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Vascular changes in autoimmunological connective tissue diseases

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Abstract

Vascular complications due to systemic connective tissue diseases pose a very difficult clinical problem. Due to the nature and location of the lesions, they very often prevent revascularization procedures and the conservative treatment is usually insufficient, which leads to a growth in the degree of ischemia and the need to amputate the limb. The authors clearly show the clinical picture of the most common diseases in this group — systemic lupus erythomatosus, systemic scleroderma, dermatomyositis, mixed connective tissue disease and Sjögren's syndrome.

Key words: connective tissue disease, vascular changes, systemic sclerosis, Raynaud's fenomenon

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Introduction

Autoimmune connective tissue disease (AI-CTDS) is a heterogeneous group of disorders having many clinical features in common as well as serological and morphological, characterized by a high diversity and variability of the clinical picture and the presence of numerous clinical forms, which can vary the course and prognosis of the disease. The most common autoimmune connective tissue diseases include systemic lupus erythematosus, systemic scleroderma, dermatomyositis, mixed connective tissue disease and Sjögren's syndrome.

The variety of clinical symptoms and laboratory abnormalities may hinder quick diagnosis, especially at the early stage of the disease. Therefore specific diagnostic criteria were created for each of them, enabling proper diagnosis. An overlap syndrome can be identified in cases where the diagnostic criteria of at least two of the diseases are met.

The pathogenesis of AI-CTDs is not well known. Its complex mechanism is emphasized, involving genetic factors, cardiovascular and immune disorders, both cell-mediated and humoral, with the presence of specific antibodies. The time between the appearance of clinical symptoms and the presence of autoantibodies is an individual characteristic, whereas an inflammatory process within the skin, internal organs and the vascular system is common in the cases of connective tissue diseases [1, 2].

Vascular changes seem to be a crucial factor causing immunological cascade and, in consequence, the development of inflammation within the tissues.

The clinical manifestation of vascular changes in systemic connective tissue diseases affects up to 20% of patients, being a group of symptoms resulting from the involvement of vessels of various size [3].

Vascular changes

Systemic sclerosis (SSc)

Systemic sclerosis is an autoimmune disease characterized by fibrosis of the connective tissue of the skin and internal organs: esophagus, heart, lung, kidney, muscle and other [4].

It is now accepted that systemic sclerosis is a disease in which certain environmental factors (toxic), within the group of patients with genetic predisposition, damage the blood vessels and cause immune cell activation, which leads to non-specific stimulation of fibroblasts and

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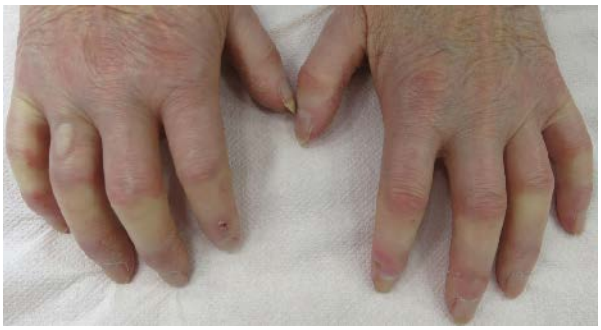

Figure 1. Raynaud's phenomenon, patient with systemic sclerosis

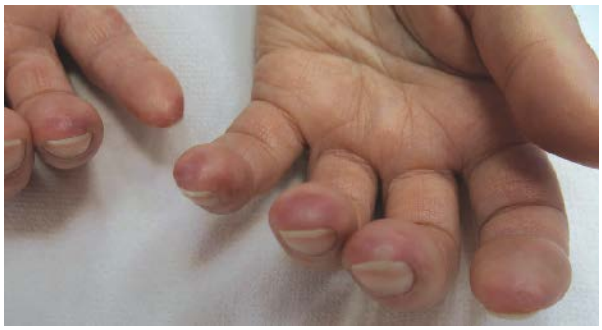

Figure 2. Finger tips with erythema, patient with systemic sclerosis

other connective tissue cells that produce components of an extracellular matrix [5].

According to the latest classification, there are three main types of scleroderma: diffused scleroderma (dSSc), limited scleroderma (lSSc) and scleroderma without sclerosis (SSc sine sclerodema, SSSC) [6].

Different types of SSc vary in the severity of skin sclerosis, process and prognosis of the disease, although the resulting changes to internal organs, bones and joints are the same.

Diffused scleroderma is usually characterized by a rapid and severe course. Vasomotoric changes eg. Raynaud's syndrome (paroxysmal paleness of the fingers, with subsequent cyanosis and swelling, occuring most frequently under the influence of cold, stress or injury, Fig. 1) appear at the same time with sclerosis or they slightly precede them [7, 8].

Sclerosis in dSSc may involve the face, neck, trunk, upper and lower limbs. Often they coexist with discoloration and telangiectasias. Facial skin sclerosis results in a thinning of the nose and lips, around which radial furrows are visible. The face becomes mask-like, and in advanced cases, eyelid movability becomes limited and mouth narrowing occurs (microstomia) [6]. Callous skin edema may initially be observed within the hand area, especially within the area of digital pulps, as well as within the regions of osteophytes. Difficult to heal erosions or ulcers appear within the areas of atrophies i.e. within the ungual phalanges and over the phalangeal joints. Hand dactylocampsis and limitations to finger movability occur, as well as trophic disturbances leading to bone destruction and ungual phalanges shortening (acro-osteolysis). The intensification of induration decreases from the circumference in the proximal direction. The less frequent symptoms of dSSc (diffuse scleroderma) include skin dryness, skin pruritus and hair loss [6]. Xerophthalmia and xerostomia, which results from the impairment of the exocrine gland's secretory function, are frequently observed in patients suffering from Ssc.

Circumscribed scleroma (lSSc) is characterized by a chronic and slow course and the development of sclerosis is preceded over many years by Raynaud syndrome. Dermal changes pertain to distal limb parts (most frequently the upper limbs) and face and resemble the changes described in the course of dSSc (diffuse scleroderma) [8]. This variety is characterized by less frequent pigmentation disturbances (skin hyperpigmentation and depigmentation). Hard subcutaneous nodules (calcinosis cutis) may occur mainly around the joints of the hands as a result of calcium compound deposition. A greater increase in telangiectasis is observed as well [6, 8]. Most frequently, the changes in the internal organs, which occur during the course of SSc, pertain to the alimentary, osteoarticular, muscular system as well as the lungs, heart and kidneys. Hypothyreosis, as the result of thyroid fibrosis or the autoimmune process occurring within it, and the disturbances within the peripheral nervous system are less frequent.

Certain authors emphasize the significant role of vascular disorders in the scleroderma pathogenesis. Damage to the blood vessels as well as chronic tissue ischemia may lead to tissue damage, which manifests itself as erosions and ulcers within limbs (mainly within the distal elements, Fig. 2), changes within the alimentary system — Gastric antral vascular ectasia, pulmonary hypertension, kidney and myocardium fibrosis. The most characteristic clinical manifestation of vascular dysfunction during the course of SSc is Raynaud syndrome defined as a sequence of colour changes most frequently within the hand area in response to cold, stress and changes in temperature. These skin colour changes include paleness ("white"), cyanosis ("blue") and hyperaemic reperfusion ("red") [9]. Raynaud syndrome is caused by reversible vascular contraction due to functional disorders in the minor arteries. However, in many SSc patients progressive structural changes developing within the minor arteries lead to permanent blood flow impairment and tissue necrosis. There is

a greater risk of thromboembolism in SSc patients. In a large-scale population study, a threefold increase in the risk of pulmonary embolism and deep vein thrombosis was observed in SSc patients, when compared to the control group, taking into account the risk factors such as age, sex and recent hospitalization [10].

Systemic lupus erythematosus (SLE)

This is a disease covering a vast array of dermal changes and organ disorders. The SLE complex pathogenesis is characterised by genetic factors, vascular and immunological disorders.

The vital factor affecting the course of the disease is UV radiation (UVR). In all forms of SLE one may observe the way UVR hypersensitivity leads to pathological changes [11]. Mostly women are affected by SLE (80–90% of the ailing) between 20–40 years of age, with an average morbidity age of 29. Children and aged persons are less prone to be affected. The illness usually causes distinctive symptoms such as skin changes, joint pains and cytopenia (anaemia, leucopenia, trombocytopenia). The symptoms may be associated with non-distinctive symptoms such as weakness, tiredness, raised temperature or fever, loss of weight, lymphadenopathy, splenomegaly, pleuritis or pericarditis, kidney disorder symptoms, Raynaud symptoms, excessive hair loss, and reoccurring obstetric failures especially in young women. The sickness is most severe when the central nervous system or kidneys are infiltrated [12]. In 2012, new SLE classification criteria were designed by the SLICC group (Systemic Lupus International Collaborating Clinics), which include 11 clinical criteria and 6 immunological criteria. SLE can be detected when at least 4 clinical and immunological criteria from the SLICC group are met, including at least one clinical and one immunological criterion or when the patient is diagnosed with lupus nephritis and the presence of ANA antibodies and anti-dsDNA is confirmed by biopsy [12]. In SLE, the ailing process may affect both big and small vessels. The basic mechanism, which plays the key role in the inflammation ofthe blood vessel wall, is immune complex build-up.

During the ailment, clinically we observe vascular changes in the form of erythema appearing on the face, hemorrhagic changes, atrophy focal points, erythema marks and erosions (Figs. 3, 4), and exteroceptive ulceration, mainly located on the distal parts of the limbs. Additionally, teleangiectasias, ecchymosis and Raynaud symptoms can be observed in the area of the fingers and toes [3, 13]. Cardiovascular system disorders mainly lead to the development of exudative pericarditis. The build-up of immunological complexes on the walls of the glomerulonephritis capillaries may lead to kidney malfunction and the development of renal lupus in a short time. The symptoms appearing in the central nervous system are present in the form of micro cardiac infarction and postapoplectic focal points. Vascular changes in the area of the lungs are mainly intervesicular bleeding and the development of renal hypertension. Small ocular vessels may also be included in the ailment process, which even leads to multiple bleeding entering the retina [14].

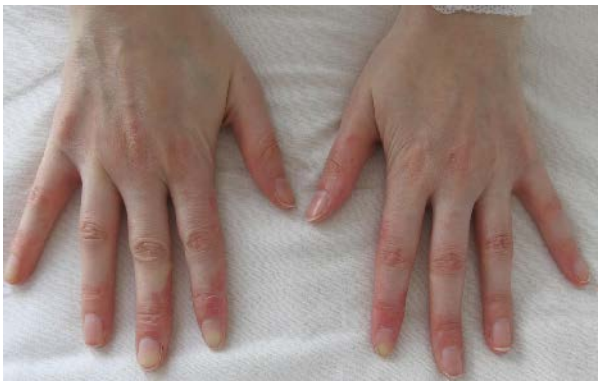

Figure 3. Fingers with erythema, patient with systemic lupus erythematosus

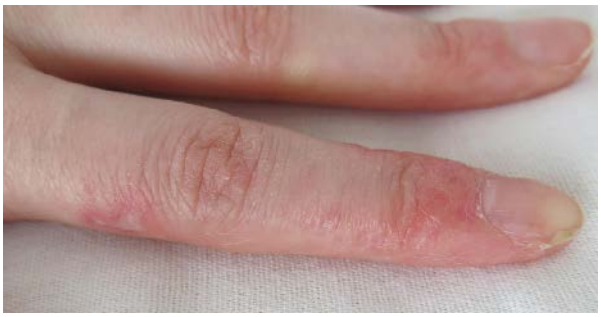

Figure 4. Fingers with erythema, patient with systemic lupus erythematosus

Dermatomyositis (DM)

This is a polymyositis especially affecting the muscles of the shoulder and pelvic girdle, as well as causing typical skin changes. The pathogenesis of this ailment is not fully known as yet. It seems that the changes occur on immunological grounds, which is justified with the presence of antibodies located around the striated muscle and the presence of immunological complex in the affected muscles and skin. In patients over 40 years of age, DM may be a tumor revelator [15]. The clinical impact of the ailment, apart from muscle weakness, includes erythematous edema changes that are predominant in the facial area, especially close to the eyelids (alleged binoculars), erythema on the cleavage, erythematous lumps over the small hand limbs (Gottron's lumps, Fig. 5) as well as telangiectasis around the nail shafts. Organ changes involve the digestive system (affecting smooth muscles), heart, respiratory system, (affecting the intercostal muscles and diaphragm).

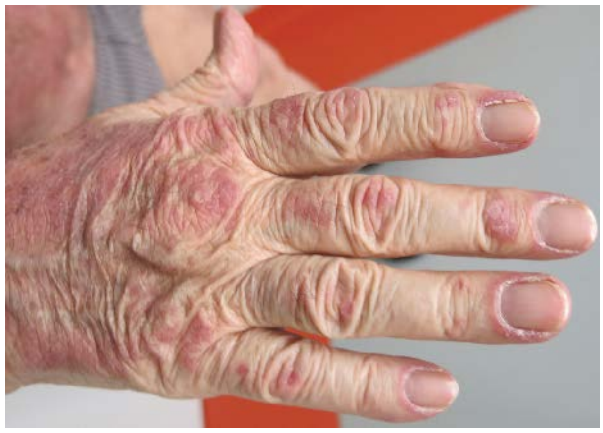

Figure 5. Gottron's papules in dermatomyositis

Figure 6. Nailfold changes in dermatomyositis

The ailment may take a severe form characterized by the presence of general symptoms in the form of a fever, weakness, and fast or chronic course of the illness with the presence of muscular atrophies, scieroderma-like or poikiloderma-like skin changes and calcifications [3].

The assessment of vasculopathy involvement includes symmetric erythema on the cheeks and nose, telangiectasia on the nailfolds (Fig. 6) with dendritiform capillaries identified with a capillaroscopy test, subungual petechiae, Raynaud phenomenon and erosions of the affected skin [10].

Sjögren's syndrome (SS)

Sjögren's syndrome is a chronic autoimmune inflammatory disorder most common in middle-aged women. It is characterized by lymphocytic infiltration of the exocrine glands (mostly salivary and lacrimal), which causes dryness of the eyes and mouth. Besides typical sicca syndromes, Sjögren's syndrome may involve other organs such as the kidneys, osteoarticular system, muscles, digestive system, respiratory system and nervous system. Other vascular symptoms in SS related with the inflammation include Raynaud phenomenon, petechiae, purpura or vascular urticaria.

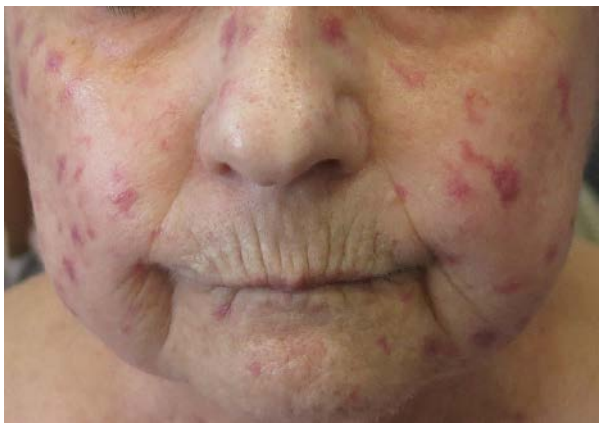

Figure 7. Vascular changes on the face in mixed connective tissue disease

During the course of cryoglobulinemia, this group of patients can develop leukocytoclastic vasculitis [16].

Mixed connective tissue disease (MCTD)

This is a disease that has signs and symptoms of lupus erythematosus, scleroderma and polymyositis. It is characterized by the presence of a distinctive autoantibody anti-U1 ribonucleoprotein RNP (U1RNP). As in SLE and SSc, it appears to be most common amongwomen. MCTD patients present clinical and immunological symptoms of AI-CTDs in varying degrees of severity.

Raynaud's phenomenon, which is a characteristic clinical symptom of MCTD, usually overtakes other symptoms. More than 50% of patients with MCDS have abnormalities of the nailfold vessels identified by a capillaroscopy exam. Erythema of the face, as well as telangiectasia of the nailfolds (Fig. 7), face and cleavage are the dominant symptoms of the clinical picture of MCTD.

Summary

Autoimmune connective tissue diseases are closely related to different manifestations of vascular lesions, mainly inflammatory-related. Symptoms mainly occur within the skin, but can also involve the vessels of internal organs. Vascular lesions seem to be a significant factor, which releases an immunological cascade and, subsequently, inflammation in the tissues. Vasculitis associated with AI-CTDs is a symptom of disease activity and an unfavorable prognostic factor. In the treatment of each of these diseases, vasodilators and medications improving the rheological parameters of the blood play an important role.

It should be noted that theyinclude calcium-channel blockers [6], angiotensin-converting-enzyme inhibitors [17], pentoxifylline [18], sulodexide [20, 23], prostaglandin PGE1 and alprostadil [6–8].

The treatment should be comprehensive, including education of the patient, pharmacological treatment, rehabilitation and sometimes even surgical intervention (skin calcinosis).

In the case of dominant vascular changes (involving the peripheral vessels, Raynaud's syndrome, or ulceration of the finger tips) calcium-channel blockers as well as intravenous analogs of pentoxifylline, sulodexide and selective phosphodiesterase inhibitors efficiently reduce the frequency and the severity of ischaemic episodes [19, 20, 22, 23].

When skin calcinosis occurs, calcium-channel blockers are the main choice for slowing down calcification, minocycline and colchicine tend to be helpful in the healing and anti-inflammatory process. Some authors mention the efficacy of warfarin at the early stage of changes [20, 24].

Kidney complications are treated mainly with high doses of angiotensin converting enzyme inhibitors. In the case of organ failure, dialysis is used [20, 21].

Cardiovascular complications like arrhythmias and heart failure require special cardiological treatment where antiarrhythmics, diuretics and ACEIs are administered. In the case of pulmonary arterial hypertension, phosphodiesterase inhibitors, endothelin receptor analogues and prostacyclin analogues are recommended. If this therapy is insufficient, surgical treatment, or lung and heart transplants are required [19, 21].

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