

Systemic Sclerosis, Transient Neurological Symptoms, and Macrovascular Disease

Marc R. Fournier, Brian J. Schmidt, David B. Robinson

Can. J. Neurol. Sci. 2010; 37: 121-124

Systemic sclerosis (scleroderma) is a chronic autoimmune disorder of unknown etiology, characterized by sclerotic skin and /or multisystem internal organ involvement. Severe secondary Raynaud's phenomenon due to vasospasm and intimal proliferation in small vessels frequently leads to digital ulceration and ischemia. Internal organ manifestations variably involve the gastrointestinal, renal, cardiac, and pulmonary systems.

Neurological symptoms are uncommon but include myopathy, cranial neuropathies, peripheral neuropathy and, rarely, myelopathy^{1,2}. Cerebrovascular symptoms are particularly rare and usually attributed to complications of renal or cardiopulmonary disease². We describe a patient with systemic sclerosis who presented with cerebral and ocular ischemic symptoms and occlusive disease involving multiple large vessels at the base of the neck.

CASE REPORT

During the course of an eighteen month period, a 46-year-old woman experienced three identical episodes consisting of

sudden “graying-out” of vision in the left eye, lasting three to five minutes, with complete recovery from each episode and no other associated neurological symptoms. There was no history of headache nor migrainous visual phenomena. Two days after the third episode of visual disturbance, while sitting, she experienced left upper limb weakness lasting several minutes that prompted her to present to the emergency room. She did not notice face or lower limb weakness with the episode. She denied being able to provoke neurological symptoms in response to left upper limb exercise and had no history of left upper limb pain or claudication. Her medical history included diffuse cutaneous systemic sclerosis diagnosed at age 30 associated with pulmonary fibrosis, advanced skin changes, sclerodactyly, digital ischemia and resorption, and dysphagia secondary to esophageal dysfunction. Medications included aspirin 81 mg and losartan for digital ischemia, and mycophenolate mofetil for interstitial lung disease with previous intolerance of cyclophosphamide and azathioprine. She never smoked and had no history of hypertension, elevated lipids, or heart disease. Family history was unremarkable for cerebrovascular and cardiovascular



Figure 1: A: Digital subtraction angiogram showing occlusion of the left subclavian artery (short arrow) and approximately 50% stenosis of the origin of the left common carotid artery (long arrow). Later films B and C show filling of the left axillary artery (short arrow in C) via retrograde flow in the left vertebral artery (long arrow in C).

From the Department of Internal Medicine, Sections of General Internal Medicine (MRF), Neurology (BJS), Rheumatology (DBR), University of Manitoba, Winnipeg, Manitoba, Canada.

RECEIVED JUNE 8, 2009. FINAL REVISIONS SUBMITTED JULY 27, 2009.

Correspondence to: Brian J Schmidt, Room F-543, Section of Neurology, Department of Internal Medicine, Faculty of Medicine, University of Manitoba, 820 Sherbrook Street, Winnipeg Manitoba R3A 1R9, Canada.



Figure 2: Digital subtraction angiogram time series A through D. Selective injection of the right vertebral artery (A) results in filling of the left axillary artery via retrograde flow from the left vertebral artery.

disease apart from her father having a myocardial infarction at 60 years of age.

On examination, severe sclerodermal involvement of the face and all four limbs, as well as contractures and ischemia of the digits, was noted. Mental status and language function was normal. The blood pressure was 170/90 mm Hg in the right upper limb and 130/70 mm Hg on the left. Bilateral cervical bruits originated at the base of the neck and radiated to the angle of the mandible. Bruits were also detected over both supraclavicular fossae. Heart sounds were normal. Visual acuity was 20/20 bilaterally, visual fields were intact on confrontation, and fundoscopic examination was normal. Apart from face and limb movement limitations secondary to scleroderma-related contractures, the remainder of the cranial nerve and general neurological examination was intact.

Computed tomography of the brain was normal. A computed tomographic angiogram showed occlusion of the left subclavian artery, 50% narrowing at the origin of the left common carotid artery, and patent internal carotid, vertebral and intracranial arteries. Magnetic resonance imaging of the brain, including diffusion-weighted images, revealed no abnormalities. A digital subtraction catheter angiogram confirmed left subclavian artery occlusion (Figure 1) and 50% stenosis at the origin of the left common carotid artery. Also demonstrated was filling of left axillary artery via retrograde flow from the left vertebral artery (Figure 2). The distal segments of the left and right common carotid arteries showed irregular caliber without significant stenosis. The proximal cervical segments of both internal carotid arteries were abnormally straight but without stenosis. The right brachiocephalic and subclavian arteries were normal, but there was irregular caliber of the right axillary artery without stenosis. Mild stenosis of the origin of the right vertebral artery was present. Intracranial vessels were normal. Pertinent laboratory investigations included the following: erythrocyte sedimentation rate 87mm/hr, C-reactive protein 42.2mg/L, anti-nuclear antibodies 1:1280, and anti-DNA antibodies 17 (normal 0-34). Antibodies to extractable nuclear antigens were negative with the exception of a "strongly positive" Scl-70 antibody level, consistent with a diagnosis of scleroderma. Molecular testing for the factor V Leiden mutation and prothrombin G20210A were

negative as was the lupus inhibitor test. The homocysteine level was 16 $\mu\text{mol/L}$. Serum total cholesterol was mildly elevated cholesterol at 5.76 mmol/L. A 12-lead electrocardiogram was normal and a transthoracic echocardiography revealed no abnormality suggestive of embolic phenomena. Upon hospitalization, she was started on clopidogrel, continued on the previously prescribed mycophenolate mofetil, and has remained free of further neurological or visual symptoms for the past 14 months (up to the time of preparing this report).

DISCUSSION

Small and medium size vessel pathology is a well-established component of systemic sclerosis and underlies classical features of the condition such as Raynaud's phenomenon and digital ischemia. However, the present case illustrates that, although rare, patients with systemic sclerosis can also develop severe stenotic disease involving large vessels originating in the root of the neck. Alusik et al described a 39-year-old woman with asymptomatic left subclavian artery occlusion³. Das et al reported a 19-year-old woman with bilateral carotid stenosis and bilateral cerebral hemispheric infarcts⁴. Merino et al described a 48-year-old woman with systemic scleroderma who developed right hemiplegia associated with segmental stenosis of the left common carotid artery; she also had right subclavian artery stenosis⁵.

Three patients with scleroderma and Takayasu arteritis have been reported⁶⁻⁸. The diagnosis of Takayasu arteritis is based on clinical, not pathological, criteria set by the American College of Rheumatology, of which a minimum of three of the six criteria must be present⁹. Thus, our patient might be considered to have Takayasu arteritis, as she meets three of the criteria (bruits over the subclavian arteries, arteriographic evidence of narrowing and occlusion of large primary branches of the aorta, and brachial artery blood pressure difference >10 mmHg between arms). However, the pathological mechanism of her macrovascular disease is unknown, and may or may not be similar to pathology reported in patients with Takayasu arteritis; therefore we have not committed to the label "Takayasu arteritis". Regardless of whether or not one considers our patient to have Takayasu

arteritis, her treatment with mycophenolate mofetil for systemic sclerosis is also appropriate for Takayasu arteritis¹⁰.

Carotid duplex scanning of patients with systemic sclerosis showed an increased prevalence of carotid artery disease compared with control subjects (64% vs. 35%)¹¹, and a significant reduction in the elastic properties of the artery¹². Another study showed that the carotid artery intima is thicker in patients with systemic sclerosis compared to healthy controls¹³. However, to date, no studies have demonstrated an increased prevalence of stroke in patients with systemic sclerosis.

Cases of scleroderma and macrovascular disease outside the cervico-cranial distribution have been reported, with and without thrombosis. These cases have involved renal^{5,14}, external iliac³, femoral¹⁵, popliteal^{16,17}, anterior tibial¹⁵, posterior tibial¹⁸, and mesenteric arteries¹⁶. Among 31 patients with limited scleroderma for at least five years, Youssef et al reported a prevalence of peripheral vascular disease of 58% compared to 9.6% in 31 matched control subjects¹⁹. In another study, intermittent claudication of the calf was more prevalent in patients with scleroderma compared to the general population (22% vs. 4.5%)²⁰. Ulnar arteries may be particularly vulnerable to occlusive disease in patients with scleroderma²¹.

Histological analysis of an ulnar artery resected from a patient with systemic sclerosis showed luminal narrowing and occlusion by acellular material as well as fragmentation of the internal elastic lamina¹⁵. The posterior tibial artery from another patient showed similar changes including intimal thickening and prominent transmural inflammatory infiltrate of lymphocytes¹⁹. These findings suggest a mechanism other than atherosclerosis. Marked intimal hyperplasia has also been found in posterior tibial¹⁷ and renal arteries^{5,14}.

Lee and Haynes reported a 43-year-old patient with scleroderma who died one month after a cerebral infarct²². Postmortem examination of the stenotic carotid artery demonstrated thickening by fibrous proliferation without cellular infiltration in the wall of the artery. However, inflammatory changes were seen in the vasa vasorum and connective tissue surrounding the carotid and proximal middle cerebral arteries leading to the authors to suggest that an arteritis was present. Other reports of patients with scleroderma and intracranial vascular disease have also attributed the pathology to "arteritis" and/or an autoimmune pathogenesis, although the involved vessels in these cases were not examined histologically²³⁻²⁶. On the other hand, a recent review of the vascular pathology in scleroderma suggests that although mild vasculitic changes are sometimes observed, and there is a role for the immune system, the pathology "is not necessarily inflammatory" in nature²⁷. Additional factors may include a pro-thrombotic state that predisposes patients with systemic sclerosis to thrombus formation^{16,28}.

With respect to the present case, the precise mechanism of her episodes of transient left monocular blindness, and the episode of left upper limb weakness is unknown. Although reverse flow from the left vertebral artery supplied the axillary artery distal to the subclavian occlusion, our patient's symptoms are not likely a direct consequence of a subclavian steal phenomenon. Patients with subclavian or innominate artery occlusive disease and episodes of transient visual disturbance have been described²⁹⁻³². However, these cases feature a more definable mechanism such as transient monocular blindness of the right eye related to

stenosis of the right carotid artery combined with left subclavian occlusion³⁰, or a steal syndrome from the right carotid artery in the presence of innominate artery occlusion^{29,31}, or a visual field deficit related to occipital ischemia³² which might be misinterpreted as a monocular vision problem. Given that our patient had only 50% stenosis of the origin of the left common carotid and no significant stenosis of the left internal carotid or right carotid systems, her ocular and cerebral ischemic systems can not be accounted for by hemodynamic factors in the anterior circulation. Thromboembolic disease, including artery-to-artery emboli from abnormal vessels (see above) remains a possibility. Theoretically, vasospasm might be considered, given that altered vasoreactivity is a pathophysiological feature of scleroderma, contributing not only to Raynaud's phenomenon, but also to sclerodermal renal crises and cardiac dysfunction in some patients³³. However, we are unaware of any reports to date documenting vasospasm as a cause of neurological symptoms in patients with scleroderma. Regardless of the precise mechanism of her symptoms, this case illustrates that disease of the macrovascular blood supply to the brain can occur in systemic sclerosis and should be considered in the differential diagnosis of such patients when they present with neurological symptoms.

REFERENCES

1. Nadeau SE. Neurological manifestations of connective tissue disease. *Neurol Clin N Am.* 2002; 20: 151-78.
2. Shah AA, Wigley FM. Often forgotten manifestations of systemic sclerosis. *Rheum Dis Clin N Am.* 2008; 34: 221-38.
3. Alusik S, Kovac J, Peregrin J. Large artery involvement in scleroderma – a case report. *J Vasc Dis.* 1990; 41: 973-6.
4. Das CP, Prabhakar S, Kharbanda PS. Scleroderma, stroke, optic neuropathy: A rare association. *Neurol India.* 2002; 50: 504-7.
5. Merino J, Casaneuva B, Piney E, Val Bernal F, Rodriguez-Valverde R. Hemiplegia and peripheral gangrene secondary to large and medium size vessels involvement in C.R.E.S.T. syndrome. *Clin Rheumatol.* 1982; 4: 295-9.
6. Passiu G, Vacca A, Sanna G, Cauli A, Laudadio M, Garau P, et al. Takayasu's arteritis overlapping with systemic sclerosis. *Clin Exp Rheum.* 1999; 17: 363-5.
7. Yago T, Ota S, Nishinarita M. A Case of systemic sclerosis complicated by Takayasu's arteritis. *Ryumachi.* 2002; 42: 605-9.
8. Kocabay G, Tiryaki B, Ekmekci A. Takayasu arteritis associated with systemic sclerosis. *Med Rheum.* 2006; 16: 120-1.
9. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. *Arthritis Rheum.* 1990; 33: 1129.
10. Shinjo SK, Pereira RMR, Tizziani VAP, Radu AS, Levy-Neto M. Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. *Clin Rheumatol.* 2007; 26: 1871-5.
11. Ho M, Veale D, Eastmond C, Nuki G, Belch J. Macrovascular disease and systemic sclerosis. *Ann Rheum Dis.* 2000; 59: 39-43.
12. Cheng K-S, Tiwari A, Boutin A, Denton CP, Black CM, Morris R et al. Carotid and femoral arterial wall mechanics in scleroderma. *Rheumatol.* 2003; 42: 1299-1305.
13. Bartoli F, Blagojevic J, Bacci M, Fiori G, Tempestini A, Conforti ML, et al. Flow-mediated vasodilation and carotid intima-media thickness in systemic sclerosis. *Ann NY Acad Sci.* 2007; 1108: 283-90.
14. Borra SI, Kleinfeld MJ. Bilateral renal artery occlusion in a patient with progressive systemic sclerosis. *Angiology.* 1980; 31: 142-5.
15. Youssef P, Englert H, Bertouch J. Large vessel occlusive disease associated with CREST syndrome and scleroderma. *Ann Rheum Dis.* 1993; 52: 464-6.
16. Furey NL, Schmid FR, Kwaan HC, Friederici HH. Arterial thrombosis in scleroderma. *Brit J Derm.* 1975; 93: 683-93.

17. Dorevitch MI, Clemens LE, Webb JB. Lower limb amputation secondary to large vessel involvement in scleroderma. *Brit J Rheumatol*. 1988; 27: 403-6.
18. Hasegawa M, Nagai Y, Tamura A, Ishikawa O. Arteriographic evaluation of vascular changes of the extremities in patients with systemic sclerosis. *Br J Derm*. 2006; 155: 1159-64.
19. Youssef P, Brana T, Englert H, Bertough J. Limited scleroderma is associated with increased prevalence of macrovascular disease. *J Rheumatol*. 1995; 22: 469-72.
20. Veale DJ, Collidge TA, Belch JJ. Increased prevalence of symptomatic macrovascular disease in systemic sclerosis. *Ann Rheum Dis*. 1995; 54: 853-5.
21. Stafford I, Englert H, Gover J, Bertouch J. Distribution of macrovascular disease in scleroderma. *Ann Rheum Dis*. 1998; 57: 476-9.
22. Lee JE, Haynes JM. Carotid arteritis and cerebral infarction due to scleroderma. *Neurology*. 1967; 17: 18-22.
23. Estey E, Lieberman A, Pinto R, Meltzer M, Ransohoff J. Cerebral arteritis in scleroderma. *Stroke*. 1979; 10: 595-7.
24. Pathak R, Gabor AJ. Scleroderma and central nervous system vasculitis. *Stroke*. 1991; 22: 410-13.
25. Kanzato N, Matsuzaki T, Komine Y, Saito M, Saito A, Yoshio T, et al. Local scleroderma associated with progressing ischemic stroke. *J Neurol Sci*. 1999; 163: 86-9.
26. Lucivero V, Mezzapesa DM, Petruzzellis M, Carella A, Lamberti P, Federico F. Ischaemic stroke in progressive systemic sclerosis. *Neurol Sci* 2004; 25: 230-3.
27. Fleming JN, Schwartz SM. The pathology of scleroderma vascular disease. *Rheum Dis Clin N Am*. 2008; 34: 41-55.
28. Renard D, Heroum C. Carotid thrombus formation and extension during anticoagulation: a case report of large vessel disease and hypercoagulable state in systemic sclerosis. *Acta Neurol Belg*. 2007; 107: 55-7.
29. Heyman A, Young WG, Dillon M, Goree JA, Klein LJ, Tindall G. Cerebral ischemia caused by occlusive lesions of the subclavian or innominate arteries. *Arch Neurol*. 1964; 10: 581-9.
30. Siekert RG, Millikan CH, Whisnant JP. Reversed blood flow in the vertebral arteries. *Ann Int Med*. 1964; 61: 64-72.
31. Aasen J, Kerty E, Russel D, Bakke SJ, Nyberg-Hansen R. Amaurosis fugax: clinical, Doppler and angiographic findings. *Acta Neurol Scand*. 1988; 77: 450-5.
32. Rampini P, Alimehmeti R, Egidio M, Locatelli M, Zavanone M. Left quadrantanopsia caused by traumatic subclavian steal syndrome. *J Trauma*. 2004; 56: 1342-4.
33. Wigley FM. Vascular disease in scleroderma. *Clinic Rev Allerg Immunol*. 2009; 36: 150-75.