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Cerebral Angioendotheliomatosis: A Report of Two Cases and Review of the Literature

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Cerebral angioendotheliomatosis is a rare form of vascular neoplasia characterized by rapidly progressive dementia and multifocal neurologic deficits. Histologically there is proliferation of neoplastic cells within the lumina of arteries, arterioles, capillaries, and venules, which results in multiple infarcts within the brain and spinal cord. Although rare, angioendotheliomatosis should be considered in the differential diagnosis of multifocal vascular disease and rapidly progressive dementia. We report the neuroradiologic findings in two cases of angioendotheliomatosis and review the literature on this disease.

Case Reports

Case 1

A 67-year-old man developed progressive personality change and memory loss punctuated by intermittent vertigo and ataxia over several months. Neurologic examination on admission revealed a marked organic mental syndrome, weakness of the left arm and leg, and ataxia. Electroencephalography revealed slow wave activity in the left frontotemporal region. A skull series showed demineralization of the sella turcica. Isotopic brain scan showed increased radionuclide activity in the left frontotemporal region. Computed tomography (CT) was not available (1967). Routine laboratory studies were unremarkable except for 1%–2% blast forms in the peripheral blood smear. Lumbar puncture revealed a normal opening pressure with total protein concentration of 107 mg/dl. A left common carotid angiogram showed minimal shift of the anterior cerebral artery from left to right and small-vessel irregularities ascribed to atherosclerosis. Multiple middle cerebral artery branches were occluded.

The patient's hospital course was characterized by progressive obtundation, seizures, and death. General autopsy revealed numerous neoplastic cells within the lumina of the vessels in visceral organs including the lungs, heart, adrenals, and kidneys. The lymph nodes, bone marrow, and spleen did not show evidence of lymphoma. The brain was grossly unremarkable. Microscopic examination revealed numerous malignant cells within the lumina of many cerebral blood vessels and occasionally infiltrating the adjacent parenchyma. All areas of the brain were involved, including the brainstem and cerebellum.

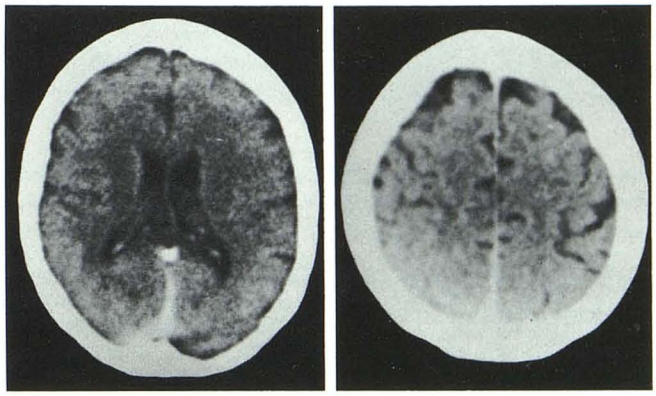

Fig. 1.—Case 2. Initial (admission) CT scan of brain with contrast enhancement at level of lateral ventricles (**A**) and at level of high convexity (**B**). Scan was interpreted as normal.

Case 2

A 60-year-old man with no significant medical history developed intermittent headaches, nausea, and vomiting accompanied by vertigo, with symptoms increasing in frequency over 10 months. Two months before admission he had a generalized seizure and was placed on Dilantin. Symptoms stabilized temporarily, but 1 month before admission he had another generalized seizure. CT, brain scan, and lumbar puncture at an outside institution were normal. The patient became increasingly confused and developed a gait disturbance over the last 2 weeks before admission.

Neurologic examination on admission revealed a confused man who was oriented to person only. He had a broad-based gait but otherwise a normal motor and sensory examination. Repeat lumbar puncture and CT with and without contrast enhancement were interpreted as normal (fig. 1). The patient gradually became more demented, continued to have seizures, and developed bouts of fever to 103°F (39.4°C). Laboratory studies revealed persistently elevated alkaline phosphatase and SGOT. Cerebral angiography showed multiple distal vascular occlusions of the right middle cerebral artery and irregular narrowing of several opercular vessels of the left middle

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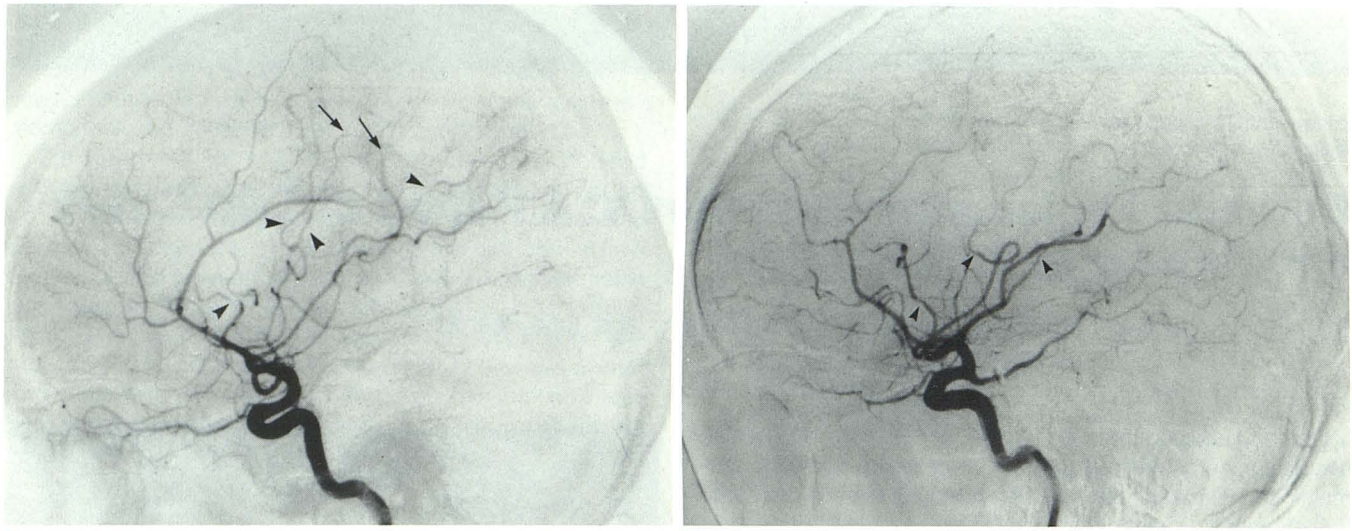

Fig. 2.—Case 2. Femorocerebral arteriogram on admission. Right (**A**) and left (**B**) internal carotid injections. Distal vascular occlusions of right middle cerebral artery (*arrows*); areas of arterial irregularity (*arrowheads*) in branches of both middle cerebral arteries.

cerebral artery (fig. 2). These findings were thought to be consistent with either thromboembolic cerebrovascular disease or a cerebral vasculopathy. Biopsies of the temporal artery and the gastrocnemius muscles showed no evidence of vasculitis.

Repeat lumbar puncture demonstrated a progressive rise in the protein concentration with few cells and negative cytology. A brain biopsy from the right frontal lobe including some small blood vessels was unremarkable except for a moderate increase in lymphocytes in the perivascular area, considered to be nonspecific. An electron microscopic study of the biopsy provided no additional information. CT of the thorax and abdomen; a liver biopsy; and repeat blood and urine cultures were all normal, and no source of fever was ever identified. Two weeks after admission and despite the institution of steroid therapy, the patient deteriorated, making no spontaneous motor or verbal responses and responding only to painful stimuli; he had bilateral extensor plantar responses and a dilated, nonreactive right pupil.

A repeat CT scan of the brain at 1 month after admission (figs. 3A and 3B) showed cerebral atrophy and ventricular dilatation. The sylvian and interhemispheric fissures were widened, and there was a slight increased lucency to the cerebral white matter. A course of vidarabine produced no improvement. A CT scan at 1½ months after admission (figs. 3C and 3D) showed marked periventricular white-matter lucency consistent with demyelination and atrophy as compared with the initial scan. No mass effect was present. The patient died 2 months after admission.

General autopsy was unremarkable on gross examination. Microscopic examination revealed pleomorphic cells with large vesicular nuclei, prominent nucleoli, scant cytoplasm, and numerous mitotic figures in the blood vessels of all organs examined. The organs involved included the heart, lungs, liver, pancreas, spleen, adrenals, kidneys, testes, thyroid, and gastrointestinal tract. The lymph nodes were unremarkable. The bone marrow was mildly hyperplastic with several bizarre cells phagocytizing red blood cells. Neuropathologic examination revealed multiple areas of hemorrhagic necrosis in the cerebral white matter and multiple infarcts in the convolutional and deep white matter of the frontal, temporal, and occipital lobes. The brainstem, cerebellum, and pituitary were also involved. Microscopic examination revealed numerous medium-sized blood vessels as well as branches of the middle cerebral artery filled with neoplastic cells (fig. 4). Arterioles, veins, and capillaries were involved in all sections examined. In most specimens the tumor cells were free of the wall except where tethered by fibrin strands. In some vessels there was a transition between intraluminal tumor and abnormal endothelium. Occasionally the full thickness of the vessel wall was involved. The white matter showed marked rarefaction, necrosis, and edema. In many gray-matter regions, vascular plugging by tumor existed in the absence of ischemic changes in the neurons.

Discussion

Cerebral angioendotheliomatosis is a rare clinicopathologic entity characterized by rapidly progressive dementia and multifocal neurologic deficits. The disease is considered to represent a multifocal primary neoplasm of endothelial cells throughout the vascular system. Evidence for considering the tumor to be derived from endothelium lies in its occasional continuity with atypical endothelium, its intravascular location, the absence of any suggestion of an extravascular source, and usually minimal extravascular involvement. The tumor cells in the brain fail to stain with peroxidase-antiperoxidase immunoperoxidase technique for factor VIII–related antigen. Factor VIII is an antigenic marker found in endothelial cells and immunocytochemically detectable in the normal lining cells of vessels in patients with these diseases. Vessels occasionally show cuffing with lymphocytes, which raises the possibility of a relation to lymphoma, but lymph nodes are unaffected and immunocytochemical markers for lymphocytic cells are not present. The tumor differs from angiosarcoma in that it does not have cohesive sheets of cells, intravascular papillae, or neoplastic vascular budding; it shares with angiosarcoma the absence of the factor VIII marker. Recent electron microscopic studies have confirmed the malignant nature of the intraluminal cells and suggested their endothelial origin by the detection of intracytoplasmic tubular organelles similar

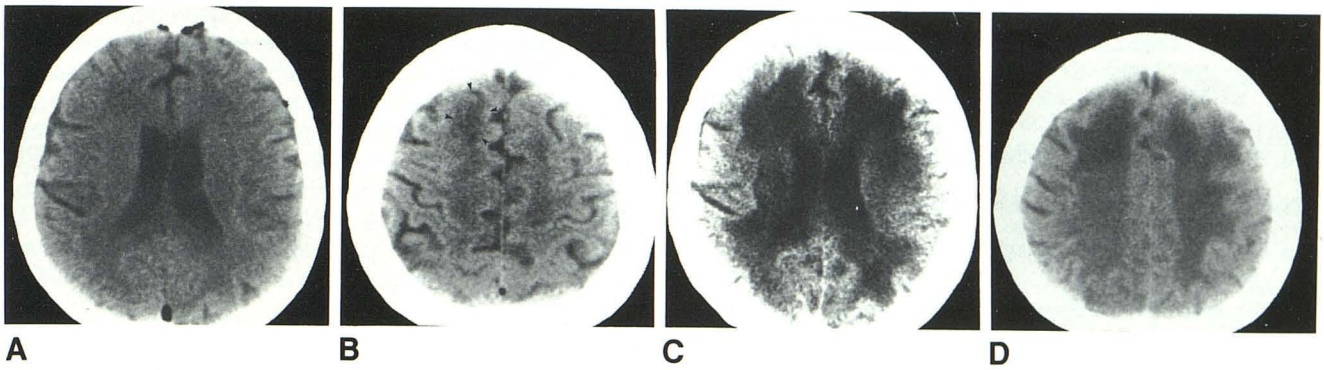

Fig. 3.—Case 2. Unenhanced CT scans at 1 month (**A** and **B**) and 1½ months (**C** and **D**) after admission. **A**, At level of lateral ventricles. Dilatation of cortical sulci. (Intracranial air was secondary to recent brain biopsy.) **B**, At level of high convexity. Early white-matter lucency (*arrowheads*). **C**, At level of lateral ventricles. Marked periventricular white-matter lucency consistent with diffuse demyelination. **D**, At level of centrum semiovale.

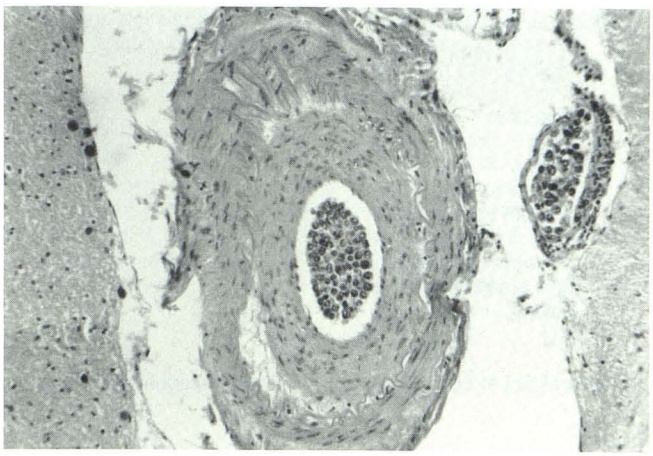

Fig. 4.—Case 2. Photomicrograph of autopsy specimen of branch of middle cerebral artery. Neoplastic cells consistent with angioendotheliomatosis.

to Weibel-Palade bodies (cytoplasmic structures that are relatively specific for endothelial cells) [1–3].

Many organs throughout the body are affected. The kidneys and lungs are most often involved, followed by the heart, adrenals, skin, liver, lymph nodes, spleen, and bone marrow [1]. The meninges are considered most sensitive for biopsy [1]. The multifocal nature of the disease is considered a primary feature, not a manifestation of peripheral emboli. It has been hypothesized that the aberration in angiogenesis might be the result of a circulating angiogenic factor [4].

Diagnosis is rarely made in life. A nonspecific progressive loss of cerebral function, sometimes associated with focal motor or sensory deficits, gives little clue to the underlying disease. Peripheral blood examination and bone-marrow and cerebrospinal-fluid cytology usually show no tumor cells. Cerebrospinal fluid usually is remarkable only for elevated protein. The disease is universally fatal with a mean survival of 13 months [3]. Steroid therapy produces transient symptomatic improvement but does not alter the course of the disease [2, 5, 6]. Other treatments have met with little success. One case [7] showed spontaneous regression of the intraluminal tumor cells at autopsy 20 months after a diagnostic brain biopsy. Intraluminal tumor cells were found only in vessels of the pituitary stalk.

The neuropathologic findings in both of our cases explain the arteriographic findings. Only two previous case reports [3, 7] had similar findings of small-vessel irregularity indicative of vasculopathy. Angiographic studies in six other cases [1, 3, 5, 6, 8] were normal or showed nonspecific mass effect. The clinical and radiographic findings previously reported in this condition are summarized in table 1. On CT, several cases [2, 3] showed low-attenuation absorption abnormalities and mild mass effect consistent with areas of infarction or demyelination. The CT scan in our case 2 was normal at the time when angiography was performed, but became positive later in the course of the disease, when it had the appearance of leukoencephalopathy. The rapid and widespread demyelination of the cerebral white matter in case 2 is most unusual and is attributed to the plugging of numerous vessels by neoplastic cells, resulting in widespread necrosis, rarefaction, and edema (as confirmed by autopsy). Involvement of the posterior fossa explains the late clinical symptomatology in case 2.

Differential diagnostic consideration of the CT findings includes multiinfarct dementia, congenital leukodystrophies (Krabbe, metachromatic, and adrenoleukodystrophy), glioblastoma diffusum, herpes encephalitis, chemotoxicity leukodystrophy, and Binswanger disease. The adult onset of this rare neoplasm eliminates the congenital leukodystrophies. The rapid progression of changes of the white matter with the lack of a source for thromboembolism excludes multiinfarct dementia. Binswanger disease or subcortical white-matter atherosclerosis has similar CT findings, but the clinical progression is less rapid and the demyelination seen on serial CT scans in angioendotheliomatosis has not been reported in Binswanger disease. No chemotherapeutic agent was administered to our patient, so a chemotoxic leukodystrophy cannot be implicated in the demyelination process that occurred. Herpes encephalitis usually follows a more rapid fulminating course with abundant cells in the cerebrospinal fluid; this was not observed in our patient. Rare malignant tumors that infiltrate the cerebral parenchyma diffusely have been observed, but the CT findings in such cases exhibit

TABLE 1: **Summary of Clinical and Radiographic Findings in Reported Cases of Angioendotheliomatosis**

Series: Age, Gender	Findings			
	Clinical	Angiographic	CT	Other
Stroudth et al. [8]:				
42, M	MMSD, dementia	Normal*	...	Pneumoencephalogram: normal†
63, M	MMSD, dementia	Normal	...	Brain scan: normal
Reinglass et al. [5]:				
59, F	MMSD, dementia	*Initial:* normal *Repeat:* 5-mm shift with focal mass effect, R parietal	...	Focal uptake R parietal, consistent with infarct; pneumoencephalogram: mass effect
Petito et al. [1]:				
66, F	MMSD, dementia	Normal*	Mild cortical atrophy	Myelogram, brain scan: normal
Dolman et al. [6]:				
66, M	MMSD	Normal†	...	Brain scan: consistent with occipitotemporal infarct
79, F	MMSD	...	...	Brain scan, myelogram: normal
Ansbacher et al. [2]:				
42, F	Dementia	...	*Initial:* multiple areas of decreased attenuation bilaterally with mild mass effect, consistent with infarction *Repeat at 2 months:* persistence of R frontal lesion with increased mass and rim enhancement *Repeat at 6 months:* L hemorrhagic infarction; multiple areas of low attenuation	Brain scan: multiple areas of increased uptake
Wick et al. [3]:				
39, M	MMSD, dementia	Normal	...	...
64, M	MMSD, dementia	Irregular narrowing of frontal cortical arteries	Generalized atrophy	Pneumoencephalogram: normal
41, F	MMSD, dementia	...	Mass effect and areas of decreased attenuation in bifrontal and R parietal regions	...
71, F	Hemiparesis	...	Mass effect in L frontoparietal region	...
LeWitt et al. [7]:				
52, F	MMSD	Multifocal distal artery stenosis in anterior and middle cerebral distribution, more pronounced on R	Focal atrophy, R parietal region; bifrontal lucencies	...
Schonfeld et al:				
67, M	MMSD	Mild L-to-R shift; small-vessel irregularity; multiple small-vessel occlusions	...	Brain scan: increased activity in L parietooccipital region
60, M	Dementia, seizures	Multiple distal vascular occlusions of R middle cerebral artery; irregular narrowing of several opercular vessels of L middle cerebral artery	*Initial:* normal *Repeat at 1 month:* increased white-matter lucency; atrophy *Repeat at 1½ months:* marked periventricular white-matter lucency; atrophy	...

Note.—MMSD = mixed motor and sensory deficits; R = right; L = left.
* Examination was performed three times.
† Examination was performed twice.

prominent mass effect with marked cisternal and ventricular compression, and have not been observed to progress from a normal CT appearance to one of white-matter lucency with diffuse cerebral atrophy as in angioendotheliomatosis.

Although rare, cerebral angioendotheliomatosis should be considered in the differential diagnosis of arterial irregularity and multifocal white-matter lucency, especially when the clinical picture suggests this entity. Biopsy of the meninges, brain, or multiple visceral organs may then be performed to confirm the diagnosis and direct therapeutic trials.

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REFERENCES

1. Petito CK, Gottlieb GJ, Dougherty JH, Petito FA. Neoplastic angioendotheliosis: ultrastructural study and review of the literature. *Ann Neurol* **1978**;3:393–399
2. Ansbacher L, Low N, Beck D, Boarini D, Jacoby C, Cancilla PA. Neoplastic angioendotheliosis: a clinicopathological entity with multifocal presentation. *J Neurosurg* **1981**;54:412–415
3. Wick MR, Scheithauer BW, Okazaki H, Thomas JE. Cerebral angioendotheliomatosis. *Arch Pathol Lab Med* **1982**;106:342–346
4. Person J. Systemic angioendotheliomatosis: a possible disorder of a circulating angiogenic factor. *Br J Dermatol* **1977**;96:329–331
5. Reinglass JL, Muller J, Wissman S, Wellman H. Central nervous system angioendotheliosis: a treatable multi infarct dementia. *Stroke* **1977**;8:218–221
6. Dolman CL, Sweeney VC, Magil A. Neoplastic angioendotheliomatosis: the case of the missed primary? *Arch Neurol* **1979**;36:5–7
7. LeWitt PA, Forno LS, Brant-Zawadzki M. Neoplastic angioendotheliosis: a case with spontaneous regression and radiographic appearance of cerebral arteritis. *Neurology* (NY) **1983**;33:39–44
8. Strouth JC, Donahue S, Ross A, Aldred A. Neoplastic angioendotheliosis. *Neurology* (NY) **1965**;15:644–648