Chapter 7
Raynaud's Phenomenon

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What Is Raynaud's Phenomenon?

Whereas the majority of medical eponyms describe a constellation of clinical symptoms and signs around a single disease, the term Raynaud's phenomenon (RP) is used to describe a symptom complex that can be present in virtually any form of digital vascular compromise. The existing classification of RP applies the same eponym to both the relatively benign functional vasospasm of primary RP and the more complex (and usually severe) vasospastic, obliterative and vaso-occlusive microangiopathy of systemic sclerosis (SSc). The breadth of pathology associated with the term RP can be traced back to Maurice Raynaud's original treatise which assembled a large number of disparate cases around the common theme of peripheral digital vascular compromise [1]. SSc-RP is generally considered a more severe form of digital vasculopathy than primary RP and can result in impaired dermal nutri-

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tional flow resulting in tissue injury such as digital ulceration disease and necrosis.

The Clinical Features of Raynaud's Pheneomen

The clinical features of Raynaud's phenomenon are caused by digital ischaemia. Traditional definitions have focussed on the vasospastic component (often precipitated by cold exposure) resulting in discrete 'attacks' manifesting as digital colour changes (white, blue/purple and red) that reflect digital tissue perfusion and oxygenation during vasoactive changes within the digital arteries, arterioles and post-capillary venules. It is sensory symptoms of pain and numbness that result in impaired hand function and reduced quality of life. In SSc-RP, there is a vasospastic component with acute RP 'attacks' (typically precipitated by cold exposure but also the sympathomimetic effects of emotional stress) but also more persistent background digital ischaemic symptoms caused by the obliterative and vaso-occlusive microangiopathy of scleroderma.

The Relevance of Raynaud's Phenomenon in Scleroderma

Endothelial injury is considered an important initiating event in the pathogenesis of systemic sclerosis (SSc) [2]. Evidence of digital vasculopathy is present in virtually all patients at baseline assessment; manifesting as clinical symptoms of digital vascular compromise and confirmed through identification of morphological abnormal capillaries at the nailfold [3, 4]. Indeed, such is the importance of digital vasculopathy, the presence of objective evidence of Raynaud's phenomenon (RP) and nailfold capillaroscopic abnormalities are sufficient to fulfil classification criteria for early SSc [5] and feature, alongside anti-nuclear antibodies and puffy fingers, in the preliminary criteria for very early diagnosis of systemic sclerosis (VEDOSS) [6]. The absence of RP symptoms should

prompt clinicians to consider the possibility of a 'SSc mimic' when evaluating a patient with sclerosing skin disease [7].

The Burden of Raynaud's Phenomenon in Systemic Sclerosis

Whilst non-life threatening, SSc-RP is a major cause of disease-related morbidity [8]. Patient survey have ranked RP as the highest disease-specific manifestation of SSc in terms of overall frequency and impact [9]. SSc-RP results in pain, numbness, impaired hand function, emotional distress, impaired health-related quality of life and reduced social participation [10]. The principle goal of treatment is reduce the daily burden of SSc-RP symptoms but it is also hoped that vasoactive medications might modify disease progression. Challenging to demonstrate within the constraints of a clinical trial, observational data from large registries has suggested a lower prevalence of vascular complications of SSc in patients established on calcium channel blockers (CCBs) early in the disease course, offering a tantalising glimpse of the potential disease-modifying potential of such treatments when used over extended periods [11].

Clinical Vignette

Case History

A 72 year old lady presented to the scleroderma clinic in 2014 with an 18-month history of tri-phasic RP and gastro-oesophageal reflux symptoms. Past medical history included hypothyroidism managed with a stable dose of levothyroxine. Clinical examination revealed cool peripheries and grade I sclerodactyly but no other features of SSc. Antinuclear antibody testing revealed an anti-nucleolar stain on indirect immunofluorescence but no SSc-specific autoantibodies were identified using solid phase immunoassays. Nailfold capillaroscopy revealed good preservation of capillary density

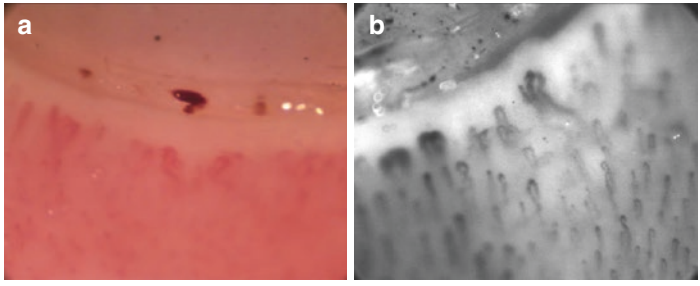

Figure 7.1 Nailfold capillary morphology in early systemic sclerosis. (**a**) Left ring finger with evidence of a giant capillary, a few elongated tortuous capillaries and a microhaemorrhage. (**b**) Right ring finger with a few enlarged capillaries. Similar changes were evident in other digits

but there was evidence of SSc changes with the occasional giant capillary, some aberrant neovascularisation and the occasional microhaemorrhage (consistent with 'early' SSc changes using the classification proposed by Cutolo et al.) (Fig. 7.1). A diagnosis of limited cutaneous SSc (lcSSc) was made and low dose nifedpine (5 mg daily) was commenced for Raynaud's symptoms (with a view to dose titration depending on tolerability and efficacy) but not tolerated (vasoactive side effects). Amlodipine 2.5 mg daily was better tolerated and increased to 5 mg daily but stopped after it was concluded it had not helped her RP symptomatically. Her RP remained problematic and treatment was commenced with sildenafil 25 mg daily which was better tolerated and effective at reducing Raynaud's symptoms. In December 2018, she attended a routine clinic review and reported more intrusive Raynaud's symptoms. Clinical examination revealed cool peripheries with patchy blanching and areas of dusky cyanosis affecting several digits (Fig. 7.2). A few small telangiectases were now evident on the palmer aspects of the fingers. There was no overt digital ulceration but minor fissuring of the thumb and index finger of the right hand was noted (Fig. 7.2). Cardiopulmonary screening has remained normal. The sildenafil dose was increased to 50 mg daily, with the opportunity to increase the dose to 50 mg twice daily depending on tolerability and efficacy.

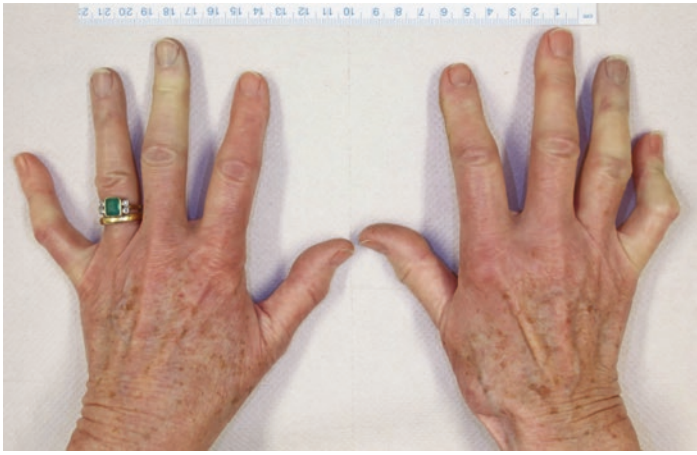

FIGURE 7.2 Appearance of the digits at routine clinic review. Raynaud's is not easily assessed in the clinic setting but the digits may appear cool to touch and there may be visible discolouration of the digits. There is some fissuring of the skin of the right index finger and thumb which reflects impaired digital perfusion

Point for Consideration

The initial presentation included a number of potential 'red flags' to suggest the presence of an underlying autoimmune rheumatic disease including late-onset Raynaud's, gastro-oesophageal reflux symptoms, positive ANA and a history of organ-specific autoimmunity (hypothyroidism). A clinical diagnosis of lcSSc was made based on the distribution of skin involvement and presence of scleroderma-pattern capillaroscopic abnormalities on nailfold microscopy. The patient would have fulfilled classification criteria for early SSc [5] and the preliminary criteria for VEDOSS [6] at presentation. First-line treatment with calcium channel blockers (CCBs) was abandoned due to inefficacy of low-dose therapy and issues around tolerability using higher doses. Despite this, second line treatment with phosphodiesterase V inhibitors (PDEVi) has been better tolerated at low doses and attempts are underway to increase the dose according tolerability and efficacy. The decision to initiate and escalate treatment for SSc-RP is

generally based on patient-reported symptom severity. Clinical findings such as visible digital discolouration, cool peripheries, reduced capillary refill and trophic cutaneous changes suggestive of ischaemic damage (e.g. cutaneous fissuring) should prompt enquiry about Raynaud's symptoms and discussion around treatment escalation. Initiation of vasodilator therapy should start with low doses with the aim of escalating the dose depending on tolerability and efficacy. Unwanted transient vasoactive effects (e.g. headaches) can sometimes be overcome with patient education, gradual up-titration from a starting low dose and reassurance that come adverse effects (such as headaches) have a tendency to disappear with repeated dosing; allowing patients to benefit from effective treatments that might otherwise have been stopped prematurely. The preservation of capillary density on nailfold microscopy ('early' changes) was consistent with the early stage of her disease (5 years since first RP symptoms) but may also have accounted for the absence of more overt digital ischaemic lesions such as digital ulcers and normal cardiopulmonary screening. It is possible proactive management of RP symptoms may modify disease progression in SSc.

Assessment and Management of Scleroderma-Related Raynaud's Phenomenon

RP occurs in virtually all patients with SSc and is an important feature of early disease. RP is not life-threatening but is a significant cause of disease-related morbidity and should be treated with the same care as other disease-specific manifestations of SSc. Patient education and advice on important aspects of self-managment (cold avoidance, core temperature control, smoking cessation etc.) are vital, particularly in the early stages of SSc. Patients become adept at cold avoidance and adopting strategies to prevent and/or ameliorate Raynaud's symptoms which can lead to a reduction in the burden of SSc-RP with advancing disease duration; sometimes despite progression of the microangiopathy of SSc [10].

There are a number of available vasodilator therapies that can be used in the management of SSc-RP. Data from large patient registries indicates clinicians do not fully exploit the therapeutic options available (with respect to treatment initiation and optimising dosing) in the management of SSc-RP [12]. Physician attitudes and prescribing practices for SSc-RP management vary considerably. A fifth of SSc experts in one survey considered treatment for RP unnecessary in around half of their SSc patients [13]; surprising given the very high reported burden of RP symptoms reported in surveys capturing the needs of SSc patients [9]. Physician attitudes towards the importance of intervention may be a contributory factor to the significant variation in prescribing practices for SSc-RP [14]. Despite CCBs being recommended for the management of SSc-RP [13, 15], only approximately half of patients have ever received CCB therapy [16, 17]. Variation in clinical practice is even more marked for prostanoid therapy. Despite also being recommended in the management of SSc-RP [13, 15], prostanoid therapy is subject to marked geographic differences in reimbursement policies with higher use at units in Europe compared with North America [16, 17]. The use of PDEVi was not recommended for the management of SSc-RP in the original EULAR recommendations of 2009 [18]. The findings of a subsequent meta-analysis of PDEVi use in SSc-RP (despite indicating only a modest benefit to PDEVi over placebo [19]) have led to PDEVi forming part of the updated 2017 EULAR recommendations [15]. The positioning of PDEVi in the management of SSc-RP is gradually evolving. Previous consensus best practice guidelines proposed PDEVi therapy for SSc-RP in patients for whom prostanoids were ineffective or not tolerated [20]. Clinical experience gained from using PDEVi for SSc-related pulmonary arterial hypertension, the advantages of oral administration and the falling cost of generic preparations have encouraged the earlier use of PDEVi (increasingly in advance of prostanoid therapies) in SSc-RP. A practical approach to the management of SSc-RP and current positioning of the major classes of vasodilator therapy considered useful in SSc-RP is presented in Fig. 7.3.

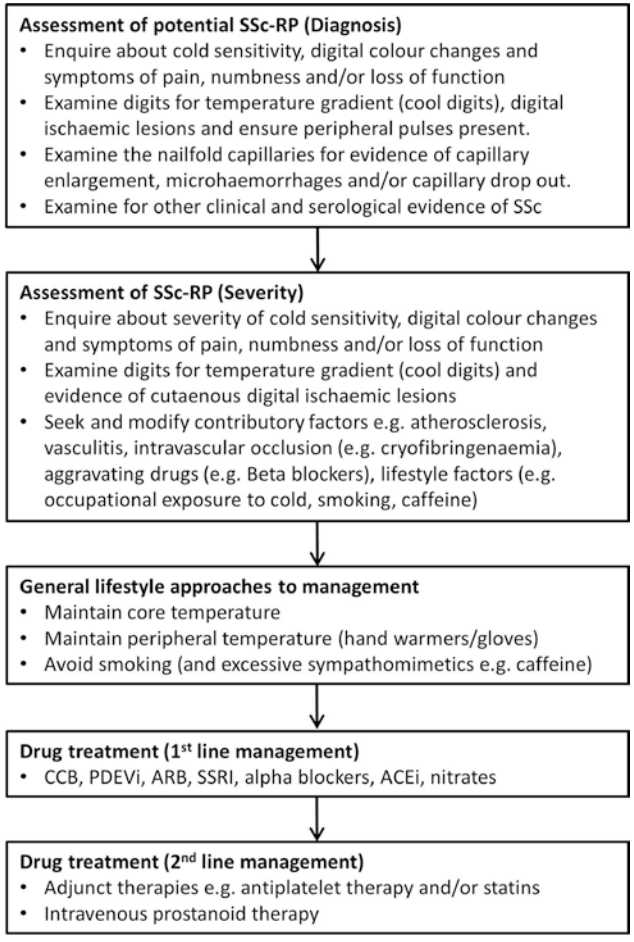

FIGURE 7.3 A practical approach to assessment and management of SSc-RP. Adapted from [20]. The assessment and management of SSc-RP starts with careful assessment for contributory factors and patient education. Medication use includes a range of vasoactive medications to improve digital perfusion by either preventing vasoconstriction or encouraging vasodilation. *SSc-RP*, Systemic sclerosis-related Raynaud's phenomenon; *CCB*, calcium channel blockers; *PDEVi*, phosphodiesterase V inhibitors; *ARB*, angiotensin receptor blocker; *SSRI*, selective serotonin receptor inhibitor; *ACEi*, angiotensin converting enzyme inhibitor

Conclusions

Raynaud's phenomenon occurs in virtually all patients with SSc. RP is typically the earliest clinical manifestation of SSc and the identification of digital vasculopathy (clinically manifest as RP and through objective assessment of abnormal capillary morphology) is an important part of SSc diagnosis. RP is not life-threatening but is a major cause of disease-related morbidity. Clinicians should take a proactive approach to RP management, initiating vasodilator therapy and switching to alternative classes of vasodilators where necessary to establish a regime that is effective for the patient. Careful management of SSc-RP can reduce the impact and burden of digital vasculopathy. It may also modify disease progression in SSc.

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