Scleroderma (progressive systemic sclerosis) is a multisystem disease affecting the skin, lungs, kidneys, vascular system, myocardium, nervous system, and gastrointestinal tract. Most case reports and texts describing the effects of the disorder on the nervous system have focused on the peripheral nervous system and the cranial nerves. Central nervous system (CNS) dysfunction secondary to the vascular effects of scleroderma is recognized and considered a rare manifestation of the disorder. When cerebral ischemia is a manifestation of scleroderma, it is generally associated with evidence of renal failure and severe hypertension. We describe a patient with CREST syndrome (a variant of scleroderma characterized by calcinosis cutis, Raynaud’s phenomenon, esophageal reflux, sclerodactyly, and telangiectasia) and CNS vasculitis who was treated with high-dose immunosuppressive therapy, resulting in dramatic clinical improvement.

**Case Report**

A 45-year-old right-handed woman with previously diagnosed CREST syndrome and primary biliary cirrhosis was admitted to the University of California, Davis Medical Center in late February 1988 because of severe frontotemporal headaches of 3 days' duration. The intense headaches were characterized by sudden onset and were throbbing in character. Two days prior to admission a computed tomogram (CT scan) of the head showed a small area of subarachnoid hemorrhage in the left parietal region.

At age 21 years the patient developed Raynaud's phenomenon. Medications for this afforded no relief, and in 1966 a bilateral sympathectomy was performed. Bilateral subclavian bypass surgery was performed in 1978 in continuing attempts to improve circulation in the upper extremities. The symptoms of Raynaud's phenomenon persisted, however, and the patient lost the distal portions of two fingers of each hand. No further symptoms of peripheral ischemia occurred. In 1980 she developed esophageal reflux, and abnormal liver function tests were recorded. Four liver biopsies at different institutions followed, resulting in a diagnosis of primary biliary cirrhosis. Calcific subcutaneous nodules were first noted in 1987, resulting in the diagnosis of CREST syndrome. The patient was discovered to be hypertensive in 1974 and had been receiving 80 mg/day propranolol. Her blood pressure 3 months prior to admission was recorded as 148/94 torr.

At the time of admission, the patient's blood pressure was 122/60 torr, her temperature was 36°C, her pulse was 64/min, and respirations were 16/min. The patient had telangiectasias on her face, chest, and extremities. Subcutaneous nodules could be palpated over her extremities and hips. Bilateral carotid bruits and a systolic murmur were present. Her liver was palpable 2 cm below the costal margin, and her spleen was enlarged.

She was fully alert and oriented. There was no evidence of dysarthria or dysphasia. The results of funduscopic examination were normal. A left lateral rectus palsy due to an old eye injury was present. The remainder of the neurological examination was normal. A repeat CT scan was normal, and spinal fluid examination revealed a protein content of 77 mg% with no cells and no evidence of xanthochromia or increased pressure.

To determine if the patient had an intracranial aneurysm, cerebral angiography was performed the
morning after admission. The study had to be discontinued after bilateral carotid injections, however, because the patient developed a severe headache and disorientation associated with hypertension (blood pressure of 230/130 torr).

The angiogram demonstrated 50% stenosis of the left common carotid artery at its origin. Slight narrowing was present in the left internal carotid artery just above the carotid bulb. No irregularities were noted in either carotid siphon. These findings were interpreted as characteristic of atherosclerotic disease. Narrowing of several distal medium-sized and small arteries was seen in the anterior and middle cerebral artery distributions on the left and in a small distal branch of the middle cerebral artery on the right. An occluded medium-sized branch of the middle cerebral artery was also seen on the left. Both posterior cerebral arteries filled from the carotid injections and showed no abnormalities. These findings were reported as evidence of arterial spasm or vasculitis.

During angiography, the patient became confused, disoriented, and unable to follow two-step commands. After angiography her blood pressure continued to fluctuate (230–109/120–55 torr) for 12 hours, and elevations in pressure were accompanied by severe throbbing headaches despite antihypertensive therapy (propranolol, sublingual and oral nifedipine, and intravenous hydralazine). A generalized convulsive seizure occurred, and she was treated with phenobarbital. Another spinal fluid examination only confirmed an elevated protein content of 83 mg% with no evidence of xanthochromia. The patient's blood pressure was controlled (135/86 torr), but her confusion and disorientation did not improve. Because of the absence of clinical improvement and despite the uncertainty of the radiological diagnosis, 100 mg i.v. methylprednisolone every 4 hours was started 48 hours after angiography because of the suspicion of CNS vasculitis. Within 6 hours her mental status began to improve, and within the next 14 hours the patient was alert, oriented, and free of headache with a normal mental status. The steroid dosage was reduced to prednisone 60 mg/day. She continued to do well, and 2 days later angiography was performed again to visualize the vessels of the basilar circulation.

The angiogram showed multiple long segments of smooth, symmetrical narrowing in large and medium-sized vessels of the posterior circulation; the most prominent of these were in the superior cerebellar arteries near their origins (Figure 1). The 0.5–1.5-cm-long narrowed arterial segments were thought to be characteristic of vasculitis as opposed to nonspecific arterial spasm such as might occur in association with subarachnoid hemorrhage.

Skin biopsy was performed to document systemic vasculitis and showed epidermal and dermal changes associated with scleroderma, but no evidence of vasculitis. The patient remained free of symptoms and was discharged 3 days later receiving 60 mg prednisone and 12.5 mg captopril per day.

Two weeks later the prednisone dosage was reduced to 50 mg/day following a tapering program. Two days later the patient began to have episodes of numbness of her right arm and shoulder, each episode lasting 1–5 minutes. She was brought to the emergency room on March 29, 1988, following an episode of numbness of her right face, arm, and leg associated with expressive aphasia. Examination confirmed the aphasia and hemianalgesia, and a blood pressure of 186/130 torr was recorded. Methylprednisolone 100 mg i.v. was administered, resulting in resolution of her neurological symptoms within 30 minutes; her blood pressure returned to baseline levels (140/90 torr). During her first week of hospitalization methylprednisolone was replaced with prednisone 60 mg/day.

The results of a leptomeningeal and cortical biopsy obtained to confirm the presence of CNS vasculitis were normal. Because of cushingoid facies, nausea, vomiting, depression, and intermittent confusion (all considered to be side effects of steroid therapy) as well as the negative biopsy results, the prednisone dosage was tapered to 50 mg/day. No further neurological symptoms occurred for 2 days, and the patient was discharged.

During the first week at home the patient again began to experience episodes of right facial and upper extremity paresthesias associated with expressive aphasia. She continued to have clinical symptoms of ischemia, and now hyperglycemia was added to the other side effects of steroid therapy. Because of poor therapeutic response to moderate-dosage steroid therapy and the unacceptable side effects of higher dosages of steroids, the patient was started on cyclophosphamide 100 mg/day and the steroid dosage was reduced to 40 mg/day. Over the next 1.5 months the cyclophosphamide dosage was gradually increased to 175 mg/day and the prednisone dosage was gradually decreased to 20 mg/day. The patient became symptom-free after starting cyclophosphamide therapy and remained so for 2 months. In early August, however, she began to experience 1–2-minute episodes of numbness of the right angle of her mouth and her right hand. The cyclophosphamide dosage was increased to 200 mg/day, and the prednisone dosage was gradually tapered to 10 mg/day. Episodes of neurological deficit did not recur, but 1.5 months later a white blood cell (WBC) count of 2,300/mm$^3$ and a total platelet count of 61,000/mm$^3$ required discontinuation of the cyclophosphamide and the prednisone dosage was increased to 60 mg/day.

Within 2 weeks after discontinuing cyclophosphamide therapy the patient was experiencing frequent falls and numbness of her left face and hand. Being unable to restart cyclophosphamide therapy, we increased the prednisone dosage to 120 mg/day. In November her WBC count was 7,000/mm$^3$ and monthly cyclophosphamide pulse therapy was initiated (700 mg/mo). The prednisone dosage was de-
FIGURE 1. Vertebral angiogram demonstrating multiple areas of symmetrical segmental narrowing of superior cerebellar arteries (1, arrows). Narrowed portions of arteries are 0.5-1.5 cm long. Distal branch of superior cerebellar artery terminates abruptly (2, arrow). Other examples of segmental arterial narrowing and abruptly terminating vessels could also be identified on original roentgenograms.

increased to 60 mg/day and then tapered at a rate of 2.5 mg/wk. On this regimen the patient had only two brief episodes of right facial numbness during the next 3 months.

In January 1989 the patient was seen in the emergency room because of right abdominal pain, fever, chills, and a cough. Her WBC count was 27,000/mm³, and she had severe metabolic acidosis. She did not improve, and ultimately an exploratory laparotomy was performed in search of a source of sepsis. During surgery the patient became hypotensive and suffered irreversible cardiac arrest. Permission for autopsy was denied.

Pertinent laboratory data included rheumatoid factor positive at 1:160, with normal complement levels and absent Sjögren's antibodies SS-A and SS-B; results of an antinuclear antibody (ANA) screen were negative. Her liver function tests revealed an alkaline phosphatase level of 600-700 units/l, an aspartic transaminase level of 100 units/l, a γ-glutamic transaminase level of 1,700 units/l, a total bilirubin content of <1.0 mg%, a cholesterol content of 471 mg%, and a triglyceride content of 101 mg%. Her blood urea nitrogen and creatinine levels were always normal, as was her plasma renin level. Her erythrocyte sedimentation rate was normal or slightly elevated (20–39 mm/hr). Creatinine clearance was elevated at 168 ml/min. Thyroid function tests and α-fetoprotein levels were normal. Assay for hepatitis B surface antigen was negative; the rapid plasma renin test and microhemagglutination test for Treponema pallidum were normal.

Discussion

Primary CNS involvement in scleroderma is rare and unusual, leading some to argue that CNS dysfunction is either secondary to end-organ failure or, if vasculitis is present, it is associated with evidence of systemic vasculitis. The rarity of CNS vasculitis associated with scleroderma in addition to the underestimated significance of the angiographic data resulted in diagnostic uncertainty and delayed appropriate medical intervention for our patient. Further uncertainty resulted from the subsequent normal findings on leptomeningeal biopsy, which had been recommended to confirm the angiographic findings. Only the repeated, prompt, dramatic benefits of
immunosuppression ultimately led to appropriately focused therapy.

This case is instructive in the following ways:
1. When cerebral vasculitis is a diagnostic consideration, four-vessel angiography is required rather than restricting the study to only the anterior or posterior circulations. The most dramatic angiographic changes are neither restricted to nor necessarily maximal in areas suggested by focal or lateralized neurological signs and symptoms.
2. When there is angiographic evidence of vasculitis a leptomeningeal biopsy is of value to confirm the diagnosis, but the findings may well be normal. The absence of pathological changes should not be construed as contradicting angiographic evidence of vasculitis.
3. CNS vasculitis occurs in association with scleroderma and is not necessarily associated with renal disease or malignant hypertension.

The amount of steroids and cyclophosphamide required to control our patient's symptoms were more than generally considered adequate. The immediate benefits of immunosuppressive therapy in this patient are clear and can be considered lifesaving. For this patient the benefits were temporary (11 months), and the side effects of the medication may have contributed to her death.

Two additional patients with scleroderma and isolated CNS vasculitis have been reported. Both were females in the first half of the fifth decade of life, as was our patient. Immunosuppressive therapy was effective in reversing the signs and symptoms in one of the patients. Our patient is therefore the third demonstrating the association of CNS vasculitis with scleroderma and the first patient with CNS vasculitis and CREST syndrome.

References

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