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АЛОПЕЦИЯ В СТРУКТУРЕ КЛИНИЧЕСКИХ ПРОЯВЛЕНИЙ ЭНДОКРИНОПАТИЙ: ПАТОГЕНЕТИЧЕСКИЕ И ДИАГНОСТИЧЕСКИЕ АСПЕКТЫ

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Alopecia and Clinical Presentation of Endocrinopathies: Pathogenetic and Diagnostic Aspects

Резюме

В обзоре рассмотрены ключевые аспекты патогенеза алопеции при патологии эндокринной системы. Продемонстрирована роль целого ряда гормонов, факторов роста, цитокинов и других биологически активных веществ. Показано, что клиническое значение алопеции — весьма распространенного в популяции симптома — далеко не исчерпывается геронтологической проблематикой, и может быть проявлением эндокринопатий. Указанное обстоятельство диктует проведение в целом ряде случаев широкого дифференциально-диагностического поиска, выполнение которого наиболее перспективно при условии реализации мультидисциплинарного подхода с участием эндокринолога, гинеколога, андролога, дерматолога / трихолога и других специалистов.

Ключевые слова: *алопеция, эндокринная система, эндокринопатии, трихология, мультидисциплинарный подход*

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Abstract

The review examines the key aspects of the pathogenesis of alopecia in endocrine system pathology. The role of hormones, growth factors, cytokines and other biologically active substances has been demonstrated. Alopecia is a frequent symptom that can be the result of not only gerontological, but also endocrinological problems. Therefore, time-consuming differential diagnosis is often necessary. Diagnosis is more effective if a team of specialists is involved: endocrinologist, gynecologist, andrologist, dermatologist / trichologist, and others.

Key words: *alopecia, endocrine system, endocrinopathies, trichology, multidisciplinary approach*

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5-AR — 5-alpha reductase, AGA — androgenetic alopecia, HF — hair follicle, SHBG — sex hormone binding globulin, DHT — dihydrotestosterone, DHEA-S — dihydroepiandrosterone sulfate, TE — telogen effluvium, BMI — body mass index, IGF-1 — insulin-like growth factor-1, LH — luteinizing hormone, MS — metabolic syndrome, DM — diabetes mellitus, PCOS — polycystic ovary syndrome, TRH — thyrotropin-releasing hormone, TNF-alpha — tumor necrosis factor-alpha

In the clinical practice, there are quite often cases when a symptom that should serve as a key to a correct and accurate diagnosis escapes the doctor's analytical field due to its low specificity and the diagnostic procedure based on it seems unpromising. An example is alopecia, which can be the only sign and nevertheless deserves close attention and requires a comprehensive examination of the patient. Diagnostic search should include a range of diseases and conditions that can cause this symptom. The type of alopecia can also have a diagnostic value, and hair loss itself can serve as the first symptom of the disease.

Optimal treatment of the patient requires an understanding of the hair loss progression and awareness of the plurality of its possible causes. An individual treatment plan can be implemented if work with the patient is carried out sequentially: starting with the most simple and obvious tasks and gradually moving on to more complex ones. It should be borne in mind that hair loss is most often caused not by a single cause but by a whole range of factors [1].

Alopecia is a term that refers to any hair loss. The daily rate of hair loss is about 100, and hair loss can be defined as a condition in which more than 100 hairs fall per day. However, given the individual physiological processes, excessive hair loss, not typical for a particular person, can be called alopecia [2]. There are two main groups of alopecia: reversible and irreversible (scarring, in which hair cannot be restored, and the goal of therapy is to achieve remission to prevent the expansion of the lesion). Reversible forms include AGA, telogen and anagen effluvium, and alopecia areata.

The hair follicle (HF) is a highly organized structure with a high mitosis rate. It is sensitive to many factors, such as growth factors (insulin-like growth factor, endothelial vascular growth factor, fibroblast growth factor), cytokines (interleukin 1-alpha, TNF-alpha, etc.) and the state of the endocrine system, which largely regulates hair growth via androgens, prolactin, thyroid hormones, melanocyte-stimulating hormone, etc.

This article discusses the main points of hormonal regulation of HF functioning.

Androgens

Testosterone is produced not only in the adrenal glands and gonads from its predecessors — androstenedione, dihydroepiandrosterone and dihydroepiandrosterone sulfate, but also locally by the dermal papilla. Therefore, the hair follicle is not only the target but the site of testosterone synthesis [3].

The link between androgens and alopecia was first noted by Hamilton J. B. (1960), stating that AGA did not develop in eunuchs and boys castrated before puberty [4, 5]. However, with severe testosterone deficiency, telogen effluvium (TE) may develop. Most likely, this is due to its anabolic effect on the formation of protein structures, which are also the hair shaft. The relationship between the androgen receptor gene with androgenic insensitivity and hair loss has been shown in Kennedy's disease, which is a neurodegenerative disease that triggers muscular atrophy of the spine, testicular atrophy and reduced virilization [3]. Significant improvement in hair condition was also shown in patients taking tamoxifen for breast

cancer. Therefore, in the absence of genetic sensitivity of the HF to dihydrotestosterone (DHT), hormone replacement therapy with testosterone can have a positive effect on hair growth [6, 7].

During puberty, young men and women develop terminal hair (secondary sexual characteristics) in the axillary, pubic areas, and lower extremities, and young men in the trunk and beard (the so-called androgen-dependent hair growth zones). In these areas, androgens extend the hair growth phase, change the ability of keratinocytes to divide and increase the pigmentation and size of the dermal papilla.

These processes involve 5-alpha reductase (5-AR), enzyme that converts testosterone to dihydrotestosterone. It can also convert 4-androstenedione and progesterone into their corresponding reduced forms. 5-AR is synthesized in two molecular forms, each encoded by a separate gene. The distribution of 5-AR of the first and second types, their ratio and expression intensity vary in different areas. The expression of second-type 5-AR is higher in the dermal papilla of the HF on the head, which intensifies the negative effect of androgens.

A five-fold increase in the androgenic activity of testosterone due to its conversion to DHT demonstrates the important role of 5-AR in androgen action. With a genetic predisposition under the influence of DHT, microinflammation develops in the perifollicular zone in the scalp skin. This leads to the gradual miniaturization of the follicle and a shorter hair growth phase, and the development of fibrosis, with slow replacement of the follicle with connective tissue. Therefore, with high activity of the 5-AR and HF genetic sensitivity to DHT, a type of hair loss called AGA develops. In contrast, in rare cases of 5-AR deficiency syndrome, hair loss on the head was not observed [3]. In this regard, finasteride, a second-type 5-AR inhibitor mainly used to treat benign prostatic hyperplasia, is effective in treating AGA.

The role of androgens in the development of AGA in women is contradictory. Most studies have shown no hyperandrogenism in more than 60% of women with AGA [6].

Estrogens

Estrogen (and androgen) receptors are located on epidermal keratinocytes, dermal fibroblasts, sebaceous glands and HF. On the scalp, the predominant estrogen receptors are beta-estrogen receptors [6]. Estradiol alters the metabolism of androgens in the pilosebasial structures, which itself exhibits a noticeable activity of aromatase, a key enzyme in the conversion of androgens to estradiol. In addition, estradiol can affect androgen metabolism by inhibiting aromatase activity, which determines the conversion of testosterone and androstenedione androgens to estrogens estradiol and estrone [8]. That is, the HF is simultaneously a target for estrogens and their source [9].

Estrogens are believed to have a positive effect on the prolongation of the hair growth phase by binding to locally expressed estrogen receptors, stimulating the synthesis of glycosaminoglycans, elastin, and collagen in the skin [10]. This partially explains the active postpartum hair loss due to a drop in the system level of estrogen (and progesterone). The same applies to women during menopause: with a drop in estrogen levels, changes in the skin and hair are significantly accelerated, accompanied by loss of turgor, dryness, thinning and hair loss due to depletion of the microvasculature of the dermis, trophic innsufficiency of the dermal papilla, relative increase in androgenic effect, activation of pro-inflammatory cytokines with the formation of zones of chronic inflammation in the HF [3]. Most women receiving aromatase inhibitors develop some form of alopecia (androgenetic or diffuse) [11].

With a genetic predisposition, a violation of the ratio of estrogens and androgens can be a triggering factor in hair loss in women [12]. Combined oral contraceptives or hormone replacement therapy with androgenic progestogens (norethisterone, levonorgestrel, tibolone) often cause hair loss, especially in genetically predisposed women [1, 13–15]. In the overwhelming majority of cases, severe hair loss occurs after oral contraceptives are discontinued, and AGA often occurs, which argues against prescribing these drugs to treat alopecia (not to mention other side effects — changes in blood rheology and lipid profile, increased SHBG level, gonadotropin synthesis inhibition by the hypothalamus, acne, hirsutism, decreased libido, osteoporosis, adrenal gland dysfunction, impaired venous outflow, and vaginal atrophy) [1, 16].

AGA in women, which differs externally from men, is also explained by the fact that scalp skin in women has higher aromatase activity and more estrogen receptors [17]. On the other hand, a mouse study showed that parenteral and local estrogen agonists cause deep and long-term inhibition of hair growth, while estrogen antagonists stimulate hair growth by initiating anagen, that is, an active growth phase [4]. Therefore, unlike androgens, the role of estrogens in the regulation of hair growth is debatable.

Progesterone

The effects of progesterone that have an impact on the phases of hair growth include vasodilating and anti-inflammatory effect (due to inhibition of lipid peroxidation, TNF-alpha, mast cells), suppression of the effects of excess testosterone and estrogen, as well as inhibition of

5-AP activity. It was shown that the topical application of progesterone to the scalp skin significantly reduces 5-AR activity and the level of DHT in the perifollicular zone (the synthesis of DHT is inhibited by 97% and estradiol by 41%) [18]. The effect of progesterone, which partially intensifies hair growth, is also due to its central action via inhibiting the secretion of luteinizing hormone (LH), which, in turn, causes a decrease in the stimulation of ovarian theca cells (androgen synthesis) [8].

Progesterone is considered a female steroid hormone. However, since it is also produced in the testes and adrenal glands in men (in lesser amounts than in women), it also has its biological effects (anti-inflammatory, antioxidant activity, and participation in the synthesis of neurohormones). Progesterone could be a tool in hormonal modulation and treatment of hair loss in men and treating disorders caused by high activity of 5-AR of both types and system hyperestrogenia (which leads to gynecomastia, prostate hyperplasia, and erectile dysfunction) [19]. Therefore, progesterone deficiency affects the course of AGA in women and, to a lesser extent, in men.

Among the main reasons for a decrease in progesterone are an increase in estrogen and cortisol levels, polycystic ovary syndrome, oral contraceptives and cortisone use, menopause, and vitamin D deficiency.

Prolactin

Prolactin levels also affect the pilosebial structures: on the phases of hair growth and sebaceous gland, affecting the follicle not only directly, but also indirectly, through an increase in the proandrogen content in the adrenal cortex and tissue androgen metabolism [20]. Consequently, hyperprolactinemia can be the cause of not only TE, but also AGA, as well as acne and hirsutism [21, 22]. A decrease in blood prolactin levels to physiological values usually offsets symptoms of hyperandrogenism.

Human scalp hair follicles express prolactin receptors. Exposure of the follicle to high doses of prolactin leads to significant inhibition of anagen and premature development of catagen, along with a decrease in proliferation and increased apoptosis of hair follicle keratinocytes. The significant inhibitory in vitro effect of high doses of prolactin suggested that prolactin acts as an autocrine inhibitor of hair growth [23]. This may explain hair loss in patients with high prolactin levels. Hyperprolactinemia is one of the possible causes of TE in women in the postpartum period [2].

Thyroid Hormones

The thyroid diseases accompany more than half of alopecia cases. The main functions of thyroid hormones are the maintenance of basic metabolism and the regulation of tissue respiration: they increase general metabolism, oxygen consumption and heat production in tissues. It has been shown that thyrotropin-releasing hormone (TRH) acts as an inducer of hair growth and pigmentation [24, 25]; TRH and thyroid-stimulating hormone are powerful promoters of mitochondrial activity and regulators of keratin expression [25], and triiodothyronine and tetraiodothyronine stimulate hair growth by regulating the function of stem cells of the dermal papilla and prolonging anagen [26]. Working mainly at the level of the cell nucleus, they can directly affect processes in the mitochondria and the cell membrane, stimulating RNA formation and leading to stimulation of protein synthesis, which is manifested by both growth and differentiation reactions [25]. Since thyroid hormones affect the growth and differentiation of tissues, the metabolism of many substrates, vitamins, hormones, oxygen consumption, protein synthesis, mitosis, they are of great importance for the formation and growth of hair.

Hypothyroidism occurs ten times more often in women than men. With hypothyroidism, hair is dry, dull, coarse, brittle, and TE, growth retardation, loss of lateral areas of the eyebrows (madarosis) develop. With a genetic predisposition, AGA may occur, and the probable development mechanism involves a decrease in SHBG and an increase of free androgens in plasma [27, 28].

The most common symptoms of hyperthyroidism are systemic, not cutaneous, and are caused by the state of hypermetabolism. TE is observed in 20–40% of cases, and axillary hair loss in 60%. The severity of hair loss does not correlate with the severity of thyrotoxicosis. The hair itself is thin, soft, straight, and not amenable to permanent waving. It should be borne in mind that hair loss can result from side effects of drugs used for treatment (carbimazole, methyluracil, levothyroxine, lithium, amiodarone, etc.) [1, 29].

D-Hormone

The outlook on vitamin D has expanded significantly in recent decades. In terms of its chemical structure, metabolic characteristics and interaction with nuclear receptors, vitamin D has more similarities with steroid hormones than with vitamins, which is why it is called D-hormone in many publications [30, 31]. The hormone-active form of vitamin D reportedly acts as a regulator of a number of enzymes involved in the metabolism of steroid hormones: both adrenal and sex hormones [32, 33].

In experiments on animals, on cell cultures and in vivo, it was shown that the vitamin D receptor gene is expressed in ovarian tissues, modulating the steroidogenesis pathway in granulosa cells, which can lead to improved follicular development and maturation [31,

34]. The expression of these genes in keratinocytes is necessary for the regulation of the hair follicle cycle, and vitamin D deficiency leads to impaired epidermal differentiation and regulation of hair growth [35, 36]. It was shown that alopecia develops in mice and humans due to the inactivation of vitamin D receptors [2, 37].

It was found that the biologically active form of vitamin D — 1,25(OH)2D — stimulates the production of progesterone, estrone and, in synergy with insulin, increases the production of estradiol by 60% [38]. In autoimmune diseases, vitamin D stimulates apoptosis of immune cells, inhibits NO production, reduces T-helper tissue infiltration and T-cell activation, and inhibits the maturation of antigen-presenting cells, thus possessing a powerful immunomodulatory effect [39]. Therefore, vitamin D may be a defense factor in some autoimmune diseases, including alimentary and fibrotic alopecia [40]. In particular, in patients with alopecia areata, the vast majority of cases involve a critically low level of 25(OH)D (6 to 15 ng/l using liquid chromatography and tandem mass spectrometry). In patients with fibrotic forms, the correlation is not so obvious. The study conducted by Aksu Ceman, et al. (2014) showed that vitamin D deficiency is detected in 91% of patients with alopecia areata and correlates with the severity of the disease [41].

A meta-analysis of recent studies showed that vitamin D deficiency plays an important role in the pathogenesis of irreversible alopecia — TE, AGA, alopecia areata: most studies showed a decrease in serum vitamin D concentration in patients with various forms of alopecia compared with control groups [42].

Growth Hormone

Growth hormone affects the growth and differentiation of cells, playing a role in the development of hair follicles and hair growth. It was found that insulin-like growth factor 1 (IGF-1) is produced in the dermal papillae, and the presence of matrix RNA of the IGF-1 receptor in keratinocytes has been proven. IGF-1 in the presence of insulin is believed to induce hair growth by stimulating the proliferation of hair follicles and inhibiting apoptosis [43]. For example, hypertrichosis is observed in acromegaly [44].

In Laron's syndrome (mutation in the IGF-1 encoding gene), the hair is thin, with a significantly shorter growth phase [45]. Growth hormone enhances the effect of androgens on hair growth in areas of secondary sexual characteristics. Therefore, boys with growth hormone deficiency require five times more testosterone to induce axillary hair than hypogonadal boys with a sufficient amount of it. The effects of growth hormone are probably mediated by insulin, similar to growth factor 1 [43, 46].

Insulin

The anabolic effects of insulin have a positive effect on prolonging the hair growth phase (similar to growth hormone). In particular, its dose-dependent stimulating effect was shown in the in vitro study [43], but its ability to initiate type-2 5-AR activity aggravates the course of AGA in the presence of genetic predispositions.

The development of hyperinsulinemia (insulin resistance) intensifies glycation mechanisms (oxidation of substrates by glucose acting as a free radical), which leads to an increase in oxidative stress at the cellular level, while maintaining inflammation in the perifollicular zone and contributing to diffuse hair loss. The course of AGA worsens as the blood insulin level increases since insulin has a stimulating effect on 5-AR, and, therefore, the level of DHT increases [47]. Therefore, through the stimulation of 5-AR, hyperinsulinemia promotes the development of AGA in genetically sensitive individuals with DHT, and through the development of inflammation and oxidative stress in combination with comorbidity, it can trigger diffuse hair loss.

There are numerous studies showing the relationship between metabolic syndrome (MS) and AGA in both men and women [62]. The early onset of AGA in young men indicates, among other things, excessive activity of 5-AR and the development of related conditions in the future (erectile dysfunction, prostate hyperplasia); a significant relationship between AGA and coronary disease was also found. In young men with MS and AGA, total cholesterol, blood pressure, and insulin resistance index are significantly higher than in men without AGA [48]. It is well known that insulin resistance and MS in women have a clear association with polycystic ovary syndrome, which is the most common cause of hyperandrogenism, accompanied by anovulation. Starka L., et al. (2005) suggested that the combination of early AGA and insulin resistance can be a male analogue of polycystic ovary syndrome [49].

In addition, according to Cannarella R., et al. (2020), a hormonal profile similar to that of polycystic ovary syndrome (PCOS) and characterized by a decreased level of follicle-stimulating hormone (FSH) and sex hormone binding globulin (SHBG), increased levels of LH, androstenedione and 17α-hydroxyprogesterone (17α OHP), as well as hypertension, insulin resistance, and weight gain, is also characteristic of men with early onset of AGA [50]. It is noteworthy that all patients with early AGA had a significantly higher body mass index (BMI) and seru, 17 α-hydroxyprogesterone level compared with the control group ($p < 0.05$). The authors report a tendency to an increase in dehydroepiandrosterone sulfate (DHEA-S), a decrease in the level of total testosterone, as well as a higher percentage of sperm apoptosis compared with the control group ($p < 0.05$) [50]

Androgenetic Alopecia (AGA)

AGA is usually divided into male type and female type hair loss. Androgen-dependent zones (forehead, crown, and, in some cases, temporal zones) are identified on the scalp skin, where the amount of 5-AR and DHT is significantly higher. Despite the similarity of mechanisms in the development of AGA in both sexes, hair loss in women is characterized by less pronounced zonality, which is associated with greater aromatase activity in the scalp skin and a large number of estrogen beta-receptors [51, 52].

It is already established that 287 genes are responsible for the development of AGA, i.e., polygenic multifactorial inheritance takes place. However, the main gene is located on the X chromosome [17]. Polymorphism of one of the two main hair loss susceptibility genes in men — the androgen receptor gene EBA2R on the X chromosome — is associated with the early onset of AGA [11]. The role of aromatic compounds CYP19A1 genes has been suggested but not confirmed [6].

AGA in both men and women should raise concern over the development of metabolic syndrome, and coronary disease. Possible mechanisms explaining the relationship between these conditions are the presence of 5-AR and receptors for DHT in blood vessels [6, 53]. Studies have confirmed a significant relationship between body mass index, systolic and diastolic blood pressure, levels of aldosterone, cholesterol, triglycerides, glucose, fasting insulin and AGA. MS was observed significantly more often in patients with AGA — in 60% of men and 48.6% of women (12.5% and 8.1% without AGA, respectively, $p < 0.0001$) Patients with AGA also have more significant atheromatous plaques [54, 55].

A 2020 case-control cross-sectional study by Jingwen Ma et al. showed the following results: men with AGA (n = 1,312) had a higher mean uric acid level (6.25 mg/dl versus 5.97 mg/dl; $p < 0.001$) and a higher prevalence of hyperuricemia (25.0% versus 15.6%; $p < 0.001$) than men without AGA (n = 2,624). A significant relationship between the severity of AHA and hyperuricemia was not demonstrated ($p = 0.295$) [56]

Figure 1. *Androgenetic alopecia (female-type hair loss)*

In a population-based prospective cohort study, the relationship between the mortality rate from diabetes mellitus (DM) and cardiovascular diseases and the severity of AGA was evaluated in 7,252 participants After about five years of follow-up, there was a significantly higher risk of mortality from diabetes and cardiovascular diseases with moderate and severe AGA compared with normal or moderate AGA in men and women after adjusting for age, a family history of diabetes mellitus or cardiovascular disease and MS (adjusted risk ratio: 2.97 and 2.28, respectively). Therefore, despite the different mechanisms of alopecia in men and women, the occurrence of cardiovascular diseases and mortality from them increases in both gender groups [55].

In the event of AGA, men should be wary of the development of metabolic, coronary syndromes, prostate diseases, which underlines the importance of preventive measures, especially in young men and adolescents with AGA.

In the case of AGA in women and adolescent girls, the following should be excluded: polycystic ovary syndrome (the most common endocrine disease in women with AGA [6]), congenital adrenal cortical dysfunction, hyperprolactinemia and other causes of systemic hyperandrogenism (often also accompanied by acne and/or hirsutism, galactorrhea, anovulation), insulin resistance and type 2 DM. As in the case of male hair loss, in women, more than half of the cases do not show any concomitant disease; only a genetic predisposition is detected. In this case, a family history is important.

In the presence of a genetic predisposition, the androgen-estrogen ratio can play a decisive role. However, in clinical practice, among patients diagnosed with AGA, the majority have a reduced/normal level of testosterone in the blood and a normal/undetectable level of DHT. This is because 5-AR is a tissue enzyme, and the conversion of testosterone to DHT occurs directly in the skin (this phenomenon is called "cutaneous hyperandrogenism"). Therefore the measurement of DHT in the blood is of no diagnostic value in the absence of systemic disorder [57].

Sugar-lowering drugs have a positive effect on the course of AGA [24], again proving the relationship between this condition and hyperinsulinemia. Among these drugs, one of the most effective is metformin, since besides regulating carbohydrate metabolism, it has a positive effect on the microvasculature.

In 2017, a hypothesis was published. It summarized a large number of studies and suggested that the thinning

and hair loss characteristic of AGA is a consequence of fibrosis, which develops due to calcification of the microvasculature due to systemic vascular disorders in patients with heart diseases accompanied by hypercholesterolemia and deposition calcium in the walls of the arteries. Fibrosis is usually believed to be a consequence of perifollicular microinflammation as a result of the damaging effect of DHT [58]. However, regardless of the sequence of processes, it was found that metabolic disorders and AGA are associated, and AGA may be one of the markers of MS and cardiovascular risks [59.60].

AGA usually does not reverse itself, and patients need lifelong therapy with topical and systemic drugs after all possible comorbid conditions are excluded, or during treatment.

Telogen Effluvium (TE)

It is a common condition that is not associated with increased sensitivity to DHT, in which there is no progressive thinning of the hair shaft. Alopecia does not have a clear zonality; hair loss occurs evenly throughout the scalp. TE has various causes, mostly endocrine: thyroid diseases (hypo- and hyperthyroidism), Addison's disease and hypopituitarism. The severity of hair loss usually does not correlate with the severity of endocrine disease, and for a long time, may be the only symptom of the disease [6].

In TE management, treatment of the underlying disease is crucial. When the triggering factor is eliminated, complete hair restoration occurs.

Alopecia Areata

Alopecia areata is an immune-mediated disease characterized by sudden onset of hair loss from any area without scarring. This is a fairly common condition without hazard to life.

It has long been known that focal alopecia occurs in various autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes mellitus, vitiligo, systemic lupus erythematosus, thyroiditis, pemphigus vulgaris, pernicious anemia and celiac disease. There is evidence of impaired thyroid function or the presence of autoantibodies to thyroid tissue in 24% of examined children with focal alopecia. In adult patients with focal alopecia, antibodies to thyroid peroxidase were detected in 17.7% of cases.

The meta-analysis of 2019 studied the relationship between alopecia areata and thyroid disease. It was shown that the prevalence of thyroid diseases in patients with alopecia areata is significantly higher than in the control group (odds ratio 3.66; 95% confidence interval 2.90–4.61; p 0.001 [61].

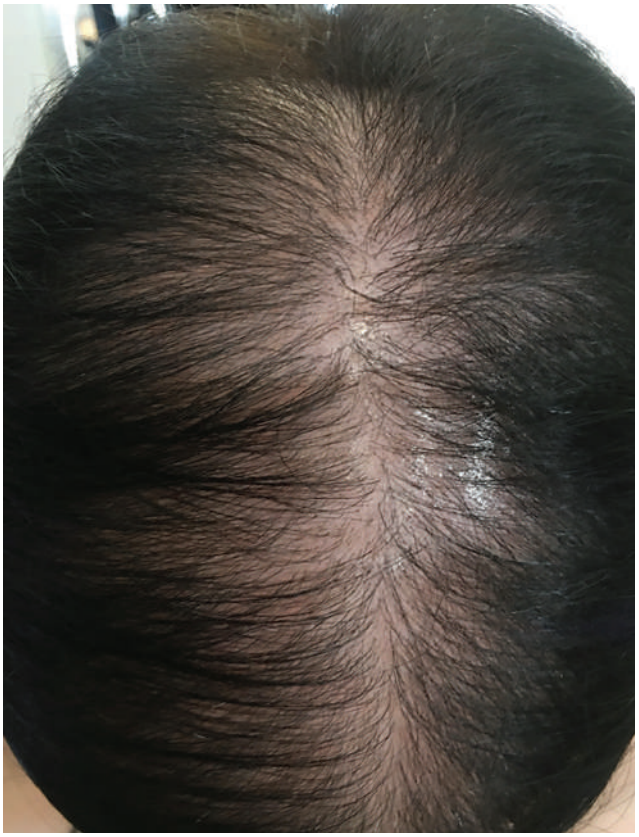

Figure 2. *Androgenetic alopecia in a patient with polycystic ovary syndrome*

Figure 3. *Diffuse telogen hair loss in hypothyroidism*

The overwhelming majority of patients with alopecia areata also have a critically low level of 25 (OH) D [59].

Treatment of alopecia areata is associated with the treatment of the underlying disease (if detected). However, in most cases, it is impossible to detect any causes of alopecia areata, while at the same time. The doctor is required to conduct a screening examination to exclude health-threatening conditions during the initial examination of such a patient.

Conclusion

Alopecia is a very common symptom in the population, and in a number of cases, it is a sign of endocrine diseases. The causes of alopecia and the clinical context of this symptom may be ambiguous in different cases. At the same time, there is no doubt that alopecia as a symptom should be subjected to clinical and diagnostic evaluation and not be ignored in the process of diagnostic search as a "purely age-related" phenomenon.

According to the information presented in the review, the problem under consideration does not always have an exclusively gerontological basis. Therefore, in most cases, the diagnostic search and the choice of therapeutic approach should be multidisciplinary with the participation of an endocrinologist, gynecologist, andrologist, dermatologist/trichologist and other medical specialists.

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Figure 4. *Alopecia Areata, multifocal form*

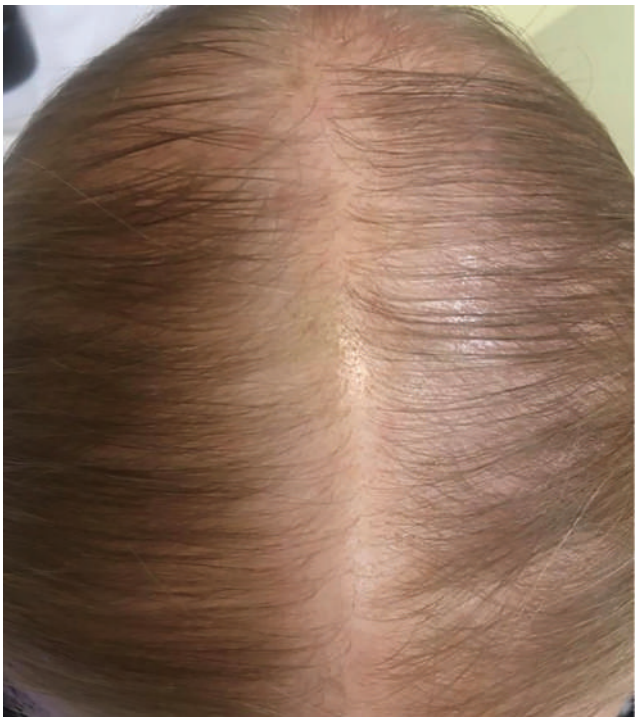

Figure 5. *Alopecia Areata, diffuseform*

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ДИСТАНЦИОННЫЙ МОНИТОРИНГ АРТЕРИАЛЬНОГО ДАВЛЕНИЯ КАК ИНСТРУМЕНТ ПОВЫШЕНИЯ КАЧЕСТВА ДИСПАНСЕРНОГО НАБЛЮДЕНИЯ ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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The Distance Monitoring of Blood Pressure as a Tool for Improving of the Quality of Follow-Up Observation of Patients with Arterial Hypertension

Резюме

В статье рассматриваются преимущества дистанционного мониторинга артериального давления у пациентов с артериальной гипертензией. Многочисленные исследования подтверждают увеличение риска сердечно-сосудистых осложнений даже при незначительном превышении показателей артериального давления. И наоборот, снижение значений артериального давления даже на 5 мм рт.ст. уменьшает риск летального исхода. В этой связи важным аспектом является не только назначение корректно подобранной антигипертензивной терапии, но и дистанционный мониторинг достижения и удержания целевых уровней артериального давления. Диспансерное наблюдение пациентов с артериальной гипертензией является эффективным инструментом профилактики сердечно-сосудистых осложнений. Однако, до настоящего времени охват динамическим контролем и достижение целевых показателей артериального давления у пациентов с артериальной гипертензией является одним из наиболее проблемных аспектов.

Результаты исследований отечественных и зарубежных авторов показывают высокую эффективность применения предлагаемых подходов дистанционного мониторинга артериального давления. Положительные результаты в отношении достижения таргетного артериального давления уже через 3 месяца показаны при применении технологии телемониторирования артериального давления и дистанционном консультировании больных артериальной гипертензией. Особого внимания заслуживает технология мобильного здравоохранения (mHealth), которая обеспечивает более гибкую платформу для улучшения самообслуживания пациентов.

***Ключевые слова**: артериальная гипертензия, дистанционный мониторинг артериального давления, технология мобильного здравоохранения, телемедицина*

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Abstract

This article focuses on the distant blood pressure monitoring for patients with arterial hypertension. As numerous studies show, even slightly elevated blood pressure significantly raises the risk of cardiovascular complications. And, vice versa, a 5 mmHg decrease in blood pressure reduces the lethality risk. Therefore, it is not enough to prescribe the right medication but also it is of paramount importance to monitor patients' compliance with the treatment. Clinical observation of patients with arterial hypertension is an effective tool for the prevention of cardiovascular complications. However, to date, the coverage of follow-up and the achievement of blood pressure targets in patients with arterial hypertension is one of the most problematic aspects. Distance monitoring of blood pressure opens more opportunities for the doctor's involvement, timely assessment and adjustment of the medication. The results of domestic and foreign research show high efficacy of the distance blood pressure monitoring. Positive results regarding the achievement of target blood pressure after 3 months are shown when using the technology of blood pressure monitoring and distance counseling of patients with arterial hypertension. In particular, the article considers the technology of mobile health care (mHealth), which is a more flexible platform for a patient's continuous self-care.

***Key words**: arterial hypertension, distance monitoring of blood pressure, mobile health technology, telemedicine*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, BP — blood pressure, FU — follow-up, RFU — remote follow-up, DBP — diastolic blood pressure, CHD — coronary heart disease, CVA — cerebrovascular accident, SBP — systolic blood pressure, DM — diabetes mellitus, CVD — cardiovascular diseases, TMRC — telemonitoring and remote consultation, RF — risk factors, COPD — chronic obstructive pulmonary disease, EML — electronic medical log, EMR — electronic medical records

Over the past 50 years, cardiovascular diseases (CVD) have been the main cause of mortality in the population [1]. According to the ESSE epidemiological study, which covered ten Russian regions, elevated blood pressure is the number one risk factor (RF) of CVD — 33.8% (Fig. 1) [2].

According to the results of the MMM17 (MAY MEASUREMENT MONTH 2017) multicenter study, controlled target BP could not be achieved in 46% of patients with hypertension who received antihypertensive therapy [3].

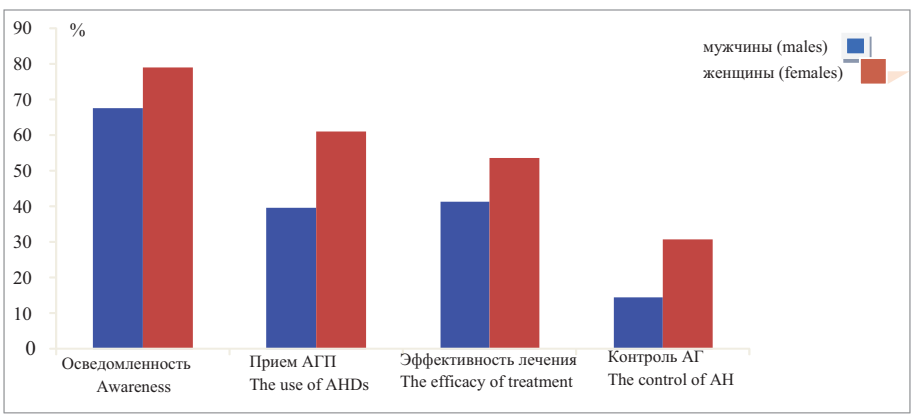

***Figure 1.** The trial ESSE-RF: the awareness of the presence of arterial hypertension, frequency of antihypertensive drugs uses and blood pressure control*

Uncontrolled hypertension is ranked first among risk factors of mortality and is the cause of more than 50% cerebrovascular accidents (CVA) and almost half of coronary heart disease (CHD) cases. The risk of death from CVD doubles if systolic blood pressure (SBP) increases by 20 mm and diastolic blood pressure (DBP) increases by 10 mm [4].

A meta-analysis of 61 prospective observational studies (1 million adults who had not been previously diagnosed with vascular diseases, 12.7 million person-years) showed that a decrease in mean SBP by 2 mm Hg leads to a 10% reduction in the risk of death from CHD and CVA or other vascular causes [5].

According to a large-scale study by Ettehad D. et al. (2016), a decrease from the initial SBP of 130–139 mm Hg by 10 mm Hg (that is, when the level of SBP reaches less than 130 mm Hg during treatment) leads to a significant decrease in the risk of the unfavorable cardiovascular impact of hypertension: CHD — by 12%, CVA — by 27%, heart failure — by 25%, major cardiovascular complications — by 13%, and death from any cause — by 11% [6].

According to the Program of State Guarantees, 43.8 million EMS calls are made annually in Russia. According to the Moscow EMS, CVD-related calls account for 18.8% of that number, of which 60% are due to hypertensive crises [7].

Follow-up (FU) of patients with hypertension is an effective tool for the prevention of cardiovascular complications**.** However, the coverage of FU and the achievement of target BP in patients with hypertension remains one of the most challenging tasks.

Active preventive measures can reduce the risk of adverse cardiovascular events, subsequent disability and mortality.

Primary care physicians shoulder most of the burden in implementing preventive programs and FU [8, 9]. Given the current shortage of primary care physicians, a number of disadvantages of FU can be identified: its limited scope and low quality, which may be associated, in addition to the shortage of manpower, with a low level of their expertise [9, 10].

In this connection, improving the FU procedure in hypertension is relevant, both in terms of increasing its coverage and improving its quality (achieving and maintaining target levels of health indicators), as well as reducing the number of cardiovascular complications.

The most relevant and acceptable model is remote monitoring, aimed at the simultaneous analysis of a large number of patients using automatic or semi-automatic information summarizing. Remote follow-up (RFU) can theoretically help to reduce the number of visits associated with exacerbation of diseases, as well as unfavorable life-threatening consequences [9].

Therefore, information technologies, including RFU, for solving primary and secondary prevention problems are becoming increasingly relevant [9].

The Experience of Remote BP Monitoring in Russia

To ease the social and economic burden of NID [non-infectious diseases] at the national level as part of international cooperation, Saratov researchers from the Research Institute of Cardiology conducted a study involving the use of BP analysis in 97 hypertensive patients undergoing active outpatient treatment and 102 patients receiving standard outpatient care. The aim of the study was to compare the clinical efficacy of active outpatient care, supported by short message services and mobile telephone technology, with standard outpatient management of patients with hypertension. The study included the analysis of blood pressure, body weight and smoking history. In the group of active outpatient care, 35 (36%) patients with hypertension were excluded from the study during the year: 18 patients with hypertension lost interest in the study, 12 patients declined for technical reasons and five patients refused for an unknown reason. According to the results of one year of observations, 48 (77%) patients from the active treatment group reached the target BP level. This was more than five times higher than in the group receiving standard outpatient care ($p = 0.03$). Odds ratio of achievement and maintenance of target BP in patients receiving treatment (control group) was 5.44; 95% CI 3.2–9.9; $p = 0.005$). The introduction of active outpatient care with the support of short message service and mobile phone technology improves the quality of outpatient care for patients with hypertension. The proposed method is the most affordable way to switch from standard outpatient care to active outpatient care for patients with hypertension (Fig. 2) [11].

For the rapid implementation of effective, innovative methods in large target groups of the population and/or even among the entire population (national or population level), it is necessary to use information technology in healthcare (e-health). The use of such technologies in practical healthcare can contribute to:

- improving the medical literacy of the population, including target groups and healthcare workers on innovative methods of diagnosis, prevention and control of NID and their RF;
- remote consultations/meetings on the provision of specialized medical care, including high-tech medical care;
- monitoring the use of guidelines and their effectiveness in relation to target health indicators [12].

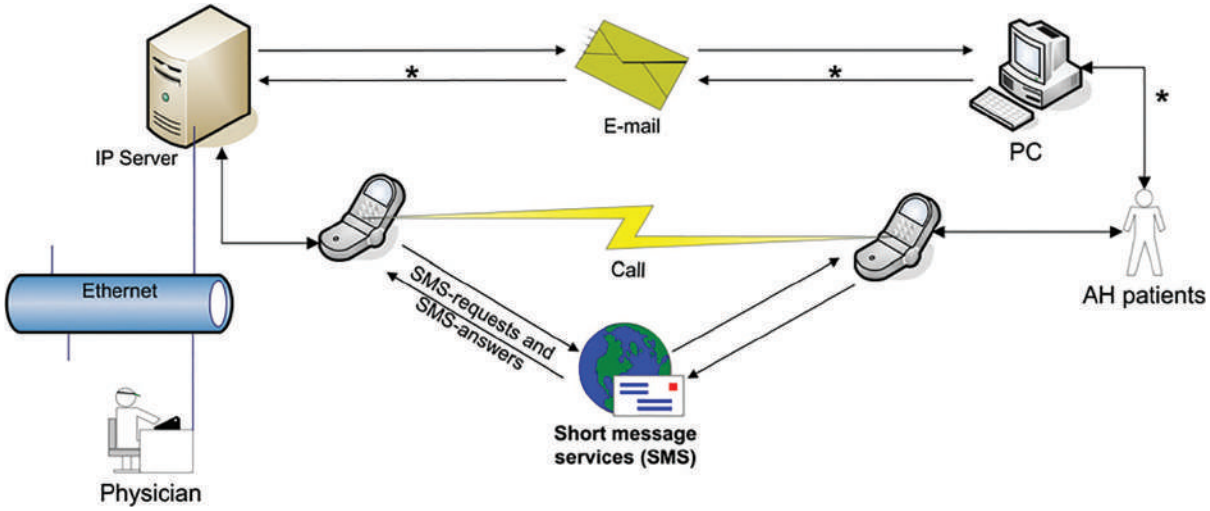

Figure 2. *Scheme of information technology system with SMS and mobile phone technology for active ambulatory care management.*

Note: * Only for arterial hypertension (AH) patients who did not return the data. IP, internet protocol; PC, personal computer

Analysis of data obtained in controlled clinical trials on hypertension in Russia showed the effectiveness of long-term management in achieving target blood pressure levels [13]. In real clinical practice, one of the important issues is maintaining the target BP values, which primarily depends on the patient's adherence to treatment and working with the doctor [14].

For these reasons, most countries have an insufficient level of BP control [15, 16]. The introduction of telemonitoring in practice can solve the problem of maintaining blood pressure within acceptable limits. In this regard, the remote monitoring of blood pressure at home has become widespread [17].

The undoubted advantages of using BP telemonitoring are presented in a pilot study conducted by M.V. Ionov et al. at the Federal State Budgetary Institution Almazov National Medical Research Center of the Ministry of Health of the Russian Federation. Cardiologists analyzed the effectiveness of achieving target BP and patient-oriented endpoints in telemonitoring BP and remote counseling (TMRC) of patients with hypertension. During the study, special TMRC programs were used with a follow-up every three months from one month to one year (the first and last visits were mandatory). Most patients chose a three-month follow-up period. After three months, a significant decrease in "office" SBP and DBP was recorded in the TMRC group compared with the control group ($p = 0.002$). By the end of the observation, BP self-monitoring in the TMRC group had decreased from 142 ± 17 to 128 ± 12 mm Hg (SBP), and from 88 ± 8 to 79 ± 6 mm Hg (DBP). Therefore, a decrease in SBP by –14 ± 10 mm Hg (95% CI [–11 to –17], $r = 0.819$, $p < 0.0001$) and in DBP by –9 ± 6 mm Hg (95% CI, [–7 to –11], $r = 0.647$, $p < 0.0001$) was achieved (Fig. 3). In addition, according to the Hospital Anxiety and Depression Scale (HADS), there was a decrease in the degree of anxiety and depression. As a result, there was an overall improvement in the patients' state. Therefore, the convenient, reliable TMRC technique for patients with uncontrolled hypertension is more effective than the standard approach used in routine clinical practice. However, the authors noted that its widespread implementation requires additional decisions: the inclusion of telemedicine consultations in the payment of compulsory (CMI) and voluntary (VMI) medical insurance, providing remote consultative care to patients in remote areas and in a stable condition, but with the need for regular follow-up, as well as the creation of a legal framework for the use of telemedicine in clinical practice [18].

In the scientific literature, besides the remote transmission of physiological data, the conditions of their subsequent management by medical personnel by phone are considered. Moreover, remote counseling of patients for the purpose of prevention is becoming more widespread [19].

In the Federal State Budgetary Institution National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Health of the Russian Federation, Kontsevaya A. V. et al. (2017) created a mathematical model of social and economic efficiency of remote BP monitoring in the region with a population of 1 million people. According to the model, BP monitoring would prevent up to 1,940 deaths over five years with 90% remote monitoring coverage of patients with hypertension and 645 deaths with 30% coverage [20].

In the study by Bubnova M. G. et al. (2019), which included 342 patients with hypertension, significant advantages were determined in remote monitoring

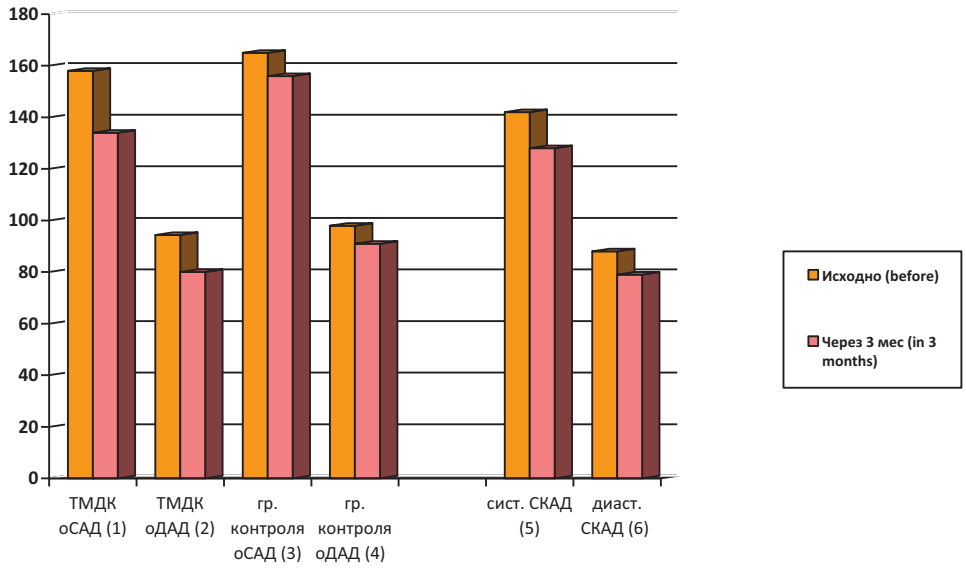

Figure 3. *The indicators of «office» and home blood pressure in the study groups*
Notes: of SBP — «office» systolic blood pressure; oDBP- «office» diastolic blood pressure; TMDC — telemonitoring of blood pressure and distance consultation; SMBP — self-monitoring of blood pressure. * before — исходно, in 3 months — через 3 месяца
1 — TMDC oSBP; 2 — TMDK oDBP; 3 — control group oSBP; 4 — control group oDBP; 5 — syst. SMBP; 6 — diast. SMBP

groups according to the number of EMS calls, hospitalizations, and the time spent on sick leave. After 12 months, in the main group, the target BP level was achieved in 92.2% of patients, in the control group — only in 43.3% [21].

Therefore, the domestic experience of using remote blood pressure monitoring demonstrates a number of advantages: it increases the proportion of patients with hypertension who have reached target BP values, improves adherence to treatment, reduces the duration of temporary disability and hospitalization, which is economically beneficial, primarily due to fewer requests for medical care and the preservation of human resources in the economy [20]. Based on the cost-benefit analysis of remote blood pressure monitoring in the Russian Federation, it can be concluded that the project should be considered not only effective but also fast-payback and fully viable for regional implementation [20].

Currently, there are some challenges with the implementation of remote BP monitoring in clinical practice. Several electronic medical services have been proposed to solve the monitoring problem. Although they are more patient-oriented and often effective, they still need wired connections to a personal computer with Internet access and navigation, which significantly reduces access for many elderly patients [21].

Remote BP Monitoring in Other Countries

Continuous BP monitoring over the entire FU period in patients with hypertension can be facilitated via mobile health technology (mHealth — Mobile Health), which is a more flexible platform for improving patient self-care. The World Health Organization (WHO) classifies mHealth under both medical practice and public health practice. The mHealth application is supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices [22]. In addition, the American Telemedicine Association (ATA) considers mobile healthcare as a form of telemedicine [23].

The success of using the mHealth application directly depends on adherence to monitoring schedules and prescribed treatment procedures [24]. A group of scientists from the University of Toronto (Canada) showed that not only in hypertension, but also in other chronic conditions, the use of mHealth contributed to the improvement in indicators reflecting the general condition of the patients [25].

It is known that for accurate diagnosis of hypertension, repeated measurement of blood pressure is recommended, as demonstrated by a group of American researchers [26]. Patients were randomized into three groups. In each group, it was proposed to record the results of BP measurements in an electronic medical log (EML). In the second and third groups, SMS (Short Message Service) messages were used as a reminder to communicate with the patient, including feedback, asking them to send blood pressure measurement results. The report recommended to perform 14 BP measurements. Among 121 patients, 14 measurements were performed more often in the feedback group compared with the first and second groups. The study showed that bidirectional

automated text messaging is an effective way to collect data on the patient's BP. Only text reminders turned out to be an effective way to encourage patients to take BP measurements [26].

Electronic medical records (EMR) and smart computer systems are increasingly having an impact on established approaches in medicine [27]. As a result, the combination of extensive EMR and computer analysis allows to automate the collection of information, data synthesis and feedback from the clinician. These systems, organized in the form of a complex cloud network, allow data sharing using, among other things, mobile online access. It is likely that these approaches will increasingly have an impact on medical education. Since smart computer systems can analyze a large amount of data and share the results of the analysis with suppliers, the focus of medical training can shift for the better. Guidelines will be formed on the use of electronic systems for the treatment of patients. Considering the influence of data processing technologies on many aspects of everyday life, computer technologies adapted in the medical environment will affect the model of the relationship between the doctor and the patient, which will bring potential benefits to both individuals and large groups.

At the same time, foreign researchers also note limitations in the implementation of remote BP monitoring in practice. Clinical decision making depends on complex human factors and personal preferences. In the short term, approaches with automated data collection and machine learning will likely play a largely supporting role in the doctor-patient relationship [27]. In cases of high BP, mHealth improved patients' adherence to antihypertensive drug therapy and contributed to its decrease [27].

McGillicuddy J. W. et al. (2013) conducted a study in which 20 participants were monitored for three months using the prototype mobile healthcare. A BP self-monitoring system was used. Adherence to treatment, usability and results were evaluated. Compared with the control group, the mHealth intervention group showed a significant improvement in adherence to therapy and a significant decrease in the clinical SBP measured monthly. During the three-month trial, the doctors performed more adjustments of antihypertensive treatment in the mHealth group compared to the standard group (seven adjustments in five patients versus three adjustments in three patients) based on the information provided in the weekly reports [28].

The adherence index (degree of the patient's compliance with the doctor's recommendations), previously described by Russell C. L. et al., was used to assess the use of prescribed drugs at the recommended time [29]. Adherence to treatment increased significantly after three months of using mobile healthcare compared to standard medical care. SBP decreased from 138 to 122 mm Hg and DBP from 88 to 81 mm Hg when using mobile healthcare; in the control group, SBP increased from 132 to 139 mm Hg and DBP increased from 76 to 79 mm Hg after three months. Limitations of the study were associated with the small sample size from one clinical center [29].

The SimCard Study (SimCard trial, 2015) was a randomized, controlled, follow-up study of 2,086 patients over 40 years of age with a high risk of CVD, who reported CHD, stroke, or diabetes mellitus or SBP ≥ 160 mm Hg. Participants in the follow-up group were monitored by health professionals using the Android application monthly; treatment was limited to two medications and lifestyle adjustment. The control group had access to free drugs in primary care centers. Compared to the control group, the comparison group showed a higher incidence of antihypertensive drug use (by 25.5%; $p < 0.001$). In addition, significant differences were found in the assessment of secondary endpoints: an increase in aspirin intake (17.1%; $p < 0.001$) and a decrease in SBP by an average of 2.7 mm Hg ($p=0.04$). This multicenter study showed that mobile technologies are potentially useful for improving adherence to treatment among resource-limited populations [30].

McInnes D. K. et al. (2014) considered the use of mobile phone text messages for veterans in nursing homes to increase their adherence to treatment and reduce the number of no-shows for appointments. To this end, two text message reminders were sent to 20 participants of the study before each of their outpatient visits to the city medical center for veterans [31]. The assessment included questionnaires before and after the visit, open-ended questions (interviews) and a review of medical records. The questions concerned social and demographic characteristics, the experience of using mobile phones (how often), the reasons for making calls on a mobile phone and sending text messages, and the barriers to using a mobile phone. The cost and cost-effectiveness of large-scale implementation were also evaluated. The study participants were pleased to receive text messages, had few technical difficulties and were interested in continuing receiving the reminders. There was a downward trend in the cancellation of visits and no-shows from 53 to 37 and from 31 to 25, respectively ($p = 0.03$). There was also a decrease in admissions to emergency departments ($p = 0.01$) and the number of hospitalizations from 3 to 0 ($p = 0.08$). Researchers concluded that text message reminders were beneficial for veterans.

Telemedicine is increasingly used for remote and timely provision of clinical care, and some studies have shown its effectiveness in treating the most common chronic diseases [32]. Tholomeus is an online telemedicine service that passed clinical testing and is certified for Internet medicine. The service facilitates a closed cycle of

communication between patients and caregivers in accordance with interdisciplinary and complex interventions. Evidence on the effectiveness of the service has been collected over the past decade in 1,471 health facilities. More than 135,000 patients have documented the usefulness of the service in improving access to medical care and improving the screening and treatment of hypertension, CVD, COPD and obstructive sleep apnea. In addition to professional diagnostic tests, the AndroidTM Tholomeus® app, which has been used by 3,654 consumers over the past three years, has helped to record the high incidence of impaired glucose tolerance, overweight or obesity, dyslipidemia, or uncontrolled BP among users. According to experts, the use of telemedicine in the management of chronic diseases is currently characterized by a high heterogeneity of solutions, often not supported by reliable evidence of clinical efficacy and safety. Tholomeus® meets current recommendations for software designed to be used as a medical device [32]. Today, Tholomeus® is widely used in Italy. The positive experience of Italian colleagues could help ramp up the implementation of the project in Russia. Unfortunately, the web portal is still available only in Italian and English. And this is the only obstacle that limits the ability of Russian patients to actively use the online service to assess their health status.

WHO declared the novel coronavirus disease (COVID-19) pandemic in 2020. Patients with hypertension, DM, cerebrovascular diseases, CHD and COPD are at high risk of COVID-19 complications [33, 34]. One side effect of the measures taken to curb the spread of COVID-19, which involves a range of restrictions, is the late referral in case of life-threatening conditions, as well as an increase in hospitalizations, for example, for hypertension or diabetes [35, 36].

According to the recommendations of the consensus of experts of the Russian Society for the Prevention of Non-Communicable Diseases, Specialized Commission on Therapy and General Medical Practice of the Ministry of Health of the Russian Federation and Specialized Commission on Medical Prevention of the Ministry of Health of the Russian Federation "Providing Outpatient Medical Care to Patients with Chronic Diseases Subject to Follow-Up in the Context of the COVID-19 Pandemic", it is advisable to provide patients with a high risk of complications due to hypertension with personal medical devices (telemedicine tonometers). These devices enable wireless data transmission of diagnostic results to a medical institution, taking into account the accumulated experience of remote monitoring of patients with hypertension, which is the main factor in developing heart attack, stroke and other cardiovascular complications. A telemedicine tonometer can be delivered to a patient via a courier, with the involvement of volunteers. It can also be delivered by medical professionals when providing medical care to a patient with exacerbation of the disease (during referral to a healthcare facility, in-home medical care, discharge from the hospital, and providing first aid) [37].

Conclusion

The implementation of remote BP monitoring will significantly improve the existing model of diagnosis and treatment of patients with chronic diseases. It will also increase the number of patients observed at each therapeutic site without increasing the follow-up time and encourage the working-age population to utilize primary prevention of cardiovascular diseases. The use of active remote monitoring of patients with hypertension receiving antihypertensive therapy (both in domestic and foreign practice) enables to achieve target BP values with subsequent monitoring of health indicators, as well as timely delivery of medical care.

The data obtained demonstrate an improvement in patients' adherence to antihypertensive treatment with remote monitoring of blood pressure, as well as an increase in the population's satisfaction with the quality of medical care.

The experience of foreign clinicians proves the high efficiency of using mHealth technology for remote BP monitoring in patients with hypertension, focusing on the continuous interaction with the doctor through feedback. Clinical and economic studies, including using mathematical modeling, support the economic feasibility of the widespread implementation of remote monitoring in clinical practice due to a reduced incidence of cardiovascular complications and, as a result, reduced cost of emergency care, hospitalization, and rehabilitation.

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Шарапова Ю.А. (ORCID ID: https://orcid.org/0000-0002-4269-2143): сбор, анализ и интерпретации данных, научное редактирование

Author Contribution:

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

Starodubtseva I.A. (ORCID ID: https://orcid.org/0000-0002-4665-2966): the review and analysis of literary sources in domestic and foreign databases, formation of ideas and structure, generalization and comparative analysis of the results, final approval of the manuscript for publication, responsible for all aspects of the work.

Sharapova Yu.A. (ORCID ID: https://orcid.org/0000-0002-4269-2143): the collection, analysis and interpretation of data, scientific editing

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ФАКТОРЫ РИСКА ГОСПИТАЛЬНОЙ ЛЕТАЛЬНОСТИ ПРИ ОСТРОМ КОРОНАРНОМ СИНДРОМЕ С ПОДЪЕМОМ СЕГМЕНТА ST, ОСЛОЖНЕННОМ КАРДИОГЕННЫМ ШОКОМ

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Risk Factors for Hospital Mortality in Acute ST-Segment Elevation Coronary Syndrome Complicated by Cardiogenic Shock

Резюме

Цель исследования. Изучить факторы риска госпитальной летальности у больных острым коронарным синдромом с подъемом сегмента ST (ОКСпST), осложненным кардиогенным шоком (КШ). **Материал и методы.** Исследовались 104 пациента с ОКСпST, осложненным КШ. В группу наблюдения (I группу) вошли 58 (55,8%) умерших в стационаре больных (средний возраст 71,8±7,31 лет), в группу сравнения (II группу) — 46 (44,2%) пациентов, прошедших лечение и выписавшихся (средний возраст 59,5±6,18 лет). Всем больным проводились общеклинические исследования, определялся уровень тропонинов, липидов, глюкозы, креатинина плазмы, выполнялась электрокардиография и эхокардиография. Экстренно проводили коронароангиографию и чрескожное коронарное вмешательство (ЧКВ). Для выявления факторов риска госпитальной летальности использовали метод бинарной логистической регрессии с определением для каждой достоверной переменной отношения шансов и его 95% доверительного интервала. **Результаты.** В I группе больных с КШ, по сравнению со II группой, значимо чаще наблюдались пациенты в возрасте старше 70 лет (32 (55,2%) vs 10 (22,7%), p=0,0004), с сопутствующей хронической болезнью почек (32 (55,2%) vs 9 (19,6%), p=0,0002), постинфарктным кардиосклерозом (30 (51,7%) vs 9 (19,6%), p=0,001) и хронической сердечной недостаточностью III-IV функционального класса (32 (55,1%) vs 11 (23,9%), p=0,001). Исходные уровни лейкоцитов, тропонина и креатинина плазмы были достоверно выше у умерших больных с КШ. Фракция выброса левого желудочка ниже 40% отмечалась чаще в группе наблюдения, чем в группе сравнения (46 (79,3%) vs 27 (58,7%), p=0,022). В I группе, по сравнению со II группой, была выше частота трехсосудистого поражения венечного русла (36 (75%) vs 12 (26,1%), p=0,0001) и хронической окклюзии коронарной артерии, несвязанной с ОКСпST (25 (52,1%) vs 12 (26,1%), p=0,009). Такая же тенденция отмечалась при оценке среднего числа стенозов и окклюзий коронарных артерий. ЧКВ выполнено 43 (74,1%) умершим и 43 (93,5%) выжившим больным ОКСпST с КШ (p=0,009). В группе наблюдения, чем в группе сравнения, была выше частота безуспешного ЧКВ (13 (30,2%) vs 3 (7%), p=0,001) и проведенного позднее 6 часов от начала ангинозного приступа (28 (65,1%) vs 6 (14%), p=0,0001). **Выводы.** Госпитальная летальность у больных ОКСпST, осложненным КШ, ассоциировалась с наличием у них фракции выброса левого желудочка менее 40%, трехсосудистого поражения коронарного русла и проведением ЧКВ позднее 6 часов от начала болевого приступа.

Ключевые слова: *кардиогенный шок, острый коронарный синдром с подъемом сегмента ST, госпитальная летальность, факторы риска, предикторы, прогноз*

Конфликт интересов

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

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Abstract

The aim. To study the risk factors for hospital mortality in patients with acute coronary syndrome with ST-segment elevation (STEACS) complicated by cardiogenic shock (CS). **Materials and methods.** A total of 104 patients with STEACS complicated by CS were studied. The follow-up group (group I) included 58 (55,8%) patients who died in hospital (mean age 71,8±7,31 years), the comparison group (group II) — 46 patients, who have been treated and discharged (mean age 59,5±6,18 years). All patients underwent general clinical studies, the level of troponins, lipids, glucose, creatinine in plasma was determined, electrocardiography and echocardiography were performed. Coronary angiography and percutaneous coronary intervention (PCI) were urgently performed. The method of binary logistic regression with the determination of the odds ratio and its 95% confidence interval for each reliable variable was used to identify risk factors for hospital mortality. **Results.** In group I patients with CS, compared with group II, patients over the age of 70 (32 (55,2%) vs 10 (22,7%), p=0,0004), with concomitant chronic kidney disease (32 (55,2%) vs 9 (19,6%), p=0,0002), postinfarction cardiosclerosis (30 (51,7%) vs 9 (19,6%), p=0,001) and chronic heart failure of III-IV functional class (32 (55,1%) vs 11 (23,9%), p=0,001) were significantly more often observed. Baseline levels of plasma leukocytes, troponin and creatinine were significantly higher in deceased patients with CS. Left ventricular ejection fraction below 40% was observed more often in the follow-up group than in the comparison group (46 (79,3%) vs 27 (58,7%), p=0,022). In group I, compared with group II, there was a higher incidence of three-vessel coronary lesions (36 (75%) vs 12 (26,1%), p=0,0001) and chronic coronary artery occlusion unrelated to STEACS (25 (52,1%) vs 12 (26,1%), p=0,009). The same trend was observed when assessing the average number of stenoses and occlusions of the coronary arteries. PCI was performed in 43 (74,1%) of the deceased and 43 (93,5%) of the surviving STEACS patients with CS (p=0,009). The follow-up group had a higher rate of unsuccessful PCI (30,2%) vs 3 (7%), p=0,001) and performed later than 6 hours after the onset of an angina attack (28 (65,1%) vs 6 (14%), p=0,0001). **Summary.** Hospital mortality in patients with STEMI complicated by CS was associated with the presence left ventricular ejection fraction less than 40%, three-vessel coronary lesion and performing PCI later than 6 hours from the beginning of the pain attack.

Key words: *cardiogenic shock, acute ST-segment elevation coronary syndrome, hospital mortality, risk factors, predictors, prognosis*

Conflict of interests

The authors declare no conflict of interests

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CS — cardiogenic shock, ACSST — acute coronary syndrome with ST segment elevation, PCI — percutaneous coronary intervention

Due to the significant success in medical care for patients with acute coronary syndrome with ST-segment elevation (ACSST), widespread routine percutaneous coronary interventions (PCI) have reduced in-hospital mortality in recent years [1]. Today, in-hospital ACSST mortality in leading clinical centers does not exceed 2–2.3% [2]. However, despite advances in treatment, cardiogenic shock (CS) remains the leading cause of death in these patients [3]. CS accounts for 76% of lethal outcomes in myocardial infarction with ST segment elevation in the first seven days [4]. CS incidence in ACSST in recent decades has not significantly decreased and amounts to 4–15% [5, 6], and mortality is not less than 50% [7, 8]. In this regard, the identification of predictors of adverse outcome in patients with ACSST complicated by CS and the search for methods for their management that could increase the survival of these patients is relevant.

Study purpose — to study the risk factors for in-hospital mortality in patients with ACSST complicated by CS.

Material and Methods

This prospective, open-label, observational study included 104 patients with ACSST complicated by CS admitted to the Cardiology Department of the Vascular Center of Ivanovo Regional Clinical Hospital in 2019. CS was diagnosed based on systolic blood pressure decrease below 90 mm Hg for more than 30 minutes or the need for infusion of vasopressors to maintain systolic pressure above 90 mm Hg and due to the signs of hypoperfusion. Among the studied patients with CS, 58 patients died in the hospital (55.8%). Therefore, all the patients were divided into two groups. The study group I included

58 deceased patients with ACSST complicated by CS, and the comparison group (group II) included 46 patients with ACSST with CS who underwent treatment and were discharged from the hospital. All enrolled patients with ACSST at admission were diagnosed with myocardial infarction with ST segment elevation.

Inclusion criteria: ACSST complicated by CS; men and women; signing of voluntary informed consent.

Exclusion criteria: acute coronary syndrome without ST segment elevation on the electrocardiogram; intercurrent somatic disease, which has an independent negative impact on the prognosis (severe hepatocellular and respiratory failure, metastatic cancer, cerebrovascular accident during the month before or during this hospitalization); refusal of the patient to be included in the study.

Upon admission to the hospital, the study patients underwent physical examination; blood troponins, lipids, glucose, and creatinine were determined and electrocardiography and echocardiography were performed. Coronary angiography and PCI were urgently performed.

The patients were examined based on informed voluntary consent in accordance with order No. 3909n of the Ministry of Health and Social Development of the Russian Federation of April 23, 2012 (registered by the Ministry of Justice of the Russian Federation on May 05, 2012, under No. 240821) in compliance with ethical principles.

Statistical data were processed using the IBM SPSS Statistics 23 software. The normal distribution of the sample was checked using the Shapiro—Wilk test. Quantitative signs are presented as the arithmetic mean of the variation series and its standard deviation (M ± SD) in the normal distribution or the median and interquartile range (Me [Q25; Q75]) in the distribution other than normal. Qualitative data are expressed as absolute and percentage values (n (%)). Analysis of the statistical significance of differences between quantitative indicators was performed using the parametric Student's t-test or the non-parametric Mann—Whitney U-test, between the qualitative characteristics — χ^2 criterion. Factors associated with the likelihood of in-hospital mortality were identified using simple logistic regression. Multiple logistic regression was used to detect predictors that independently affect in-hospital mortality. Differences were considered significant at $p < 0.05$.

Results

The mean age of deceased patients with CS was significantly higher than that of survivors (71.8 ± 7.31 and 59.5 ± 6.18 years, respectively, p = 0.003) (Table 1). There were 32 (55.2%) patients older than 70 years in group I, which is significantly higher than in group II (10 (22.7%), p = 0.0004). Among the studied patients with ACSST complicated by CS, men predominated, but in the group of deceased patients, there were fewer of them than among survivors (32 (55.2%) and 34 (73.9%), respectively, p = 0.049), due to the increased number of women (26 (44.8%) and 12 (26.1%), respectively, p = 0.049).

There were no significant differences between the groups in the incidence of such cardiovascular risk factors as smoking, hypertension, diabetes mellitus, obesity and dyslipidemia. Chronic kidney disease diagnosed before the development of ACSST was more common in deceased patients with CS than among survivors (32 (55.2%) and 9 (19.6%), respectively, p = 0.0002). The incidence of acute kidney injury was higher in the observation group than in the control group (39 (67.2%) and 22 (47.8%), respectively, p = 0.046). A history of myocardial infarction was observed in 30 (51.7%) patients of group I and in 9 (19.6%) patients of group II (p = 0.001). Prior to the development of ACSST, among deceased patients with CS, chronic heart failure with reduced ejection fraction was observed more often than among survivors (36 (62.1%) and 12 (26.1%), respectively, p = 0.0001); NYHA III–IV (32 (55.2%) and 11 (23.9%), respectively, p = 0.001). There were no significant differences between the compared groups in the frequency of PCI and cerebrovascular accident history, as well as in the localization of acute ischemic changes in the electrocardiogram.

Compared with surviving patients with CS, deceased patients with ACSST complicated by CS had significantly higher blood levels of leukocytes (13.1 ± 1.01 and 10.2 ± 0.95 10^9/l, respectively, p = 0.0001) and troponin (7,905.1 ± 710.22 and 6,134.3 ± 811.18 pg/ml, respectively, p = 0.001) (Table 2). Initially, before CAG and PCI in patients of group I, plasma creatinine was significantly higher (138.2 ± 12.12 and 116.8 ± 10.22 μmol/l, respectively, p = 0.002), and the glomerular filtration rate was lower (45.7 ± 4.36 and 51.3± 3.12 ml/min/1.73 m^2, respectively, p = 0.016) in comparison with group II. There were no significant differences between the groups in terms of lipid profile, as well as blood level of hemoglobin and glucose.

At admission, ejection fraction of the left ventricle below 40% was observed in 46 (79.3%) and 27 (58.7%) patients of group I and II, respectively (p = 0.022). Significant differences were found between the observation and comparison groups in terms of end-systolic (48.7 [47.9; 49.4] and 47.9 [47.3; 48.5] mm, respectively, p = 0.013) and end-diastolic (58.5 [57.9; 59.1] and 57.1 [56.7; 57.2] mm, respectively, p = 0.012) size of the left ventricle.

Urgent coronary angiography was performed in 48 (82.8%) deceased patients and in 46 (100%) survived patients with ACSST complicated by CS (p = 0.003).

Table 1. *Initial comparative characteristics of patients with acute coronary syndrome with ST-segment elevation complicated by cardiogenic shock*

Sign	Group I (n=58)	Group II (n=46)	p
Age, years (M±SD)	71,8±7,31	59,5±6,18	0,003
Age >70 years, n (%)	32 (55,2)	10 (21,7)	0,0004
Female, n (%)	26 (44,8)	12 (26,1)	0,049
Male, n (%)	32 (55,2)	34 (73,9)	0,049
Smoking, n (%)	33 (56,9)	24 (52,2)	0,635
AH, n (%)	52 (89,7)	35 (76,1)	0,064
Diabetes mellitus, n (%)	20 (34,4)	10 (21,7)	0,157
Obesity, n (%)	23 (39,7)	17 (36,9)	0,781
Dyslipidemia, n (%)	46 (79,3)	34 (73,9)	0,521
AKI, n (%)	39 (67,2)	22 (47,8)	0,046
History of CKD, n (%)	32 (55,1)	9 (19,6)	0,0002
PICS, n (%)	30 (51,7)	9 (19,6)	0,001
CHF with preserved EF, n (%)	2 (3,4)	15 (32,6)	0,00004
CHF with intermediate EF, n (%)	12 (20,7)	14 (30,4)	0,259
CHF with low EF, n (%)	36 (62,1)	12 (26,1)	0,0002
History of CVA, n (%)	4 (6,9)	6 (13,0)	0,295
History of PCI, n (%)	5 (6,9)	4 (8,7)	0,989
Localization of acute ischemic changes on the ECG:			
- anterior, n (%)	24 (41,4)	15 (32,6)	0,364
- anterolateral, n (%)	7 (12,0)	5 (10,9)	0,317
- inferior, n (%)	27 (46,6)	26 (56,5)	0,851
Time from the beginning of the pain syndrome to PCI, min (Me [Q25;Q75])	418,8 [379,1;458,6]	214,5 [171,9;257,1]	0,0001

Note: AH — arterial hypertension; AKI — acute kidney injury; CKD — chronic kidney disease; PICS — postinfarction cardiosclerosis; CHF — chronic heart failure; EF — ejection fraction; FC — functional class; CVA — acute cerebrovascular accident; PCI — percutaneous coronary intervention; ECG — electrocardiography

Table 2. *Primary laboratory and instrumental indicators in patients with acute coronary syndrome with ST-segment elevation complicated by cardiogenic shock (Me [Q25;Q75])*

Indicator	Group I (n=58)	Group II (n=46)	p
Leukocytes, 10^9/l	13,1 [12,1;14,1]	10,2 [9,3;11,2]	0,0001
Hemoglobin, g/l	139,8 [129,6;150,01]	143,9 [131,6;156,2]	0,124
Troponin, pg/ml	7905,1 [7194,9;8615,3]	6134,3 [5323,1;6945,5]	0,001
Creatinine, μmol/l	138,2 [126,1;150,3]	116,8 [106,6;127,02]	0,002
GFR, ml/min/1,73 m^2	45,7 [41,3;50,06]	51,3 [48,2;54,4]	0,016
Glucose, mmol/l	6,8 [5,7;7,9]	6,7 [5,7;7,7]	0,264
Total cholesterol, mmol/l	5,7 [5,3;6,1]	5,5 [5,2;5,8]	0,132
LDL, mmol/l	3,3 [3,1;3,6]	3,2 [2,9;3,5]	0,074
HDL, mmol/l	1,05 [0,96;1,14]	1,11 [0,98;1,22]	0,102
Triglycerides, mmol/l	2,3 [1,7;2,8]	2,2[1,7;2,7]	0,208
LV ejection fraction, %	33,5 [30,3;36,7]	36,4 [32,1;40,8]	0,048
LVESD, mm	48,7 [47,9;49,4]	47,9 [47,3;48,5]	0,013
LVEDD, mm	58,5 [57,9;59,1]	57,1 [56,7;57,2]	0,012

Note: GFR — glomerular filtration rate; LDL — low-density lipoproteins; HDL — high-density lipoproteins; LV — left ventricular ejection; LVESD — left ventricular end systolic diameter; LVEDD — left ventricular end diastolic diameter

CAG in the observation group was not performed in 10 (17.2%) patients due to the extremely serious state at admission and death within an hour from the moment of hospitalization.

According to the results of CAG, in patients of group I, three-vessel lesion of the coronary arteries was significantly more often diagnosed than in patients of group II (36 (75%) and 12 (26.1%), respectively, p = 0.0001), while single-vessel was less often (1 (2.1%) and 27 (58.1%), respectively, p = 0.0001). Compared with survivors, deceased patients with CS had a significantly higher average number of occlusions (1.58 [0.97; 2.19] and 1.13 [0.51; 1.75], respectively, p = 0.001) and hemodynamically significant stenoses (2.5 [1.75; 3.25] and 2.1 [1.48; 2.72], respectively, p = 0.033) of the coronary arteries. Chronic occlusion of the coronary artery unrelated to ACSST was observed in 25 (52.1%) patients of group I and 12 (26.1%) of patients of group II (p = 0.009). Hemodynamically significant stenosis of the left main coronary artery stem was observed in 9 (18.8%) and 2 (4.3%) patients of the observation and comparison group, respectively (p = 0.03).

PCI was performed in 43 (74.1%) deceased and 43 (93.5%) survived patients with ACSST with CS (p = 0.009). In all cases, the intervention resulted in the stenting of the infarct-related artery. The mean number of implanted stents in the observation group was 1.52 [0.81; 2.23], and in the comparison group — 1.43 [0.73; 2.13] (p = 0.004). In the remaining patients of group I and II (5 (10.4%) and 3 (6.5%), respectively, p = 0.023), stenting was not performed due to multiple coronary bed lesions and/or technical impossibility of intervention. Unsuccessful PCI was observed in 13 (30.2%) deceased and 3 (7%) survived patients with ACSST complicated by CS (p = 0.001) and was characterized primarily by the no-reflow phenomenon in both groups (10 (23.3%) and 3 (7%), respectively, p = 0.007), as well as acute stent thrombosis and death on the operating table in the observation group (2 (4.7%) and 1 (2.3%), respectively).

The mean time from the onset of pain to the intervention was greater in the group of deceased patients (418.8 [379.1; 458.6] and 214.5 [171.9; 257.1] minutes, respectively, p = 0.0001). The same trend was observed in the study of the frequency of PCI, performed more than six hours from the onset of angina (28 (65.1%) and 6 (14%), respectively, p = 0.0001).

Intraaortic balloon counterpulsation was performed in 12 (20.7%) patients of group I and in 6 (13%) patients of group II (p = 0.301).

Using the simple logistic regression method, we identified factors associated with in-hospital mortality in patients with ACSST complicated by CS (Table 3).

A multiple logistic regression analysis, which incrementally included the above-mentioned signs, identified

Table 3. *Factors associated with hospital mortality in patients with acute coronary syndrome with ST-segment elevation complicated by cardiogenic shock*

Sign	OR	95% CI	p
Age >70 years	4,43	1,85-10,59	0,001
History of CKD	5,06	2,07-12,37	0,00001
PICS	4,41	1,81-10,75	0,001
CHF III-IV FC	3,92	1,64-9,19	0,001
LV ejection fraction <40%	2,69	1,12-6,41	0,031
Three-vessel lesion	8,51	3,36-21,49	0,00001
Chronic CA occlusion	3,08	1,29-7,34	0,012
PCI later 6 hours after the onset of pain	11,51	3,96-33,44	0,00001
Unfulfilled PCI	5,02	1,35-18,53	0,01
Unsuccessful PCI	5,78	1,51-22,10	0,011

Note: OR — odds ratio; CI — confidence interval; CKD — chronic kidney disease; PICS — postinfarction cardiosclerosis; CHF — chronic heart failure; FC — functional class; LV — left ventricle; CA –coronary artery; PCI — percutaneous coronary intervention

Table 4. *Independent predictors of hospital mortality in patients with acute coronary syndrome with ST-segment elevation complicated by cardiogenic shock*

Sign	OR	95% CI	Wald χ^2	p
LV ejection fraction <40%	1,99	1,11-5,86	7,797	0,007
Three-vessel lesion	5,91	1,55-22,53	6,769	0,009
PCI later 6 hours after the onset of pain	3,50	1,88-13,89	8,255	0,005

Note: OR — odds ratio; CI — confidence interval; LV — left ventricle; PCI — percutaneous coronary intervention

significant independent variables that influence an adverse outcome in patients with ACSST complicated by CS (Table 4). For the model as a whole, Wald chi square was 6.676, p <0.01.

Discussion

According to the literature, elderly age is an independent predictor of an adverse outcome in patients with ACSST complicated by CS, which is associated primarily with progressive left ventricular dysfunction in patients with ACS [3, 9, 10]. Age older than 65–70 years in patients with ACSST is associated with a high incidence of CS, the history of cardiovascular diseases [9] and such organizational aspect as adherence to a conservative management of older patients [10]. In the presented analysis, the majority of deceased patients with CS were older than 70 years, and the mean age in the observation group was 71.8 ± 7.3 years.

According to some authors, the female sex is a factor of in-hospital mortality in patients with CS in ACSST [9]. Other researchers noted that women with myocardial infarction complicated by CS were more likely to have unfavorable clinical characteristics such as old age, diabetes mellitus, hypertension and low cardiac output; however, the female sex was not identified as an independent predictor of in-hospital mortality in patients with CS [11, 12, 13]. According to our results, there were significantly more women in the group of deceased patients than among survivors. However, logistic regression analysis did not confirm the hypothesis that female sex may be a risk factor for in-hospital mortality in patients with ACSST complicated by CS (OR 2.3, 95% CI 0.99–5.32; p = 0.065).

Our findings that the clinical and anamnestic predictors of death in patients with ACSST with CS are chronic kidney disease, cardiosclerosis and high-NYHA chronic heart failure are consistent with the results of other studies [3, 7, 14, 15].

In the groups we analyzed, the blood level of leukocytes and troponins on the first day after hospitalization was significantly higher in deceased patients with CS. According to the literature, a systemic inflammatory reaction plays a role in the development and progression of CS in myocardial infarction. It occurs in cardiac muscle necrosis and progressive tissue hypoxia during shock, and contributes to the progression of myocardial dysfunction [16]. The blood level of proinflammatory cytokines (interleukin-6, tumor necrosis factor-α, C-reactive protein and others) and leukocytes correlated with the severity of CS and adverse outcome in patients with myocardial infarction [16, 17]. Some studies note that the degree of blood troponin increase in patients with ACS has prognostic value in the development of CS and early mortality [18].

A high level of plasma creatinine is associated with an unfavorable prognosis in ACSST complicated by CS [3, 14]. According to our data, the initial serum creatinine was higher before PCI and the glomerular filtration rate was lower in deceased patients.

The pathogenesis of CS in myocardial infarction is based on a decrease in myocardial contractility in conditions of acute ischemia and cardiac muscle necrosis. This creates a vicious circle, that is, a decrease in cardiac output and aggravation of myocardial ischemia, which, in turn, further worsens the systolic function of the heart [16]. In this regard, it was proved that a decrease in the ejection fraction below 40% is an independent factor of fatal outcome in patients with ACSST, complicated by CS [3, 15]. This is also reflected in our study.

The analysis of coronary angiograms showed that a multiple, three-vessel lesion of the coronary bed and chronic occlusion of the coronary artery was more common in deceased patients with CS than in survived patients. A number of publications evaluate multi-vessel coronary lesion and chronic occlusion of an infarct-unrelated artery as risk factors for poor prognosis in patients with CS [16, 19]. These factors seem capable of aggravating myocardial ischemia and systolic dysfunction that already exist in patients with ACSST with CS.

According to current recommendations, primary PCI is the preferred method of reperfusion in ACSST complicated by CS [1]. Refusal of intervention or its inefficiency is associated with a high incidence of early mortality in this category of patients [10, 15]. In addition, the timing of PCI also has prognostic value. The superiority of early revascularization was proven [12, 15]: intervention within six hours after the onset of chest pain was associated with the lowest mortality in patients with CS [16]. In our study, the time between the onset of pain to PCI was significantly longer in the group of deceased patients with CS and averaged seven hours. The data obtained on the possible effect of such factors as failure to perform the intervention, unsuccessful intervention or intervention after six hours from the onset of angina on in-hospital mortality in patients with ACSST complicated by CS are consistent with the literature data. The effect of these PCI-associated predictors on in-hospital mortality in this group of patients can be associated with the volume of viable myocardium, the degree of systolic dysfunction of the left ventricle, and the severity of CS.

According to our results, multiple stenting of coronary arteries was more often performed in deceased patients with CS than in the comparison group. This observation can be explained by the severity of the coronary bed lesion, multiple stenoses and occlusions of coronary arteries in these patients, which required implantation of two or more stents for adequate myocardial reperfusion.

Conclusion

According to the study results, the risk of in-hospital mortality in patients with ACSST complicated by CS is associated with ejection fraction decrease below 40%, a three-vessel coronary lesion, and PCI after six hours from the pain onset. The identification of predictors of an unfavorable CS course can help optimize risk stratification and select the optimal management strategy for patients with ACSST in order to improve their treatment outcomes and prognosis.

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РЕВМАТОИДНЫЙ АРТРИТ: КЛИНИКО-ЛАБОРАТОРНЫЕ И УЛЬТРАЗВУКОВЫЕ ПАРАЛЛЕЛИ

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Rheumatoid Arthritis: Clinical-Laboratory and Ultrasound Parallels

Резюме

Цель. Установить взаимосвязь показателей сывороточного адипонектина и лептина у больных ревматоидным артритом с клиническими данными, серологическими показателями, активностью заболевания, результатами ультразвукового исследования опорно-двигательного аппарата и рентгенологическим поражением суставов. **Материалы и методы.** В статье представлена сравнительная характеристика уровней адипокинов среди 64 женщин с диагнозом ревматоидный артрит (I группа) и 30 здоровых женщин (II группа). У больных ревматоидным артритом выявлена зависимость уровней адипокинов от клинико-лабораторных, ультразвуковых и рентгенологических изменений. **Результаты.** Концентрация адипонектина была значительно выше у больных ревматоидным артритом по сравнению с группой здоровых ($p < 0,0001$) и имела достоверные корреляционные связи с рентгенологическими изменениями в суставах ($r=0,4$; $p < 0,001$) и длительностью приема метотрексата ($r=0,4$; $p < 0,001$) и глюкокортикостероидов ($r=0,3$; $p < 0,05$). Уровень лептина у больных ревматоидным артритом и контрольной группы был примерно одинаковым. Однако, были отмечены положительные взаимосвязи между уровнем лептина и числом болезненных суставов ($r=0,5$; $p < 0,0001$), уровнями С-реактивного белка ($r=0,3$; $p < 0,05$) и интерлейкина-17 ($r=0,3$; $p < 0,05$), индексом Disease Activity Score 28 ($r=0,4$; $p < 0,001$), а также усилением кровотока при допплерографии ($r=0,4$; $p < 0,001$). **Заключение.** Таким образом, у больных ревматоидным артритом отмечается значительное повышение уровня адипонектина по сравнению с группой здоровых, что связано с выраженными деструктивными изменениями в суставах и длительностью приема метотрексата и глюкокортикостероидов. Однако, положительная взаимосвязь между показателями активности заболевания и наличием допплеровского сигнала отмечается только у лептина.

Ключевые слова: *адипонектин; лептин; ультразвуковое исследование суставов*

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

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Abstract

Purpose. To establish the relationship of serum adiponectin and leptin with clinical data, serological parameters, disease activity, results of ultrasound examination of the musculoskeletal system and X-ray damage of joints in rheumatoid arthritis patients. **Materials and methods.** The article presents a comparative characteristic of adipokine levels among 64 women diagnosed with rheumatoid arthritis (group I) and 30 healthy women (group II). The dependence of adipokine levels on clinical, laboratory, ultrasound and radiological changes was revealed in patients with rheumatoid arthritis. **Results.** The concentration adiponectin level was significantly higher in rheumatoid arthritis patients compared to the control group ($p < 0.0001$) and had significant correlations with radiological changes in the joints ($r=0.40$; $p < 0.001$) and the intake duration of methotrexate ($r=0.4$; $p < 0.001$) and glucocorticosteroids ($r=0.3$; $p < 0.05$). The level of leptin in the blood serum of women with rheumatoid arthritis and healthy individuals was approximately the same. However, there were positive correlations between the level of leptin and of the tender joint count ($r=0.5$; $p < 0.0001$), the levels of C-reactive protein ($r=0.3$; $p < 0.05$) and interleukin-17 ($r=0.3$; $p < 0.05$), the index Disease Activity Score 28 ($r=0.4$; $p < 0.001$) and increased blood flow during Doppler imaging ($r=0.4$; $p < 0.001$). **Conclusion.** Thus, patients with rheumatoid arthritis have a significant increase in the level of adiponectin compared to the health group, which is associated with pronounced destructive changes in the joints and the intake duration of methotrexate and glucocorticosteroids. However, a positive relationship between the indicators of disease activity and the presence of a Doppler signal is observed only in leptin.

Key words: *adiponectin; leptin; ultrasound examination of joints*

Conflict of interests

The authors declare no conflict of interests

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Anti-CCP — anti-cyclic citrulinated peptide antibodies, GCS — glucocorticosteroids, IL-17 –interleukin-17, BMI — body mass index, WJ — wrist joint, MTX — methotrexate, NSAIDs — non-steroidal anti-inflammatory drugs, RA — rheumatoid arthritis , CRP — C-reactive protein, US — ultrasound examination, TJC — tender joint count, SJC — swollen joint count, TNF-α — tumor necrosis factor-α, PD — power Doppler, DAS28 — Disease Activity Score 28

Introduction

Rheumatoid arthritis (RA) is one of the most common severe immune-mediated inflammatory diseases in humans. It is characterized by chronic erosive arthritis and systemic damage to internal organs, which leads to early disability and shorter life expectancy. This, in turn, determines the high social significance of the disease [1]. The pathogenetic mechanisms of RA are still being studied. A number of studies have shown that adipose tissue is actively involved in the development of systemic inflammation in RA, producing pro-inflammatory cytokines and adipose tissue hormones (adipokines), which can independently modulate inflammatory and destructive processes in joints [2, 3].

However, data on the pro- and anti-inflammatory role of adipokines in the pathogenesis of RA remain poorly understood, which makes this study relevant.

Objective

To establish the relationship between serum adiponectin and leptin in patients with RA with clinical data, serological parameters, disease activity, results of ultrasound examination (US) of the musculoskeletal system and radiological damage to the joints.

Materials and Methods

Clinical, laboratory and ultrasound examinations of 64 women with RA confirmed according to the classification criteria of RA (American College of Rheumatology / European League Against Rheumatism, 2010) [1] were performed in the Orenburg State Medical University Hospital from September 2018 to September 2020. The average age of patients with RA was 46.1 ± 7.1 years; the average duration of the disease was 8.3 ± 5.8 years. Most of the examined patients 52 (81.3%) were seropositive for rheumatoid factor (RF).

Inclusion criteria: the patient's age over 18 years.

The exclusion criteria were hand injury and surgery during the last six months, another concomitant rheumatic disease, cancer, pregnancy and lactation, acute or exacerbation of chronic infections at the time of examination, and diabetes mellitus.

The study was approved by the local ethics committee of the Federal State Budgetary Educational Institution of Higher Education of the Orenburg State Medical University (Protocol No. 208 of September 28, 2018). All patients signed Informed Consent.

Patients with RA underwent a physical examination, which included estimation of the tender joint count (TJC) (mean value 10.0 ± 7.4), swollen joint count (SJC)

(mean value 4.4 ± 2.8), duration of morning stiffness (mean value 100.8 ± 54.4 min), a general assessment of the intensity of pain using a 100-mm visual-analogue scale [1] (mean value 46.2 ± 23.5). Disease activity was assessed by the DAS28 (Disease Activity Score 28) [1] (mean value 4.4 ± 1.7): remission, low, medium and high disease activity were observed in 11 (17.2%), 9 (14.0%), 32 (50.0%) and 12 (18.8%) patients, respectively. The X-ray stage was determined according to the modified Steinbrocker classification [1]: I, II, III and IV radiological stages of the disease were detected in 6 (9.4%), 37 (57.8%), 17 (26.6%) and 4 (6.3%) patients, respectively. The functional status of the musculoskeletal system was evaluated according to the clinical classification criteria of RA (2007) [1]: Functional classes I, II, III, and IV were determined in 6 (9.4%), 36 (56.3%), 20 (31.3%), and 2 (3.1%) patients, respectively.

The control group consisted of 30 women without inflammatory joint diseases, similar in gender, age and body mass index (BMI) to patients with RA.

The BMI index was calculated using the formula: $ИМТ = \frac{\text{weight (kg)}}{\text{height (m)}^2}$ [4]. The mean BMI in patients with RA was 26.3 ± 6.2 kg/m^2, in healthy individuals — 24.6 ± 5.0 ($p > 0.05$).

The following laboratory tests were performed in all study subjects: serum RF, anti-cyclic citrullinated peptide antibodies (anti-CCP), and C-reactive protein (CRP).

The concentrations of tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), adiponectin and leptin were determined by ELISA on a Bio-Rad Model 680 microplate photometer using commercial Bender MedSystems kits (Austria — USA), Mediagnost (Germany) and Diagnostics Biochem Canada Inc. (Canada), respectively.

We performed ultrasound examination to determine the inflammatory and destructive changes in 30 joints in each patient with RA (wrist (Wrist joint), from the first to fifth metacarpophalangeal joints, from the second to fifth proximal and distal interphalangeal joints and the first interphalangeal joint on the palmar and dorsal sides of both hands) using the Philips EPIQ 7 device with a multi-frequency linear transducer with a frequency of 4–18 MHz and power Doppler (PD). US exam included the detection of joint effusion, synovial hypertrophy and angiogenesis (the presence of a vascular signal), erosive changes in the hand joints, as well as the assessment of periarticular tissues to detect tenosynovitis on the palmar and dorsal hand sides. We examined 1920 joints in patients with RA.

In our work, we used the term "synovitis", which combines the concepts of "joint effusion" and "hypertrophy of the synovial membrane".

At the time of examination, 29 (45.3%) patients with RA received treatment with disease-modifying antirheumatic drugs (methotrexate (MTX) in combination with folic acid, hydroxychloroquine, leflunamide); seven patients (10.9%) received glucocorticosteroids (GCS) orally; 12 patients (18.8%) received a combination of disease-modifying antirheumatic drugs and GCS. Nine (14.1%) patients with RA received non-steroidal anti-inflammatory drugs (NSAIDs).

STATISTICA 12.0 software was used for statistical analysis. Qualitative results are given as the absolute number and percentage of the total number. Mann—Whitney U-test was used to assess the significance of differences between values. To identify the relationships between the variables, the Spearman pair correlation coefficient was calculated. Values were considered significant at $p \le 0.05$. To determine the agreement between the results of the two examination methods, the Cohen's kappa coefficient (κ) was used, the values of which at $\kappa < 0.2$ reflect poor, 0.2–0.40 — mediocre, 0.41–0.60 — moderate, 0.61–0.80 — good and > 0.81 excellent agreement [5].

Results

Table 1 presents a comparative assessment of the results of physical and ultrasound examination of patients with RA.

B-mode ultrasound revealed inflammation in the form of synovitis and tenosynovitis in 965 (50.3%) joints in patients with RA, while clinical manifestations of arthritis (TJC and SJC) were noted in 755 (39.3%) (Table 1). No ultrasound signs of inflammation were detected in 210 (10.9%) joints in RA during physical

Table 1. *Comparative assessment of clinical symptoms of arthritis and US signs of inflammation in WJ and small joints of the hands by B-mode US in RA, n (%)*

RA (n=1920)				
US-signs	Clinical manifestations of inflammation in the joint			
	TJC and SJC	TJC	SJC	No TJC and SJC
Synovitis and tenosynovitis	96/5,0	11/0,6	4/0,2	13/0,7
Only synovitis	154/8,0	58/3,0	96/5,0	167/8,7
Only tenosynovitis	123/6,4	186/9,7	27/1,4	30/1,6
Absence of US-signs	6/0,3	58/3,0	4/0,2	887/46,2

Table 2 *Comparative assessment of clinical symptoms of arthritis and signs of hypervascularization of synovial stratum in the WJ and small joints of the hands detected with using PD US in RA, n (%)*

RA (n=1920)				
US-signs	Clinical manifestations of inflammation in the joint			
	TJC and SJC	TJC	SJC	No TJC and SJC
Signal present	146/7,6	96/5,0	68/3,5	90/4,7
Signal absent	248/12,9	215/11,2	58/3,0	995/51,8

Table 3. *Adipocytokine concentrations in the blood serum of RA patients and the control group*

Adipocytokine	RA patients (n=64)	Control group (n=30)	p
Adiponectin (ng/ml), M±σ	40,9±13,6	22,8±11,3	p <0,0001
Leptin (ng/ml), M±σ	18,1±14,0	16,6±11,4	nr

Note: nr — not reliable

examination (Table 1). At the same time, swelling and/or pain in 68 (3.5%) joints in patients with RA noted during physical examination were not confirmed with US (Table 1).

When comparing the data of physical examination and US, the agreement was observed in 85.5% of cases (κ = 0.7) in patients with RA.

The Doppler signal was detected in 400 (20.8%) joints in RA, of which clinical signs of arthritis were found in 310 (16.2%) joints (Table 2). The Doppler signal was not detected in 1,516 (78.9%) joints in RA, of which swelling and/or tenderness were noted in 521 (27.1%) joints, respectively (Table 2).

The agreement between the results of the physical examination and US in the PD mode was 68.3% (κ = 0.3) in RA.

When determining the relationship between ultrasound and clinical/laboratory data, correlations between US signs of synovitis were detected in B-mode and PD ($r = 0.4$; $p < 0.001$) and SJC ($r = 0.5$; $p < 0.0001$). Significant correlations were determined between the presence of the Doppler signal and CRP ($r = 0.5$; $p < 0.0001$) and anti-CCP ($r = 0.3$; $p < 0.05$) levels, as well as higher DAS28-CRP ($r = 0.5$; $p < 0.0001$).

The serum level of adiponectin in patients with RA was significantly higher compared with the control group ($p < 0.0001$). The serum leptin level in women with RA and healthy individuals was approximately the same (Table 3).

In RA, there was a negative correlation between the concentrations of adiponectin and leptin ($r = -0.3$; $p < 0.05$). The level of serum adiponectin negatively correlated with the level of CRP ($r = -0.3$; $p < 0.05$). In this case, significant correlations between the X-ray stage of RA and adiponectin level were found ($r = 0.4$; $p < 0.001$). Additional correlations were observed between adiponectin level and duration of MTX treatment ($r = 0.4$; $p < 0.001$) and GCS ($r = 0.4$; $p < 0.001$) (Table 4).

We noted a positive correlation between the level of leptin and BMI ($r = 0.6$; $p < 0.0001$). In addition, significant correlations were found between the level of serum leptin and the duration of morning joint stiffness ($r = 0.3$; $p < 0.05$), TJC ($r = 0.5$; $p < 0.0001$), as well as the level of CRP ($r = 0.3$; $p < 0.05$) and the DAS28 index ($r = 0.4$; $p < 0.001$) in patients with RA. In patients with RA, an increase in the concentration of IL-17 was associated with an increase in the level of leptin ($r = 0.3$; $p < 0.05$).

Table 4. *Correlations between adipocytokine levels in RA patients and clinical manifestations of the disease, laboratory parameters, disease activity, US-signs of joint inflammation and X-ray stage*

Indicators	Adiponectin (ng/ml)	Leptin (ng/ml)
	r	r
Age (years)	0,2	0,1
BMI (kg/m²)	-0,1	0,6****
Duration of disease (years)	-0,1	-0,1
Morning stiffness (min)	-0,1	0,3*
ЧБС/ТЈС	0,1	0,5****
SJC	-0,2	0,1
DAS28-CRP	-0,2	0,38**
CRP (mg/l)	-0,2	0,32*
RF (U/mL)	0,2	-0,1
A-CCP (U/mL)	0,1	-0,2
TNF-α (pkg/ml)	-0,1	0,1
IL-17 (pkg/ml)	-0,2	0,3*
X-Ray stage	0,4***	-0,2
US-signs:		
Synovitis	-0,2	0,1
Tenosynovitis	-0,2	0,1
Hypervascularization of synovia	-0,2	0,4****
Intake duration of MTX (years)	0,4***	0,1
Intake duration of GCS (months)	0,4**	0,2
Intaking NSAIDs	0,1	0,1

Note: * — p ≤0.05; ** — p <0.01; *** — p <0.001; **** — p <0.0001

However, we did not find any significant correlations between the concentrations of serum adipokines and the levels of RF and anti-CCP (Table 4).

As shown in Table 4, along with BMI, serum leptin showed high correlations with TJC, levels of CRP, as well as the DAS28, indicating disease activity. At the same time, adiponectin had significant correlation with radiological changes in the joints and drugs used (MTX and GCS).

Also, a positive correlation was observed between the concentration of leptin and the presence of the Doppler signal ($r = 0.4$; $p < 0.001$) (Table 4).

Discussion

Most of the previous studies have shown that the concentrations of serum leptin [2, 6, 7] and adiponectin [2, 7] are higher in patients with RA than in healthy individuals. At the same time, low levels of these adipokines in RA were also recorded [2, 6]. Our results show a significant increase in adiponectin level in patients with RA ($p < 0.0001$) compared to the control group. However, there was no tendency to leptin concentration increase in women with RA.

A number of authors note the anti-inflammatory role of adiponectin in the human body. However, in RA, the level of this adipokine does not directly correlate with disease activity [7, 8], as confirmed by our study.

We noted a significant correlation between the level of adiponectin and the radiological stage of RA ($p < 0.001$), which is consistent with a number of studies that note the relationship between high levels of adiponectin and radiological markers of joint destruction (erosion and narrowing of the joint space) [9, 10].

In the present study, the level of adiponectin in serum significantly correlated with the duration of MTX and GCS treatment, which is consistent with other authors [3, 7]. A number of researchers reported that TNF-α reciprocally inhibits adiponectin production in adipose tissue. Since MTX and GCS inhibit the production of proinflammatory cytokines, including TNF-α, they can cause an increase in serum adiponectin in patients with RA [3].

Most previous studies established a positive correlation between the level of leptin and BMI [2], which is also observed in our study. It has been suggested that leptin may play the role of the pro-inflammatory cytokine in RA [2, 7]. We identified significant positive relationships between the level of leptin and disease activity (TJC, CRP level, DAS28-CRP) and morning stiffness of joints, which is consistent with the results of several authors [2, 6, 7]. Also, in our study, the level of serum leptin positively correlated with the concentration of proinflammatory cytokine (IL-17). Deng J. et al. suggested that leptin stimulates the differentiation of CD4+ T-lymphocytes along the Th-17 pathway [11], which explains the obtained results.

Such concepts as "subclinical synovitis" and "subclinical tenosynovitis" emerged with the development of imaging techniques [12, 13]. A number of researchers noted the discrepancy between the results of clinical and ultrasound assessments of inflammatory changes in the joints [14, 15], which was confirmed in our study: US showed more joints with signs of inflammation than physical examination in patients with RA ($p < 0.0001$). At the same time, the proportion of false-negative results was insignificant and amounted to 3.5% in RA.

Ceponis A. et al. note the correlation between the ultrasound signs of synovitis and tenosynovitis in the study in B-mode and PD and SJC [16] in patients with RA, which is consistent with the results of our study.

When determining the relationship between ultrasound and laboratory findings, we found a close correlation between increased blood flow and levels of CRP and anti-CCP ($p < 0.0001$; $p < 0.05$) and higher DAS28-CRP ($p < 0.0001$). Our results were confirmed by studies Xu H. et al. [14], showing that PD reflects the activity of the disease better than the B-mode. Also, a positive correlation was observed between the concentration of leptin and the presence of the Doppler signal ($p < 0.001$), which is consistent with the results of a study by Sherin H.N. et al. [17], who observed a moderate increase in the average serum leptin level in patients with increased blood flow according to Doppler US.

The obtained data suggest a pathogenetic relationship between adipose tissue hormones and inflammatory and destructive processes in the joints.

Conclusion

There is a significant increase in the level of adiponectin in patients with RA compared with the healthy group, which is associated with severe destructive changes in the joints and the duration of MTX and GCS treatment. The concentration of leptin in patients with RA and healthy individuals is approximately the same. However, there is a positive relationship between the level of leptin and disease activity (TJC, level of CRP and IL-17, DAS28-CRP) and increased blood flow, which suggests its role as a pro-inflammatory cytokine.

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ИЗУЧЕНИЕ ВАРИАБЕЛЬНОСТИ РИТМА СЕРДЦА У БОЛЬНЫХ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ И ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ.

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Study of Heart Rate Variability in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease

Резюме

Цель. Изучить вариабельность ритма сердца (ВРС) у больных хронической сердечной недостаточностью (ХСН) и хронической обструктивной болезнью легких (ХОБЛ) во взаимосвязи: с уровнем насыщения крови кислородом, параметрами функции внешнего дыхания (ФВД), концентрацией Nt — proBNP в плазме крови. **Материалы и методы.** Обследовано 128 амбулаторных пациентов обоего пола. Возраст больных составил от 45 до 70 лет. 1 группа — основная (60 больных) с ХСН ишемического генеза II–III функционального класса по NYHA и ХОБЛ GOLD I–III степени ограничения воздушного потока (классификация GOLD 2019) в стадии стойкой ремиссии, 2 группа — контрольная (63 пациента), с изолированной ХСН. Все, включенные в исследование больные с ХСН, перенесли инфаркт миокарда (ОИМ) давностью от 1 года до 5 лет. Статистически значимых различий по тяжести ХСН между 1 и 2 группами не было. **Результаты.** У пациентов с ХСН и ХОБЛ, в отличие от больных с изолированной ХСН, выявлено достоверное преобладание частоты встречаемости гиперсимпатикотонического типа вегетативной регуляции. Достоверно более низкие показатели вариабельности ритма сердца были в группе больных с сопутствующей ХОБЛ в сравнении с пациентами с изолированной ХСН. Выявлены статистически значимые корреляционные связи между показателями ВРС и параметрами ФВД, уровнем насыщения крови кислородом, концентрацией NT-proBNP в крови. При проведении многофакторного регрессионного анализа установлена достоверная зависимость показателей ВРС от параметров ФВД и концентрации NT-proBNP в крови в группе больных с ХСН и ХОБЛ.

Ключевые слова: *хроническая сердечная недостаточность, хроническая обструктивная болезнь легких, вариабельность ритма сердца*

Конфликт интересов

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

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Abstract

Aim. To study heart rate variability (HRV) in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) in relation to: blood oxygen saturation level, parameters of respiratory function (RPF), Nt — proBNP concentration in blood plasma. **Materials and methods.** We examined 128 outpatients of both sexes. The patients' age ranged from 45 to 70 years. Group 1 — main (60 patients) with CHF of ischemic genesis of NYHA functional class II — III and GOLD COPD of I — III degree of airflow restriction (GOLD 2019 classification) in the stage of stable remission, group 2 — control group (63 patients), with isolated CHF. All patients with CHF, who were included in the study, had myocardial infarction (AMI) from 1 to 5 years ago. There were no statistically significant differences in the severity of CHF between groups 1 and 2. **Results.** In patients with CHF and COPD, in contrast to patients with isolated CHF, a significant prevalence of the frequency of occurrence of the hypersympathicotonic type of autonomic regulation was revealed. Significantly lower indicators of heart rate variability were in the group of patients with concomitant COPD in comparison with patients with isolated CHF. Statistically significant correlations were revealed between HRV parameters and RPF, parameters of blood oxygen saturation level, NT-proBNP concentration in blood. Multivariate regression analysis showed a significant dependence of HRV parameters on the parameters of HRV and the concentration of NT-proBNP in the blood in the group of patients with CHF and COPD.

Key words: *chronic heart failure, chronic obstructive pulmonary disease, heart rate variability.*

Conflict of interests

The authors declare no conflict of interests

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CHF — chronic heart failure, COPD — chronic obstructive pulmonary disease, CCP — chronic cor pulmonale, HRV — heart rate variability, AMI — acute myocardial infarction, ANS — autonomic nervous system, PFT — pulmonary function test

Introduction

Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are common diseases in clinical practice. CHF in COPD can be associated with both concomitant cardiac disease (in particular, coronary heart disease) and decompensation of chronic cor pulmonale (CCP) [1].

The prevalence of CHF among COPD patients is on average 10–20%. The incidence of COPD in CHF is 9–13%. CHF worsens the prognosis and increases the frequency of hospitalizations in patients with COPD. On the other hand, the prevalence of CHF and cardiovascular complications increases as the severity of COPD increases. Cardiovascular events are one of the main, if not the primary, reasons for the hospitalization of patients with COPD [2].

In COPD, a chronic inflammatory process in the tracheobronchial tree is observed due to the toxic effects of inhaled pathogenic particles or gases, leading to microhemocirculation disorders, increased endothelial dysfunction, the elevation of C-reactive protein, development of atherosclerosis, regression of capillary networks, blood stasis and tissue hypoxia [3, 4].

Hypoxia, inflammation, oxidative stress, activation of neurohumoral systems (renin-angiotensin-aldosterone (RAAS) and sympathoadrenal (SAS)systems) are associated with direct and indirect cytotoxic effects that contribute to CHF and aggravation of its clinical course [1, 2].

As a result of the cascade of pathophysiological reactions, the activity of the sympathetic and parasympathetic components of the autonomic nervous system (ANS) changes. A number of studies described a decrease in heart rate variability (HRV) and the predominance of the sympathetic nervous system activity, both in patients with CHF and patients with COPD [5–9].

However, we did not see any studies of heart rate variability in relation to blood oxygen saturation, the severity of airway obstruction, and blood NT-proBNP level in patients with CHF and COPD.

The aim of the study was to assess heart rate variability in patients with CHF and COPD in relation to blood oxygen saturation, pulmonary function test (PFT) results, and plasma NT-proBNP level.

Materials and Methods

Our prospective, open-label, controlled study included 123 outpatients, both men and women. Group 1 — main (60 patients), NYHA II–III CHF of ischemic genesis and GOLD I–III (GOLD classification 2019) COPD in the stage of stable remission; group 2 — control (63 patients), isolated CHF. All enrolled patients with CHF had a history of myocardial infarction (AMI) in the past 1–5 years. The age of participants ranged from 45 to 70 years.

***Table 1**. Characteristics of the patients included in the study, Me [Q25; Q75]*

Variable	1st group (main)	Group 2 (control)	p
Number of patients, n	60	63	p >0,05
Average age, years	64 [60; 68]	62 [58; 69]	p >0,05
Men, n (%)	48 (80,0)	53 (84,1)	p >0,05
Women, n (%)	12 (20,0)	10 (15,8)	p >0,05
BMI	29,7 [26,1; 34,2]	30,4 [26,5; 33,3]	p >0,05
AHA, %	100	100	p >0,05
SBP, mm Hg	130 [120; 140]	130 [120; 130]	p >0,05
DBP, mm Hg	80 [75; 80]	80 [75; 80]	p >0,05
Heart rate, beats / min	67 [60; 72]	64 [59; 71]	p >0,05
CHF duration, years	2 [1; 4]	2 [1; 5]	p >0,05
FC, years	2,0 [2,0; 3,0]	2,0 [2,0; 3,0]	p >0,05
NT-proBNP, fmol /ml	231,7 [187,2; 383,0]	227,1 [164,4; 300,8]	p >0,05
LVEF, %	48,5 [42,0; 54,5]	52,0 [44,0; 57,0]	p >0,05
HFpEF,%	45,0	58,0	p >0,05
HFmrEF, %	38,3	29,0	p >0,05
HFrEF, %	16,7	13,0	p >0,05
LA, mm	38,0 [36,0; 43,0] x 55,0 [54,0; 56,0]	37,0 [35,0; 41,0] x 54,0 [50,0; 57,0]	p >0,05
RA, mm	37,0 [35,0; 41,0] x 56,0 [48,0; 62,0]	35,0 [34,0; 37,0] x 51,0 [45,0; 54,0]*	p <0,05
RV, mm	39,0 [36,0; 41,5]	28,0 [27,0; 34,0]*	p <0,05
EDD, mm	54,0 [48,0; 58,0]	52,0 [47,0; 57,0]	p >0,05
LVDS, mm	37,0 [35,0; 42,0]	35,0 [32,0; 40,0]	p >0,05
ICH, years	30 [0; 40]	15 [0; 27,5]*	p <0,05
SpO_2, %	96% [95; 97]	97% [96; 98]*	p <0,05
FVC, %	58,0 [45,0; 71,0]	85,0 [76,0; 89,0]*	p <0,05
FEV_1, %	52,0 [41,0; 64,0]	90,0 [83,0; 95,0]*	p <0,05
VC, %	68,0 [55,0; 77,0]	88,0 [78,0; 93,0]*	p <0,05
FEV_1/FVC, %	65,0 [59,0; 67,0]	88,0 [84,0; 93,0]*	p <0,05
MEF 25%	39,0 [25,0; 52,0]	94,0 [72,0; 109,0]*	p <0,05
MEF 50%	31,0 [20,0; 41,0]	93,0 [77,0; 106,0]*	p <0,05
MEF 75%	34,0 [24,0; 43,0]	78,0 [70,0; 103,0]*	p <0,05
Enalapril, mg /day	5,0 [5,0; 10,0]	5,0 [5,0; 10,0]	p>0,05
Bisoprolol, mg /day	2,5 [2,5; 5,0]	5,0 [2,5; 5,0]	p>0,05
Veroshpiron, mg /day	25,0	25,0	p >0,05
Torasemide, mg / day	2,5	2,5	p >0,05
Atorvastatin, mg /day	20 [10,0; 20,0]	20 [10,0; 20,0]	p >0,05
Acetylsalicylic acid, mg /day	100 [75; 100]	100 [75; 100]	p >0,05
Isosorbide mononitrate, mg	40 [20,0;40,0]	40 [20,0;40,0]	p >0,05
Ivabradine, %; mg /day	7,6%; 5,0 [5,0; 7,5]	6,3%; 6,2 [5,0; 7,5]	p >0,05
Ipratropium bromide, mcg /day	140,0 [100,0;160,0]	-	
Budesonide+formoterol, mcg /day	160,0/4,5 мкг/сут.;	-	
Olodaterol hydrochloride+ tiotropium bromide, mcg /day	2.5 мкг/2.5 мкг сут	-	

Note: * p< 0,05, BMI — body mass index, AHA — arterial hypertension, SBP — systolic blood pressure, DBP — diastolic blood pressure, HFpEF — Heart failure with preserved ejection fraction, HFmrEF — Heart failure with midrange ejection fraction, HFrEF — heart failure with reduced ejection fraction, FC — functional class of CHF, NT-proBNP — terminal fragment of cerebral natriuretic peptide, LVEF — left ventricular ejection fraction, LA — left atrium, RA — right atrium, RV — right ventricle, EDD — end diastolic size of the left ventricle, CSR — terminal systolic size of the left ventricle, ICH — index of a smoking person, FVC% — forced vital capacity of the lungs, FEV_1% — forced expiratory volume in the first second, VC% — vital capacity of the lungs, FEV_1 / FVC% — Tiffno index, MEF 25% — instantaneous volumetric expiratory flow rate of 25% FVC, MEF 50% — instantaneous expiratory flow rate of 50% FVC, MEF 75% — instantaneous expiratory flow rate of 75% FVC

The study was conducted in accordance with the ethical principles set forth in the World Medical Association Declaration of Helsinki (2008), the ICH Harmonised Tripartite Guideline on Good Clinical Practice (ICH-GCP), and Basics of Health Protection of the Citizens in the Russian Federation. The study was approved by the regional ethics committee (protocol No. 001-2019, expert opinion No. 002/5).

Patients who participated in the study were comparable on the main clinical and demographic characteristics, the severity of CHF signs, as well as the dose regimens of the CHF treatment used. All patients with CHF and concomitant COPD in our study received baseline treatment of COPD with long-acting drugs: predominantly M-anticholinergics (tiotropium bromide) or a combination of tiotropium bromide and long-acting β2-agonist olodaterol (double bronchodilation); a number of patients (20%) took combined drugs (long-acting β2-agonist (formoterol) + inhalation GCS (budesonide)). Six patients occasionally used short-acting bronchodilators during the observation period, but in all cases, these drugs (ipratropium bromide and fenoterol hydrobromide) were withdrawn 3–4 days before the study. Patients with diabetes mellitus were not included in the study.

Clinical and demographic characteristics of patients are presented in Table 1.

HRV was studied using the Poly-Spectrum-Rhythm software module (Poly-Spectrum-8/E (Russia)). Short-term (five-minute) electrocardiogram recordings in the supine position of the patient were evaluated [10].

HRV was recorded in a state of complete rest. Before the exam, the patients were lying down for ten minutes. Then HRV data were recorded in the supine position. Time-series analysis was evaluated by the following indices: SDNN — standard deviation of all analyzed *R-R* intervals, pNN50 (%) — the percentage of consecutive NN intervals; RMSSD (ms) — the root mean square of differences of the values of successive pairs of NN intervals. Changes in RMSSD and pNN50 were used to assess the parasympathetic nervous system shift. The minimum and maximum R-R interval (R-R min and R-R max) were also determined.

To assess the tension of regulatory systems, we evaluated the stress index (SI) and tension index (TI). TI was calculated as follows [11]:

$$TI = AMo/Mo \times 2 \times (R\text{-}R\ max — R\text{-}R\ min)$$

Spectral Analysis was used to determine the contribution of periodic components to the changes in heart rate (TP — the total power of the HRV spectrum; LF/HF — the vagosympathetic balance ratio; ULF% — ultra-low-frequency component of variability as % of the total oscillation power; VLF % — very low-frequency component of variability as % of the total oscillation power; LF % — low-frequency component of variability as % of the total oscillation power; HF % — high-frequency component of variability as % of the total oscillation power) [10].

PFT was performed according to the generally accepted technique on the SPIROSOFT FUKUDA 3000 device (Japan).

SpO_2 was assessed using laser Doppler flowmetry (LDF) with spectral analysis of blood flow fluctuations using the LAKK — OP device.

The plasma level of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) was evaluated using ELISA (NT-proBNP, Bio-medica, Slovakia). The data obtained were reported in fmol/ml. For the methods used, a concentration of 150 fmol/ml was considered the upper limit for NT-proBNP.

The results are presented as Me [Q25; Q75], where Me is the median, Q25 and Q75 are 25th and 75th percentiles, respectively. Data were processed using the STATISTICA 10.0 software. When analyzing the results of independent samples, we used the Mann—Whitney test (estimation of quantitative indices) and the Fisher exact test (for qualitative indices). The differences between studied groups were considered significant at $p < 0.05$.

Results

There was a significant decrease in the following parameters in patients of the main group: SDNN, ms (33.5 [19.0; 47.0] vs 35.0 [27.0; 55.0]), CV % (3.1 [2.0; 5.1] vs 3.8 [2.7; 5.6]) and TP, ms^2 (1,185.0 [520.0; 1,863.0] vs 1,364.0 [750.0; 3,312.0]), in comparison with the control group patients. This may suggest the predominance of the sympathetic nervous system effects in comorbid patients. A significant low pNN50% value (1.1 [0.0; 5.6] vs 2.7 [0.9; 14.4]) in the group of patients with CHF and COPD indicates a decrease in the activity of the parasympathetic nervous system.

The significant predominance of the sympathetic nervous system activity in the 1st group, compared to the 2nd group, contributes to the tension of regulatory systems, which is confirmed by a significant increase in SI, c.u. (229.7 [96.7; 528.5] vs 138.9 [79.3; 265.1]), and TI, c.u. (161.7 [81.4; 435.1] vs 134.8 [58.9; 220.7]). Results are shown in Table 2.

The assessment of HRV in the study groups revealed a significant increase in the incidence of patients with hypersympathicotonia (51% vs 34.5%). The obtained data confirm the predominance of sympathetic nervous system activity in the patients of the main group and, consequently, the tension of regulatory systems, along with a decrease in the activity of the parasympathetic nervous system. Results are shown in Table 3.

Table 2. *Indicators of heart rate variability of the patients in the study*

Indicator	1st group (CHF+COPD)	Group 2 (CHF isolated)	p
SDNN, ms	33,5 [19,0; 47,0]	35,0 [27,0; 55,0]*	p <0,05
SDNN <50, n (%)	73,3%	70,0%	p >0,05
CV, %	3,1 [2,0; 5,1]	3,8 [2,7; 5,6]*	p <0,05
TP, ms^2	1185,0[520,0;1863,0]	1364,0[750,0; 3312,0]*	p <0,05
LF/ HF, u.e.	0,7 [0,48;1,3]	0,8 [0,5; 1,3]	p >0,05
ULF, %	15,4 [9,4; 26,5]	18,4 [8,2; 31,9]	p >0,05
VLF, %	13,8 [9,0; 26,8]	17,2 [9,7; 28,6]	p >0,05
LF, %	23,9 [17,8; 33,0]	25,6 [18,0; 33,4]	p >0,05
HF, %	35,8 [18,4; 51,3]	28,9 [15,7; 46,0]	p >0,05
(SI), u.e.	229,7 [96,7; 528,5]	138,9 [79,3; 265,1]*	p <0,05
pNN50, %	1,1 [0,0; 5,6]	2,7[0,9; 14,4]*	p <0,05
RMSSD, ms	25,0 [13,0; 59,0]	22,0 [15,0; 49,0]	p >0,05
RMSSD <20, n (%)	40,3%	34,6%	p >0,05
IN, c.e.	161,7 [81,4; 435,1]	134,8 [58,9; 220,7]*	p <0,05

Notes: * Differences between groups are significant (p <0,05). SDNN is the standard deviation of all analyzed R — R intervals; CV % — coefficient of variation; TP — total power of HRV spectrum; LF/HF — vagosympathetic balance coefficient; ULF% — ultra-low-frequency component of variability in% of the total oscillation power; VLF% — very low-frequency component of variability in% of the total oscillation power; LF% — low-frequency component of variability in% of the total oscillation power; HF% — high-frequency component of variability in% of the total oscillation power; SI — stress index of regulatory systems; pNN50,% — percentage of consecutive NN intervals; RMSSD — square root of the mean square of the differences in the values of consecutive pairs of NN intervals; IN — stress index

Table 3. *The background state of the autonomic nervous system*

Type of vegetative tone	Group 1 (CHF+COPD)	Group 2 (CHF isolated)	p
Wagotonia (IN <30), %	9,0	16,3	p >0,05
Eutonia (IN=30-90), %	27,3	27,4	p >0,05
Sympathicotonia (IN=90-160), %	12,7	21,8	p >0,05
Hypersympathicotonia (IN >160), %	51	34,5*	p <0,05

Notes: *p <0,05

In patients with CHF and COPD, significant correlations were established between VC % and TI, c.u., ($r = -0.27$; $p < 0.05$); VC % and SDNN, ms ($r = 0.24$; $p < 0.05$); VC % and CV % ($r = 0.20$; $p < 0.05$); VC % and RMSSD, ms ($r = 0.26$; $p < 0.05$); VC % and ULF % ($r = -0.28$; $p < 0.05$). Significant correlations were also revealed between FEV_1/FVC % and VLF % ($r = -0.19$; $p < 0.05$), FEV_1/FVC % and LF % ($r = 0.20$; $p < 0.05$). These correlations indicate a reliable relationship between the main HRV and PFT parameters. The activation of the sympathetic center of the medulla oblongata, which has a vasoconstrictive and cardiostimulating effect, could be closely associated with an increase in the degree of airway obstruction.

Blood oxygen saturation also significantly correlated with an increase in the activity of the sympathetic nervous system. Significant correlations were revealed between SpO_2% and VLF % ($r = 0.16$; $p < 0.05$), SpO_2% and LF % ($r = 0.19$; $p < 0.05$).

CHF progresses with airway obstruction and increasing hypoxia, as evidenced by the significant correlation between NT-proBNP level, fmol/ml, and SI, c.u. ($r = 0.35$; $p < 0.05$), NT-proBNP, fmol/ml, and TI, c.u. ($r = 0.30$; $p < 0.05$), NT-proBNP, fmol/ml, and SDNN, ms ($r = -0.32$; $p < 0.05$), NT-proBNP, fmol/ml, and CV % ($r = -0.28$; $p < 0.05$), NT-proBNP, fmol/ml and TP, ms^2 ($r = -0.36$; $p < 0.05$), NT-proBNP, fmol/ml, and VLF % ($r = 0.34$; $p < 0.05$), NT-proBNP, fmol/ml, and RMSSD, ms ($r = -0.23$; $p < 0.05$).

A multivariate regression analysis was performed to determine the contribution of the PFT parameters, SpO_2 and NT-proBNP in the development of HRV dysfunction. The data are presented in Table 4.

According to the results of the multivariate regression analysis, VC % ($p < 0.05$) contributes the most to the development of autonomic dysfunction (LF/HF). The degree of influence of VC % on LF/HF was 40%.

Based on the data obtained, it can be assumed that the progression of bronchial obstruction in patients with CHF and COPD significantly changes the vegetative balance due to the predominance of the sympathetic activity.

A significant effect of blood NT-proBNP on VLF % was also revealed. The degree of influence of blood NT-proBNP on VLF % was 40%. Accordingly, a high level of NT-proBNP, indicating the CHF progression, significantly changes the vegetative balance causing hypersympathicotonia.

Table 4. Multivariate regression analysis of the influence of the parameters of HRV, SpO_2, NT-proBNP on HRV parameters

Indicator		β		b		t(95)	p
		M	SE	M	SE		
SDNN, ms	member			385,06	219,80	1,75	0,08
	SpO_2,%	-0,25	0,14	-4,37	2,39	-1,82	0,07
	NT-proBNP, fmol /ml	-0,23	0,13	-0,03	0,02	-1,77	0,08
CV, %	member			46,04	27,56	1,67	0,10
	SpO_2, %	-0,25	0,14	-0,55	0,30	-1,83	0,07
	FEV_1/FVC, %	0,32	0,17	0,15	0,08	1,79	0,07
TP, ms^2	member			2590,38	12329,84	0,21	0,83
	NT-proBNP, fmol /ml	-0,24	0,13	-2,21	1,23	-1,80	0,07
LF/ HF, u.e.	member			-3,88	8,35	-0,46	0,64
	VC, %	-0,40	0,19	-0,02	0,01	-2,06	0,04*
VLF, %	member			-156,41	95,06	-1,64	0,10
	SpO_2, %	0,25	0,13	1,93	1,03	1,86	0,06
	NT-proBNP, fmol /ml	0,40	0,12	0,03	0,00	3,21	0,002*
RMSSD, ms	member			530,70	403,00	1,31	0,19
	ЖЕЛ, %	0,34	0,18	1,06	0,58	1,81	0,07

Notes: * p <0,05, SE — is the standard error; β — is the standardized equivalent of the coefficient b; b — is the regression coefficient; p — is the exact value for each regression coefficient, member — constant

Discussion

The results of the study can be explained by morphological changes in the myocardium after acute myocardial infarction with the formation of denervated areas and a secondary violation of the autonomous regulation of heart rhythm, an increase in catecholamines, as well as the progression of hypercapnia and hypoxia [5, 12].

Complex pathogenetic interactions create a vicious circle with an increased cardiac load and aggravation of CHF. Hypoxemia, hypercapnia, and acid-base imbalance increase the electrical heterogeneity of the myocardial tissue that can lead to life-threatening arrhythmias. Hypoxemia is an important factor in the pathophysiology of autonomic neuropathy and is considered the main cause of autonomic dysfunction, manifesting in the hyperactivation of the sympathetic nervous system [5, 13].

A significant increase in the stress index and tension index of regulatory systems, as well as hypersympathicotonia revealed in patients with CHF and COPD are independent predictors of the risk of sudden death and general mortality. In turn, a sharp decrease in PNN50 (which is determined by the predominant effect of the parasympathetic system) indicates a decrease in vagal activity and imbalance of autonomic influences on the sinus rhythm, which is an unfavorable sign and correlates, the same as SDNN, with an increased risk of sudden death [5, 7, 9, 14].

Reliable correlation between HRV parameters and blood oxygen saturation, parameters of PFT, and plasma NT-proBNP level confirms the inextricable relationship between pathophysiological changes occurring in concomitant CHF and COPD.

Hypoxia and hyperactivity of the sympathetic ANS trigger vasoconstriction, which exacerbates CHF and leads to complications that contribute to an unfavorable outcome in comorbid patients.

Due to the increase in airway obstruction, significantly lower blood oxygen saturation, decreased heart rate variability, and the predominance of hypersympathicotonia, patients with CHF and COPD are more difficult to manage than patients with isolated CHF; and they have a higher risk of sudden death from cardiovascular complications.

Conclusions

1. Significantly lower values of heart rate variability were observed in patients with CHF and COPD compared with patients with isolated CHF. The hypersympathicotonic type of autonomic regulation was significantly more common in the group of patients with CHF and COPD compared with patients with CHF without COPD.

2. Reliable correlations between HRV and PFT parameters, SpO_2 and blood NT-proBNP level were established in patients with CHF and COPD. An increase in the activity of the sympathetic nervous system in patients with CHF and COPD is accompanied by an increase in the blood NT-proBNP concentration, a decrease in the pulmonary function and blood oxygen saturation.

3. Multivariate regression analysis showed that VC and the blood level of NT-proBNP contribute the most to the development of autonomic dysfunction in patients with CHF and COPD.

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АНЕМИЯ У ПАЦИЕНТОВ С АКСИАЛЬНЫМИ СПОНДИЛОАРТРИТАМИ НЕ АССОЦИИРОВАНА С УВЕЛИЧЕНИЕМ РИГИДНОСТИ СОСУДИСТОЙ СТЕНКИ И ТОЛЩИНЫ КОМПЛЕКСА ИНТИМА-МЕДИА (РЕЗУЛЬТАТЫ ОДНОЦЕНТРОВОГО КРОСС-СЕКЦИОННОГО ИССЛЕДОВАНИЯ)

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Anemia in Patients with Axial Spondyloarthritis is Not Associated with an Increase of Arterial Stiffness and Intima-Media Thickness (Results of a Single-Center Cross-Sectional Study)

Резюме

Цель — изучение показателей ригидности сосудистой стенки и субклинического атеросклероза у пациентов с аксиальными спондилоартритами (аксСпА) без клинически манифестной кардиоваскулярной патологии в зависимости от наличия анемии. **Материал и методы.** Включены 102 пациента с аксСпА, возраст — 37,7±9,8 лет, длительность аксСпА — 13,5±8,7 лет, 66 (64,7%) мужчин. Рассчитаны индексы BASDAI, ASDAS-СРБ, исследованы гемограмма, скорость оседания эритроцитов (СОЭ), уровень С-реактивного белка (СРБ). Исследование параметров артериальной ригидности проводили методами осциллографии и фотоплетизмографии, оценка толщины комплекса интима-медиа (ТКИМ) осуществляли в ходе ультразвукового исследования в В-режиме согласно стандартным протоколам. **Результаты.** В ходе анализа свойств пульсовой волны статистически значимых различий показателей ригидности сосудистой стенки у пациентов аксСпА с наличием и без анемического синдрома не обнаружено. У пациентов с анемией скорость распространения пульсовой волны в аорте (PWVao) составила 7,4±1,5 м/с, индекс аугментации в аорте (Aix-ao) — 19,1±13,7%, индекс жесткости (SI) — 8,2±1,7 м/с, у пациентов без анемии — 7,4±1,4 м/с, 17,3±10,6% и 8,8±2,0 м/с, соответственно (p >0,05 для всех). Средние значения ТКИМ у пациентов с анемией составили 0,70±0,13 см, у па-

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циентов без анемии — 0,73±0,16 (p >0,05). По результатам корреляционного анализа установлены взаимосвязи между Aix-ao, PWVao, SI, ТКИМ и возрастом пациентов (r=0,488, r=0,516, r=0,289, r=0,461, соответственно, p <0,05), взаимосвязи между Aix-ao, PWVao и клиническим индексом активности BASDAI (r=0,243, r=0,253, соответственно, p <0,05). Выявлены взаимосвязи между PWVao и Aix-ao (r=0,442, p <0,001), SI (r=0,273, p=0,011) и ТКИМ (r=0,236, p=0,034). **Заключение.** В ходе настоящего исследования не подтверждено отрицательное влияние анемии на показатели ригидности сосудистой стенки и ТКИМ у пациентов с аксСпА. Полагаем, что это связано с потенциальным протективным эффектом анемии, обусловленным общеизвестными патофизиологическими паттернами — снижением вязкости крови и индукцией синтеза оксида азота. Требуется дальнейшее изучение взаимосвязей между уровнем гемоглобина и маркерами эндотелиальной дисфункции у пациентов с воспалительными заболеваниями позвоночника.

Ключевые слова: *анемия, гемоглобин, атеросклероз, артериальная ригидность, толщина комплекса интима-медиа, анкилозирующий спондилит, аксиальный спондилоартрит*

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

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Abstract

Aim: to study parameters of arterial stiffness and subclinical atherosclerosis in patients with axial spondyloarthritis (axSpA) without clinically manifest cardiovascular pathology depending on the presence of anemia. **Material and methods.** 102 patients with axSpA (mean age — 37.7±9.8 years, axSpA duration — 13.5±8.7 years, 66 (64.7%) men) were included. The BASDAI index and C-reactive protein (CRP)-based ASDAS score were measured, the hemogram, the erythrocyte sedimentation rate (ESR), and the level of CRP were studied. Parameters of arterial stiffness were studied by oscillography and photoplethysmography, intima-media thickness (IMT) was evaluated by B-mode ultrasound according to standard protocols. **Results.** During analysis of pulse wave properties, no statistically significant differences in parameters of vascular wall stiffness were found in axSpA patients with and without anemia. Aortic pulse wave velocity (PWVao) in patients with anemia was 7.4±1.5 m/sec, aortic augmentation index (Aix-ao) was 19.1±13.7%, stiffness index (SI) was 8.2±1.7 m/sec; in patients without anemia — 7.4±1.4 m/sec, 17.3±10.6% and 8.8±2.0 m/sec, respectively (p >0.05 for all). IMT in patients with anemia was 0.70±0.13 cm, in patients without anemia — 0.73±0.16 cm (p >0.05). Correlation analysis was performed and significant correlations were noted between Aix-ao, PWVao, SI, IMT and age (r=0.488, r=0.516, r=0.289, r=0.461, respectively, p <0.05); Aix-ao, PWVao and the BASDAI index (r=0.243, r=0.253, respectively, p <0.05). Significant correlations between PWVao and Aix-ao (r=0.442, p <0.001), SI (r=0.273, p=0.011) and IMT (r=0.236, p=0.034) were found. **Conclusion.** The present study did not confirm the negative effect of anemia on vascular wall stiffness parameters and IMT in patients with axSpA. We consider that potential protective effect of anemia, due to well-known pathophysiological patterns — a decrease in blood viscosity and the induction of nitric oxide synthesis, plays an important role. Further studies are required to assess relationship between hemoglobin levels and markers of endothelial dysfunction in patients with axSpA.

Key words: *anemia, hemoglobin, atherosclerosis, arterial stiffness, intima-media thickness, ankylosing spondylitis, axial spondyloarthritis*

Conflict of interest

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Aix-ao — aortic augmentation index, axSpA — axial spondyloarthritis, CRP — C-reactive protein, ESR — erythrocyte sedimentation rate, IMCT– intima-media complex thickness, PWVao — pulse wave velocity of the aorta, SI — stiffness index

Introduction

Axial spondyloarthritis (axSpA) is a group of chronic autoimmune diseases with predominant damage to the axial skeleton (spine and/or sacroiliac joints), the possible involvement of peripheral joints, enthesis, skin (psoriasis), intestines (Crohn's disease, ulcerative colitis), eyes (uveitis), heart and aorta [1]. The development of a chronic autoinflammatory status is considered the main predictor of the early development and progression of cardiovascular diseases in patients with axSpA.

The risk of cardiovascular diseases in cases of axSpA is 1.3-1.5 times higher than in the general population, while mortality due to unfavorable cardiovascular events is 20-40% higher than in the general population [2–4].

Anemia is a common comorbid disease in patients with axSpA [5–7]. Persistent systemic inflammation underlying the impairment of iron metabolism and dysfunction of erythropoiesis is also a leading cause of endothelial dysfunction, increased arterial stiffness, early development and progression of atherosclerotic lesions of the vascular wall [8].

A number of studies [9–11] describe increased arterial stiffness in patients with axSpA compared with healthy individuals. The effect of anemia on the processes of vascular wall remodeling and arterial stiffness parameters is generally understudied, and there are currently no data on the correlation between anemia and damage to arterial vessels in patients with axSpA. In this regard, it is of practical interest to study the parameters indicating changes in the rigidity of the arterial wall in patients with axSpA with and without anemia.

The **study objective** was to investigate the parameters of vascular wall rigidity and subclinical atherosclerosis in patients with axSpA without clinically manifesting cardiovascular disease, depending on the presence of anemia.

Materials and methods

The study included 102 patients with axSpA (age — 37.7±9.8 years, duration of axSpA — 13.5±8.7 years, 66 (64.7%) male subjects) who were hospitalized at the Regional Clinical Hospital (Saratov) in 2017-2020. Inclusion criteria were the following: compliance with axSpA criteria of the Assessment of Spondyloarthritis International Society, 2009 [12], age ³18, signed informed consent to participate in the study. The study did not include patients with coronary heart disease (exertional angina, previous myocardial infarction, chronic heart failure), uncontrolled arterial hypertension, atherosclerotic plaques according to duplex examination of carotid arteries, chronic kidney disease of stages 3-5, liver failure, viral hepatitis, HIV infection, tuberculosis, chronic diseases in acute phase (peptic ulcer, cholecystitis), cancer and lymphoproliferative diseases, and pregnant women.

Standard parameters of CBC and blood biochemical assay, concentration of C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were determined. Estimated glomerular filtration rate (eGFR) was defined using the CKD-EPI formula (Chronic Kidney Desease Epidemiology Collaboration, 2009) [13]. BASDAI (the Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (the Ankylosing Spondylitis Disease Activity Score) indices using CRP were calculated to determine the activity of axSpA.

Clinical features of the examined patients are presented in Table 1. Patients were comparable in age and disease duration. However, the percentage of female patients and the number of patients positive for HLA-B27 were higher among patients with axSpA and anemia. Patients with anemia more often received therapy with synthetic and/or biological disease-modifying drugs in comparison with patients without it. The percentage of patients receiving non-steroidal anti-inflammatory drugs and systemic glucocorticoids demonstrated no statistically significant difference.

Table 1. *The main clinical and demographic parameters and characteristics of drug treatment in patients with axSpA included in the study*

Parameter	All patients with axSpA (n=102)		p
	Without anemia (n = 50) M±SD / n (%)	With anemia (n = 52) M±SD / n (%)	
Age, years	37,0±9,6	38,5±10,0	0,454
Men	40 (80)	26 (50)	0,002*
Duration of axSpA, years	14,0±8,2	12,9±9,2	0,521
HLA-B27 positivity	19 (38)	32 (62)	0,04*
Smokers	16 (32)	18 (35)	0,468
BMI, kg/m^2	24,8±6,4	24,8±4,9	0,97
Obesity	10 (20)	8 (15)	0,774
Total cholesterol, mmol/L	4,8±1,0	4,8±0,9	0,843
eGFR, ml/min/1.73 m^2	88,4±14,7	86,6±17,8	0,579
Arterial hypertension	18 (36)	14 (27)	0,323
BASDAI, points	4,7±2,2	5,6±2,1	0,038*
BASDAI >4	25 (52)	38 (81)	0,003*
ASDAS-CRP, points	3,2±1,0	3,8±1,0	0,004*
ASDAS-СРБ ³2,1/ ASDAS-CRP ³2,1	39 (78)	46 (88)	0,015*
Therapy of axSpA			
NSAIDs	46 (92)	49 (94)	0,713
Glucocorticoids	21 (42)	31 (60)	0,075
DMARs, including:	24 (48)	35 (67)	0,048*
Methotrexate	8 (33)	9 (26)	0,844
Sulfasalazine	6 (25)	22 (62)	0,001*
Methotrexate + sulfasalazine	2 (8)	1 (3)	0,614
Methotrexate/sulfasalazine + bDMARDs	3 (13)	2 (6)	0,675
bDMARDs	5 (21)	1 (3)	0,109

Notes: axSpA — axial spondyloarthritis, HLA-B27 — human leukocyte antigen-B27, BMI — body mass index, eGFR — estimated glomerular filtration rate, NSAIDs — non-steroidal anti-inflammatory drugs, DMARs — disease-modifying antirheumatic drugs, bDMARDs — biological disease-modifying anti-rheumatic drugs. * — p <0,05

To assess the rigidity of the vascular wall, the oscillography method was used (TensioClinic arteriograph, Tensiomed, Hungary) with the calculation of the aortic augmentation index (Aix-ao), brachial artery augmentation index corrected for heart rate (Aix-br) and pulse wave velocity of the aorta (PWVao), as well as the photoplethysmography method (AngioScan device, AngioScan-Electronics, Russia) with determination of the stiffness index (SI) and reflection index (RI). Intima-media complex thickness (IMCT) of the right and left common carotid artery was assessed by ultrasound examination in B-mode using an Acuson 128 XP/100 device according to the standard technique [14]. Average IMCT was calculated; an increase in TCIM of ≥0.9 mm was regarded as a marker of subclinical atherosclerosis.

Statistical analysis was performed using SPSS 26.0 software (IBM SPSS Statistics, USA). Checking the distribution for compliance with the normal law was carried out using the analysis of histograms and the Kolmogorov — Smirnov test with Lilliefors correction; the distribution was considered normal at p> 0.05. To describe normally distributed quantitative parameters, the mean value and mean standard deviation (M±SD) were used; to describe the distribution of parameters different from the normal distribution, the median, upper and lower quartiles were defined (Me [Q1-Q3]). To assess the difference in quantitative parameters in two independent groups, Student's t-test was used with normal distribution of data; the Mann — Whitney test was used for distribution other than normal. The Kruskal-Wallis test was used to compare three or more groups. To assess the differences in categorical variables, the Pearson χ^2 test or Fisher's exact test was used. The correlation of two normally distributed quantitative parameters was studied using the Pearson method; for distribution other than normal, Spearman's method was used. Differences were considered statistically significant at p <0.05.

This study was approved by the Ethics Committee of the V.I. Razumovsky Saratov State Medical University of the Ministry of Health of Russia.

Results

Decreased hemoglobin level in patients with anemia corresponded to mild anemia in 49 (94%) cases, and to moderate anemia in 3 (6%) cases. Anemia of chronic disease (ACD) was revealed in 15 (29%) patients; 29 (56%) had a combination of ACD and iron deficiency anemia (IDA); in 8 (15%) patients, isolated IDA was observed. Laboratory and clinical activity of systemic inflammation, according to the obtained values of CRP, ESR, BASDAI and ASDAS-CRP indices, was statistically significantly higher in patients with anemia (Tables 1, 2).

During the analysis of pulse wave properties, no significant differences in vascular wall stiffness indices in axSpA patients with and without anemia were found (Table 3). PWVao values above 10 m/s were registered in 3 (6%) patients without anemia and in 2 (4%) patients with anemia (p=0.675). Mean SI values in patients with normal and reduced hemoglobin exceeded the reference range, while the percentage of patients with increased SI >8 m/s among axSpA patients with and without anemia was 56% and 60%, respectively (p=0.714) An increase in IMCT^{3}of 0.9 mm was observed in 8 (16%) patients with axSpA without anemia and in 4 (8%) patients with anemia (p=0.312).

According to the results of correlation analysis, statistically significant correlations were obtained between Aix-ao, PWVao, SI, IMCT and the age of patients, between Aix-ao, PWVao and BASDAI clinical activity index.

Table 2. *The main hematological parameters and traditional markers of inflammation in patients with axSpA included in the study*

Parameter	All patients with axSpA (n=102)		p
	Without anemia (n = 50) M±SD / Me [Q1-Q3]	With anemia (n = 52) M±SD / Me [Q1-Q3]	
Red blood cells, 10^{12}/L	4,7±0,3	4,2±0,5	<0,001*
Hemoglobin, g/L	138 [134-149]	116 [107-120]	<0,001*
Hematocrit, %	42,0±3,6	34,9±2,5	<0,001*
Mean corpuscular volume (MCV), fL	89 [87-95]	84 [78-89]	<0,001*
Mean cellular haemoglobin content (MCH), pg	30,5 [29,1-31,9]	27,5 [25,2-30,1]	<0,001*
Red cell distribution width (RDW), %	13,5 [12,6-14,2]	15,1 [13,6-17,2]	<0,001*
Platelets, 10^9/L	249 [218-301]	297 [250-371]	0,001*
ESR, mm/h	10 [6-15]	17 [12-28]	<0,001*
CRP, mg/L	9,5 [3,8-15,3]	16,9 [6,7-37,7]	0,003*

Notes: ESR — erythrocyte sedimentation rate, CRP — C-reactive protein. * — p <0,05

Table 3. The main indicators of arterial stiffness and IMT in patients with axSpA with and without anemic syndrome

Parameter	All patients with axSpA (n=102)		p
	Without anemia (n = 50) M±SD	With anemia (n = 52) M±SD	
Oscillography			
SBP, mm Hg	130,3±16,0	129,1±19,2	0,729
DBP, mm Hg	75,4±12,2	75,0±14,1	0,896
MAP mm Hg	93,7±13,0	93,1±15,4	0,837
PP, mm Hg	54,9±8,3	54,0±9,3	0,608
HR, beat/min	72,1±10,7	73,4±11,3	0,564
SBPao, mm Hg	122,8±19,9	119,9±20,5	0,471
	17,3±10,6	19,1±13,7	0,455
Aix-br, %	-40,2±20,9	-36,6±27,1	0,455
PWVao, m/sec	7,4±1,4	7,4±1,5	0,99
Photoplethysmography			
SI, m/sec	8,8±2,0	8,2±1,7	0,183
RI, %	60,6±15,0	54,3±16,7	0,069
Carotid ultrasound			
IMT, cm	0,73±0,16	0,70±0,13	0,421

Notes: SBP — systolic blood pressure, DBP — diastolic blood pressure, MAP — mean arterial pressure, PP — pulse pressure; HR — heart rate, SBPao — central systolic blood pressure, Aix-ao — aortic augmentation index, Aix-br — HR-corrected brachial augmentation index, PWVao — aortic pulse wave velocity, SI — stiffness index, RI — reflection index, IMT — intima-media thickness

Table 4. Relationships between Aix-ao, PWVao, SI, TCIM and traditional cardiovascular risk factors, axSpA activity indices and laboratory parameters

Parameter	Aix-ao		PWVao		SI		IMT	
	r	p	r	p	r	p	r	p
Age	**0,488**	**<0,001***	**0,516**	**<0,001***	**0,289**	**0,007***	**0,461**	**<0,001***
axSpA duration	**0,199**	**0,045***	0,156	0,116	**0,336**	**0,002***	0,167	0,135
SBP	0,032	0,752	**0,355**	**<0,001***	0,192	0,077	0,219	0,05
DBP	**0,305**	**0,002***	**0,434**	**<0,001***	**0,318**	**0,003***	0,211	0,059
BASDAI	**0,243**	**0,018***	**0,253**	**0,013***	0,003	0,981	0,179	0,117
ASDAS-CRP	0,075	0,467	0,131	0,204	0,074	0,51	0,069	0,548
Hemoglobin	-0,131	0,189	0,024	0,815	0,095	0,386	0,158	0,159
Hematocrit	-0,083	0,437	0,17	0,111	0,125	0,289	0,125	0,3
ESR	0,034	0,736	0,129	0,197	0,026	0,811	-0,199	0,077
CRP	-0,022	0,834	0,131	0,201	0,103	0,358	-0,106	0,36

Notes: Aix-ao — aortic augmentation index, PWVao — aortic pulse wave velocity, SI — stiffness index, IMT — intima-media thickness, SBP — systolic blood pressure, DBP — diastolic blood pressure, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein. * — p <0,05

No correlations between the parameters of vascular wall stiffness, IMCT and conventional laboratory markers of inflammation, and hemoglobin level were established (Table 4). Correlations were found between PWVao and Aix-ao (r=0.442, p <0.001), SI (r=0.273, p=0.011) and IMCT (r=0.236, p=0.034).

Discussion

As far as we know, this study is the first one to attempt to assess the correlation between hemoglobin level and vascular wall stiffness, subclinical atherosclerosis in patients with axSpA. The determination of IMCT and arterial stiffness parameters (their increased values are associated with the subsequent development of adverse cardiovascular events) is an important tool for stratification of cardiovascular risk and selection of adequate disease-modifying drugs in patients with axSpA. Data accumulated to date clearly demonstrate the high incidence of subclinical atherosclerosis among patients with axSpA. According to the meta-analysis performed by Yuan Y. et al. [15], IMCT in patients with ankylosing spondylitis (AS) was statistically significantly higher than in healthy controls (standardized mean difference

[95% confidence interval (CI)] = 0.725 [0.443–1.008], p <0.001). According to a systematic review and meta-analysis performed by Bai R. et al.[11] with a total of 2,882 subjects (1,535 patients with AS and 1,347 healthy individuals), a statistically significant increase in PWVao was revealed in patients with AS compared to the control group (weighted average difference [95% CI] = 0.910 [0.464-1.356], p <0.001). IMCT values and vascular wall stiffness parameters obtained during our study in patients with axSpA are consistent with literature data.

However, the objective of this study was to assess the possible correlation between hemoglobin level and the presence of subclinical atherosclerosis in patients with axSpA. At the moment, the role of anemia in the processes of vascular wall remodeling remains a subject of discussion, and study results are sometimes contradictory. On the one hand, it is known that IDA and ACD are associated with the development of oxidative stress [16], and persistent systemic inflammation makes an independent contribution to the dysfunction of antioxidant systems with underlying overproduction of reactive oxygen species [17]. The combined effect of these factors leads to impaired endothelial function, which is a key pathological pattern underlying the development of atherosclerosis [18]. In a study performed by Schwarz C. et al., a negative correlation was demonstrated between hemoglobin level and PWVao (r=-0.31, p=0.01) in patients on hemodialysis [19]. At the same time, H. Hsu et al. [20] reported a positive correlation between hemoglobin concentration and arterial stiffness in dialysis patients, while hemoglobin levels >109 g/l were significantly associated with increased PWVao >10 m/s. A survey of 807 male subjects with and without cardiovascular diseases by Kishimoto S. et al. [21] showed that both a decrease and an increase in hemoglobin, hematocrit and the number of RBC were associated with impaired endothelial function, increased brachial-ankle pulse wave velocity (baPWV) and IMCT of brachial artery. According to Kishimoto S. et al., hematocrit 42.0–49.4%, hemoglobin 147–168 g/l and RBC 4.82–5.24×10⁶/μl are optimal

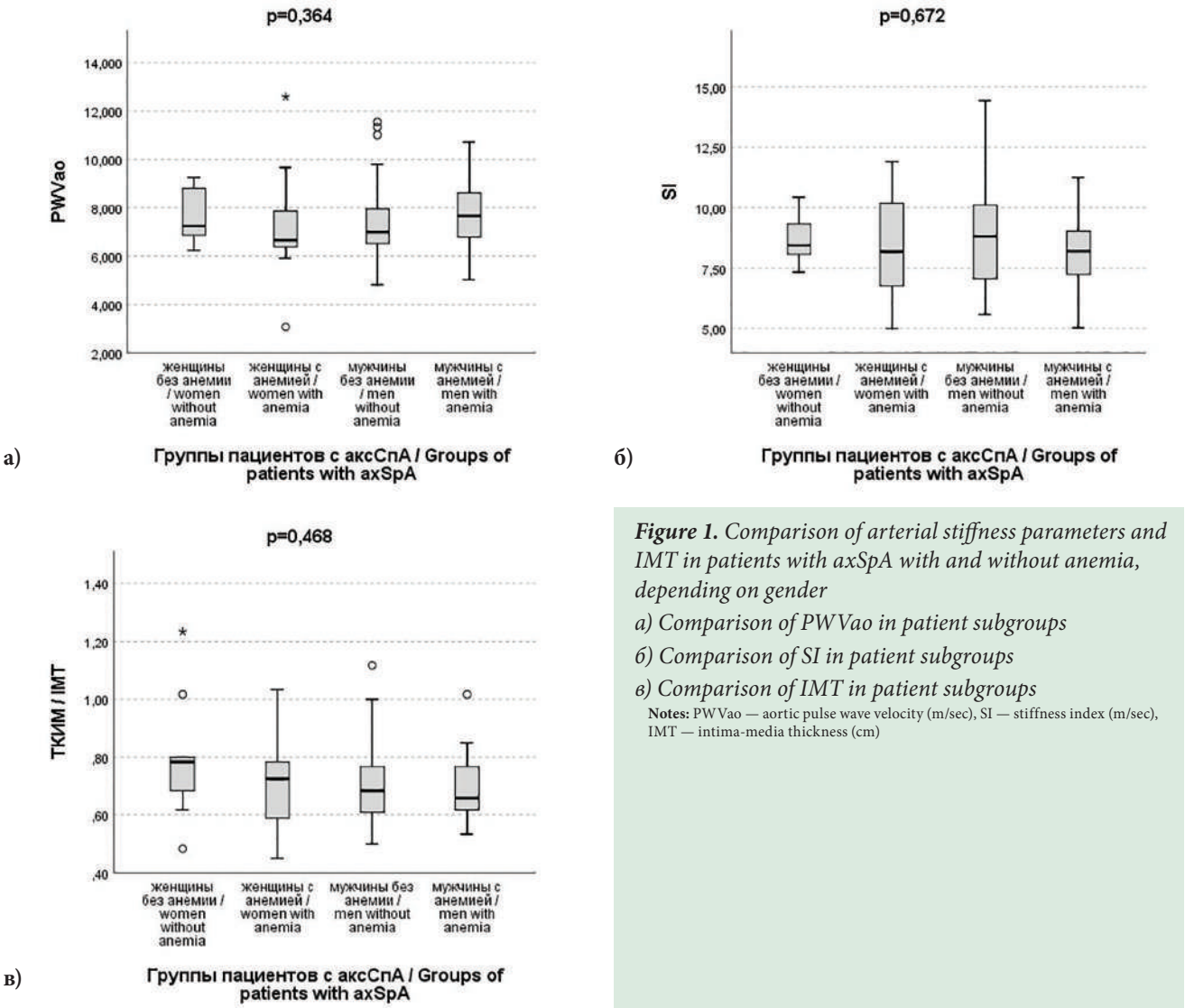

Figure 1. *Comparison of arterial stiffness parameters and IMT in patients with axSpA with and without anemia, depending on gender*

а) Comparison of PWVao in patient subgroups

б) Comparison of SI in patient subgroups

в) Comparison of IMT in patient subgroups

Notes: PWVao — aortic pulse wave velocity (m/sec), SI — stiffness index (m/sec), IMT — intima-media thickness (cm)

target levels for adequate endothelial function and state of vascular wall. A population-based Gutenberg Health Study (GHS) [22] with a total of 13,724 subjects demonstrated an independent association of higher hematocrit values with increased SI in patients of both genders; in men, hematocrit was an independent predictor of increased SI, even in the absence of cardiovascular factors. A large Chinese study by Sun P. et al. demonstrated similar results [23]: there was a significant increase in baPWV and Aix-br with increased concentration of hemoglobin and number of RBC. A group of Japanese researchers [24] obtained data that indicate the potentially protective role of a small decrease in hemoglobin levels — in female patients with mild anemia, baPWV values were lower than in females with normal and increased hemoglobin levels.

Interestingly, despite the significantly higher inflammatory activity of axSpA in patients with anemia (Tables 1, 2), this study did not reveal significant differences between the studied markers of vascular wall remodeling in comparison with patients without anemia. The negative effect of highly active systemic inflammation registered in patients with anemia was probably partially offset by the relative improvement in blood rheological properties due to decreased blood viscosity, as well as increased nitric oxide production induced by hypoxia [25]. Of course, further study of markers of endothelial dysfunction in patients with axSpA and anemia is necessary to determine correlation with parameters of arterial stiffness and subclinical atherosclerosis. It is also worth noting that the percentage of female patients in our study among patients with anemia was higher compared to patients without anemia, 50% and 20%, respectively (p=0.002). However, during the analysis of subgroups by gender, no significant differences between the parameters of arterial stiffness and IMCT in men and women depending on the presence of anemia were found (Fig. 1).

Conclusion

This study could not confirm a correlation between anemia and vascular wall stiffness, IMCT in patients with axSpA. It is possible that the decrease in hemoglobin did not lead to a further increase in the rigidity of the vascular wall due to the potential protective effect of anemia via well-known pathophysiological patterns — decreased blood viscosity and induction of nitric oxide synthesis, which is an endogenous vasodilator and has a strong antiatherogenic effect. Further study of the correlation between hemoglobin levels and markers of endothelial dysfunction in patients with inflammatory diseases of the spine is required.

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ТРУДНОСТИ ДИФФЕРЕНЦИАЛЬНОЙ ДИАГНОСТИКИ БРОНХООБСТРУКТИВНОГО СИНДРОМА

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The Difficulties of Differential Diagnosis of the Bronchial Obstruction Syndrome

Резюме

Бронхообструктивный синдром представляет собой нарушение бронхиальной проходимости функционального или органического происхождения, который проявляется одышкой, приступами удушья, кашлем, тахикардией. Наиболее распространёнными причинами бронхообструктивного синдрома являются хроническая обструктивная болезнь легких и бронхиальная астма. В некоторых случаях причиной бронхиальной обструкции являются опухоли или метастазы опухолей в легкие. В статье описан клинический случай бронхообструктивного синдрома, показывающий, что все больные с бронхиальной астмой, при отсутствии эффекта от назначенной адекватной базисной терапии, с отсутствием контроля над заболеванием, должны быть хорошо обследованы на предмет альтернативного диагноза. В нашем случае тщательное обследование больной позволило врачу аллергологу диагностировать центральный рак легкого с метастазами в лимфоузлы средостения. Особенностью случая является первичная резистентность к ингибиторам тирозинкиназы, выявленная при генетическом исследовании, что определило схему дальнейшей полихимиотерапии. Данный клинический случай доказывает необходимость проведения дифференциальной диагностики, с комплексным подходом и использованием различных методик обследования.

Ключевые слова: *бронхиальная астма, бронхообструктивный синдром, ингибиторы тирозинкиназ, немелкоклеточный рак легких, рецептор эпидермального фактора роста*

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

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Abstract

Bronchial obstructive syndrome is a violation of bronchial patency of functional or organic origin, which is manifested by shortness of breath, suffocation attacks, cough, tachycardia. The most common cause of bronchial obstructive syndrome is chronic obstructive pulmonary disease and bronchial asthma. In some cases, the cause of bronchial obstruction is tumors or tumor metastases to the lungs. The article describes a clinical case of bronchial obstructive syndrome, showing that all patients with bronchial asthma, in the absence of an effect from the prescribed adequate basic therapy, with no control over the disease, should be well examined for an alternative diagnosis. In our case, a thorough examination of the patient allowed the allergist to diagnose central lung cancer with metastases to the lymph nodes of the mediastinum. A feature of the case is the primary resistance to tyrosine kinase inhibitors, revealed during a genetic study, which determined the scheme of further polychemotherapy. This clinical case proves the need for differential diagnosis, with a comprehensive approach and the use of various examination methods.

Key words: *bronchial asthma, bronchial obstruction syndrome, tyrosine kinase inhibitors, non-small cell lung cancer, epidermal growth factor receptor*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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TKI — tyrosine kinase inhibitors, VC — vital capacity, FEV_1 — forced expiratory volume in one second

Introduction

Bronchial obstructive syndrome is a complex of symptoms associated with impaired bronchial patency of functional or organic origin. The most common complaints in bronchial obstruction are: dyspnea, asthma attacks, productive or unproductive cough, and tachycardia [1].

According to literature data, bronchial obstructive syndrome is a challenging diagnosis that combines a heterogeneous group of diseases and a variety of risk factors, prognosis and treatment methods [2].

Chronic obstructive pulmonary disease and bronchial asthma are the most common causes of bronchial obstructive syndrome [3]. One of the common causes of bronchial obstruction is tumors or their metastases in the lungs. Most lung cancers are known as primary tumors, which include carcinomas that originate from epithelial cells. The clinical picture of lung cancer during physical examination in most cases manifests itself in the late stages. The earliest signs of a lung tumor are: persistent cough (can be either unproductive or productive), dyspnea (inspiratory or mixed) without chest pain, hemoptysis, general weakness, and fatigue [4].

In clinical practice, computed tomography is used to diagnose lung cancer. Morphological verification of the diagnosis is performed using fibrobronchoscopy with biopsy, which allows diagnosing central lung cancer in the absence of X-ray signs [4].

Both standard chemotherapy regimens and targeted drugs — 1st and 2nd generation EGFR tyrosine kinase inhibitors (TKI) (Gefitinib, Erlotinib, Afatinib) — are used to treat patients with non-small-cell lung carcinoma. In 60% of cases, resistance occurs after 8–12 months of using these drugs. For this reason, tyrosine kinase inhibitors are prescribed as second-line therapy. If a mutation in the EGFR gene is detected during molecular genetic research prior to the prescription of TKI, resistance is regarded as primary. The T790M mutation (replacement of the amino acid residue of threonine with methionine at position 790) makes TKI use ineffective [5].

Case report

We present a clinical case from the Department of Allergology of the Regional Clinical Hospital in Krasnoyarsk. Patient H., 58 years old, was referred to an allergist at the Regional Clinical Hospital to clarify the diagnosis in November 2018 with complaints of paroxysmal cough in the morning with difficulty to discharge mucus sputum and following hoarseness, occasional feeling of heaviness, chest congestion, wheezing, inspiratory dyspnea when climbing stairs up to the 2nd floor.

The first symptoms appeared after emotional stress in November 2017. Patient took acetylcysteine on her own. She did not have nocturnal symptoms of suffocation; she did not use bronchodilators. She was examined by a local allergist in January 2018. According to the medical history, the patient's maternal grandfather suffered from bronchial asthma. Patient does not smoke. During the last four years, a paroxysmal unproductive cough was noted upon contact with household chemicals. During the last 1.5 years, a dry paroxysmal cough was noted after a viral infection. History of allergy to beta-lactam antibiotics (anaphylactic shock and urticaria). The patient lives in a panel building, sleeps on a polyester pillow, has a dog.

Spirometry and bronchodilator test results, dated January 31, 2018: vital capacity (VC) was 101%; forced expiratory volume in 1 second (FEV1) — 89%; FEV1/VC) — 86; test with salbutamol 400 mg — negative, increase in FEV1 — by 2%. Conclusion: external respiration function within normal. Scarification tests were performed with household, epidermal and pollen allergens. Sensitization was not detected. Based on the clinical picture, medical history, physical examination and further investigations, non-allergic bronchial asthma was diagnosed first. Controller medications were prescribed: beclomethasone / formoterol 100/6 μg, 1 inhalation twice a day; salbutamol 100 μg, 1–2 inhalations on demand in case of suffocation. Despite the therapy, episodes of labored breathing persisted, as well as dyspnea at moderate physical exertion; episodes of dry cough became more frequent; wheezing labored breathing appeared at night, and hoarseness of the voice was noted; a decrease in body weight (four kg loss in two months) was observed with preserved appetite.

In October 2018, the patient was repeatedly attended to by an allergist at a local outpatient clinic. According to the data of thyroid ultrasound and chest X-ray, no abnormality was revealed. The patient was prescribed the following treatment: ipratropium bromide/fenoterol 1 ml four times a day via a nebulizer, methylprednisolone 4 mg — three tablets per day for seven days, montelukast 10 mg at night. During therapy, the frequency of asthma attacks decreased, but coughing, wheezing, and hoarseness persisted. Due to the lack of monitoring the symptoms of bronchial asthma, she was referred for consultation with an allergist at the Regional Clinical Hospital in Krasnoyarsk and was hospitalized on November 21, 2018, in the Allergology Department for symptom management and controller medication adjustment.

Physical examination findings: at auscultation — harsh breathing is conducted over all pulmonary fields, rales are not heard, respiratory rate is 21 per minute, SaO_2 97%. Laboratory findings were within normal limits. Spirometry and bronchodilator test revealed mixed dysfunction of external respiration: VC — 53–75%; FEV1 — 47–50%; FEV1/VC — 73-77; bronchodilation test (salbutamol 400 μg) negative, increment — 3%. Chest X-ray in two projections: the pulmonary fields are characterized with increased pneumatization, without shadowing, the pulmonary pattern is diffusely strengthened, the roots are structural, the mediastinal shadow is not displaced, the aorta is compressed, elongated, the interlobar pleura is densified on the right. The diaphragm contour is clear, even, the sinuses are free (Fig. 1).

Despite the presence of allergic history, respiratory symptoms, dysfunction of external respiration with a moderate decrease in VC, a negative bronchodilation test, and the absence of the effect of the prescribed therapy required further investigations. Tracheobronchoscopy revealed bilateral diffuse moderate bronchitis with mild hypersecretion. Deformation of the right middle lobe and lower lobe bronchi. A biopsy of the middle lobe and lower lobe bronchi was conducted (Fig. 2).

On November 30, 2018, multislice computed tomography (MSCT) of the chest was performed, mass lesion in the root of the right lung, measuring 30.2 × 33.8 × 42.5 mm, with cord-like tuberous contours was defined. The lobe bronchi are compressed due to the lesion, the stump of the middle lobe bronchus is determined. In the right middle lobe, signs of lymphangitic carcinomatosis are determined. Mediastinum structures are preserved, not displaced. No enlarged lymph nodes. There is no

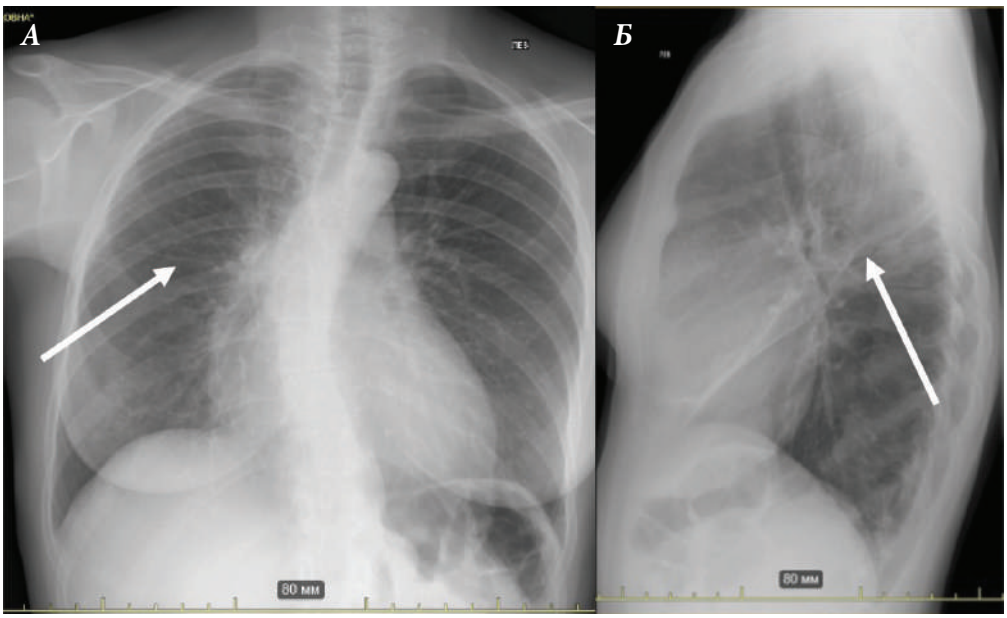

Figure 1. *Radiography of chest organs in 2 projections dated 23.11.2019.*
a) direct projection,
b) lateral projection

pleural effusion. Pericardial effusion, pericardium thickness is 27.4 mm (Fig. 3).

When examined by an otorhinolaryngologist, no abnormality was detected. Three-fold cytological examination of sputum did not reveal Mycobacterium tuberculosis. Histopathological examination of the bronchus showed gland-like structures representative of bronchial adenocarcinoma. The patient was diagnosed with central cancer of the right lung. The patient was referred to an oncologist at the A. I. Kryzhanovsky Krasnoyarsk Regional Clinical Oncology Center (KRCOC).

In April 2019, the patient was diagnosed with stage IIIa (T3NxM0) central cancer of the right lung. Deformation of the right middle lobe and lower lobe bronchi. Mediastinal lymph node metastases. The EGFR+ mutation was detected at the KRCOC during the cytogenetic examination of the lung biopsy specimen, the T790M mutation, ALK — negative. Therefore, the patient has primary resistance to tyrosine kinase inhibitors. According to the histological conclusion, a polychemotherapy course was prescribed in the EC regimen (Etoposide and Cisplatin).

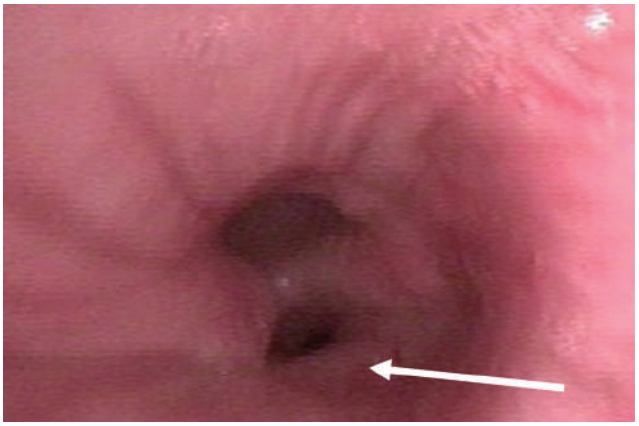

Figure 2. *Tracheobronchoscopy dated 26.11.2018*

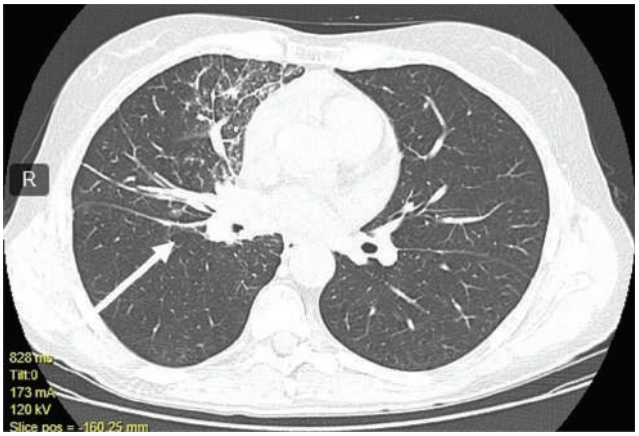

Figure 3. *MSCT of thoracic organs dated 30.11.2018*

Discussion

The incidence of lung cancer has increased dramatically in many countries around the world in recent years. More than 1.2 million new cases of lung cancer are reported annually in the world. In Russia, lung cancer also ranks 1st among oncological diseases, accounting for 12% of cases. Central lung cancer accounts for 60–80% of all cancer cases [6, 7]. Incidence statistics are sex-related. In men, lung cancer is the most common cancer and accounts for 16.7% of all cases. In women, it is significantly lower and amounts to 8.8% [7].

Among the risk factors for central lung cancer, smoking ranks first — 79.1%, and followed by occupational hazards (metal processing — 8.3%; chemical production — 5.6%, etc.) [8]. Therefore, primary care physicians should be less stereotypical about the central lung cancer diagnosis and suggest this disease in such cases.

The early clinical symptom in patients with central lung cancer is cough: according to the literature, it occurs in up to 70% cases. The second most common symptoms are chest pain (38%) and dyspnea (37.9%) [8]. In this case, cough upon contact with chemicals in the patient appeared four years before the diagnosis was established. However, since the above-described stereotype and characteristic medical history data (grandfather with BA, allergic history), BA appeared to be a more suitable diagnosis.

Current difficulties in central lung cancer diagnosis are also associated with the predominance of its peribronchial form, which, for a long time, does not cause significant narrowing of the bronchus lumen or its obstruction [6]. In this case, clinical signs of bronchial obstructive syndrome appeared 1.5 years before the diagnosis. The presence of bronchial obstructive syndrome and the absence of the effect of the BA controller medications made it possible to doubt the earlier diagnosis. Further investigations (tracheobronchoscopy and chest MSCT) revealed signs of central lung cancer. The patient was referred to an oncologist for further treatment.

Conclusion

The presented clinical case suggests that all patients with bronchial asthma, if the prescribed treatment has no effect and without monitoring the disease, should be carefully examined for an alternative diagnosis. The described clinical case proves the need for differential diagnosis with an integrated approach and the use of various examination methods. The clinician should remember that bronchial tumors are a common cause of persistent bronchial obstructive syndrome. The focus should be on the fact that cancer must be excluded if the prescribed controller medications are ineffective.

Вклад авторов

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СОЧЕТАНИЕ ИНФЕКЦИОННОГО ЭНДОКАРДИТА И ИНФЕКЦИИ COVID-19 У МОЛОДОЙ ПАЦИЕНТКИ

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Combination of Infective Endocarditis and Covid-19 Infection in a Young Patient

Резюме

Инфекционный эндокардит нативного митрального клапана с множественными кардиоэмболическими инфарктами головного мозга и миокарда при сочетании с новой коронавирусной инфекцией тяжелого течения стал причиной неблагоприятного исхода у молодой женщины. Причинами этого стали как поздняя диагностика ИЭ (несвоевременное выполнение трансторакальной эхокардиографии), так и синергия патогенетических механизмов двух тяжелых заболеваний, наиболее ярко проявившаяся в развитии гемореологических нарушений, повреждении миокарда, легких и головного мозга.

Ключевые слова: *инфекционный эндокардит, новая коронавирусная инфекция, SARS COV 2, COVID19*

Конфликт интересов

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

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Abstract

Infective endocarditis of the native mitral valve with multiple cardioembolic cerebral infarctions and myocardial infarctions against the background of a severe new coronavirus infection caused an unfavorable outcome in a young woman. The reasons for this were both the late diagnosis of IE (untimely performance of transthoracic echocardiography) and the synergy of the pathogenetic mechanisms of two serious diseases, which was most clearly manifested in the development of hemorheological disorders, damage to the myocardium, lungs and brain.

Key words: *infective endocarditis, new coronavirus infection, SARS COV 2, COVID19*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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BP — blood pressure, HIV — human immunodeficiency virus, WHO — World Health Organization, DU — duplex ultrasound, MI — myocardial infarction, ACEI — angiotensin converting enzyme inhibitors, IL-6 — interleukin-6, CT — computed tomography, MK — mitral valve, MRI — magnetic resonance imaging, NIV — non-invasive ventilation, CF — circulatory failure, PCR — polymerase chain reaction, RNA — ribonucleic acid, PASP — pulmonary artery systolic pressure, CRP — C-reactive protein, RR — respiration rate, HR — heart rate, ECG — electrocardiogram, EchoCG — echocardiography, LVEF — left ventricle ejection fraction, FC — functional class, SpO_2 — oxygen saturation, SARS-CoV-2 — Severe acute respiratory syndrome-related coronavirus 2, COVID-19 — Coronavirus Disease 2019, IE — infective endocarditis

The novel coronavirus pandemic declared by WHO on March 11, 2020 [1] made us focus on the state of the cardiovascular system in SARS-CoV-2 patients [2]. The most frequently discussed and obviously most significant cardiovascular disorders are acute coronary syndrome, diffuse myocarditis and acute myocardial damage [2, 3]. These conditions are caused by coagulation dysfunction, endothelial damage, exposure of the myocardium to the virus, pro-inflammatory cytokine release, hypoxia, stress, and other factors [3]. There is no information and evidence of specific COVID-19-mediated endocardial damage. There are few data on other types of endocardial damage, in particular, the incidence of infective endocarditis (IE) during the SARS-COV-2 pandemic [4]. Cases of IE during this period are presented in the publications mainly as clinical observations [5]. Studies devoted to this issue present data indicating, on the one hand, a decrease in the number of reported cases of IE at the peak of the pandemic compared to the same previous period, and on the other hand, a significant increase in in-hospital mortality [6]. IE has an unfavorable prognosis and high mortality [7] even in the absence of concomitant diseases. The similarity of clinical symptoms of severe viral (COVID-19) and bacterial (IE) infections, systemic inflammatory response syndrome, late access to medical care due to severe restrictions on the movement of patients and shifting the focus of the healthcare system to the treatment of coronavirus disease are additional factors contributing to the diagnosis of IE and worsening of its prognosis and outcomes [8].

In the presented clinical case, left-sided IE with embolic syndrome and concomitant severe COVID-19 in a young woman led to an unfavorable outcome.

A 34-year-old woman was admitted to the Infections Department with complaints of general weakness, mixed dyspnea at moderate exercise and rest, and fever up to 38 °C. She had no previous health problems. Two months before hospitalization, two weeks after cesarean section, febrile fever appeared. Ceftriaxone injections, 4 g/day, were prescribed and an improvement in overall well-being and relief of fever were noted. A week later, the patient noted febrile fever with chills again, as well as dyspnea during normal physical exertion; cefepime 4 g/day was prescribed and body temperature returned to normal. Nasal and throat swabs for COVID-19 were negative. Deterioration of the condition on the day of admission: weakness increased sharply, dyspnea at rest appeared. Chest computed tomography (CT) was performed, bilateral pneumonia, 25–35% lung involvement, bilateral pleural effusion were detected, pulmonary infarction could not be excluded.

The patient's state at admission was severe. Oxygen saturation (SpO_2) 94%. Orthopneic position. Lethargy. Pale gray skin. Dense edema and cyanosis of the right lower limb. Muffled, rhythmic heart sounds. At the apex of the heart, I tone is weakened, systolic murmur radiates to the axillary region. II tone accent over a. pulmonalis. Heart rate (HR) and pulse rate is 100 bpm. BP 110/60 mm Hg. In the lungs, breathing is harsh, weakened in the lower parts, no rales. Abdomen is soft, nontender. Diuresis rate is reduced. Complete blood count: RBC 3.63×10^{12}/l, HGB 75 g/l, PLT 113×10^9/l, WBC 7.7×10^9/l, ESR 31 mm/h. Blood creatinine 225 mmol/l. Troponins are positive. D-dimer is positive. C-reactive protein (CRP) 175 mg/l. Ferritin 590 μg/l. PCR for COVID-19 at admission is negative. Procalcitonin 0.85 ng/ml. Blood cultures for sterility are negative. HIV antibodies and viral hepatitis markers are negative.

Electrocardiography (ECG) findings: focal changes in the myocardium of the left ventricle lower wall. When performing echocardiography (EchoCG), akinesia of all segments of the lower wall of the left ventricle was detected, ejection fraction (EF) of the left ventricle (LV) was 36%, pulmonary artery systolic pressure (PASP) was 31 mm Hg. In the projection of the anterior cusp of the mitral valve (MV), a hyperechoic formation 1.4 × 1.1 cm in diameter is visualized. According to the duplex

ultrasound (DU) of the veins of the lower extremities: iliofemoral deep vein thrombosis on the right. Magnetic resonance imaging (MRI) findings: multiple lacunar cerebral infarcts. A gynecologist did not detect any abnormality.

The diagnosis was: Infective endocarditis of the native mitral valve with grade 3 mitral regurgitation. 1st degree pulmonary hypertension.

Coronavirus infection, virus not identified, severe course.

Complications: CF II B (IV FC) according to the Russian classification. Acute kidney injury. Acute respiratory failure. Bilateral pneumonia. Bilateral pleural effusion. Pulmonary embolism. Multiple lacunar cerebral infarcts. Myocardial infarction. Ileofemoral DVT on the right.

In the hospital, antibiotics (imipinem + cilastatin 3 g/day), anticoagulants (fraxiparin 0.3 ml twice times a day) were prescribed, as well as angiotensin-converting enzyme inhibitors (ACEI), beta-blockers, diuretics, gastroprotective agents, mucolytics, oxygen therapy and prone position. Due to bacterial septicemia, steroids and IL-6 inhibitors were not used.

Temperature returned to normal on the third day, weakness and shortness of breath persisted. On day 10, tachycardia (HR 120), hypotension (BP 85/60 mm Hg), and respiratory failure (RR 26 per minute, SpO_2 88%) progressed. As a result, the patient was transferred to the intensive care unit. Due to unstable hemodynamics, dopamine infusion at a dose of 12 μg/kg/min (BP on infusion was 100/60 mm Hg, heart rate — 135 per minute) was prescribed, and non-invasive ventilation (NIV) was initiated. SpO_2 increased up to 90%. The patient was examined by a cardiac surgeon, conservative management was recommended, decision on surgery was delayed until the patient's stabilization. Repeated chest CT revealed bilateral interstitial pneumonia, CT score 3/4 (55–75%), bilateral pleural effusion (Fig. 1).

Repeated throat and nasal swab for COVID-19 was positive. Respiratory and heart failure increased; cardiac arrest in the form of asystole occurred, CPR was without effect. The patient died on the 20th day of hospitalization (10th day in the intensive care unit).

During pathological examination, the myocardium weighs 340 g. The endocardium is smooth, shiny and translucent. On the mitral valve, the overlays are of light yellow color measuring 0.8 × 0.5 cm in size (Fig. 2).

The myocardium is pale red in color, a bluish area measuring 2 × 3 cm is determined on the posterolateral wall of the left ventricle (Fig. 3).

Coronary arteries are not macroscopically altered. The airness of the lungs is reduced, the density is doughy; and the incision of the right lower lobe and left upper and lower lobes showed induration of the tissue of dark red color — lung infarctions (Fig. 4).

In the brain, multiple lacunar small foci are defined, measuring from 1 to 1.5 cm in size, flabby, light yellow in color (Fig. 5).

Histological examination on the mitral valve revealed fibrin masses with the presence of leukocytes (Fig. 2), accumulation of microorganisms; in the myocardium, vacuole and granular dystrophy of cardiomyocytes, foci of necrosis, areas of young and mature granulation tissue along the periphery of necrosis are defined (Fig. 3).

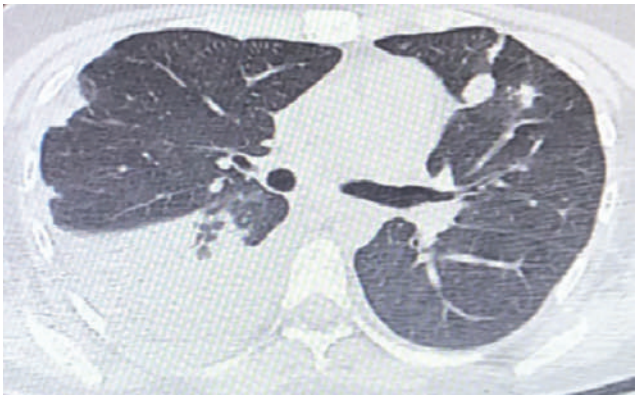

Figure 1. *Computed tomography of a patient's lungs (description in text)*

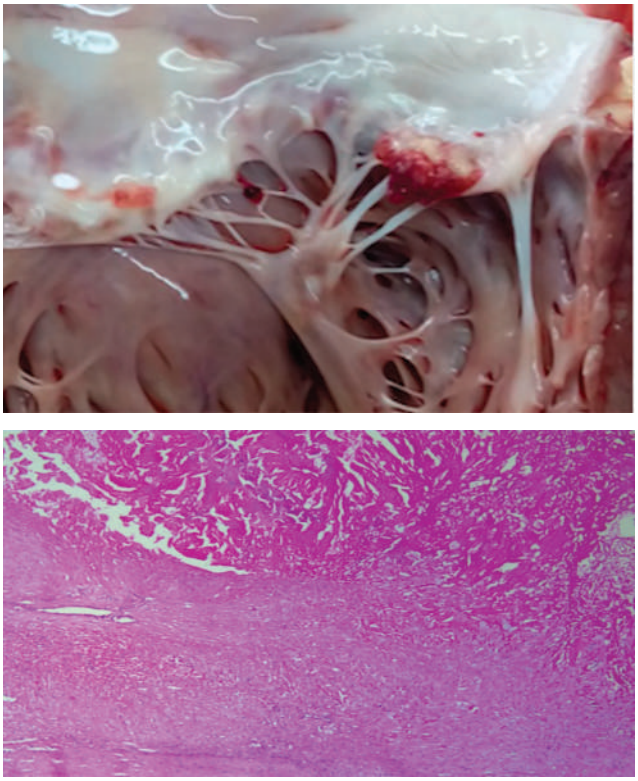

Figure 2. *Vegetations on the mitral valve (photo) and histological signs of fibrin application (hematoxylin/eosin staining)*

In the lungs intra-alveolar edema, multiple pulmonary infarctions of varying onset time were detected; in the lumens of the alveoli, there were accumulations of a large number of hyperplastic desquamated alveolocytes, fibrin masses, lymphocytes and leukocytes (Fig. 4). Multiple small foci of necrosis were found in the brain. SARS-CoV-2 RNA was detected in all the specimens, except for the spleen: in lungs, bronchi, trachea, and myocardium. Unfortunately, the cardiac valve specimen was not examined for the presence of RNA. The pathological diagnosis was the following:

The primary disease: 1. Infective endocarditis of the native mitral valve with grade 3 mitral regurgitation. 1st degree of pulmonary hypertension.

2. Novel coronavirus infection, the virus is identified, acute exudative phase of diffuse alveolar damage.

Primary disease complications: Multiple cerebral infarctions in the left hemisphere. Multiple pulmonary infarctions of varying time of onset. Acute myocardial infarctions (varying periods of onset). Pulmonary edema. Acute kidney injury in the diuretic phase: acute tubular necrosis. Bilateral viral pneumonia.

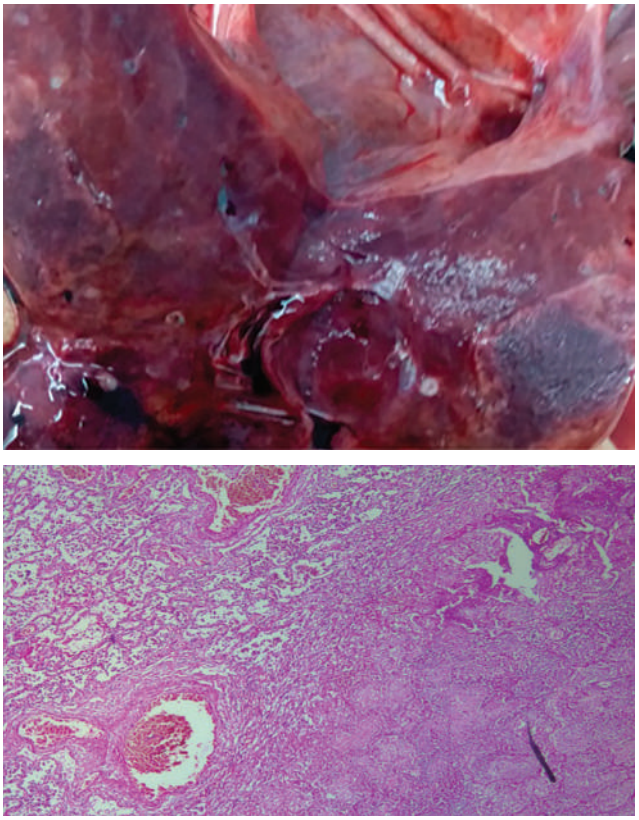

Figure 4. *Lung infarcts (macromedicine and histologicalmedicine)*

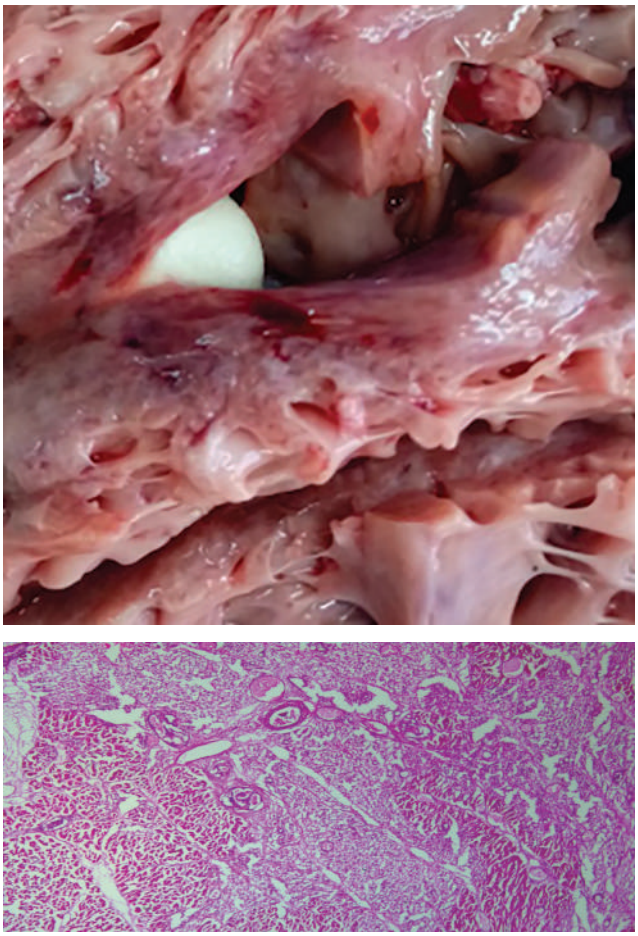

Figure 3. *Left ventricular myocardial infarction (macromedicine and histologicalmedicine)*

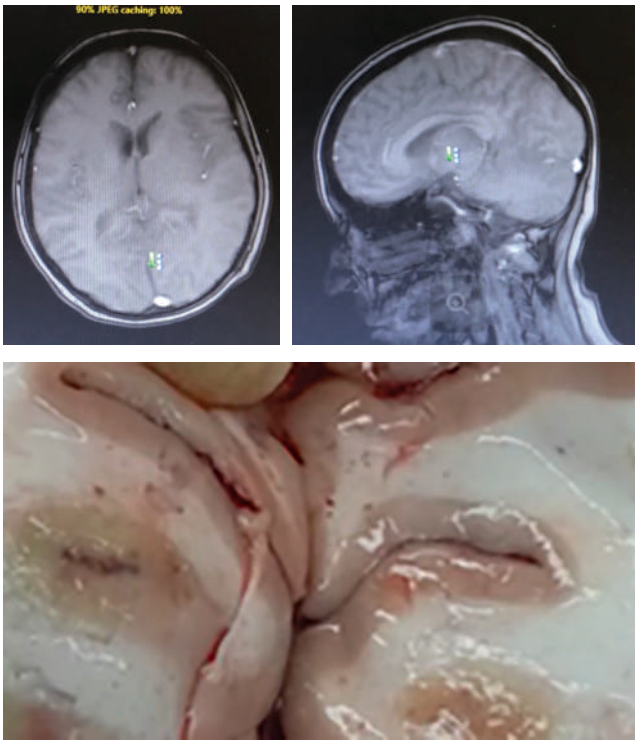

Figure 5. *Cardioembolic lacunar brain infarcts (on MRT and autopsy)*

Discussion

Several aspects of the possible interaction of SARS-COV-2 and IE in this clinical case should be discussed.

Chronology of Severe Viral and Bacterial Infections

An analysis of the sequence of events (febrile wave-like fever with chills, negative PCR results at the time of confirmation of mitral valve IE) suggests the high probability that IE preceded SARS-COV-2 infection. This is indirectly evidenced by the large size of vegetations on the mitral valve and the macroscopic changes in the valve, which take time to form. The late diagnosis of IE, not uncommon at other times [7], during the SARS-COV-2 pandemic is due to the most frequent explanation of any fever by the assumption of this particular infection [6]. This circumstance meant echocardiography was not performed on time, though it was undoubtedly indicated and probably would have been performed at a different time. The simultaneous occurrence of two diseases is not excluded. There is no doubt that they are approximately equal in degree to thanatogenesis (progressive lung damage, multiple thrombosis and myocardial damage characteristic of SARS-COV-2 infection, and cardioembolic cerebral infarctions in left-sided IE).

The Possibility of Endocardial Damage and IE Due to Exposure to Coronavirus

The literature has previously discussed the viral etiology of IE. Fournier P.E. described a case of recurrent IE of presumably enteroviral genesis in a four-month-old baby [9]. However, the viral etiology of IE is justifiably questioned: the direct cytopathic effect of the virus on the endocardium and its incorporation into cells has not been proven. This is particularly why IE is considered an almost exclusively bacterial infection [7], which, in this case, is confirmed by microorganisms in the surface layer of vegetation. Unfortunately, in this specific case, we did not have methods of morphological verification of possible viral damage to the myocardium and endocardium (electron microscopy, immunohistochemistry). Apparently, in this case, the cause of negative blood culture in IE, as discussed in the literature [7, 10], was the previous use of antibiotics.

The State of the Coagulation System and the Use of Anticoagulants

Multiple venous thromboses, damage to the microvascular bed, and signs of systemic hypercoagulation, observed in this particular case, are characteristic of novel coronavirus infection, often cause death and require continuous treatment with anticoagulants [11]. Hypercoagulation and vasculitis are also characteristic of IE. However, the use of anticoagulants is not recommended for the treatment of IE patients or should be used with caution for strict indications, primarily due to the high risk of hemorrhagic stroke. This led to certain challenges in deciding on the use of this group of drugs. Hypercoagulation and large vegetations on the mitral valve contributed to the development of thromboembolic complications of the brain, lungs, and heart.

Synergy of Visceral Lesions and Interpretation of Their Origin in SARS-COV-2 Concomitant with IE

First of all, severe myocardial damage (significant decrease in global contractility and widespread impairment of local myocardial contractility, focal ECG changes) is noteworthy. The possibility of such a lesion exists both with novel coronavirus infection and with IE, and an unambiguous interpretation of the predominant role of either disease in a particular case is difficult even after morphological examination. Damage to the endothelium and thrombosis of large and small branches of the coronary arteries are considered a key mechanism of myocardial damage in SARS-COV-2 infection [11]. In case of novel coronavirus infection, the term "acute myocardial damage" (AMD) is used to refer to conditions accompanied by symptoms of heart failure, rhythm and conduction disturbances, hypotension, and tachycardia with significant increase in serum troponins [12]. Morphologically, this can correspond to diffuse myocarditis, Takotsubo cardiomyopathy, and coronarogenic myocardial necrosis [3, 4, 11]. AMD in COVID-19 occurs with a frequency of 7 to 45%. It often requires hospitalization in the ICU and is always a predictor of an unfavorable outcome [3, 12]. ECG and EchoCG changes characteristic of myocardial infarction (MI), as well as an increase in myocardial damage markers can also be interpreted as a manifestation of coronary embolism in IE with the development of type 2 myocardial infarction [12]. However, in this specific case, macroscopic changes in coronary arteries, as well as microbial emboli in their lumen were not detected. The role of SARS-COV-2 in myocardial damage was likely predominant (decrease in ejection fraction, detection of RNA in the myocardium), which was one of the reasons to avoid surgical treatment of IE.

Conclusion

Infective endocarditis of the native mitral valve with multiple cardioembolic cerebral and myocardial infarctions and concomitant severe novel coronavirus infection caused an unfavorable outcome in the young woman. This was caused by both the late diagnosis of IE (untimely transthoracic echocardiography) and the combination of damaging pathogenetic mechanisms of two serious diseases that mostly affected hemorheology and damaged the myocardium, lungs and brain.

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Пономарева Е.Ю. (ORCID http://orcid.org/0000-0001-6187-7525): интерпретация и анализ данных, подбор литературы, редактирование статьи

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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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КАРБУНКУЛ ПОЧКИ У ПАЦИЕНТКИ С ПЕРВИЧНЫМ СИСТЕМНЫМ AL-АМИЛОИДОЗОМ И НЕФРОТИЧЕСКИМ СИНДРОМОМ

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Kidney Carbuncle in a Patient with Primary Systemic Al-Amyloidosis and Nephortic Syndrome

Резюме

Диагностика и лечение системного амилоидоза остается значимой клинической проблемой для врачей различных специальностей. Инфекционные осложнения и сепсис составляют до 8% причин смерти больных амилоидозом. Приведенный клинический случай демонстрирует развитие изначально имевшейся бессимптомной моноклональной гаммапатии неясного значения с исходом в системный AL-амилоидоз, течение которого осложнилось формированием карбункула почки после проведения первых циклов химиотерапии. Было установлено значительное расхождение между тяжестью общей клинической картины пациентки и изменениями в лабораторных показателях. Объективных факторов для восходящего распространения инфекции мочевыводящих путей или гематогенной диссеминации из других очагов выявлено не было, в связи с чем была предположена первичная бактериемия.

Ключевые слова: *AL-амилоидоз, карбункул, почка, нефротический синдром, МГНЗ*

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Конфликт интересов

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

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Abstract

The diagnosis and treatment of systemic amyloidosis remains a significant clinical problem for physicians of various specialties. Infectious complications and sepsis account for up to 8% of deaths in amyloidosis patients. This clinical case describes the development of an initially asymptomatic monoclonal gammopathy of unclear significance into systemic AL-amyloidosis, which was complicated by the formation of a renal carbuncle after the first cycles of chemotherapy. There was a significant discrepancy between the severity of the patient's overall clinical state and changes in laboratory parameters. There were no objective factors for the ascending spread of urinary tract infection or hematogenous dissemination from other foci, so a primary bacteremia was assumed.

Key words: *AL-amyloidosis, carbuncle, kidney, nephrotic syndrome, MGUS*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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CRP — C-reactive protein, CT — computed tomography, GFR — glomerular filtration rate, MGUS — monoclonal gammopathy of undetermined significance, US — ultrasound

Introduction

Amyloidosis is a heterogeneous group of hereditary and acquired diseases with pathogenesis based on the deposition of an insoluble fibrillar glycoprotein, amyloid, in the extracellular space [1]. There are 36 known types of human amyloidosis today; their classification is based on the structure of amyloid fibrils and their precursor proteins. Structural variants of amyloidosis are associated with both the systemic and localized nature of the disease. Amyloidosis types with immunoglobulin light (AL) or heavy (AH) chains and procalcitonin (Acal) as precursors can involve one or multiple organs in the process of amyloid infiltration [2]. Localized types are much less common than systemic types, including those in cases of AL amyloidosis [2, 3].

AL amyloidosis, previously defined as primary, is the most common type of systemic amyloidosis in developed countries with an incidence of 5-10 cases per 1,000,000 individuals annually. Its prevalence has been increasing over the past nine years [4, 5]. AL amyloidosis is significantly more common in patients aged over 65, with a slight predominance of male patients. The relative risk of AL amyloidosis is eight times higher in patients with plasma cell dyscrasia and asymptomatic monoclonal gammopathy of undetermined significance (MGUS) [6]. Abnormal clones of plasma cells that produce nephrotoxic paraprotein are not an exclusive feature of AL amyloidosis. Identification of a non-malignant clone of B-cell differentiation line generally defines a group of pathological conditions characterized by specific variants of kidney damage — monoclonal gammopathies of renal significance [7, 8].

Amyloid infiltration in AL amyloidosis can affect almost any organ; however, it mainly affects the heart, kidneys, liver, spleen, and, to a lesser extent, the gastrointestinal tract and nerve fibers, with the exception of the central nervous system [2, 9]. The clinical presentation of this disease is usually extremely obscure

and includes fatigue, weight loss, peripheral edema; dyspnea and orthostatic hypotension are often found. Symptoms highly specific for AL amyloidosis include macroglossia and periorbital purpura (raccoon's eyes), which can be observed in 15% of cases and have low sensitivity [10]. The detection of diastolic myocardial dysfunction and isolated proteinuria over 0.5 g/day without objective and common causes, i.e., a long history of arterial hypertension and/or diabetes mellitus, enables to include systemic amyloidosis in the differential diagnosis. The onset of secondary cardiorenal syndrome (type 5) is a key stage in the development of a vicious pathophysiological circle in cases of AL amyloidosis. Therefore, for most patients, myocardial damage with the development of chronic heart failure, rhythm disturbances, and amyloid nephropathy with the progression of chronic kidney disease (CKD) are the most significant issues in terms of the quality of life and poor prognosis [11].

The diagnostic algorithm in cases of suspected AL amyloidosis primarily includes serum or urine immunofixation for paraprotein in order to exclude plasma cell dyscrasia. Final verification of the diagnosis is based on morphological examination. The sensitivity of rectal or gastric mucosa biopsy is about 75–80%, and it is second only to percutaneous renal biopsy with sensitivity and specificity close to 100%. Subcutaneous adipose tissue (SAT) aspiration is less invasive and is the most preferred method. Detection of amyloid protein in subcutaneous fat aspirate in a patient with known plasma cell dyscrasia is sufficient for the final confirmation of the diagnosis of amyloidosis [12, 13]. The disadvantage of this biopsy site is the impossibility of typing amyloid fibrils, which does not allow excluding ATTRwt-amyloidosis without immunohistochemical examination or laser microdissection. The sensitivity of SAT aspiration is significantly lower in the presence of a low "amyloid load" of the whole body [13, 14].

Despite the established correlation between MGUS and amyloidosis and recommendations for screening monoclonal gammopathies in risk groups, many patients are diagnosed with amyloidosis when amyloid infiltration of the heart and kidneys becomes clinically significant. Mortality among patients with MGUS is largely determined not only by the progression of amyloidosis but also by the high risk of malignant paraproteinemias (multiple myeloma, Waldenstrom macroglobulinemia), rapidly progressing coronary heart disease, and, not least, severe bacterial and viral infections [15]

In the given clinical case, we describe the history of the development of AL amyloidosis with underlying chronic glomerulonephritis with MGUS with the course complicated by a renal carbuncle of unknown etiology.

Case report

Patient N., female, 62, was urgently hospitalized in the Internal Medicine Department of a multidisciplinary hospital with complaints of high body temperature of up to 39°C accompanied by shaking chills, sweating and general weakness.

She considers herself ill since 2016 when she was diagnosed with chronic glomerulonephritis with severe urinary syndrome and monoclonal gammopathy of unknown origin with preserved renal function: glomerular filtration rate (GFR) according to CKD-EPI 104 ml/min/1.73 m^2.

She was followed up by a hematologist and a nephrologist. On February 14, 2018, she visited the Treatment and Rehabilitation Center for swelling of the right lower limb; occlusive thrombosis of muscular venous sinus, of the right posterior tibial vein with flotation into popliteal vein was revealed. Anticoagulant therapy was started — enoxaparin 80 mg twice a day, with further dose adjustment. Control examination on March 29, 2018, demonstrated positive changes with complete recanalization of thrombus. In June 2018, due to persisting complaints of leg edema, she was hospitalized for examination: with underlying exacerbation of chronic glomerulonephritis accompanied by nephrotic syndrome (daily proteinuria — 7.3 g/day, total cholesterol — 11.8 mmol/l), cryoglobulinemia was revealed, GFR CKD-EPI 96 ml/min/1.73 m^2. After transfer to the Nephrology Department, upon further examination, the following diagnosis was made: primary AL amyloidosis with damage of kidneys (nephrotic syndrome with preserved kidney function), gastrointestinal tract, nervous system, adrenal glands. CKD C1 A4 (GFR CKD-EPI 91.6 ml/min/1.73m^2). The diagnosis was confirmed by a puncture biopsy of the right kidney. The results of the histological exam of the rectal and gastric mucos membrane for amyloid were negative. After stabilization of the condition, four courses of chemotherapy were carried out according to the bortezomib-melphalan-dexamethasone scheme (cycle of 28 days). Two weeks before the current hospitalization, she was discharged from the Nephrology Department in satisfactory condition after the last treatment course.

The current deterioration was acute and manifested as a febrile fever that persisted for five days, with no catarrhal respiratory signs. Self-administered antipyretic therapy (indomethacin 100 mg per rectum) had no significant effect; therefore on November 18, 2018, the patient called an ambulance team and was hospitalized for examination and treatment.

Patient's life history: retired, lives with her husband and children, denies bad habits. No history of allergies. Epidemiological history was unremarkable.

Comorbidities:

– arterial hypertension for 20 years with maximum values of 180/100 mm Hg. Constant medication therapy with amlodipine 5 mg, valsartan 80 mg per os helps to maintain target blood pressure values (120/70 mm Hg); the patient also constantly takes atorvastatin 10 mg, rabeprazole 20 mg, rivaroxaban 20 mg once daily
– bilateral gonarthrosis since 2004. In 2015, arthroscopic debridement, meniscectomy of left knee joint was performed, in 2016 — total arthroplasty of left knee joint, in 2017 — total arthroplasty of right knee joint with a satisfactory result.

Objective status on admission: condition of moderate severity. Clear consciousness. Active position. T = 38.7° C. Skin, visible mucosae are pale, no rash. Harsh breathing is heard in lungs, no wheezing, respiratory rate 18 per minute. Heart sounds are muffled, rhythmic, heart rate (HR) — 80 bpm, blood pressure — 118/78 mm Hg. Abdomen is soft, painless in all parts on palpation. No peripheral edemas. Costovertebral angle tenderness was absent on both sides. Urination is free, painless.

CBC on admission — mild leukocytosis 10.9×10^9/l, no anemia. Blood biochemistry revealed hypoalbuminemia, hypercholesterolemia, hyponatremia, and mild hypokalemia, as well as increased C-reactive protein (CRP) level: total protein — 50 g/l, albumin — 26.5 g/l, urea — 8.0 mmol/l , creatinine — 91 μmol/l, **glucose — 10.64 mmol/l, total cholesterol — 5.94 mmol/l**, total bilirubin — 3.8 μmol/l, AST — 43.2 U/l, ALT — 44.2 U/l, **potassium — 3.41 mmol/l, sodium — 132.6 mmol/l, CRP — 153.3 mg/l**, procalcitonin < 0.5 ng/ml. N-terminal pro-brain natriuretic peptide **(NT-proBNP) — 292 pg/ml**. Coagulogram: increased concentration of fibrinogen to 5.28 g/l. Clinical urinalysis: proteinuria (1.0 g/l), leukocyturia (80 — 100 per HPF) and erythrocyturia (100 — 120 per HPF). Urine analysis by Nechiporenko: RBC 37.500 — U/ml, WBC — 77.500 U/ml.

According to the results of computed tomography (CT), no reliable data for inflammatory changes in lungs were obtained; a region of decreased pneumatization of ground-glass opacity was revealed in S1+2 of left lung.

Echocardiography: slightly increased left atrial cavity up to 4.0×5.0 cm (normal: 3.9×4.8); LV parameters: end diastolic dimension — 4.6 cm (normal: 3.8 — 5.5), end systolic dimension — 3.0 cm (normal: 2.2 — 4.0), posterior wall — 0.9 cm (up to 1.1); dimensions of right atrium in 4-chamber view — 3.2×4.3 cm (normal: 3.8×4.6); average diameter of right ventricle in 4-chamber view — 2.3 cm (normal up to 3.6); diastolic size of interventricular septum — 1.0 cm (normal up to 1.1). Global myocardial contractility is satisfactory, ejection fraction — 63%. Type 1 left ventricular diastolic dysfunction. Grade 1 mitral regurgitation. Grade 1 tricuspid regurgitation. Atrial septal aneurysm.

Electrocardiography: sinus rhythm, HR — 83 per minute, normal QRS axis, no acute focal lesion.

Abdominal ultrasound: moderate hepatosplenomegaly. Liver is enlarged due to the right lobe (vertical oblique size of right lobe — 20.5 cm, height of left lobe –5.0 cm), with sharp and even contours; its lower edge is somewhat rounded and localized at the level of navel. Liver tissue of a homogeneous fine-grained structure, of normal uniform echogenicity, with no focal changes, vascular pattern without changes. Portal and splenic veins are not dilated — 12 mm and 7.5 mm, respectively. Spleen is elongated, moderately enlarged, 14.6×4.2 cm, homogeneous, of normal echogenicity.

Ultrasound of kidneys and ureters on admission: kidneys are located symmetrically and typically, with sharp and even contours, moderately enlarged — mostly, right kidney: right kidney at least 13.5×7.5×6.0 cm, left kidney 13.0×6.4×5.3 cm. Renal sinuses are not dilated, of normal structure and echogenicity on the left side. In the renal sinus of right kidney, single oblong cysts with the largest size up to 1.5 cm were found. In different segments of the right kidney, there are single (at least, three) simple cysts, the largest one of irregularly rounded shape, the largest size is up to 2.0 cm, localized in the anterior middle segment of the kidney; the largest size of other cysts does not exceed 1.0 cm. In the lower segment of left kidney, a simple cyst with a diameter of 0.6 — 0.7 cm was found (2.0 — 2.5 cm in different segments). There is slightly increased echogenicity of renal parenchyma and decreased size of several pyramids. Pelvicalyceal system was not dilated, no calculi found. Ureters are not dilated, with active peristalsis, no calculi in the examined areas. Conclusion: ultrasound presentation of bilateral cysts with underlying moderately pronounced nonspecific diffuse changes in kidneys.

Due to signs of systemic inflammatory reaction syndrome of unclear etiology in the absence of an objective focus of infection, empiric antibacterial therapy with levofloxacin 500 mg i/v drip was started. In addition, the patient received albumin 10% — 100 ml, enoxaparin sodium 40 mg subcutaneously once a day, omeprazole 20 mg twice a day, spironolactone 25 mg twice a day per os; when body temperature increased to 38°C — paracetamol 1000 mg — 100 ml.

In the course of ongoing therapy on day 2 after hospitalization, laboratory tests revealed negative changes: leukocytosis 13.7×10^9/l with a neutrophilic shift to the left, mild normochromic normocytic anemia (hemoglobin — 108 g/l, RBC 3.7×10^{12}/l, hematocrit — 37%, MCV — 87 fl, MCH — 29.4 pg, MCHC — 38 g/l),

erythrocyte sedimentation rate (ESR) — 72 mm/h, proteinuria — 2.8 g/l. No clinical changes since admission.

Due to no effect of therapy and a high risk of sepsis (ESR — 78 mm/h, CRP — 165.6 mg/l, procalcitonin — 10 ng/ml), levofloxacin was replaced with meropenem 2000 mg 3 times a day i/v drip.

On day 3, along with stable clinical presentation, slight positive changes of laboratory parameters were registered: CRP — 133.4 mg/l, potassium — 4.43 mmol/l, sodium — 143.3 mmol/l, lactate dehydrogenase — 524 U/l, urea — 7.0 mmol/l, creatinine — 81 μmol/l, hemoglobin — 107 g/l. Fecal occult blood test — negative. Blood and urine cultures — negative.

On November 21, 2018, CT scan of abdominal organs with intravenous enhancement was performed: in the parenchyma of the middle segment of right kidney, a lesion of reduced fluid density is visible, with ill-defined contours, 2.7×2.4×2.3 cm; in the arterial phase, there is decreased vascularization of the surrounding parenchyma with impaired corticomedullary differentiation. When compared with the results of native CT of thoracic organs from November 18, 2018, there was an increase in the size of the cyst in the right kidney from 1.6×2 cm to 2.4×2.7 cm (determined at the edge of visualization area); there is also an area with decreased corticomedullary differentiation in the lower segment of the right kidney, in the arterial phase, with ill-defined contours, about 3×3.6 cm in size. CT presentation corresponds to a carbuncle with signs of developing abscess. The diagnosis was confirmed by a control ultrasound of the right kidney. The patient was transferred for further treatment to the Urology Clinic of Sechenov First Moscow State Medical University. During observation period, the patient's condition remained stable. During transfer, there were no signs of heart failure, the patient was hemodynamically stable.

Final clinical diagnosis.

Main: Primary AL amyloidosis with damage of kidneys (nephrotic syndrome), gastrointestinal tract, nervous system, adrenal glands. Condition after chemotherapy with bortezomib-melphalan-dexamethasone (4 courses).

Complications: Carbuncle of right kidney. Systemic inflammatory response syndrome. Mild normochromic normocytic anemia of mixed genesis. Chronic kidney disease stage 2 (GFR CKD-EPI 67 ml/min/1.73m^2).

Secondary: Hypertensive disease stage II, grade 3 (achieved grade of AH 1), risk of cardiovascular complications is very high. Occlusive thrombosis of the muscular venous sinus of the right lower leg in recanalization stage. Condition after total arthroplasty of left and right knee joints 2016 — 2017

Discussion

Based on the examination and the patient's medical history, no objective data for acute or chronic urinary tract infection were revealed, making it unlikely that renal carbuncle will develop with underlying pyelonephritis. Hematogenous dissemination was not confirmed due to the absence of other foci of infection. One should take into account the high risk of previous bacteremia due to repeated venipunctures during the last four months with the development of immunosuppression during chemotherapy. It is possible that acute focal bacterial nephritis was the starting point for the development of renal carbuncle. In the case of an abscess, an intervention to drain and sanitize the focus in the right kidney with sampling for histopathological and bacteriological tests is critical not only for a favorable outcome for the patient but also for determining the etiology of renal carbuncle.

The described clinical case includes two clinically important issues: diagnosis of suppurative diseases of renal parenchyma, as well as the significance of MGUS for the risk of systemic amyloidosis.

Renal carbuncle and abscess are relatively rare pathologies — about 5-10 cases per 10,000 hospitalizations. Before the widespread use of ultrasound and CT, mortality in certain patient groups was as high as 50%. But even now, with the widespread use of imaging techniques in modern diagnostic algorithms, mortality remains at 9–10% [16]. This is largely due to nonspecific symptoms at the disease onset and to its long course when complaints and physical examination results usually do not indicate the severity and extension of purulent fusion of kidney tissue. The greatest danger for such patients is the high risk of urogenic sepsis. Persistent fever, high CRP level, urinary syndrome, and unsatisfactory effect of empiric antibiotic therapy suggest a purulent and inflammatory process in the kidney, but these are not prerequisite criteria. CT remains the most sensitive method for making the final diagnosis [16].

The main pathogenetic mechanism of renal carbuncle is the ascending extension of the pathogen along the urinary tract, in particular, with pyelonephritis. The hematogenous mechanism is much less common and is directly associated with secondary or primary bacteremia. The best described are cases of secondary bacteremia with the development of a kidney abscess during the removal of a microbial embolus from a detected focus of infection in another organ. Primary bacteremia remains a subject of discussion since, in the overwhelming majority of cases, the port of infection cannot be defined; such cases are classified as a renal abscess or carbuncle of unknown etiology [17]. In some cases, renal carbuncle may not be a primary morphological

element but the next stage in the development of acute focal bacterial nephritis [18].

In urological practice, most patients with renal abscess or carbuncle have one or more predisposing factors: nephrolithiasis, congenital renal anomalies, recurrent urinary tract infections, diabetes mellitus, autoimmune diseases [16]. Several clinical cases include the development of a renal abscess in patients with drug addiction and multiple injections. A case of multiple aseptic abscesses in a patient with MGUS accompanied by a clinical presentation typical for bacterial infection, is of particular interest [19].

According to the results of retrospective studies, patients with MGUS have twice the risk of developing spontaneous viral and bacterial infections compared to the general population. Within ten years from their diagnosis, patients with MGUS have a high risk of developing pneumonia, osteomyelitis, pyelonephritis, and septicemia [20]. Chemotherapeutic treatment of patients with amyloidosis can play a significant role in the development of an infectious process. Basic chemotherapeutic regimens used in the management of plasma cell dyscrasias often inevitably lead to the development of immunosuppression, which contributes not only to possible bacteremia but also to infectious complications. Analysis of literature data revealed no systematic reviews or clinical cases describing renal carbuncle or abscess in patients with systemic amyloidosis. In this regard, data required for an objective assessment of the risk of severe suppurative diseases in patients with already developed AL amyloidosis are extremely limited.

Due to the possibility of a long course of previous asymptomatic MGUS and nonspecific clinical presentation at the onset of AL amyloidosis, the diagnosis is established on average 12 months after the first manifestation of symptoms [4, 6]. Several laboratory panels were developed for screening for MGUS but they are not widespread and, in most cases, are used only when there is clinical evidence to suspect MGUS [21]. A five-year randomized population-based study on screening the population of Iceland aged over 50 for monoclonal gammopathy is in its final stage. At present, this is the only global study seeking to create an optimal strategy for diagnosing and monitoring patients with known MGUS, assess the effect of screening for MGUS on overall survival, and develop a model for determining the risk of progression [22].

Conclusion

MGUS and amyloidosis remain an important interdisciplinary issue, since the clinical manifestations of the disease are diverse, and different specialists can encounter them in their practice. Considering the regular development of nephropathy and cardiomyopathy in systemic amyloidosis, one should also take into account the possible risks of infectious complications associated both with the course of underlying disease and with the therapy performed. Prevention of bacteremia can reduce the potential risks of poor outcomes for patients with amyloidosis. Implementation of effective screening programs will allow detecting systemic forms of amyloidosis at early stages, which will help reduce the number of deaths from amyloidosis and its complications.

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КАРДИАЛГИЯ У БОЛЬНОЙ С АРТЕРИЕЙ LUSORIA: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Chest Pain in the Patient with Arteria Lusoria: A Case Report

Резюме

Самой частой аномалией развития дуги аорты и ее ветвей является аберрантное отхождение правой подключичной артерии — arteria lusoria. Обычно клинически проявляется дисфагией, одышкой или кашлем. **Цель:** обратить внимание практических врачей на необходимость исключения аномалий ветвей дуги аорты, в том числе артерия lusoria, у больных с кардиалгиями неясного генеза. **Клинический случай.** Пациентка, 18 лет, без хронической патологии в анамнезе была госпитализирована с клиникой давящих болей в грудной клетке после эмоционального стресса, длившихся в течение одного часа. На ЭКГ регистрировался синусовый ритм с частотой 50 ударов в минуту, нормальное направление электрической оси сердца, неполная блокада правой ножки пучка Гиса, отрицательный зубец Т в III отведении. После исключения острого коронарного синдрома, тромбоэмболии легочной артерии, при проведении компьютерной томографии органов грудной клетки с контрастированием выявлена аномалия дуги аорты — артерия lusoria. **Заключение.** Артерия lusoria может сопровождаться болями в грудной клетке. У пациентов с кардиалгией неясного генеза необходимо исключать аномалии развития дуги аорты и ее ветвей, в том числе аберрантное отхождение правой подключичной артерии — a. lusoria.

Ключевые слова: *кардиалгия, стенокардия, дифференциальная диагностика, аномалия развития дуги аорты, аберрантная правая подключичная артерия, артерия lusoria, правая подключичная ретроэзофагеальная артерия*

Конфликт интересов

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

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Abstract

The most common anomaly of the aortic arch and its branches is the aberrant right subclavian artery — arteria lusoria. Usually, it produces dysphagia or dyspnea and chronic coughing. **Our purpose** is to underline that it is necessary to exclude the anomalies of the branches of the thoracic aorta, including arteria lusoria, in the patients with cardialgia of unknown origin. **Clinical case.** An 18-year-old female patient without a previously diagnosed chronic pathology was admitted to a hospital with chest pain after emotional stress for about an hour. The ECG revealed a sinus rhythm with a heart rate of 50 per minute, the normal direction of the electrical axis of the heart, the incomplete right bundle branch block, the negative T wave in the lead III. After excluding ischemic heart disease, acute coronary syndrome, pulmonary embolism, contrast-enhanced chest computed tomography revealed an aortic arch anomaly — a. lusoria. **Conclusion.** A. lusoria may manifest by cardiac pain. In patients with chest pain of unknown origin, it is advisable to include anomalies of the aorta and its branches, including the presence of the lusoria artery, in the range of differential diagnostics.

Key words: *aberrant right subclavian artery, right subclavian retroesophageal artery, arteria lusoria, anomaly of the development of the aortic arch and its branches, cardialgia, chest pain, differential diagnostics*

Conflict of interests

The authors declare no conflict of interests

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BP — blood pressure, CT — computed tomography, ECG — electrocardiogram, ECHO-CG — echocardiography, LV — left ventricle, PE — pulmonary embolism

Introduction

The most common abnormal development of the aortic arch and its branches is the aberrant origin of the right subclavian artery — arteria lusoria (right subclavian retroesophageal artery). Lusoria comes from the Latin expression “lusus naturae”, which means “freak of nature” [1]. This anatomical anomaly was first identified in 1735 by P. Hunauld. Dysphagia associated with it was described by D. Bayford; he defined it as dysphagia lusoria in 1794 [1, 2]. According to major studies, the incidence of this anomaly varies from 0.5 to 2.5% [1]. This anomaly (a. lusoria) accounts for 17% of all cases of the abnormal development of the aortic arch and its branches [1, 2]. This anomaly is often observed in women (55.3–58%) than in men (42–44.7%) [3]. In most cases, a. lusoria is combined with other developmental anomalies of the cardiovascular system (such as truncus bicaroticus, right aortic arch, coarctation of the aorta, patent ductus arteriosus, tetralogy of Fallot, transposition of the great arteries, ventricular and atrial septa defect, aneurysms, hypoplastic left heart, congenital mitral stenosis, pulmonary valve stenosis, arterioesophageal fistula, and genetic syndromes — Down, Edwards, DiGeorge) [1].

A. lusoria is a consequence of impaired embryonic development (Fig. 1) [1, 4].

In patients with a. lusoria, four arteries branch from the aortic arch in the following sequence: right common

carotid artery, left common carotid artery, left subclavian artery, and more distal — aberrant right subclavian artery. The brachiocephalic trunk, which normally branches from the aorta first and is divided into right common carotid and right subclavian arteries, is absent. A. lusoria branches from the proximal part of the descending aorta in the left chest and goes up and to the right. . In 80-84% of cases, the aberrant right subclavian artery is situated behind the esophagus, in 4.2-5% of cases — in front of the trachea, in 12.7-15% — between these two organs. This vessel can be damaged during various surgical interventions, including tracheostomy, thyroid surgery, transcardial interventions on coronary vessels.

Sixty percent of patients have a. lusoria dilated at the point of branching. This conical dilation of the proximal part of the aberrant subclavian artery near its branching from the aorta is called Kommerell diverticulum, "lusoria diverticulum", or "lusoria root". It was described by B.F. Kommerell in 1936. It occurs in 14.9-60% of patients with a. lusoria.

According to the classification by Adachi and Williams, there are four types of a. lusoria: 1) G-1 type, when a. lusoria branches from the distal part of the aortic arch, other branches are not changed. 2) CG-1 type, when a. lusoria branches from the distal part of the aortic arch, left vertebral artery branches directly from the aortic arch; 3) H-1 type, when a. lusoria branches from the distal part of the aortic arch, there is a truncus bicaroticus; and 4) N-1 type, when there is a mirror image of type G-1 with the right aortic arch and left subclavian artery similar to a. lusoria (Fig. 2) .

The average age of patients diagnosed with a. lusoria, is 49.9 years: 54 years for women, 44.9 years for men. Between 60% and 80% of patients have a. lusoria with no clinical symptoms. Clinical manifestations may develop in three cases:

1. If a. lusoria runs between behind the esophagus and trachea and in the front of truncus bicaroticus
2. If there is an aneurysm of a. lusoria
3. In the elderly, due to atherosclerotic lesions or fibromuscular dysplasia of arteries

When a. lusoria runs behind the esophagus, it can compress it, which is manifested by dysphagia (dysphagia lusoria). Dysphagia is the most common symptom; it develops in 71.2% of patients. It is characterized by difficulty in swallowing solid food.

In younger patients, a. lusoria can be manifested by frequent respiratory infections, respiratory failure due to trachea compression.. Shortness of breath is observed in 18.7% of patients. Less common signs are retrosternal chest pain (17.0%), cough (7.6% due to tracheal compression), weight loss (5.9%), epigastric pain, back pain, numbness of the right upper limb, torticollis, neck enlargement, hoarseness. The clinical presentation of a. lusoria can resemble that of pericarditis, endocarditis, aortic dissection.

A. lusoria can be diagnosed by chest x-ray: with the esophagus contrasting with barium, there is a rounded localized lesion in the lateral view, continuously connected with the upper edge of the aortic arch with pulsation (Fig. 3). A. lusoria is diagnosed mainly by multisite computed tomography (Fig. 4) and magnetic resonance angiography. Sometimes it is diagnosed with angiography

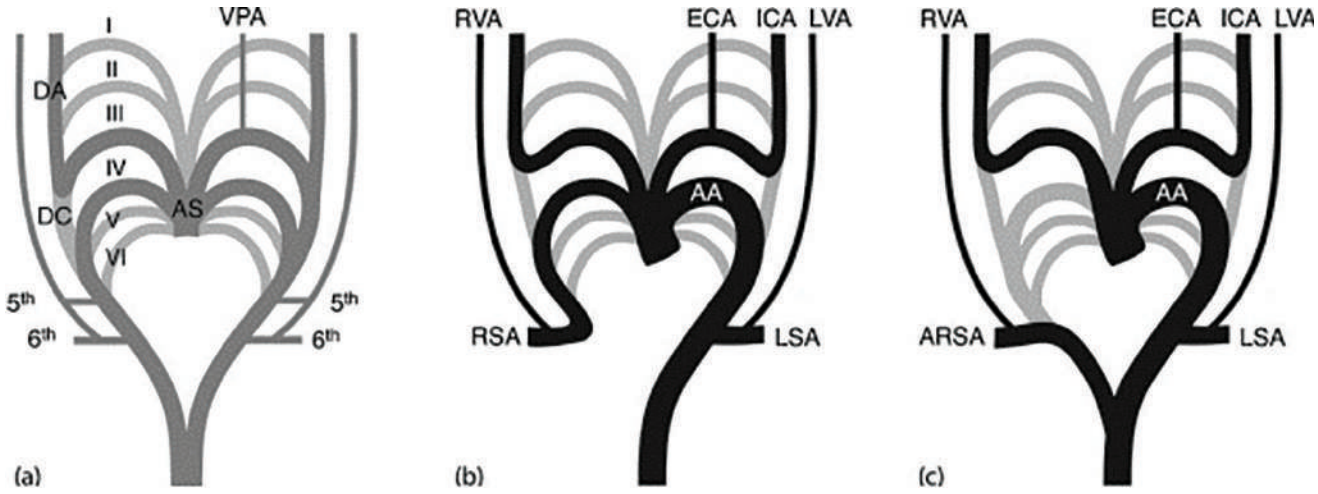

Figure 1. *Development of arteria lusoria; a: embryological development of the aortic arches; b: normal adult situs; c: arteria lusoria situs. I: first branchial arch. II: second branchial arch. III: third branchial arch. IV: fourth branchial arch. V: fifth branchial arch. VI: sixth branchial arch. 5th: fifth cervical intersegmental artery. 6th: sixth cervical intersegmental artery. AA — aortic arch, AS — aortic sinus, ARSA — aberrant right subclavian artery, DA — dorsal aorta, DC — ductus caroticus. ECA — external carotid artery, ICA — internal carotid arter, LSCA — left subclavian artery, LVA — left vertebral artery, RSCA — right subclavian artery, RVA — right vertebral artery, VPA — ventral pharyngeal artery*

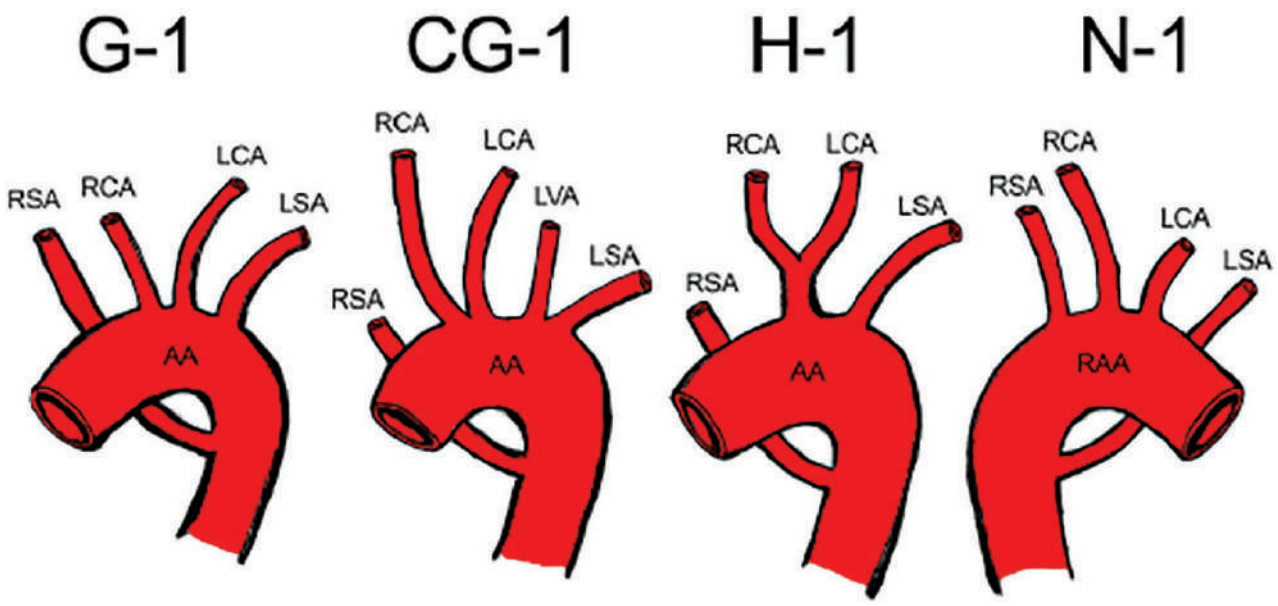

Figure 2. *Variants of anomalies of the right subclavian artery according to the Adachi-Williams classification. AA: aortic arch; RAA: right aortic arch; RSA: right subclavian artery; RCA: right common carotid artery; LCA: left common carotid artery; LVA: left vertebral artery; LSA: left subclavian artery (1)*

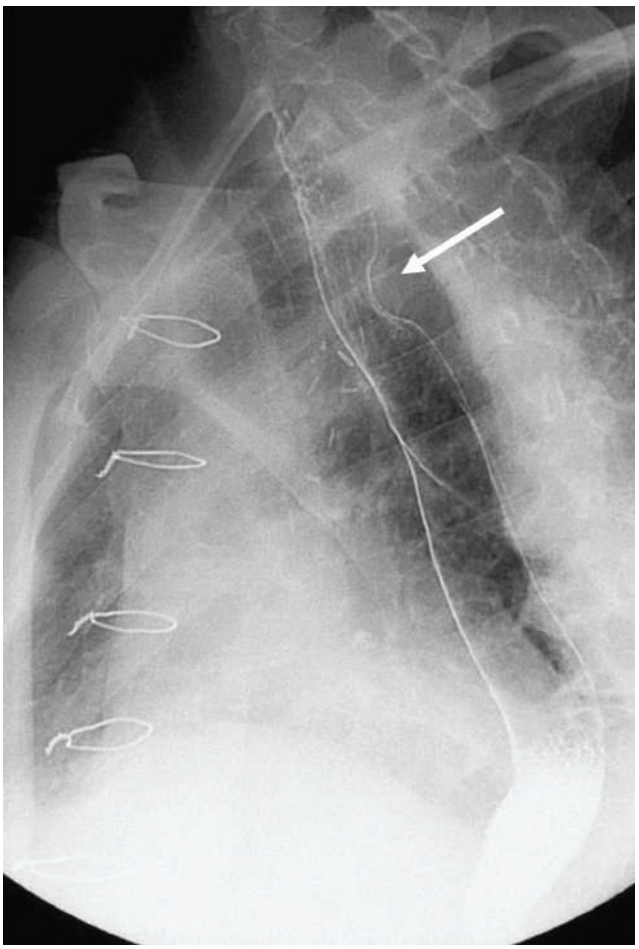

Figure 3. *X-ray of the chest organs in lateral projection. The aberrant right subclavian artery (arteria lusoria) deflects the contrasted esophagus, shown by the arrow. Made by the doctor Kemezh Yu.V.*

and surgery. Due to the predominantly asymptomatic course of a. lusoria, its life-time diagnosis is quite rare; it is often found during autopsy.

Most asymptomatic patients require no treatment. However, the probability of death and rupture in patients with an aneurysm of a. lusoria is 44-57%, which requires more aggressive management. All patients with severe clinical symptoms and complications are subject to surgical treatment of a. lusoria. Endovascular approaches are possible. With moderate dysphagia, slow and thorough chewing of food is recommended. There are no specific recommendations for the diagnosis and surgical treatment of patients with this anomaly.

Case history, clinical, laboratory and X-ray examination data

A 18-year female patient, with no previously diagnosed chronic disease, was hospitalized with a clinical presentation of retrosternal pressing pains, without irradiation, which developed after emotional stress lasting about one hour. There were no data for elevated blood pressure (BP) during hospitalization and in history, no symptoms or signs of heart failure, anemia. Electrocardiogram (ECG) demonstrated sinus rhythm with heart rate of 52 per minute, normal QRS axis, negative T wave in lead III (Fig. 5). Concentration of creatine kinase MB (mass fraction) was 3.0 μg/l (normal 2.0-7.2), troponin I in blood <0.01 ng/ml (normal range <0.01 ng/ml), low density lipoprotein cholesterol — 3.36 mmol/l, D-dimer — 542 μg/l (normal range 64-550 μg/l). Chest

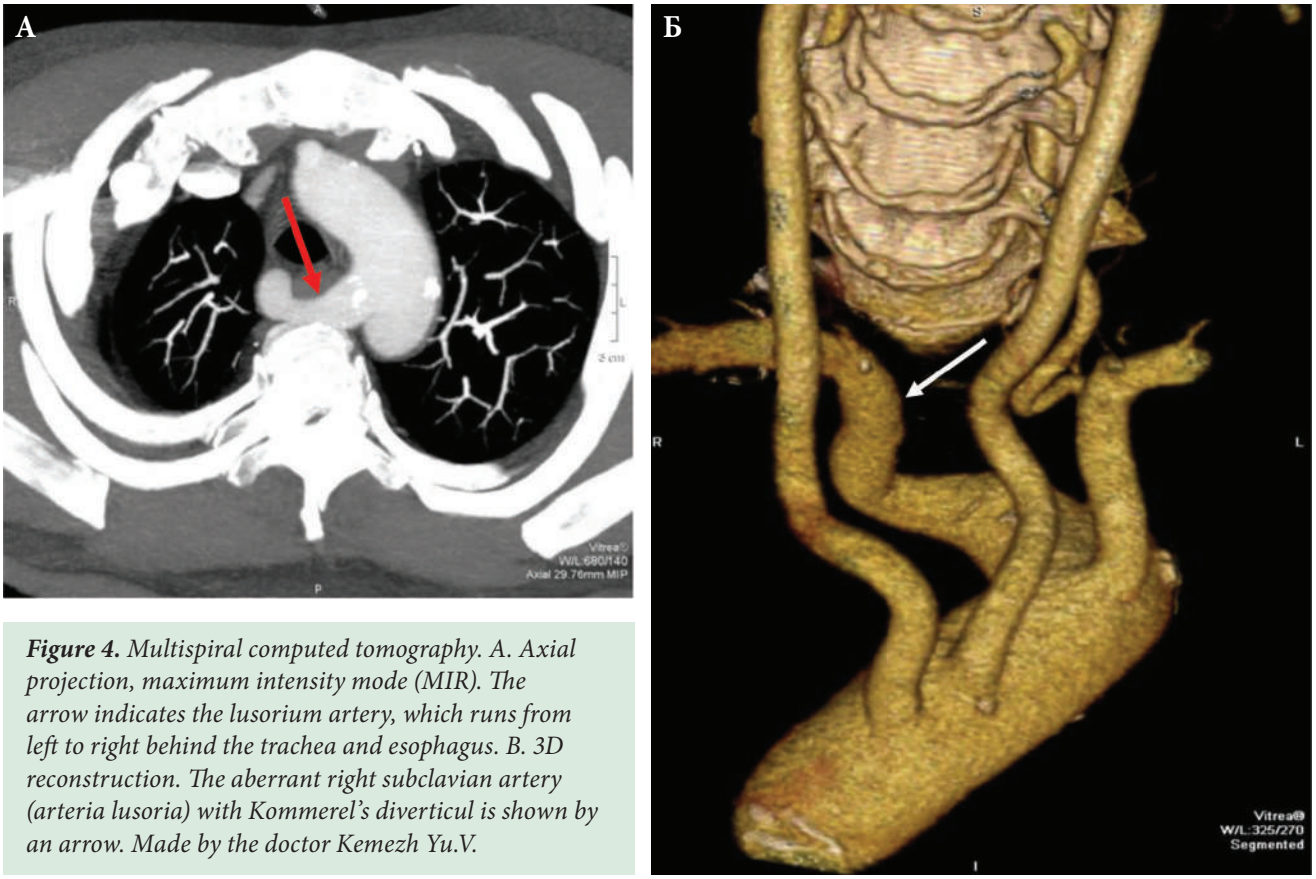

Figure 4. *Multispiral computed tomography. A. Axial projection, maximum intensity mode (MIR). The arrow indicates the lusorium artery, which runs from left to right behind the trachea and esophagus. B. 3D reconstruction. The aberrant right subclavian artery (arteria lusoria) with Kommerel's diverticul is shown by an arrow. Made by the doctor Kemezh Yu.V.*

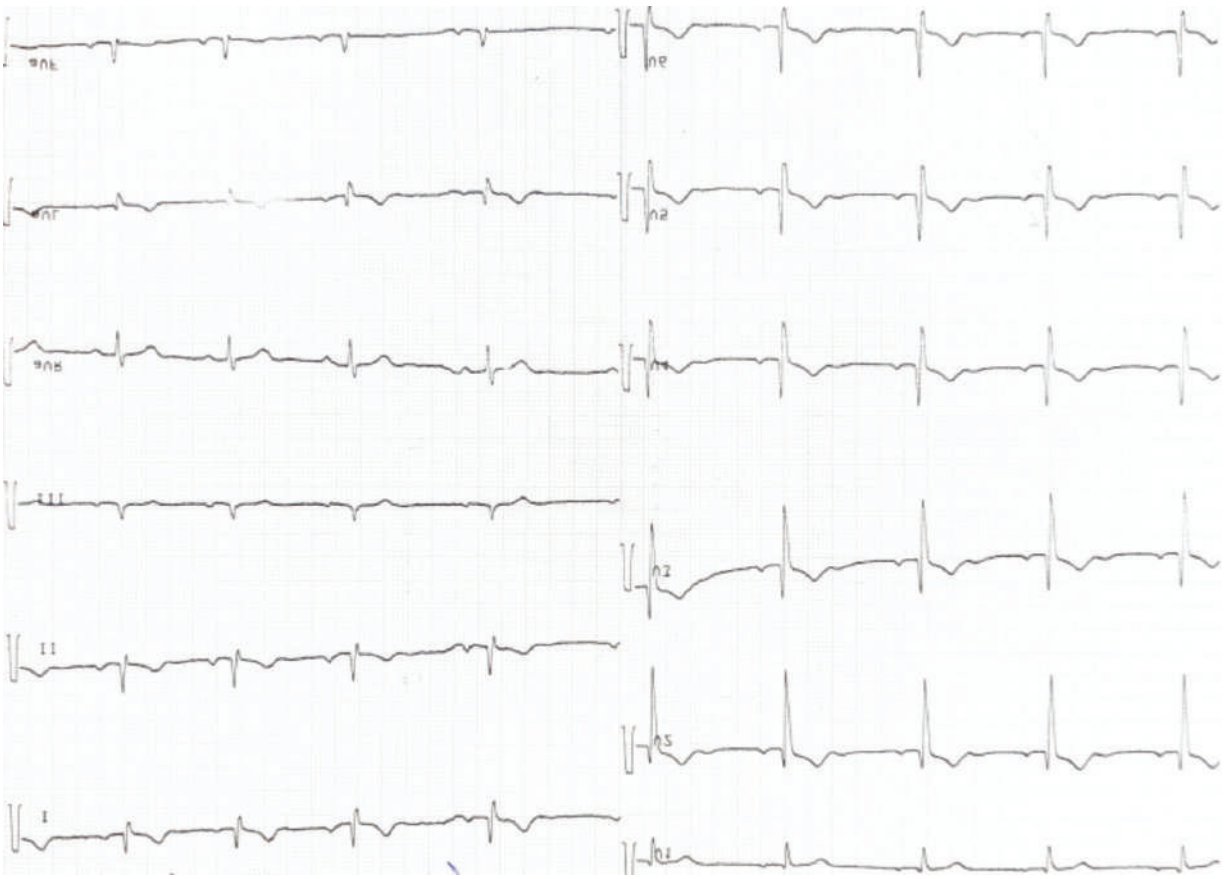

Figure 5. *Electrocardiogram at the admitting*

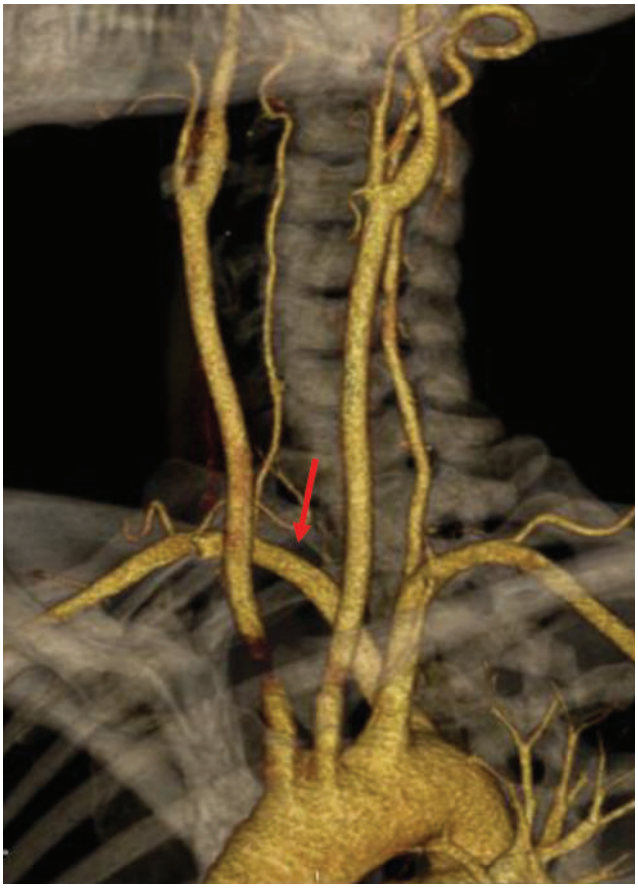

Figure 6. *Multispiral computed tomography, 3D resconstruction. The aberrant right subclavian artery (arteria lusoria) is shown by an arrow*

x-ray, ultrasound of the vessels of lower limbs, as well as ultrasound of kidneys and retroperitoneal space and esophagogastroduodenoscopy: within normal.

During echocardiography (ECHO-CG), normal myocardial contractility, normal sizes and volumes of cardiac cavities, pulmonary artery pressure and valve function were observed. LV ejection fraction was 55%, maximum aortic valve pressure gradient — 15 mm Hg, and peak aortic valve velocity — 1.82 m/s. 24-hour ECG monitoring revealed sinus rhythm with an average rate of 68 bpm, minimum — 44 bpm, maximum — 118 bpm; 4 supraventricular extrasystoles. No pauses, ventricular extrasystoles or ST segment dispositions were registered. During cardiac stress test, the patient developed pressing chest pain that lasted for 5 minutes, without changes on ECG, exercise tolerance was moderate (100 W), BP response of normotonic type, no rhythm or conduction disturbances. Chest multislice computed tomography (CT) revealed aortic arch anomaly — a. lusoria (Fig. 6).

Discussion

Chest pain is one of the most common reasons for seeking medical attention. The main causes of heartburn are disease of the heart, blood vessels, respiratory organs, gastrointestinal tract, musculoskeletal system, nervous system, mammary glands, blood system, etc. (Table 1).

Table 1. *The diseases with cardiac pain*

Causes	Nosology
1. Heart pathology	• Myocardial infarction *, acute coronary syndrome *
	• Stable angina
	• Pericarditis *
	• Myocarditis
	• Infective endocarditis (thromboembolism in the coronary arteries by pieces of vegetation, shielding of the orifices of the coronary vessels, decreased oxygen delivery in severe aortic regurgitation) *
	• Congenital and acquired heart defects (aortic stenosis, insufficiency; mitral stenosis, coarctation of the aorta, etc.).
	• Cardiomyopathy (hypertrophic, etc.)
	• Arterial hypertension
	• Arrhythmias
	• Coronaryitis (with polyarteritis nodosa, Kawasaki disease and other systemic vasculitis)
	• Spasm of the coronary arteries (in cocaine or amphetamine addicts)
	• Mitral valve prolapses
2. Vascular pathology	• Aortic dissecting aneurysm *
	• Pulmonary embolism*
	• A. lusoria and other developmental anomalies of the aorta and its branches

3. Pathology of the respiratory system	• Pleurisy, mediastinitis • Pneumothorax *, pneumomediastinum * • Pneumonia • Lung tumor
4. Pathology of the gastrointestinal tract	• Reflux esophagitis • Spasm of the esophagus • Ruptured esophagus * • Hernia of the esophageal opening of the diaphragm • Mallory-Weiss syndrome • Peptic ulcer • Cholecystitis • Pancreatitis • Biliary colic
5. Pathology of the musculoskeletal system	• Costochondritis (Tietze's syndrome) • Rib fracture • Dorsopathy of the cervical spine • Osteoarthritis of the shoulder joints and spine • Spasm / injury of intercostal muscles • Anterior scalene muscle syndrome (Naffziger syndrome) • Pectoralis syndrome (Wright's syndrome) • Subacromial bursitis • Tendonitis of the supraspinatus and deltoid tendons • Rheumatic polymyalgia • Dermatomyositis • Myalgia • Myogelosis • Tumors of the chest wall • Bone metastases
6. Pathology of the nervous system	• Intercostal neuralgia • Damage to intercostal nerves during thoracotomy, thoracoscopy • Neurinoma • Spinal cord compression • Herpes zoster • Pleurodynia
7. Diseases of the mammary glands	• Mastopathy • Mammary cancer
8. Pathology of the blood system	• Anemia • Erythremia
9. Psychogenic	• Anxiety disorders • Depressive disorders
10. Other	• Sappho Syndrome (SAPHO) • Mondor's disease

Note: * — conditions requiring immediate hospitalization of the patient

Description of chest pain typical for different conditions

Myocardial infarction

- **Type:** pressing, constricting; intense pain
- **Triggers** — stressful event, physical activity
- **Localization:** behind the sternum or in the left half of the chest, in the epigastrium
- **Irradiation:** into the arm (usually along the medial side of the forearm down to the little finger), interscapular region, neck, or lower jaw
- **Associated symptoms:** cold clammy sweat, shortness of breath, sometimes nausea or vomiting, arterial hypotension, unusual weakness, feeling faint
- **Duration:** more than 20 minutes.
- **Treatment:** narcotic analgesics

Angina

- **Type:** pressing, constricting; heavy feeling, sometimes aching or burning (however, one should keep in mind that pains of any type can be anginal)
- **Triggers:** pain during physical or psychoemotional stress; the pain ceases when the stress stops. Pain can be triggered by a large meal, exposure to the cold, wind, or other factors that increase heart rate (mismatch between myocardial oxygen demand and oxygen delivery).
- **Localization:** behind the sternum or in the left half of the chest; when asked to show the place where the pain is, the patient demonstrates typical Levine's sign (a clenched fist or palm held over the sternum or across the anterior chest wall)
- **Irradiation:** into the shoulder, arm (both left, often along the medial side of the forearm down to the little finger), interscapular region, neck, lower jaw, rarely — epigastric region
- **Associated symptoms:** inability to breathe deeply
- **Duration:** 5 minutes for stable angina; 5-10 minutes for unstable angina
- **Treatment:** pain eases at rest or with the help of nitrates

Pericarditis

- **Type:** pain is not intense, heavy feeling, there may be a sharp stabbing pain
- **Triggers:** pain intensifies in a horizontal position, during inspiration (like pleural pain), during coughing, raising legs, swallowing or extending neck; becomes less when bending forward
- **Localization:** pain can be behind the sternum, in the left side of the chest, in the neck and abdomen
- **Irradiation:** pain can irradiate along the phrenic nerve to the upper abdomen (sometimes similar to cholecystitis, pancreatitis), left shoulder blade, shoulder, neck
- **Duration:** constant, long-term
- **Associated symptoms:** often after a cold, viral infection (Coxsackie viruses A and B, echovirus, adenovirus, human immunodeficiency virus); less common — oncological disease (breast cancer, lung cancer, lymphoma), uremia, radiation, acute myocardial infarction, connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis), trauma; rare — tuberculosis, bacterial infection, drug-induced effect (procainamide, isoniazid, phenytoin), and inflammatory bowel diseases

Angina syndrome

Pain in angina syndrome is no different in its characteristics from pain in angina.

Angina syndrome is often observed with affected heart valves (aortic stenosis, insufficiency), hypertrophic cardiomyopathy (especially idiopathic hypertrophic subaortic stenosis), arterial hypertension. The reason is left ventricular (LV) myocardial hypertrophy, which is associated with increased myocardial oxygen demand. Also, due to the obstruction of the aortic opening in cases of aortic stenosis, LV outflow tract in idiopathic hypertrophic subaortic stenosis, and blood regurgitation into the LV cavity in diastole, oxygen delivery to myocardium decreases.

During auscultation in cases of aortic stenosis, a rough systolic murmur is heard in the second intercostal space to the right of the sternum. It spreads to neck vessels accompanied by a weakening and slowing down of the increase in the pulse wave on carotid arteries and by a sharp weakening or the absence of tone II. In cases of idiopathic hypertrophic subaortic stenosis, the sound at the Erb's point is conducted along the left edge of the sternum. In cases of aortic insufficiency, diastolic murmur in the second intercostal space to the right of the sternum is conducted to the apex.

Arrhythmia

Pain during arrhythmia is acute, located in precordial region, irradiates to the throat, starts and ends with an arrhythmia attack.

Mitral valve prolapse

Pain accompanying mitral valve prolapse is mild, often long-term, in the left side of the chest.

Aortic dissection and aneurysm

- **Type:** pain develops suddenly, quickly reaches its maximum, is tearing or ripping
- **Localization:** pain is localized in the chest or back (depending on the site of dissection)
- **Specific features:** often pulses together with heartbeats. The pain is most intense at its onset. Asymmetry of BP values on arms is typical.

- **Irradiation:** pain can irradiate into the abdomen, legs, and move to the back.
- **Duration:** lasts for hours, does not depend on body position or breathing.
- **Treatment:** high doses of narcotic analgesics.

Pulmonary embolism (PE).

- **Type:** dull pain, heavy feeling with massive PE; tearing, rubbing pain, sometimes resembles angina in cases of pulmonary embolism of small branches.
- **Onset:** acute
- **Localization:** severe pain in the center of the chest, behind the sternum — with massive PE; in lateral sections with deep breathing (of pleural nature) with PE of small branches.
- **Associated symptoms:** pain is associated with acute shortness of breath, tachycardia; the patient feels anxiety, sweats, hemoptysis is possible.
- **Duration:** long-term
- **Risk factors:** Main risk factors for venous thromboembolism: long period of strict bed rest, immobilization of extremities, surgery.

Pleuritis

- **Type:** stabbing, sharp, tearing, changing with breathing.
- **Triggers:** pain intensifies with deep breathing and coughing.
- **Localization:** unilateral with irradiation into the shoulder or epigastric region.
- **Associated symptoms:** cough, fever due to lung infection.
- **Specific features:** eases in a position of the body bending towards the affected side.

Pneumothorax

- **Type:** sharp, tearing, changing with breathing
- **Onset:** sudden
- **Duration:** long-term
- **Localization:** unilateral, in the lateral parts of the chest
- **Associated symptoms:** pain is associated with acute shortness of breath, tachycardia. The disease develops spontaneously or with underlying bronchial asthma, pulmonary emphysema, tuberculosis, cystic fibrosis, sarcoidosis, blunt or penetrating chest trauma.

Pneumonias

Sharp long-term pain associated with breathing, shortness of breath, fever with chills, cough, either dry or wet. Unilateral pain irradiating into the shoulder or epigastric region.

Chest diseases

Costochondritis, Tietze syndrome — inflammation of sternocostal joints. Costochondritis is a common cause of chest pain in childhood and adolescence and accounts for 10-30% of all chest pain at this age. Most often occurs between 12-14 years. Pain is usually of moderate intensity, stabbing or dull, one-sided, short-term (from a few seconds) to long-term (several days). The patient can accurately point with a finger at the site of the pain, which is most often located at the level of the 2nd-3rd sternocostal joint. Pain is not associated with movements. Local tenderness is observed when pressing on the corresponding parts of the chest. Pain decreases with the use of non-steroidal anti-inflammatory drugs (NSAIDs).

Radicular chest pain

With a herniated disc in the cervical spine, pain can irradiate along the radial nerve. Pain becomes intense when walking, when moving arms or head.

Intercostal pain often develops after thoracic surgery, especially when the intercostal nerves are damaged by thoracoscopy.

Herpes zoster is a common cause of chest pain. Pain may start several days before the skin manifestations. Postherpetic neuralgia can last up to several months or years.

Epidemic pleurodynia (Bornholm disease, or epidemic myalgia) is caused by Coxsackie virus B; and often manifests as interosseous neuralgia. Pain is acute, severe, paroxysmal over lower ribs or in the sub-sternal region.

Esophageal spasm

- **Type:** pain in cases of esophageal spasm can be similar to that typical for angina — compressive chest pain
- **Irradiation:** pain can irradiate from the upper part of the epigastrium to the chest region, upper chest, upper limbs
- **Treatment:** taking nitroglycerin brings quick relief, similar to angina. Differential diagnosis, in this case, is based on the proven absence of exertional angina and the identified relationship with food intake.

Reflux esophagitis

- **Type:** burning pain, rarely very severe. It may be dull, similar to angina.
- **Triggers:** pain increases in the supine position or when bending over, after taking aspirin or other NSAIDs, drinking alcohol, spicy, fried foods
- **Localization:** precordial and epigastric region
- **Associated symptoms:** pain is usually not associated with profuse sweating or shortness of breath,

is often accompanied by heartburn, dysphagia, belching undigested food, weight loss
- **Duration:** pain in cases of reflux esophagitis lasts from a few minutes to several hours
- **Treatment:** decreases when taking antacids, water, hot beverages, in sitting position

Ruptured esophagus

Excruciating sharp pain, often after vomiting, followed by fever, shock; long-term; in the precordial region with irradiation to the back.

Hiatus hernia

Typical feature is development and aggravation of pain in the supine position.

Peptic ulcer
- **Localization:** in the epigastrium or behind the sternum
- **Triggers:** pain arises 1-1.5 hours after eating and decreases a few minutes after taking antacids or milk.

SAPHO syndrome

SAPHO syndrome (SAPHO — Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis) is a rare autoinflammatory disease characterized by a correlation between neutrophilic skin lesions and chronic osteomyelitis. The age of onset ranges from childhood to elderly; on average, between 30 and 40 years. Inflammation in adults develops mainly in the anterior chest wall, as well as in the spine, less often — in the lower jaw and ilium. It may be accompanied by chest pain or swelling of the affected area. There is no clear description of chest pain in this syndrome.

Mondor's disease

Mondor's disease is characterized by thrombophlebitis of the superficial lateral veins of the chest. There is no clear description of chest pain in this syndrome. There is no clear description of chest pain in this syndrome.

Psychogenic chest pain
- **Type:** aching or pressing, rarely intense
- **Triggers:** not related to physical activity, undulating. May be associated with fatigue or periods of intense emotional stress
- **Localization:** behind the sternum or in the apex of the heart
- **Duration:** there are two types: acute short-term, "piercing", does not allow drawing a breath, or long-term (more than 30 minutes), aching, sometimes almost constant, not related to physical exertion

Differential diagnosis

The primary goal of diagnosis in patients with chest pain is to identify or exclude coronary heart disease, dissecting aortic aneurysm and PE. In cases of acute, persistent pain, one should determine whether the patient is in danger of shock, circulatory arrest, or acute respiratory failure, and should start appropriate intensive therapy, if required. Then the differential diagnosis may be performed.

Considering newly diagnosed anginal pain in the described patient, as well as the connection with emotional overstrain and duration of the attack, a differential diagnostic search was carried out to exclude coronary heart disease, acute coronary syndrome, pulmonary embolism, and congenital anomalies of the cardiovascular system. CT angiography of the thoracic aorta revealed a developmental anomaly of the aortic arch — an aberrant right subclavian artery that manifested as heartburn in the 18-year-old patient.

A. lusoria is usually manifested by dysphagia (in 71.2% of patients) and shortness of breath (in 18.7%), less common — by cough (in 7.6%), loss of body weight (in 5.9%), even less common — pain in the epigastrium, back, numbness in the right upper limb [1, 5]. Retrosternal pain syndrome that led to the hospitalization in the described patient is observed in 17% of patients [5].

Conclusion

It is reasonable to include anomalies of the aorta and its branches, including arteria lusoria, in the range of differential diagnosis in patients with chest pain of unknown origin, after excluding common diseases. Timely diagnosis is important to prevent the threat of rupture of the aneurysm of this vessel. Knowledge of the anatomical variants of aortic arch branches minimizes the risk of intraoperative complications and improves the patient's prognosis.

Вклад авторов:

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