Review paper

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Haematological abnormalities in systemic sclerosis

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Abstract

Systemic sclerosis (SSc) is a connective tissue disease characterised by extremely high heterogeneity. This heterogeneity concerns the organ involvement, course of disease and prognosis. Unlike in some other systemic connective tissue diseases, especially systemic lupus erythematosus, in SSc haematological disorders occur rarely. When they develop, they affect erythrocytes, leucocytes and platelets. The most common cause of this pathology of erythrocyte abnormalities is microcytic anaemia resulting from micro-haemorrhages with telangiectasias within the digestive mucosa in patients with SSc. In SSc patients with severe haematological disturbances, the differential diagnosis should include overlapping with another systemic connective tissue disease or a haemato-oncological disease (lympho/myeloproliferative syndrome). In SSc patients with monoclonal proteins or cryoglobulins, it is essential to consider a haemato-oncological disease. In such cases, the differential diagnosis should be focused on a paraneoplastic syndrome, especially when the haematological symptoms develop shortly after the diagnosis of SSc and in the elderly.

Key words: systemic sclerosis, lymphoma, haematological abnormalities.

Introduction

Systemic sclerosis (SSc) is a disease with a highly diverse clinical picture. The disease is considered an autoimmune condition; nevertheless, beside the activity of the immune system with non-specific inflammation, endothelial damage with vascular dysfunction as well as uncontrolled proliferation of fibroblasts and progressive fibrosis play an essential role in it. Any organ can be involved, yet the most common lesions affect the skin, lungs, heart, skeletomuscular system, gastrointestinal tract, and kidneys [1].

Contrary to some other connective tissue diseases, e.g. systemic lupus erythematosus, rheumatoid arthritis or mixed connective tissue disease, systemic sclerosis is rarely associated with haematological disturbances [2]. When they develop, they affect erythrocytes, leukocytes, or platelets (Table I).

Erythrocyte abnormalities in systemic sclerosis

According to literature data, the most common cause of erythrocytic system pathology in systemic sclerosis patients is microcytic anaemia associated with iron deficiency and resulting from relatively common gastrointestinal microhaemorrhages and gastric antral vascular ectasia (GAVE), also known as watermelon stomach, endoscopically characterised by red stripes in the lining [3–5].

In systemic sclerosis, gastrointestinal involvement is most frequently observed; fibrosis of the gastrointestinal wall and slow peristalsis result in absorption disorders, e.g. of vitamin B12 and folic acid. Therefore, systemic sclerosis patients can develop megaloblastic anaemia. Anaemia may be observed during severe malabsorption syndrome. Gastrointestinal involvement and impaired gut motility found in systemic sclerosis promote small intestinal bacterial overgrowth, resultant malabsorption syndrome with deficiency of vitamins (e.g. B12, folic acid), and development of severe anaemia [6–10].

Another relatively rare pathology is microangiopathic haemolytic anaemia during scleroderma renal crisis with the presence of schistocytes and reticulocytosis [11]. About 25% of patients with systemic sclerosis may develop anaemia in chronic inflammatory diseases. Moreover, the overlap syndromes of systemic sclerosis

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Table I. Haematological abnormalities in systemic sclerosis

Haematological abnormalities		Causes
Erythrocyte abnormalities	Microcytic anaemia	Microhaemorrhages from telangiectasias within the gastrointestinal mucosa, severe malabsorption syndrome
	Megaloblastic anaemia	Malabsorption of folic acid, vitamin B12, severe malabsorption syndrome
	Haemolytic microangiopathic anaemia	Scleroderma renal crisis
	Anaemia in chronic inflammatory diseases	Chronic inflammation in an autoimmune disease
	Anaemia in overlapping syndromes	Overlapping of systemic sclerosis with rheumatoid arthritis or systemic lupus erythematosus
Leucocyte abnormalities	Leucopenia	Overlapping of systemic sclerosis with systemic lupus erythematosus, Sjögren's syndrome, immunosuppressive treatment, severe malabsorption syndrome
	Leucocytosis	Advanced lung fibrosis, recurrent infections, neoplastic disease, lymphoproliferative disease
Platelet abnormalities	Thrombocytopenia	Scleroderma renal crisis, overlapping syndrome of systemic sclerosis with systemic lupus erythematosus, antiphospholipid syndrome
	Thrombocythemia	Neoplastic disease, inflammation

and systemic lupus erythematosus or rheumatoid arthritis should be mentioned [12].

According to Frayha et al. [12], who examined 180 patients with systemic sclerosis, anaemia was found in about 25% of patients while severe anaemia with haemoglobin < 10 g/dl was found in 10% of them. Still another clinical issue is iron deficiency in systemic sclerosis patients.

Ruiter et al. [13] found iron deficiency in about 40% of systemic sclerosis patients. The authors found that iron deficiency was associated with worse prognosis and shorter survival, as compared to systemic sclerosis patients with normal levels of iron. Moreover, the lung function parameters in systemic sclerosis patients with iron deficiency were worse than in those in systemic sclerosis patients with normal iron levels [13].

Leucocyte abnormalities in systemic sclerosis

In systemic sclerosis, leucocytosis is found more commonly than leucopenia. The causes of increased leucocyte counts include leucocytosis during advanced lung fibrosis or other severe organ complications, recurrent infections, particularly of the respiratory system, often originating from an interstitial lung disease, as well as neoplastic diseases or lymphoproliferative syndromes [14]. Leukopenia in systemic sclerosis is relatively rare and can accompany the overlap syndromes of systemic sclerosis and systemic lupus erythematosus or Sjögren's syndrome.

Furthermore, there are cases of decreased leucocyte counts caused by immunosuppressive treatment or severe malabsorption syndrome. According to Frayha et al. [12], leucocytosis was present in 25/180 (14%) patients with systemic sclerosis, including 10/25 patients with overlapping myositis while leukopenia was present in 5.5% of patients. The abnormalities in white blood cell subsets are worth mentioning. Increased absolute neutrophil counts may be elicited by recurrent infections, while lymphocytosis or eosinophilia may be elicited by lymphoma.

Neutropenia and lymphopenia may result from immunosuppressive treatment. Decreased absolute lymphocyte counts are likely to be associated with systemic lupus erythematosus overlapping systemic sclerosis. Furthermore, in systemic sclerosis, there are abnormalities in B lymphocyte homeostasis, with increased expression of activation markers (CD80, CD95, HLA-DR) on some B-cell subsets, mainly the memory B-cells [15].

Moreover, some data have revealed altered T-cell homeostasis in systemic sclerosis. Giovannetti et al. [16] demonstrated significantly higher proliferation of CD4+ T-cells, lymphocyte apoptosis and incidences of CD4+ regulatory T (Treg) cells in systemic sclerosis patients, as compared with controls, and significantly correlated with clinical phenotypes of disease and clinical progression parameters, i.e. diffusing capacity of the lung for carbon monoxide (DLCO) and disease activity. The above-mentioned data indicate that the evaluation of T-cell homeostasis can be a valuable prognostic tool in systemic sclerosis patients, useful to distinguish between limited and diffuse phenotypes [16, 17].

Platelet abnormalities in systemic sclerosis

Thrombocytosis in systemic sclerosis can result from a concomitant neoplastic disease or chronic inflammation, e.g. in cases of overlapping with rheumatoid arthritis. The overlapping of systemic sclerosis and another autoimmune disease, particularly systemic lupus erythematosus or antiphospholipid syndrome, can lead to thrombocytopenia [12, 18–21].

Thrombocytopenia can also occur in scleroderma renal crisis; in such cases, the development of thrombocytopenia with microangiopathic haemolytic anaemia is observed. The above condition is characterized by the presence of haemolysed erythrocytes, increased LDH activity, reduced concentration of haptoglobins, thrombocytopenia, increased activity of renin, reduced concentration of fibrinogen and the presence of fibrin degradation products [22].

The symptoms are turbulent; patients develop acute kidney failure with oliguria, sudden arterial hypertension, often accompanied by retinopathy symptoms or hypertensive encephalopathy, circulatory insufficiency, vision disturbances caused by haemorrhages to the retina or generalized seizures due to hypertensive encephalopathy [23].

Thrombotic microangiopathy can also be caused by infectious factors, neoplastic diseases, and other autoimmune diseases, such as systemic lupus erythematosus or antiphospholipid syndrome [24]. Thrombocytopenia with microangiopathic haemolytic anaemia during scleroderma renal crisis should be differentiated from idiopathic thrombotic thrombocytopenic purpura, caused by congenital or acquired ADAMTS-13 deficiency, which lead to endothelial injury and capillary microthrombi. In such cases, systemic sclerosis marker antibodies or nailfold capillaroscopy-detected changes (sclerotic microangiopathy-like) or other symptoms of systemic sclerosis are not observed [25].

Association of systemic sclerosis with myeloproliferative and lymphoproliferative diseases

According to the literature data, the incidence of neoplasms in patients with systemic sclerosis is twice as high compared to that in the general population and increases 7–10 times in the elderly. The most common neoplasms accompanying systemic sclerosis are lymphomas.

Colaci et al. [26], who analysed a group of 130 systemic sclerosis patients with haematological cancers, demonstrated B-cell non-Hodgkin lymphoma in about 50% of them; multiple myeloma, chronic lymphocytic and myeloid leukaemia were found in a high percentage of patients. In single cases, Hodgkin disease, T-cell lymphoma, as well as myelofibrosis and polycythaemia vera, were diagnosed.

Moreover, in over 7% of patients, overlapping of systemic sclerosis with another autoimmune disease was determined, including about 60% with Sjögren's syndrome overlapping. The authors reported that haematological cancers were significantly more common in men than in women (28% of male patients); no correlation between the type of sclerosis and haemato-oncological disease was observed. Furthermore, the highest incidence of haematological cancers was found in the 6th decade of life; in 60% of cases, the neoplastic disease was diagnosed within 5 years following the diagnosis of systemic sclerosis [26].

In another study, Vettori et al. [27] analysed a group of 251 patients with systemic sclerosis; 0.5% of them were diagnosed with non-Hodgkin lymphomas.

Moreover, haematological complications were demonstrated to be more common in older age in diffuse cutaneous systemic sclerosis, and lymphoma was diagnosed within the first years of systemic sclerosis. Gastrointestinal lymphomas constituted a substantial percentage of all the lymphomas diagnosed [27, 28].

Systemic sclerosis and the prevalence of monoclonal protein

Patients with systemic sclerosis and monoclonal protein are at a particularly high risk of haematological neoplastic transformation. Hypergammaglobulinaemia in systemic sclerosis is relatively rare; its presence may evidence an active inflammatory process, overlapping of systemic sclerosis with other autoimmune diseases, especially Sjögren's syndrome, or may precede the development of lymphoma.

According to Trad et al. [29], who analysed 244 patients with systemic sclerosis, 50% of them had diffuse systemic sclerosis. In this group, 41% were found to have hypergammaglobulinaemia while 13% had monoclonal protein.

The group of patients with systemic sclerosis and the presence of monoclonal protein was older and was characterized by worse lung function parameters; moreover, they were demonstrated to have higher incidence of pulmonary arterial hypertension, cancers, including non-Hodgkin lymphomas, and the presence of anti-β2-glycoprotein I antibodies [29] (Table II).

Monoclonal gammopathy in systemic sclerosis should be differentiated from the rare POEMS syndrome (i.e. polyneuropathy, organomegaly, endocrinopathy,

Table II. Symptoms suggestive of lymphoproliferation in systemic sclerosis

Haematological abnormalities		Characteristic features and clinical symptoms
Hypergammaglobulinaemia		Overlapping of systemic sclerosis with another autoimmune disease, particularly Sjögren's syndrome
Presence of monoclonal protein		Older age, short duration of the disease, diffuse cutaneous systemic sclerosis, worse lung function parameters, pulmonary arterial hypertension
Presence of cryoglobulins	Type I	An extremely high risk of lymphoma, severe course of systemic sclerosis, worse prognosis, lower-limb ulcerations, kidney failure, vasculitis
	Type II	Ulcerations, symptoms of vasculitis, severe course of systemic sclerosis, worse prognosis
	Type III	

monoclonal protein, skin changes). The skin lesions in this syndrome may resemble the changes during systemic sclerosis observed on nailfold capillaroscopy; additionally, there are no marker antibodies for systemic sclerosis, digital ulceration or telangiectasias [30].

Systemic sclerosis and the prevalence of cryoglobulins

One of the well-known risk factors of the development of lympho-proliferative disease in systemic sclerosis patients is the presence of serum cryoglobulins. Giuggioli et al. [31] studied the frequency of cryoglobulin occurrence in patients with systemic sclerosis. They analysed 246 systemic sclerosis patients. Seven patients (2.8%) were demonstrated to have cryoglobulins; 2/7 had trace concentrations of them while 5 had mixed cryoglobulinaemia type II; four of the third group developed severe vasculitis. The entire group of 7 patients was characterised by limited systemic sclerosis with the presence of anti-centromeric antibodies, pulmonary arterial hypertension, severe non-healing ulcerations of the lower limbs and poor prognosis.

The symptoms of systemic sclerosis developed 3–17 years prior to vasculitis. Summing up, the incidence of mixed cryoglobulinaemia in systemic sclerosis patients is relatively rare, ranging between 0.3% and 2%; such cases are characterised by a severe course and poor prognosis [31] (Table II).

Conclusions

Haematological disorders in systemic sclerosis are relatively rare, as compared to other systemic connective tissue diseases. In cases with severe haematological abnormalities during systemic sclerosis, the differential diagnosis should involve overlapping of systemic sclerosis with another systemic connective tissue disease or haemato-oncological disease.

In some cases, haematological disorders (leucopenia, thrombocytopenia) may be caused by immunosuppressive treatment. Patients suffering from systemic sclerosis should be diagnosed for a haematological disease, especially elderly patients and during the first years of the disease.

The presence of severe haematological abnormalities, cryoglobulins or monoclonal protein, especially in the early stage of the disease, is likely to be suggestive of a paraneoplastic syndrome rather than systemic sclerosis. However, in cases of paraneoplastic syndromes, marker antibodies for systemic sclerosis or sclerotic microangiopathy-like capillaroscopic changes are not found.

The authors declare no conflict of interest.

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