CONCISE REPORTS

Vasculitis in patients with systemic sclerosis and severe digital ischaemia requiring amputation

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Abstract

***Objectives*—To document the incidence of histological vasculitis in amputation specimens from patients with severe digital ischaemia secondary to systemic sclerosis (SSc), and to look for an association between anticardiolipin (aCL) antibodies and severe digital ischaemia in SSc.**

***Methods*—This was a retrospective review of patients with SSc who underwent amputation for digital ischaemia over a three year period.**

***Results*—Five of nine patients had histological vasculitis, four of whom had aCL antibodies, although these were not present in high titre.**

***Conclusion*—Vasculitis does occur in SSc, at least in that subgroup with severe peripheral ischaemia. These findings could have implications for treatment of this subgroup of patients with SSc.**

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Ischaemia is a predominant manifestation of systemic sclerosis (SSc), and characteristically the digits are most obviously affected. Severely affected patients progress to permanent digital ischaemia and a minority may require amputation.

The characteristic histological finding in involved blood vessels is non-inflammatory intimal thickening and fibrosis: unlike in other connective tissue disorders, an inflammatory component is rarely recognised. However, we report histological vasculitis in several patients with SSc undergoing amputation because of severe digital ischaemia. Because of a possible association between anticardiolipin (aCL) antibodies and arterial and venous disease these antibodies were sought in patients who required amputations.

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Patients and methods

A large number of patients with SSc are referred to The Rheumatic Diseases Centre. We reviewed the case notes and histological findings of all patients fulfilling the American Rheumatism Association Criteria for SSc[1] who had amputation for severe peripheral ischaemia over a three year period (1988–91), with particular reference to disease subtype (diffuse or limited disease, and possibility of an overlap syndrome), severity of peripheral ischaemia and aCL antibody status. When no aCL antibody result was available, then this was assayed either retrospectively on serum stored at −20°C or at the patient's next clinic visit.

Blocks were taken from the skin and soft tissue resection margins of the amputated specimens and sections stained with haematoxylin and eosin and elastic Van Geison for histological examination. Additional blocks were taken from the soft tissues of the digits where appropriate, always from sites remote from necrotic areas.

Antibodies to cardiolipin were analysed using an ELISA technique as previously described.[2] All results were calculated using the same standard sera. The values of the individual isotypes were expressed as IgG and IgM aCL: the upper reference limits were 5 and 3 units respectively.

Results

PATIENTS' CLINICAL CHARACTERISTICS

Nine patients with SSc required amputation during the three year period because of severe peripheral ischaemia. All were female and their median age at the time of the first amputation was 40 years, range 27 to 61 years. All had the limited cutaneous variant of SSc (eight were anticentromere antibody positive) and all had severe disease. Several patients had had amputations before the three year study period and over 30 amputations, mostly of digits, had been performed in this patient group (table).

Three patients had dry eyes and a dry mouth (patients 3, 4 and 9, all anti-Ro and anti-La antibody negative), and patients 3 and 4 had had histologically proven myositis. Patients 3 and 4 had sclerodactyly and nail pitting, and patient 9 had had proximal skin involvement. All three had telangiectasiae and oesophageal involvement, and none had anti-RNP antibodies. Therefore clinically these three patients fulfilled the ARA criteria for SSc and were not felt to have an overlap syndrome: the myositis and symptoms of sicca syndrome were in all cases believed to be a manifestation of the SSc. Patient 7 was unusual as she had a left subclavian artery stenosis which was surgically treated and which may have contributed to left sided digital ischaemia. However, clinically she had limited cutaneous SSc and was anticentromere antibody positive, and both upper limbs showed similar ischaemic features.

Antibodies to the extractable nuclear antigens Ro, La, Sm, RNP and Scl-70 were not present in any of the patients' sera. Four of the

Amputations and aCL antibody status in nine patients with SSc

Patient	Age*		Amputations	ACL antibody titre	
				IgG (n < 5)	IgM (n < 3)
1	27	1984	right index finger	Neg	25†
		1988	right middle finger (V)		
		1989	right little finger		
			left middle finger		
			left ring finger		
2	38	1984	left middle finger	Neg	Neg
		1986	right middle finger		
		1989	right ring finger		
			left middle finger stump		
			left ring finger		
		1990	right lower leg (T)		
			left little finger (T)		
3	58	1989	left index finger (T)	14	Neg
		1990	right index finger		
		1991	right little finger (V)		
			left middle finger**		
4	61	1988	right below knee (T)	Neg	9
			left below knee (V)		
		1990	left above knee**		
5	47	1975	left fifth toe**	N/K	N/K
			right fifth toe**		
		1988	left fourth toe		
			left hallux (V)		
			right second toe (V)		
		1990	right hallux (V)		
			right third toe (V)		
			right fourth toe (V)		
6	40	1980	right index finger	Neg	Neg†
		1988	right ring finger		
			right ring finger stump		
7	39	1972	right index finger**	Neg	Neg
		1987	right third toe**		
		1991	left little finger		
			left ring finger		
			left little finger stump**		
8	28	1988	left second toe	Neg	Neg†
		1990	right fourth toe		
9	57	1990	left index finger (V)	Neg	19
		1991	right middle (T)		

*At time of first amputation
**No histology available
†Blood sample for aCL antibody assay taken more than three months after last amputation.
V = vasculitis; T = thrombosis; N/K = not known.

patients had lymphopenia at the time of the last amputation (lymphocyte count ranging between 1·0 and $1{\cdot}4 \times 10^9$/l) but none had suppression of the total white blood count. One of these patients (patient 3) was on prednisolone.

Only one patient (patient 4, IgM aCL antibody weakly positive) has so far developed clinically evident vasculitis – a florid vasculitic rash of her left thigh (fig 1). This could not be biopsied because of the risk of poor wound healing, but it improved with oral steroids. She was the only one of the eight patients tested for this antibody who was known to be significantly ANCA positive, titre >1/64 (pANCA).

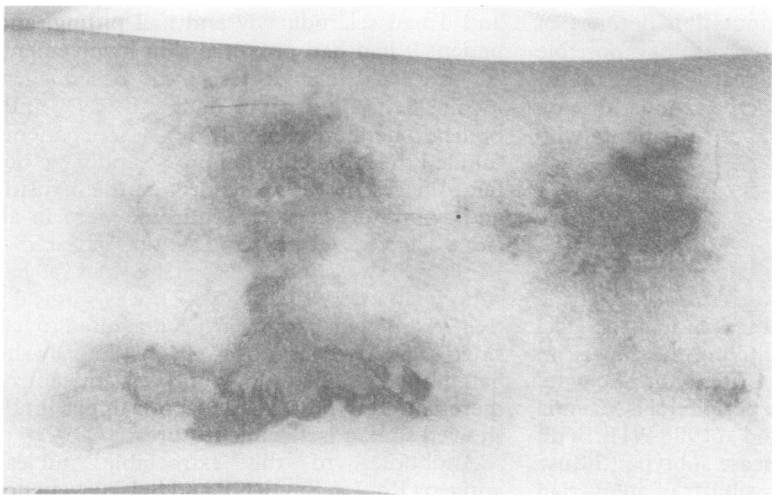

Figure 1 Vasculitic rash of thigh of patient 4 – this responded to oral steroids.

Five of the patients continued to smoke cigarettes against medical advice and two others had stopped smoking around the time of their first amputation. None of the patients were on beta-blockers. One patient was on prednisolone for myositis (patient 3) and two were on stanozolol.

HISTOLOGY

Typical vascular changes of SSc consisting of concentric obliterative intimal thickening due to proliferation and swelling of the endothelial cell, the appearance of collagen and mucoid ground substance in the subendothelial tissue and an intact internal elastic lamina were present in the small arteries of all patients; the dermal microvessels were decreased in number and showed basement membrane thickening. A variety of other morphological changes were, however, also observed in the vessels of these patients. In particular, a vasculitis involving small sized vessels was identified in five of the nine patients (table). Both arteries and veins were involved in three cases, whereas in the other two, the vasculitis was limited to the dermal veins.

In serial sections the inflammatory infiltrate was focal, mononuclear and associated with medial oedema and endothelial swelling (fig 2). A leucocytoclastic vasculitis was observed in one patient (patient 3). The vasculitic process was generally mild, but there was disruption of the connective tissue framework of the vessel wall with oedema and an increase in collagen. The changes were more pronounced in the arterial lesions, where there was discontinuity and disorganisation of the internal elastic lamina.

Arterial thrombosis was present in four patients (table), showing organisation in two, whilst the other two had recanalised (fig 3). Recanalisation was also observed within the media in two arteries occluded by intimal fibrosis (patients 3 and 4).

A 'Masson' type lesion comprising irregular narrow collagen cores covered by hypertrophic endothelial cells projecting into the lumen or crossing the vessel completely was seen in the dermal veins in three patients (patients 3, 4 and 5).

ACL ANTIBODIES

ACL antibodies were detected in four patients; all had histological vasculitis. The fifth patient shown to have vasculitis has since died and whether she had aCL antibodies is unknown. Three of the four patients with histological thrombosis had aCL antibodies. In three of the four patients with aCL antibodies these were of the IgM isotype (table).

Because this was a retrospective study, aCL antibodies were not always assayed at the time of admission for amputation. ACL antibodies were assayed within three months of amputation in five patients, and 15 months, two

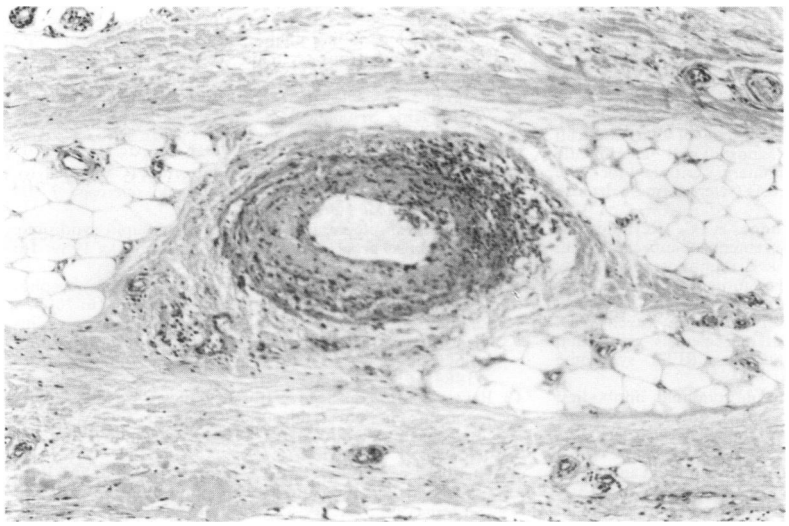

Figure 2 Focal chronic inflammatory cell infiltrate of an arterial wall (haematoxylin and eosin stain, magnification ×400).

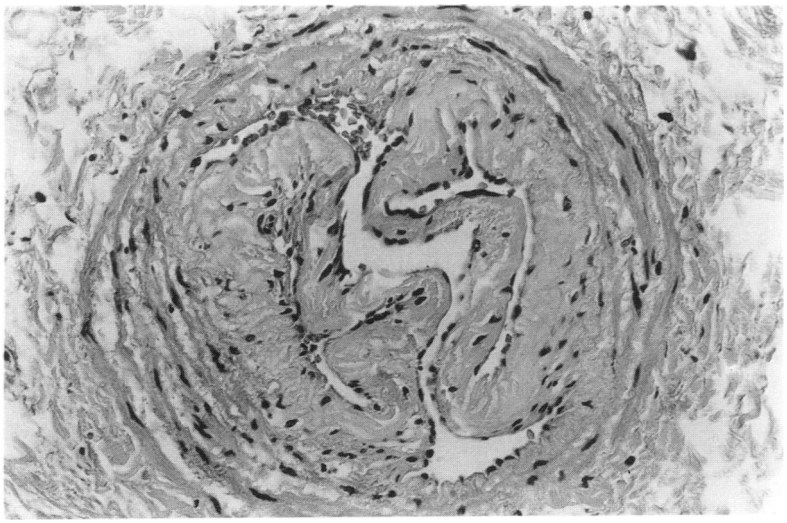

Figure 3 An artery with a recanalised organised thrombus (haematoxylin and eosin stain, magnification ×1000).

years and three years later in the three other patients.

Discussion

Our observations suggest that vasculitis does occur in SSc, and that at least in the subgroup with severe digital ischaemia vasculitis occurs histologically when not apparent clinically. Previously it has been thought that vasculitis is a rare finding in SSc, and that when it does occur this is usually in association with the CREST variant and features of Sjögren's syndrome.[3]

We have also found that a proportion of patients with severe peripheral ischaemia have aCL antibodies (four of the eight patients tested), and in our experience these were always associated with at least one amputation specimen showing vasculitis. These patients had levels of aCL antibodies outside the reference range for normal healthy controls, but did not have the very high levels found in acute arterial and venous thrombotic states sometimes associated with SLE or a primary antiphospholipid syndrome (in our laboratory such patients would typically have aCL IgG levels in excess of 50 units/ml). Three of the four patients with aCL antibodies had evidence of thrombosis histologically, but not in association with vasculitis in individual biopsies. Admittedly patient numbers are small and vasculitis was not a consistent finding in every amputation specimen from patients with aCL antibodies, but SSc is a rare disease and only a very small minority of affected patients require amputation. We therefore feel that our findings in this rare group of patients are important. By requiring amputation these patients provided a unique opportunity for histological examination.

ACL antibodies have now been reported in a wide variety of disorders, including SSc.[4] The proportion of SSc patients found to have aCL antibodies varies greatly between studies,[5-9] and the well recognised interlaboratory variability in aCL methodology will have contributed to these differences. Whether occlusive vascular disease associated with antiphospholipid antibodies is primarily due to thrombosis or vasculitis had been debated,[10] but not specifically in patients with SSc. A small number of patients with vasculitis in association with antiphospholipid antibodies have been reported.[11-14]

It is recognised that various infective and inflammatory states are associated with rises in aCL antibodies[4] which may be transient. Similarly in our patients low grade inflammation, such as we have demonstrated histologically, appears to be associated with aCL antibodies. What is unclear at present is whether the vasculitis leads to the formation of aCL antibodies, or whether low levels of these antibodies can, in the long term, predispose to the chronic vascular problems present in this patient group. Perhaps a combination of both factors occurs. It may well be that these aCL antibodies are not pathogenic, but a marker of vascular events occurring in patients with SSc. A prospective study is required to clarify the relationship between systemic sclerosis, vasculitis, thrombosis, and aCL antibodies. If a definite association is shown, then the demonstration of aCL antibodies may indicate prophylaxis with long term low dose aspirin as in coagulopathies associated with other aCL syndromes.

The most important finding from our study, however, is that inflammatory change does occur in the blood vessels of a significant proportion of SSc digits that are so ischaemic that they require amputation. Evidence for vasculitis should be carefully looked for in this patient group. Perhaps in patients with SSc at risk of severe digital ischaemia immunosuppressant treatment to suppress this inflammation may be justified, in an attempt to minimise digit loss. However, caution is indicated because of the potential toxicity of these drugs, and of particular concern is that steroid therapy may, in some instances, be associated with worsening of vasculitis.[15] Unfortunately, the small number of SSc patients with peripheral ischaemia so severe as

to need amputation means that controlled clinical trials concerned with this issue are unlikely to be mounted.

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