CASE REPORT

Blue toe syndrome as a first sign of systemic sclerosis

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SUMMARY

We describe an unusual case of blue toe syndrome as the primary and solitary manifestation of systemic sclerosis. The possible cause was long-term occupational exposure in construction work. Blue toe syndrome is a small vessel disease, characterised by the sudden development of painful, blue discolouration in one or more toes. The most common aetiology is atheroembolic disease; however, it can also appear in several conditions ranging from hypercoagulability disorders to underlying systemic diseases such as vasculitis or autoimmune diseases. Here, we describe the case of a 57-year-old man who presented with blue toe syndrome without underlying atheroembolic disease. He was found to have positive anticentromere antibodies, which indicated that systemic sclerosis was the likely primary underlying cause. An extensive systemic evaluation and a thorough physical examination revealed no other symptoms associated with systemic sclerosis. He was prescribed nifedipin and rosuvastatin, and showed complete resolution of symptoms after 3 months.

BACKGROUND

The term 'blue toe syndrome' was initially introduced in 1976; it was described as a sudden onset of acute pain and cyanosis in one or more toes.¹

The syndrome may be defined as a small vessel disease, characterised by the development of blue or violaceous discolouration in one or more toes in the absence of obvious trauma, serious cold-induced injury or disorders that produce generalised cyanosis.² The affected digits are usually painful, and during physical examination the peripheral pulses are characteristically well preserved. When ischaemia becomes pronounced, ulceration, tissue loss, infection and gangrene may develop, which sometimes lead to amputation.

Although a common cause of blue toe syndrome is the embolisation of cholesterol crystals derived from atherosclerotic plaques, it may present as a symptom of several underlying diseases such as hypercoagulability disorders, vasculitis and autoimmune disorders.² Another possibility is systemic sclerosis (SSc), a rare autoimmune disorder of the connective tissue and microvessels. It is characterised by skin fibrosis, vascular abnormalities and alterations in the gastrointestinal tract, lungs, heart and kidneys.^{3,4} Although both genetic and environmental factors have been implicated, the aetiology remains relatively unknown.⁵ A detailed history of the patient revealed that occupational exposure was a possibly causative risk for developing SSc.

CASE PRESENTATION

An otherwise healthy 54-year-old Caucasian man was referred to the emergency department by his primary physician due to the sudden onset of petechiae on both legs.

At initial presentation, the patient had painful, blue discolouration in numerous toes on both feet. His medical history was uneventful and he did not use any medication.

The patient was a social drinker, had a history of cigarette smoking (30 pack-years) and had worked as a construction worker most of his life. Family history was positive for hypercholesterolaemia.

Physical examination of the lower extremities showed small blue, non-blanching spots (approximately 0.5 cm in diameter) on the toes of both feet, which were sporadically painful (figure 1). No purpura or livedo reticularis was found. The peripheral artery pulses were present on both lower extremities. His blood pressure was 107/66 mm Hg and his pulse was 80 beats/min. Results of neurological, cardiac and pulmonary examinations were unremarkable. An examination of the upper extremities was also normal.

Figure 1 Initial presentation. Painful, blue discolouration and ulceration in the toes on both feet.

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Table 1 Autoimmune disease and thrombophilia work-up to investigate the cause of blue toe syndrome

Antinuclear antibodies	Positive
Lupus anticoagulant	Negative
Anticardiolipin antibodies	IgG<10 E/mL; IgM<7 E/mL
MPO antibodies and PR3 antibodies	<5 U/mL
Anti-double-stranded DNA	Negative
Anticentromere antibodies A and B	Strongly positive (+++)
Antibodies to anti-Scl70; anti-RNA polymerase III, anti-fibrillarin; anti-Th/To and anti-Ku	All negative
Anti-CCP antibodies	Negative
Anti-beta2 glycoprotein antibodies	Negative

Routine laboratory investigations included a full blood count and measurement of inflammatory markers, which showed the following: haemoglobin=9.1 mmol/L, erythrocyte sedimentation rate=40 mm in the first hour, thrombocytes= 411×10^9 /L, leucocytes= 12.4×10^9 /L and C reactive protein=40 mg/L.

The urinalysis was normal and the chest X-ray showed no infiltrative abnormalities.

With a primary diagnosis of blue toe syndrome, vascular imaging was performed to rule out embolic occlusion due to atherothrombotic material from proximal arterial sources or cardiac abnormalities such as a myxoma or a patent foramen ovale. Doppler ultrasound and angiography scanning of the lower limbs showed no abnormalities. The ankle/arm indexes of the right and left foot were 1.22 and 1.26 (normal values >0.90), respectively. Ultrasound of the abdomen showed no signs of abdominal aortic aneurysm. Electrocardiography and transoesophageal echocardiography results were normal; they demonstrated normal ventricular volumes and no signs of pulmonary hypertension.

DIFFERENTIAL DIAGNOSIS

Additional laboratory testing was performed to investigate further into the primary cause of blue toe syndrome in this patient. Results of serology for vasculitis and autoimmune diseases are shown in [table 1](#). We found no conditions associated with a hypercoagulable state such as essential thrombocytosis, antiphospholipid syndrome and hyperhomocystinaemia ([table 2](#)).

Testing for systemic autoimmune disease showed positive results for antinuclear antibodies (ANAs) and anticentromere antibodies (ACAs), type A and B. These were mainly detected by immunofluorescence, which showed the typical staining pattern for ACA. Western blot analysis for ACA was positive, further confirming these results. Antibodies against anti-Scl70 were negative. Tests were negative for antibodies against double-stranded DNA and CPP. Antineutrophil cytoplasmic antibodies (ANCA) were absent, and we did not detect cryoglobulinaemia.

These results pointed to a diagnosis of SSc. On presentation, there were no signs of Raynaud's phenomenon, such as vaso-spastic attacks or triphasic colouring of the skin. His hands and

fingers did not reveal abnormalities such as skin thickening (ie, sclerodactyly), ulcers or puffy fingers. No scars, hyperpigmentation or calcinosis of the skin or joints were noted at that time. There were no signs of teleangiectasia.

TREATMENT

The patient was started on rosuvastatin and nifedipine. At 1-week follow-up in the outpatient clinic, there was a moderate improvement of the symptoms.

OUTCOME AND FOLLOW-UP

At 3 months' follow-up, a slow but complete healing of the toes was observed. While the patient remained symptom-free at 6 months' follow-up, at 12 months' follow-up thickened skin and puffy fingers were observed in both hands.

DISCUSSION

The sudden development of the cyanotic lesions in this patient raised the possibility of atherosclerotic or systemic embolic disease. It prompted us to carry out a clinical investigation, which was performed in close collaboration with a vascular surgeon and a cardiologist. Although the patient was a smoker and had a family history of hypercholesterolaemia, we could not find an embolic or atherosclerotic source. Subsequently, we considered a number of medical conditions, including thrombophilia and systemic diseases such as autoimmune diseases and vasculitis, as the primary trigger for the microvascular presentation of disease.

As mentioned above, we identified the presence of ANA and ACA. These findings suggested an autoimmune disease as the underlying cause of the syndrome.

The pathogenesis of SSc remains incompletely understood although immune activation, vascular damage and fibrosis are three factors known to be important in the development of this illness.⁵

With regard to humoral immune activation, numerous antibodies have been associated with SSc, including ACA, which is present in 80%–90% of patients with the type of SSc associated with limited cutaneous involvement. Moreover, anti-Scl70 is almost exclusively found in the diffuse cutaneous type of SSc. Coexistence of ACA and anti-Scl70 in the same patient is rarely found.⁴ It has been reported that patients with SSc may develop ANCA-associated vasculitis.⁶ Our patient showed no signs of a second small vessel disease, such as polyangiitis or a rheumatic overlap syndrome.

These immunological alterations, together with vascular changes, lead to the deposition of increased amounts of structurally normal collagen, causing fibrosis as the final step, which is responsible for a number of clinical manifestations. Our patient, however, did not present with the typical scleroderma of the skin of his fingers or other clinical manifestations at first. According to literature, a small number of patients with SSc marker auto-antibody positivity will present with Raynaud's phenomenon or ulceration without any further signs of skin involvement.^{7,8} This condition, referred to as early SSc, may precede manifestation of symptoms and involvement of internal organs by many years.^{8,9} By performing capillaroscopy, we found abnormal nailfold capillaries suggestive for microvascular disease.

Importantly, vascular involvement characterised by endothelial dysfunction and microvascular disease, in contrast to macrovascular (atherosclerotic) injury, is a principal feature of SSc.¹⁰ The latter diagnosis differs from other disorders such as rheumatoid arthritis or systemic lupus erythematosus (SLE) in which macrovascular disease is well documented. Particularly in the

Table 2 Conditions associated with a hypercoagulable state, which may be related to blue toe syndrome

JAK two mutation	Negative
Homocysteine	11.4 µg/L
Cryoglobulins	Negative
Cold agglutinins	Negative
M-Protein	Negative

early type of SSc, the presence of atherosclerotic disease remains a matter of debate.^{10 11} Taking into account these arguments, we assumed that early SSc was the trigger for the blue toe syndrome in our patient. Although one cannot definitely exclude atherosclerotic lesions, extensive work-up did not show any sign of macrovascular disease. Identifying an early manifestation of SSc might be essential for a more thorough clinical follow-up and early detection of internal organ involvement. Indeed, at 1-year follow-up, our patient developed thickening of the skin and significant swelling of the fingers, the so-called 'puffy fingers'. All findings were included in the revised, 2013 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) SSc classification criteria. Consequently, based on the appearance of the new clinical findings, our patient fulfilled the criteria of having 'definite scleroderma' according to the 2013 ACR/EULAR SSc classification.¹² Given his clinical and laboratory manifestations, we suspected that he has the limited subtype of SSc.

An intriguing aspect of this case remains the occupation of the patient. Although the aetiology of SSc remains relatively unknown, both genetic and environmental factors have been implicated.^{4 5} Based on results from meta-analyses and case-control studies, several exogenous factors such as silica, solvents and epoxy resins have been suggested to play a role in the development of SSc. However, to date, we have only a limited understanding of the link between these exogenous factors and the development of SSc due to the lack of methods for quantitatively assessing environmental exposures or the potential role of gene-environment interactions in this disease.¹³

As a construction worker for many years, our patient was exposed to several substances including silica dust and epoxy resins. In the literature, silica was one of the earliest substances

associated with SSc development. A recent meta-analysis, which included 15 case-control studies and four cohort studies, examined the risk of occupational silica exposure; they found that silica exposure was associated with significant risk for developing SSc, with an overall OR of 2.81 (95% CI 1.86 to 4.23; $P < 0.001$). Moreover, that association was found to be higher in men than in women.¹⁴

Contributors All authors (RN, MW, SG, AD) participated in the preparation of the manuscript and the revised version as well. The literature survey was performed by SG. RN wrote the initial version. RN and AD wrote the final version. MW and AD treated and followed the patient in the outpatient clinic.

Competing interests None declared.

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REFERENCES

- 1 Karmody AM, Powers SR, Monaco VJ, *et al.* "Blue toe" syndrome. An indication for limb salvage surgery. *Arch Surg* 1976;111:1263–8.
- 2 Hirschmann JV, Raugi GJ, Blue RGJ. Blue (or purple) toe syndrome. *J Am Acad Dermatol* 2009;60:1–20. quiz 1–2.
- 3 Bovenzi M, Barbone F, Pisa FE, *et al.* A case-control study of occupational exposures and systemic sclerosis. *Int Arch Occup Environ Health* 2004;77:10–16.
- 4 Allanor Y, Avouac J, Denton CP, *et al.* Systemic sclerosis. In: Bijlsma JWJ, ed. *EULAR textbook on rheumatic diseases*. London: BMJ Group, 2012.
- 5 Smith V, Vanthuyne M, Vander Cruyssen B, *et al.* Over-representation of construction-related occupations in male patients with systemic sclerosis. *Ann Rheum Dis* 2008;67:1448–50.
- 6 Rho YH, Choi SJ, Lee YH, *et al.* Scleroderma associated with ANCA-associated vasculitis. *Rheumatol Int* 2006;26:369–75.
- 7 Galluccio F, Matucci-Cerinic M. Two faces of the same coin: Raynaud phenomenon and digital ulcers in systemic sclerosis. *Autoimmun Rev* 2011;10:241–3.
- 8 Valentini G. Undifferentiated connective tissue disease at risk for systemic sclerosis (SSc) (so far referred to as very early/early SSc or pre-SSc). *Autoimmun Rev* 2015;14:210–3.
- 9 Picillo U, Marcialis MR, Matarazzo A, *et al.* Digital gangrene and anticomplement antibodies without scleroderma. *Br J Rheumatol* 1998;37:1352–3.
- 10 Cannarile F, Valentini V, Mirabelli G, *et al.* Cardiovascular disease in systemic sclerosis. *Ann Transl Med* 2015;3:8.
- 11 Psarras A, Soulaïdopoulos S, Garyfallos A, *et al.* A critical view on cardiovascular risk in systemic sclerosis. *Rheumatol Int* 2017;37:85–95.
- 12 Araújo FC, Camargo CZ, Kayser C. Validation of the ACR/EULAR classification criteria for systemic sclerosis in patients with early scleroderma. *Rheumatol Int* 2017;37:1825–33.
- 13 Mora GF. Systemic sclerosis: environmental factors. *J Rheumatol* 2009;36:2383–96.
- 14 Rubio-Rivas M, Moreno R, Corbella X. Occupational and environmental scleroderma. Systematic review and meta-analysis. *Clin Rheumatol* 2017;36:569–82.

Learning points

- A detailed, multidisciplinary investigation of blue toe syndrome, including vascular and immunological pathways, is required to avoid missing potential surgical or medical causes of large and small vessel disease.
- In the patient described herein, our results suggested that blue toe syndrome was related to an early presentation of systemic sclerosis, possibly associated with his occupation as a construction worker.

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