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Review

Macro- and microvascular disease in systemic sclerosis

Niloufar Kavian [a,b,*], Frédéric Batteux [a,b]

[a] Faculté de Médecine Paris Descartes, Sorbonne Paris Cité, INSERM U 1016, Institut Cochin, Paris, France
[b] Laboratoire d'immunologie biologique, Hôpital Cochin, Groupe Hospitalier Paris Centre, AP-HP, 75679 Paris cedex 14, France

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ABSTRACT

Vasculopathy is common in patients with connective tissue disease and can be directly implicated in the pathogenesis of the disease. Systemic sclerosis is an auto-immune multiorgan connective tissue disorder characterized by fibrosis of the skin and visceral organs and vascular disease. Micro- and macro-vessels are a direct target of the disease. In this review, we present the various clinical manifestations of the vasculopathy that can be present in SSc patients, and then discuss the various aspects of the pathophysiology of the vascular disorders.

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Contents

1. Introduction

Vascular involvement is frequent in patients with connective tissue disorders and can represent an important cause of death in established disease. Vasculopathy can be directly implicated in the pathogenesis of the disease, representing an acute manifestation of

* Corresponding author at: Laboratoire d'Immunologie, Hôpital Cochin, 27 Rue du faubourg St Jacques, 75679 Paris cedex 14, France.
E-mail address: niloufar.kavian@cch.aphp.fr (N. Kavian).

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lupus (e.g., antiphospholipid syndrome (APS), lupus vasculitis), rheumatoid arthritis (e.g., vasculitis), or systemic sclerosis (SSc) (e.g., pulmonary arterial hypertension, digital ulcers).

Vasculitis is common to various connective tissue disorders and is triggered by a vascular inflammatory process of the vessel walls that may take many clinical forms due to its capacity to affect vessels of different sizes (arteries, veins, and/or capillaries) and sites (involving either skin or internal organs), with a prognosis that may range from mild to life-threatening [1].

Besides vasculitis, auto-immune connective diseases can also be associated with a large spectrum of cardiovascular manifestations affecting myocardium, cardiac valves, the pericardium, the conduction system, [2]. These cardiovascular manifestations can have various impacts on the patients' condition: from clinically silent to increasing considerably the co-morbidity and mortality.

In SSc, the vascular disease is fundamental to the physiopathology of the disease all along its development from early onset to late complications. Indeed, vasculopathy represents one of the three key features that characterize the connective tissue disorder SSc, along with fibrosis and auto-immunity. Two clinical forms of the disease are distinguished on the basis of skin involvement, that both display symptoms of vasculopathy [3–5]. On one hand, patients with limited SSc (lSSc) display a skin involvement that is confined to the face, neck, and areas distal to elbow and knees. On the other hand, in patients with diffuse SSc (dSSc) the skin involvement extends proximally to involve upper arms, thighs and/or trunk. Blood vessels are a direct target in this disease, as shown by the various clinical manifestations that occur from the initiation to the propagation of the disease, and have an important effect on the quality of life of the patients.

These typical features of the vascular disease in SSc can differ when SSc co-exist with Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. ANCA-associated vasculitis is a multi-organ autoimmune disease associated with ANCA production and inflammation of small vessels. Any organ can be affected but more particularly the respiratory tract, skin, heart, nervous system and kidneys. The incidence of ANCA auto-antibodies in patients with SSc has been evaluated to be about 7% [6–8]. Though, there are only few case reports of ANCA-associated vasculitis in SSc [9,10]. In the case of ANCA-associated vasculitis occurring in overlap with SSc, patients can present with ANCA-associated necrotizing glomerulonephritis, that can be confused with scleroderma renal crisis, making the diagnosis challenging. Derrett-Smith et al. interestingly reported in a small cohort that shared HLA haplotypes may be present in patients who develop both scleroderma and ANCA-associated vasculitis [10].

In this review, we will briefly present the clinical manifestations directly linked to the micro- and macro-vascular involvement of the disease and then focus on the cellular and molecular aspects defining the pathophysiology of the vascular disease in SSc, including the modifications of the microvasculature, the endothelium, the pericytes, the impaired angiogenesis and vasculogenesis, the activation of the coagulation system, the role of auto-antibodies and atherogenesis, and the dysfunction of recently involved transcription factors.

2. Manifestations of the microvascular and macrovascular diseases in SSc

Several organs can be affected by the vascular disease in SSc including the lungs, kidneys, heart and digital arteries, leading to various clinical manifestations in SSc patients.

2.1. SSc microvascular manifestations

Raynaud's phenomenon is one of the first clinical manifestations observed in SSc. This microvasculature disorder affects mostly the fingers and toes but can also affect other extremities. Over 95% of SSc patients display evidence of Raynaud's phenomenon, that can begin many years before any other clinical symptoms of SSc. Raynaud's phenomenon is due to hypoxia in the extremities in response to cold and is characterized by a triphasic color pattern: pallor (constricted blood-flow), cyanosis (tissue hypoxia) and rubor (reperfusion) [11]. Evidence suggests that Raynaud's phenomenon is triggered by endothelial injuries in association with dysregulations in the production of nitric oxide and vasoactive factors [12].

Raynaud's phenomenon can lead to the formation of digital ulcers that is also one of the earliest complications of the disease. Healing of digital ulcers is often difficult and the most threatening complication is the loss of digits that is secondary to infections.

Telangiectasias are also frequent in SSc patients, reflecting the systemic microvascular involvement of the disease. They are caused by a dilatation of postcapillary venules [13]. They are localized on the hands, face, lips and oral cavity, reflecting the systemic microvascular disease in SSc.

Pulmonary vascular involvement in the form of pulmonary arterial hypertension (PAH), diagnosed by right-heart catheterization, occurs in approximately 12% of patients with SSc, and is seen in both lcSSc and dcSSc [14,15]. SSc-PAH occurs as a consequence of progressive remodeling of the small- to medium-sized pulmonary vasculature leading to pulmonary artery vasoconstriction and cellular proliferation. Hypoxemia and ischemia–reperfusion injury in the pulmonary vasculature maintain the vascular remodeling, fibrosis, and intraluminal microthrombosis [16]. These phenomena result in a progressive increase in pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular pressure overload. Compensatory mechanisms in the right ventricle eventually lead to cardiac failure, making PAH life-threatening.

The vascular disease can also affect renal vessels and cause scleroderma renal crisis that affects approximately 10% of patients with diffuse scleroderma and 2% of patients with limited scleroderma. This vascular complication is frequently associated with the presence of anti-RNA polymerase III antibodies [17]. Scleroderma renal crisis typically presents as an acute onset of severe hypertension and renal failure, caused by a proliferative obliterative vasculopathy of arterioles leading to a glomerular ischemia, as shown by histopathological studies of renal biopsies.

Likewise, vascular malformations of the gastro-intestinal mucosa closely resembling telangiectasias (Gastric Antral Vascular Ectasia) can induce gastro-intestinal manifestations in SSc patients [18]. GAVE or watermelon stomach has a typical microscopic aspect characterized by dilatation of mucosal capillaries, focal fibrin thrombosis, fibromuscular hyperplasia, and fibrohyalinosis. This typical gastrointestinal feature can be observed in autoimmune connective tissue disorders including SSc, but is also associated with liver diseases. Various reports estimate its prevalence in SSc population between 1 and 20% [18–22].

2.2. SSc macrovascular manifestations

Macrovascular disease is considered very rare in SSc and the prevalence of vascular abnormalities in SSc is inversely proportional to the size of the blood vessels [23]. The heart is one of the major organs involved in SSc macrovascular disease [24], but histology examinations or coronary angiography show that coronary arteries are rarely involved [25–28]. Vasospasm of the coronary arteries with or without the presence of structural vascular abnormalities could be observed in patients with SSc [13,14]. This phenomenon is due to a transient nonperfusion because of arrythmias or Raynaud's phenomenon of the coronary arteries. Improvement of myocardial perfusion after oral nifedipine administration supports the hypothesis of myocardial RP in SSc [77,78]. Endothelial dysfunction and local hyperreactivity are involved in its pathogenesis [79].

Contradicting data have been reported regarding the prevalence of cerebrovascular involvement in SSc, but the current opinion is that it is very low [29,30].

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