Cerebral Arteritis in Scleroderma

ELIHU ESTEY, M.D., ABRAHAM LIEBERMAN, M.D., RICHARD PINTO, M.D., MARTIN MELTZER, M.D., AND JOSEPH RANSOHOFF, M.D.

SUMMARY Central nervous system (CNS) involvement is rare in scleroderma unless there are concomitant abnormalities in renal or lung function or malignant hypertension. A 43-year-old woman with typical scleroderma developed subacute encephalopathy despite absence of the above abnormalities. Cerebral angiography demonstrated a focal arteritis. The patient improved while being given corticosteroids. We believe this case indicates that cerebral arteritis can occur in scleroderma.

PROGRESSIVE systemic sclerosis (PSS; scleroderma) is characterized by increased amounts of collagen in skin, peripheral blood vessels, and visceral organs. Neurologic involvement is uncommon, unlike in systemic lupus erythematosus (SLE) or polyarteritis nodosa (PAN). For example, in one large series 6 out of 727 patients with PSS had clinical involvement of the nervous system. Likewise, in postmortem studies the incidence of brain lesions is similar in patients with PSS and in matched controls in a general autopsy population. Neurologic disease, when it does occur in PSS, is usually a consequence of accelerated (malignant) hypertension, uremia, or pulmonary disease. Although examples of primary involvement of cerebral arteries in PSS have been reported, such examples are rare. Therefore, we report a patient with PSS who developed a diffuse and reversible CNS disorder secondary to cerebral arteritis in the absence of classic malignant hypertension, uremia or marked pulmonary disease.

Case Report

The patient is a 43-year-old, right-handed, white female who was admitted to the New York University Medical Center with focal and generalized seizures beginning one day prior to admission (pta).

Two years pta the patient noted onset of pain in her proximal interphalangeal joints and puffiness of hands and fingers. She experienced partial symptomatic relief with aspirin and further relief with corticosteroids. Corticosteroids were maintained at 9 mg methylprednisolone daily. One year pta her blood pressure was 170/100 torr. At this time her skin was firm and tight over all fingers and both wrists. There were no other skin changes. Six months pta her fingertips would, at intervals, turn white in the cold. Three months pta her skin was dry and tight over all fingers and both wrists. There were no other skin changes. Six months pta her finger-tips would, at intervals, turn white in the cold. Three months pta her skin was dry and tight over all fingers and both wrists. There were no other skin changes. Six months pta her fingers, wrists, forearms, arms, thighs, and face. The lungs were clear and there was a soft apical systolic murmur. There was no organomegaly or lymphadenopathy. The patient was restless; she failed to respond to verbal stimuli but responded appropriately to noxious stimuli. The optic disc margins were blurred; arterioles were narrowed diffusely, veins were full but pulsed spontaneously; there were scattered flame hemorrhages (some with white centers). Pupils were 3 mm and reacted to light; there was full range of motion of the extraocular muscles. There was no extrenzy paresis; deep tendon reflexes were symmetrically hyperactive with bilateral extensor plantar responses. Gait, cerebellar, and sensory functions could not be tested.

Hemoglobin and hematocrit were normal. White blood count (WBC) was 21,000 with an increase in polymorphonuclear (PMN) forms. Erythrocyte sedimentation rate was 20 mm/h on admission, 13 mm/h on the second hospital day, 50 mm/h on the ninth day, 60 mm/h on the fourteenth day. Electrolytes, BUN, creatinine, glucose, calcium, liver function tests and arterial blood gases were normal. VDRL was non-reactive; latex fixation was positive in a 1:40 dilution and gave a speckled pattern on immunofluorescence. Testing of renin levels demonstrated that 20 nanograms of aldosterone were generated per ml/h incubation (normal up to 1). Multiple blood cultures were negative. Multiple urinalyses demonstrated no cells or casts. Mean 24 h urinary protein excretion was 500 mg (range 100 mg to 1,300 mg). Chest roentgenogram revealed an enlarged heart. An upper gastrointestinal series revealed absence of normal esophageal peristaltic activity. Pulmonary function tests showed a mildly decreased diffusing capacity: skin biopsy revealed sclerodermatos changes without histological or immunofluorescent evidence of vasculitis. Lumbar puncture on admission was slightly traumatic; opening pressure was 380 mm of water and a closing pressure of 140 mm; there were 470 RBCs/mm$^2$ and 8 WBCs (4 PMNs and 4 lymphocytes); the protein was 100
mg%; and glucose was 92 mg% (simultaneous blood glucose was 118 mg%).

Gram stain and acid fast stains were negative; bacterial and fungal cultures showed no growth. Electroencephalogram (EEG) recorded paroxysmal 2-3 Hz slow waves bilaterally. Computerized tomography indicated no hemorrhage or abnormal lucencies. Ventricles were normal and there was no shift of midline structures.

Cerebral angiography via catheter 2 days after admission with blood pressure (BP) 140/90 torr demonstrated diffuse attenuation in the caliber of both the right and the left middle cerebral opercular branches. The posterior parietal and angular branch of the middle cerebral as well as the posterior communicating artery and posterior cerebral artery were uninvolved as were the supraclinoid carotid artery and the horizontal segment of the middle cerebral artery. No mass effect was seen. The extracranial vessels were normal (fig. 1A, B; the left carotid angiogram was similar in appearance to the right).

The patient was begun on 250 mg intravenous methylprednisolone every 6 h. Mental status remained unchanged until the third day when the patient, although agitated and confused, spoke and recognized her family. On the fourth day she was much less confused and by the tenth day her mental status and neurological exam were normal; daily corticosteroids were tapered to 30 mg methylprednisolone by mouth. Temperature was normal by the second day. Blood pressure ranged from 140-190/80-105 torr during the first 4 days. Blood pressure rose to 230/140 torr on the fifth day but fell spontaneously within a few minutes to 190/110 torr. The patient was begun on hydralazine, hydrochlorothiazide and alphamethyldopa. Blood pressure fell to 130/80 torr and remained at this level during the remainder of her hospital stay. Hydralazine was discontinued and the patient maintained on hydrochlorothiazide and alphamethyldopa.

She continued to do well and was discharged after a normal neurological examination.

Subsequent to discharge she was consistently hypertensive, with elevations in blood pressure up to 160/90 torr. However, azotemia never developed. In February, 1978, she suffered a similar, although milder, encephalopathic episode at another hospital. She died in February, 1978, of heart failure.

**Comment**

The combination of skin changes, Raynaud's phenomenon, aperistaltic esophagus, and decreased pulmonary diffusing capacity established the diagnosis of PSS in our patient with onset 2 years prior to the development of CNS dysfunction. Although the elevated renin levels and fundoscopic examination are compatible with malignant hypertension, the blood pressure levels recorded during the initial days of hospitalization, when the patient was most confused, are not the levels associated with malignant hypertension. Normal arterial blood gases make lung disease an unlikely contributing factor. Although the findings on lumbar puncture suggest an aseptic meningoencephalitis as a possible cause, the angiographic findings of a focal arteritis confined to the opercular branches of the middle cerebral artery and the rapid recovery make encephalitis unlikely. The angiographic findings are unlike those seen with vascular disease. The latter is characterized by a more diffuse elongation, tortuosity and irregularity of intracranial vessels and microaneurysms of the lenticulostriate arteries. Thus, we believe that our patient's encephalopathy was the result of a primary cerebral arteritis independent of blood pressure, renal or pulmonary function or CNS infection.

The intermittently elevated blood pressure in the hospital and the persistent hypertension after discharge indicate that the patient had renal scleroderma.
However, despite the hypertension, hyperreninemia and retinopathy, the patient did not have malignant hypertension (secondary to renal scleroderma). Patients with malignant hypertension either have renal failure or develop it within a short period of time. Our patient never became azotemic. Furthermore, the life expectancy of patients with malignant hypertension and renal scleroderma averages 1 month (range 0.1–7 months). Our patient lived an additional 19 months after discharge. In the absence of classic malignant hypertension, the role of renal scleroderma in the pathogenesis of the encephalopathy in our patient is doubtful.

Discussion

Few case reports of cerebral involvement in scleroderma in the absence of hypertension or renal disease have appeared. Lee and Haynes reviewed the literature and described a patient with scleroderma who developed aphasia and a right hemiparesis after a generalized seizure. A left carotid angiogram revealed narrowing of the internal carotid artery to the level of the siphon. The patient did not recover and died a month later. Postmortem examination revealed thickening of all 3 layers of the wall of the internal carotid artery with inflammatory changes. The walls of the anterior and middle cerebral arteries were normal, but there was fibrosis of the cerebral arterioles and capillaries and occasional occlusion of these small vessels with collagenous material. There were numerous microinfarcts throughout the brain.

Formerly the main pathologic feature of PSS was thought to be fibrosis. The absence of CNS involvement was ascribed to the absence of connective tissue in the brain. However, our case indicates that cerebral vessels can be involved in PSS as they can in SLE and PAN. This involvement is consistent with recently changed concepts of the pathogenesis of scleroderma. Attention has shifted to vascular involvement as the initial event preceding the development of fibrosis. It has been proposed that an unknown agent incites a mononuclear cell inflammatory reaction periarternially, which in turn leads to abnormal proliferation of fibroblasts in the interstitium and perhaps abnormal proliferation of endothelial cells in the intima. These abnormally behaving cells then secrete increased amounts of connective tissue components producing the characteristic fibrosis. If this proposed mechanism is correct then the rarity of cerebral scleroderma would have to be explained in a different way than previously with specific attention to cerebral vessels. Perhaps there are subtle differences between endothelial cells in cerebral and non-cerebral vessels. This might account for the failure of cerebral endothelial cells to proliferate in response to the proposed stimulus or perhaps there is no stimulus to mononuclear cell inflammation.

References

Cerebral arteritis in scleroderma.
E Estey, A Lieberman, R Pinto, M Meltzer and J Ransohoff

Stroke. 1979;10:595-597
doi: 10.1161/01.STR.10.5.595

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/10/5/595

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/