42-5
www.onebook.ru

The journal is included in Russia Science Citation Index (RSCI)

Journal data are published on website of Russian General Scientific Electronic Library www.elibrary.ru

Subscription index in the catalogue «Ural-Press Okrug» 87732

DOI: 10.20514/2226-6704-2024-6

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http://www.medarhive.ru/jour/about/submissions#authorGuidelines

DOI: 10.20514/2226-6704-2024-14-6-405-418
УДК 616.24-002.155-056.43-07-085
EDN: LYHBFO

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ИДИОПАТИЧЕСКИЙ ЛЕГОЧНЫЙ ФИБРОЗ И ГИПЕРСЕНСИТИВНЫЙ ПНЕВМОНИТ: НОВЫЙ ВЗГЛЯД НА РОЛЬ ГЕНЕТИЧЕСКИХ И ЭПИГЕНЕТИЧЕСКИХ ФАКТОРОВ В РАЗВИТИИ И ТЕЧЕНИИ ЗАБОЛЕВАНИЙ

E.E. Arkhangelskaya[1], S.V. Lyamina[2], E.O. Kozhevnikova[2], I.V. Kozlova[1], T.G. Shapovalova[1], G.L. Yurenev[2]

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Idiopathic Pulmonary Fibrosis and Hypersensitive Pneumonitis: A Fresh View on The Role of Genetic and Epigenetic Factors in The Development and Course of Diseases

Резюме

Учитывая повсеместно прогрессирующий характер и неблагоприятный прогноз, интерстициальные заболевания легких (ИЗЛ), особенно такие часто встречающиеся варианты, как идиопатический легочный фиброз (ИЛФ) и гиперсенситивный пневмонит (ГП), оправданно привлекают значительное внимание клиницистов и ученых по всему миру. В последние годы все большую актуальность приобретает необходимость углубленного изучения клинических и патогенетических особенностей ИЗЛ, совершенствование существующих и разработка новых эффективных персонализированных подходов тактики ведения этой категории пациентов, на основе наиболее перспективных мишеней воздействия, среди которых все более активно рассматриваются генетические и эпигенетические варианты. Авторами проведен нарративный, описательный обзор литературы, направленный на систематизацию данных об основных известных генетических и эпигенетических механизмах, вовлеченных в патогенез и формирование специфических клинических проявлений ИЛФ и ГП. Отдельно выделены мутации в генах, кодирующих теломеразы, синтез факторов фиброгенеза, полиморфизмы генов муцина, сурфактанта легких, основные эпигенетические изменения, вовлеченные в процессы фиброгенеза. Проанализированы перспективы генетических и эпигенетических исследований для новых фармакологических подходов и мониторинга эффекта уже доступных методов лечения. Поиск литературных источников проводился по базам данных Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, CyberLeninka и РИНЦ, по ключевым словам, «интерстициальные заболевания легких», «идиопатический легочный фиброз», «гиперсен-

ситивный пневмонит», «семейный легочный фиброз», «генетический», «эпигенетический», «прецизионная диагностика», «терапия» с глубиной поиска 20 лет.

Ключевые слова: *интерстициальные заболевания легких, идиопатический легочный фиброз, гиперсенситивный пневмонит, семейный легочный фиброз, генетический, эпигенетический, MUC5B, TERT, теломеры, сурфактант, терапия*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 22.08.2024 г.
Одобрена рецензентом 23.09.2024 г.
Принята к публикации 14.10.2024 г.

Для цитирования: Архангельская Е.Е., Лямина С.В., Кожевникова Е.О. и др. ИДИОПАТИЧЕСКИЙ ЛЕГОЧНЫЙ ФИБРОЗ И ГИПЕРСЕНСИТИВНЫЙ ПНЕВМОНИТ: НОВЫЙ ВЗГЛЯД НА РОЛЬ ГЕНЕТИЧЕСКИХ И ЭПИГЕНЕТИЧЕСКИХ ФАКТОРОВ В РАЗВИТИИ И ТЕЧЕНИИ ЗАБОЛЕВАНИЙ. Архивъ внутренней медицины. 2024; 14(6): 405-418. DOI: 10.20514/2226-6704-2024-14-6-405-418. EDN: LYHBFO

Abstract

Given their ubiquitous progressive nature and unfavorable prognosis, interstitial lung diseases (ILD), especially such common variants as idiopathic pulmonary fibrosis (IPF) and hypersensitivity pneumonitis (HP), rightly attract considerable attention from clinicians and scientists worldwide. In recent years, the need for an in-depth study of the clinical and pathogenetic features of ILD, improvement of existing approaches and development of effective personalized approaches to the management of this category of patients, based on the most promising targets of action, among which genetic and epigenetic variants are increasingly being considered, has become increasingly important. The authors conducted a non-systematic, descriptive review of the literature aimed at systematizing data on the main known genetic and epigenetic mechanisms involved in the pathogenesis and formation of specific clinical manifestations of IPF and HP. Mutations in genes encoding telomerase, synthesis of fibrogenesis factors, polymorphisms of mucin genes, lung surfactant are highlighted separately, and the main epigenetic changes involved in fibrogenesis processes are highlighted separately. Prospects of genetic and epigenetic studies for new pharmacological approaches and monitoring the effect of already available treatment methods are analyzed. The search for literature sources was conducted in the Scopus, Web of Science, MedLine, The Cochrane Library, EMBASE, Global Health, CyberLeninka, and RSCI databases by the keywords "interstitial lung diseases", "idiopathic pulmonary fibrosis", "hypersensitivity pneumonitis", "familial pulmonary fibrosis", "genetic", "epigenetic", "precision diagnostics", "therapy" with a search depth of 20 years.

Key words: *interstitial lung diseases, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, familial pulmonary fibrosis, genetic, epigenetic, MUC5B, TERT, telomeres, surfactant, therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 22.08.2024
Reviewer approved 23.09.2024
Accepted for publication on 14.10.2024

For citation: Arkhangelskaya E.E., Lyamina S.V., Kozhevnikova E.O. et al. Idiopathic Pulmonary Fibrosis and Hypersensitive Pneumonitis: A Fresh View on The Role of Genetic and Epigenetic Factors in The Development and Course of Diseases. The Russian Archives of Internal Medicine. 2024; 14(6): 405-418. DOI: 10.20514/2226-6704-2024-14-6-405-418. EDN: LYHBFO

HSP — hypersensitive pneumonitis, CD — Christian's disease, DIP — desquamative interstitial pneumonia, ILD — interstitial lung disease, IIP — idiopathic interstitial pneumonia, IPF — idiopathic pulmonary fibrosis, COP — cryptogenic organizing pneumonia, LAM — lymphangioleiomyomatosis, LIP — lymphocytic interstitial pneumonia, PF — pulmonary fibrosis, NIP — non-specific interstitial pneumonia, AIP — acute interstitial pneumonia, RB — respiratory bronchitis, ILD RB — interstitial lung disease-associated respiratory bronchitis, SCTD — systemic connective tissue diseases, FPF – family history of idiopathic pulmonary fibrosisa, TNF-α — tumour necrosis factor alpha, FNIP – fibrous non-specific interstitial pneumonia, AE2 — alveolar epithelium type II cells, ECM – extracellular matrix, EMT — epithelial-mesenchymal transition, FGFR — fibroblast growth factor, GWAS — genome-wide association study, HAT — histone acetyltransferase, HDAC — histone deacetylase, HDACi — histone deacetylase inhibitors, HDM — histone demethylase, HLA — major histocompatibility complex, HMT — histone methyltransferase, IL — interleukin, NGS — next generation sequencing, PDGFR — platelet growth factor, siRNA — small interfering RNA, SNP – single nucleotide polymorphism, SP — surfactant protein, SP-A — surfactant protein A, SP-D — surfactant protein D, TGF-β — tumour growth factor beta, TLR — Toll-like receptor, VEGFR – vascular endothelial growth factor

Introduction

Currently, the term "interstitial lung disease" (ILD) combines a heterogeneous group of pulmonary diseases associated with non-infectious infiltrates, mostly in pulmonary interstitial tissue and alveoli, which sometimes manifest as altered pulmonary pattern and irreversible fibrosis. To date, over 200 clinical entities of ILD are known, which account for over 15 % of all pulmonary

pathologies [2]. Morphologically, interstitial pulmonary fibrosis is associated with progressive replacement of pulmonary tissue with fibrous scar tissue due to excessive release of collagen by mesenchymal cells, myofibroblasts. Over time, this process alters the architecture and function of the organ, which, together with the associated autoimmune inflammation in the lung interstitial tissue, promotes development of marked respiratory distress, which gradually progresses along with the spread of the inflammatory process and aggravation of fibrous changes in the lungs [2], causing a number of unfavourable clinical and prognostic effects [8]. The course and outcome of the disease significantly depend on the specific clinical entity of ILD; therefore, early disease verification and forecasting the course of the disease are crucial (Fig. 1).

There is currently a group of ILDs with known causes, which includes HSP associated with exposure to various organic (mould spores, particulate bird droppings, non-tuberculous mycobacteria, etc.) and non-organic substances (silicone dioxide, asbestos, coal mine dust, beryllium and solid metals), as well as a number of medicinal products. Also, this group includes ILDs caused by systemic autoimmune rheumatic disorders [8, 42]. A new classification of chronic HSP proposes to separate non-fibrous and fibrous variants. In terms of clinical, functional and visual properties, the latter can be non-progressive or progressive [3]. There are reports of ILDs with progressive drug-induced fibrosis, for instance, caused by amiodarone [8], and also in patients with rheumatoid arthritis and systemic scleroderma [41]. Among ILDs with unknown origin, or idiopathic interstitial pneumonias (IIP), there is a subgroup of diseases with chronic fibrous X-ray morphologic pattern, which includes usual interstitial pneumonia (UIP) and fibrous non-specific interstitial pneumonia (FNIP). An excellent example of an ILD with X-ray morphologic pattern of UIP is IPF, which is progressive in 100 % of cases. For reference, FNIP is progressive only in 65 % of cases. The majority of IIPs are sporadic; however, according to the contemporary view, genetic susceptibility can have a significant role not only in manifestation, but also in the variant of ILD course [3, 8, 42].

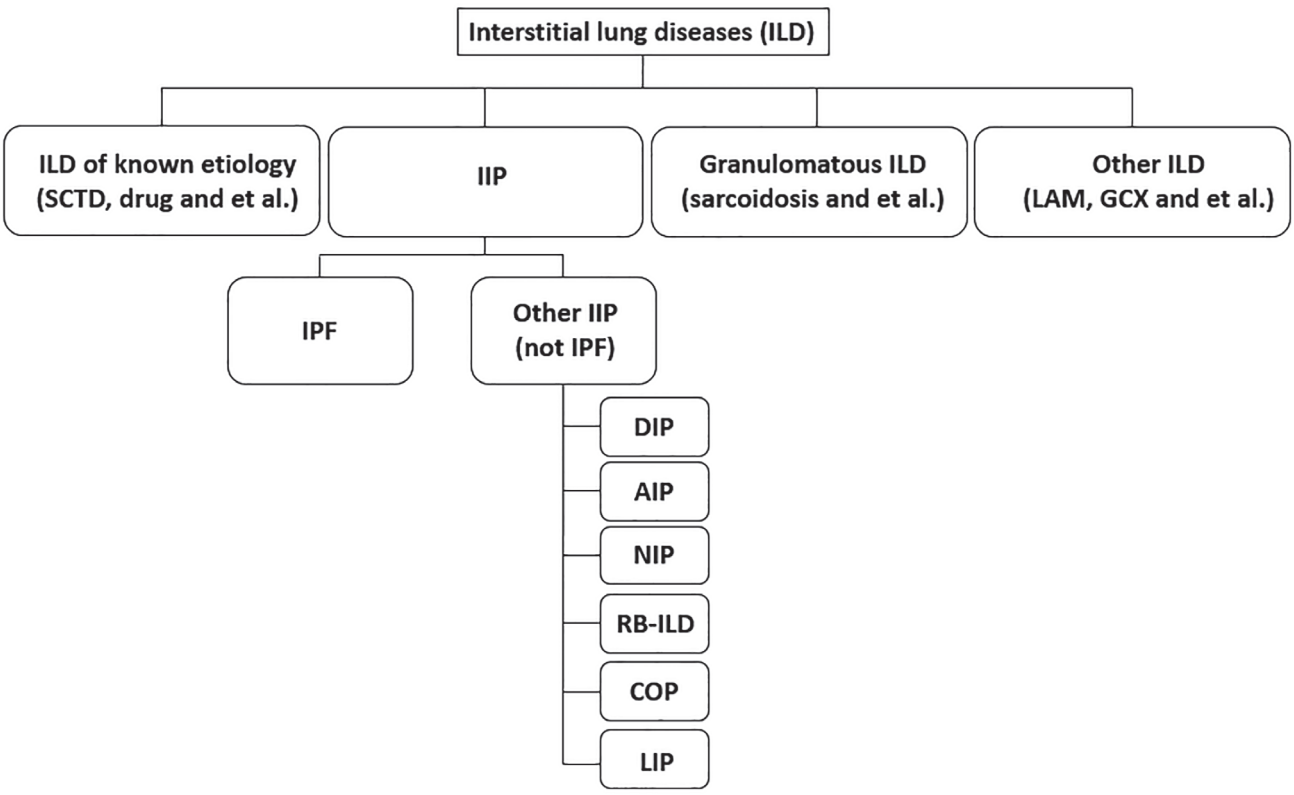

Figure 1. *Classification of ILD*

Note. ILD — interstitial lung diseases, IPF — idiopathic pulmonary fibrosis, IIP — idiopathic interstitial pneumonia DIP — desquamative interstitial pneumonia, RB-ILD — respiratory bronchitis associated with interstitial lung disease, AIP- acute interstitial pneumonia, COP — cryptogenic organizing pneumonia, NIP — non-specific interstitial pneumonia, LIP — lymphoid interstitial pneumonia, SCTD — systemic connective tissue diseases, LAM — lymphangioleiomyomatosis, GCX — histiocytosis X

Given the commonly progressive nature and unfavourable prognosis, ILD rightfully draws the attention of scientists and clinicians all over the world. The incidence of ILD varies between 0.63 and 7.6 per 100,000 people in the USA and Europe [45, 47], with a significant rise in the numbers with population ageing. A recent study of the global disease burden demonstrated that the ILD share in the increase in all-cause deaths in 2017 was 0.26 %, while the number of ILD-associated loss of years of life rose by 86 % over the past two decades [14]. According to the WHO, pre-COVID-19 social losses from ILD were comparable with losses from lung cancer [10].

Given the high rates of disablement and deaths in individuals of employable age resulting from ILD progression and development of irreversible pulmonary fibrosis, where health protection is of utmost importance because of existing demographical fluctuations in the Russian Federation, recently the need in deep studies of the clinical and pathogenetic features of ILD, as well as improvements of the existing and development of efficient approaches to manage this category of patients have become of immediate interest [4, 44]. Nevertheless, despite a number of achievements in the understanding of the pathogenetic mechanisms of the disease, the origin of diseases in this group is understudied, irrespective of the obvious understanding of its complexity and a combination of effects from genetic and epigenetic factors.

Modern idea of the pathogenesis of ILDs

Scientists and clinicians have been actively discussing the role of genetic susceptibility [53], environmental factors [58] and changes related to fast ageing [22] in the development of IPF and HSP, the combination of which results in a complex epigenetic re-programming, promoting aberrant activation of epithelial cells. When activated, epithelial cells release a lot of mediators, which promote migration, proliferation and activation of fibroblasts and myofibroblasts. These cells are resistant to apoptotic mechanisms and continue releasing extracellular matrix components [36]. Extracellular matrix holds a number of growth factors involved in the upregulation mechanisms and acting as components of cross signal pathways, which also adds to steady remodelling of lung tissue and fibrosis progression [36].

A pathologic result is replacement of the normal elastic extracellular matrix of the lungs with modified matrix rich in fibrillar collagen [61].

Overall, heterogeneous genetic variants can promote development of altered bronchopulmonary tissue, which becomes more susceptible to recurring microdamages under the influence of various potential environmental factors.

This objective of this review is to analyse the results of the modern genetic and epigenetic studies in patients with IPF and HSP, which makes it possible to identify the potential targets for interventions in the course and outcomes in patients with ILDs, most commonly dealt with by a pulmonologist, such as IPF and HSP.

Genetic factors of IPF and HSP development

To date, patients with IPF underwent three genome-wide association studies (GWAS), which identified single nucleotide polymorphisms (SNP) in several loci, associated with predisposition to IPF [19, 38]. These variants included mutations in gene *MUC5B* [35, 48, 54]; in genes related to the innate immunity functioning (*TOLLIP, TLR3, IL1RN, IL8, TGFB1*) [22, 40] and barrier function of epithelial tissue (*DSP, DPP9*) [4, 22], as well as in genes maintaining telomere integrity (*TERT, TERC, OBFC1, TINF2, DKC1, RTEL1, PARN*) [6, 13, 29, 31, 57], surfactant production (*SFTPC, SFTPA2, ABCA3*) [23, 38] and cell cycle regulation (*KIF15, MAD1L1, CDKN1A*) [7, 42] (Fig. 2).

For example, SNP rs35705950 in the promoter region of mucin gene 5B (*MUC5B*) was first identified back in 2011 during a genome-wide association study and is associated with a 7-fold increase in the risk of IPF [37]. After 2011, this SNP in gene MUC5B was verified in numerous independent studies and is still the most significant risk factor associated with development of IPF [23, 43, 48, 54]. Also, several authors reported a paradoxical advantage in the survival rates of patients with IPF, who are heterozygous carriers of a minor allele of this gene, as compared to patients who do not have it [7, 19]. However, other groups of patients with ILD demonstrated that the same mutation variant results in poorer survival rates in patients with interstitial pneumonia with autoimmune manifestations and a trend to poorer survival rates in patients with ILD associated with a connective tissue disorder or chronic HSP [5, 35].

In 2013, the same GWAS identified SNP of two other genes associated with cell-cell adhesion — *DSP* (desmoplakin) and *DPP9* (dipeptidyl peptidase 9), associated with IPF [19]. It has been demonstrated that mutations, which cause loss of function in other desmosome genes, including *DSG1*, boost production of proinflammatory cytokines and promote phagocyte attraction [22, 37].

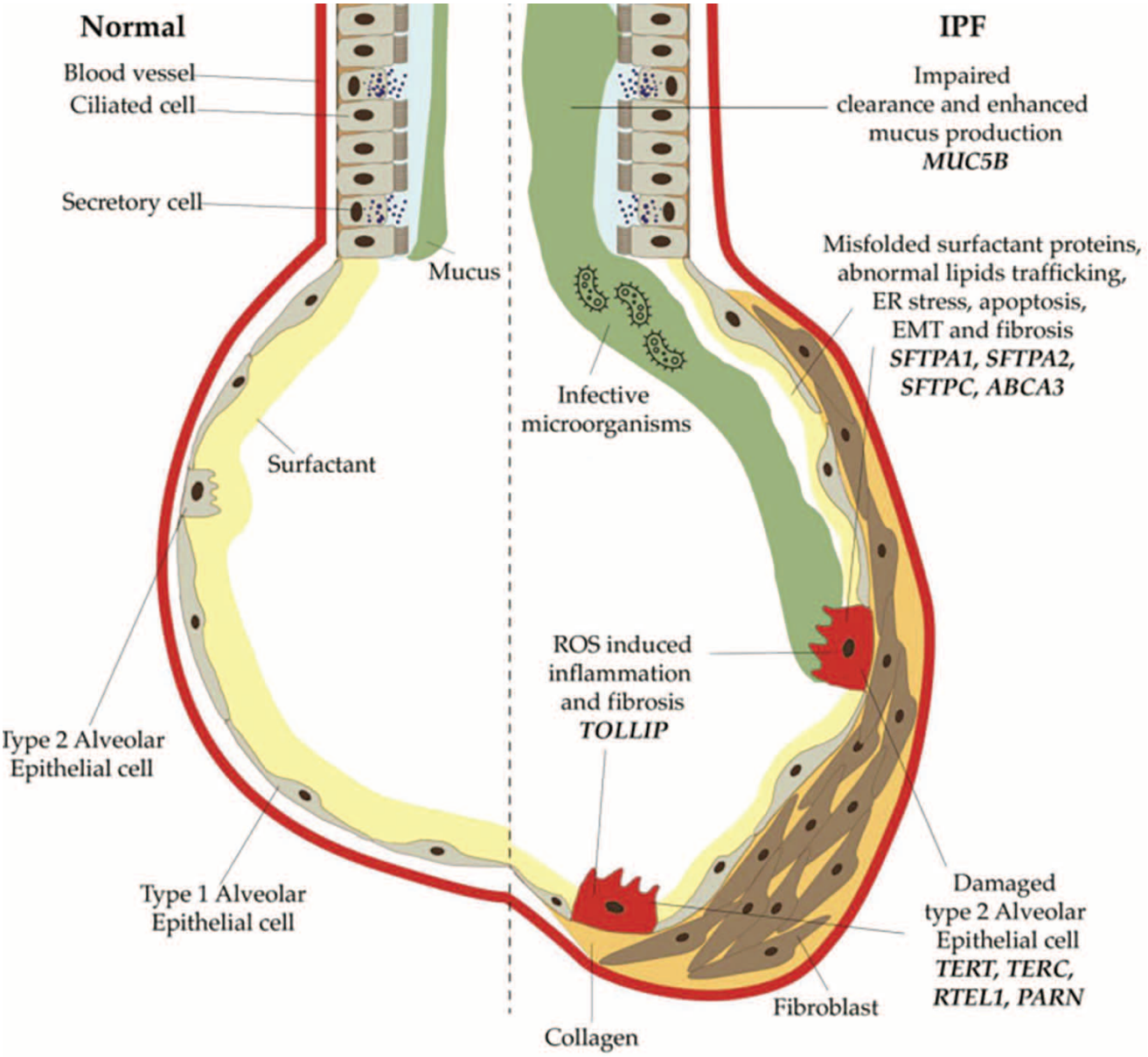

Figure 2.
Key profibrotic mechanisms secondary to mutations or polymorphisms in the genes of telomerase, surfactant proteins, mucin 5B.

Note. Mutations in *TERT, TERC, PARN* and *RTEL1* reduce telomerase activity, which leads to increased telomere shortening. *SFTPC, SFTPA1, SFTPA2, ABCA3* are involved in the modulation and stabilization of alveolar surfactant tension; when altered, they can cause increased endoplasmic reticulum stress, which ultimately leads to epithelial-mesenchymal transitions and apoptosis of type II alveolocytes. Polymorphisms in the *MUC5B* gene are responsible for mucociliary dysfunction with impaired clearance and increased mucus production, predisposing to bacterial overgrowth and infection [63, modified]).

Cytokines, produced both by damaged epithelial cells and activated alveolar cells, including such cytokines as IL-1β, IL-6 and IL-8, facilitate this cyclic damage process [38]. As a result, the epithelial layer of alveoli loses its barrier function, both due to genetic predisposition and stronger inflammatory signals.

Some authors also demonstrated that IPF is associated with impaired regulation of signalling of auto-inflammatory Toll-like receptors as a link between innate and adaptive immune response [23, 38]. Ten functional TLRs have been identified, which have distinct receptor/ligand associations, at the same time they are localised either on the cell membrane (TLR1, 2, 4, 5, 6) or in endosomal compartments (TLR3, 7, 8, 9) in order to recognise various extracellular and endocellular signals, respectively [42]. Genetic risk variants, which impact signalling of TLR family related to IPF, are presented below (Fig. 3).

In 2013, GWAS identified three more common SNPs (rs111521887, rs5743894, rs574389) of the protein gene interacting with Toll-like receptors (*TOLLIP*), which were associated with a high risk of IPF, and one of them (rs5743894) was also associated with high mortality rates

in patients with this disease [19]. TOLLIP is known to be expressed mostly by alveolar macrophages and epithelial cells. Each of the identified SNPs was associated with 20–50 % reduction in *TOLLIP* mRNA expression [19]. Since *TOLLIP* and *MUC5B* are related genes in chromosome 11p15.5 region, there are conflicting data whether their variants are in linkage disequilibrium or ensure independent associations to bring about the risk of IPF [18, 35, 43, 48]. Nevertheless, their expression in epithelial cells is higher in IPF, which is probably a result of long-term exposure to pathogens [16, 24, 25, 39, 40, 43, 52].

An integral part of the normal human lung function and prevention of alveolar collapse during respiration is surfactant protein (SP). It is a well-known fact that surfactant protein is a phospholipid-rich substrate, which is produced by distal parts of the airways, alveolocytes. Approximately 10 % of surfactant consists of proteins produced and released by alveolar epithelium type II cells (AE2) and terminal secretory cells of the airways [8, 42]. Fractions of surfactant protein A (SP-A) and D (SP-D) belong to a specific group of innate immune proteins called collectin, named after calcium-binding C-terminal lectin domain, which recognises respective receptors on pathogen surface [23, 38]. It has been demonstrated that SP-A and SP-D opsonize common bacterial and viral pathogens and promote phagocyte destruction by innate immune cells, such as macrophages and neutrophils. Sparse SNP in two adjacent genes encoding SP-A, *SFTPA1* and *SFTPA2* were described in several cases of family pulmonary fibrosis [4, 33]. However, the role of these and other surfactant-associated SNP in the development of sporadic IPF is still unclear. Several authors reported that patients with IPF had lower SP-A concentration in bronchoalveolar lavage compared to healthy volunteers, and SP-A levels are inversely correlate with patient survival rates [7, 38].

Unlike IPF, patients with HSP did not undergo any large-scale GWAS; however, some studies with target genotyping showed a number of genes responsible for

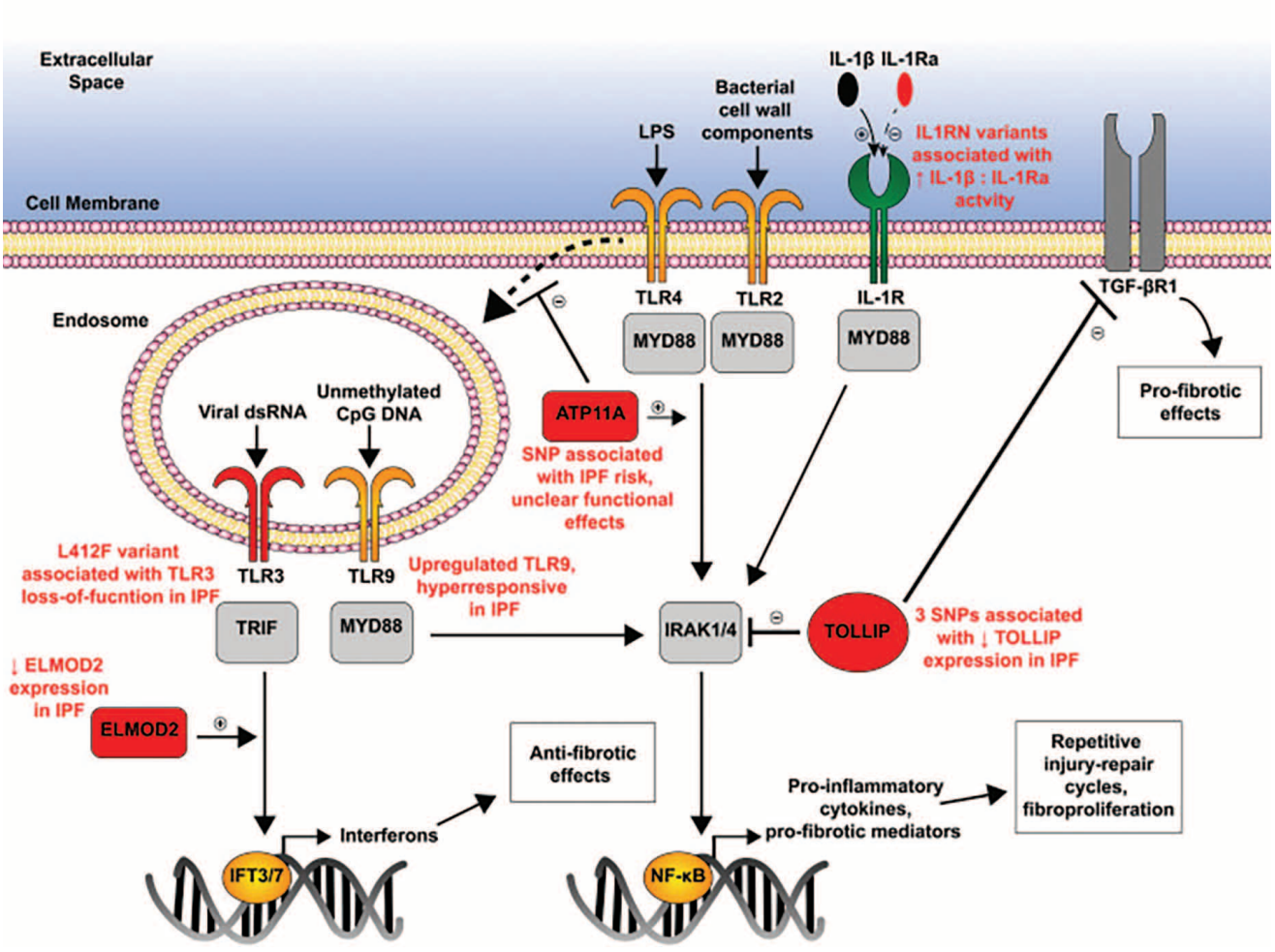

Figure 3. *Pro-fibrous transmission of TLR signals [36, changed]*

higher susceptibility to this disease with an unfavourable outcome. For instance, a test was performed in order to identify SNP in genes of the major histocompatibility complex (HLA) [18]. Gene HLA-DRB1 in patients with HSP had several SNP associated with carrier status of specific antigens and production of tumour necrosis factor alpha (TNF-α) [18].

B. Ley et al. demonstrated that SNP of promoter MUC5B associated with predisposition to IPF is found in a significantly larger number of patients with HSP, as compared to healthy controls [35]. However, unlike patients with IPF, the latter was associated with a higher risk of death in patients with HSP, and the degree of this association varies in various cohorts.

GWAS identified gene polymorphisms which can impact the susceptibility to IPF. A transcriptome analysis of RNA separated from the lung tissue and peripheral blood showed expression of genes involved in the pathogenesis and outcomes of IPF and HSP. These studies demonstrated that, while patients with IPF had higher regulation of genes involved in tissue remodelling, apoptosis and fibroblast signalling, patients with HSP had higher regulation of genes, which are important for the immune function, including genes transmitting T-cell signals and other which are associated with the major histocompatibility complex functioning [38].

Further transcriptome studies of lung and peripheral blood samples of patients with IPF confirmed the role of genes involved in the alveolar epithelium damage and remodelling, i.e. pathogenesis of IPF [23].

As for additional criteria to differentiate IPF and ILDs for the development of a tool to genomically forecast survival rates in patients based on peripheral blood data, transcriptome analysis was used. By using a two-stage multicenter approach to identification and validation, J.D. Herazo-Maya et al. identified a gene signature consisting of 52 differentially expressed genes, which is able to efficiently classify patients with a high or low risk of death during the 4-year follow-up period. This gene signature had test efficiency characteristics similar to those of the validated model of clinical forecasting [23] and significantly improved the existing clinical model. Then these researchers verified the 52-gene signature at six sites across the USA and Europe. It was demonstrated that antifibrotic therapy initiation was associated with favourable gene signature modulation. The majority of differentially expressed genes, which were identified using this approach, are essential for immunological enhancement. It is assumed that impaired immune response regulation can greatly contribute to IPF progression [50].

Studies of large families with several affected family members allowed identifying a number of genes associated with monogenetic forms of family idiopathic pulmonary fibrosis (FPF) and improved our understanding of the genetic basis of this ILD. Currently, there are seven known genes associated with telomeres, which were involved in the development of FPF in adults (*TERT, TERC, RTEL1, PARN, NAF1, TINF2, DKC1*) [15, 33, 42, 59]. Pathogenic variants of genes related to telomeres are associated with extremely short age-adjusted length and predispose to multisystem organ dysfunction, including PF, hepatic dysfunction and bone marrow failure [50].

Pathogenic variants related to telomeres were found in approximately 30 % of all family members with FPF, and *TERT* is the most frequently affected gene, which accounts for up to 20 % of FPF cases [40, 50]. Inheritance of a pathogenic variant related to telomeres results in a considerable risk of ILD; however, other factors, such as age, sex, environmental conditions and telomere length, also contribute to penetration variability [35, 58, 59]. At the same time, correlation between genotype and ILD phenotype in patients with pathogenic telomere-associated variants is weak. Despite the fact that IRF is the most common clinical diagnosis in relatives with FPF, it accounts for less than a half of all cases. The other part includes ILD both with known (HSP and ILD associated with connective tissue disorders) and unknown origin (idiopathic non-specific interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis). Interesting to note that the presence of a rare telomere-associated variant in *TERT, TERC, PARN* or *RTEL1* was associated with rapid disease progression and low survival rates irrespective of the diagnosis [59]. This observation allows assuming that the presence of a pathogenic variant in the telomere-associated gene prevails over the clinical manifestation of the disease, including ILD variant and overall prognosis. The accumulated data show that telomere dysfunction not only predisposes to disease manifestation, but it can also impact the rate of disease progression and the intrazonal nature of fibrosis [15, 59].

Epigenetic effects in IPF and HSP

No doubt that genetic predisposition alone is not sufficient for PF development, and the group of ILDs cannot be characterised without assessment of epigenetic effects. Gene expression is controlled by a number of epigenetic mechanisms, which coordinate activation and suppression of gene transcription (Fig. 4). Epigenetics impacts gene expression modulation irrespective of

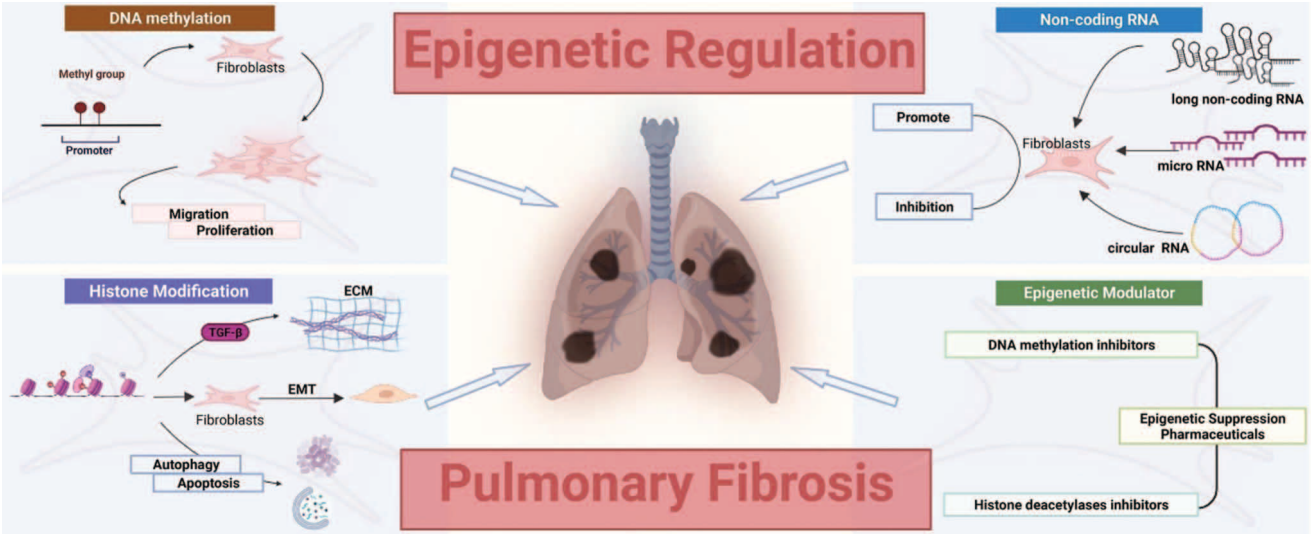

Figure 4. *Key mechanisms of epigenetic changes in the development and course of pulmonary fibrosis [modified, 67]*
Note. ECM — extracellular matrix, EMT — epithelial-mesenchymal transition, TGF-β — transforming growth factor beta)

DNA sequence. Currently, epigenetic modifications can be grouped into three types: DNA methylation in CpG sites, posttranslational modifications of histones and non-coding RNA. A number of studies demonstrated that several genes are differentially expressed in the lungs of ILD patients; this concerns mostly endocellular signal pathways of tumour growth factor beta (TGF-β), epithelial-mesenchymal transition, fibroblast proliferation [28, 55, 62].

The use of *TGF-β*, the main factor promoting ILD development, increases DNMT1 and DNMT3a levels in pulmonary fibroblasts without changing their mRNA expression, using various posttranscriptional mechanisms [31]. Upon interaction with TGF-β1, DNMT3a production increases due to increased protein synthesis and translation. To the contrary, TGF-β1 inactivates glycogen synthase kinase-3β, which causes inhibition of DNMT1 ubiquitination and its proteosomal degradation in pulmonary fibroblasts. The data from the study demonstrate the significant role of DNA methylation in the pathogenesis of ILDs. The most common histone modifications include methylation and acetylation. Histone methylation is regulated by dynamical interaction between two sets of enzymes: histone methyltransferases (HMT) and histone demethylases (HDM). Signature of histone acetylation in a cell plays a role in chromatin structure modulation and gene expression. This dynamic process is regulated by a balance between histone acetyltransferase (HATs) and histone deacetylase (HDAC) activity. Among HATs, the most well-studied protein is p300, which is associated with transcriptional activation of numerous genes in response to cell signalling. It has been demonstrated that increased p300 activity and expression are associated with various diseases, including PF [49] and acute respiratory distress syndrome [12]. Also, it has been shown that genetic deficit and pharmacological inhibition of p300 eliminate pulmonary fibrosis both in vitro and *in vivo* [9]. The role of non-coding RNAs in the pathogenesis of ILD is well-recognised. MicroRNAs are associated with almost all stages of ILD pathogenesis. For instance, let-7d, miR-200, miR-26a and miR-375 are associated with lung epithelium reparation, epithelial to mesenchymal transition (EMT); miR-21, miR-155, miR-26a, miR-27a-3p, miR-9-5p are associated with fibroblast activation and their transdifferentiation to myofibroblasts; and miR-320a is associated with AECII cell ageing and collagen production regulation. Currently available data confirm the dual pathogenetic role of microRNA and involvement both in fibrotic and antifibrotic processes in ILD [9]. Numerous environmental factors, such as behavioural patterns, patient's diet, and drugs taken (widely defined as exposome), ageing factors, which are currently evaluated on the molecular level, can cause epigenetic modifications, thus impacting gene expression.

All biological characteristics of pulmonary fibrosis can be explained by impaired gene expression regulation associated with epigenetic modifications. Given that epigenetic modifications are dynamic, they are an attractive therapy target, because epigenetic markers can be reversed using specific therapies, e.g., histone deacetylase inhibitors (HDACi) [11].

Moreover, individual episignatures actually become disease-specific, and epigenetic profile can be used to

verify clinical diagnosis. Identification of altered methylation, caused by disease progression, is particularly important for pathologies closely related to environmental exposure, like in IPF. Epidemiological studies demonstrated the relationship between exposure to inhaled environmental agents and IPF development, which is true for cigarette smoke, chip dust, metallic dust, silica particles, textile dust, and possibly pollutants found in agricultural, farming and cattle-breeding areas [17, 60, 63]. Cigarette smoke is the highest risk factor of disease development, allowing to assume that it has a significant epigenetic effect, especially in cases of genetic predisposition to the disease [57, 63]. Studies of genome methylation in IPF are ongoing; they aim at identification of specific modified methylation models, which can shed light on the role of environmental impact and pathogenetic mechanisms underlying PF development. Epigenetic signatures can be potential biomarkers for clinical diagnosis verification, identification of new drug therapies in order to reverse epigenetic changes and monitoring effects of available therapies.

Modern approaches to ILD therapy, taking into account possible effects of genetic factors

A recent study, which was based on the next generation sequencing (NGS) results and bioinformatic approaches, described some genetic and epigenetic pathways, which can be affected by an antifibrotic agent nintedanib [56].

Nintedanib is a tyrosine kinase inhibitor, which possesses antifibrotic properties due to the impact and interference with fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and potential inhibition of TGF-β signalling for ECM suppression [61]. It is worth noting that, following nintedanib therapy, authors identified four genes with reduced expression and one gene with increased expression, which impact the following microRNA/mRNA interactions: *E2F1*, *NPTX1*, *DDX11*, *PLXNA4* (reduced expression) and *SLC25A23* (increased expression).

The presence of relatively rare variants of telomere-associated single nucleotide polymorphisms or short telomeres promote faster disease progression both in IPF and HSP patients; however, currently there are no sufficient data on the efficacy of specific therapies.

Another remarkable recent study evaluated the efficacy and safety of nintedanib and pirfenidone in a cohort of PF patients with telomerase gene mutations. The authors found that both antifibrotic therapies were associated with less reduced forced vital capacity without any unexpected side effects [27]. However, the current strategy of immunosuppressive agent use varies depending on the type of lung involvement; for instance, immunosuppressive agents are often prescribed to patients with progressive HSP, while it is not indicated in patients with IPF [30]. The safety and efficacy of immunosupression in patients with short telomerases were not tested systematically. Small samples of patients with rare *TERT* and *TERC* variants allowed assuming that immunosuppressure therapy after lung transplantation due to ILD can be associated with a high rate of side effects, including bone marrow failure, hepatic toxicity and infections [15]. It brings about the question of safety and tolerability of this therapeutic strategy for patients with short telomeres in a wide range of ILDs. Antifibrotic agents, including pirfenidone and nintedanib, are effective in slowing down pulmonary function impairment in patients with IPF [30]. Pirfenidone was well tolerated by a small group of *TERT* carriers, but larger studies are required to identify its efficacy in patients with IPF with telomere dysfunction. One study demonstrated that pirfenidone can slow down the rate of EMT progression by modulating several gene-induced profibrotic pathways [34]. Pirfenidone can suppress enzymes involved in EMT, such as SULF2, and boost the activity of antifibrotic genes, such as Gremlin 2 (GREM2), which then cause restoration of the damaged alveolar epithelium via fibroblast growth factor-10, thus preventing fibrosis. Moreover, the levels of EDN1 and 5-HTR2B, two profibrotic genes, which are associated with collagen deposits and fibroblast proliferation, drop under the effect of pirfenidone.

Since the available medicinal products cannot cure IPF, several studies sought to use gene therapy as a potential strategy in attenuation of a wide array of processes involved in fibrosis. Despite the possible advantages of gene therapy, no studies for the treatment of IPF have been conducted to date. Development of new medicinal products for treatment of IPF is really challenging because of the complex pathogenesis of the disease and sophisticated disease modelling in animals. The currently available animal models are not specific to IPF, they just reproduce some aspects of PF, artificially caused by various chemicals (e.g., bleomycin, FTIC and lipopolyssacharide). Early studies to evaluate the potential use of gene therapy in IPF patients were focused on induction of the targeted gene overexpression using both nanoparticles and viral vectors [46, 64]. This approach

was mainly aimed at inflammatory pathways, including TGF-β and FGF7 signalling pathways [5, 41].

Most recently, the use of gene suppression with siRNA (small interfering RNA) for the management of PF was studied in several studies, which described the efficacy of some siRNA combined with antifibrotic compounds in the therapy of several aspects of PF [20]. Very few studies evaluated the use of miRNA to induce gene expression suppression in PF patients [64, 65]. These studies showed that miRNA-based therapy can have huge potential for simultaneous suppression of several genes associated with fibrosis. However, the pleiotropic effects of miRNA for various gene transcripts (not all of them have been characterised yet) raise concerns about the safety of therapeutic use of these ncRNAs.

In general, these studies confirm the applicability of gene therapy in suppression of fibrosis progression. However, to date, not a single gene therapy approach has demonstrated the ability to reverse confirmed fibrosis.

Future study outlooks

The possibilities of a more thorough study of the genetic and epigenetic principles of PF are the current clinical and scientific task, the addressing of which can help both in diagnostics and gene therapy development for the management of pulmonary diseases associated with fibrosis.

It is obvious that the genetic data can significantly complement the existing algorithms of ILD diagnosis, acting as a molecular foundation for morphological, clinical and instrumental data. According to the diagnostic manoeuvre roadmap proposed by experts at the European Respiratory Society (ERS) and Pulmonary Fibrosis Foundation [26], the current indications for genetic testing are: unexplained ILD in childhood; presence of ILD, first-degree and second-degree family members with ILD; any patient with a relative, who is a carrier of a pathogenic/possible pathogenic ILD variant; any patient with suspected telomere shortness (short telomere syndrome includes pulmonary fibrosis, haemotological disorders and hepatic diseases); any patient with short telomeres, where telomere length is analysed prior to the test; any patient with idiopathic fibrotic interstitial lung disease below 50 years of age.

In addition to the proposed genetic diagnostic roadmap, the European Respiratory Society also considers a possibility of diagnostic testing to identify predisposition to ILD in patients with Hermansky-Pudlak syndrome, because, provided considerable amount of genome data is interpreted correctly, they will be used for diagnostic evaluation of risks of the disease and prevention of its rapid progression and patient incapacitation [32]. At the moment, there are genetic diagnostic testing approaches, which are panels including a specific genome set, e.g., a test panel Interstitial Lung Disease manufactured by Blueprint genetics (USA), comprising the following genes: *ABCA3 (16p13.3), CSF2RA (Xp22.33), CSF2RB (22q12.3), DKC1 (Xq28), ELMOD2 (4q31.1), HPS1 (10q24.2), HPS4 (22q12.1), ITGA3 (17q21.33), NF1 (17q11.2), NKX2-1 (14q13.3), PARN (16p13.12), RTEL1 (20q13.33), SFTPA1 (10q22.3), SFTPA2 (10q22.3), SFTPB (2p11.2), SFTPC (8p21.3), SLC34A2 (4p15.2), SLC7A7 (14q11.2), SMPD1 (11p15.4), STAT3 (17q21.2), TERC (3q26.2), TERT (5p15.33), TINF2 (14q12), TSC1 (9q34.13), TSC2 (16p13.3)* [1]. New data on genetic variants of predisposition to ILD have been accumulated, which help to improve and make new genetic diagnostic panels.

Interference with epigenetic changes contributing to the development and progression of PF is also an interesting scientific and research perspective for target precision therapy in this category of patients [9].

Conclusion

The significance of genetic and epigenetic studies is becoming more and more important for the study of pathogenesis, identification of disease progression and prognosis in patients with ILD. A lot of genes and pathways involved in PF development have been found as a result of genome-wide studies. A major part of currently available genome data is associated with patients with IPF. As far as patients with HSP and other forms of ILD are concerned, very few similar studies have been conducted. To date, there is no unified standardisation of diagnostic criteria for ILD variants. Also, it is still unclear how to classify these groups of patients depending on the risk of disease progression and death, including identification of genetic factors, namely predictors of unfavourable disease outcome in patients with HSP. More and more articles study the effects of epigenetic modifications, which can alter the risk of the disease in the presence of environmental triggers. Besides, epigenetic mechanisms can impact development and prognosis of PF. DNA methylation in CpG sites, posttranslational histone modifications and suppression of non-coding RNA genes are the mechanisms, actively studied in fibrogenesis to search for potential clinical use as biomarkers and targets for drug therapy, because epigenetic markers can be reversed.

Finally, there are data on molecular pathways both on genetic and epigenetic levels, which are the foundation for the efficient antifibrotic therapy.

Вклад авторов:

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

Архангельская Е.Е.: формулирование идеи, разработка методологии исследования, сбор, анализ и систематизация данных, подготовка и оформление текста рукописи

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Юренев Г.Л.: редактирование текста

Author contribution:

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

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Lyamina S.V.: formulation of the idea, development of the research methodology, collection, analysis and systematization of data, preparation and design of the manuscript

Kozhevnikova E.O.: preparation of the manuscript text, design of the manuscript text, work with graphic material

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DOI: 10.20514/2226-6704-2024-14-6-419-434
УДК 616.5-006.6-073.5-085
EDN: ASZIKP

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ДИАГНОСТИКА И МАРШРУТИЗАЦИЯ ПАЦИЕНТОВ С ПОДОЗРЕНИЕМ НА ЗЛОКАЧЕСТВЕННЫЕ НОВООБРАЗОВАНИЯ КОЖИ В УСЛОВИЯХ ПЕРВИЧНОГО ЗВЕНА ЗДРАВООХРАНЕНИЯ: ПРОБЕЛЫ И ПЕРСПЕКТИВЫ

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Diagnosis and Routing of Patients with Suspected Skin Cancer in Primary Care Settings: Gaps and Perspectives

Резюме

Ранняя диагностика злокачественных опухолей кожи остается актуальной проблемой здравоохранения во всем мире. В первичном звене здравоохранения заподозрить у пациента злокачественное новообразование (ЗНО) кожи можно на основании данных анамнеза, осмотра, физикального обследования. Для исключения или подтверждения онкологического процесса необходимо провести дерматоскопическое исследование, которое выполняет врач-дерматовенеролог. Далее, если онкологический процесс исключить нельзя, пациента направляют к онкологу. Четко организованная маршрутизация выявленных пациентов улучшает благоприятный прогноз. Однако, для снижения показателей высокой запущенности по злокачественным образованиям кожи и оптимизации маршрутизации пациентов после обращения к врачу первичного звена здравоохранения необходимо обратить внимание на следующие моменты: обязательное прохождение периодического профилактического осмотра, особенно в возрасте старше 40 лет; полное физикальное обследование с тщательным сбором анамнеза и полный осмотр кожи терапевтом в рамках диспансеризации на приёме в первичном звене здравоохранения; применение обязательного дерматоскопического исследования для ранней диагностики ЗНО кожи врачом-дерматовенерологом, а при возможности — динамическое картирование кожи с анализом искусственным интеллектом; повышение профессиональной и коммуникативной подготовки медицинского персонала при общении с пациентом, особенно с впервые диагностированным ЗНО кожи, поскольку психосоциальные факторы влияют на отношение пациента к собственному здоровью; поддержание преемственности в работе врачей-терапевтов и врачей-дерматовенерологов для повышения качества и ускорения оказания квалифицированной медицинской помощи; создание в поликлиниках школ «Здоровая кожа» для повышение медицинской грамотности населения с обязательным информирование об опасности для здоровья и жизни ЗНО кожи, обучением навыков самообследования кожи; привлечение технологий электронного здравоохранения в качестве дополнительного источника информации.

Ключевые слова: *рак кожи, меланома, диагностика, первичное звено здравоохранения, профилактика, дерматоскопия, дерматоскопическое исследование, злокачественные новообразования кожи, маршрутизация пациентов*

Конфликт интересов

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

Соответствие принципам этики

Информированное согласие не требуется в силу невозможности идентифицировать пациента

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 08.06.2024 г.
Одобрена рецензентом 24.09.2024 г.
Принята к публикации 22.10.2024 г.

Для цитирования: Гайдина Т.А., Дворников А.С., Ларина В.Н. и др. ДИАГНОСТИКА И МАРШРУТИЗАЦИЯ ПАЦИЕНТОВ С ПОДОЗРЕНИЕМ НА ЗЛОКАЧЕСТВЕННЫЕ НОВООБРАЗОВАНИЯ КОЖИ В УСЛОВИЯХ ПЕРВИЧНОГО ЗВЕНА ЗДРАВООХРАНЕНИЯ: ПРОБЕЛЫ И ПЕРСПЕКТИВЫ. Архивъ внутренней медицины. 2024; 14(6): 419-434. DOI: 10.20514/2226-6704-2024-14-6-419-434. EDN: ASZIKP

Abstract

Early accurate detection of skin cancer is a growing global problem of health's services throughout the world. Malignant skin formation can be suspected by using an anamnesis, visual inspection of the skin, and diffrent types of investigations in primary care settings. The dermatoscopic examination is necessary for exclusion or confirmation skin cancer, which is performed by a dermatovenerologist. The patient is referred futher to an oncologist in case the cancer cannot be excluded. Well-organized identification of patients with suspected skin cancer is accociated with favorable prognosis. However, in order to reduce the rates of high neglect for malignant skin tumors and optimize the routing of patients after visiting a primary care phisician, it is worth to pay attention to the following points: annual medical check-up examinations, especially among people of age is over than 40 years; a complete physical examination, including thorough history and full body skin examination by general practition as part of a clinical examination in a primary care settings; the use of mandatory dermoscopic examination by a dermatovenerologist for early diagnosis of skin cancer, and, if possible, dynamic skin mapping with artificial intelligence analysis; increasing the professional and communicative skills, especially needed in managing newly diagnosed skin cancer, since psychosocial factors influence the patient's attitude towards his/her own health; maintaining continuity between general practitioners and dermatovenerologists to improve the quality of medical care; creation of "Healthy Skin" schools in clinics to increase the medical literacy of the population concerning the education regarding the danger of skin cancer, training in skin self-examination skills; using e-health technologies as an additional source of information.

Key words: *cancer, melanoma, diagnosis, primary care settings, prevention, dermatoscopy, dermatoscopic examination, malignant neoplasms of the skin, patient routing*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

Informed consent is not required due to the inability to identify the patient

Article received on 08.06.2024
Reviewer approved 24.09.2024
Accepted for publication on 22.10.2024

For citation: Gaydina T.A., Dvornikov A.S., Larina V.N. et al. Diagnosis and Routing of Patients with Suspected Skin Cancer in Primary Care Settings: Gaps and Perspectives. The Russian Archives of Internal Medicine. 2024; 14(6): 419-434. DOI: 10.20514/2226-6704-2024-14-6-419-434. EDN: ASZIKP

MA — malignancy, SBHI — State Budget Healthcare Institution, US — ultrasound, MSPCDC — Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology, OCCC — Outpatient Cancer Care Center, CME — continuous medical education, UVR — ultraviolet radiation, FSAEI HE RSRMU n.a. N.I. Pirogov, Ministry of Health of Russia — Federal State Autonomous Educational Institution of Higher Education Russian State Research Medical University named after N.I. Pirogov, Ministry of Health of the Russian Federation, HLS — healthy lifestyle, FSBEI HE PRMU — Federal State Budget Educational Institution of Higher Education Privolzhsky Research Medical University, CNN — Convolutional Neural Network

Introduction

Despite advancements in the diagnosis of skin malignancies (MA) in Russia within the latest decade, the high prevalence of visually located advanced tumors are preserved.Skin melanoma is not the most prevalent tumor; however, mortality reported within a year since the diagnosis of melanoma in 2022 was 7.5 % [1]

The comparative analysis of MA-associated mortality in Moscow (2019-2021) demonstrated that skin melanoma is a leading pathology among skin MAs regarding the contribution to deaths among the total number of people died [2].

In 2022, the diagnosis of Stage III skin melanoma in Russia was established in 11.3 % of all first detected

cases, Stage IV — in 7.9 %[1]. The advanced melanoma parameter in 2022 was 19.2 % [1]. The number of multiple primary MAs, including those of skin, increases annually [3]. In 2002, 68,165 multiple primary tumors were diagnosed in Russia, i.e. 10.9 % of all first detected Mas [1].

One of the leading issues of increased skin disease prevalence is low awareness of the population about risk factors and lifestyle features that can lead to skin pathologies, including MAs. Prophylactic and awareness-raising procedures have an especially important value in adolescence — a period when behavior stereotypes are still formed [4].

Global actual healthcare issues still include the analysis of factors affecting the advanced state of skin MAs and the search for new solutions for improving the quality of early diagnosis and prevention. These article objectives include the review of possible causes of high advanced skin MA prevalence, including melanoma, search for approaches to perfecting the patient routing after visiting the primary care physician, and the possibility of skin MA prevention in primary care.

Methodology of literature search

The search for open-access full-text publications in Russian and English published in 2016-2024 were conducted in Elibrary and National Library of Medicine databases using the following keywords and their combinations: skin malignancies, melanoma, diagnosis, health literacy, primary healthcare, prevention. 51 publications concerning the issue analyzed were included into the final analysis.

Skin malignancies

The skin is the largest organ of the human body, with a total weight up to 3.6 kg and area of approximately 2 m^2 in adults [5]. The skin is composed of three layers: epidermis (consisting of keratinocytes (95 %) and several other cell lineages (melanocytes, Merkel cells, Langerhans cells); derma, consisting of collagen, elastic fibers, blood vessels, nerve fibers, glands; hypoderma, using which derma interacts with underlying tissues [5, 6].

Skin diseases affect millions of people globally in all age groups and include various pathologies, including acute and chronic diseases, benign and malignant disorders of the skin and its appendages [7, 8].

Neoplastic changes of the skin and its appendages are very variable and may emerge in all layers and cells. Depending on the histogenesis, skin MAs are divided into epithelial (basal cell carcinoma, squamous cell carcinoma, skin appendage cancer) and non-epithelial (melanoma, sarcoma, fibrosarcoma, leiomyosarcoma, angiosarcoma, sarcoma of unknown origin) [9]. When compiling reports about the condition of cancer care and analysis of statistical parameters, all MAs of the skin and its appendages are divided into melanoma and non-melanoma tumors, accounting for high mortality rates in melanoma within a year since the moment of diagnosis.

Melanoma is a rather dangerous tumor developing as a result of malignant transformation and uncontrollable proliferation of melanocytes. Melanoma is characterized by aggressive growth, enhanced tendency to quick lymphogenous and hematogenous metastasizing, unfavorable prognosis with the untimely treatment onset. Four clinical cutaneous melanoma forms exist: superficially spreading, nodular, malignant lentigo-melanoma, and acral-lentiginous melanoma [10]. Approximately 70 % of all cutaneous melanomas are superficially spreading and characterized by two growth phases: radial and vertical [10]. The 5-year survival of patients with the superficially spreading melanoma in the radial phase with the timely treatment is 95 %; if the radial phase transforms to the vertical one, the survival decreases to 40-60 % [11, 12]. As melanocytes are also located in the hair follicle bulbs, retina, internal ear, central nervous system, non-cutaneous melanoma forms may develop — these are characterized by progressive growth and unfavorable course [13-18].

Arnold M. et al. conducted a population epidemiological study, analyzing statistical data for 2020, and concluded that melanoma incidence is mainly reported in highly developed countries predominantly populated with fair-skinned people and, thus, a higher risk and a higher susceptibility to carcinogenic solar radiation effects. Researchers detected significant geographical differences in morbidity and mortality parameters by countries and global regions; with that, the highest cutaneous melanoma incidence was observed among the fair-skinned population in Australia, New Zealand, Western and Northern European countries (Denmark, Norway, the Netherlands), and North America. On the other hand, cutaneous melanoma remained rare in the majority of African, South and Central American, Asian countries. The largest melanoma-related mortality was reported in New Zealand: 5 cases per 100,000 patient-years. Nevertheless, the global proportion of deaths relative to the sick people remained disproportionately high in Asia and Africa compared to other world regions [19].

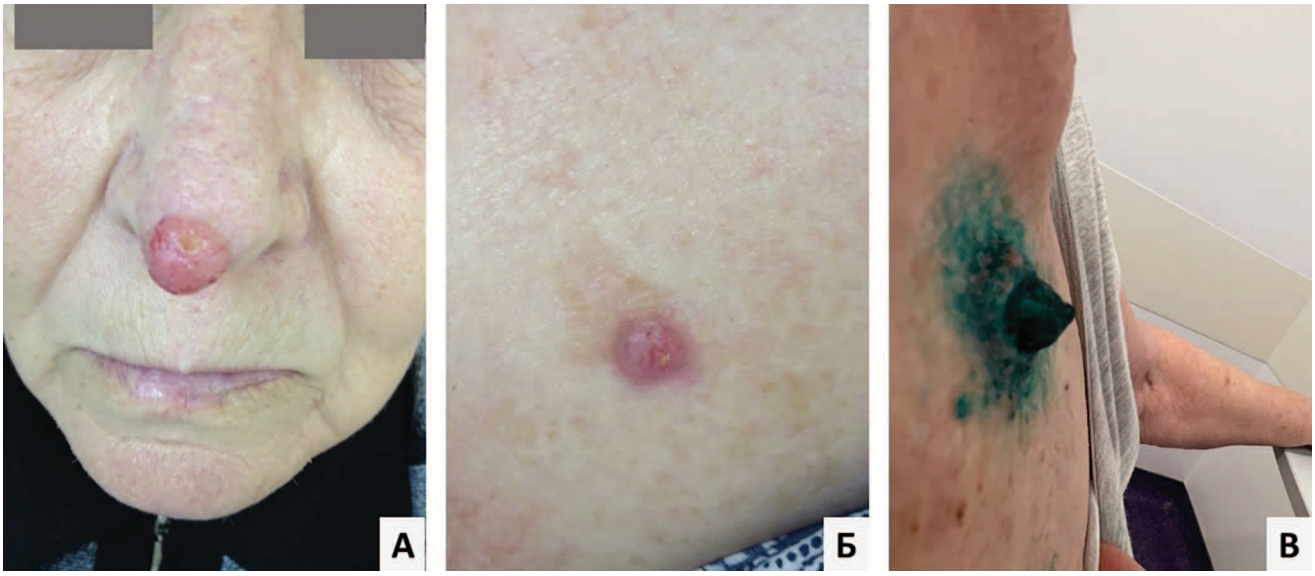

Figure 1. *A — Macro photograph: basal cell carcinoma of the nasal skin, nodular form, pT1N0M0, II art.; B — Macro photograph: basal cell carcinoma of the skin of the abdomen, nodular form pT1N0M0, I art.; C — Macro photograph: squamous cell carcinoma of the skin of the anterior chest wall, pT2N0M0, II art*

Based on authors' data, in 2020 melanoma was globally diagnosed in 325,000 people (174,000 males, 151,000 females), and almost 57,000 people (32,000 males, 25,000 females) died from this disease. Out of all newly diagnosed cases in 2020, 259,000 (79.7 %) people were over 50 years of age, while out of all deaths in 2020, 50,000 people (87.7 %) were over 50 years of age. According to Arnold M. et al., by 2040 the number of newly diagnosed cases of melanoma will have increased by more than 50 % — up to 510,000. Similarly, based on estimates, melanoma-related mortality will increase approximately by 68 % — from 57,000 in 2020 to 96,000 in 2040 — provided 2020 parameters remain stable. These predictions were calculated exclusively assuming changes in the world population count and age structure, but they did not account for possible changes in the age-related global or country-specific mortality. Global morbidity and mortality decrease should exceed 2 % to guarantee that the number of melanoma cases in 2040 will be less than that in 2020.

The most common non-melanoma skin MAs include basal cell carcinoma and squamous cell carcinoma, which are characterized by variable clinical signs (Figure 1).

At the end of 2021, the amount of Russian patients on constant follow-up with non-melanoma skin MAs was 10.8 %, being second after breast MAs, while first in the total morbidity structure for both sexes (12.7 %) [1]. Early diagnosis of non-melanoma cutaneous MAs significantly improves the prognosis and quality of life of patients [20].

Modern possibilities of skin MA diagnosis in primary care conditions

Visually located tumors, primarily skin tumors, are possibly diagnosed in a patient already upon visiting the primary care physician [21]. Simple and comprehensible (for primary care physicians) symptoms exist that provide timely cancer suspicion. Thus, the "ugly duckling" symptom may be detected upon the general examination of the patient's skin without using a special equipment (Figure 2).

Upon timely control routing from the primary healthcare to the cancer service, diagnosis and further treatment can be done for the patient before the emergence of metastases and life-threatening conditions.

Without significant clinical signs of the malignant process in the skin, cutaneous MAs may be suspected based on history, complete physical examination, including lymph node palpation, dermatoscopy.

When collecting history, it is necessary to determine whether the patient is in the risk group for cutaneous MAs. This conclusion can be made based on the following questions: Did you or your relatives have skin MAs? How long do you stay in the active sun annually? Do you have any occupational hazards? Have you developed any new skin lesions over the past 6 monts? How have your existing nevi changed lately? Do you attend tanning salons? Do you take immunosuppressive therapy? Postoperative scars on the skin require thorough

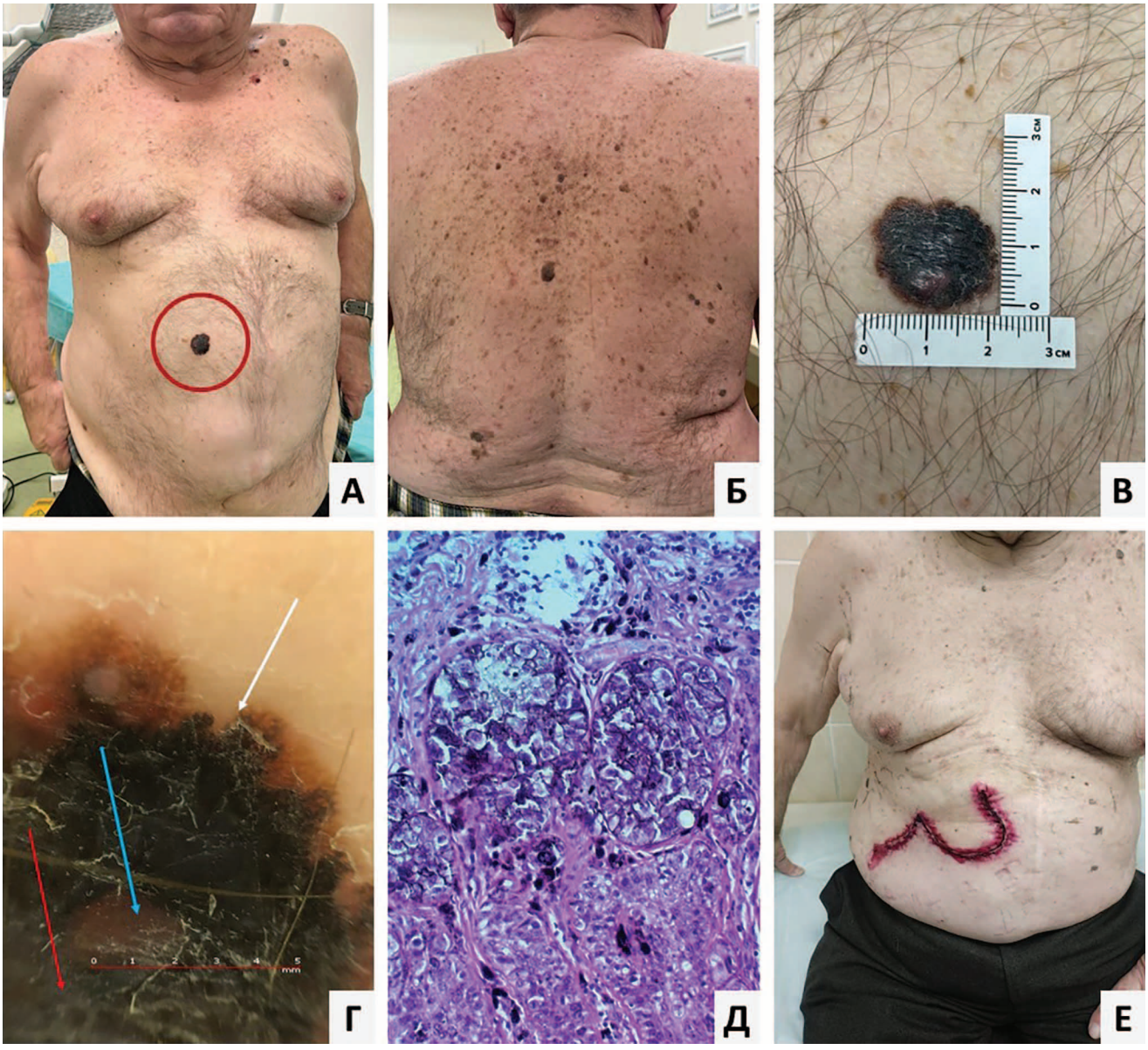

Figure 2. *A — Overview macro photograph of the patient's abdominal skin.*

Note. A bright brown spot is marked on the skin of the abdomen with a red circle, which differs significantly from other skin formations. The symptom of the "ugly duckling". Postoperative scar on the skin of the abdomen (mature cell lymphoma of the spleen in 2015, splenectomy); Б — Overview macro-image of the skin of the patient's back. There are multiple formations of different diameters on the skin of the back, of the same type in their structure; В — A macro photograph of melanoma of the skin on the patient's abdomen, C43.5, TxNxM0; Г — A dermoscopic image of melanoma of the skin on the abdomen, magnification × 20. A white arrow marks the uneven edge of the formation; a red arrow indicates a blue-white veil; a blue arrow indicates polychromy; Д — Histological examination of the removed material: nests of atypical melanocytes with uneven pigmentation, some cells without pigment, in others the pigment accumulates in the form of granules in the cytoplasm. Magnification x 200; Е — Overview macro-image of the patient's abdominal skin after surgical wide excision of skin melanoma with repair of the defect with a musculoskeletal flap on the vascular pedicle

interrogation concerning the history of malignancies, as the number of multiple primary MAs steadily increases, and cancer alertness concerning patients that underwent cancer surgeries should be increased [3] (Figures 2, 3).

When examining the skin in primary healthcare, the clinical diagnosis of melanoma may be suspected based on the combination of results of three pigmented lesion analyses: visual analysis of each separate lesion — examination with a naked eye (ABCDE mnemonic); intraindividual comparative analysis — search for the pigmented neoplasm not similar to others in the same patient ("ugly duckling", "Little Red Riding Hood" sign); chronological analysis of changes — search for quick and recent changes of this pigmented lesion, which can be confirmed by the patient or documentally, compared to prior photographs [22].

Dermatoscopy should be arranged if the cutaneous MA is suspected. According to the Order of the Ministry of Health of Russia dated November 15, 2012 No. 924n, On Approving the Procedure for Providing Medical Care in Dermatovenerology to the Population, dermatoscopy is conducted by the dermatovenerologist as part of primary specialized medical care; the dermatoscope

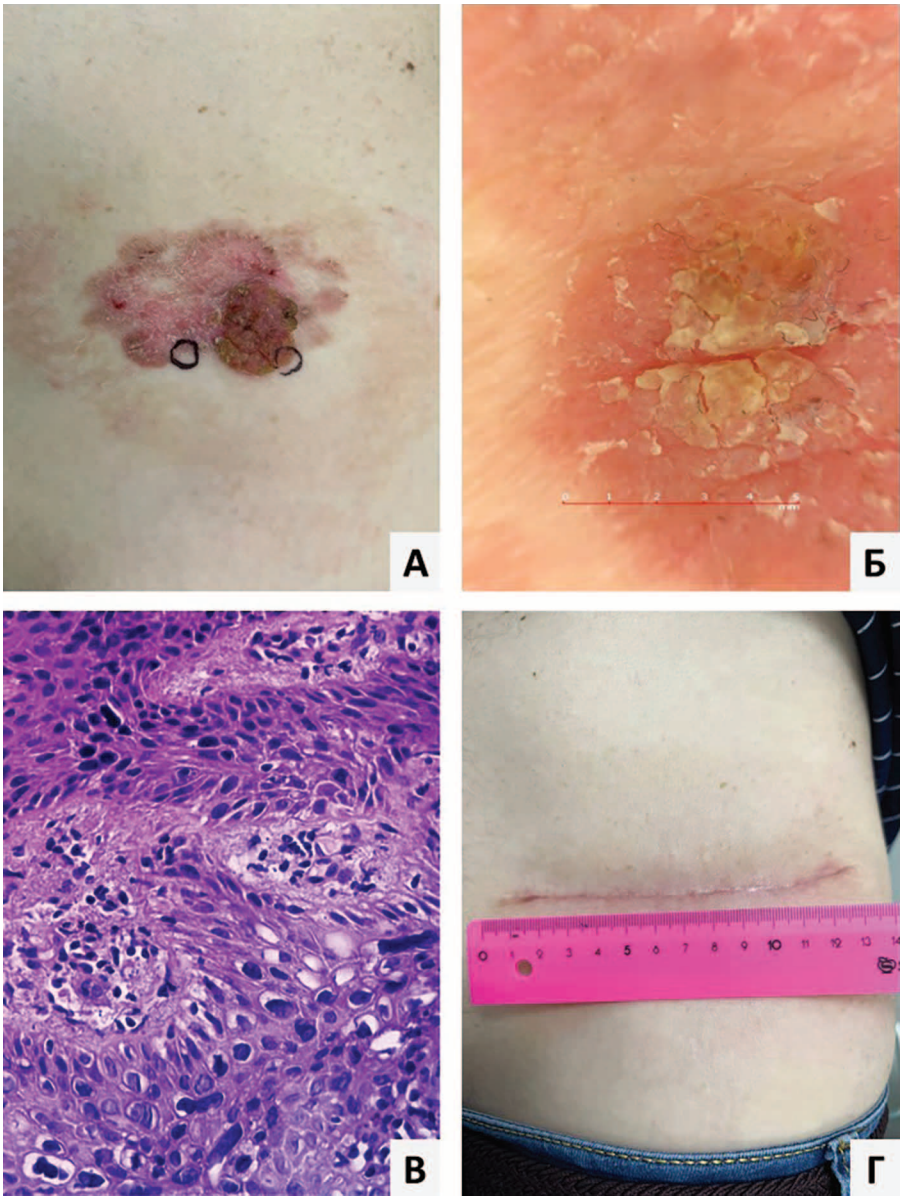

Figure 3. *A — Macro-image of abdominal skin formation in a patient undergoing surgical treatment for rectal carcinoma in 2021.*

Note. The black line encircles the places where the punch biopsy was taken; Б — Dermatoscopic image of the formation of the abdominal skin, magnification × 20; В — Histological examination of the punch biopsy material: skin fragments with invasive growth of squamous cell carcinoma G2 with focal keratinization; Г — A macrograph of the abdominal skin after surgical treatment. Postoperative scar

is included into the equipping standard of the consulting-diagnostic department of the dermatovenerology dispensary [23]. Patients from primary care are routed to the dermatovenerologist (Figure 4).

The targeted dermatoscopy of skin lesions suspicious of malignancies requires deep knowledge and professional experience from the dermatovenerologist — it is most effective for the early diagnosis of superficially spreading melanomas. Dermatovenerologists do not belong to primary care, and so the general practitioner arranges dermatoscopy in the outpatient setting, which can decrease the diagnostic significance due to incorrect interpretation of the data obtained. Besides, significant time is required for dermatoscopy of the whole skin with description and photography of the images obtained — it takes from 20 minutes to 2 hours per one patient, depending on the number of lesions. The issue of dermatoscopic image photography and storage of images obtained in the patient's medical chart is not solved in primary care. Herath H.M.M.T.B. et al. (2018) arranged a survey of general practitioners working in the National Hospital of Sri Lanka and obtained data that over 95.2 % of physicians did not consider dermatoscopy mandatory in routine practice at primary visits. It was demonstrated that only 10 % of primary care physicians conducted the complete

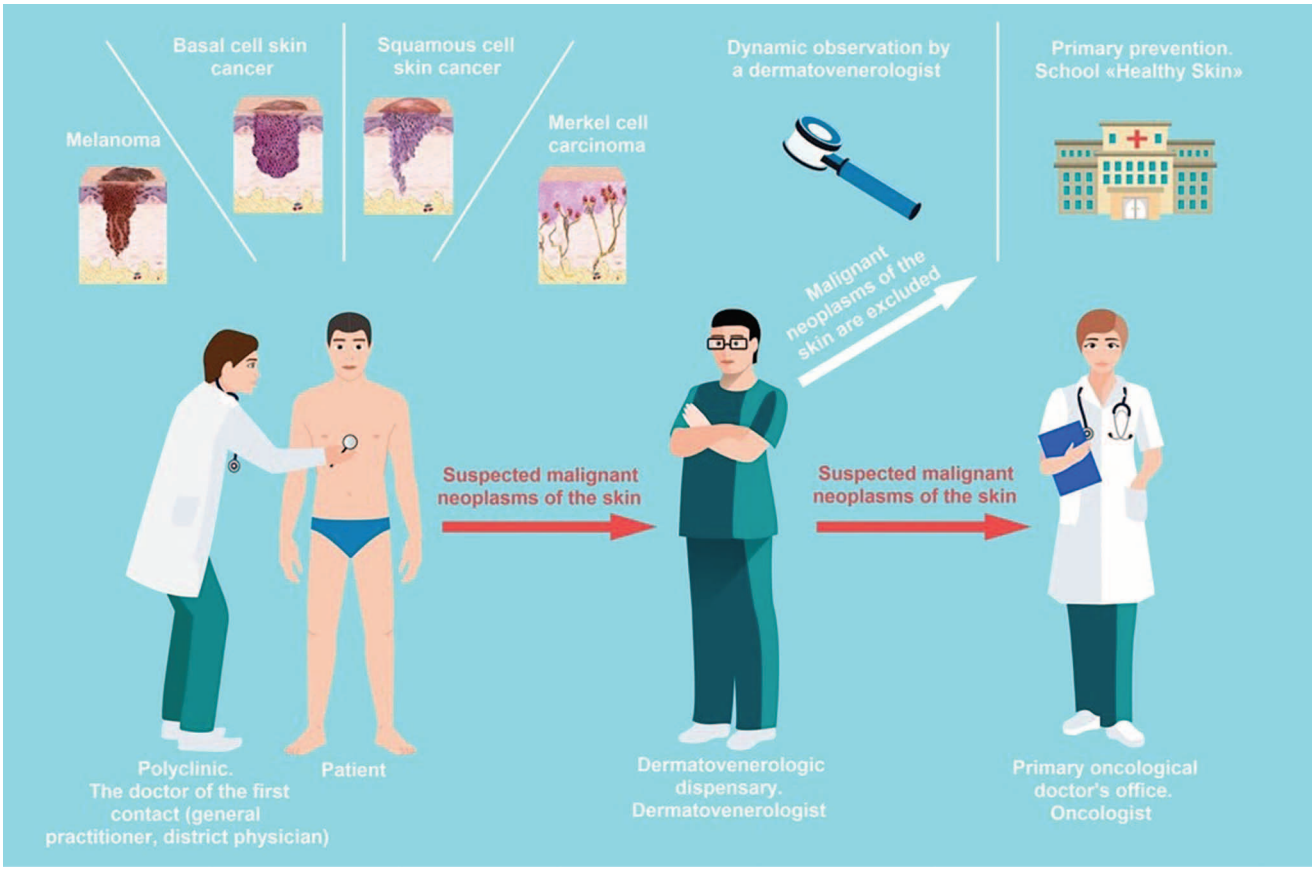

Figure 4. *Patient routing algorithm in case of suspected malignant neoplasms of the skin*

examination of the whole skin, and only 18 % of physicians arrange awareness procedures, informing patients about the risk of excessive solar exposure without corresponding protection [24].

The example of early cutaneous MA diagnosis efficacy with the help of dermatoscopy arranged by the dermatovenerologist was provided by the colleagues from the oncodermatology department of SBHI Center of Specialized Medical Care named after V.P. Avaev (Tver, Russia). According to the retrospective analysis of medical charts from 500 outpatient patients aged 16 to 85 years that visited the dermatovenerologist, the leading reason for visits was the prophylactic examination [25]. Using dermatoscopy with subsequent histological confirmation of the diagnosis, skin MAs were detected in 9.8 % of patients. Out of them, cutaneous melanoma was diagnosed in 18.3 % cases, basal cell carcinoma — in 75.5 % cases, squamous cell carcinoma — in 6.2 % cases. The majority of patients (96 %) with skin MAs were over 40 years of age. The results of the study conducted confirm the feasibility of using dermatoscopy for early cutaneous neoplasm diagnosis and the necessity of mandatory periodic prophylactic examinations, especially in persons over 40 years of age.

One of the legislative acts regulating the organization of oncology medical care in state medical organizations on primary care (in particular, in the Moscow healthcare system) is the Order of the Department of Healthcare of Moscow City dated January 15, 2020 No. 16, On Providing Medical Care in Oncology in Medical Organizations of the Moscow City State Healthcare System. The document approves the list of examinations (Table 1) for the patient with complaints or signs typical for cutaneous MAs, periods of examination and counseling of the oncologist when confirming the preliminary diagnosis of MA. For skin MAs, this period is 6 days.

If any complaint/sign of MA is present, patients are routed according to the algorithm stated in the table (Table 2).

To increase the quality of medical care with the purpose of early diagnosis and effective treatment of cancers, the project “Personal Assistant” providing patient assistance in the period from diagnosis in the primary care until dispensary follow-up by the oncologist has been developed.

To diagnose cutaneous MAs, primary care physicians of the Moscow healthcare use available clinical examination methods (“naked eye” examination) and weakly

Table 1. List of complaints/signs of malignant neoplasm of the skin requiring immediate examination of the patient

№	Complaint/objective examination data
1.	Pigmented formation with rapid growth
2.	Pigmented formation with a change in the configuration of the boundaries
3.	Pigment formation with different shades of color within a given formation
4.	Itching in the area of pigment formation
5.	Burning sensation in the area of pigment formation
6.	Long-term non-healing skin ulcer
7.	Painful and bleeding ulcers, seals, crusts on the surface of the skin (especially the scalp, neck)
8.	Sealing of the local area of the skin
9.	A red border around any volumetric formation

Table 2. List of examination / consultations in the presence of any complaint / sign of malignant neoplasm of the skin

N	Destination	Mandatory examination	Additional examination
1.	Polyclinic	Doctor's examination	Dermatoscopy
2.	MSPCDC Branch	Doctor's examination Dermatoscopy	Fluorescent diagnostics
3.	MSPCDC	Doctor's examination Dermatoscopy	Videodermatoscopy Fluorescent diagnostics Ultrasound of the skin
4.	OCCC	Doctor's examination	

Note: MSPCDC — Moscow Scientific and Practical Center of Dermatovenereology and Cosmetology, OCCC — Outpatient Cancer Care Center

magnifying optical systems (magnifying glass) that are included into the mandatory list of general practitioner devices. Dermatoscopy is conducted as part of complex patient examination in "Healthy Moscow" pavilions and medical prophylaxis rooms.

Possible approaches to advancements in the routing of patients after visiting the primary care physician

Patients not visiting the dermatovenerologist and/or oncologist after visiting the primary care physician is a significant issue in the routing of patients with suspected cutaneous MAs. Some patients, even with the correct diagnosis of melanoma established by the primary care physician or dermatovenerologist, prefers not to visit the oncologist due to subjective reasons: fear, no free time for prolonged treatment, unwillingness to present their diagnosis to relatives and colleagues, other diseases considered primary based on the patient's opinion, limited mobility, anosognosia, etc. Finally, these patients still visit the oncologist, but when malignancy is advanced, and the possible care is significantly limited. The probability of unfavorable prognosis increases if the period between the moment of diagnosis and the surgical intervention exceeds two months [26]. When visiting commercial clinics and cosmetologists, the physician does not usually have a possibility to route the patient using the Form No. 057/u to the primary oncologist, only recommending to visit the oncologist orally. Further responsibility for timely oncologist attendance lies on the patient him/herself. From their part, patients may postpone further examinations and treatment, which is significantly more efficient with timely visits, due to various reasons [27].

The study of O'Shea S.J. et al. (2017) [28] was devoted to the identification of factors associated with late physician visits. The study authors accentuated the attention on the necessity to inform wide population strata about the existence of cutaneous MAs and the possible transformation of existing nevi, mainly changes in the diameter (D)

to ≥ 6 mm and evolution (E). 159 patients (47 % males) aged 24 to 90 years (mean 62 years) answered the questionnair. In 15 % of them, melanoma was located in the head and neck area, in 30 % — on the torso, in 24 % — on upper extremities, and in 28 % — on lower extremities. The location was not defined in 5 patients. 40 (27 %) patients noted late physician visit (3 months later). The most common sign of melanoma reported by the interviewed people was increased nevus diameter. Over half of respondents (55 %) reported factors that precluded them from attending the physician: confidence of low disease risk for them, absence of general malaise, unwillingness to disturb the physician. With that, patients aged ≥65 years had a higher incidence of timely physician visits, and they rarely delayed the treatment compared to persons aged below 40 years.

Currently, psychosocial factors (work responsibilities, child care) are discussed as possible obstacles for timely physician visits among younger persons. Thus, a more balanced approach to the evaluation of the psychosocial patient's well-being may increase the efficacy of communication with the patient, persuading him/her to attend the physician timely [29].

Barinova A.N. et al. (2023) conducted a study of awareness of physicians belonging to different specialties and persons without higher medical education concerning the risk factors of cutaneous MAs, procedure of patient routing, and preventive measures. 463 people aged 20 to 72 years (81 % females) participated in the survey. Correct answers were reported in 72.7 % cases, however correct answers to all questions were provided by only 0.9 % respondents. The worst (incorrect) answers concerned prophylactic examinations [30]. In authors' opinion, it is necessary to arrange additional education of the medical staff, including in the CME (continuous medical education) system, differential diagnosis of cutaneous MAs, procedure for routing detected patients, and preventive measures.

Besides, a wider implementation of educational online-courses based on principles of early cutaneous MA diagnosis may also additionally contribute to the improvement of the epidemiological situation [31].

Approaches to cutaneous MA prevention

The issue of cutaneous MA prevention is global. Euromelanoma Pan-European Organization has developed primary prevention aimed at stimulating and awarding the correct behavior of persons exposed to ultraviolet radiation (UVR). To unite and increase the efficacy of work of specialists in the analysis, prevention, treatment, and rehabilitation of patients with the diagnosis of melanoma, the Russian Association of Melanoma Specialists "Melanoma PRO" has been working since 2016 [3]. The "Melanoma Day" is arranged annually in many Russian medical institutions, as part of which all willing persons can undergo early diagnosis of cutaneous MAs for free. The example of this event is the "Melanoma Day" arranged at FSAEI HE RSRMU n.a. N.I. Pirogov, Ministry of Health of Russia (Federal State Autonomous Educational Institution of Higher Education Russian State Research Medical University named after N.I. Pirogov, Ministry of Health of the Russian Federation), which is conducted by the Department of Dermatovenerology named after Academician Yu.K. Skripkin of the Medical Faculty. The experience of foreign colleagues from Australia can be presented as an example of preventive work — in that country commercial tanning salons have been banned on the legislative level since 2015, which, in conjunction with other preventive measures, has led to the decreased invasive melanoma mortality in persons below 40 years of age [32, 33].

The prevention of cutaneous MAs presumes a complex of various measures aimed at preserving and strengthening the human health. The inseparable prevention components include following healthy lifestyle (HL) principles, prophylaxis of potentially hazardous risk factors, elimination of exposure of negative environmental factors on the human health. The priority preventive measures should include the complex of measures providing the HL promotion, sanitary & anti-epidemic measures, periodic prophylactic examinations, dispensary follow-up. Prophylactic events are usually arranged individually with each person separately or in a group of patients in the medical organization, while at the population level these spread among the whole population, including adolescents. In general, such approaches form the basis of preserving the public health [34].

The awareness raising with patients in the risk group for melanoma presumes the active implementation of primary, secondary, and tertiary prophylaxis methods (Figure 5) [35-37].

The general main objective of primary cutaneous MA prevention is the limited skin exposure to the ultraviolet radiation (UVR) [38]. The secondary prevention objectives include dispensary follow-up and prophylactic examinations, periodic follow-up of suspicious cutaneous neoplasms, dermatovenerologist examinations with the purpose of early diagnosis. The tertiary prevention objectives include the prevention of cutaneous MA relapses, decreased risk factor exposure, increasing

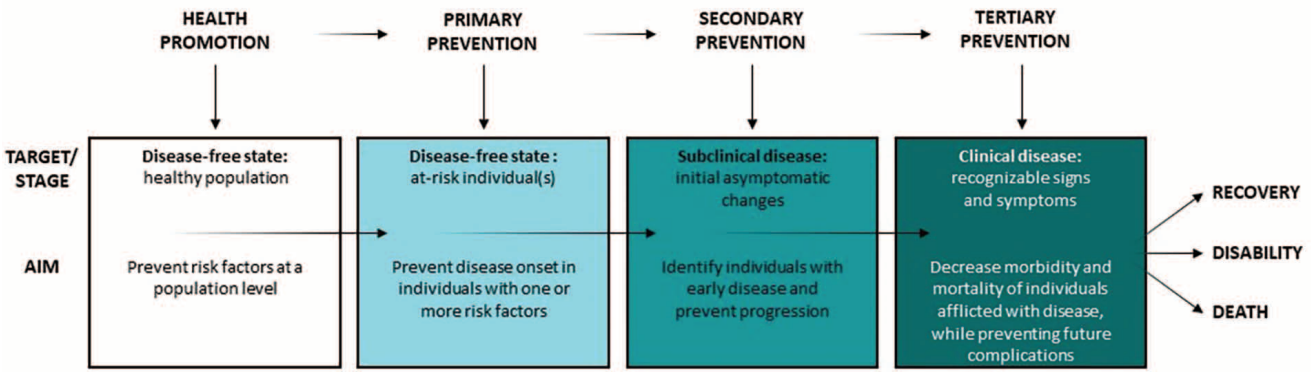

Figure 5. *Methods of primary, secondary and tertiary prevention. Adapted from Perez M., Abisaad J.A., Rojas K.D. et al. Skin cancer: Primary, secondary, and tertiary prevention. Part I. J Am Acad Dermatol. 2022;87(2):255-268. doi: 10.1016/j.jaad.2021.12.066*

patient's quality of life, compliance with HL principles, regular visits and compliance with dermatovenerologist, oncologist recommendations.

The formation of a correct concept of responsibility towards the proper health (i.e. compliance with HL, physician recommendations on the examination and treatment) is an important moment in the prevention of cutaneous MAs. A more attentive attitude of the patient to his/her health will help to change the negative attitude to the physician recommendations, being more responsible regarding the prescriptions and recommendations, in particular routing after cutaneous MA detection [39].

Undoubtedly, mortality can be decreased after elimination the possible causes of cutaneous MAs, due to which increased population awareness of health issues is one of the priority objectives in the tactics of patient management in primary healthcare [40].

Sufficient time for the patient contact (asking targeted questions, demonstration of skin self-inspection and lymph node examination methods) is also a very important condition for prophylaxis and increased medical literacy. Skin self-inspection as an efficient behavior strategy is considered a potentially beneficial instrument to decrease the risk of relapse and serious melanoma complications, i.e. patients can detect suspicious nevi, skin lesions or changes themselves. It has been proven that patients with melanoma that detected melanoma relapses themselves had better survival than patients in whom relapse was diagnosed by the physician [41].

Medical literacy skills represent a degree in which people can obtain, process, and understand the main medical information necessary for the corresponding decisions concerning the proper health preservation and strengthening. The active and constant familiarization of physicians (especially in primary healthcare) and wide population strata with signs and criteria of cutaneous MAs in early development stages: pamphlets with melanoma images and photographs in the radial growth stage in various body areas on the physician's worktable, publication of articles in scientific-practical journals for general practitioners and therapeutic physicians on principles and possibilities of the early cutaneous melanoma detection, available and correct information in the official websites, educational webinars organized by independent healthcare experts and attended by physicians — can serve an effective method of increasing awareness of cutaneous MAs [42].

Patients with the newly diagnosed cutaneous MAs should be provided with the complete and comprehensive information about the disease, compulsory treatment, and compliance with the attending physician recommendations. Stege H. et al. (2022) had the objective of retrospective medical chart analysis among 714 patients (40.9 % females) with cutaneous MAs aged 18 to 89 years (mean age 61.8 years) and analyzing the health information sources. Malignant melanoma was diagnosed in the majority of patients (76.9 %). Regardless of age, patients obtained the main information about the disease from the oncologist (n=526) and the general practitioner (n=374). 301 people obtained the information from the Internet, however the rate of using Internet resources decreased with age (p=0.052). And on the other hand, persons aged over 65 years obtained the information more often from the general practitioner rather than younger participants (p=0.043). Thus, younger patients are more prepared to search the information about health in the Internet. Besides, more educated participants significantly improved the understanding of health-related information. Electronic healthcare technologies become more

and more represented as the main source of information; due to this, it is really important to educate patients with cutaneous MAs, including in the electronic healthcare sphere, to make independent, justified decisions and to obtain larger confidence in life with their disease [43].

Another important aspect is to analyze the association of medical literacy skills and the level of perception of negative information about the health condition by patients with cutaneous MAs. It has been demonstrated that medical literacy skills affect the cognitive perception of information about the disease (OR 0.75, 95 % CI 0.58, 0.96), while persons with higher education think about genetic test results less frequently (β=-0.66) and are less prone to stresses (β=-1.15). The association ($p < 0.001$) has been detected between the medical literacy and the risk of melanoma affecting the frequency of thoughts about test results [44].

Thus, prophylactic measures may delay the cutaneous MA progression, while the increased medical literacy of the population in the complex of measures on decreasing cutaneous MA advancement requires further enhancement and detailed review of this issue.

Prospects of improving early skin MA diagnosis

Modern innovative methods of early cutaneous MA diagnosis are currently developed and implemented in Russia. However, to decrease the indicator of high advanced cutaneous MA incidence, one should improve the work in primary healthcare concerning the control routing of patients with suspected cutaneous MAs to the specialized oncology institution, as well as increase the occupational and communicative preparation of medical staff along with increasing the medical literacy of the population.

Foreign colleagues also note several aspects that should be enhanced in primary healthcare to increase the quality of early cutaneous MA diagnosis, including:

1. prevention (regular prophylactic examination in melanoma high risk groups, monitoring patients with skin lesions from UVR exposure and/or occupational risk factors);
2. early diagnosis (increased quality of dermatoscopy interpretation, regular skin mapping in risk groups);
3. routing (decreased delay between the primary physician counseling and biopsy, biopsy sending and diagnosis, diagnosis presentation to the patient, decreased referral time to the oncologist and treatment onset);
4. process of interpersonal physician/patient relations (patient communication aspects) [45].

The self-inspection skill is a significant factor for early skin MA detection. New IT-products with neural networks and the newest software (including for smartphones) are currently actively developed — these allow users to conduct the remote screening of skin lesions independently, also helping to decide upon the necessity of an off-line physician visit. The example of such mobile application may be the «Pro Rodinki» application developed at the Department of Skin and Venereal Diseases of FSBEI HE Privolzhsky Research Medical University (PRMU). As a rule, non-congenital melanocytic nevi emerge in childhood, grow in the early adult years, and then stop growing; their diameter is usually less than 5 mm. The evolution of existing skin nevi is interpreted ambiguously by patients. On the one hand, some patients suffer from cancerophobia; on the other hand, some patients ignore even significant changes (transformations of the shape, borders; size increase), not paying attention to them. Some nevi located on the skin of the scalp, back, genitals, are difficult to be examined during the self-inspection by the patient, and the continuous changes may be left unnoticed for a long time. The «Healthy Skin» schools in polyclinics managed by the dermatovenerologist are considered progressive; these are intended for awareness raising among wide population strata.

The most efficient diagnostic method for early cutaneous MAs, including those of rare locations, is still the prophylactic examination of the patient by the dermatovenerologist using dermatoscopy [46]. The digital dermatoscopy has been implemented recently into the clinical practice of dermatovenerologists — it is characterized by high sensitivity and specificity, and also enhanced by the artificial intelligence, which helps to decide during prophylactic examinations and further routing of patients with suspicious cutaneous neoplasms [21, 47-49]. To evaluate the transformation of melanocytic nevi and to determine *de novo* cutaneous neoplasms, skin mapping with the photography of dermatoscopic images is applied [50]. The skin mapping is more efficient in patients with multiple (≥ 50) cutaneous nevi due to several reasons: routine dermatoscopy of each nevus requires a lot of time, it is rather difficult to describe the accurate location of nevi, the photography of changes is difficult. Currently the skin mapping procedure is the most convenient one, although it requires rather costly equipment.

Artificial neural networks have found their use in many spheres of human life, including the medical care system. The mathematical model of an artificial neural network and remote medical technologies provide early

cutaneous MA diagnosis in digital images among wide population strata. High-precision artificial neural networks (Convolutional Neural Network, CNN) have demonstrated high potential in the automatic diagnosis of cutaneous MAs thanks to the analysis of images with a spatial structure [22, 47, 50, 51].

After visiting the primary care physician, mandatory informing about suspicious MAs and persuading the patient about the necessity of complying with all physician recommendations and mandatory feedback preservation seems prospective.

Conclusion

The high incidence of advanced cutaneous MAs, including melanoma, is a complex medical & social issue, including insufficient medical staff preparation; inadequate patient informing about the importance of prophylactic examinations and disease seriousness; gaps in routing patients detected in primary healthcare to the specialized oncology institution; absence of skin self-inspection skills in patients; absence of a "Healthy Skin" school for wide population strata.

To decrease the high rate of advanced cutaneous MAs, including melanoma, and the optimization of patient routing after visiting the primary care physician, the following is definitely required:

1. mandatory periodic prophylactic examinations, especially in people over 40 years of age;
2. complete physical examination with thorough history collection and complete skin examination during regular checkups in primary healthcare;
3. using mandatory dermatoscopy for early cutaneous MA diagnosis by the dermatovenerologist, if possible — repeated skin mapping with the artificial intelligence analysis;
4. enhanced professional and communicative medical staff training for patient communication, especially with those with a newly diagnosed cutaneous MA, as psychosocial factors affect the patient's attitude towards their health;
5. maintaining succession in the work of therapeutic physicians and dermatovenerologists to increase the quality and to accelerate specialized medical care;
6. creation of "Healthy Skin" schools in polyclinics to enhance the medical literacy of the population with mandatory informing about the danger of cutaneous MAs for health and life, training patients in skin self-inspection skills;
7. applying electronic healthcare technologies as an additional information source.

Вклад авторов:

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

Гайдина Татьяна Анатольевна: подготовка материала для статьи, анализ литературы, сбор, анализ данных и интерпретация результатов, подготовка черновика рукописи, внесение в рукопись существенной (важной) правки с целью повышения научной ценности статьи, одобрение финальной версии рукописи

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Author contribution:

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

Tatyana A. Gaidina: preparation of material for the article, literature analysis, collection, data analysis and interpretation of results, preparation of a draft manuscript, making significant (important) edits to the manuscript in order to increase the scientific value of the article, approval of the final version of the manuscript

Anton S. Dvornikov: data analysis and interpretation of the results; making significant (important) edits to the manuscript in order to increase the scientific value of the article, approving the final version of the manuscript

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Alexey A. Silin: data collection, analysis and interpretation of results, preparation of a draft manuscript, approval of the final version of the manuscript

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DOI: 10.20514/2226-6704-2024-14-6-435-441
УДК 616.12-008.46
EDN: DNHKNH

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ВОЗМОЖНОСТИ ИСПОЛЬЗОВАНИЯ СИСТЕМЫ REDS В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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The Possibilities of Using the Reds System in Clinical Practice

Резюме

Представлен обзор литературы, в которой описывается уникальная мобильная неинвазивная система для измерения совокупного объёма жидкости в лёгких — ReDS, исследование её эффективности на животных, добровольцах, а также опыт применения в клинической практике. Проведён анализ отечественных и зарубежных литературных источников порталов PubMed, Web of Science, Nature, опубликованных в период 2012–2024 годов. Ежегодно во всём мире наблюдается тенденция к увеличению числа больных с хронической сердечной недостаточностью. Ключевой проблемой диагностического поиска остаётся раннее выявление декомпенсации хронической сердечной недостаточности. Одним из надёжных и ранних маркеров надвигающейся острой декомпенсации хронической сердечной недостаточности служит мониторинг показателя объёма жидкости в лёгких. Определение показателя объёма жидкости может служить критерием проведения коррекции проводимой терапии, что, в свою очередь, должно повлиять на частоту повторных госпитализаций. Таким образом, жизненно необходимым для дальнейшего ведения пациентов с острой декомпенсацией хронической сердечной недостаточности является контроль волемии, а также выявление и количественное определение степени застоя. Оценка объёма жидкости является ключевым фактором при ведении пациентов с хронической сердечной недостаточностью в стационарных и амбулаторных условиях. Мониторинг ReDS значительно снижает вероятность повторной госпитализации с хронической сердечной недостаточностью в течение 3 месяцев после выписки, по сравнению с пациентами, у которых не проводилось исследование на системе ReDS.

Ключевые слова: *ReDS, отёк лёгких, сердечная недостаточность, диагностика отёка лёгких*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 14.04.2024 г.
Одобрена рецензентом 25.08.2024 г.
Принята к публикации 28.10.2024 г.

Для цитирования: Елфимов Д.А., Елфимова И.В., Харченко Д.Д. и др. ВОЗМОЖНОСТИ ИСПОЛЬЗОВАНИЯ СИСТЕМЫ REDS В КЛИНИЧЕСКОЙ ПРАКТИКЕ. Архивъ внутренней медицины. 2024; 14(6): 435-441. DOI: 10.20514/2226-6704-2024-14-6-435-441. EDN: DNHKNH

Abstract

A review of the literature is presented, which describes a unique mobile non-invasive system for measuring the total volume of fluid in the lungs ReDS, a study of its effectiveness on animals and volunteers, as well as experience of use in clinical practice. An analysis of domestic and foreign literary

sources of the portals PubMed, Web of Science, Nature, published in the period from 2012–2024, was carried out. Every year around the world there is a tendency to increase the number of patients with chronic heart failure. The key problem of the diagnostic search remains the early detection of decompensation of chronic heart failure. One of the reliable and early markers of impending acute decompensation of chronic heart failure is monitoring of the fluid volume in the lungs. Determining the fluid volume indicator can serve as a criterion for adjusting the therapy, which, in turn, should affect the frequency of re-hospitalizations. Thus, vital for the further management of patients with acute decompensation of chronic heart failure is the control of volume, as well as the identification and quantification of the degree of congestion. Fluid volume assessment is a key factor in the management of patients with chronic heart failure in inpatient and outpatient settings. ReDS monitoring significantly reduces the likelihood of readmission to hospital with chronic heart failure within 3 months compared with patients not tested on the ReDS system.

Key words: *ReDS, pulmonary edema, heart failure, diagnosis of pulmonary edema*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 14.04.2024
Reviewer approved 25.08.2024
Accepted for publication on 28.10.2024

For citation: Elfimov D.A., Elfimova I.V., Harchenko D.D. et al. The Possibilities of Using the Reds System in Clinical Practice. The Russian Archives of Internal Medicine. 2024; 14(6): 435-441. DOI: 10.20514/2226-6704-2024-14-6-435-441. EDN: DNHKNH

ACCHF — acute decompensation of chronic heart failure, CHF — chronic heart failure

Introduction

There is a global annual trend towards increased number of patients with chronic heart failure (CHF). According to statistical data, in 2022 the incidence of CHF in the Russian Federation was 7.2 % [1]. CHF decompensation was a cause of admission to cardiology and medical wards in 4.9 % of all cases. In 82 % of cases, readmitted patients with CHF had decompensated pulmonary oedema [2].

Early identification of CHF decompensation is still the key diagnostic challenge. One of the reliable and early markers of imminent acute decompensation of chronic heart failure (ACCHF) is monitoring of the amount of pulmonary fluid. Measurement of the amount of fluid can be a criterion to adjust the therapy, which, in turn, should affect the frequency of hospital admissions [3].

Therefore, for the management of patients with ACCHF, it is essential to monitor the amount of fluid, as well as to detect and quantify the degree of congestion. Measurement of the amount of fluid is the key factor in the management of patients with CHF both in inpatient and outpatient settings [4].

Biophysical basis of ReDS technology

Modern non-invasive methods to evaluate the amount of pulmonary fluid include physical examination, chest X-ray and measurement of brain natriuretic peptide, type B, as well as chest CT [5].

In 2015, a non-invasive technology for the measurement of the cumulative pulmonary fluid ReDS™ (abbreviation of «remote dielectric sensing», i.e., a portable system for non-invasive measurement of the cumulative amount of pulmonary fluid) was registered in the USA, which can be an alternative to the above methods and can be used in inpatient settings, outpatient clinics, and also at home [6].

ReDS (Sensible Medical Innovations Ltd, Netanya, Israel) measures dielectric properties of tissues. This technology was developed by Israeli R&D specialists using the military technology «See through wall», which allows sensing biological objects through walls. The technology was presented to the public at the largest international ground and airborne defence and security exhibition Eurosatory only in 2022, but the first article describing the «See through wall» principle was published in 2005 [7].

A ReDS device comprises two sensors fixed to a vest, which the patient puts on for a 90-second measurement. The sensors are located on the chest (in front) and on the right side of the patient's body (on the back). The vest is connected to a monitor console with a cable. Each sensor is a small, round device, which can transmit and intercept energy reflected by the lung tissue or transmitted through it.

Non-invasive measurement of the fluid volume using ReDS is performed as follows: a sensor sends low-power electromagnetic signals to the body, and intercepted signals represent dielectric properties of tissues, impacted mostly by the fluid accumulated in them [8]. The dielectric factor of a material is a frequency-dependent complex value, which describes its interaction with electromagnetic energy, including the degree of energy

absorption, reflection and retention. Various tissues have varying dielectric factors. Since water has a very high dielectric factor (about 80), dielectric factors of tissues depend mostly on the amount of fluid in them. For instance, healthy fat tissue with a low amount of fluid has a relative low dielectric factor, whereas healthy muscular tissue, which is relatively rich in fluid, has a higher dielectric factor. The dielectric factor of the lung tissue is impacted by dielectric factors of each of its components and their concentrations (e.g., blood, lung parenchyma, air and their relative concentrations). Since air has the lowest dielectric factor, and dielectric factors of other blood components are approximately equal and significantly higher than that of air, one can assume that the lung tissue comprises two types of high-contrast components. Therefore, air makes the dielectric factor of the lung tissue a very sensitive and direct indicator of the volume ratio of fluid and air, i.e. an indicator of fluid volume. High sensitivity of this parameter to a high concentration of a fluid is a physiological basis for assumed high accuracy of the device in detection of pulmonary oedema and its progression over time [9].

Scope of ReDS application

The use of a ReDS system makes it possible to measure an absolute amount of a fluid in the lungs. High levels of a fluid in the lungs indicate decompensated CHF.

A key marker of heart failure development and diagnosis is urine output. ReDS system was tested in volunteers; the objective of the clinical trial was to evaluate the capability of ReDS system parameters to correlate both with the clinical course of ACCHF, manifesting as pulmonary congestion, and with changes in the fluid status. According to ReDS system, the levels of fluid in the lungs of patients with ACCHF strongly correlated with the urine output values. During hospitalisation, ReDS parameters demonstrated positive dynamics and corresponded to clinical improvements; when baseline ReDS values and discharge values were compared, significant improvements were noted [10].

Relative diagnostic value of ReDS system

The important task with the use of ReDS system is to compare its values with other methods measuring fluid levels in the lungs, as well as to correlate it with other methods of CHF diagnosis in general.

At the moment, the gold standard to measure fluid in the lungs is computer tomography. A study of the correlation between ReDS and CT values was conducted by a number of foreign and Russian scientists.

In 2013, a scientific article was published on an assessment of ReDS efficiency in animals and healthy volunteers. The study compared CT data with ReDS values. Results obtained with ReDS system demonstrated high sensitivity to changes in lung fluid content. A comparative analysis of ReDS values and CT data in the porcine heart failure model showed that ReDS technology is accurate in detecting changes in lung fluid concentrations, evidenced by high ICC values (intraclass correlation coefficient) and Pearson correlation of 0.95 [9].

In 2016, the International Journal of Cardiology published an article describing validation of ReDS technology for quantitative evaluation of pulmonary fluid, by comparing high-resolution chest CT scans of patients with and without acute heart failure. This study demonstrated that quantitative measurement of fluid using ReDS closely correlates with CT data in measurement of the amount of pulmonary fluid [11].

Another study comparing correlation between ReDS data and CT data demonstrated that ReDS accuracy is comparable to CT results; the level of correlation is 94 %. These data confirm potential replacement of CT with ReDS in the measurement of the absolute amount of pulmonary fluid [12].

As for other methods of CHF diagnosis, e.g., Swan-Ganz catheter, a study was published, the results of which allowed scientists to conclude that in some cases ReDS diagnostics can be used as a non-invasive alternative to Swan-Ganz catheter, since there is a correlation between ReDS values and pulmonary capillaries wedge pressure. Normal ReDS values have high prognostic value (95 %), demonstrating that the pulmonary capillaries wedge pressure is less than 18 mm Hg [13, 14].

After analysing the results and conclusions in scientific publications on this topic, we can conclude that ReDS data are accurate if compared to chest CT, which is confirmed with high coefficients of concordance.

ReDS as an indicator of ACCHF risk

ACCHF in patients with a history of CFH imminently leads to repeated hospitalisations, a high risk of complications and negatively impacts the clinical course of CHF. There is a study to evaluate the use of ReDS values as criteria of eligibility for discharge, judging by the total amount of fluid in the lungs of patients, who are clinically ready for discharge.

The ReDS study results showed premature discharge in 32 % of cases, because these patients still had higher than normal amount of fluid in their lungs. The use of ReDS as a criterion of an optimal therapy result allows preventing discharge of patients with higher than normal amount of fluid in their lungs, thus reducing the re-admission rates [4, 15, 16].

In 2012, Dan Rappaport published the first clinical study of ReDS system in healthy volunteers. ReDS values were evaluated in inpatient settings, as well as in outpatient clinics after discharge from the hospital for three months. According to ReDS, during hospitalisation, patients had lower concentrations of fluid in their lungs (by 18 ± 8 %), indicating lungs "drying". Lower ReDS values correlated with clinical manifestations (Pearson correlation = 0.85). In outpatient settings, the study of ReDS values showed clinical stability in 67 % of cases with CHF therapy. These patients had minimal changes in the values of fluid concentrations in the lungs (ReDS (2.5 ± 4)), evidenced by no need in re-admissions. In 33 % of cases, patients were re-hospitalised with pulmonary oedema 28 ± 12 days later. Changes in ReDS values demonstrated an increase in the total amount of fluid in the lungs (17 ± 7) vs. values upon discharge. Worse results in patients demonstrated by ReDS preceded re-admission 22 ± 5 days later. Based on the study results, the authors concluded that quantitative evaluation of the amount of pulmonary fluid using ReDS can be useful in the monitoring of pulmonary congestions both in inpatient settings and outpatient clinics. This fact makes it possible to use ReDS data for identifying the changes in CHF and possible development ACCHF [17].

A metaanalysis of the data of 985 patients from seven studies showed a low risk of re-admissions in patients with heart failure, who were monitored for ReDS values, as compared to patients who did not have their ReDS values evaluated [18-20].

High sensitivity of ReDS system ensures identification of pulmonary congestions prior to significant clinical (symptomatic) aggravation of CHF, thus making it possible to use ReDS as a risk indicator of ACCHF.

ReDS in the management of patients with CHF

Taking into account high correlation between ReDS values and CT findings, as well as urine output and brain natriuretic peptide values, the authors of several studies suggest that ReDS values could help in defining the management strategy in hospital settings. Changes in ReDS values correspond to the clinical course, improvement of the patient condition during hospitalisation, because pre-discharge values improve significantly vs. ReDS values upon admission, it being also confirmed with changes in brain natriuretic peptide levels. The use of ReDS allows evaluating data within a broad range of fluid levels, including the applicable clinical range [11, 21].

Also, researches insist on continued outpatient monitoring of ReDS values in patients after discharge for timely therapy adjustments [9].

In 2017, the International Journal of Cardiology published an article titled "Evaluation of remote dielectric sensing (ReDS) technology-guided therapy for decreasing heart failure re-hospitalizations". The article described a study to decrease the number of re-hospitalisations in patients with CHF and development of ACCHF, using ReDS monitoring at home [22, 23].

In 2012–2015, a study was conducted, which allowed concluding that the non-invasive ReDS technology makes it possible to alert on early detection of decompensated CHF with a relative low burden for patients. Maintaining healthy levels of pulmonary fluid after therapy adjustments using ReDS values results in decreased brain natriuretic peptide levels and lower rates of hospitalisations [24].

It has been noted that ReDS-guided therapy of CHF during the 30-day follow-up period of patients after hospitalisation for ACCHF can result in a lower (by 54 %) risk of re-hospitalisations, including cardiac causes — by 78 % [25].

A retrospective analysis of 112 medical records of patients with ACCHF demonstrated that ReDS value monitoring and therapy adjustments reduced hospitalisation duration in patients admitted with CHF and extended doctor's possibilities to adjust the therapy [26].

ReDS system was used in 2020, during the COVID-19 pandemic, in the pulmonology ward in Ospedali Riuniti Hospital in Ancona, Italy. ReDS measurements were performed at bedside. Evaluation of changes in ReDS values allowed assessing the therapy efficacy [27].

The study results confirm the potential clinical usefulness of ReDS monitoring of patients with CHF. Monitoring ReDS values and maintaining the normal total amount of pulmonary fluid result in decrease in brain natriuretic peptide levels and reduced number of re-hospitalisations. Thus, the ReDS technology is a useful tool for remote outpatient management of patients at risk of re-hospitalisation for CHF.

Advantages and drawbacks of ReDS

The distinctive features of the ReDS system are high sensitivity and rapid measurement of parameters within seconds after a minor change in pulmonary congestion, resulting from manipulations in studies simulating ACCHF [9].

Besides, the ReDS system is superior to computer tomography: rapid monitoring of changes, compact design of the device, rapid measurements, possibility of frequent measurements and diagnostics of even tiny changes in pulmonary congestion, and absence of radiation exposure. All these factors make it possible to replace CT with ReDS examinations in order to measure the absolute amount of pulmonary fluid. Since the device is portable, it can be used at home to monitor condition and possible therapy adjustments.

Also, the device is useful as ReDS can be used as an alternative to Swan-Ganz catheter, i.e., it is a potential non-invasive tool to evaluate the right and left cardiac ventricle function, monitor efficacy of the therapy of myocardial infarction, cardiogenic shock, pulmonary oedema, volume depletion and hypertension monitoring, various cardiac arrhythmias. The ReDS technology is highly sensitive and specific for the identification of abnormally high pulmonary capillaries wedge pressure and ensures timely adjustment of drug therapies [14].

The simplicity of the method, time for examination, comparable result reliability, and safety for patients and staff (the measurement uses low-power electromagnetic waves, less than 1/1,000 of the cell phone radiation) indicate an apparent advantage of the ReDS technology for early diagnosis of decompensated CHF.

However, spatial resolution prevents from telling where in the lungs fluid accumulates: intravascular, interstitial or alveolar sections [9].

The drawbacks also include high costs of the ReDS system and just a few publications in Russian journals describing the use of the technology and its advantages.

Use of ReDS in Russia and its cost-effectiveness

Russian scientists also conduct studies demonstrating the efficacy of the ReDS system in outpatient settings. For instance, ReDS values were monitored in rural areas. A dynamic study of ReDS values in outpatient settings made it possible to timely adjust the therapy, diagnose the onset of decompensated CHF and reduce the rate of re-hospitalisations. The authors of the study note that measurements with the ReDS system can be performed in a remote clinic, and a cardiologist can remotely evaluate the values and correct therapy. This medical care model improves healthcare for patients with CHF and reduces the mortality and re-hospitalisation rates [28].

In summary, drug therapy of patients with CHF can be adjusted using ReDS value monitoring.

Introduction of the ReDS technology in the federal healthcare in Russia and its use in outpatient and inpatient settings are a promising area. Clinical efficacy and cost-effectiveness are justified, since it will reduce the number of hospitalisation and save money in the healthcare starting from the third year of use. The evaluation demonstrated that in order to enrol 95 % of the population, 1,129 to 1,234 ReDS devices will be needed [6].

Conclusion

Therapy adjustment using the ReDS system can help in identifying the urine output and rate, prescription of other medicinal products, e.g., vasodilators, and in preventing early discharge of patients.

The advantages of the ReDS method in the measurement of the amount of pulmonary fluid are a non-invasive procedure, short duration of the procedure, no need in consumables and preparation of rooms. The device is portable and can be transported from one room to another (from a ward to a ward), while a CT device cannot. The device can perform measurements over clothes, at home. Also, an important factor is patient and staff safety and the possibility to perform multiple measurements during one 24-hour period.

ReDS value monitoring significantly decreases the probability of re-hospitalisation of patients with chronic heart failure within three months, as compared to patients who did not undergo ReDS measurements. The method is clinically justified and allows performing adjustment of heart failure therapy after ReDS measurements. At the same time, it is worth noting that the use of the ReDS system in comorbid patients has been understudied. The developer has provided a diagram of ReDS measurements, but it is up to the medical organisation to set the frequency of examinations. The studies do not provide any clarity as to the frequency of examinations. The use of the ReDS system in patients with CHF is clinically justified, and results are comparable to CT results; however, it is essential to develop algorithms of ReDS measurements depending on CHF severity and comorbidities.

Вклад авторов:

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

Елфимов Д.А.: создание идеи и концепции рукописи, утверждение окончательного варианта

Елфимова И.В.: создание дизайна рукописи, критический обзор материала, окончательное редактирование рукописи

Харченко Д.Д.: написание обзорной части и заключения рукописи

Чупраков А.Е.: сбор и анализ литературных данных

Тюменцева Н.В.: редактирование 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

Elfimov D.A.: creation of the idea, conceptualisation, approval of the final version

Elfimova I.V.: creation of the manuscript design, critical review of the material, final editing of the manuscript

Harchenko D.D.: writing the review and conclusion of the manuscript

Chuprakov A.E.: collection and analysis of literature data

Tjumenceva N.V.: revision of the text

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DOI: 10.20514/2226-6704-2024-14-6-442-456
УДК 616-003.829.1-06:[616.12-008.64+616.36-004]
EDN: ERQADO

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ГЕМОХРОМАТОЗ И ПОРАЖЕНИЕ СЕРДЦА

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Hemochromatosis and Heart Involvement

Резюме

Гемохроматоз при отсутствии терапии представляет собой опасное для жизни состояние, связанное с избыточным содержанием железа в организме. Выделяют первичный (наследственный) гемохроматоз, возникающий в результате мутаций генов, и вторичный (приобретенный) в результате чрезмерного потребления или поступления железа с пищей или в составе лекарственных препаратов, заболеваний печени или многократных гемотрансфузий. Отложение избытка железа в паренхиматозных тканях приводит к клеточной дисфункции и клиническим проявлениям заболевания. Чаще всего поражаются печень, поджелудочная железа, суставы, кожа, гипофиз и сердце. Гемохроматоз сердца в ряде случаев приводит к развитию сердечной недостаточности, которую потенциально возможно предотвратить. Первоначально развивается диастолическая дисфункция и нарушения ритма, на более поздних стадиях — картина дилатационной кардиомиопатии. Выявить признаки поражения сердца при гемохроматозе можно с помощью комплексной 2D- и допплеровской эхокардиографии, МРТ сердца с измерением времени релаксации T2* и других диагностических методов. «Золотым стандартом» диагностики первичного гемохроматоза является генетическое тестирование, которое должно проводиться всем пациентам с подозрением на данную патологию после исключения вторичных причин перегрузки железом. Основу терапии гемохроматоза составляют лечебная флеботомия и хелатирование железа. Средняя продолжительность жизни у нелеченых пациентов с гемохроматозом и тяжелой сердечной недостаточностью не превышает одного года. Однако при раннем и агрессивном лечении выживаемость приближается к таковой у пациентов с сердечной недостаточностью другой этиологии.

Ключевые слова: *гемохроматоз, сердце, сердечная недостаточность, аритмия, флеботомия, фиброз печени, цирроз печени, гепатоцеллюлярная карцинома, сахарный диабет, хелатирование железа, эритроцитаферез*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 11.06.2024 г.
Одобрена рецензентом 08.07.2024 г.
Принята к публикации 24.07.2024 г.

Для цитирования: Резник Е.В., Лауар М.Х.Э., Воинова В.Ю. и др. ГЕМОХРОМАТОЗ И ПОРАЖЕНИЕ СЕРДЦА. Архивъ внутренней медицины. 2024; 14(6): 442-456. DOI: 10.20514/2226-6704-2024-14-6-442-456. EDN: ERQADO

Abstract

Hemochromatosis is a life-threatening condition if left untreated, that is caused by excess iron in the body. It can be primary (hereditary) hemochromatosis, resulting from genes mutations, and secondary (acquired) as a result of excessive intake of iron from food or drugs, liver diseases or repeated

blood transfusions. Deposition of excess iron in parenchymal tissues leads to cellular dysfunction and clinical manifestations of the disease. The liver, pancreas, joints, skin, pituitary gland and heart are most often affected. Cardiac hemochromatosis is an important and potentially preventable cause of heart failure. Initially, diastolic dysfunction and arrhythmias develop, at later stages a picture of dilated cardiomyopathy can appear. Signs of heart damage in hemochromatosis can be detected using complex 2D and Doppler echocardiography, cardiac MRI with T2* relaxation time measurement and other diagnostic methods. Genetic testing is the gold standard for diagnosing hemochromatosis and should be performed after secondary causes of iron overload have been excluded. The basis of therapy is therapeutic phlebotomy and iron chelation. Median survival is less than a year in untreated patients with severe heart failure caused by hemochromatosis. However, with early and aggressive treatment, survival approaches that of patients with heart failure of other etiologies.

Key words: *hemochromatosis, heart, heart failure, arrhythmia, phlebotomy, liver fibrosis, liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, iron chelation, erythrocytapheresis*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 11.06.2024
Reviewer approved 08.07.2024
Accepted for publication on 24.07.2024

For citation: Reznik E.V., Laouar M.H.E., Voinova V.Yu. et al. Hemochromatosis and Heart Involvement. The Russian Archives of Internal Medicine. 2024; 14(6): 442-456. DOI: 10.20514/2226-6704-2024-14-6-442-456. EDN: ERQADO

MRI — magnetic resonance imaging, LVEF — left ventricular ejection fraction, ECG — electrocardiogram, NT-proBNP — N-terminal precursor of the brain natriuretic peptide, SAT — transferrin saturation coefficient, SF — serum ferritin, NAFLD — non-alcoholic fatty liver disease, HCC — hepatocellular carcinoma, CT — computed tomography, AFib — atrial fibrillation, DXA — dual-energy X-ray absorptiometry, *HFE* — Human homeostatic iron regulator gene, *HAMP* — Hepcidin anti-microbial peptide gene, *HJV* — Hemojuvelin gene, *TFR2* — Transferrin receptor 2 gene, *SLC40A1* — Ferroportin gene, *DMT1* — Divalent metal transporter 1, T2 — spin echo decay time constant, T2* — gradient echo-induced relaxation time

Introduction

Hemochromatosis is a disease characterized by the systemic iron overload and iron deposition in various organs, including the heart. Two hemochromatosis types exist: primary and secondary disease. Primary hemochromatosis is a hereditary disease, while secondary one results from the prolonged use of iron drugs or frequent hemotransfusion in anemias, liver diseases [1].

Primary hemochromatosis is a hereditary autosomal-recessive disease caused by decreased levels of the regulatory hormone hepcidin which controls iron levels or decreased hepcidin-ferroportin binding. Hepcidin regulates the activity of ferroportin, which is the only known cellular iron exporter. The most common form of hemochromatosis is caused by homozygous mutations in the *HFE* (Homeostatic Iron Regulator) gene, in particular the C282Y mutation, which occurs in over 80 % of patients with this disease form. Less common hemochromatosis forms are associated with mutations in other genes: hepcidin anti-microbial peptide gene (*HAMP*), or hemojuvelin gene (*HJV*), or transferrin receptor 2 gene 2 (*TFR2*), or ferroportin gene (*SLC40A1*), which prevent hepcidin-ferroportin binding. Increased plasma iron levels may lead to iron accumulation in parenchymatous organs and tissues, especially in hepatocytes, pancreatic cells and cardiomyocytes, pituitary gland, testes, which results in organ fibrosis and failure. The diagnosis of hereditary hemochromatosis includes genetic testing, assessment of serum iron metabolic parameters, imaging data. Hepcidin may become an innovative future approach to the treatment of this disease [2].

The main pathogenetic mechanism of primary hemochromatosis associated with the *HFE* gene mutation is the increased iron absorption in the intestine [3]. When discussing the issue of hemochromatosis, the acquired iron overload (secondary hemochromatosis) is not considered; rare genetic disorders leading to systemic iron excess due to mechanisms different from primary hepcidin deficiency are not excluded. Such disorders include ferroportin loss of function, atransferrinemia, aceruloplasminemia, or iron overload associated with divalent metal transporter 1 (*DMT1*, also known as *NRAMP2*).

Both *HFE*-associated and non-*HFE*-associated hemochromatosis lead to hepcidin deficiency, increased iron influx from the small bowel cells and splenic macrophages into plasma (Fig. 1, 2). Increased plasma iron levels lead to enhanced iron transport into parenchymatous cells (especially hepatocytes, cardiomyocytes, and pancreatic cells), which in turn leads to predominant iron overload of the liver, heart, and pancreas. Despite the role of hepcidin in the pathogenesis of hemochromatosis, its measurement is not necessary

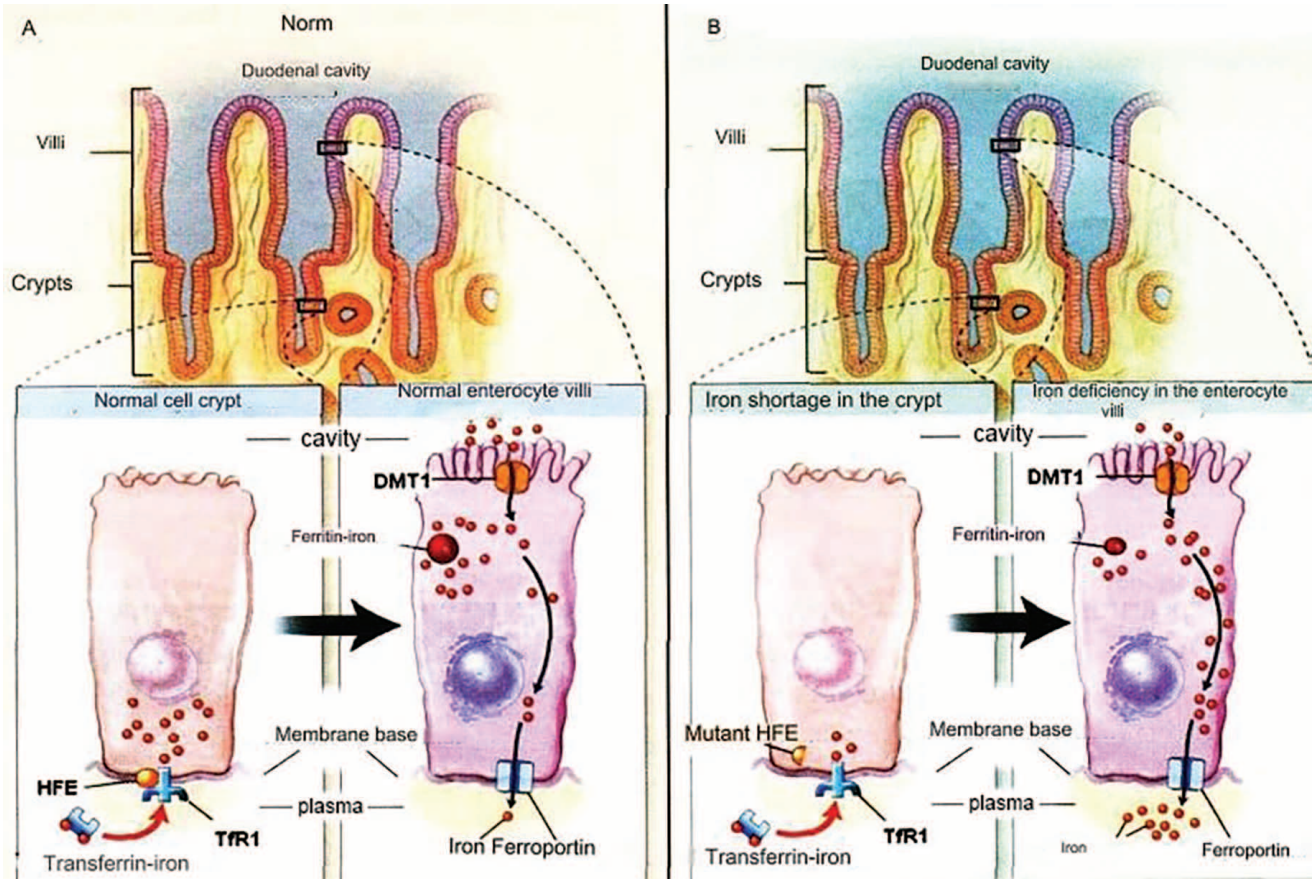

Figure 1. *The mechanism of absorption of iron from food in the duodenum. Arutyunov A.T., Ivanikov I.O., Syutkin V.E. et al. Scientific and practical journal N 9-10, 2008. [Electronic resource]. URL: http://bono-esse.ru/blizzard/img/RPP/Abdomen/Fe3.jpg. (date of the application: 30.04.2024).*

Note. A: Normal, B: With a mutation in the *HFE* gene

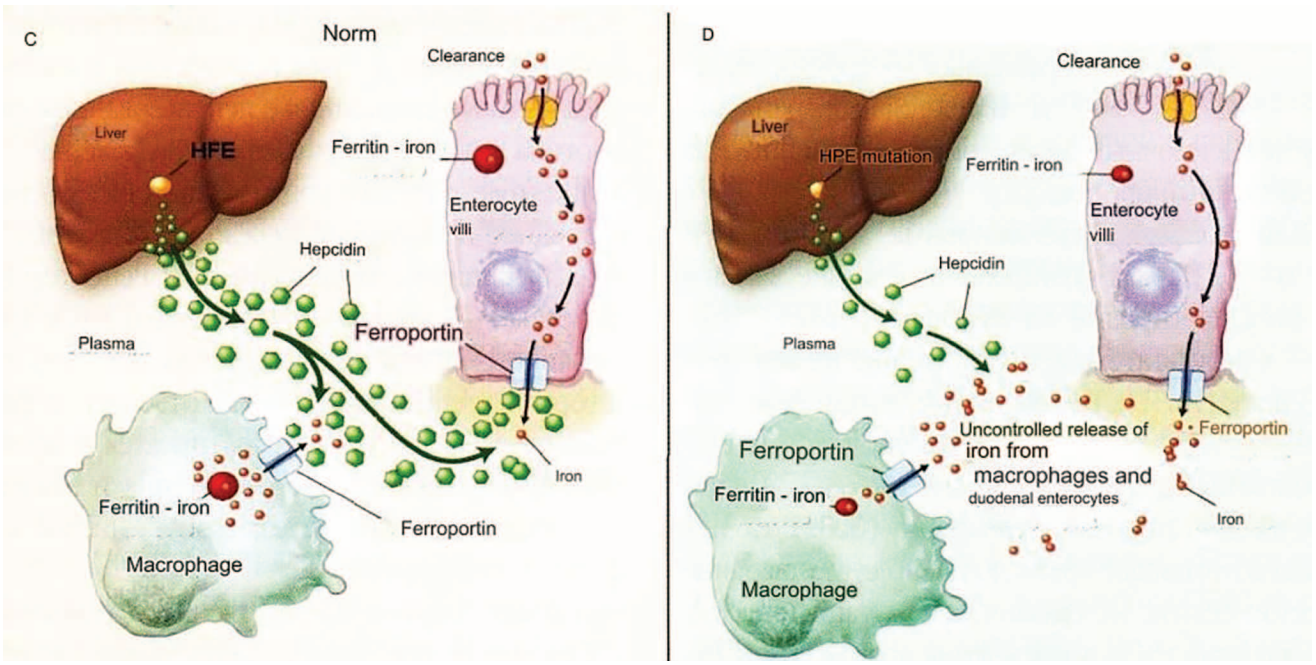

Figure 2. *Model of iron metabolism based on hepcidin. Arutyunov A.T., Ivanikov I.O., Syutkin V.E. et al. Medical advice. Scientific and practical journal N 9-10, 2008. [Electronic resource]. URL: http://bono-esse.ru/blizzard/img/RPP/Abdomen/Fe4.jpg. (date of the application: 30.04.2024).*

Note. C: Normal, D: With a mutation in the *HFE* gene

for diagnosis, as increased transferrin saturation (with iron) or increased plasma ferritin levels are considered sufficiently specific hepcidin deficiency markers. Transferrin saturation is the ratio of the number of occupied iron binding sites to the total number of plasma transferrin iron binding sites. The increase of this parameter is decisive for the diagnosis of hemochromatosis. Besides, strict interpretation of serum ferritin levels (which is the main iron depot protein in the body) should be used for diagnosis.

- **Epidemiology of hemochromatosis**

When *HFE* gene was first identified as a hemochromatosis-associated gene, the most common causes of this disease were identified as homozygous p.Cys282Tyr (C282Y) and p.His63Asp (H63D) mutations.

Homozygous p.C282Y variant in the *HFE* gene occurs among over 80 % of Caucasian people with hemochromatosis. Homozygous p.H63D mutations is detected no more frequently among patients with non-p.C282Y homozygous hemochromatosis than in the general population. The total prevalence of p.C282Y/p.H63D compound heterozygotes among patients with clinically overt hemochromatosis is 4.1 % [4]. However, p.C282Y/p.H63D compound heterozygosity itself is not sufficient to cause hemochromatosis. Phenotypic hemochromatosis develops only if this genotype coincides with additional genetic or ecological risk factors of the liver disease [5].

The incidence of hemochromatosis and its genetic cause in various populations were analyzed in multiple studies. They are summarized in Table 1. It has been demonstrated that the prevalence of the most well-known *HFE* mutations (i.e. p.C282Y and p.H63D) which may cause hemochromatosis varies depending on ethnic groups [6]. The most common cause of hemochromatosis is definitely homozygous p.Cys282Tyr substitution. Among patient with the diagnosis of hemochromatosis in Australia, UK, France, this reaches 96 %, while in Italy it is only 62 %, in Greece — 39 %. p.Cys282Tyr/p.His63Asp compound heterozygosity in the *HFE* gene is more common than p.Cys282Tyr homozygosity, though it has a much lower biochemical and clinical penetrance.

The Hemochromatosis and Iron Overload Screening Study (HEIRS) evaluated the prevalence, genetic and ecological determinants among other hemochromatosis factors in the multiethnical primary care sample among 100,000 adults within 5 years in the USA and Canada. Among 99,711 subjects not belonging to the same family, 299 people were *C282Y* homozygotes. Presumed C282Y homozygosity prevalence was 0.44 % among non-Hispanic whites, 0.11 % among Native Americans, 0.027 % among Latinos, 0.014 % among blacks, 0.012 % among Pacific Islanders, 0.000039 % among Asians. C282Y homozygosity prevalence in Ireland was 1.2 %. Besides, the average prevalence of C282Y homozygosity 0.4 % and C282Y heterozygosity 9.2 % was demonstrated in the review of 27 studies including 6302 Caucasians. The same study demonstrated the prevalence of C282Y homozygosity 0.5 % and C282Y heterozygosity 9 % in the North America. In Asia, Africa, Middle East, and among native Australasians (including indigenous persons, Vanuatu Australians, and Papuans), C282Y homozygosity was not detected (n=3752), though the prevalence of C282Y heterozygosity varied from 0 % to 0.5 %. The prevalence of C282Y/H63D heterozygosity and H63D homozygosity was 2 % both in the Caucasian population; in America, the prevalence of compound heterozygosity was 2.5 %, while the prevalence of H63D homozygosity was 2.1 %. Other studies reported the highest rate of C282Y substitution among Europeans of non-Finnish descent (5.14 % allele prevalence) [7].

Table 1. *Separate population studies of homozygous frequencies HFE p.Cys282Tyr*

Country	Studied population	Cohort size	Frequency of *HFE* p.Cys282Tyr
Australia	Workers	11 307	1 of 221
Australia	Voters of Northern European descent	29 676	1 of 146
USA	Primary Health Care Laboratory Clients	99 711	1 of 333
Great Britain	Persons, registered in the National Health Service	451 243	1 of 156
Norway	Hospitalized persons (Europeans only)	1 900	1 of 136
Spain	Blood donors	5 370	1 of 671
France	Visitors of health assessment centers	9 396	1 of 174

In the USA, almost 1 out of 300 white Caucasians suffers from hereditary hemochromatosis; 1 out of 15 persons of North American descent has at least one mutant *HFE* copy, which is the most common gene mutation associated with hereditary hemochromatosis [8]. Hereditary hemochromatosis is not associated with sex, though it is more likely symptomatic in males. In females, symptoms of hemochromatosis may develop at a later age (after menopause) due to regular menstrual blood losses. Almost 75 % of people have hemochromatis diagnosed before clinical signs develop (mainly due to genetic testing). Despite the high prevalence of *C282Y* homozygosity, only a small amount of people accumulate enough iron to cause organ damage. Accounting for *C282Y* autosomal-recessive inheritance, the prevalence of *C282Y* homozygosity in males and females is the same, though the prevalence of clinical signs differs. One study demonstrated that clinical signs of hemochromatosis were detected only in 28.4 % of males and 1.2 % of females with *C282Y* homozygosity. However, in the beginning of the study, 81.8 % of males and 55.4 % of females had increased serum ferritin levels, i.e. the biochemical penetrance should be higher than the clinical one. Other studies revealed that clinical signs of hemochromatosis developed in 25–60 % of *C282Y* homozygotes. Various factors (i.e. genetic modifiers, environmental or lifestyle factors) probably determine the phenotype in *C282Y* homozygotes [9].

The cohort study that included 22 sites from England, Scotland, Wales (British biobank; in total 451,243 Caucasians) detected 2890 (0.6 %) people with the homozygous *p.C282Y phenotype.* With that, the diagnosis of hemochromatosis was established in 21.7 % of males and 9.8 % of females. This confirms the hypothesis that *p.C282Y*-associated iron overload may be prevented and cured with the early intervention. The study of Brazilian blood donors detected the 2.1 % prevalence of *HFE p.C282Y* alleles.

- **Hemochromatosis classification**

4 hereditary hemochromatosis subtypes have been described — these result from increased iron absorption into the bloodstream from the gastrointestinal tract. Decreased hepcidin activity or synthesis cause the majority of hemochromatosis cases. Type 1 is associated with mutations in the *HFE*gene — this causes over 80 % of hemochromatosis cases, type 2A is caused by mutations in the *HJV* (or *HFE2*) gene, type 2B is caused by mutations in the *HAMP* gene, type 3 is caused by mutations in the *TFR2* gene, type 4 is caused by mutations in the *SLC40A1* gene — these lead to increased ferroportin activity (this disease was initially classified as type 4B, and it differs from the ferroportin disease which is caused by the ferroportin loss of activity and classified as type 4A) [10].

- **Clinical signs of hemochromatosis**

Clinical signs of homozygous *HFE*-associated hemochromatosis (*p.C282Y)* were initially described by A. Trousseau and F.D. von Reclinghausen. Early clinical cohort studies detected significant morbidity and mortality in this disease [11], [12].

After the *HFE* gene discovery, population studies demonstrated various biochemical and clinical signs of hemochromatosis. Crossover cohort studies demonstrated that hemochromatosis was not associated with increased mortality. Later population studies demonstrated that *p.C282Y*-homozygous males (but not females) had a significantly higher risk of death to the age of 75 years (19.5 % vs. 15.1 % in the control group). It was also detected that complex or simple *p.C282Y* and/or *p.H63D* heterozygosity was not associated with the increased risk of premature death [13, 14]. *p.C282Y* homozygosity was associated with significant dementia, delirious disorders, sarcopenia, weakness, and chronic pain in males over 60 years of age [15, 16].

HFE-associated hemochromatosis may be asymptomatic for over 30 years (even over 40 years in males and over 50 in females). In non-*HFE*-associated hemochromatosis, symptoms may emerge at the age of about 20–30 years. In general, symptoms are variable, which explains late diagnosis [17].

In hemochromatosis, iron location in different tissues is determined by several factors, including the disease stage, total iron overload value, and genetic predisposition of specific organs to iron overload. Excess tissue iron may be stored in the reticuloendothelial system until the threshold is exceeded. When this occurs, other organs (including the liver, heart, pancreas, spleen, pituitary gland) may also serve as excess iron depots. Animal studies demonstrate that the source of excess iron may partially determine the iron deposition degree in the heart.

Fatigue and arthralgia are among the most common symptoms. Skin signs mainly include melanodermia (skin pigmentation), sometimes — dry skin and nail changed (even paradoxical koilonychia, a classic sign of iron deficiency anemia). Main hepatic symptoms include hepatomegaly and mild transaminitis with the preserved liver function. Hemochromatosis may cause diabetes mellitus, hypogonadism, or hypopituitarism. It is very important to remember that *HFE*-associated

hemochromatosis occurs in Caucasian people, while non-*HFE*-associated hemochromatosis may be detected in many ethnic groups, although it is much less common [18].

The most common and significant clinical signs include liver diseases and arthritis [19]. *p.C282Y*-homozygous males (but not females) have a more than 4-fold risk of hepatic diseases compared to persons without *HFE* mutations. Male *p.C282Y* homozygotes also have an increased risk of arthritis, colorectal cancer, and diabetes mellitus. Female *p.C282Y* homozygotes also have an increased risk of arthritis, colorectal cancer, and breast cancer compared to females without *HFE* gene mutations [13].

• **Liver pathology:** Progressive liver fibrosis or cirrhosis in non-*HFE*-associated hemochromatosis is rare before the age of 45 years in the absence of other concomitant liver diseases [20]. The risk factors for liver fibrosis or cirrhosis include excessive alcohol consumption, diabetes mellitus, arthritis, serum ferritin levels over 1000 μg/L, and hepatic iron levels over 200 μmol/g [21].

In *HFE p.C282Y*-homozygous males, the lifetime risk of primary hepatic carcinoma is 12-fold compared to males without *HFE* gene mutations. *HFE p.C282Y*-homozygous females do not have increased hepatic carcinoma risks [13]. The largest risk of primary hepatic carcinoma is present in patients with liver cirrhosis [22]; liver ultrasound every 6 months is recommended for timely diagnosis [23].

• **Arthritis:** Joint lesions are detected in at least 24 % of patients with hemochromatosis. Classic arthropathy involves metacarpophalangeal joints, followed by the hip, ankle, wrist, elbow, shoulder, and knee joints, as well as the lumbar spine. It can be hard to differentiate the hemochromatosis-associated arthropathy from osteoarthritis. It is unknown why arthropathy affects only some patients with hemochromatosis. Arthritis may develop at various disease stages and even after successful phlebotomies. Risk factors for arthritis include older age, progressive liver fibrosis, prolonged periods of serum ferritin levels over 1000 μg/L and serum iron transferrin saturation ≥50 % [24].

Hepatic diseases and arthritis usually manifest simultaneously. The probability of arthritis is higher with larger iron loads or during the later stage of liver lesions [17]. The recent study demonstrated that arthritis was closely associated with significant liver fibrosis, i.e. arthritis was diagnosed in 84 % of *HFE p.C282Y* homozygotes with significant liver fibrosis, while 34 % of *p.C282Y* homozygotes with arthritis had significant liver fibrosis. It is important to note that late-stage liver fibrosis was observed only in 5 % of patients without arthritis. Thus, the absence of arthritis had a 95 % negative prognostic value for progressive liver fibrosis [25].

• **Other clinical signs:** Other conditions typical for *HFE p.C282Y* homozygous hemochromatosis include diabetes mellitus, hyperpigmentation, hypogonadotropic hypogonadism, and cardiomyopathy. Such conditions are usually treated in accordance with general clinical guidelines in combination with the iron overload treatment. Cardiomyopathy is a rare complication, which is potentially reversible with iron overload treatment [14].

• **Diagnosis of hemochromatosis**

The modern diagnostic approach to hemochromatosis is non-invasive, i.e. liver biopsy is no longer required. Hemochromatosis may be diagnosed only based on the combination of clinical, laboratory, and imaging data.

1. Laboratory tests

The most common diagnostic biochemistry tests include the following plasma parameters: iron, transferrin saturation coefficient (SAT), and serum ferritin (SF). Increased SAT is the earliest biochemical disorder in hemochromatosis, reflecting increased iron absorption. It is >45 % (often >60 % in males and >50 % in females) and should be confirmed by the repeated test. Increased SF (>300 μg/L in males and postmenopausal females, >200 μg/L in premenopausal females) is typical for hemochromatosis, but this may also occur in inflammatory processes, metabolic syndrome (especially in diabetes mellitus), alcohol consumption, and hepatic lesions [26].

2. Genetic testing

Genetic testing is arranged in patients with high SAT provided that other mechanisms are excluded, except for iron excess in the body (especially hypotransferrinemia due to hepatocellular failure, nephrotic syndrome, or malnutrition). Hemochromatosis should be considered not as a simple monogenic disease, but rather as a complex result of interactions between the environment, lifestyle, and genetic factors that have not been yet identified. It is widely thought that homozygous p.C282Y mutations in the *HFE* gene form the necessary basis for iron excess in the body. Regarding p.C282Y/p.H63D compound heterozygosity, it may predispose only to mild iron overload, and the physician should be cautious when informing the patient, as mentioning

hemochromatosis may lead to unnecessary anxiety of the patient and his/her family.

If the genetic testing for *HFE* gene mutations is negative, further genetic tests may be arranged with other genes participating in iron metabolism and hepcidin synthesis. Non-*HFE*-associated hemochromatosis is less prone to the effects of cofactors and is characterized by a more severe and uniform clinical condition manifesting at a younger age. Modern approaches based on the next-generation sequencing (NGS) expand the diagnostic possibilities of rare lesions; however, at the same time they create issues for the interpretation of results. Tertiary centers (both state and private ones) are required for the NGS technology, its costs remain high, though they tend to decrease with time [26].

It should be noted that the direct sequencing tests for *HJV*, *HAMP*, *TFR2*, *SLC40A1,* and even *HFE* genes in most hospitals is not widely available globally. Treatment usually does not depend on molecular diagnosis. Thus, it is important to remember that patients with the clinical diagnosis of hemochromatosis should not wait for the DNA test results in cases of difficult access to genetic identification to start the treatment [27]. Nevertheless, results of genetic tests are important for the prognosis of the disease course and the assessment of risk of giving birth to sick children in the family.

3. Tissue biopsy

Liver biopsy is the best method for the quantifying assessment of iron overload. However, there's no correlation between iron deposition in the liver and myocardium. Liver deposition in the myocardium progresses slower than iron absorption by the liver. Endomyocardial biopsy may be required for patients with cardiac manifestations. Increased iron levels are always detected during endomyocardial biopsy in patients with the left ventricular dysfunction associated with the cardiac hemochromatosis.

4. Imaging methods

Magnetic resonance imaging (MRI) may be useful for the detection and quantification of iron overload in the body, especially in the liver and spleen (the contrast between significant iron overload in the liver and no iron overload in the spleen is common for hemochromatosis). Laboratory tests in combination with MRI have currently replaced liver biopsy in many situations.

Liver ultrasound is often the first diagnostic step when the patient demonstrates increased liver enzyme levels, or the liver disease is suspected. Ultrasound cannot detect iron in the liver tissue, and, thus, it cannot be used to diagnose iron overload in hemochromatosis, though it may be useful in the differential diagnosis to exclude other causes of elevated liver enzymes and non-alcoholic fatty liver disease (NAFLD). Ultrasound may also be used in the diagnosis of liver cirrhosis and hepatocellular carcinoma (HCC).

Ultrasound elastography (Fibroscan®) of the liver was used to evaluate fibrosis in patients with hemochromatosis only in several studies. The issue of whether this method can be used for *HFE*-associated liver fibrosis diagnosis and follow-up should be analyzed additionally [28].

Computed tomography (CT) of the liver can detect iron in the liver parenchyma, however this method requires special scanner programming, is semi-quantitative, and has several sources of errors. After MRI implementation, CT is rarely used to detect iron concentration in the liver, though it may help to visualize focal liver lesions [29].

X-ray of joints is used to evaluate the degree of arthritis. The rheumatological evaluation system based on X-rays of hands, wrists, knees, and ankles was checked in the group of patients with hemochromatosis and arthritis.

Dual-energy X-ray absorptiometry (DXA) is used to determine the bone tissue density in the diagnosis of osteopenia and osteoporosis [30].

- **Treatment of hemochromatosis**

1. Diet therapy

Patients with hemochromatosis should not take oral iron drugs. Consumption of large vitamin C amounts quickly mobilizes iron from the heart, increases the production of free radicals, and causes lethal arrhythmias. Due to this, synthetic vitamin C should not be used in hemochromatosis, though vegetables and fruit rich in vitamin C may be consumed. Alcohol increases iron absorption, while some red wines contain large amount of iron, so they should not be consumed. The low-sodium diet is indicated for patients with cardiomyopathy and heart failure [31].

2. Iron removal

Phlebotomy. Bloodletting remains the main method of *HFE*-associated hemochromatosis treatment. Phlebotomy is also the preferable treatment method in non-*HFE*-associated hemochromatosis; however, additional oral chelation can be used in the most severe cases (e.g., in patients with juvenile hemochromatosis). Bloodletting is also efficient in the treatment of patients with ferroportin disease, though it should be less frequent, accounting for the risk of anemia due to poor iron recirculation in these patients. Many physicians and patients insist that high serum ferritin levels corresponds to iron

overload, and it should be treated with phlebotomy. However, as mentioned earlier, patients without *C282Y* homozygosity may not always have iron overload.

The aim of phlebotomy is to remove excess iron and prevent further tissue damage. Due to ethical issues, phlebotomy was not analyzed in randomized clinical trials, which makes understanding the natural course of non-treated diseases difficult. Although some persons (rarely) believe that phlebotomy use is not evidence-based, the majority of experts think that this iron store depletion form may improve chronic fatigue and cardiac function, stabilize the liver function, reverse liver fibrosis, and decrease skin pigmentation in patients with hemochromatosis. However, joint symptoms are poorly controlled by phlebotomy and may worsen. The efficacy of bloodletting is good if it was started before the development of liver cirrhosis. Adverse phlebotomy effects emerge in 37–50 % of patients and include phlebitis, malaise, fatigue. If adverse effects emerge, increased intervals between procedures are possible [32].

Phlebotomy is usually arranged in the outpatient setting by nurses. The blood volume of 400–500 mL is usually removed within 15–30 min with the patient in the supine position. This process is repeated weekly until the serum ferritin level reaches ~50 μg/L. Hemoglobin level is also assessed, and the phlebotomy regimen is altered if hemoglobin level drops below 11 g/dL (e.g., 400–500 mL during one session once every two weeks). Simultaneous oral fluid administration (e.g., a salty sports drink) in the volume equivalent to that of blood removed during phlebotomy is important to maintain the plasma volume during the procedure. The duration of induction therapy depends on the iron overload severity, spanning from several months to several years. After the induction phase, supportive phlebotomies are conducted to maintain serum ferritin at the levels of ~50 μg/L. If bloodletting is continued after serum ferritin levels reach <20 μg/L, iron deficiency may occur. Serum hepcidin levels may decrease during bloodletting [33]. Supportive phlebotomies are conducted 2–4 times per year, while this depends on the rate of iron reaccumulation, which varies in different patients. Serum ferritin levels are checked 3–6 months after the completion of induction therapy may be useful to evaluate the rate of iron reaccumulation. Serum ferritin levels may be assessed monthly during induction phlebotomy and weekly when serum ferritin levels drop below 100 μg/L. As soon as serum ferritin reaches 50 μg/L, serum ferritin levels may be assessed annually or during each supportive phlebotomy. Although evidence confirming supportive treatment use is lacking, many patients appreciate it, especially if they can become voluntary blood donors [34].

Despite successful iron depot depletion, transferrin saturation remains increased in some patients. It is proposed that normal transferrin saturation maintenance may improve symptoms greater than ferritin decrease. However, transferrin saturation may not decrease until the patient almost reaches iron deficiency; thus, maintenance of corresponding ferritin and transferrin saturation levels may be difficult [35].

Red blood cell exchange in hemochromatosis. Red blood cell exchange is the method of selective red blood cell removal with or without erythropoietin administration. This process removes iron excess from tissues twice faster than whole blood phlebotomy. When analyzing patients with hereditary hemochromatosis, therapeutic red blood cell exchange demonstrated almost 70 % decrease in the total amount and duration of treatment vs. phlebotomy. Terminal cardiomyopathy associated with hereditary hemochromatosis was successfully treated with red blood cell exchange in combination with the left ventricular assist device [36].

Chelating agents. Bloodletting is not a treatment option for patients with anemia (secondary disorders associated with iron overload) and patients with severe heart failure. Iron chelating agents are considered the treatment of choice in these patients. Iron chelating agents increase the rate of iron elimination due to binding iron in plasma and tissues, removing iron excess. Serum ferritin levels should be checked periodically. If serum ferritin levels drop below 1000 ng/mL, iron chelating agents should not be started. Deferoxamine, deferiprone and deferasirox are three iron chelating agents approved by the US Food and Drug administration for the treatment of secondary chronic iron overload.

Deferoxamine is a hexadentate molecule which directly binds to labile iron in plasma and tissues, including the heart. Deferoxamine has low bioavailability with oral administration and a short half-life. This product is administered as subcutaneous or intravenous infusions. The recommended dose for adults is 40–50 mg/kg/day, which is administered within 8–12 hours 5–7 times a week. Deferoxamine treatment decreased myocardial iron levels almost by 24 %, delays the onset of clinical cardiac hemochromatosis manifestations, reverses cardiac hemochromatosis in early stages, improves the left ventricular function, and increases survival in transfusion-dependent patients with thalassemia. However, prolonged compliance with deferoxamine treatment regimen leaves much to be desired [37].

Deferiprone is an orally active bidentate iron chelating agent approved for the treatment of iron overload in patients with transfusion-dependent thalassemia, in whom the current chelating treatment is inadequate. The starting deferiprone dose is 75 mg/kg/day, divided into 3 administrations. The maximum deferiprone dose is 99 mg/kg/day. Several studies demonstrated that deferiprone decreased myocardium levels better than deferoxamine. It was detected that combined deferiprone and deferoxamine treatment quickly decreases iron overload and improves cardiac function in patients with iron overload, heart failure, and unstable hemodynamics [37].

Deferasirox is a tridentate iron chelating agent with good oral bioavailability approved for the treatment of iron overload related to repeated blood transfusions. The starting oral deferasirox dose is 20 μg/day once daily (with the maximum dose of 40 mg/kg/day). Deferasirox decreases serum ferritin levels, decreases iron overload in the heart and liver. New iron chelating agents studied in the treatment of iron overload-associated diseases include silibine, deferitrine, and starch-conjugated deferoxamine. The transcutaneous iron and ferritin excretion using the Al-Hijama method (specific transcutaneous blood volume removal using special pots) is a new method of iron overload method in hemochromatosis, β-thalassemia, and sideroblastic anemia [38].

Investigated methods of hemochromatosis treatment

Hepcidin treatment. Murine models demonstrated that hepcidin analogues decreased iron overload and iron-induced tissue hypertoxicity. Minihepcidins represent smaller hepcidin-like peptides which decreased iron concentration in the myocardium of mice with knocked out hepcidin. Minihepcidins prevented iron overload in the model of severe hemochromatosis in mice with hepcidin deficiency. Minihepcidins may be probably beneficial in iron overload-associated disorders or when used separately for prophylaxis, or as concomitant therapy with phlebotomy or chelation. Natural hepcidin and its analogues are investigated in the treatment of iron overload with hemochromatosis.

Apotransferrin treatment. Several studies demonstrated decreased *Fam132b* (erythroferrone) erythroid gene expression, increased hepcidin gene expression in the liver, increased plasma hepcidin-25 levels, and decreased intestinal ferroportin-1 in mice with thalassemia administered apotransferrin. Apotransferrin treatment requires further analysis regarding the normalization of iron levels in the myocardium and other organs [39].

Gene therapy. Gene therapy of such diseases as β-thalassemia and sickle-cell anemia may prevent the need in blood transfusions and iron overload in tissues. *DMT1* and enterocyte ferroportin gene expression inhibition were recommended as gene therapy targets for patients with hereditary hemochromatosis. Other therapeutic approaches to be investigated include wild-type *HFE* gene overexpression in enterocytes and hepcidin (regulatory iron peptide) overexpression in the liver. Mutations in the *HFE* gene may affect the survival of patients with myelodysplastic syndrome; studies are required to determine whether such patients should be treated with powerful iron chelating agents [40].

- **Cardiac hemochromatosis**

Cardiac hemochromatosis, or primary cardiomyopathy with iron overload, is an important and potentially preventable cause of heart failure. Iron overload-associated cardiomyopathy is defined as systolic or diastolic cardiac dysfunction [41] caused by enhanced iron deposition; it is an important cause of chronic heart failure due to the increased incidence of this pathology observed in patients with thalassemia and in patients with hereditary hemochromatosis. Cardiomyocyte ferroportin regulates cellular iron homeostasis, while the location of iron deposition in the myocardium determines the severity of cardiac dysfunction [42]. Due to intensive metabolism, cardiomyocytes are especially sensitive to toxic iron effects. Consequently, iron deposition in the myocardium may lead to cardiomyopathy and heart failure, which is a relatively later, but potentially fatal manifestation of hemochromatosis [43]. Myocardium is especially sensitive to iron-induced oxidative stress due to a large amount of mitochrondria and low antioxidant levels.

The iron from transfusion sources is more likely to accumulate in the heart than the orally taken one. During cardiac iron accumulation, iron predominantly deposits in epicardial myocytes, while affecting the whole wall thickness only later. Cardiac iron overload initially leads to increased perinuclear iron deposition with subsequent deposition in the whole cell. Iron deposition is more widespread in ventricles than in atria. The cardiac conductive system is often involved. Myocardial dysfunction severity correlates with the amount of iron deposition in the myocardium. As iron deposits enhance in the myocardium, this leads to increased left ventricular wall thickness. This may lead to decreased

left ventricular compliance, decreased systolic function, and dilation [44].

Factors affecting the penetrance include sex, age, physiological and pathological blood losses, blood donation, dietary iron and alcohol consumption, hepatitis B and C, obesity, administration of dietary supplements (with iron and vitamin C) [45].

Mechanical alterations associated with myocardial hemochromatosis are aggravated by cytotoxic iron effects inside myocytes. Iron in these cells abruptly accelerates the production of hydroxyl ions, extremely reactive free oxygen radicals which may destroy the cellular lipid bilayer, lysosomes, membranes of other organelles, leading to cellular dysfunction and death.

- **Clinical features of cardiac hemochromatosis**

Clinical signs of cardiac hemochromatosis may be divided into three categories, including arrhythmias, congestive failure due to systolic dysfunction, and congestive failure due to diastolic dysfunction [43].

Hemochromatosis and arrhythmias. Patients with cardiac hemochromatosis often develop atrial and ventricular arrhythmias and blocks due to myocardial dysfunction and iron deposition in the atrioventricular node and the conductive system. Symptoms may include simple palpitations or overt syncope. Palpitations are routine and detected in 37 % of patients. Irregular palpitations may be associated with atrial fibrillation, premature atrial or ventricular contractions, or sinus arrhythmia. Regular, fast palpitations may be related to paroxysmal supraventricular tachycardia, sustained or non-sustained ventricular tachycardia, or atrial flutter. Palpitations may be accompanied by dizziness, chest discomfort, diaphoresis, and dyspnea. Several patients may develop symptoms of pre-syncope or overt syncope associated with bradyarrhythmias, including inadequate sinus bradycardia, 2nd degree (Mobitz II) or even 3rd degree atrioventricular block. Some patients may experience dizziness before losing consciousness, but in other situations no preliminary signs develop before Adams-Stokes attacks. Patients with sick sinus syndrome may manifest with palpitations due to tachycardia alternating with dizziness due to bradycardia. This tachy-brady syndrome may be the result of alternating atrial fibrillation with quick conductivity and subsequent spontaneous conversion to sinus rhythm with significant sinus bradycardia. The diagnostic evaluation in a patient with arrhythmia does not differ depending on whether arrhythmias are caused by hemochromatosis or any other disease. This includes electrocardiography with subsequent Holter monitoring or even longer cardiac event monitoring. If these test results are not decisive, cardiac catheterization and electrophysiological study may be required [43].

Chronic heart failure. By the time chronic heart failure develops due to cardiac hemochromatosis, the diagnosis of this disease has already been verified in the majority of cases based on other existing symptoms. If chronic heart failure is the main manifestation of hemochromatosis, dyspnea on physical exertion with gradually decreasing load tolerance may develop in the disease onset, followed by paroxysmal nocturnal dyspnea (the patient is in a forced position with the elevated head end of the bed (lying on high pillows) — orthopnea); later, dyspnea may emerge even at rest, and pulmonary edema may develop. Patients with higher iron deposition in the right ventricle than the left one may develop right ventricular failure. With isolated right ventricular heart failure, dyspnea is not prominent, and pulmonary congestion is absent. In such patients symptoms include peripheral edema, weakness, and fatigue. Congestive hepatomegaly may cause discomfort, which is usually described as dull pain or heaviness in the right upper abdominal quadrant or epigastrium. This pain may be caused by the hepatic capsule distension; it may be intensive with the quickly increased size of the liver in acute right ventricular failure. Physical signs of chronic heart failure in cardiac hemochromatosis also include increased jugular venous pressure, positive hepatojugular reflux, pleural effusion, and ascites. Cardiomegaly may be accompanied by the lateral point of maximum impulse shift, emergence of pathological additional S3 and S4 heart sounds (gallop rhythm), systolic murmurs or mitral and/or tricuspid regurgitation associated with dilation of the left or right ventricles. These murmurs often decrease or disappear after the restoration of the cardiac function [45].

- **Diagnosis**

Biochemistry tests. Cardiac hemochromatosis should be suspected in any patient with unexplained heart failure. Systemic iron overload should be screened for using serum ferritin and transferrin saturation. If the results of these tests correspond to iron overload, subsequent non-invasive and histological investigations are indicated to confirm organ lesions due to iron overload.

Guidelines recommend that plasma transferrin saturation levels are over 55 %, while serum ferritin levels are over 200 ng/mL in females or 300 ng/mL in males when diagnosing patients with iron overload. As serum ferritin is an acute phase reactant, it is not robust in diseases with active inflammation. Serum iron studies

are beneficial for screening for total iron overload, but are not robust in the diagnosis of organ-specific overload (i.e. cardiac iron). Serum ferritin levels do not correlate with the myocardial iron overload severity. Despite low serum ferritin levels, myocardial deposition levels may be high. A strong correlation exists between plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and iron overload parameters [46].

Tissue biopsy. Liver biopsy is the best method for the quantifying assessment of iron overload. However, there's no correlation between iron deposition in the liver and myocardium. Liver deposition in the myocardium progresses slower than iron absorption by the liver. Endomyocardial biopsy may be required for patients with cardiac manifestations. Myocardial iron is constantly detected in endomyocardial biopsy specimens in patients with left ventricular dysfunction resulting from cardiac hemochromatosis.

Electrocardiography data. Electrocardiography (ECG) is usually not of diagnostic value in early cardiac hemochromatosis. In advanced cardiac hemochromatosis, ECG demonstrates low QRS voltage and non-specific ST/T anomalies. Atrial tachyarrhythmias (especially paroxysmal atrial fibrillation) are commonly observed. Ventricular arrhythmias develop with LVEF decrease. Iron deposition in the conductive system may cause 1st degree, 2nd degree, or complete atrioventricular blocks.

Echocardiography data. In early cardiac hemochromatosis lesions, echocardiography may detect left ventricular diastolic dysfunction associated with the impaired relaxation of the left ventricle or its restriction. Signs typical for dilated cardiomyopathy (phenocopy) with reduced LVEF typically develop later. Patients with cardiac hemochromatosis may demonstrate dilation of the left or right heart chambers and reduced LVEF, or left atrium and right ventricle dilation with increased pulmonary artery pressure and normal LVEF. Eccentric left ventricular hypertrophy may develop as well. Tissue Doppler echocardiography may be used to diagnose diastolic left ventricular dysfunction in early cardiac hemochromatosis stages [29].

Cardiac magnetic resonance imaging. Although echocardiography may be used to detect myocardial iron overload, it does not accurately predict iron levels in the myocardium. MRI provides quantification of the myocardial iron loads. In patients with cardiac hemochromatosis, iron-overloaded myocardium demonstrates changes in the signal intensity and sensitivity with a shorter relaxation time and a quicker image darkening associated with paramagnetic iron effects. The relaxation time may be measured using the spin echo method, in which signals are refocused using a special radiofrequency impulse or small magnetic fields called gradients (gradient echo) in specific time intervals (echo time). Relaxation decay time constant inversely correlates with myocardial iron levels. The larger myocardial iron levels, the shorter are T2 and T2* — spin echo decay time constant and gradient echo-induced relaxation time, respectively. Spin echo is less sensitive than gradient echo to evaluate myocardial iron levels. T2* method is more sensitive and highly specific for quantification and longitudinal follow-up of myocardial iron deposition. A good inverse correlation exists between the T2* in the patient's myocardium and LVEF, as well T2* in the patient's myocardium significantly correlates with the requirements for cardiac hemochromatosis treatment [47].

T2* relaxation time is determined by iron in the hemosiderin form, but not iron in the labile cellular or ferritin form, accurately predicting myocardial iron levels. Clinical severity of myocardial iron overload in cardiac hemochromatosis is evaluated using T2* values. Patients with T2* relaxation time over 20 ms have a low risk of congestive heart failure. Patients with T2* relaxation time 10–20 ms probably have myocardial iron deposits, thus having an intermediate risk of congestive heart failure. Patients with T2* relaxation time less than 10 ms have a high risk of congestive heart failure and require chelation therapy [47].

- **Treatment of cardiac hemochromatosis**

Treatment of iron overload conditions is important to prevent or eliminate cardiac dysfunction. Iron excess removal from tissues in these patients leads to minimum formation of free radicals, decreasing organ damage. The treatment to remove excess iron stores includes therapeutic phlebotomy and iron chelating agents. Treatment of the main disease causing iron overload and diet therapy are also important when treating cardiac hemochromatosis. Diet therapy includes abstaining from taking drug-induced iron, mineral supplements, excess vitamin C, and raw seafood. Congestive heart failure should be treated using the standard drug therapy of heart failure [48].

Therapeutic phlebotomy in cardiac hemochromatosis. Phlebotomy decreases myocardial iron levels and improves left ventricular diameter, left ventricular fractional shortening, LVEF, left ventricular weight, and left atrial size in these patients. Treatment of cardiomyopathy-associated congestive heart failure and serious arrhythmias in patients with cardiac hemochromatosis

should be used until therapeutic phlebotomy (sometimes in combination with iron chelating therapy) decreases excess myocardial iron levels.

Heart transplant in cardiac hemochromatosis. Heart transplant is a therapeutic option for patients with cardiac hemochromatosis and severe heart failure refractory to optimal conservative treatment and cardiac resynchronization therapy. Out of 16 patients that underwent heart transplant associated with iron overload cardiomyopathy, etiology was distributed as follows: primary hemochromatosis in 11 patients, thalassemia major in 4 patients, Diamond-Blackfan anemia in 1 patient. 30-day mortality was 12 %, while 3 deaths were related to infectious complications. Actuarial survival (Kaplan-Meier method) in 1, 3, and 5 years was 81 %, 81 %, and 81 %, respectively. 10-year actuarial survival was 41 % [49].

Congestive heart failure after liver transplant may require the use of a biventricular assist device. Combined heart and liver transplant is indicated in patients with severe cardiomyopathy associated with iron overload and liver cirrhosis. All these patients should continue therapy to decrease iron overload and prevent hemochromatosis of the transplanted heart. In patients with secondary iron overload (i.e. myelodysplastic syndrome, sickle cell anemia, β-thalassemia, Diamond-Blackfan syndrome), hematopoietic stem cell transplant may decrease blood transfusion requirements and slow down the rate of iron overload in these patients [50].

Investigated methods of cardiac hemochromatosis treatment

Calcium channel blockers. L-type and T-type Ca2+-channels provide the main pathway for iron influx into cardiomyocytes in iron overload cardiomyopathy. It was demonstrated that amlodipine decreased iron absorption and production of free oxygen radicals in murine hearts with chronic iron overload. Therapy with calcium channel blockers (nifedipine, verapamil, efonidipine) and the divalent metal transporter 1 (ebselen) demonstrated decreased iron deposition in the heart, cardiac malonic dialdehyde and plasma non-transferrin-bound iron levels, as well as improved cardiac rhythm variability and left ventricular function in mice with thalassemia and iron overload. Efonidipine and ebselen decreased mortality in such mice. Further studies are required to determine whether calcium channel blockers may be effective in the prevention and treatment of iron overload cardiomyopathy [51].

Conclusion

Hemochromatosis is a multisystemic disease, which starting symptoms include fatigue, arthralgia, decreased libido, erectile dysfunction, signs of hepatic, cardiac lesions, and diabetes mellitus. These are subsequently followed by organ dysfunction with the emergence of such lesions as liver cirrhosis, cardiomyopathy, pancreatic fibrosis, and osteoporosis. Timely detection of this systemic disease may prevent multiple organ damage. Biochemical parameters and T2* relaxation time in cardiac MRI are not only of diagnostic value, but also help to quantify the therapeutic effect. Treatment includes phlebotomy and iron chelating agents which provide normal survival in pre-clinical and early clinical stages. Specific chelation, red blood cell exchange, and standard treatment of heart failure may demonstrate significant benefits even in the late stage. As symptoms and organ lesions are often irreversible, it is important to start the treatment as soon as possible, before symptoms and organ dysfunction develop.

Вклад авторов:

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

Резник Е.В.: идея, руководство, организация работы, редактирование рукописи

Лауар М.Х.Э.: анализ публикаций по теме, написание обзора литературы

Воинова В.Ю.: генетическое консультирование, редактирование рукописи

Голухов Г.Н.: организация работы, редактирование 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

Reznik E.V.: idea, leadership, work organization, edition

Laouar M.H.E.: literature review, writing of article

Voinova V.Yu.: genetic consulting, edition

Golukhov G.N.: work organization, edition

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DOI: 10.20514/2226-6704-2024-14-6-457-466
УДК 616.248-036.11-085.234
EDN: TZBRYB

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ДОСТИЖЕНИЕ КОНТРОЛЯ ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМЫ ПРИ ИСПОЛЬЗОВАНИИ ПРЕПАРАТА ДУПИЛУМАБ

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Achievement of Control of Severe Bronchial Asthma When Using Dupilumab

Резюме

Цель исследования оценить возможность достижения контроля тяжелой бронхиальной астмы (БА) при использовании генно-инженерной биологической терапии препаратом Дупилумаб. Материалы и методы. Обследовано 32 пациента тяжелой бронхиальной астмой (8 (25 %) мужчин, средний возраст 58 [28;65]) лет, 24 (75 %) женщин, средний возраст 50 [26;62] лет), которые получали дополнительную терапию препаратом Дупилумаб в течение 12 месяцев. Конечная точка исследования 12 месяцев терапии препаратом Дупилумаб. Аллергический фенотип заболевания регистрировался у 19 (60 %) пациентов, у четверти пациентов — неаллергический и у 5 (15 %) пациентов наблюдалась смешанная БА. Результаты. До назначения генно — инженерной биологической терапии (ГИБТ) у пациентов отмечалась крайне высокая каждодневная потребность в скоропомощных препаратах — около 9 раз в сутки, регистрировались 4 и более обострений в течение предшествующих 12 месяцев до включения в исследование. Спустя 12 месяцев дополнительной терапии препаратом Дупилумаб отмечалось значительное снижение симптомов — у 22 (70 %) пациентов полностью отсутствовали приступы удушья. У 6 пациентов (19 %) в течение последующих 12 месяцев развилось 1 обострение БА, с которым пациенты справились самостоятельно при помощи небулайзерной терапии в домашних условиях. До начала генно-инженерной биологической терапии 10 человек (31 %) получали системные глюкокортикостероиды (СГКС) в дозе от 10 до 5 мг по преднизолону. Через 4 месяца 22 (70 %) пациентам, получающим гормональные препараты, удалось от них отказаться. Через 12 месяцев ни один пациент не принимал СГКС. Заключение. В течение 12 месяцев дополнительной терапии препаратом Дупилумаб пациентам удалось полностью отказаться от приема СГКС. Обострения, требующие госпитализаций, отсутствовали у всех пациентов, включенных в исследование. Полный контроль достигли 22 (69 %) исследуемых, частичный контроль — 10 (31 %). Полностью отсутствовала потребность в короткодействующий бета-агонистов (КДБА) у 27 (85 %) исследуемых.

Ключевые слова: *тяжелая бронхиальная астма, дупилумаб, достижение контроля, генно-инженерная биологическая терапия*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Локально-этический комитет КГБУЗ «Краевая клиническая больница» г. Красноярск, и локально-этический комитет ФГБОУ ВО КрасГМУ им. проф. В.Ф. Войно-Ясенецкого Минздрава России одобрил исследование (Протокол № 122/2023 от 29 ноября 2023 года). Лекарственные препараты пациенты получали как региональные или федеральные льготополучатели

Статья получена 12.06.2024 г.
Одобрена рецензентом 02.08.2024 г.
Принята к публикации 22.10.2024 г.

Для цитирования: Казмерчук О.В., Собко Е.А., Демко И.В. ДОСТИЖЕНИЕ КОНТРОЛЯ ТЯЖЕЛОЙ БРОНХИАЛЬНОЙ АСТМЫ ПРИ ИСПОЛЬЗОВАНИИ ПРЕПАРАТА ДУПИЛУМАБ. Архивъ внутренней медицины. 2024; 14(6): 457-466. DOI: 10.20514/2226-6704-2024-14-6-457-466. EDN: TZBRYB

Abstract

The aim of the study was to evaluate the possibility of achieving control of severe bronchial asthma (BA) using genetically engineered biological therapy with Dupilumab. Materials and methods. The study included 32 patients with severe bronchial asthma (8 (25 %) men, mean age 58 [28; 65]) years, 24 (75 %) women, mean age 50 [26; 62] years) who received additional therapy with Dupilumab for 12 months. The endpoint of the study was 12 months of therapy with Dupilumab. The allergic phenotype of the disease was recorded in 19 (60 %) patients, a quarter of patients had non-allergic phenotype, and 5 (15 %) patients had mixed BA. Results. Before the introduction of genetically engineered biological therapy, patients had an extremely high daily need for emergency medications — about 9 times a day, 4 or more exacerbations were recorded during the previous 12 months before inclusion in the study. After 12 months of additional therapy with Dupilumab, a significant reduction in symptoms was noted — 22 (70 %) patients did not have asthma attacks at all. In 6 patients (19 %), 1 exacerbation of bronchial asthma developed during the next 12 months, which the patients coped with independently using nebulizer therapy at home. Before the start of genetically engineered biological therapy, 10 people (31 %) received systemic glucocorticosteroids (OCS) at a dose of 10 to 5 mg of prednisolone. After 4 months, 22 (70 %) patients receiving hormonal drugs managed to stop them. After 12 months, no patients took OCS. Conclusion. During 12 months of additional therapy with Dupilumab, patients managed to completely stop taking OCS. Exacerbations requiring hospitalization were absent in all patients included in the study. Complete control was achieved by 22 (69 %) subjects, partial control was achieved by 10 (31 %). There was no need for short-acting beta-agonists (SABA) in 27 (85 %) subjects.

Key words: *severe bronchial asthma, dupilumab, achieving control, genetically engineered biological therapy*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Conformity with the principles of ethics

The Local Ethics Committee of the Krasnoyarsk Regional Clinical Hospital and the Local Ethics Committee of the Federal State Budgetary Educational Institution of Higher Education Krasnoyarsk State Medical University named after prof. V.F. Voyno-Yasenetsky of the Ministry of Health of the Russian Federation approved the study (Protocol No. 122/2023 dated November 29, 2023). Patients received medications as regional or federal beneficiaries

Article received on 12.06.2024
Reviewer approved 02.08.2024
Accepted for publication on 22.10.2024

For citation: Kazmerchuk O.V., Sobko E.A., Demko I.V. Achievement of Control of Severe Bronchial Asthma When Using Dupilumab. The Russian Archives of Internal Medicine. 2024; 14(6): 457-466. DOI: 10.20514/2226-6704-2024-14-6-457-466. EDN: TZBRYB

ALT — antileukotrienes, BA — bronchial asthma, BT — biological therapy, LAACA — long-acting anticholinergic agents, LABA — long-acting beta-agonists, ICS — inhaled corticosteroids, NSAIDs – non-steroid anti-inflammatory drugs, FEV_1 — forced expiratory volume in one second, SCS — systemic corticosteroids, SBA — severe bronchial asthma, FVC — maximum air volume that can be exhaled after the maximum deep inspiration.

Introduction

Bronchial asthma (BA) is the second most common chronic respiratory disease in the world reported in almost 330 million patients [1]. Approximately 1.6 million patients with BA are verified just in Russia based on official historical data [2]. However, epidemiological studies demonstrate that this parameter may be significantly higher — around 6 million people [3]. The latest studies have confirmed significant economic effects of BA burden on vulnerable social population strata. Due to this, analysis of the disease course, dedicated costs, and socioeconomic factors becomes the main studied object [4, 5].

The term “socioeconomic burden” includes not only high treatment costs (direct medical expenses), but also costs associated with both temporary or permanent

disability (direct non-medical expenses), limited physical and social activity, and, thus, decreased quality of life of patients and their family members (indirect expenses) [6]. According to the World Health Organization definition, global disease burden is measured by the number of living years lost due to disability. This definition combines living years lost due to the health condition which does not comply with full health criteria and living years lost due to premature mortality [7].

Within the latest decade, severe bronchial asthma (SBA) treatment should be significantly improved thanks to the availability of biological therapy modifying specific cellular signaling pathways. In particular, Dupilumab, a fully human monoclonal antibody, blocks interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling via specific binding with the IL-4Rα-subunit which is common for IL-4 and IL-13 receptor complexes. The drug also blocks IL-4 signaling via type I receptors (IL-4Rα/γc) and IL-4/IL-13 common signaling via type II receptors (IL-4Rα/IL-13Rα). IL-4 and IL-13 are key type 2 inflammatory cytokines (including produced by Th2-lymphocytes) involved in the pathogenesis of atopic diseases [8]. The drug was approved in adults and children over 6 years of age as additional SBA treatment [9]. According to the European Medicines Registry, Dupilumab is recommended in SBA associated with Th2-inflammation, which is characterized by high eosinophil count in peripheral blood, increased nitric oxide levels (FeNO) in the exhaled air, with the requirements for systemic corticosteroids (SCS) in adult patients with allergic BA [10].

Treatment with Dupilumab demonstrates significant therapeutic effects confirmed in many randomized clinical trials (RCTs) [11, 12]. It should be noted that the additional drug therapy provided the increased probability that SCS would not be required and improved clinical outcomes regardless of the SCS dose in patients with steroid-dependent SBA [13, 14, 15].

Aim of the study

Evaluating the possibility of achieving severe bronchial asthma control when using biological therapy with Dupilumab.

Study materials and methods

32 patients with severe bronchial asthma were included into the prospective open observational single-center study: 8 (25 %) males with an average age of 58 [28;65] years and 24 (75 %) females with an average age of 50 [26;62] years followed up in the Pulmonary-Allergy Center of KSBHI "Krai Clinical Hospital" (Krasnoyarsk, Russia). All respondents had their concomitant diseases determined, pulmonary function tests and disease control level assessed, the scope of basic therapy available was clarified as well. The primary endpoint of the study was to assess the efficacy and safety of Dupilumab, to determine the possibility of achieving SBA control. Important study milestones: before starting biological therapy (BT) and 12 months after initiating BT.

Study inclusion criteria: severe BA; age 18-75 years, reversible bronchial obstruction confirmed by pulmonary function tests; basic therapy compliance, possibility of correct basic therapy use, scope of basic therapy corresponding to Steps 4-5 (GINA 2023).

Exclusion criteria: mild or moderate BA, COPD, difficult-to-control BA, malignancies, severe renal or hepatic failure, pregnant and breastfeeding females.

The study was approved by the Local Ethics Committee of KSBHI «Krai Clinical Hospital» (Krasnoyarsk, Russia) and the Local Ethics Committee of FSBEI HE KrasSMU named after Prof. V.F. Voino-Yasenetsky, Ministry of Health of Russia (Protocol No. 122/2023 dated November 29, 2023). The patients received drug products as regional or federal benefit recipients.

All patients signed consents for personal data processing.

The diagnosis of severe BA was established based on the scope of basic anti-inflammatory therapy corresponding to Step V according to GINA 2023 guidelines that was administered to patients included into the study [9, 18].

Patients demonstrated correct inhalation technique and had high compliance with the basic therapy.

It should be noted that early disease onset (before 6 years of age) was observed in 2 (6 %) patients included in the study; before 20 years of age — in 8 (25 %) patients with SBA, over 40 years of age — in 11 (34 %) patients. Prolonged disease history is worth noting: in 22 (70 %) patients BA duration was over 20 years. Allergic disease phenotype was reported in 19 (60 %) patients, non-allergic phenotype — in a quarter of patients, and mixed BA — in 5 (15 %) patients. Allergic rhinitis was predominant in the structure of comorbidities, its prevalence was 18 (56.2 %) persons; chronic rhinosinusitis polyposa — in half of patients; non-steroid anti-inflammatory drug (NSAID) intolerance — in 7 (22 %) patients. 25 (78 %), i.e. the majority of patients with SBA were overweight, while the normal body mass index was observed in 7 persons (22 %).

Table 1. Characteristics of patients with severe bronchial asthma included in the study

Indicator		Severe BA (n = 32)
Age, years Me [IQR]		56 [33; 68]
Phenotype	Allergic	19 / 60 %
	Non-allergic	8 / 25 %
	Mixed	5 / 15 %
Gender:	Female, abs/%	24 / 75 %
	Men, abs/%	8 / 25 %
Duration of the disease, years Me [IQR]		22,0 [2,0; 55,0]
Age of disease onset, years Me [IQR]		33,0 [5,0; 56,0]
Comorbid pathology:		
Allergic rhinitis, abs/%		18 / 56,2 %
NSAID intolerance, abs/%		7 / 21,9 %
Chronic polypous rhinosinusitis, abs/%		16 / 50 %
Body mass index, kg/m^2 Me [IQR]		28,5 [21,9; 44,1]

Note: BA — bronchial asthma, NSAID — non-steroidal anti-inflammatory drugs, n — quantitative characteristic accepted in mathematics, abs — absolute number of patients

The general clinical examination included the patient's interrogation (complaints, history); physical data (visual examination, auscultation). Bronchial obstruction severity was clinically evaluated by the number of daily asthma attacks, frequency of nocturnal symptoms, number of daily β2-agonist inhalations.

All patients had the allergy examination in the history, which included skin tests and/or detection of specific IgE.

The pulmonary function parameters were recorded using the ErichEger general pletysmography device (Germany). The bronchial patency condition was evaluated using the pulmonary function tests coupled with the bronchodilator test (400 μg of salbutamol). Pulmonary function tests were arranged in accordance with the quality standards of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) [19].

BA control was assessed using the ACQ-5 (Asthma Control Questionnaire — 5) questionnaire [9], which allows to determine the control level and risk of future exacerbations. The ACQ-5 test consists of 5 questions with the 6-point rating scale for answers. The total ACQ-5 score is calculated as the mean for 5 answers: 0.5-0.75 — adequate control; 0.75-1.5 — intermediate control; 1.5 — uncontrollable asthma.

BA control level was also assessed using the ACT (Asthma Control Test) test [9]. The questionnaire included 5 questions with a 5-point rating scale for answers. The total ACT score was determined as the sum of points: <20 points — no control; 20-24 points — partial control; 25 points — total control of BA symptoms.

All respondents were administered treatment corresponding to Step V (GINA 2023) [9] and demonstrated high treatment compliance. All concomitant diseases were compensated.

The criterion for administering additional Dupilumab treatment presumed not achieving BA control with the standard treatment scope. Administration of the biological agent Dupilumab is recommended in patients aged ≥12 years with the eosinophilic asthma phenotype (eosinophil count in peripheral blood ≥150 cells/μL) or in patients with hormone-dependent asthma administered oral corticosteroids (regardless of the eosinophil count in peripheral blood).

Data were statistically processed using Microsoft Office Excel, 2010 (version 14.0.7261.5000) and 2009 software. Quantifiable values were presented as medians (Me) and the interquartile range (Q1 and Q3), where Q1 corresponded to the 25th percentile, and Q3 — to the 75th percentile. When analyzing samples for normal distribution using the Kolmogoroff-Smirnoff method and the Shapiro-Wilk test, all data were distributed non-normally. In the comparative group analysis based on quantifiable signs, the non-parametric Wilcoxon test was used ($p < 0.05$). The comparative analysis of differences in qualitative signs was provided with the χ^2 test and the Yates' correction.

Cost calculations. Costs were calculated using the model built in the Microsoft Office Excel, 2010 software. The time horizon of 12 months was used for the scenario of the analysis presented in the article. Compulsory medical insurance system costs based on the existing tariffs were calculated as part of evaluating costs for each patient's treatment strategy. We evaluated only direct medical expenses in our study. Accounting for the fact that SBA is a chronic disease requiring prolonged treatment and follow-up, the analysis included the evaluation of costs at several stages, the final formula was as follows:

$$Cost = Cost\ (basic\ therapy) + Cost\ (outpatient\ treatment) + Cost\ (inpatient\ treatment) + Cost\ (ambulance\ calls),$$

where Cost is the total treatment costs,

Cost (basic therapy),

Cost (outpatient treatment),

Cost (inpatient treatment),

Cost (ambulance calls).

Medical care costs for adult patients with SBA were evaluated accounting for direct medical expenses (drug treatment and various medical care types) [16].

Study results and discussion

Clinical and functional characteristics of patients with SBA included in the study are presented in Table 2. Before initiating BT, patients had very high everyday requirements in emergency drugs — approximately 9 times a day. Patients had daytime symptoms up to 7 times a day and nocturnal awakenings due to BA attacks up to twice a night. At least 4 exacerbations were recorded within 12 months preceding the study inclusion, and most of them required inpatient hospitalization. Ambulance team calls were reported in each patient with SBA (at least 5 times during the previous year).

Significantly decreased symptoms were observed 12 months after additional Dupilumab treatment. Thus, 22 (70 %) patients had no attacks, while in 10 (30 %) patients asthma attacks developed 3-4 times a week. 1 BA exacerbation developed in 6 (18 %) patients within the following 12 months, though patients coped with them spontaneously using nebulizer therapy at home.

Clinical symptoms were objectified with ACQ-5 and ACT tests, which results (see Table 2) confirm no BA control in each patient included into the study (ACQ-5 > 1.5 points, ACT-test < 20 points).

Table 2. *Clinical and functional indicators of patients with severe bronchial asthma included in the study, before the appointment of GIBT and 12 months after the appointment of GIBT*

Indicator	Before the appointment of the GIBT	12 months after appointment GIBT	The significance of differences
	Me [Q_1; Q_3]	Me [Q_1; Q_3]	
Number of daytime attacks, o/day	7,0 [4,0; 13,0] *	1,0 [0,0; 1,0] *	P_{1-2} = 0,003
Number of night attacks, o/day	2,0 [1,0; 5,0] *	0,0 [0,0; 0,0] *	P_{1-2} = 0,008
Need for SABA, o/day	9,0 [8,0; 16,0] *	1,0 [0,0; 1,0] *	P_{1-2} = 0,003
Number of exacerbations, o/year	4,0 [3,0; 7,0] *	1,0 [0,0; 1,0] *	P_{1-2} = 0,005
Number of hospitalizations, o/year	4,0 [4,0; 7,0] *	0,0 [0,0; 0,0] *	P_{1-2} = 0,01
Number of visits to the clinic, o/year	3,0 [2,0; 6,0] *	0,0 [0,0; 1,0] *	P_{1-2} = 0,001
Number of EMS calls, o/year	5,0 [2,0; 12,0] *	0,0 [0,0; 0,0] *	P_{1-2} = 0,003
ACQ-5, point	3,0 [1,5; 5,0] *	0,0 [0,0; 1,0] *	P_{1-2} = 0,009
ACT, point	15,0 [8,0; 19,0] *	24 [22,0; 25,0] *	P_{1-2} = 0,007
FEV1, %	63,11 [21,1; 86,8]	90,6 [51,0; 119,9]	P_{1-2} = 0,1
FEV1/FVC, %	63,6 [46,9; 75,3]*	72,3 [51,2; 79,4] *	P_{1-2} = 0,055
Growth, %	21,2 [2,4; 40,3]	9,4 [4,8; 17,9]	P_{1-2} = 0,1
Growth, ml	223 [162,0; 219,0]	31,0 [0,0; 180,0]	P_{1-2} = 0,12

Note. p* — differences between groups in quantitative characteristics were carried out using the Wilcoxon test for two dependent samples (p <0.05), GIBT — genetic engineering biological therapy, SABA — short-acting beta-agonists, EMS — emergency medical care, ACQ — Asthma Control Questionnaire–5 / asthma control questionnaire, ACT — Asthma Control test / asthma control test; FEV1 — forced expiratory volume in the first second, FEV1/FVC — the ratio of the forced expiratory volume in the first second to the forced vital capacity of the lungs, o/day — number of times during the day, o/year — number of times during the previous year

The majority of patients achieved maximum control levels, with the ACQ-5 parameter of 0 points in 12 months (p=0.009). Meanwhile, ACT results increased from 15 to 22 points (p=0.007).

Before biological therapy, FEV_1 level <80 % was reported in 20 (62 %) people. 13 (41 %) people had fixed respiratory pathway obstruction, with FEV_1/FVC parameters below 70 %. When evaluating pulmonary function parameters after 12 months of additional Dupilumab treatment, FEV1 increased to reference levels in 22 (70 %) patients. Fixed respiratory pathway obstruction (FEV_1/FVC < 70 %) was determined only in 6 (18 %) patients included in the study.

12 months of additional treatment with Dupilumab led to significant decrease in the number of asthma attacks (p=0.003), nocturnal asthma attacks (p=0.008), daily SABA requirements (p=0.03), and ambulance calls (p=0.003) (Table 2).

Results of analysis of the basic therapy scope in patients with severe asthma, before initiating BT, and after 12 months after initiating BT are presented in Table 3.

Before starting biological therapy with Dupilumab, 10 (30 %) humans were administered SCS in doses of 10 to 5 mg (equivalent to prednisolone). 12 months later, no patients required daily SCS use (p=0.017). Such progressive results are associated with the fact that the majority of patients used small prednisolone doses. BT administration provided the possibility of increasing the number of patients using the double ICS + LABA combination from 10 (31 %) to 23 (72 %) (p=0.03).

Thus, almost complete control achievement did not only decrease the scope of situational SABA requirements, but also provided the possibility of complete SCS discontinuation and decreased the basic therapy scope.

Comparative analysis of direct medical expenses

During the first step, direct medical expenses for BT were determined for the current clinical practice.

For the modeled practice of using Dupilumab in adult patients with SBA, the following dosing regimen was accounted for: starting dose 600 mg subcutaneously (2 injections x 300 mg), followed by 300 mg subcutaneously once every two weeks. This means that one patient required 13 Dupilumab packages, while 32 patients — 416 packages within 12 months. The cost of 1 Dupilumab package is 87,536 rubles, thus the annual Dupilumab costs are 36,414,976 rubles per 32 patients with severe bronchial asthma.

Basic therapy costs in patients with SBA included in the study before BT initiation were 1,101,136 rubles, basic therapy costs after 12 months of BT treatment were 918,600.2 rubles (Table 4). For all drugs included into the List of Vital and Essential Drugs (LVED), registered

Table 3. *Volume of basic therapy received by patients with severe bronchial asthma, before the appointment of GIBT and 12 months after the appointment of GIBT*

Indicator	Before the appointment of the GIBT	The significance of differences GIBT	The significance of differences
Inhaled glucocorticosteroids + long-acting beta-agonists (ICS + LABA)	10 / 31 %	23 / 72 %	P_{1-2} = 0,003
Inhaled glucocorticosteroids + long-acting beta-agonists + systemic glucocorticosteroids (ICS + LABA + OCS)	7 / 22 %	0 / 0 %	P_{1-2} = 0,017
Inhaled glucocorticosteroids + long-acting beta-agonists, + antileukotrienes (ICS + LABA + ALT)	2 / 6 %	1 / 3 %	P_{1-2} =0,5
Inhaled glucocorticosteroids + long-acting beta-agonists + long-acting anticholinergics (ICS + LABA + LAMA)	5 / 16 %	5 / 16 %	P_{1-2} =0,7
Inhaled glucocorticosteroids + long-acting beta-agonists + antileukotrienes + long-acting anticholinergics (ICS + LABA + ALT + LAMA)	5 / 16 %	3 / 9 %	P_{1-2} =0,7
Inhaled glucocorticosteroids + long-acting beta-agonists + antileukotrienes + long-acting anticholinergics + systemic glucocorticosteroids (ICS + LABA + LAMA + ALT + OCS)	1 / 3 %	0 / 0 %	P_{1-2} =1
Inhaled glucocorticosteroids + long-acting beta-agonists + long-acting anticholinergics + systemic glucocorticosteroids (ICS + LABA + LAMA + OCS)	2 / 6 %	0 / 0 %	P_{1-2} =0,47

Note: p* — differences between groups in qualitative characteristics were carried out using the $\chi 2$ criterion with Yates Amendment (p <0.05), GIBT — genetic engineering biological therapy, ICS — Inhaled glucocorticosteroids, LABA — long-acting beta-agonists, LAMA — long-acting anticholinergics, OCS — systemic glucocorticosteroids, ALT — antileukotrienes.

prices with VAT and regional wholesale uplift were accounted for; distributor data were considered for other drugs. Costs were calculated based on the international nonproprietary name (INN) accounting for the dosage form.

The annual number of SBA exacerbations requiring inpatient treatment was 166 hospitalizations for all patients included into the study. According to the Tariff Agreement of the Territorial Department of Compulsory Medical Insurance of Krasnoyarsk Krai (Russia), the cost for 1 completed SBA inpatient treatment case was 50,000 rubles. Costs per 1 outpatient (therapeutic) physician visit was 405 rubles (primary visit) and 1673 rubles (repeated counseling). With that, an average of 2 outpatient visits is required for the treatment of 1 SBA exacerbation episode. It should be noted that the elective (therapeutic) physician visits are arranged 3 times yearly for all patients with SBA. Costs for 1 ambulance call concerning bronchial obstruction syndrome are 3500 rubles.

Thus, annual regional healthcare expenses for the outpatient and inpatient treatment of SBA exacerbations are 9,309,024 rubles for patients administered the standard basic therapy scope corresponding to GINA Step V. Meanwhile, after initiating BT, costs for outpatient follow-up in SBA patients achieving almost total control decreased 239-fold to 38,880 rubles (Table 5).

Thus, the total costs for treatment and medical care in the analyzed patient group before initiating BT was 10,410,160 rubles. After initiating BT with Dupilumab, total costs were 37,372,456 rubles.

Table 4. *Cost of basic therapy received by patients with severe bronchial asthma before the appointment of GIBT and 12 months after the appointment of GIBT*

Basic therapy before prescribing GIBT		Cost per month, RUB	Cost per year, RUB	Basic therapy 12 months after the appointment of GIBT		Cost per month, RUB	Cost per year, RUB
ICS + LABA, person	10	18305	219660	ICS + LABA, person	23	42101,5	505218
ICS + LABA + SGCS, person	7	13667,5	164010	ICS + LABA + OCS, person	0	0	0
ICS + LABA + ALT, person	2	4675	56100	ICS + LABA + ALT, person	1	2337,5	28050
ICS + LABA + LAMA, person	5	18622	223464	ICS + LABA + LAMA, person	5	18622	223464
ICS + LABA + ALT + LAMA, person	5	21068,5	252822	ICS + LABA + ALT + LAMA, person	3	12641,1	151693,2
ICS + LABA + LAMA + ALT + OCS, person	1	4353,7	52244,4	ICS + LABA + LAMA + ALT + OCS, person	0	0	0
ICS + LABA + LAMA + OCS, person	2	7693,4	92320,8	ICS + LABA + LAMA + OCS, person	0	0	0
LABA, person / aerosol	32/219	3376,25	40515	LABA, person / aerosol	32/55	847	10175
Итого, руб			1101136				918600,2

Note: GIBT — genetic engineering biological therapy, ICS — inhalational glucocorticosteroids, LABA — long-acting beta-agonists, ALT — antileukotrienes, OCS — systemic glucocorticosteroids, LAMA — long-acting anticholinergics, person/aerosol — number of canisters of the preparation per person, RUB — ruble

Table 5. *Costs of medical care received by patients with severe bronchial before the appointment of GIBT and 12 months after the appointment of GIBT*

	Before the appointment of the GIBT		12 months after the appointment of the GIBT	
	Quantity	Cost, RUB	Quantity	Cost, RUB
Hospitalizations	166	8 300 000	0	
Scheduled visits to the clinic	1 215	38 880	1 215	38 880
Additional visits to the clinic	128	214 144	0	
Calls to the ambulance team	216	756 000	0	
Total, RUB		9 309 024		38 880

Note: GIBT — genetic engineering biological therapy, RUB — ruble

The following formula was used to calculate the cost-effectiveness ratio [17]

$$CER = Cost : Ef,$$

(1) CER is the cost-effectiveness ratio of the technology;
(2) Cost presumes the costs associated with the technology (in money equivalent);
(3) Ef is the clinical efficacy of the technology in corresponding units. The parameter defines the scope of costs for achieving a treatment benefit unit, which is expressed, e.g., with the quality of life index. The lower the parameter, the higher is the cost benefit [17].

Complete control over SBA symptoms is equal to 1.0 of the treatment efficacy for this disease. Meanwhile, no control, frequent hospitalizations, low scores of validated questionnaires (ACT-test, ACQ-5) equals 0.2 of efficacy.

Thus, the cost-effectiveness in the group of patients with SBA before initiating BT was 52,050,800 rubles based on the formula above, while the cost-benefit 12 months after initiating BT was 37,372,456 rubles.

To conclude, the use of Dupilumab not only leads to control over disease symptoms, significantly decreasing medical care needs, increasing the quality and duration of patients' lives, but also demonstrates a more economically beneficial treatment strategy.

Discussion

According to the data obtained, after 12 months of Dupilumab treatment the maximum control level was achieved by the majority of patients: the ACQ-5 parameter was 0 points in 12 months. Meanwhile, ACT results increased from 15 to 22 points. All respondents were able to discontinue SCS completely. Such progressive results are associated with the fact that the majority of patients used small prednisolone doses. The administration of additional Dupilumab treatment statistically significantly decreases daily SABA requirements; the number of daily and nocturnal asthma attacks, and ambulance calls vs. standard treatment.

Similar results were obtained in other studies as well. Thus, significant decreases not only in the daily prednisolone dose, but also in the rate of daily exacerbations within a year were observed after Dupilumab administration in the study of Dupen C. et al. (2020) [20]. The study of Pelaia C. et al. (2021) demonstrated significant decrease in the SCS administration in already 4 weeks after the start of Dupilumab administration [21].

The possibility of administering additional treatment to patients with SBA not controlled using the standard scope of treatment is the most efficacious treatment vector. Analyzing the economic efficacy of BT use is the actual issue of modern medical community. Krysanov I.S. et al. (2020) conducted a study of target drugs used in SBA and demonstrated the least indirect and direct costs for Dupilumab treatment. The cost per 1 prevented exacerbation case for Dupilumab was significantly less than for other BT drugs [22]. In this study we have demonstrated the analysis of direct economic costs in patients with SBA administered standard basic therapy scope and additional BT with Dupilumab. We observed the increase in general expenses for the patient's drug provision, which is associated only with high Dupilumab costs. When calculating the cost-effectiveness ratio, additional BT demonstrated a more economically beneficial treatment strategy.

The current study was limited by the time frame of 12 months, and only direct economical treatment expenses were analyzed. Only SBA patients administered Dupilumab were included into the study. Long-term BT effects were not analyzed. In future studies we will recruit more patients with SBA administered Dupilumab. Patients will be included into the study for a longer follow-up period to evaluate long-term effects and economic Dupilumab efficacy.

Conclusions

The results of this study demonstrated high Dupilumab efficacy: higher symptom control parameters, improved pulmonary function parameters, and decreased scope of SCS use were reported after 12 months of therapy.

Thus, Dupilumab is an economically justified option for additional severe bronchial asthma treatment, demonstrating not only significantly decreased economic expenses, but also improved functional parameters and control levels.

Вклад авторов:

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

Казмерчук О.В.: написание текста, подготовка публикации

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Демко И.В: окончательное утверждение 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

Kazmerchuk O.V.: text writing, preparation of a publication

Sobko E.A.: text editing

Demko I.V.: final approval of the manuscript

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DOI: 10.20514/2226-6704-2024-14-6-467-472
УДК 616.124.2-008.31-073.7-085
EDN: UPHGBH

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СЛУЧАЙ РАЗВИТИЯ СИНДРОМА ТАКОЦУБО ПОСЛЕ ПЛАНОВОЙ ЭЛЕКТРОИМПУЛЬСНОЙ ТЕРАПИИ

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A Case of The Development of Takotsubo Syndrome After Electropulse Therapy

Резюме

В статье приводится описание клинического наблюдения синдрома такоцубо с развитием кардиогенного шока у пациента 77 лет с персистирующей формой фибрилляции предсердий после проведения плановой электроимпульсной терапии для восстановления синусового ритма. Диагноз синдром такоцубо был подтверждён на основании лабораторно-инструментальных данных: изменений на электрокардиограмме (элевация сегмента ST в отведения V3-4 на 2-3 мм), повышения уровня тропонина (456,8 нг/л), выявленных нарушений сократимости левого желудочка по данным эхокардиографии (акинез всех верхушечных сегментов, передних, передне- и нижнее-перегородочных сегментов на срединном уровне, гипокинез остальных сегментов на срединном уровне) с последующим полным восстановлением сократимости левого желудочка в динамике, результатов коронароангиографии (значимых стенозов/тромбозов не выявлено) и данных магнитно-резонансной томографии сердца с гадолинием (отсутствуют признаки миокардита, рубцовых изменений в миокарде).

Представленный клинический случай еще раз подчеркивает важность осведомленности специалистов о возможном риске развития синдрома такоцубо после электроимпульсной терапии, так как это позволит своевременно установить диагноз и инициировать соответствующее лечение. Пациентам с такими факторами риска развития синдрома такоцубо, как с наличие в анамнезе психических или неврологических заболеваний, бронхиальной астмы, хронической обструктивной болезни легких, диффузного узлового зоба, гипо-/гипертиреоза, после проведения кардиоверсии, по-видимому, требуется более тщательное и длительное наблюдение. Подобная тактика, вероятно, позволит своевременно диагностировать это осложнение для предотвращения серьезных последствий, однако требуется дальнейшее изучение этого вопроса.

Ключевые слова: *синдром такоцубо, электроимпульсная терапия, фибрилляция предсердий*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «Случай развития синдрома такоцубо после плановой электроимпульсной терапии» для журнала «Архивъ внутренней медицины», подписав информированное согласие

Статья получена 07.07.2024 г.
Одобрена рецензентом 05.08.2024 г.
Принята к публикации 09.09.2024 г.

Для цитирования: Евдокимов Д.С., Быкова Е.Г., Болдуева С.А. и др. СЛУЧАЙ РАЗВИТИЯ СИНДРОМА ТАКОЦУБО ПОСЛЕ ПЛАНОВОЙ ЭЛЕКТРОИМПУЛЬСНОЙ ТЕРАПИИ. Архивъ внутренней медицины. 2024; 14(6): 467-472. DOI: 10.20514/2226-6704-2024-14-6-467-472. EDN: UPHGBH

Abstract

The article describes a clinical observation of takotsubo syndrome with the development of cardiogenic shock in a 77-year-old patient with persistent atrial fibrillation after planned electrical impulse therapy to restore sinus rhythm. The diagnosis of ST was confirmed based on laboratory

and instrumental data: changes in the electrocardiogram (ST segment elevation in leads V3-4 by 2-3 mm), increased troponin levels (456.8 ng/l), identified left ventricular contractility disorders according to echocardiography (akinesis of all apical segments, anterior, anterior and inferior septal segments at the median level, hypokinesis of the remaining segments at the median level) followed by complete restoration of left ventricular contractility over time, coronary angiography results (no significant stenosis/thrombosis detected) and magnetic resonance imaging data of the heart with gadolinium (no signs of myocarditis, cicatricial changes in the myocardium).

The presented clinical case once again emphasizes the importance of awareness of specialists about the possible risk of developing takotsubo syndrome after electrical impulse therapy, as this will allow timely diagnosis and initiation of appropriate treatment. Patients with such risk factors for the development of takotsubo syndrome as a history of mental or neurological diseases, bronchial asthma, chronic obstructive pulmonary disease, diffuse nodular goiter, hypo-/hyperthyroidism, after cardioversion, apparently require more careful and long-term monitoring. Such tactics will probably allow timely diagnosis of this complication to prevent serious consequences, but further study of this issue is required.

Key words: *takotsubo syndrome, electropulse therapy, atrial fibrillation*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article « A Case of The Development of Takotsubo Syndrome After Electropulse Therapy» for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

Sources of funding

The authors declare no funding for this study

Article received on 07.07.2024
Reviewer approved 05.08.2024
Accepted for publication on 09.09.2024

For citation: Evdokimov D.S., Bykova E.G., Boldueva S.A. et al. A Case of The Development of Takotsubo Syndrome After Electropulse Therapy. The Russian Archives of Internal Medicine. 2024; 14(6): 467-472. DOI: 10.20514/2226-6704-2024-14-6-467-472. EDN: UPHGBH

BP — blood pressure, CAG — coronary angiography, LV — left ventricle, MRI — magnetic resonance imaging, ACS — acute coronary syndrome, AHF — acute heart failure, TS — Takotsubo syndrome, HF — heart failure, HECGM — Holter electrocardiogram monitoring, AFl — atrial flutter, EF – ejection fraction, AFib — atrial fibrillation, GDS — gastroduodenoscopy, ECV — electrical cardioversion, ECG — electrocardiogram, EchoCG — echocardiography, VR — ventricular rate

Introduction

Atrial fibrillation (AFib) is the most common type of supraventricular tachyarrhythmias globally [1]. This arrhythmia correlates with the 5-fold increase in the stroke risk and the 2-fold mortality risk [2], thus, the rhythm control strategy is considered preferable [3]. Electrical cardioversion (ECV) is considered the most efficient method providing quick sinus rhythm restoration in paroxysmal AFib [3]. According to the clinical guidelines, this procedure is considered safe even in pregnancy [3]. 23% of complications after ECV are related to possible irritation, pain, and/or burns in the places of skin contact with electrodes [1], however, cases of Takotsubo syndrome (TS) development after ECV have been published in the recent years [1].

Takotsubo syndrome is an acute reversible heart failure (HF) with a transient left ventricular (LV) dysfunction, which is often clinically equivalent to the acute coronary syndrome (ACS) [4, 5]. For the first time the term “takotsubo” (“octopus trap” in Japanese) was introduced by Sato H. et al. in 1990, as the LV shape based on echocardiography data is similar to that of the fisher’s trap in this syndrome [4]. The most common TS trigger is the psychoemotional stress; however, in some cases it can be triggered by the new onset or exacerbation of the pre-existing chronic disease, drug product administration, or the medical intervention [5, 6], including ECV. Based on the latest data, the prevalence of this syndrome associated with ECV is 2.7 cases per 10,000 ECV procedures in AFib [1]. Clinical signs of the transient LV dysfunction manifest within 24-48 hours after ECV with signs of acute HF, up to cardiogenic shock [1].

Let’s get acquainted with the case study of TS after the elective electrical cardioversion in paroxysmal AFib with subsequent circulatory arrest and cardiogenic shock.

Clinical case study

A 77-year-old male was hospitalized electively for additional examination and determining further management tactics.

He had a long history of essential hypertension, with maximum blood pressure (BP) values of 180/90 mm Hg; hypotensive treatment led to BP values of 120/70 mm Hg. The patient denied the history of myocardial infarction, cerebrovascular diseases, diabetes mellitus, angina and dyspnea; he tolerated physical loads satisfactorily, however he noted decreasing tolerance within the previous two months.

The first atrial flutter (AFl) paroxysm was reported in 2011, which was treated with radiofrequency catheter ablation of the cavotricuspid isthmus (2012). In 2018 the

patient developed AFl relapse, which was treated with ECV; the anti-relapse treatment included sotalol (160 mg in the morning, 80 mg in the evening), with concomitant dabigatran 150 mg twice daily, losartan 25 mg/day, spironolactone 25 mg/day. After that, when AFib paroxysm developed 5 years later (on November 15, 2022), cardioversion was provided by amiodarone administration.

A week after that, the patient was electively hospitalized for examination and treatment correction. The Holter ECG monitoring (HECGM) recorded a sinus rhythm with a mean ventricular rate (VR) of 54/min, 130 single ventricular extrasystoles per hour; no significant pauses were detected, with the mean QT (Bazett) duration of 456 ms. Stress-echocardiography (EchoCG) yielded negative results. Mild iron deficiency anemia was detected based on the laboratory tests. During the diagnostic search of anemia etiology, acute gastric ulcer and esophageal candidiasis were detected during gastroduodenoscopy (GDS). Thus, treatment with rabeprazol, rebamipide, and fluconazole was initiated. As concomitant use of fluconazole and sotalol may lead to prolonged QT interval duration, it was decided to switch sotalol to metoprolol succinate 100 mg. The dose of dabigatran was also reduced (to 110 mg twice daily) for two months due to the increased risks of ulcer hemorrhage.

A year later (in December 2023), during the hospitalization due to acute gastroenteritis, the patient noticed dyspnea on moderate physical exertion and arrhythmic palpitations. The electrocardiogram (ECG) recorded AFib with VR of 120-140 bpm. As COVID-19 infection was detected during this hospitalization (with the polymerase chain reaction method), the patient was discharged to outpatient treatment. However, as AFib persisted, the patient referred to another medical institution to consider the cardioversion tactics.

Complaints of tachyarrhythmias and dyspnea preserved during the elective hospitalization as of January 11, 2024. Physical examination: the patient's consciousness was clear, his condition was relatively satisfactory; skin and visible mucous membranes were normal, no peripheral edema or cyanosis was detected. BP 115/70 mm Hg, VR 116 bpm, arrhythmic pulse; cardiac tones were muffled, but without pathological murmurs. The respiratory rate was 15 per min; on auscultation, the breathing was harsh, but auscultated in all areas, without rales or wheezing. The abdomen was soft and non-tender.

The day after the hospitalization, transesophageal EchoCG was arranged, which revealed no thrombi, with spontaneous Grade 2 contrasting. Based on the clinical and historical data, it was decided to restore the sinus rhythm using ECV, and the patient was transferred to the cardiac intensive care unit.

After the electrical cardioversion (300 J), the ECG demonstrated sinus rhythm with VR of 72/min; however, 2 min later, bradycardia with VR of 25-30/min developed, followed by asystole. The external cardiac massage was started, 1 mg of atropine and 1 mg of epinephrine were administered. This led to cardiac activity restoration, though with preserved hypotension (BP approximately 70/40 mm Hg), due to which vasopressor support was initiated (norepinephrine up to 0.3 μg/kg/min, epinephrine up to 0.03 μg/kg/min).

When evaluating follow-up ECG, 2-3 mm ST segment elevation was recorded in leads V_{3-4} along with sinus rhythm with VR of 82/min (Fig. 1). The urgent EchoCG detected significantly decreased LV ejection fraction (EF). Evaluation of local kinetic disorders of LV walls was considered incorrect with the significantly decreased global contractility (Table 1). It was decided to arrange coronary angiography (CAG), which yielded no significant stenoses/thromboses. After CAG, ECG revealed sinus rhythm with HR of 82/min without significant ST deviation. Elevated troponin levels (Table 2) were reported, which were most likely due to myocardial damage (ECV, external cardiac massage, CAG) and hemodynamic disorders.

The common blood count demonstrated neutrophilic leukocytosis (15.77×10^9/L) and elevated platelet count of 476×10^9/L. Biochemistry: hyperglycemia up to 7.3 mmol/L (N 4.1-5.9), creatinine — 111 μmol/L, C-reactive protein — 16.98 mg/L (N 0-5), potassium — 5.88 mmol/L (N 3.5-5.1), decreased albumin to 26.6 g/L (N 35-52) and total protein to 45.5 g/L (N 66-83). Thyroid-stimulating hormone: 1.76 μIU/mL (N 0.35-4.94). Lipid profile: total cholesterol — 3.71 mmol/L, low-density lipoproteins — 2.21 mmol/L, triglycerides — 1.16 mmol/L. The urinalysis and coagulation panel were normal. All blood parameters normalized with the treatment administered by Day 14.

The EchoCG repeated next day (January 13, 2024) revealed increasing LVEF, though akinesis of all apical segments, midline akinesis of anterior, antero- and inferoseptal segments, midline hypokinesis of other segments was reported (Table 1, Fig. 2). Contrast-enhanced computed tomography of the chest was arranged to exclude pulmonary embolism: no signs suggestive of the neoplasm, acute inflammatory and disseminated pulmonary diseases were detected, although bilateral hydrothorax was visualized.

During the magnetic resonance imaging (MRI) of the brain on January 15 (signs of single focal lesions of vascular origin in the brain matter, left-sided exudative sinusitis), hypotension (60/40 mm Hg) and relapsing AFib (VR 140-160 bpm) emerged due to forced

halt of inotropic and vasopressor support. Diuresis also decreased, and this led to the replacement of epinephrine with dobutamine (treatment continued as follows: dobutamine — 14 μg/kg/min, norepinephrine — 0.9 μg/kg/min); albumin, gelofusin infusions were administered. HECGM demonstrated AFib-AFl with irregular and regular 2:1 conduction, transient tachycardia-dependent complete right bundle branch block with an average VR of 151/min, QT of 378-511 ms; no significant pauses were recorded.

The history of recent viral infection (December 2023) and high anti-coronavirus antibody titers (IgG — 25,291 U/mL) provided a possible diagnosis of active myocarditis with cardiac conduction disorders. This was an indication to gadolinium-enhanced cardiac MRI, which demonstrated no signs of myocarditis or scarring lesions.

The follow-up EchoCG revealed increasing EF with the normalization of functional parameters and restoration of motion in all LV walls (Table 1, Fig. 3, Fig. 4).

Table 1. *Echocardiography data during dynamic observation*

	29.12.23 г.	12.01.24 г.	13.01.24 г. (Fig. 2)	17.01.24 г. (Fig. 3)	19.01.24 г. (Fig. 4)	22.01.24 г.
Left ventricular ejection fraction, %	60 %	25 %	31 %	40 %	50 %	70 %
Local contractility of the left ventricle	No local contractility disorders were detected	The assessment of local kinetics against the background of a marked decrease in global contractility is not correct	Akinesis of all apical segments, anterior, anterior and inferior septal segments at the median level, hypokinesis of the remaining segments at the median level	Diffuse myocardial hypokinesia, no local contractility disorders detected	Mild hypokinesia of the anterior septal and anterior walls of the left ventricle	No local contractility disorders were detected

Table 2. *Dynamic troponin level data*

	12.01.24 г.	13.01.24 г.	14.01.24 г.	15.01.24 г.	20.01.24 г.
Troponin, ng/l	24,6	370	456,8	414,4	97,1

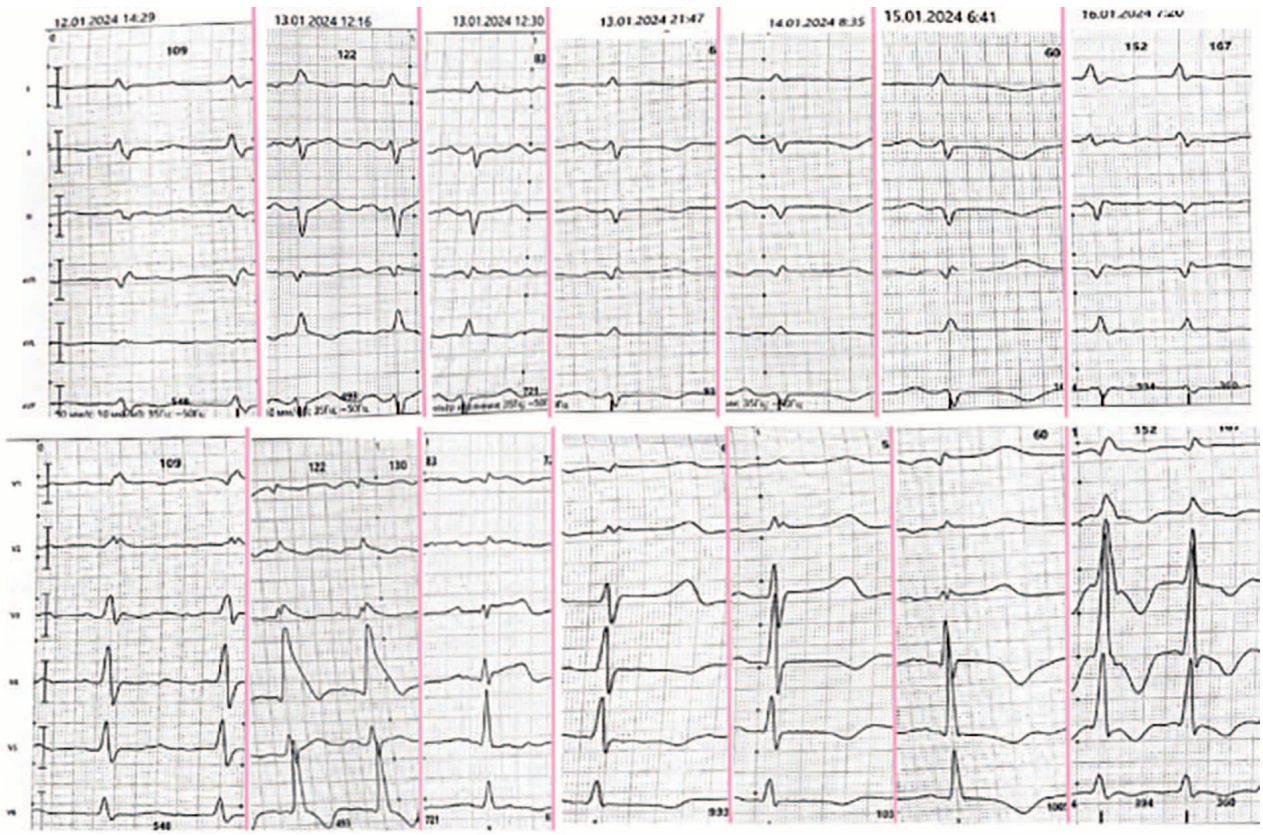

Figure 1. *ECG data in dynamics*

By January 22, hemodynamics stabilized with restoring LV contractility and VR decreasing to 90-100 bpm — after that, inotropic and vasopressor support was discontinued. The patient was transferred to the cardiology department for further follow-up and deciding on the management tactics.

When analyzing the time course of clinical and laboratory-instrumental data, secondary TS that had developed in response to ECV was suspected.

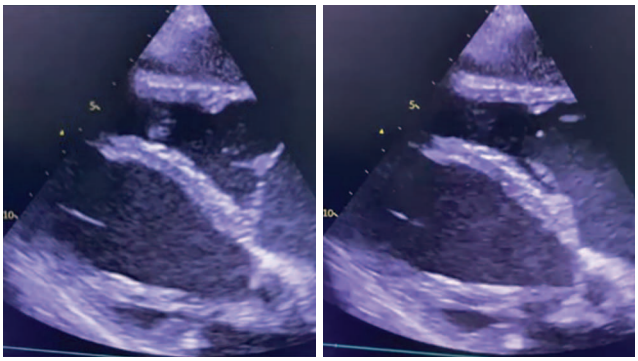

Figure 2. *Echocardiography from 13.01: akinesia of all apical segments, anterior, anterior and inferior septal segments at the median level, hypokinesis of the remaining segments at the median level*

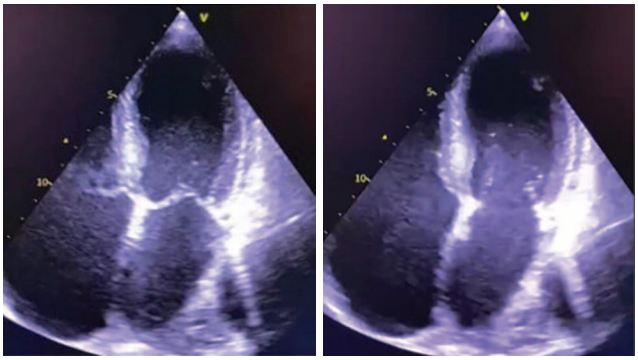

Figure 3. *Echocardiography from 17.01: diffuse myocardial hypokinesia, no local contractility disorders detected*

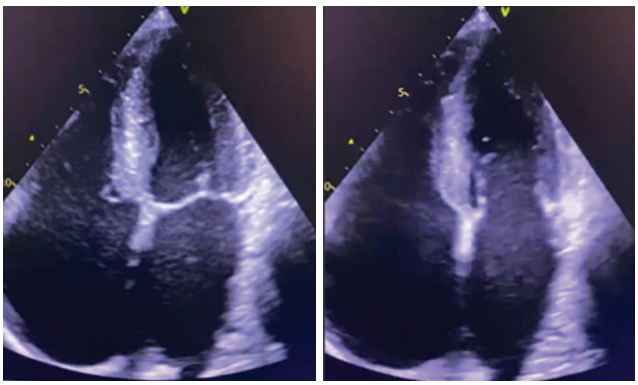

Figure 4. *Echocardiography from 19.01: mild hypokinesia of the anterior septal and anterior walls of the left ventricle*

During the hospital stay, the active patient regimen was extended, HF signs did not progress, while HECGM revealed persisting AFib with an average VR of 80-90 bpm. The following rate control and supportive treatment was administered: metoprolol succinate 150 mg/day, apixaban 5 mg twice daily, losartan 25 mg/day, spironolactone 25 mg/day, torasemide 5 mg/day, atorvastatin 20 mg/day, omeprazol 20 mg/day. The patient was discharged with the recommendation of elective hospitalization in 3 months to discuss the necessity of cardioversion.

Diagnosis upon discharge: Grade 3 essential hypertension, controlled hypertension, very high risk of cardiovascular complications (4). Persistent atrial fibrillation, paroxysm dated December 2023. Cardioversion with ECV on January 13, 2024. Takotsubo syndrome (January 13, 2024). Cardiogenic shock (January 13, 2024). Circulatory arrest (January 13, 2024). New-onset tachycardia-dependent complete right bundle branch block. Paroxysmal AFib (January 15, 2024), not controlled. EHRA 2b. CHA2DS2-VASc 4 points. HAS-BLED: 2 points.

Discussion

The presented case study demonstrates that ECV may become a trigger for TS with severe hemodynamic complications.

The pathogenesis of this ECV-associated condition has not been studied well, though it is presumed that electrical myocardial damage may activate the classic reaction cascade with hypercatecholaminemia, hypersympathetic tone, mytochondrial dysfunction, thus initiating the transient LV dysfunction [7].

The severity of the patient's condition after the ECV was probably related to a prolonged history of AFib. This point of view correlates with the literature data analyzing this issue — it is stated that the emergence of TS in patients with the history of this arrhythmia is an AHF predictor, as AFib directly correlates with worsening hemodynamics. Based on the results presented by I. El-Battrawy et al., it was also demonstrated that compared to patients without AFIb, patients with TS and AFib developed cardiogenic shock (requiring urgent treatment, including the intraaortic balloon pump) more frequently, with a more significant hospital mortality [2].

Conclusion

The case study presented emphasizes the importance of the physician awareness about the possible risk of TS after ECV. Such approach enables the timely diagnosis with the initiation of the corresponding treatment.

Probably, a more thorough and prolonged follow-up is required after cardioversion for patients with various TS risk factors, including the history of psychiatric or neurological diseases, asthma, chronic obstructive pulmonary disease, diffuse nodular goiter, hypo-/hyperthyroidism [8, 9, 10]. Such tactics will possibly enable the timely diagnosis of this complication to prevent serious complications; however, this issue has to be analyzed more thoroughly.

Вклад авторов:

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

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Author Contribution:

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

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Boldueva S.A.: editing the text of the article, approval of the final version of the manuscript

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DOI: 10.20514/2226-6704-2024-14-6-473-478
УДК 616.24-006.363-07-085
EDN: XFVWEA

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ПАЦИЕНТКА С ДОБРОКАЧЕСТВЕННЫМ ЛЕЙОМИОМАТОЗОМ ЛЁГКИХ: ЕСТЬ ЛИ СЛОЖНОСТИ ДИАГНОСТИКИ И ВЕДЕНИЯ?

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A Patient with Benign Lung Leiomyomatosis: Are There Any Difficulties in Diagnosis and Management?

Резюме

Приводится клиническое наблюдение пациентки 48 лет, обратившейся в отделение пульмонологии в связи со случайно выявленными очаговыми образованиями в легких. Несмотря на неоднократные консультации специалистов узкого профиля и выполнение визуализирующих методов обследования диагноз был поставлен только спустя четыре года после трехкратного пересмотра гистологических блоков и исключения других причин очаговых легочных диссеминаций. Данный клинический случай демонстрирует редко встречаемую патологию и сложности дифференциальной диагностики, с которыми могут столкнуться врачи всех специальностей. Диагностика заболевания представляет трудность как для врачей широких специальностей, так и для узкопрофильных специалистов. Особенности заболевания и трудности дифференциальной диагностики определяют необходимость мультидисциплинарного подхода к ведению пациентов с данной патологией.

Ключевые слова: *лейомиоматоз легких, доброкачественная метастазирующая лейомиома матки, метастазы, редкие болезни, диагностика*

Конфликт интересов

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

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Соответствие принципам этики

Пациент дал согласие на опубликование данных лабораторных и инструментальных исследований в статье «Пациентка с доброкачественным лейомиоматозом лёгких: есть ли сложности диагностики и ведения?» для журнала «Архивъ внутренней медицины», подписав информированное согласие

Статья получена 05.06.2024 г.
Одобрена рецензентом 09.09.2024 г.
Принята к публикации 24.09.2024 г.

Для цитирования: Кирносова О.А., Кароли Н.А. ПАЦИЕНТКА С ДОБРОКАЧЕСТВЕННЫМ ЛЕЙОМИОМАТОЗОМ ЛЁГКИХ: ЕСТЬ ЛИ СЛОЖНОСТИ ДИАГНОСТИКИ И ВЕДЕНИЯ? Архивъ внутренней медицины. 2024; 14(6): 473-478. DOI: 10.20514/2226-6704-2024-14-6-473-478. EDN: XFVWEA

Abstract

The article presents a clinical observation of a 48-year-old patient who applied to the Department of pulmonology in connection with accidentally detected focal formations in the lungs during a preventive examination. In the presented clinical case, the patient's disease was asymptomatic for a long time, for the first time, focal formations in the lungs were identified in 2020 and only a year later non-specific symptoms joined. Despite multiple consultations with narrow-profile specialists and the implementation of visualization methods of examination, the diagnosis of «lung leiomyomatosis» was made only four years later after a three-fold revision of histological blocks and the exclusion of other causes of focal pulmonary dissemination. This clinical case demonstrates a rare pathology and the complexity of differential diagnosis that doctors of all specialties may encounter. The features of the disease and the complexity of differential diagnosis determine the necessity of a multidisciplinary approach to the treatment of patients with this pathology.

Key words: *leumiomatos pulmonary, leiomyomatosis of lungs and uterus, metastases, lung, rare diseases, diagnosis*

Conflict of interests

The authors declare no conflict of interests

Conformity with the principles of ethics

The patient consented to the publication of laboratory and instrumental research data in the article «A Patient with Benign Lung Leiomyomatosis: Are There Any Difficulties in Diagnosis and Management? » for the journal «The Russian Archives of Internal Medicine» by signing an informed consent

Sources of funding

The authors declare no funding for this study

Article received on 05.06.2024
Reviewer approved 09.09.2024
Accepted for publication on 24.09.2024

For citation: Kirnosova O.A., Karoli N.A. A Patient with Benign Lung Leiomyomatosis: Are There Any Difficulties in Diagnosis and Management? The Russian Archives of Internal Medicine. 2024; 14(6): 473-478. DOI: 10.20514/2226-6704-2024-14-6-473-478. EDN: XFVWEA

SHI — State Healthcare Institution, BML — benign metastasizing leiomyoma, CO — chest organs, RCH — Regional Clinical Hospital, FEV_1 — forced expiratory capacity during the 1st second, CT – computed tomography, FVC — forced (expiratory) vital capacity of lungs

Introduction

The issue of differential diagnosis of focal pulmonary lesions is one of the most important objectives in modern medicine. Neoplastic dissemination has a specific place in the structure of pulmonary dissemination; the former one includes a benign metastatic leiomyoma (BML, ICD-O-3 8898/1) or, correctly speaking, "pulmonary leiomyomatosis", thus emphasizing the systemic and independent character of the disease [1]. For the first time this pathology was described in 1939 by the physician Paul Steiner in a 36-year-old female. In his study "Metastasizing fibroleiomyoma of the uterus: Report of a case and review of the literature", the author presented a thorough characteristics of the disease course, radiological signs, and results of histopathological examination in a patient with progressive uterine fibroleiomyoma and pulmonary metastases [2]. Starting from this period, less than 1,000 cases have been described in literature. According to the current concepts, pulmonary leiomyomatosis is a rare pathology which belongs to the group of "systemic leiomyomatoses". Based on the data of Russian and foreign authors, the incidence of this disease has been steadily increasing within the latest decade, while each five years the number of publications on this topic almost doubles, which may be related both to improved diagnosis and the true incidence growth [3-4].

The World Health Organization considers pulmonary leiomyomatosis as a variant of benign mesenchymal smooth muscle tumors that are prone to metastases, with specific groups of leiomyomas, grown pattern variant, and smooth muscle tumors of uncertain malignant potential [5]. Besides pulmonary leiomyomatosis, benign uterine diseases metastasizing into lungs also include lymphangioleiomyomatosis and thoracic endometriosis, which modern primary diagnosis is less difficult than that of leiomyomatosis due to more precise diagnostic criteria [6]. As the location of benign tumor "metastases" may differ, the disease terminology varies from peritoneal leiomyomatosis (in abdominal leiomyomas) to intravascular or intravenous leiomyomatosis (if leiomyomas are located in cardiac chambers and blood vessels). Leiomyomatous nodules are most commonly detected in lungs, though they may be found in the retroperitoneal space, pelvic cavity, lymph nodes, central nervous system, and muscles of extremities [7, 8]. Several authors describe cases of cardiac involvement or very rare forms of intravenous leiomyomatosis which has some signs of malignancies (e.g., higher predisposition to atypia, increased mitotic activity) [9, 10].

Regarding clinical signs, patients with pulmonary leiomyomatosis predominantly present with the asymptomatic course — most commonly pulmonary nodules

resembling metastases are detected accidentally on routine chest X-ray. With that, the disease itself most often has a favorable course, without growth or with a very slow increase in the focal lesion diameter, usually without the increase in their number; however, several patients develop some typical complications with time, i.e. hemoptysis, signs of bronchial obstruction (if neoplastic nodules are located in bronchial walls), pneumothorax (with subpleural location of foci), obstructive emphysema, superficial and deep vein thrombosis. In specific patients the disease may have a quite unfavorable course — several authors describe clinical cases with multiple uterine leiomyoma "metastases". In such situations, besides pulmonary nodules, intravenous leiomyomatosis with aggressive growth (see above) is somewhat common — as a result of massive venous lesions, significant vascular symptoms are possible, while if neoplastic thrombi are located in cardiac chambers and the inferior vena cava, acute vascular accidents may emerge (even with sudden death) [7-10].

The nature and pathogenesis of systemic leiomyomatosis have not been sufficiently analyzed. The vast majority of authors believe that the mechanism of BML development is similar to that of endometriosis, paying specific attention to the implantation therapy and associating the emergence of leiomyomatosis nodules in various organs and tissues with the vascular embolism with smooth muscle cells occurring as a result of uterine surgeries. This theory is mainly based on statistical data, as leiomyoma "metastases" are most commonly detected in females who have a history surgical uterine myoma treatment (myomectomy or hysterectomy) [11]. The next theory explains the disease development from the position of asynchronous smooth muscle tissue proliferation in various organs, i.e. the uterus, lungs, or other muscles; in this case, BML is considered as a variant of a nodular dyshormonal hyperplasia. According to this point of view, leiomyomatosis is a pathological condition with impaired differentiation and increased smooth muscle tissue volume as a result of hormonal imbalance in the body (similar to, e.g., cystic mastopathy or hepatic adenomas). With that, genetic predisposition in specific persons is of special value, while such processes as hormonal disorders or uterine myomectomy are considered proliferation triggers [4]. The third theory presumes the development of BML as a result of hormonal overstimulation. It is considered that estrogen is a driving force of muscle tissue proliferation, provoking "metastasizing" and subsequent growth of the primary tumor "metastases". Based on the data of Russian authors, clinical, morphological, and immunophenotyping studies of neoplastic nodules in patients with BML foci in lungs confirm the high estrogen and progesterone receptor expression in leiomyoma "metastases". For example, specific clinical observations demonstrate the increased diameter of foci with the increased endogenous estrogen levels or estrogen effects as part of replacement therapy. The hormonal dependence of these tumors is also confirmed by the described cases of neoplastic nodule regression in patients during pregnancy or with the natural menopause, as well as when using gonadotropin- and releasing-hormone agonists, P-450 aromatase inhibitors, estrogen inhibitors, or after ovariectomy. However, despite the fact that estrogens play a significant role in the development and progression of leiomyomatosis, they should considered not as an etiological factor, but rather as one of the components of the systemic process pathogenesis [12, 13]. Some researchers still consider BML as a subtype of hamartomas, which in their turn are classified based on the predominance of a specific component into several histological types: lipomatous, chondromatous, and leiomyomatous hamartomas. It should be noted that according to the researchers' opinion, it is really important to differentiate these subtypes, as the management tactics depends on that. If for the first two forms scientists incline towards the theory of disembryogenesis (with exclusively surgical treatment), when speaking about leiomyomatous pulmonary hamartomas, one should note that their etiology, pathogenesis, hormonal dependence, and treatment prognosis are currently not well analyzed, and the attempts of their treatment in many cases should be started from the conservative strategy [13]. Due to the differences defined, the attempt to assign BML to hamartomas is rather conditional, and currently pulmonary leiomyomatosis is usually considered as an independent disease. All theories pay special attention to genetic predisposition to leiomyomatosis. Researches from all over the world search for the typical genetic aberrations, analyzing the expression of hormone receptors in females with uterine myoma. Several authors underline the high expression of a regulatory anti-apoptotic gene bcl-2 and a gene-suppressor of malignancies p53, with a low Ki67 (marker of the proliferative activity in tumor cells) [12, 14]. Despite a plenty of theories, currently the disease is considered multifactorial; due to this, the following pathogenetic events of BML should be considered for the correct establishment of diagnosis: prolonged hormonal stimulation (prolonged oral contraceptive use, pregnancy, menstrual disorders), possibility of lymphogenous and hematogenous dissemination or intraperitoneal implantation (as a result of uterine surgeries), family history, other signs of nodular hyperplasia.

Currently, no common treatment standards and protocols exist for systemic leiomyomatosis, including pulmonary leiomyomatosis. Recommendations based on Russian and foreign medical platforms include thorough patient follow-up, surgical resection of "metastatic" lesions, medication-induced or surgical termination of ovarian function using aromatase inhibitors, estrogen receptor antagonists, tyrosine kinase inhibitors, and gonadotropin-releasing hormone (GnRH) agonists. Determining the hormonal status of female patients is mandatory before starting the treatment. Several reports of efficient treatment with the immunosuppresant "sirolimus" have been observed in young females that wish to preserve the ovarian function; however, additional clinical trials are required for its active implementation into the treatment practice of this disease [1, 2, 12, 13].

Case study

The patient L. (born August 12, 1975) was hospitalized into the pulmonology department in December 2023. She complained of dry cough and sensation of incomplete inspiration. Life history revealed no data concerning bad habits, household or occupational hazards; the patient denied the coronavirus infection and corresponding vaccinations. The patient underwent hysterectomy due to a myoma (2010), suffered from breast fibroadenoma. Focal pulmonary lesions were detected in January 2020 during the scheduled chest X-ray; she was counseled by the tuberculosis specialist — no signs of tuberculosis were detected. In February 2020, she was referred to the pulmonology department: based on the results of the computed tomography of chest organs (CT CO), bilateral pulmonary lesions sized 4 to 22.6 mm were detected (Fig. 1 a, b). Pulmonary function tests revealed FVC 74 % of reference values, FEV_1 74 % of reference values, FEV_1/FVC 98 %, laboratory tests were normal.

The patient underwent additional examination to exclude the neoplastic process and tuberculosis — both diagnoses were refuted. Videothoracoscopy was arranged, according to the histological examination results, the pulmonary tissue contained areas of fibrosis, mild lymphocytic, perivascular, and peribronchial inflammatory infiltration. "Lymphocytic pneumonia" was established. CT of CO was conducted twice in 2020, without any changes detected. The patient took several cycles of acetylcysteine (ACC) within a year. During the hospitalization into the pulmonology department in June 2021, the diagnosis was changed to "sarcoidosis". Prednisolone was administered in the dose of 15 mg/day, though the patient stopped taking it spontaneously

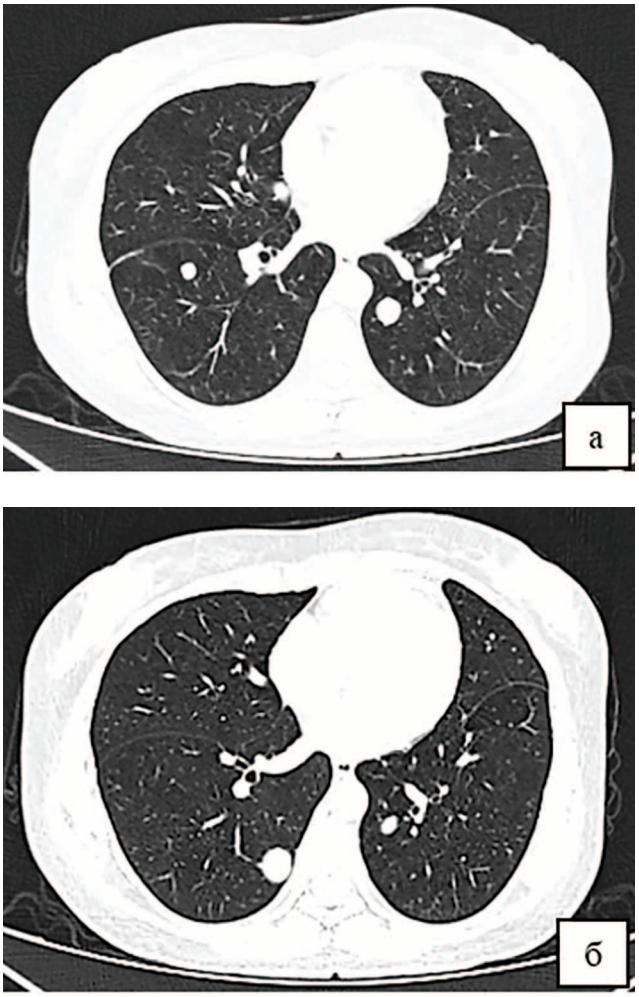

Figure 1. *CT scan of the chest (a, б)*
Note. Multiple rounded neoplasms of both lungs, with a diameter from 4 to 22.6 mm, the largest of them in the right lung (б)

several weeks later. In July 2021, she underwent another diagnostic surgery (atypical right lung resection) in the surgical department of SHI RCH, Samara, the histological examination revealed hamartomas. In January 2022, the follow-up CT demonstrated negative progression — lesions increased in size (Fig. 2 a, b).

Due to negative CT progression, it was decided to review histological blocks during the hospitalization in December 2023 in the Federal State Budget Institution Scientific-Research Pulmonology Institute, Federal Medical & Biological Agency of Russia (acknowledgements: M.V. Samsonova, A.L. Chernyaev). After review, the following description was obtained: presence of neoplastic tissue represented by multidirectional bands of spindle-like cells with multiple cavities lined with the single-layer cubical epithelium. Layers of the myxoid connective tissue were occasionally detected. The pulmonary tissue with thin interalveolar septa of the normal structure was found along the periphery of the tumor. The diagnosis of benign metastasizing leiomyoma was concluded.

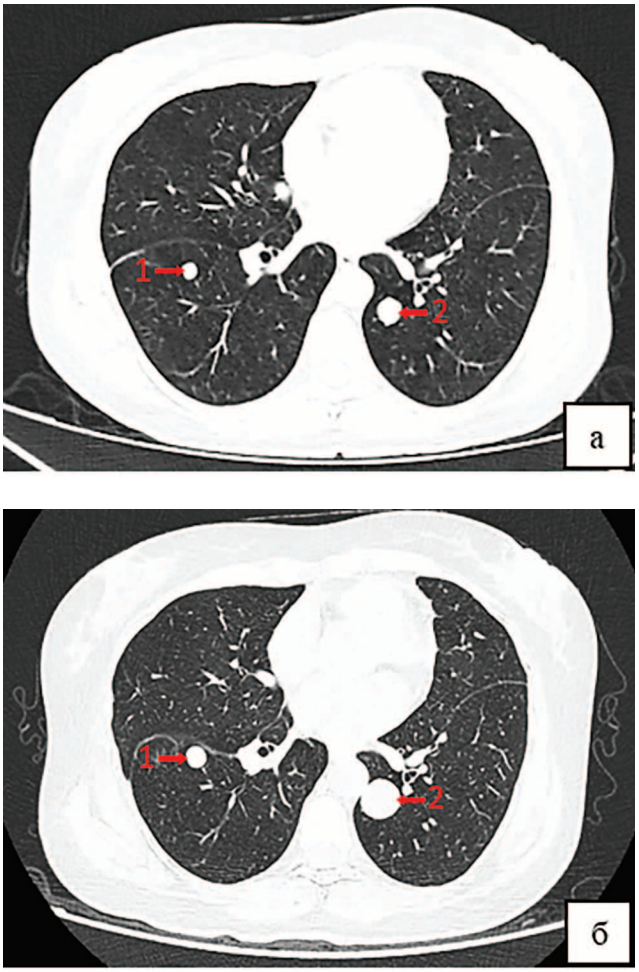

Figure 2. *CT of the chest*
Note. а — multiple rounded soft-tissue neoplasms, number 1 — diameter 9.41 mm, number 2 — diameter 14.86 mm, (02.13.2020);
б — negative dynamics, diameter of neoplasm number 1 — 12.44 mm, diameter of neoplasm number 2 — 23.85 mm, (01.24.2022)

The patient was counseled in the Federal State Budget Institution National Medical Research Radiology Center, where the histological material was reviewed again, and adenoleiomyomatous hamartomas were confirmed in lungs. According to the consilium results, daily anti-estrogen therapy (tamoxifen 40 mg) was administered, and the hormonal profile assessment was recommended — if the hormone levels corresponded to functioning ovaries, termination of the ovarian function (using the surgical or medication-induced method) would be recommended with subsequent letrozole treatment and further follow-up. The patient underwent ovariectomy, and letrozole was administered.

Discussion

In the case study presented, the disease in the patient was asymptomatic for a long time: focal pulmonary lesions were detected for the first time in 2020 during the prophylactic examination, while non-specific symptoms emerged only a year later. Despite several episodes of counseling by specializing physicians and imaging methods, the diagnosis was established only four years later after a three-fold review of histological blocks and exclusion of other causes of focal pulmonary disseminations.

Another problem presumed patient triaging after the conclusion of a benign metastasizing leiomyoma. Who should manage this patient? Unfortunately, city gynecologists and oncologists were not ready to decide upon the patient's fate and her treatment. Only after the remote (and subsequently offline) counseling one could receive recommendations about the further tactics of her management. However, the issue of further patient follow-up is considered not solved.

Conclusion

The differential diagnosis of pulmonary leiomyomatosis requires complex approach and high qualification of physicians. This case study demonstrates a rare pathology and complexity of differential diagnosis, which can be tackled by physicians of all specialties. The disease diagnosis is difficult both for general practitioners and specializing physicians. The low incidence of the pathology, lack of physician experience with the category of patients with this disease, insufficient awareness of the aforementioned risk factors, small number of publications in Russian journals concerning the diagnosis and treatment of systemic leiomyomatosis and its manifestations lead to the absence of timely diagnosis and adequate treatment of diseases, which in turn results in complications and subsequent massive surgeries. It is almost impossible to establish such diagnosis alone without morphological verification and follow-up. However, even morphology does not demonstrate the final result from the start; in such cases, the attending physician should be tolerant and provide a personalized approach, arrange counseling with other specialists, and send the histological material for review (if possible). The disease features and difficulties in the differential diagnosis determine the necessity of a multidisciplinary approach to the management of patients with this pathology.

Вклад авторов:

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

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Author Contribution:

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

O.A. Kirnosova: Research concept and design, obtaining data, analyzing and interpreting data, writing articles, approving the final version of the publication

N.A. Karoli: Research concept and design, obtaining data, analyzing and interpreting data, writing articles, approving the final version of the publication

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КАФЕДРА ПСИХИАТРИИ, ПСИХОТЕРАПИИ И ПСИХОСОМАТИЧЕСКОЙ ПАТОЛОГИИ РУДН им. Патриса Лумумбы

Уважаемые коллеги!
Приглашаем Вас 21-22 марта 2025 года посетить

XI Всероссийскую межвузовскую научно-практическую конференцию

«ПСИХОСОМАТИЧЕСКАЯ МЕДИЦИНА В РОССИИ- 2025: МЕЖДИСЦИПЛИНАРНАЯ СИМФОНИЯ»

Почему эта конференция важна не только для психиатров и неврологов, но и для врача первичного звена?

Современные научные данные и клиническая практика все более убедительно доказывают, что практически все соматические и неврологические заболевания тем или иным способом связаны особенностями характера человека, его психологическим и психическим состоянием.

Врачи всех специальностей все чаще обращают внимание на особенности психического статуса своих пациентов.

Психические расстройства могут способствовать формированию, провоцировать обострения, сопровождать и осложнять соматические заболевания, а даже имитировать их.

Любому специалисту будет полезно узнать о вариантах влияния психики на соматоневрологическое состояние его пациентов, а также о том, чем и как именно он может помочь больному, что назначить, как и к какому специалисту по психическому здоровью направить?

Для того, чтобы ответить на эти и многие другие вопросы, чтобы познакомить врачей с работой друг друга и вместе создать «маршруты» наших общих, психосоматических, больных, мы и проводим нашу конференцию вот уже 11 лет подряд!

Председатель Организационного комитета-
Заведующий кафедрой психиатрии, психотерапии и психосоматической патологии ФНМО МИ РУДН В.Э. Медведев

ФОРМАТ: гибридный — 21 марта онлайн, 22 марта — очно с трансляцией на регионы

АУДИТОРИЯ: психиатры, терапевты, неврологи, ВОП (семейные врачи), кардиологи, гастроэнтерологи, пульмонологи, дерматологи, эндокринологи, психотерапевты, наркологи и др.

РЕГИСТРАЦИЯ: предусмотрена предварительная электронная регистрация участников

ПОСЕЩЕНИЕ: свободное

АККРЕДИТАЦИЯ: программа конференции подается на аккредитацию в Координационный совет НМО при МЗ РФ для получения зачетных единиц (кредитов) в рамках Программы по непрерывному медицинскому и фармацевтическому образованию.

ТЕМАТИКИ ДОКЛАДОВ:

- Болезни сердца и сосудов — психосоматический подход
- Сахарный диабет, метаболический синдром и гиперпролактинемия
- Язвенная болезнь, диспепсия, раздраженный кишечник и ГЭРБ
- Зуд, дерматит, аллергия
- Репродуктивное здоровье и психические расстройства: от предменструального синдрома до постменопаузы
- Нездоровый «здоровый» образ жизни (ЗОЖ)
- Расстройства сна
- Хроническая усталость, астения и синдром выгорания

и др.

В составе лекторов признанные специалисты в области психиатрии, кардиологии, эндокринологии, гастроэнтерологии

Помимо лекционной части, на конференции можно узнать о новейших лекарственных препаратах и посетить медицинскую выставку