Granulomatous Angiitis
An Unusual Etiology of Stroke

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SUMMARY A 43-year-old man, who died five months after the onset of left-sided sensory deficit, had angiographical and pathological evidence of an angiitis confined largely to the distribution of the right middle cerebral artery. Histological examination identified this process to be intracranial noninfectious granulomatous angiitis. Although certain clinical and pathological features of this disorder overlap with other vasculitides which affect the central nervous system, the disease nevertheless retains sufficient individuality to warrant status as an entity, and should be considered in the differential diagnosis in adults with lesions which produce focal neurological deficits and signs of increased intracranial pressure.

The definitive answer regarding an infectious etiology will come only from detailed culture studies of the affected vessels.

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Introduction

GRANULOMATOUS ANGIITIS is an inflammatory disorder of unknown etiology whose curious preference for vessels of the central nervous system may be expressed clinically as stroke. This report describes the clinical and pathological manifestations of this disorder and considers its nosological position among the other vasculitides which may affect the central nervous system.

Report of a Case

Clinical History

The patient was a 43-year-old black man who was first admitted to Duke University Medical Center on November 9, 1970, for evaluation of repetitive attacks of numbness of the left side of the body which had begun two months previously. The initial attack of 20 minutes' duration was characterized by numbness of the left foot, staggering gait, difficulty with speech, and decreased use of the left arm and leg. Within a week the numbness extended to the entire left side of the body, at which time there was urinary urgency with precipitate micturation, anorexia, and a six-pound weight loss. The patient denied seizure activity, headache, visual disturbance, or loss of consciousness. The past medical history contained no relevant illnesses. Specifically, there was no history of asthma, allergies, sinusitis, or lesions of the skin.

The patient was well developed and cooperative, and did not appear ill. The blood pressure was normal. Decreased deep tendon reflexes and plantar responses were present.

References

decreased sensation to pinprick and touch over the left hand and forearm to the elbow and in the left leg from the knee distally. Position sense was impaired in the left great toe and vibratory sensation was diminished in the left hand. The patient walked with a very slight limp of the left leg.

Normal routine laboratory data included complete blood count with WBC differential, urinalysis, serologic test for syphilis, and serum chemical examinations including blood urea nitrogen. A brain scan revealed increased tracer activity in the right posterior parietal area. The ECG, EEG, and roentgenographic examinations of the chest and skull were normal. On the fourth hospital day, a right carotid arteriogram revealed a fusiform dilation of the intracavernous portion of the right carotid artery in the absence of other arterial abnormalities. The venous phase of this examination disclosed a 4-cm avascular area in the right parietal region. A neoplasm producing focal signs and sensory seizures was suspected, but the patient refused pneumoencephalography and rejected the suggestion of surgery. Therefore, he was discharged from the hospital with prescriptions for Dilantin and phenobarbital.

On December 1, 1970, the patient returned to the clinic with the complaint of occipital headache, but appeared well otherwise. Increased weakness of the left arm was apparent to the examiner.

On February 11, 1971, the patient was readmitted to the hospital because of headache, persistent vomiting, confusion, and left hemiplegia of sudden onset four hours earlier. Somnolence, confusion, and disorientation characterized his general state. The pulses were full and there were no cranial or cervical bruits. The right pupil was slightly greater than the left, but both reacted to light. The left corneal reflex was decreased. Left central facial weakness and left hemiplegia were noted. There were bilateral papilledema and retinal hemorrhages. There were no motor responses to pinprick on the entire left side.

A right carotid arteriogram again revealed an avascular area in the right parietal region, and in addition, for the first time, also demonstrated irregular beaded luminal profiles with focal occlusions in the parietal branches of the middle cerebral artery (fig. 1). Retrograde pial collaterals extended toward the region of avascularity. The internal cerebral vein and anterior cerebral arteries were shifted to the left and there was downward displacement of the middle cerebral artery at the sylvian point. Steroid therapy was begun.

On the second hospital day, a left ventricular tap revealed clear cerebrospinal fluid at an opening pressure of 60 mm H2O. Ventriculography demonstrated a 1-cm shift of the right lateral ventricle to the left. Because of the deteriorating neurological status indicative of uncal herniation, an exploratory right parietal craniotomy was performed. The dura was extremely tense and when incised in the anteroinferior parietal region the brain ruptured spontaneously through the pia. The inferior portion of the right parietal lobe was yellow and avascular. A ventricular needle was introduced in an attempt to locate an intracerebral hematoma, but none was encountered and the operative procedure was terminated. The patient died shortly thereafter.

Pathological Findings

The contours of the 1,450-gm brain were distorted by a large, soft, recent infarct in the right frontoparietal area. The expansile character of this lesion had induced subfalcine and transtentorial herniations and had produced a groove in the ipsilateral third cranial nerve. Although confined largely to the parietal and posterior frontal lobes, the infarct extended into the anterior portion of the occipital lobe and also involved the superior temporal gyrus. Within this recent lesion, there were scattered older (2 to 3 cm) cystic infarcts. Petechiae were dispersed throughout both cerebral hemispheres, but were most prominent on the right.

The large vessels at the base of the brain were unremark-
able and essentially free of atherosclerosis. The peripheral branches of the middle cerebral arteries over the cerebral convexities, especially on the right, showed segmental nodular thickenings associated with marked reductions in luminal diameters.

The recent cerebral infarcts were characterized microscopically by myelin pallor, neuronal eosinophilia and karyolysis, and marked perivascular and perineuronal vacuolation. The older lesions were either cystic or filled with gitter cells, and sometimes surrounded by hemosiderin-laden macrophages and mineralized neurons.

Throughout both cerebral hemispheres, but to a much greater extent on the right in the distribution of the middle cerebral artery, there was a striking, severe granulomatous inflammation of arteries, arterioles, and, to a lesser extent, veins and venules (figs. 2 to 7). The angiitis was much more prominent in the pial vessels, but also affected those within the parenchyma. The basic lesions were aggregates of epithelioid cells containing occasional multinucleated forms. These aggregates involved either the entire vascular circumference (fig. 2) or just a sector (fig. 3) and were noteworthy for their segmental distributions (figs. 4 and 5). Small clusters of these epithelioid cells sometimes appeared independent of vessels so as to simulate intraparenchymal tubercles, but adjacent sections usually demonstrated a vascular association, or a reticulin stain disclosed the outlines of a vessel in the midst of the epithelioid response.

The epithelioid aggregates in arteries were usually positioned within the outer media and adventitia (figs. 2, 3, and 4). Although the intima sometimes shared in the epithelioid response, more often it showed only thickening by fibrous tissue, foam cells, lymphocytes, and recent and old thrombi (figs. 2 and 4). The exact position of the epithelioid cells in veins was more difficult to define and their infiltration was more often transmural (figs. 5 and 6). Distinguishing arterial or venous landmarks were sometimes obliterated by the severity of involvement. Conspicuous lymphocytic aggregates containing a rare eosinophil cuffed both the affected vessels and smaller vessels throughout the parenchyma.

Although the vast majority of the granulomatous lesions were noteworthy for the absence of necrosis, in two vessels, deeply eosinophilic granular necrotic areas were surrounded by elongated epithelioid cells.

In addition to the scattered multinucleated forms that were randomly dispersed within the epithelioid aggregates, other larger multinucleated cells were aligned along the inner media where they cradled or surrounded amorphous basophilic material (fig. 7). These masses were stained positively for elastic tissue or, less commonly, for iron, and were sometimes noted along the intima without the epithelioid response. These were not consistent findings, however, and the media of many vessels were overrun by epithelioid cells in the absence of any apparent abnormalities in the internal elastic lamellae. One artery contained multiple giant cells that surrounded lucent, birefringent fibers similar to those presumed to be cotton fibers sometimes noted after cerebral arteriography.1

In addition to the active lesions described above, many vessels, especially the larger pial branches of the right mid-
FIGURE 4. Longitudinal sections of the wall of a large cerebral artery show, in a Masson preparation (right) (×170), the presence of epithelioid cells in the media and associated thickening of the underlying intima. The resultant disorganization of the media is better appreciated in an adjacent section stained for reticulin by the Wilder technique (left) (×170). I = intima, M = media, A = adventitia.

die cerebral artery, showed lesions of greater chronicity as evidenced by organized thrombi, scant inflammatory infiltrates, and mural and perithelial fibrosis.

PAS and methenamine silver stains on histological sections from multiple areas failed to disclose fungi; similarly negative were stains for acid fast bacilli, gram negative or positive organisms, and spirochetes.

The brain stem, cerebellum, and spinal cord were free of vasculitis. The latter showed Wallerian degeneration of the left lateral corticospinal tract.

The general autopsy revealed the aorta and carotid arteries in the neck to be unremarkable. The heart was normal and showed no evidence of valvular disease or mural thrombus formation. There were multiple small old infarcts in both kidneys.

Careful examinations of multiple histological sections disclosed only one extracranial focus of angiitis which appeared as a nodular aggregate of epithelioid cells within the intima of a lobar vein in the right kidney (fig. 8). One lymph node at a pulmonary hilum contained a cluster of epithelioid and giant cells without necrosis. No acid fast bacilli or fungi were identified within either of these granulomatous foci.

Discussion

The clinical course, the angiographical findings, and the postmortem examination of the present case document the presence and effect of an angiitis largely confined to the nervous system and characterized by a vascular infiltration of epithelioid cells, giant cells, and lymphocytes in the absence of a demonstrable infectious agent. As such, this case conforms to the "entity" of granulomatous, or giant-cell granulomatous, angiitis.29 Similar, and possibly identical, lesions have been reported under the term giant-cell arteritis.10-12

Granulomatous angiitis has rather distinctive characteristics that appear to define it as a clinicopathological entity. However, its true individuality rests on the differentiation of this disorder from the other vasculitides which affect the central nervous system. Notable among the latter are the collagen vascular diseases, sarcoidosis, giant-cell (temporal) arteritis, granulomatous angiitis associated with Hodgkin's disease, allergic angiitis, infectious angiitis, Takayasu's disease, and rheumatoid arthritis. Some of these are readily distinguished from the granulomatous angiitis in question, others are not.
The vascular lesions of the collagen-vascular diseases of polyarteritis nodosa\textsuperscript{12-17} and systemic lupus erythematosus\textsuperscript{18} are known for their predominant extracranial positions and, in the case of lupus, for a predilection for young women. By contrast, granulomatous angiitis is predominantly intracranial, affects the sexes in approximately equal incidence, and usually occurs later in life. Furthermore, the acute necrotizing character of polyarteritis,\textsuperscript{12-17} and to a lesser extent lupus, the propensity of lupus to involve smaller vessels,\textsuperscript{18} and the tendency, although not absolute,\textsuperscript{17} of polyarteritis to spare veins are distinguishing features. It is of interest that the small aneurysms which characterize the extracranial vessels in polyarteritis may in certain cases also be visualized roentgenographically in the cerebral vessels.\textsuperscript{16}

As evidenced by cases reported as sarcoidosis, but which could also be interpreted as granulomatous angiitis,\textsuperscript{19-20} or vice versa by cases reported as granulomatous angiitis which might be sarcoidosis,\textsuperscript{6} these two entities are not always readily distinguished. Both are or may be systemic diseases and are characterized by non-caseating granulomatous inflammation. Sarcoïdosis, moreover, may feature a prominent vasculitis in other organs.\textsuperscript{21} The character of sarcoidosis with its epithelioid cells, giant cells, and elastic membrane degeneration is unquestionably very similar to that of granulomatous angiitis. Sarcoïdosis, however, usually is positioned at the base of the brain, although disseminated lesions may occur,\textsuperscript{22} and is noted more for discrete perithelial tubercles rather than the unrestrained epithelioid cell proliferation of granulomatous angiitis.\textsuperscript{23} While not a conspicuous part of the latter entity, necrosis is still more prominent than in most cases of sarcoidosis.

A number of cases of intracranial arteritis similar, if not identical, to granulomatous angiitis have been reported as...
cranial involvement. Other allergic vasculitides are known for systemic distribution and marked necrotizing vascular changes. In one case in which there was extensive extracranial involvement, a renal vein; its morphology and position resemble, but are not entirely identical to, the intracranial vasculitis (H & E, X250).

“giant-cell arteritis.” By either statement or implication, it has been suggested that these cases bear identity with giant-cell arteritis of the temporal arteries. Certainly, the presence of giant cells and elastic membrane degeneration is common to both granulomatous angiitis and temporal arteritis, the age of incidence is similar, and there are well-documented examples of concomitant temporal arteritis and intracranial angiitis wherein veins may also show involvement. Elevated erythrocyte sedimentation rates are also seen frequently in both conditions. However, in general, temporal arteritis is known for its aversion of the central nervous system, it eschews venous involvement, and pathologically it is not characterized by the marked granulomatous response of granulomatous angiitis. Unfortunately, the temporal arteries were not examined in the present case.

Rarely, a cerebral vasculitis of granulomatous nature characterized by epithelioid cells, giant cells, and lymphocytes in small arteries and veins is associated with Hodgkin’s disease. Although this angiitis is in many respects identical to the cerebral granulomatous angiitis in the present report, its relationship, if any, to the latter entity remains uncertain.

An entity described as allergic granulomatosis shares the epithelioid cell response of granulomatous angiitis, but in the original report it was noted for extracranial disease and a close association with asthma. Although asthma has not been documented in most cases of granulomatous angiitis, it was present in one case in which there was extensive extracranial involvement. Other allergic vasculitides are known for systemic distribution and marked necrotizing vascular changes.

A granulomatous vasculitis is frequently a component of tuberculous meningitis, but is distinguished by the presence of acid fast bacilli together with necrosis. Because of their ability also to elicit granulomatous responses, other microorganisms such as Listeria monocytogenes and Treponema pallidum have been evaluated as etiologic agents in granulomatous angiitis. Serologic tests for syphilis in patients with the latter disorder have, with only rare exception, however, been negative, and no organisms have been cultured from the cerebrospinal fluid or identified in tissues. Aspergillosis and phycymycosis (mucormycosis) are noteworthy for vasculitis, but these infections most frequently occur in the immunologically compromised patient or diabetic, pursue a rapid course, and are caused by the unmistakable large hyphae.

Takayasu’s disease and other diseases of the aortic arch often produce prominent cerebral symptoms, but do so by their stenosing effect on the aorta and its large extracranial branches. Aortic arch disease, furthermore, has not been associated with documented intracranial granulomatous angiitis and the pathological findings, although not completely characterized and usually evaluated in the chronic stage, are predominantly those of chronic inflammation and fibrous scarring rather than the exuberant epithelioid response of granulomatous angiitis.

Changes consistent with cerebral vasculitis have been documented by angiography in rheumatoid arthritis, but there has been no consistent history of significant joint disease associated with intracranial granulomatous angiitis. Thus a number of arteritides share clinical and/or pathological features of granulomatous angiitis. For the reasons enumerated above, we suggest that intracranial granulomatous angiitis be viewed as an entity, at least until more compelling data are at hand to establish its relationship to other forms of extracranial or intracranial angiitis.

In the present case, this disorder usually presents in adults in the fifth through eighth decades with mental changes and localized neurological deficit in accompaniment with signs and symptoms of increased intracranial pressure — a combination which may initiate concern about a neoplasm. The cerebrospinal fluid has consistently revealed lymphocytosis and elevated protein. Cerebral arteriography in at least one previous case designated as “giant-cell angiitis” demonstrated changes similar to those of the present case. The disorder ordinarily terminates fatally in from 1 to 12 months, although the course in some patients is more prolonged.

Although usually restricted to the central nervous system, complete autopsies in some of the previous cases have shown a systemic component by the demonstration of cardiac, aortic, lymphatic, pulmonary, or abdominal visceral granulomatous angiitis. The present case includes the kidney among these extracranial sites. The nodal focus of granulomatous inflammation within a mediastinal lymph node in this case is a common autopsy finding, so that although it may relate to the granulomas in the kidney and the brain, it may also be coincidental.

The etiology of granulomatous angiitis is unknown. The failure to demonstrate stainable organisms within the tissue or recover infectious agents in the cerebrospinal fluid has encouraged the use of the prefix “noninfectious.” However, like sarcoid, the intense granulomatous response is tantalizing to those accustomed to associate such inflammation with...
infection. Kolodny et al. have noted a similarity between this human disease and a cerebral angiitis associated with mycoplasma infection in young turkeys, but, like many others, are more inclined to view human granulomatous angiitis as an autoimmune phenomenon. One case has responded favorably to steroids. Clearly, the definitive answer regarding an infectious etiology will come only from detailed culture studies of the affected vessels.

Addendum

Since this manuscript was submitted, two case reports of granulomatous angiitis have appeared which bear on the possible infectious etiology of this entity. Reyes et al. (Neurology 26: 797-799, 1976) identified intranuclear "virus-like" particles in brain tissue obtained postmortem. Scully et al. (New Engl J Med 295: 944-950, 1976) discussed the pathological findings in a cortical biopsy specimen and reported negative results of culture for tubercle bacilli and other infectious agents.

References


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