Ulnar Artery Involvement in Systemic Sclerosis (Scleroderma)

MARIAN H. TAYLOR, JOHN A. McFADDEN, MARCY B. BOLSTER, and RICHARD M. SILVER

ABSTRACT. ***Objective.*** Microvascular disease is one of the hallmarks of systemic sclerosis (SSc, scleroderma), but macrovascular involvement also exists in some patients. Patients with SSc may have severe Raynaud's phenomenon (RP) characterized by refractory digital ulcerations. We investigated if large artery involvement, that is, ulnar artery occlusion, has a role in the development of refractory digital ulcerations, and if both screening for this involvement and revascularization of the ulnar artery occlusive disease may improve digital ulcer healing.

Methods. A retrospective chart review was performed of 15 patients with SSc, all of whom had severe RP and digital ulceration, together with a positive Allen test and ulnar artery occlusive disease documented by angiography.

Results. Women outnumbered men 2:1, with limited disease predominating (7), 5 patients having diffuse cutaneous disease and 3 overlap syndromes. All patients had positive antinuclear antibody and capillary microscopy findings consistent with SSc. Antiphospholipid antibodies were present in 4 of 6 patients tested. Tobacco use was seen in 5 patients, only 2 of whom were current smokers. All patients failed conventional medical therapy (nitrates, calcium channel blockers, antiplatelet agents) for RP and digital ulceration. Only 1/8 patients improved with stellate ganglion block, and one patient had no improvement following digital sympathectomy. Eight patients underwent ulnar artery revascularization combined with digital sympathectomy, and 8 experienced dramatic improvement in RP and healing of digital ulcers.

Conclusion. An Allen test should be performed routinely on all SSc patients with severe RP and refractory digital ulceration to investigate the possibility of ulnar artery occlusive disease. If suspected ulnar artery occlusion is confirmed by angiography or ultrasonography, ulnar artery revascularization with or without digital sympathectomy should be considered in patients who fail conventional medical therapy. (J Rheumatol 2002;29:102–6)

Key Indexing Terms:
SYSTEMIC SCLEROSIS RAYNAUD'S PHENOMENON VASCULAR DISEASE

Systemic sclerosis (scleroderma, SSc) is a disease of unknown etiology characterized by tissue fibrosis and microvascular abnormalities. Raynaud's phenomenon (RP) and digital ulceration are common examples of microvascular disease. Both structural and functional alterations are thought to contribute to the vasculopathy of SSc. Pathologic specimens reveal marked intimal hyperplasia and adventitial fibrosis in digital arteries, as well as in the arteries and small arterioles of internal organs, and the latter may be extensive enough to account for visceral RP[1-3]. Histopathology of surgical specimens from patients with SSc suggests that the vasculopathy is not atherosclerotic[4,5]. Biopsy specimens and autopsy studies have revealed a spectrum of changes ranging from vacuolization and destruction of capillary endothelial cells to severe intimal hyperplasia and fibrosis of digital arteries[6]. Functional alterations are important as well in the pathophysiology of microvascular disease and include cellular mediators that play a role in vasospasm. Enhanced expression of adhesion molecules on endothelial cells, platelet activation, sympathetic hyperactivity, and influence of vasoactive molecules such as endothelin and nitric oxide are some of the proposed functional alterations contributing to RP in patients with SSc[7,8].

Macrovascular disease and its role in the morbidity of SSc has been less well studied. Case reports have described SSc patients with large vessel involvement including anterior tibial, superficial femoral, and ulnar arteries[4,5]. Serologic studies of SSc patients with large vessel disease have revealed associations with antiphospholipid antibodies, anticentromere antibodies, and antiendothelial cell antibodies[4,9,10]. Large vessel involvement may lead to the need for extremity amputation, and an association has been shown between the presence of antiphospholipid antibodies and large vessel disease requiring amputation[9]. An increased prevalence of macrovascular

From the Department of Medicine, Division of Rheumatology and Immunology, and the Department of Orthopaedic Surgery, Medical University of South Carolina, Charleston, South Carolina, USA.

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M.H. Taylor, MD, Clinical Fellow; M.B. Bolster, MD, Assistant Professor of Medicine; R.M. Silver, MD, Professor of Medicine and Pediatrics, Department of Medicine, Division of Rheumatology and Immunology; J.A. McFadden, MD, Assistant Professor of Surgery and Orthopaedic Surgery.

Address reprint requests to Dr. M.H. Taylor, Department of Medicine, Division of Rheumatology and Immunology, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite 912, PO Box 250623, Charleston, South Carolina 29425.

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disease, particularly in patients with CREST syndrome, with anticentromere antibody has also been reported[4]. Severe digital ischemia and pulmonary hypertension have been associated with increased antiendothelial cell antibodies in patients with diffuse cutaneous SSc[10].

A large number of patients have been referred to our institution with severe RP and refractory digital ulcerations. We used the Allen test as a screening tool to identify patients with large vessel arterial disease that might be amenable to surgical revascularization to enhance the potential for digital ulcer healing[14].

MATERIALS AND METHODS

This study presents a retrospective analysis of 15 patients meeting American College of Rheumatology (ACR, formerly American Rheumatism Association) criteria for SSc[13] seen in the outpatient rheumatology clinic at MUSC between 1989 and 1998, where about 450 scleroderma patients are seen annually. The Allen test evaluates arterial flow to the hand. It is performed by asking patients to repeatedly clench the fist as tightly as possible while the physician firmly compresses the radial and ulnar arteries at the wrist. The patient's fingers are then extended and relaxed, avoiding hyperextension that can cause a false-positive test. The hand appears bloodless while the 2 arteries are compressed. The examiner then releases compression over one artery and blood flow, evidenced by return of pink coloration to the hand, is evaluated. Return of color is normally complete in less than 5 seconds. The maneuver is then repeated with the opposite artery. A positive Allen test is said to occur when color does not return to the hand after 5 seconds after release of either artery[14]. All 15 patients were selected for the presence of refractory digital ulceration and abnormal Allen tests on physical examination. Patients unresponsive to medical therapy for RP underwent upper extremity arteriograms to evaluate the extent of vessel involvement. Arteriography was preferred over ultrasonography by the hand surgeon because visualization of the vasculature was needed to assess the potential for revascularization. Arteriography was performed via the right femoral artery using a single wall technique. A pigtail catheter was placed in the ascending aorta and a frontal arteriogram was performed. An H1 catheter was then exchanged for the pigtail catheter, and bilateral upper extremity arteriograms were performed via the subclavian arteries. Vasodilatory agents, tolazoline or nitroglycerin, were injected during the procedure to aid visualization of the vessels. An ulnar artery specimen from one patient with SSc was obtained during ulnar revascularization to examine histopathology. The artery was examined longitudinally and in cross section.

RESULTS

Clinical characteristics of the patient population, including atherosclerotic risk factors, are shown in Table 1. There were 10 patients with limited cutaneous SSc — 3 had overlap syndromes with systemic lupus erythematosus (SLE) or myositis, and 5 had diffuse cutaneous SSc. All patients had a positive antinuclear antibody (ANA) titer > 1:640, with anticentromere pattern being most common. Four patients with diffuse cutaneous disease were Scl-70 positive, and no patient had SSc renal crisis. No patient was being treated with immunosuppressive therapy. Two patients had a history of prednisone use; one was treated for myositis and one for lupus symptoms. Fasting lipids were normal in 3 patients tested. One patient had systolic hypertension and 5 of the 15 patients had a history of tobacco use.

Because the 15 patients with ulnar artery involvement did not improve significantly with conservative measures, including behavioral modification and multiple medical therapies, and because Raynaud's phenomenon and digital ulcers requiring antibiotic therapy continued, arteriography and surgical intervention were undertaken. Ulnar occlusion was documented by arteriography in all 15 patients. Nine patients had bilateral ulnar artery occlusion. Ten had incomplete filling of the superficial palmar arch, and 4 had interruption of the deep palmar arch. Digital artery disease was seen in all patients. Eight of the 15 patients underwent revascularization procedures; 4 had bilateral ulnar artery revascularization. Two patients were deemed to have distal microvascular disease too severe for revascularization. Periarterial sympathectomy was performed on 2 patients without revascularization due to severe distal disease. Three patients deferred surgery, wishing to continue medical therapy. Figure 1 shows a representative bilateral upper extremity arteriogram with occlusion of the right ulnar artery.

Table 1. Clinical characteristics of SSc patients with ulnar artery occlusive disease.

Characteristics	N (number tested)
RP/digital ulcers	15
SSc	
Diffuse	5
Limited	7
Overlap	3
ANA+	
Centromere	9
Nucleolar	3
Speckled	2
Smooth	1
Scl-70+	4 (10)
aPL/LAC+	4 (6)
Cardiovascular risk factors	
Tobacco use	5 (15)
Systolic hypertension	1 (15)
Fasting lipids (normal)	3 (3)

RP: Raynaud's phenomenon, ANA: antinuclear antibody, aPL: Antiphospholipid antibody, LAC: lupus anticoagulant, Scl-70: Antiscleroderma antibody.

Reversed saphenous vein grafts were used for revascularization predominately with tie-ins to the superficial palmar arch. Healing of ulcers and improvement in severity of Raynaud's phenomenon attacks were achieved. The patient who reported no improvement in symptoms had postoperative complications during the healing process. Three-year followup is available for the earliest cases.

Microscopic examination of the ulnar artery specimen revealed fibrosis of the intima (Figure 2A). Verhoeff-van Gieson (VVG) connective tissue staining revealed intimal proliferation that was described as chronic (Figure 2B). A thinner, more internal layer of connective tissue containing collagen and some degree of smooth muscle was present, lined by the final thin layer of endothelium. The muscular wall

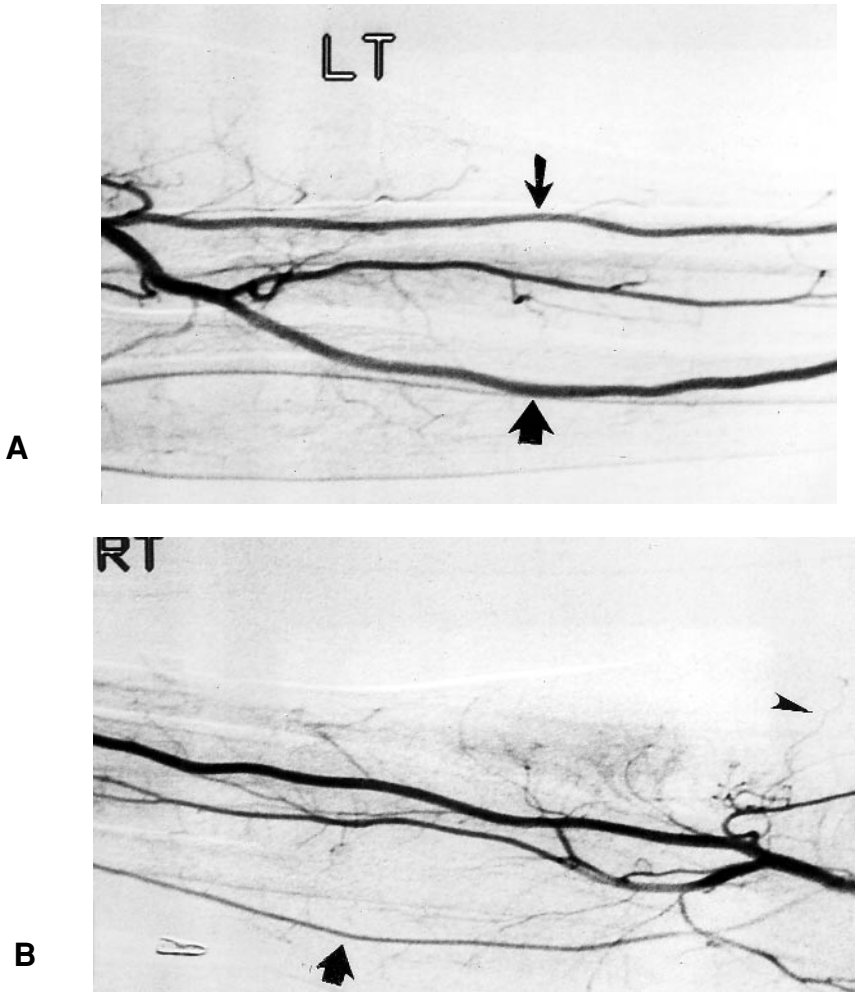

Figure 1. The patient is a 51-year-old white male with diffuse cutaneous SSc and a history of tobacco use (none currently). A. Arteriogram of the left upper extremity shows widely patent radial (thin arrow) and ulnar (thick arrow) arteries. B. Arteriogram of the right upper extremity reveals thinning and eventual occlusion of the ulnar artery (thick arrow). Proximal right upper extremity is labeled (arrowhead).

was perhaps slightly hypertrophied but structurally normal. The adventitia was normal. Amyloid stain was negative. Pathology of the ulnar artery specimen showed intimal fibrosis and narrowing of the lumen consistent with the histological changes seen in microvascular disease and concurred with the Doppler ultrasound findings described by Stafford and colleagues[12].

DISCUSSION

Our data support the presence of ulnar artery occlusion as an under-recognized phenomenon in SSc, and we believe that ulnar occlusive disease may contribute significantly to refractory digital ulceration. The Allen test is a screening tool for possible underlying ulnar artery disease. Patients with both limited and diffuse cutaneous SSc were found to be affected.

Atherosclerotic risk factors in our patients included tobacco use; 2 patients were current smokers. Hypertension was less common. Unfortunately, homocysteine, blood sugar, and antiphospholipid antibodies were not checked in all patients. Although initially negative, antiphospholipid antibody titers subsequently became positive in one patient. Hypercoagulable

Table 2. Therapy in SSc patients with ulnar artery occlusive disease.

Medication	N
Calcium channel blockers	13
NTG paste	14
Aspirin	12
Dipyridamole	9
Pentoxifylline	6
Prednisone	2
Coumadin	2
Ticlopidine HCl	1
Heparin	1
Interventional	
Stellate ganglion blocks	8
Digital sympathectomy	2

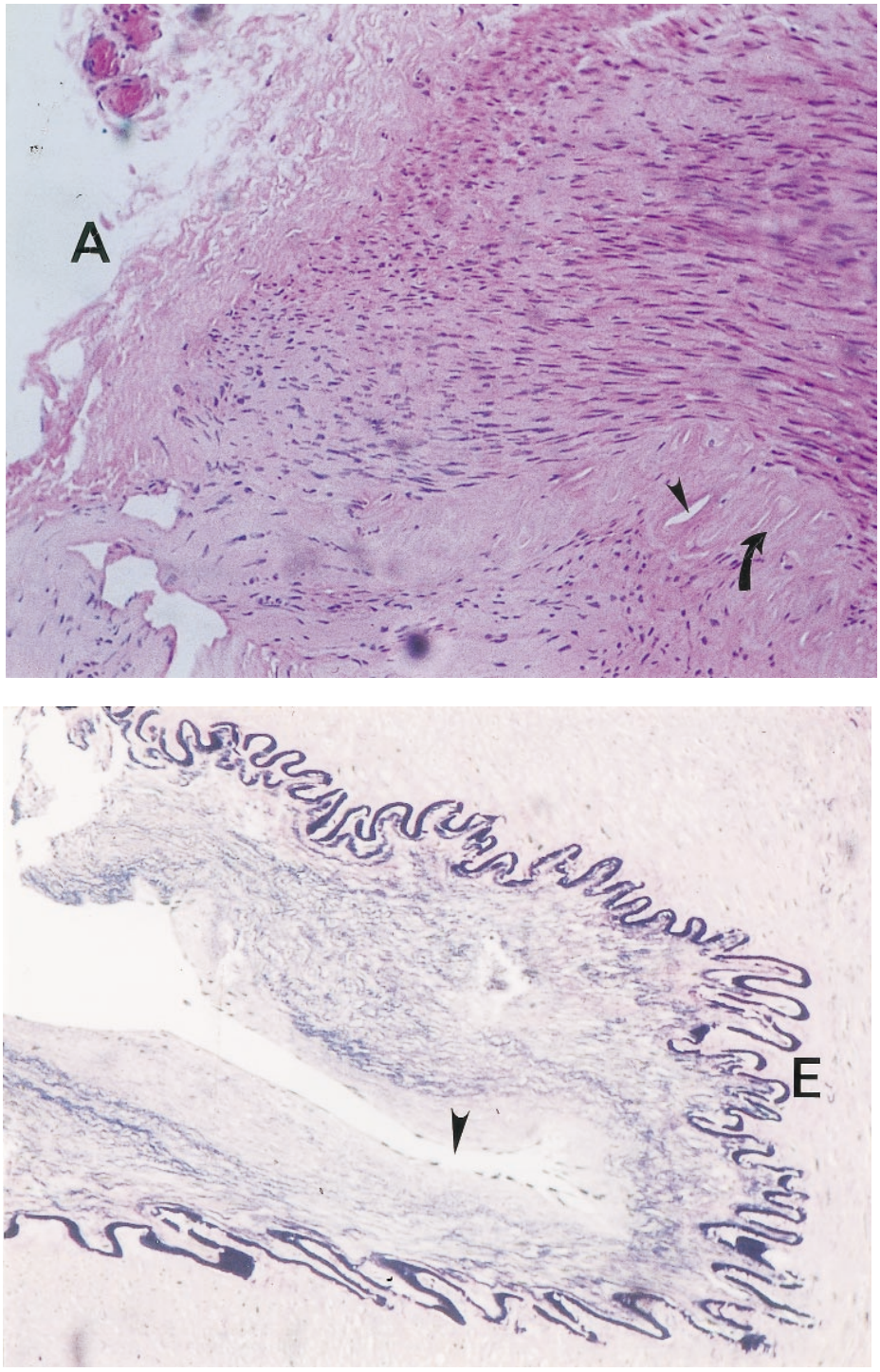

Figure 2. The patient is a 63-year-old white female with limited cutaneous SSc: ulnar artery segment excised at the time of the revascularization procedure. A. Cross section of ulnar artery reveals marked intimal thickening/fibrosis (arrow) resulting in a very small lumen (arrowhead). The muscularis is slightly hypertrophied but strictly normal. The adventitia (A) is normal (H&E stain). B. Longitudinal section of ulnar artery shows intimal proliferation and disruption of the elastic membrane (E). Again the narrowed lumen is notable (arrowhead) (Verhoeff-van Gieson stain).

testing was not performed in each patient; the extent to which hypercoagulability contributed to disease requires further examination.

Both medical and surgical approaches to management were utilized. We stressed cessation of smoking and conservative measures to maintain core body warmth including use of

mittens and layered clothing. Pharmacotherapy involved a minimum of 3 agents; many patients were prescribed 5 or 6 medications (Table 2). Aspirin, calcium channel blockers, and nitroglycerin paste were most commonly prescribed. Surgical treatment included stellate ganglion blocks performed at the discretion of the hand surgeon in 9 patients; 3 patients experienced temporary relief of symptoms. Digital sympathectomy in 2 patients did not result in healing of digital ulcerations.

Clinical evidence for large vessel disease in SSc has been described by Veale and colleagues, who found intermittent lower extremity claudication occurring more frequently in patients with SSc compared with healthy controls[11]. In 1998, Stafford and colleagues used Doppler ultrasound to compare the large vessels in the extremities, neck, and abdomen in 20 scleroderma patients and 20 controls (patients with rheumatic diseases excluding SLE and vasculitis)[12]. Arteries were assessed quantitatively using a body surface area adjusted measurement of intraluminal diameter, as well as qualitatively, by describing characteristics of the vessel walls. A significant increase in the prevalence of ulnar artery stenosis in patients with SSc was found, with smoothly thickened vessel walls compared to the control group[12]. Their ultrasound findings correspond to the histopathologic findings described by Youssef and colleagues[5].

Strikingly, ulnar revascularization resulted in healing of digital ulcers and improvement of Raynaud's phenomenon in all but one case. Although 3 year followup is available for the early cases, it is still too early to determine the longterm success of ulnar revascularization in this subset of SSc patients. Of the patients who underwent revascularization, 2 have died — both from causes unrelated to their scleroderma, and 3 have been lost to followup. One patient who underwent bilateral ulnar artery revascularization has experienced recurrence of digital ulcers on one hand, although to a much lesser extent than previously. We believe, however, that an Allen test should be performed on SSc patients who have Raynaud's phenomenon with refractory digital ulcerations. The presence of an abnormal Allen test in such patients is an indication for visualization of upper limb arteries by either arteriography or ultrasonography. If ulnar artery occlusion is found, then ulnar revascularization should be considered. It is unknown how many SSc patients with poorly healing digital ulcerations and normal Allen tests have angiographic abnormalities and might benefit from surgical revascularization.

It is notable that patients with SSc develop ulnar artery occlusion when only rare occlusions have been reported in other large vessels. If intimal fibrosis or hyperplasia is the culprit, it is of interest why ulnar arteries are affected symptomatically at a higher rate than other arteries. One possible explanation relates to the phenomenon of intimal hyperplasia as it occurs in response to increased arterial pressure secondary to downstream small vessel occlusion or spasm, similar to the phenomenon seen in pulmonary hypertension. A study of radial artery characteristics in patients with SSc compared to normal patients found the internal diameter significantly decreased, with resultant decreased circumferential wall stress, perhaps favoring a downstream occlusive mechanism in patients with SSc and Raynaud's phenomenon[15]. A hypercoagulable process could be responsible for ulnar artery occlusive disease, but pathological specimens, although few, do not suggest that clotting mechanisms are at work. These questions will hopefully be elucidated as pathological specimens are examined and the etiology of ulnar artery occlusion is revealed.

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