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Modern View on the Problem of Systemic Lupus Erythematosus with and without Comorbid Lesions of the Circulatory System (Literature Review, Clinical Case Description) – First Notice

Introduction. Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by the accumulation of pathogenic autoantibodies produced by hyperreactive B cells, causing organ damage due to the formation of immune complexes [72]. There are several phenotypes of SLE with different clinical manifestations – from mild mucosal cutaneous to severe multi-organ lesions [81], in particular, the circulatory system can be affected [7]. SLE is a potentially life-threatening disease that depletes the patient, leads to reduced working capacity, disability and, in many cases, death [68].

According to the literature review, the prevalence and incidence of SLE in the world is significant. In particular, in the United States the SLE incidence is 1.0 - 7.6 cases per 100 thousand population per year, the prevalence - 53.3-149.5 patients per 100 thousand population (in average - 81.1), in the United Kingdom - 4.9 and 65.0, respectively [110, 111]. In Ukraine, according to the results published in 2017, the incidence was 0.7 cases per 100 thousand population, prevalence - 17.1 per 100 thousand people [69].

In recent years, there has been a tendency of the SLE prevalence increase, which may be a result of the early diagnosis improvement and timely detection of mild forms of the disease, increasing the treatment effectiveness and life expectancy of patients [163].

To a large extent, success in solving this urgent problem depends on timely, thorough diagnosis and treatment of SLE, taking into account the clinical and pathogenetic features of syntropic lesions of the circulatory system, which the literature review and clinical case description of this article is dedicated to.

The aim of the study. To analyze the literature, dedicated to the modern view on the problem of systemic lupus erythematosus with and without comorbid lesions of the circulatory system, describe the clinical case.

Materials and methods. Content analysis, method of systemic and comparative analysis, bibliosemantic method of studying the current scientific studies on modern principles of diagnosis and treatment of patients with SLE are used. 167 literature sources in Ukrainian, English and Russian were analyzed. Sources were searched for in scientometric medical databases: PubMed-NCBI, Medline, ResearchGate, CochraneLibrary, EMBASE by keywords: SLE, circulatory system lesions, atherosclerosis, diagnosis and treatment of SLE. A clinical case is described.

Results. The etiology of SLE remains unknown today. Genetic predisposition is the important factor in the occurrence of the disease, as evidenced by the increase of SLE incidence of 10.3 times in relatives of the first degree of kinship. SLE occurs more often in monozygotic twins (25.0–30.0 %) than in dizygotic twins (5.0 %). The association of SLE with the region located on the long arm of chromosome-1 (1q 23-24) was also revealed [135]. The importance of innate immunity in the development of SLE is also studied. Involvement of such genes as interferon-regulating factor 5 (T-receptors' signals), gene encoding protein 1, rich in H-leucine, which is repeated (gene for N-leucine-rich-repeat protein - NALP1), interferon-induced helicase C domain 1 gene - 1990760 (interferon-induced helicase 1 rs1990760 - IFIH1 rs1990760), N-acetyltransferase 2 gene (N-acetyltransferase 2 - NAT2) was also confirmed. Interferon is thought to be important in the pathogenesis of SLE as well [73, 76, 79, 80, 121, 126].

Female gender and hormonal exposure are important risk factors for SLE. Estrogens and prolactin promote autoimmunity, increase the production of B-cell activating factor and modulate the activation of lymphocytes and plasma dendritic cells (PDC) [129]. The use of estrogen-containing contraceptives and hormone replacement therapy in the postmenopausal period may cause exacerbation

in patients with SLE and is associated with the diseases incidence increase. In patients with SLE there is an increased content of prolactin, which correlates with the disease activity. Instead, androgens are considered to be protective substances. Low endogenous estrogen concentrations reduce the risk of SLE, and the use of exogenous estrogens increases it [59]. Cyclic fluctuations of the disease activity during the menstrual cycle were revealed. In postmenopausal women, the activity of the disease decreases, so in case if SLE occurs during this period, it will have lower activity, and the prognosis will be more encouraging. The presence of a defect in the hypothalamic-pituitary system functioning in women with SLE who were not treated has been proven. It is believed that women have a single nucleotide polymorphism, disruption of the methylation of deoxyribonucleic acid (DNA) and histone modification. In case of intestinal dysbiosis, microorganisms can produce increased amount of estrogen [13, 31, 166].

Some authors state that the incidence of SLE increases with age, reaching a peak in 30–70 years with a subsequent gradual decrease [111]. The highest prevalence of SLE is in the representatives of Negroid race, the lowest – in Caucasian [79].

Environmental triggers play an important role in the occurrence of SLE [40].

Many drugs, such as hydralazine and procainamide, which are aromatic amines, can trigger lupus-like syndrome, especially in individuals who are genetically determined to be slow acetylators. Aromatic amines, hydrazines, and their derivatives are found in tobacco and tobacco smoke, hair dye, and numerous compounds used in agriculture and industry. Individuals who come into contact with these compounds are prone to lupus-like syndrome [53, 131].

The occurrence of both cutaneous lupus erythematosus and SLE is exacerbated by ultraviolet (UV) radiation, especially of B spectrum. One possible mechanism of influence is that UV radiation affects the structure of DNA, increasing its immunogenicity. In addition, due to the influence of UV radiation on keratinocytes, clusters of apoptotic cells are formed, containing both cytoplasmic and nuclear antigens. This is the manifestation of the own antigens presentation to the immune system mechanism, which provokes the autoimmune process [40,70].

Many investigations have studied the role of infectious agents in the pathogenesis of SLE, including herpesviruses, which theoretically provoke the initiation of SLE exacerbations by B-lymphocyte activation, tissue damage, and autoantigen release. Besides, an important role is played by the viruses triggering properties, in particular M. E. Epstein - I. Barr virus, parvovirus and cytomegalovirus, which are largely common in patients with SLE. They can cause disease by activating the autoimmunity through structural or functional molecular mimicry that encodes proteins that provoke cross-immune reactions with their own antigens or modulate the activation or apoptosis of B and T cells, macrophages or dendritic cells. However, the evidence base of the infectious theory of SLE development is insufficient and this issue needs further study [1, 27, 42, 60]. In addition, some infectious agents, such as malaria, Toxoplasma gondii and Helicobacter pylori, may have a protective effect. Vaccination may play a dual role in protecting or provoking the onset or exacerbation of SLE symptoms [113].

A case of Herpes zoster infection in a patient with SLE and antiphospholipid syndrome (APLS) has been described. The frequency of Herpes zoster infection in patients with SLE is increased; however, its presence in patients with APLS have not been previously reported. The combination of these diseases requires early and adequate treatment. In addition, extreme caution should be observed when monitoring patients, especially those with antiphospholipid antibodies (APLA) or diagnosed with APLS, in which infection increases the risk of new thrombotic complications [99].

The main links in the pathogenesis of SLE are inflammation, blood vessel abnormalities, in particular, occlusive vasculopathy, vasculitis and deposition of immune complexes. The most specific pathohistological changes for SLE occur in the kidneys. Lesions of other systems and organs in case of SLE are of mostly nonspecific inflammatory and vascular origin. However, immune dysfunction and autoantibody production play a leading role in the development of SLE.

In B-lymphocytes of patients with SLE, autotolerance is impaired and there is excessive production of antibodies directed against several intrinsic molecules contained in the nucleus, cytoplasm, cell membrane, as well as soluble molecules such as immunoglobulin G (immunoglobulin G – Ig G) and coagulation factors. The most typical are antinuclear antibodies (ANA), which are found in 95.0 % of patients with SLE, antibodies to double-stranded DNA (anti-dsDNA) and antibodies to Smith antigen (Anti-Smith - Anti-Sm) are the most specific for SLE [30, 134].

The association of anti-dsDNA with lupus nephritis is important. Studies have shown that most patients with active lupus nephritis have a significant increase of anti-dsDNA titer and the complement content decrease. The accumulation of anti-dsDNA occurs mainly in the kidneys, which helps to conclude that DNA immune complexes - anti-dsDNA are the main mediators of inflammation. According to the literature analysis, the correlation between the content of anti-dsDNA and lupus nephritis is incomplete. Anti-dsDNAs have different properties, including different isotopes, different ability to fix to complement and bind to glomeruli, causing pathological changes. Only part of the anti-dsDNA is pathogenic [167].

Cell-free DNA (cfDNA) is a small part of the total amount of DNA that circulates freely in the blood in both normal and pathological conditions. Study results suggest that cfDNA plays an important role in the pathogenesis of SLE and hypomethylation may be crucial for its immunogenic properties. Although differences in quantification methods prevent comparison of results between studies, cfDNA was found to be significantly increased in patients with SLE and correlated with different antibody titers but not with the disease activity. However, the cfDNA concentration increase may be associated with active

lupus nephritis. Most studies have confirmed apoptosis as the main mechanism of cfDNA release under different conditions, but the formation of extracellular neutrophil traps can significantly contribute to the formation of cfDNA in patients with SLE. Therefore, cfDNA testing for the diagnosis and prediction of SLE remains questionable [143].

The pathogenesis of SLE manifestations other than lupus nephritis has not been sufficiently studied. It is believed that its main mechanism is the corresponding local accumulation of immune complexes and complement activation. Another possible mechanism may be the direct damaging influence of antibodies and cellular cytotoxicity on the "target tissues".

Patients with SLE have an impaired immune response, involving B-, T-lymphocytes and cells of monocyte origin. It results into polyclonal activation of B-lymphocytes, antibody-producing cells number increase, hypergammaglobulinemia, production of autoantibodies and the immune complexes formation. Patients with SLE have pathological activation of B-lymphocytes, which is manifested by their content increase in the peripheral blood, and they can be at different stages of activation. B-lymphocytes in patients with SLE compared to the control group of almost healthy individuals are more sensitive to the stimulating effects of cytokines, in particular interleukin (Interleukin - IL)-6. Thus, B-lymphocytes in patients with SLE are capable of polyclonal activation due to stimulation by antigens, cytokines, etc. [22].

Changes in the T-lymphocytic branch of the immune system have also been found in patients with SLE. Their content in the peripheral blood decreases. This is caused by the influence of antilymphocytic antibodies. The functional activity of T-lymphocytes changes, which is manifested in most cases by the stimulating effect on B-lymphocytes with increased production of antibodies, as well as the decrease of the ability to proliferate in response to mitogenic stimulation and IL-2 production [52, 84, 136].

In patients with SLE the synthesis of IL-2, IL-6, IL-10, IL-15, IL-16, IL-18 increases, production of IL-12 decreases. Proinflammatory cytokines, in particular tumor necrosis factor-α (TNF-α), have been shown to act as inducers of acute-phase inflammatory enzymes. A direct correlation between the content of this cytokine and the disease activity degree was found, which allows its use as a marker of inflammation.

In case of SLE the changes in immune regulation are revealed. The uptake of immune complexes by phagocytes is disturbed, it is caused by the decrease of the number of complement receptors type 1 (CR1) - complement receptors and functional defects of receptors on the cell membrane. In patients with SLE, the deterioration of the apoptotic cells phagocytosis has been demonstrated, the remnants of which may be an immunogen for the induction of autoreactive lymphocytes or an antigen for immune complexes. Synthesis and secretion of pathogenic autoantibodies in patients with SLE is regulated by the interaction between T-lymphocytes classification determinants (CD) 4+, CD8+, as well as between double-negative T-lymphocytes (CD4-, CD8-) and B-lymphocytes [87, 142].

The role of interferon-α, -β, -γ in the pathogenesis of SLE was studied [165].

The possible role of purinergic receptors, in particular purinergic ionotropic receptors type 2, subtype 7 (P2X7R), in the pathogenesis of SLE was also studied. Purinergic signaling plays a crucial role in immunity and autoimmunity. The P2X7 receptor (P2X7R) has an indisputable role because it is expressed in high levels by immune cells, causes the release of cytokines and modulates the differentiation of immune cells [33].

Various methods to assess the degree of SLE activity (scales of SLE Disease Activity Index - SLEDAI, SLEDAI-1K, SLEDAI-2K), Safety of Estrogens in Lupus Erythematosus National Assessment - SELENA-SLEDAI, SLEDAT, the classic index of the British Isles Lupus Assessment Group (BILAG), the European Consensus Lupus Activity Measurement (ECLAM)), which is based on the assessment of the severity of the patient's condition based on the combination and degree of clinical and laboratory manifestations of the disease have been developed [77].

To assess the frequency of irreversible changes in organs and systems in patients with SLE, the damage index of Systemic Lupus International Collaboration Clinics of American College of Rheumatology (SLICC/ACR Damage ACR) is used [25].

The results of research indicate that inflammation plays a key role in the pathogenesis of atherosclerosis from initial endothelial dysfunction to the rupture of atherosclerotic plaques. The increase of the atherosclerosis incidence in patients with SLE is probably caused by the complex interaction of traditional and disease-associated, such as drugs, process activity, as well as inflammatory and immunogenic risk factors [139, 156].

Patients with SLE often develop APLS with the formation of APLA and other hemostasis disorders, hyperhomocysteinemia [122, 155].

It was found that the increased content of anticardiolipin antibodies, transforming growth factor 1β, which correlates with the degree of activity, course, stage, duration of the disease, indicates the chronic heart failure severity increase. Therefore, their definition can be used as a marker of the circulatory system diseases.

The role of anticardiolipin antibodies as a risk factor for vascular lesions is also the subject of studies [35]. Phospholipid binding proteins (rather than phospholipid molecules), such as β-2-glycoprotein-1 (β-2-Glycoprotein 1 - β2GP1) and prothrombin, are thought to be the primary link for antibody damage. The interaction of antibodies with β2GP1 of endothelial cells membranes causes damage of the endothelium and triggers a chain of subsequent events that provoke endothelial dysfunction and cardiovascular complications. Some researchers believe that APLA are an independent risk factor for cardiovascular events in case of coronary artery disease and hypertension. At the same time, other authors deny this hypothesis. Information of the role of APLA in the formation of atherosclerotic lesions in patients with APLA is also contradictory.

A link between the different classes of APLA and cardiovascular disease has been reported. Strokes and heart attacks, arterial thrombosis of the lower extremities, vascular headache and valvular heart disease were probably more common in patients with high levels of APLA or β2GP1. There is a relationship between the presence of APLA and subclinical manifestations of atherosclerotic vascular lesions [10].

The clinical manifestations of SLE are very diverse. Specific lesions of the skin, mucous membranes and serous membranes, joints, lungs, nervous system, kidneys, heart, digestive organs can be seen [6, 15, 45]. The problem of comorbidity and syntropy of lesions is relevant, as in such cases their course deteriorates, the number of complications, mortality, and medical costs also increase [4, 5, 50, 153].

The results of the literature analysis show that the range of lesions of the circulatory system is extremely wide [7].

It was found that the heart injury is based on the following factors: inflammatory syndrome, microcirculation disorders, activation of autoimmune, immunocomplex processes [43, 44, 47].

Studies in recent years indicate a close association of heart disease in case of SLE with antibodies to cytoplasmic antigen (antigen of H. S. C. Sjögren's syndrome type A or antigen of H. S. C. Sjögren's syndrome type B (anti-Ro/Sjögren syndrome type A antigen, anti-La/Sjögren syndrome type B antigen - anti-Ro/SS-A and anti-La/SS-B), which lead to direct damage of the structures, and vasculitis, due to trophic disorders, and exudative processes - to indirect damage [74, 78].

Lesions of the cardiovascular system in the case of SLE can manifest itself in the form of pericarditis, myocarditis, endocarditis, lesions of the heart valves, coronary arteries, aorta, conduction system, pulmonary hypertension occurrence [48, 54, 100, 149, 151, 164].

Pericarditis was thought to be the most common heart disease in patients with SLE. Thus, during pathomorphological examinations of patients' hearts, pericardial lesions were observed in 83.0 % of cases, and endocardial lesions in 22.0% [105]. In the modern study, pericarditis was detected in 29.0 % of cases, myocarditis - in 26.0 %, endocardial lesions - in 37.0 % [23].

Pericarditis in case of SLE can be dry or exudative. Clinically pronounced pericarditis in patients is revealed in about 25.0 % of cases. This diagnosis is based on the complaints (cardiac pain of various origin, which is exacerbated in the supine position, shortness of breath), percussion of the chest (expansion of relative cardiac dullness), auscultation - weakening of heart sounds, pericardial friction murmur, electrocardiogram (ECG) - elevation of the ST segment, depression of the PQ segment, decrease of the waves voltage in all leads, X-ray examination - increase of the cardiothoracic index. During echocardiographic examination, pericarditis was revealed in 38.0 % of cases, recording the presence of pathologically increased amount of effusion in the pericardial cavity, which corresponds to the diastolic separation of pericardial leaves and their thickening [37].

Endocardial and valvular lesions diagnosed by echocardiography are present in 60.0 % of patients with SLE and are manifested by heart defects of varying origin and severity. Previously, their structure was dominated by endocarditis of E. Libman - B. Sacks, but with the use of glucocorticosteroids, its frequency significantly decreased [20]. According to the information from other literature sources, the structure of heart valvular lesions in patients with SLE diagnosed by echocardiography looked as follows: thickening of the valvular flaps - in 4.0-51.0 %, valvular vegetations - in 4.0-43.0 %, valvular insufficiency - in 25.0 % (mitral valve - in 39.0 %, aortic valve - in 13.0 %, tricuspid - in 87.0 %), valvular stenosis - in 4.0 % of patients [23, 128].

Valvular vegetations according to the results of histological examination consist of platelets, fibrin, active fibroblasts, newly formed vessels and fibrous tissue, and the valves may have signs of fibrosis and calcification.

The prevalence of myocardial lesions in patients with SLE, as evidenced by the analysis of the literature, has not been definitively determined. Myocarditis was detected during autopsy in 26.0 % of cases [105]. Histological changes in the myocardium bioptate are perivascular or interstitial infiltration by macrophages and lymphocytes. Cardiomyocyte degeneration, focal myocardial infiltration by immune cells, and diffuse or focal sclerosis or fibrosis are also possible. Cardiomyopathies induced by antimalarial drugs may occur as well [9, 26].

Clinical manifestations of myocardial damage in patients with SLE are vague. They can be detected only by tachycardia during objective or instrumental examination of the patient [2]. Echocardiography revealed a weakening of the contractility of the myocardial wall in 20.0 % of patients with SLE. Due to its vague clinical signs, and therefore - underdiagnosis, which consequently results in failure to prescribe the appropriate treatment, myocarditis can eventually lead to heart failure and complicate the course of the main disease.

Patients with SLE develop dystrophic processes in the myocardium due to the impaired trophy of cardiomyocytes caused by occlusion of small intramyocardial vessels due to vasculitis. This can result in the disturbance of systolic and diastolic function of the ventricles, structural and functional reorganization of the heart with the formation of concentric and eccentric hypertrophy of the left ventricular myocardium [140].

Some studies have shown that patients with SLE more often than the general population have disorders of lipid metabolism, metabolic syndrome and hyperhomocysteinemia [90, 119, 158].

The course of SLE is accompanied by the risk of circulatory lesions due to the increased atherogenesis, inflammatory lesions of the vascular wall and other complications caused by many pathogenetic factors [41, 106, 154]. Early onset of atherosclerotic cardiovascular disease in patients with SLE is most often associated with autoimmune vascular endothelial damage and APLS, as well as dyslipidemia and atherosclerotic process activation caused by the inflammatory markers increased production

[49, 63, 117]. However, the above list of vascular damage factors in patients with SLE is incomplete [101]. Recently, the pathogenetic significance of acquired and genetically induced disorders of homocysteine metabolism, platelet hyperreactivity, disorders in the protein C system and other risk factors in the formation of vascular lesions in patients with SLE has been actively studied. The role of cytomegalovirus in the pathogenesis of systemic sclerosis and atherosclerosis has been described [34]. It is likely that most patients have a combination of different risk factors, which determines the individual prognosis [124].

The main targets of adverse effects of metabolic risk factors are blood vessels. They have different pathogenetic mechanisms of influence on the vascular system or hemostasis system. Excess of homocysteine has a toxic effect on vascular endothelium and vasoconstrictor, proaggregating and procoagulant properties.

Disorders of lipid metabolism are also accompanied by vascular damage due to endothelial dysfunction and the formation of atherosclerotic plaques [148]. APLA causes damage to endothelial cells, which leads to the inflammatory reaction in blood vessels, endothelial dysfunction and atheromatosis.

Differences in the relationship strength between metabolic risk factors and the presence of clinically severe cardiovascular disease were identified. The group of factors with the greatest influence on the cardiovascular lesions occurrence include lipid risk factors (total cholesterol, low-density lipoprotein cholesterol, triglycerides), markers of the inflammatory process (TNF-α), hyperhomocysteinemia and APLS. Medium-strength factors included platelet hyperreactivity, hyperfibrinogenemia, soluble vascular cell adhesion molecule-1 (sVCAM-1) and L-selectin; low-risk groups included high-density lipoprotein cholesterol content and methylenetetrahydrofolate reductase gene polymorphism.

The most sensitive metabolic risk factors for coronary artery disease (myocardial infarction, angina) are: total cholesterol, low-density lipoprotein cholesterol and TNF-α, for cerebrovascular diseases (ischemic stroke, transient ischemic and ischemic attacks) - content of homocysteine and antibodies to β-2-glycoprotein-1.

There are also significant correlations between dyslipidemia and markers of inflammation. Dyslipoproteinemias are most associated with the content of cellular adhesion molecules (sVCAM-1, L-selectin), less - the content of pro-inflammatory cytokines IL-1, IL-2 and TNF-α [51].

As a result of increased atherogenesis and arterial hypertension in patients with SLE, the lesions of the coronary and cerebral arteries are observed [3, 56, 107, 154, 161]. This can lead to coronary artery disease, including at a young age (myocardial infarction, angina), as well as stroke, transient ischemic attack, lower extremities peripheral vessels damage, and so on. Therefore, in young patients with SLE, the risk of acute myocardial infarction increases by 5-10 times. Thrombosis or thromboembolism of the coronary arteries in case of APLS and their sclerosis in the presence of coronary arteritis is also possible [108].

In case of SLE, there are changes in the vascular wall in the form of thickening of the intima-media complex and the common carotid arteries stiffness index compared to healthy people, which directly correlates with the duration of the disease, glucocorticoids use duration and their cumulative dose [21].

It has been shown that such patients have endothelial dysfunction according to the results of the brachial artery endothelium-dependent dilatation test and the determination of the sVCAM-1 content in the serum. Endothelial dysfunction continues to persist even in the absence of the pathological process activity. Changes in the microcirculatory tract in patients with SLE have been identified by digital capillaroscopy of the nail bed [89].

It is known that the formation of endothelial dysfunction and adverse changes in the structure of blood vessels and the heart is the earliest manifestation of vascular damage and appears long before the occurrence of cardiovascular events, both in patients with atherosclerosis and in patients with SLE [98].

To diagnose subclinical atherosclerosis, such markers as the thickness of the carotid tissue intima-media complex, calcium of the coronary artery are determined. Recent studies have described the association of osteoprotegerin as a biomarker of subclinical atherosclerosis in patients with SLE. Osteoprotegerin is a type of tumor necrosis factor receptor. It has recently been shown to be produced by a variety of tissues, including the circulatory system (heart, arteries, veins), lungs, kidneys, immune tissues, and bones. The osteoprotegerin signaling pathway is strongly associated with vascular calcification [36, 64].

Men with SLE have an increased risk of coronary arteries calcification. Among the patients with SLE, the increased risk is caused by the age, chronic diseases (diabetes, etc.) number increase and the cumulative effect of glucocorticoids [116].

About 10.0 % of patients with SLE have arrhythmias and conduction disorders in various manifestations. According to the information from other sources, 13.0–50.0 % of patients with SLE are diagnosed with tachycardia, and its occurrence is explained by myocarditis or autonomic nervous system disorders [114].

Thrombocytopenia, which is associated with cardiovascular disease, has been reported in patients with SLE. Thrombocytopenic syndrome, which was seen in 7.0–30.0 % of patients with SLE, leads to hypocoagulable disorders of the hemostasis system and is manifested by thrombotic thrombocytopenic purpura accompanied by bleeding. However, sometimes thrombocytopenia may be accompanied by hypercoagulation. In patients with SLE, thrombocytopenia is associated with the presence of autoantibodies to platelet antigens - glycoprotein IIb/IIIa (glycoprotein IIb/IIIa - GPIIb/IIIa) and thrombopoietin receptor (TPOR) [125]. However, there is still no consensus on how thrombocytopenia affects the increased susceptibility to thrombosis in patients with SLE [137].

Treatment of patients with SLE remains a complex problem of modern rheumatology.

The general principles of treatment are:

1. The primary goal is to prolong life, prevent organ damage and improve the life quality, which can be achieved by controlling the disease activity, as well as minimizing

comorbidities and drug toxicity [17, 55, 157]. All patients are recommended dosed exercise, normalization of body weight, diet with increased content of polyunsaturated fatty acids, smoking cessation, protection from excessive sunlight, control of blood pressure, glucose, lipid profile, routine vaccination [38, 115].

2. There are treatment aimed at achieving the remission, or if it is not possible - the lowest possible activity, and maintenance treatment, which should prevent the recurrence of the disease [75, 144, 146].

3. Drugs: glucocorticoids (GC) are used with the possible simultaneous administration of other immunomodulatory and immunosuppressive drugs, which allows reducing the dose of GC and increasing their effectiveness. You should try to use GC in the lowest doses or cancel them if possible, due to the possible side effects, in particular, avascular osteonecrosis, osteoporotic fractures, diabetes mellitus, cataract [112, 118]. The selection of drugs and their doses depends on the dominant changes in clinical signs and disease exacerbation [14, 82, 138]:

1) mild form - do not use induction treatment; GC (calculating by prednisolone) - 0.1–0.2 mg/kg/day in combination with antimalarial drugs (eg, hydroxychloroquine 200.0–400.0 mg/day); in case of long-term remission, the possibility of gradual withdrawal of GC and continued treatment with antimalarial drugs should be considered [11, 104]. The main side effect is retinopathy, for the early diagnosis of which optical coherence tomography of the retina is now used [120].

2) moderate form - GC (calculating by prednisolone) - initially 0.2-0.5 mg/kg/day in combination with immunosuppressive drugs (prescribed depending on the clinical manifestation dominance);

3) severe form, including severe exacerbations (eg, vasculitis, severe widespread skin changes (including subacute cutaneous lupus erythematosus), polyserositis, myocarditis, alveolar hemorrhage, interstitial pneumonia, severe lupus nephritis, severe hematological disorders, central nervous system (CNS) lesions, acute peripheral neuropathy, significant general symptoms): GC - 1.0–2.0 mg/kg/day p/o or iv (calculating by prednisolone) or GC, most often methylprednisolone iv 500.0–1000.0 mg/day for 3–5 days, then prednisone, prednisolone or methylprednisolone p/o 1.0–1.5 mg/kg/day. Once improvement is achieved, the dose of GC should be gradually reduced by approximately 10.0 % per week. After reaching a dose of 30.0 mg/day, the reduction is 2.5 mg/week, 10.0 mg/day - 1.0 mg/week, to the minimum dose that will control the symptoms of the disease. The use of pulse therapy is possible if the infectious process is excluded [29, 70, 127]. In many cases, treatment with cyclophosphamide is started at the same time, which, after achieving remission, can be replaced by another immunosuppressive drug (eg, azathioprine, cyclosporine, mycophenolate mofetil) [57, 152]. Belimumab, rituximab, sifalimumab or other drugs from this group can be used in patients with persistently high disease activity, despite standard treatment (but only in case of severe lupus glomerulonephritis and CNS damage absence) [46, 58, 133, 159].

In case of severe kidney and CNS damage, severe thrombocytopenia, the accession of a bacterial infection IV immunoglobulin and plasmapheresis can be used [24, 132].

A new retrospective study presented at the Congress of the European League Against Rheumatism (EULAR) showed that in some patients with SLE, immunosuppressive treatment can be stopped without the further disease exacerbation if remission is achieved. It is known that modern guidelines for the treatment of SLE do not contain recommendations - when and how to stop using immunosuppressants. The solution of this problem leans on the practitioners' shoulders. The results of studies confirm that discontinuation of treatment often has the risk of serious side effects [71].

4. Prevention of exacerbations. Exposure to sunlight should be avoided, UV protection should be used: wearing of hats and protective clothing, UV blocking films should be applied at home and in the car, anti-UV of A and B type broad-spectrum creams and lotions should also be used. Antioxidants administering, melanogenesis activating substances, stimulation of tanning by thymidine nucleotides as experimental protective measures are used as well. For prophylactic purposes, drugs that cause SLE should be avoided, antimalarial drugs can be used; correction of hypovitaminosis D should be conducted [32].

5. Additional measures: osteoporosis prevention [92]; avoiding the risk factors for cardiovascular disease exposure. The effectiveness and safety of atorvastatin and rosuvastatin in order to prevent the aggravation of atherosclerosis and the occurrence of cardiovascular and cerebrovascular events and diseases in these groups of patients have been proven [18]. Statins are prescribed to patients with a low-density lipoprotein cholesterol content of more than 3.4 mmol/l, and if content is between 2.6 and 3.4 mmol/l - the hypocholesterolemic diet, phytostanols, the possibility of treating SLE with aminoquinol drugs (have lipid-lowering properties) and GC dose reduction are recommend. If these measures are ineffective, statins should be prescribed. Further clinical studies are needed to clarify the place of statins in the treatment of patients with SLE [39].

Prophylactic vaccinations should be used (only if the disease is inactive) - especially against influenza and pneumococci; other vaccinations - depending on the individual risk assessment. The use of vaccines containing live microorganisms is generally prohibited [28, 96]. In some patients who have been vaccinated with combined vaccines against typhoid, meningococcus, tetanus, rubella, anthrax, measles, mumps, SLE occurred two to three weeks after re-immunization. The trigger for SLE can be any bacterial or viral component of the vaccine or a chemical component of the adjuvant.

Women of childbearing potential taking immunosuppressive drugs should be informed of the need for effective contraception (the presence of APLA/APLS is a reason to prohibit hormonal contraception containing estrogen). Azathioprine can be used during pregnancy [12, 38, 70].

Antiplatelet drugs and/or hydroxychloroquine should be considered in patients with persistently high APLA

titers. In situations of increased risk of deep vein phlebothrombosis of the lower extremities, low molecular weight heparins should be used in prophylactic doses.

Viral infections, skin changes, hematological disorders, joint and muscle pain, arthritis, serositis, lupus glomerulonephritis, SLE caused by drugs should also be treated [83, 86, 109].

The most common causes of death in the early period of the disease: infections and severe changes in the organs (CNS, circulatory system disorders, acute lupus pneumonia, severe nephropathy), in later period: complications of treatment (infection) and the consequences of accelerated atherosclerosis, thrombosis [70]. Patients with SLE have an increased risk of cervical cancer [19]. It is known that over the past 25-30 years, the occurrence of the following cardiovascular lesions caused by the premature aggressive atherosclerosis: coronary artery disease, myocardial infarction, cerebrovascular events (stroke, transient ischemic attack) is one of the main causes of death among patients with SLE. The incidence of atherosclerotic vascular events increases from 1.8 % at the early stages of SLE to 27.0 % in the late post-diagnosis period. Stroke occurs in 15.0 % of patients, coronary artery disease - in 6.0-9.0 %. It has been found that patients with SLE have a 50-fold higher risk of myocardial infarction than the general population. The results of histopathological studies show that the real prevalence of cardiovascular diseases among the patients with SLE is much higher. The severity of organ damage depends largely on the occurrence of hypertension and the use of GC; plaquenil has a positive effect [65].

In case of adequate diagnosis and treatment, approximately 85.0 % of patients will survive for 10 years, and 75.0 % - for 20 years. The prognosis is worse in patients with lupus nephritis – despite treatment, the end-stage renal disease develops in 20.0 % of patients. Recurrence of SLE in a transplanted kidney occurs extremely rarely (in 2.0 %) [103]. The total standardized mortality rate (SMR) in patients with SLE is 2.6, SMR from infectious diseases - 4.98, from kidney diseases - 4.89, from circulatory system lesions - 2.23, from tumors - 1.16 [135].

Thus, despite the undoubted progress in understanding the etiology and pathogenesis of SLE, its diagnosis and treatment, the mortality of patients, including ones at young and working age, is higher than in the general population, and circulatory system lesions are ones of its main reasons in these cases.

Conclusions. The results of the literature review indicate the importance of the problem of systemic lupus erythematosus, due to its widespread prevalence among young and people of working age, lack of accurate knowledge about the etiology and pathogenesis of the disease, comorbid lesions of many organs and systems, including circulatory system, the development of severe and often life-threatening manifestations, the lack of clear recommendations that would predict the differentiated use of drugs taking into account comorbid syntropic lesions, which is also demonstrated in the described clinical case. Given this, systemic lupus erythematosus needs further in-depth study.

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Conflict of interest
The authors of this article arque that there is no conflict of interest

Modern View on the Problem of Systemic Lupus Erythematosus with and without Comorbid Lesions of the Circulatory System (Literature Review, Clinical Case Description) – First Notice

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Introduction. The prevalence and incidence of systemic lupus erythematosus (SLE) in the world is significant. In recent years, there has been a tendency of the SLE prevalence increase. despite the undoubted progress in understanding the etiology and pathogenesis of SLE, its diagnosis and treatment, the mortality of patients, including ones at young and working age, is higher than in the general population, and circulatory system lesions are ones of its main reasons in these cases.

The aim of the study. To analyze the literature, dedicated to the modern view on the problem of systemic lupus erythematosus with and without comorbid lesions of the circulatory system, describe the clinical case.

Materials and methods. Content analysis, method of system and comparative analysis, bibliosemantic method of studying the current scientific investigations on modern principles of diagnosis and treatment of patients with SLE are used. A clinical case is described.

Results. The article presents modern ideas about the etiological factors and pathogenesis of the disease. The clinical manifestations of SLE are very diverse. The problem of comorbidity and syntropy of lesions is relevant. Lesions of the cardiovascular system in the case of SLE can manifest itself in the form of pericarditis, myocarditis, endocarditis, lesions of the heart valves, coronary arteries, aorta, conduction system, pulmonary hypertension occurrence. The basic principles of drug therapy are also briefly considered.

Conclusions. The results of the literature review indicate the importance of the problem of systemic lupus erythematosus, due to its widespread prevalence among the young and people of working age, lack of accurate knowledge about the etiology and pathogenesis of the disease, comorbid lesions of many organs and systems, including circulatory system, the development of severe and often life-threatening manifestations, the lack of clear recommendations that would predict the differentiated use of drugs taking into account comorbid syntropic lesions, which is also demonstrated in the described clinical case. Given this, systemic lupus erythematosus needs further in-depth study.

Keywords: SLE, circulatory system lesions, atherosclerosis, diagnosis and treatment of SLE.

Сучасний погляд на проблему системного червоного вовчака без і з коморбідними ураженнями системи кровообігу (огляд літератури, опис клінічного випадку) – повідомлення перше

Л. О. Кобак, О. О. Абрагамович, У. О. Абрагамович, В. В. Чемес

Вступ. Системний червоний вовчак (СЧВ) – потенційно небезпечна для життя хвороба, яка виснажує хворого, призводить до зниження працездатності, інвалідизації та, у багатьох випадках, до смерті. Поширеність і захворюваність на СЧВ у світі є значною. Упродовж останніх років спостерігається тенденція до зростання поширеності СЧВ. Незважаючи на безсумнівні успіхи в розумінні етіології і патогенезу недуги, її діагностики та лікування, смертність серед хворих є вища, ніж у загальній популяції, а однією із основних причин у цих випадках є ураження органів системи кровообігу.

Мета. Проаналізувати літературу, присвячену сучасному погляду на проблему системного червоного вовчака без і з коморбідними ураженнями системи кровообігу.

Матеріали й методи. Використано контент-аналіз, метод системного та порівняльного аналізу, бібліосемантичний метод вивчення актуальних наукових досліджень щодо сучасних принципів діагностики та лікування хворих на СЧВ.

Результати. Відомо багато чинників (генетична схильність, лікарські засоби та інші хімічні речовини, ультрафіолетове випромінювання, інфекції тощо), які призводять до виникнення, або пришвидшують виникнення СЧВ чи вовчакоподібного синдрому, проте етіологія хвороби досі остаточно не вивчена. Основними ланками патогенезу СЧВ є імунна дисфункція та продукція автоантитіл, спрямованих проти декількох власних молекул, які містяться у ядрі, цитоплазмі, клітинній мембрані, а також до розчинних молекул, таких як імуноглобуліни Джі та фактори коагуляції. Частіше на СЧВ хворіють жінки, проте перебіг хвороби у чоловіків тяжчий. 30–70 років – пік захворюваності на СЧВ.

Клінічні прояви СЧВ дуже різноманітні. Найбільш характерні ураження шкіри, слизових та серозних оболонок, суглобів, легенів, нервової системи, нирок, серця, органів травлення. Актуальною є проблема коморбідності уражень, оскільки погіршується їх перебіг, зростають кількість ускладнень, смертність, а також медичні витрати.

Спектр уражень системи кровообігу надзвичайно широкий. У хворих на СЧВ може виникати перикардит, міокардит, ендокардит, артеріальна гіпертензія, ураження клапанів серця, вінцевих артерій, аорти, провідної системи, зокрема, через активізацію атеросклерозного процесу, вазоактивних речовин із прозапальними властивостями.

Способи лікування СЧВ відомі, але немає чітких рекомендацій, які б передбачали диференційоване застосування лікарських засобів із урахуванням коморбідних синтропічних уражень, у тому числі життєво важливих органів і систем. Серед причин смерті хворих на СЧВ ураження органів системи кровообігу посідає третє місце після інфекційних хвороб та хвороб нирок.

Висновки. Результати огляду літератури вказують на важливість проблеми системного червоного вовчака через його значне поширення серед людей молодого та працездатного віку, брак точних знань про етіологію і патогенез хвороби, виникнення коморбідного ураження багатьох органів і систем, зокрема, системи кровообігу, виникненням тяжких і часто небезпечних для життя проявів, відсутність чітких рекомендацій, які б передбачали диференційоване застосування лікарських засобів із урахуванням коморбідних синтропічних уражень. Із огляду на це СЧВ потребує подальшого детального дослідження.

Ключові слова: СЧВ, ураження органів системи кровообігу, атеросклероз, діагностика та лікування СЧВ.

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