Digital Ulcers, Vasculopathy and Internal Organ Involvement

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Introduction

Systemic sclerosis (SSc) is an autoimmune connective tissue disorder that is characterized by a complex interplay of vascular abnormalities, immune system activation and an uncontrolled fibrotic response. Vascular component is often referred to as vasculopathy and is seen as having a key role in the early pathogenesis of SSc. Furthermore, generalized peripheral microvascular and cardiovascular alterations contribute to some later complications of the disease with converging data supporting that the SSc outcomes depend on the extent and severity of vascular lesions [1].

Patients with SSc develop a broad spectrum of vascular manifestations including the almost universal Raynaud's phenomenon (distal vasospasm), commonly digital ulceration and more rarely critical digital ischaemia. In parallel, within this very heterogeneous disease, some patients will develop some vascular-related organ damages leading to heart or kidney failure. It is still unclear whether there is a continuum between peripheral vasculopathy promoting digital ulceration (DU) or critical ischemia and some other vascular-related complications [2, 3]. The objective of this chapter is to address this question by analysing whether severe digital vasculopathy could be a surrogate for some more severe damages.

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Generalized Microvascular Damages

SSc vasculopathy depends on the complex interaction of various pathological processes including autoimmunity, impaired compensatory vasculogenesis, angiogenesis, endothelio-mesenchymal transition, endothelial dysfunction and impaired coagulation/fibrinolysis system. SSc vasculopathy is characterized by a variety of such changes that affect primarily the microcirculation and small arterioles.

The hallmark of functional abnormalities related to SSc vasculopathy is Raynaud's phenomenon. It is characterized by exaggerated but reversible vasospasm in response to cold exposure, stress or emotional upset. It must be pointed out that although it is mainly recognized at the digital level, it is well established that all microcirculatory systems can be affected (heart, nose, etc.) [2]. By example, cardiac imaging showed abnormal perfusion related to small coronary artery disturbances after cold stress [4].

With the progression of structural vascular changes, functional alteration of vascular cells includes endothelial apoptosis, endothelial dysfunction, impaired coagulation/fibrinolysis system, aberrant expression of soluble factors and cell adhesion molecules leading to the pathological inflammation. The next steps include altered neovascularization and vascular remodelling due to the impairment of compensatory vasculogenesis and exaggerated angiogenesis [5–10]. Circulating levels of various angiogenic/angiostatic factors are largely altered, and, so far, most of studies have revealed that pro-angiogenic factors are increased throughout the disease course, especially in the active stage of the disease [5–10]. Regarding the capillaries, structural vascular disease is characterized by distorted and irregular capillary loops in all the involved organs, including in particular the kidneys, lungs and heart. This reflects the systemic nature of the microvascular disorder, even in sites not affected by fibrosis.

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Therefore, destructive vasculopathy characterized by progressive loss of capillaries, leading to tissue hypoxia and dermal fibroblast activation, can co-exist or progress to proliferative obliterative vasculopathy featured by proliferation of vascular cells (endothelial cells, pericytes and vascular smooth muscle cells) [3]. The damages then lead to the occlusion of arterioles and small arteries with fibro-proliferative change and permanent hypoxia which might further promote surrounding fibrosis [11]. Another hallmark of functional abnormalities related to SSc vasculopathy is impaired endothelial function. The vasodilatory response to blood flow-associated shear stress is a useful parameter to quantify endothelial function. In SSc patients, several studies have demonstrated the reduction of flow-mediated dilation (FMD) values supporting impaired nitric oxide production [12].

Altogether, these findings support a generalized microvascular impairment in SSc. One may ask whether the digits might be primarily affected and the exposure to cold of this body area supports some more important or earlier damages that could explain the high risk for digital ulceration. Nevertheless, the pathogenesis of vasculopathy and the findings of abnormal circulating markers as previously highlighted, such as the inverse correlation of FMD values with pulmonary arterial pressure and the association of decreased FMD values with the presence of pulmonary arterial hypertension and digital ulcers, all show some generalized abnormalities [13, 14]. Therefore, it is needed to evaluate in depth the natural course of the disease to see whether proliferative obliterative vasculopathy may gradually and sometimes subclinically progress along with disease duration and eventually become clinically evident with variable degrees of severity leading to recurrent DU, pulmonary arterial hypertension (PAH) and heart failure of renal crisis.

Cross-Sectional Analyses of SSc Patients Having Digital Ulcerations

In order to investigate the clinical manifestations occurring in patients with digital ulceration (DU), the characteristics of SSc-DU patients versus the non-affected patients have been analysed in the report including large series.

A study looking at the natural history of SSc-DU was based on 103 patients among whom 46 had a history of DU. The mean duration of follow-up from the first non-Raynaud SSc symptoms was about 12 years. In 43% of cases, the first DU occurred within 1 year following the first non-Raynaud SSc symptoms and within 5 years in 73% of cases. In multivariable analysis, younger patients at occurrence of first non-Raynaud SSc symptoms and with higher skin score (such has being classified with a diffuse cutaneous subset) experienced earlier DU occurrences. It must also be pointed out that DU was delayed when vasodilator therapy was offered (mainly calcium channel blockers or ACE inhibitors). Pulmonary arterial hypertension (PAH) occurred in 11 patients (11%) during the course of the disease, and its prevalence was comparable between the subgroups (14% PAH in the DU subgroup and 9% PAH in the no DU subgroup; $p = 0.53$) [15].

In a French multicentre study, a cross-sectional analysis of 599 patients with SSc found that 53% had prior or current DU. Looking at associated variables, DU appeared to occur more frequently among males, patients with a higher Rodnan skin score, patients with early onset of disease, patients with carbon monoxide lung diffusion capacity (DLCO) < 60% predicted and patients with anti-topo I antibodies. It must be highlighted that sex and skin disease were the strongest associated variables. The frequency of PAH was not higher in patients with prior or current DU than in those never affected [16].

DLCO measures gas exchanges through the alveolar membrane and can be influenced by the thickness of the alveolar membrane and lung capillary volume. Therefore, a reduced DLCO in the absence of impairment in pulmonary function may represent a surrogate marker of vasculopathy. The association of DLCO impairment and current digital ulcers may indicate the pathophysiological link between vasculopathy and digital ulcers. However, no relationship between prior or current DU and PAH was observed. One of the main studies that highlighted the link between DLCO and vasculopathy was based on the large Pittsburgh Scleroderma Databank from which 106 patients who had the diagnosis of PAH were matched with 106 controls by SSc skin subtype, age, sex, race, disease duration and the mean time to the diagnosis of PAH after the initial Pittsburgh visit. If a decline in DLCO pre-empted PAH, PAH patients and controls had a similar frequency of Raynaud's phenomenon, digital tip ulcers and digital gangrene. However, visual ana-

logue scales for Raynaud's phenomenon showed that cases had significantly higher values for both the severity of Raynaud's phenomenon and the severity of digital tip ulcers [17].

The German network has provided some data derived from 1880 patients from whom 1690 were evaluable for DU. Out of these, 408 (24%) had active DU at the time of entering the registry. In multivariate analysis, datasets from 1164 patients were used and revealed that male sex was the most powerful independent predictor for the presence of DU and that PAH, anti-Scl70 antibodies (but not ACA), involvement of the mouth or oesophagus, elevated erythrocyte sedimentation rate or onset of Raynaud's phenomenon at a young age were all risk factors for the presence of DU. Diffuse skin sclerosis in combination with PAH was the most powerful predictor for the occurrence of DU [18].

In another national project, a total of 19 Spanish centres participated in the recruitment of 1326 SSc patients; out of these, 552 SSc patients had prior or current DU. Multivariate analysis identified that history of prior/current DU in patients with SSc was independently associated to younger age at SSc diagnosis, diffuse cutaneous SSc and peripheral vascular manifestations such as Raynaud's phenomenon, telangiectasia and acro-osteolysis [19]. However, history of DU was not associated with any visceral vasculopathy such as PAH or scleroderma renal crisis.

The Canadian registry was used to determine features associated with DU and their complications and to determine if there were associations of digital ulcers with other evidence of vasculopathy such as PAH and scleroderma renal crisis (SRC). Among 938 SSc patients, 8% had a digital ulcer currently, 44% had a digital ulcer ever, and 53% had digital pitting scars. In the multivariate analysis, the most important variables to predict DU were younger age of onset, ILD, higher hand and finger skin score and higher HAQ score [20]. There was no significant association between the history of digital ulcers and any definition of PAH (prevalence measured at 9%) and neither with renal crisis (prevalence of 5%).

If microcirculation impairment is fundamental in SSc vasculopathy, large vessel disease may contribute although there are still debates about the potential role of atherosclerosis in SSc vascular damages. A Japanese cross-sectional study looked at 254 patients among whom 48 SSc patients had prior or current DU (19%). There were no multivariable analyses performed, but it is of interest to point out that carotid atherosclerosis was not more common in patients with DU as compared to SSc patients without DU. Regarding SSc characteristics, DU were more common in males; in DcSSs, mRSS was higher in patients with a history of DU confirming previous findings coming from other geographical populations [21]. A focus was then done on heart disease, showing no more PAH in DU-SSc patients (9% vs 10% in DU-SSc versus non-DU-SSc). After exclusion of the PAH patients, those with DU had more commonly elevated natriuretic peptide or more mild cardiac abnormalities such as EKG changes or coronary artery disease [21].

The carotid-femoral pulse wave velocity (PWV) is a marker of aortic stiffness that holds prognostic significance in various vascular conditions, including systemic hypertension, renal failure and heart failure. The augmentation index (Aix_75), defined as the amplitude of the reflected wave from the periphery to the heart, can be measured by applanation tonometry and depends on several factors including large artery but also medium and small arteries stiffness. Radial applanation tonometry has been investigated in a group of 63 SSc patients to look at potential association of PWV or Aix_75 with active DU that was observed in 10 SSc patients. No differences existed in baseline characteristics between SSc-DU versus SSc non-DU patients, regarding cutaneous subset of the disease and disease duration, renal and pulmonary function, cardiovascular risk factors, heart function and pulmonary artery pressure [22]. SSc patients with DU versus those without had increased Aix_75, while there was no difference in PWV. The results of the multivariate logistic regression revealed that age, sex, erythrocyte sedimentation rate, aortic pulse pressure and DU were independently associated with Aix_75 [22]. Collectively these results suggest the existence of increased small and medium arteries stiffness in SSc patients with DU without significant aortic increased stiffness, when compared to SSc patients without DU.

Cutaneous telangiectasia is common in SSc and part of the classification criteria. A cross-sectional study aimed at determining whether the number and size of cutaneous telangiectasia were associated with the pattern of microvascular lesions assessed by nailfold videocapillaroscopy (NVC) and markers reflecting the severity of SSc-related vasculopathy.

Among the total of 87 patients, profuse and pseudotumoral cutaneous telangiectasias were both associated with capillary loss and severe neoangiogenesis on NVC [23]. In multivariate analysis, profuse pseudotumoral cutaneous telangiectasias were independently associated with past or current digital ulcers, whereas pseudotumoral cutaneous telangiectasias were independently associated with the late NVC pattern and PAH [23].

Regarding another vascular organ complication, there are few studies about the risk factors of renal crisis; however, none did suggest so far that DU or PAH may be risk factors for such event [24].

The main results of the above studies are summarized in Table 8.1 where associations observed in multivariable analyses are highlighted.

Table 8.1 Digital ulcer associations through multivariable analyses in large multicentre series of SSc patients

Variable	ItinerAIR-SSc (2009) (n = 599 patients)	German network (2009) (n = 1690)	Canadian network (2011) (n = 938)	Spanish registry (2016) (n = 1326)
Definition of DU (and prevalence)	Prior or current DU (53%)	Active DU at inclusion (24%)	Past or present DU (44%)	Prior or current DU (42%)
Age	+	–	+	+
Male sex	+	++	–	–
Smoking	–	Not studied	–	–
Disease duration	+	–	–	–
Severe skin involvement	+	NA	+ (finger mRSS)	–
DcSSc	–	–	–	+
Anti-topoisomerase	–	+	–	–
Erythrocyte sedimentation rate	Not studied	+	–	Not studied
Esophageal involvement	Not studied	+	+/–	Not studied
DLCO	+ (<60%)	NA	–	–
Interstitial lung disease	(Severe ILD and exclusion criteria)	–	+	+
Pulmonary hypertension	(Exclusion criteria)	+	–	–
Renal crisis	–	–	–	–
HAQ score	Not studied	Not studied	+	Not studied

Longitudinal and Prospective Studies

Another way to explore if DU may be a surrogate for generalized vasculopathy is to look at prospective data to see whether SSc patients with DU at baseline develop more organ vasculopathy than non-affected patients.

In EULAR Scleroderma Trials and Research (EUSTAR) cohort, it was showed that at presentation, 1092/3196 patients had a history of DU (34.1%). Follow-up at 3 years was the cut-off time to look at the occurrence of complications [25]. In multivariable analyses adjusting for age, gender and other parameters considered potentially significant, a history of DU was strongly predictive for the presence of active DUs at prospective visits but also for an elevated systolic pulmonary arterial pressure on heart ultrasound, for any cardiovascular event (new DUs, elevated US-PAPs or left ventricular failure and for death). Overt PAH could not be analysed and there was no prediction for renal crisis [25].

The German network has also looked at prospective data regarding DU and showed various progressions according to SSc characteristics. Unfortunately, no details are provided about other outcomes unless a statement that the weak or lack of association of DUs with pulmonary hypertension or heart and renal involvement indicates that the vasculopathy in digital arteries and the renal and pulmonary vasculature seem to be affected by different pathophysiological pathways [26].

In the Australian PAH registry, among 1636 patients with SSc, 194 (11.9%) had PAH proven by right heart catheter including 160 who were detected prospectively by screening. The study primarily looked at the outcomes of patients according to the screening programmes, but the characteristics of SSc-PAH are detailed and analysed using univariate analyses. The data show that SSc patients with PAH were older, had longer disease duration from the first non-Raynaud clinical manifestation and were more likely to be anticentromere positive and to have telangiectasia, calcinosis and joint contractures [27]. Furthermore, digital ulcers were more frequent (53% in PAH-SSc patients and 42% in SSc non-PAH patients), but the strength of association is not very strong, and multivariable analyses would be required to determine independency in prediction.

Biomarker Studies

Many studies investigated in these recent years candidate biomarkers. If some were mainly descriptive using cross-sectional design, some others were based on longitudinal data allowing prediction of vascular risk [28].

The pentraxins are a very conserved family of proteins with a unique architecture. In humans, the two main members of this family are C-reactive protein and serum amyloid

P. Pentraxin 3 (PTX3) is expressed predominantly in atherosclerotic lesions that involve various cells such as macrophages, neutrophils, dendritic cells or smooth muscle cells. Interestingly, PTX3 has been examined, as a novel biomarker for inflammatory cardiovascular disease. In SSc, circulating PTX3 but also fibroblast growth factor 2 (FGF-2) levels has been found to be significantly higher in SSc patients than in healthy control subjects [29]. Of the most interest, PTX3 was elevated in SSc patients who had digital ulcers or PAH, while FGF-2 was reduced in SSc patients with PAH. Multivariate analysis identified elevated PTX3 as an independent parameter associated with the presence of digital ulcers and PAH. Furthermore, PTX3 levels were a useful predictor of future occurrences of digital ulcers, and reduced FGF-2 was independently associated with the presence of PAH. Chemokine CXCL4 levels have been found to be correlated with skin and lung fibrosis and also with pulmonary arterial hypertension. No data were provided regarding DU. But among chemokines, only CXCL4 predicted the risk and progression of systemic sclerosis [30]. Using a cohort of 100 patients and a follow-up of 3 years, vascular biomarkers of new events were investigated, primarily to predict the development of new DU that occurred in 17 SSc patients. Both angiogenic and vasculogenic markers were measured. Using various multivariable models, first the history of previous DU but also placenta growth factor (PlGF) levels and endothelial progenitor cell count were independent predictors of the development of DU [31]. The prediction of other cardiovascular end points were studied suggesting stimulating clues with these markers, but the number of events was low not providing a high statistical power. Interestingly, another study confirmed the interest in regulators of angiogenesis, confirming the promise of PlGF and also of Flit1 as measures of pulmonary hypertension in SSc patients [32].

Angiotensin II type 1 receptor (AT1R) and endothelin 1 type A receptor (ETAR) are functional autoantibodies directed against vascular receptors. A majority of SSc patients have increased levels of anti-AT_1R and anti-ET_AR antibodies compared to healthy donors. Moreover, in SSc patients, the autoantibodies are associated with various vascular symptoms of the disease such as PAH, digital ulcers and renal crisis. Nevertheless, the antibodies are also associated with the diffuse cutaneous subtype as well as with lung fibrosis. Altogether, these data suggest a possible role of the antibodies in disease mechanisms, but their use in clinical practice for predicting damages remains to be established although in the context of DU, it has been shown that anti-ETAR autoantibodies can be used together with the presence of current or past DU to identify patients with SSc who are at risk for the development of subsequent DU [33, 34].

Imaging may also provide some tools to predict DU and vascular outcomes. Few studies have been performed so far, but capillaroscopy was found to be an interesting candidate, and a prospective study of 6 months identified that the mean number of capillaries per millimetre in the middle finger of the dominant hand, the number of DU at enrolment and the presence of critical digital ischemia at enrolment were risk factors for the development of new DUs. Other cardiovascular outcomes were not measured on that duration [35].

Conclusion

Vascular injury and subsequent vascular dysfunction are among the earliest alterations in SSc and are considered to act within the initiating steps in SSc pathogenesis. Microcirculation impairment is the hallmark of the disease, but larger vessels may be affected even if the reality of increased prevalence of atherosclerosis in SSc remains controversial. The process is undoubtedly generalized and all vascular territories are affected. This is strongly supported by autopsy studies that showed lung and kidney vessels involvement despite the lack of any evidence of organ involvement [36]. Nevertheless, DU is the most common clinical expression of advanced vasculopathy. It remains unclear why this area is mostly affected although the permanent exposure to external stress might contribute to its severity. Some have thought that DU could be a marker of damage (vascular and fibrotic changes), but the epidemiological studies do not clearly and reproducibly demonstrate a strong link between DU and other vascular complications. Indeed, cross-sectional studies show that SSc-DU patients have a more severe disease, but there is no demonstration of higher frequency of PAH or renal crisis. The longitudinal studies further support poorer outcomes of SSc-DU patients but do not explicitly found definite higher risk. The main results suggest a potential link between DU and subsequent DU, but several methodological issues preclude firm conclusion. Indeed, the definition of the events differs between the studies; the time of observation is usually not very long for PAH which is usually a mate complication; and because of the scarcity of major cardiovascular events, the sample size may be an issue.

Biomarker studies highlight the systemic component of vasculopathy and suggest some links between DU and PAH, but it seems that additional further and potential regional factors might contribute to more severe remodelling in the fingers or in the lung or in the kidney. Autoantibodies might contribute to these specificities, and it is of interest to see that DU is more common in DcSSc and probably anti-topoisomerase-positive patients, whereas anti-centromere antibodies are reproducibly found in SSc-PAH patients and that anti-RNA polymerase 3 antibodies are strong markers of renal crisis. The role of others and functional antibodies are interesting clues in this context.

One might also add that the natural course of vasculopathy and its complications are moving in the recent years and the recent findings about DU recurrence showing faster healing and less relapse should stimulate further studies to reshape current patients' outcomes and management [37, 38]. Therefore, SSc-DU patients have worse outcomes than non-affected patients, and they should be managed as patients having a severe form of the disease [39]. However, the reason why vasculopathy may be mainly expressed in digital arteries in some patients and in pulmonary or kidney arteries in others remains unclear. Improving the knowledge in the field would distress this part of the disease that is a huge contributor to excessive morbidity and mortality.

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