Granulomatous Angiitis of the Central Nervous System ***—A Case with Recurrent Intracerebral Hemorrhage—***

Kinzo IWATA, Norio MISU and Yoshiharu NARA*

*Department of Neurosurgery, Atsumi Hospital, Aichi; *Department of Pathology,
Nagoya University School of Medicine, Nagoya*

Abstract

Granulomatous angiitis of the central nervous system occurred in a 43-year-old male presenting with recurrent intracerebral hemorrhage confirmed by computed tomography. A surgical specimen obtained at hematoma removal revealed granulomatous angiitis. Systemic investigation found no underlying cause for the hemorrhage. Although the incidence is very low, this condition should be considered in cases of recurrent intracerebral hemorrhage with unknown cause. When surgery is indicated, biopsy of the brain and leptomeninges should be obtained, because involvement of the leptomeninges has occurred in virtually all autopsy cases.

Key words: granulomatous angiitis, vasculitis, intracerebral hemorrhage

Introduction

Granulomatous angiitis of the central nervous system (GANS) is a pathologically distinct disease characterized by necrotizing vasculitis restricted to small to medium-sized blood vessels of the brain and spinal cord, sometimes extending to the venous system.^{8,9,17,18,22,23,30,37)} GANS usually carries a poor prognosis, typically with progressive deterioration and death within weeks to months.^{9,19,23)} Diagnosis is often made only at autopsy due to the rarity and absence of clinical characteristics.^{18,36-38)}

We report a case of GANS with intracerebral hemorrhage which recurred in the contralateral hemisphere to the initial event after 1 year.

Case Report

A 43-year-old male presented with a 1-week history of progressive headache accompanied by nausea and vomiting. On admission, he had no neurological deficits and was normotensive. His temperature was 36.7°C, sedimentation rate was 5 mm/hr, and white blood cell count was 9800/mm³. He denied any history of hypertension. Computed tomographic (CT) scans of the brain disclosed a hematoma in

the right frontal lobe near the Sylvian fissure (Fig. 1). Cerebral angiograms showed a minor focal irregularity of the middle cerebral artery, but no aneurysm (Fig. 2). The hematoma was not large, but craniotomy was performed to remove the hematoma and to obtain a tissue diagnosis for the source. The postoperative course was uneventful and the histological specimen was nondiagnostic. Postoperatively, systemic or local infection was ex-

Fig. 1 *left*: Precontrast CT scan on first admission, demonstrating right frontal intracerebral hematoma. *right*: Postcontrast CT scan, demonstrating no abnormal enhancement.

Received January 17, 1992; Accepted April 14, 1992

Author's present address: K. Iwata, M.D., Department of Neurosurgery, Jichi Medical School, Tochigi, Japan.

Fig. 2 Oblique right carotid angiogram on first admission, showing minor focal irregularity (arrows) of the middle cerebral artery, but no aneurysm.

Fig. 3 Precontrast CT scan on second admission, demonstrating left frontal intracerebral hematoma.

cluded. Signs of inflammation were absent, so he was maintained only on prophylactic phenytoin.

Eighteen months later, he complained of a headache and speech difficulties for 5 days. On second admission, he had mild right hemiparesis and expressive aphasia. CT scans showed a hematoma in the left frontal lobe (Fig. 3). He was normotensive, with sedimentation rate 8 mm/hr, white blood cell count 13,300/mm³, normal coagulation tests including coagulation factors VIII and IX of 106 and 146% (normal range, 50–150 and 60–140%), negative autoimmune complex, and normal angiotensin-converting enzyme level of 12.7 IU/l (normal range, 8.3–21.4 IU/l). Cerebral angiograms revealed deformed Sylvian triangle and avascular mass. The vessel walls were normal in appearance (Fig. 4).

Fig. 4 Left carotid angiograms, lateral (left) and anteroposterior (right) views, showing normal vessels although the Sylvian triangle was deformed by the mass effect from the intracerebral hematoma.

Craniotomy was again performed. The postoperative course was difficult with recurrent bleeding requiring reoperation. He was discharged with minor right hemiparesis and expressive aphasia. He is now receiving low-dose corticosteroid therapy.

Brain and leptomeningeal specimens obtained at the second operation revealed GANS, mainly located in the meningeal blood vessels. Granulomas were composed of epithelioid cells, Langerhans' type giant cells, and a few small lymphocytes. One granuloma was enclosed in fibrous stroma but no prominent causative necrosis was seen (Fig. 5 upper). Neither nucleolar nor cytoplasmic inclusion bodies were present (Fig. 5 lower). No bacilli were present in sections stained by the Zeihl-Neelsen and periodic acid-Schiff methods. GANS was diagnosed based on the clinical course.

Discussion

GANS is a rare disorder of unknown etiology, with only 80 reported cases.^{5,36,37} Only two cases with or without concomitant cerebral amyloid angiopathy have been reported in Japan.^{20,24} GANS is possibly associated with immune compromised state, mycoplasma infection, herpes zoster infection,^{3,10,30,31,37} malignant lymphoma,^{13,25,28,30,37} and sarcoidosis.^{4,33} Electron microscopy has demonstrated particles resembling herpesvirus (varicella-zoster) and mycoplasma-like structures.^{1,11,21,29,36} A similar disorder was induced in turkey poults by intravenous injection of *Mycoplasma gallisepticum*, so inflammation resulting from this pathogen may be a cause.^{6,32}

Fig. 5 Photomicrographs of the surgical specimen. *upper*: Low magnification, showing granuloma composed of epithelioid cells, Langerhans' type giant cells, and a few small lymphocytes. One granuloma was enclosed in fibrous stroma, but no prominent causative necrosis was present. HE stain, $\times 100$. *lower*: High magnification, showing no nucleolar or cytoplasmic inclusion bodies. HE stain, $\times 400$.

GANS probably indicates a non-specific immunopathological response to a variety of antigens in the immunosuppressed state. This theory is also supported by improvement of the disease following corticosteroid therapy or a combination of corticosteroid, radiation, and chemotherapy.^{9,14,17,28)}

The average age of onset is 50 years old, with a slight predilection for males.²⁰⁾ The symptoms of GANS are usually saltatory and progressive. Non-focal symptoms of headache, obtundation, or dementia appear first, followed by findings referable to specific areas of central nervous system (CNS) damage. This sequence results from vessels narrowing secondary to the inflammatory process, with subsequent ischemic injury. The improvement in symptoms achieved by steroid treatment may reflect reduced vessel-wall inflammation and the concomitant increase in residual diameter. Severe thickening of the vessel walls may result in occlusion and in-

farction with or without hemorrhage. Saccular aneurysms may occur due to focal damage of vessel walls due to GANS, but subarachnoid hemorrhage is uncommon.¹⁴⁾ There is no predilection for any particular region of the CNS, and lesions can occur within the cerebrum, cerebellum, brainstem, or spinal cord.^{2,37)} Consequently, the presentation can mimic a tumor,^{19,34)} stroke,⁴⁾ unexplained cerebritis or encephalitis,³⁷⁾ or myelitis.^{9,20,26,37)} Recurrent intracerebral hemorrhage, as in our case, has also occurred.⁵⁾ GANS usually has a poor prognosis. Typically, patients progressively deteriorate and die within weeks to months.^{9,19,23)} In many cases, final diagnosis was made at the postmortem examination.^{2,8,15,23,29,30)}

No laboratory test is specific for the diagnosis of GANS. Even the cerebrospinal fluid (CSF) can be normal in the presence of inflammation.^{15,19)} CSF may demonstrate pleocytosis, elevated levels of protein, and normal levels of glucose. Elevated CSF pressure and hypoglycorrhachia may occur.^{8,9,15,23,27,29)} In contrast to other vasculitis, tests for antinuclear antibodies, rheumatoid factor, circulating immune complexes, and cryoglobulins are normal.^{19,37)} Although not specific, the erythrocyte sedimentation rate tends to increase in most GANS cases.

Mass effect due to infarction or hemorrhage may require surgery. In such cases, biopsy of the brain and overlying meninges is justified in the absence of another explanation for a clinical syndrome of encephalopathy evolving over days or weeks, especially with focal cerebral signs or abnormal CSF with pleocytosis and high protein content.^{15,35,38)} Seventeen biopsies of 50 GANS cases were reported, but only seven were diagnostic.¹⁸⁾ This low antemortem diagnostic accuracy is a problem and may be related to the segmental nature of the lesion.^{4,18,37)} When surgery is indicated, leptomeningeal biopsy may also be a useful diagnostic procedure because involvement of the leptomeninges occurred in virtually all autopsy cases.^{2,9,14,15,19,28,34,35)}

GANS is characterized histologically by chronic inflammatory cells: predominantly histiocytes, mononuclear cells, lymphocytes, epithelioid cells, and multinucleated giant cells.^{17,19,23,37)} Histological differentiation from neurosarcoidosis may be difficult. Other histological differential diagnoses include temporal arteritis, allergic granulomatosis, nodular polyarteritis, Takayasu's disease, and vasculitis due to tuberculosis, syphilis, mycosis, and allergic reaction to drugs.^{9,18)}

Cerebral angiographic findings have been claimed as diagnostic,^{4,12,14)} but this seems to be dubi-

ous.^{1,7,15,16)} In one-third of the cases, the angiograms are normal, and in one-fourth vessel narrowing and beading, and multiple dilatations have been reported. Other angiographic findings include aneurysms¹⁴⁾ and avascular mass lesions.^{2,19,28,34,37)} No specific angiographic finding alone can be considered diagnostic of GANS. CT is more sensitive than angiography, and in most cases either low-density area, mass effect, hemorrhagic area, atrophic area, or a combination are present.^{5,10-13,18,34,37,38)}

As the true etiology of GANS is unknown, therapy is directed against the inflammatory process. Steroids are the primary method of medical management.^{9,15,17,28,37)} Refractory or progressive cases may respond to immunosuppressive agents such as cyclophosphamide⁹⁾ or azathioprine.¹⁴⁾ Long-term administration of steroids may reduce the likelihood of further hemorrhage, and aggressive chronic steroid treatment appears to improve the otherwise dismal natural history of the disease.^{5,9,13,18,38)}

As in ours and other cases, a survival of more than 18 months without adequate corticosteroid treatment is rare, and spontaneous remission is exceptional. Recent claims of improved survival with early initiation of combined cyclophosphamide and corticosteroid therapy are based on cases diagnosed by angiography,¹⁹⁾ several without confirmation. Controlled therapeutic trials after biopsy are required for unequivocal evaluation,^{9,13,14,18,19,30)} but the condition is so rare that a multicenter trial is needed.

References

- 1) Arthur G, Margolis G: Mycoplasma-like structures in granulomatous angiitis of the central nervous system. *Arch Pathol Lab Med* 101: 382-387, 1977
- 2) Beresford HR, Hyman RA, Sharer L: Self-limited granulomatous angiitis of the cerebellum. *Ann Neurol* 5: 490-492, 1979
- 3) Blue MC, Rosenblum WI: Granulomatous angiitis of the brain with herpes zoster and varicella encephalitis. *Arch Pathol Lab Med* 107: 126-128, 1983
- 4) Burger PC, Burch JG, Vogel FS: Granulomatous angiitis: An unusual etiology of stroke. *Stroke* 8: 29-35, 1977
- 5) Clifford-Jones RE, Love S, Gurusinge N: Granulomatous angiitis of the central nervous system: A case with recurrent intracerebral hemorrhage. *J Neurol Neurosurg Psychiatry* 48: 1054-1056, 1985
- 6) Clyde WA, Thomas L: Pathogenesis studies in experimental mycoplasma disease. *Ann NY Acad Sci* 225: 413-424, 1973
- 7) Craven RS, French JK: Isolated angiitis of the central nervous system. *Ann Neurol* 18: 263-265, 1985
- 8) Cravioto H, Feigin I: Noninfectious granulomatous angiitis with predilection for the nervous system. *Neurology (Minneapolis)* 9: 599-609, 1959
- 9) Cupps TR, Moore PM, Fauci AS: Isolated angiitis of the central nervous system: Prospective diagnostic and therapeutic experience. *Am J Med* 74: 97-105, 1983
- 10) De Reuck J, Crevits L, Sieben G, DeCoster W, vander Eecken H: Granulomatous angiitis of the nervous system: A clinicopathological study of one case. *J Neurol* 227: 49-53, 1982
- 11) Doyle PW, Gibson G, Dolman CL: Herpes zoster ophthalmicus with contralateral hemiplegia: Identification of cause. *Ann Neurol* 14: 84-85, 1983
- 12) Faer MJ, Mead JH, Lynch RD: Cerebral granulomatous angiitis: Case report and literature review. *AJR* 129: 463-467, 1977
- 13) Greco FA, Kolins J, Rajjoub RK, Brereton HD: Hodgkin's disease and granulomatous angiitis of the central nervous system. *Cancer* 38: 2027-2032, 1976
- 14) Griffin J, Price DL, Davis L, McKhann GM: Granulomatous angiitis of the central nervous system with aneurysms on multiple cerebral arteries. *Trans Am Neurol Assoc* 98: 145-148, 1973
- 15) Harrison PE: Granulomatous angiitis of the nervous system. *J Neurol Sci* 29: 335-341, 1976
- 16) Hughes JT, Brownell B: Granulomatous giant-celled angiitis of the central nervous system. *Neurology (Minneapolis)* 16: 293-298, 1966
- 17) Kolondny EH, Rebeiz JJ, Caviness VS, Richardson EP: Granulomatous angiitis of the central nervous system. *Arch Neurol (Chicago)* 19: 510-524, 1968
- 18) Koo EH, Massey EW: Granulomatous angiitis of the central nervous system: Protean manifestation and response to treatment. *J Neurol Neurosurg Psychiatry* 51: 1126-1133, 1988
- 19) Kristoferitsch W, Jellinger K, Bock F: Cerebral granulomatous angiitis with atypical features. *J Neurol* 231: 38-42, 1984
- 20) Kusaka H, Hirano A: Two cases of granulomatous angiitis of the nervous system. *Shinkei Naika* 21: 38-45, 1984 (in Japanese)
- 21) Linnemann CC Jr, Alvira MM: Pathogenesis of varicella-zoster angiitis in the CNS. *Arch Neurol* 37: 239-240, 1980
- 22) Moore PM, Cupps TR: Neurological complications of vasculitis. *Ann Neurol* 14: 155-167, 1983
- 23) Nurick S, Blackwood W, Mair WPG: Giant cell granulomatous angiitis of the central nervous system. *Brain* 95: 133-142, 1972
- 24) Okamoto K, Yamazaki T, Hirai S: Cerebral amyloid angiography associated with granulomatous angiitis of the central nervous system. *No Socchu* 10: 509-512, 1988 (in Japanese)
- 25) Rajjoub RK, Wood JH, Ommaya AK: Granulomatous angiitis of the brain: A successfully treated case. *Neurology (Minneapolis)* 27: 588-591, 1977
- 26) Rawlinson DG, Braun CW: Granulomatous angiitis of the nervous system first seen as relapsing

- myelopathy. *Arch Neurol* 38: 129-131, 1981
- 27) Reik L Jr, Grunnet ML, Spencer RP, Donaldson JO: Granulomatous angiitis presenting as chronic meningitis and ventriculitis. *Neurology* 33: 1609-1612, 1983
  - 28) Rewcastle NB, Tom MI: Non-infectious granulomatous angiitis of the nervous system associated with Hodgkin's disease. *J Neurol Neurosurg Psychiatr* 25: 51-58, 1962
  - 29) Reyes MG, Fresco R, Chokroverty S, Salud EQ: Virus like particles in granulomatous angiitis of the central nervous system. *Neurology (Minneapolis)* 26: 797-799, 1976
  - 30) Rosenblum WI, Hadfield MG: Granulomatous angiitis of the nervous system in cases of herpes zoster and lymphosarcoma. *Neurology (Minneapolis)* 22: 348-354, 1972
  - 31) Rosenblum WI, Hadfield MG, Young HF: Granulomatous angiitis with preceding varicella zoster. *Ann Neurol* 3: 374-375, 1978
  - 32) Thomas L, David S, McClusky RT: Studies of PPLO infection: I. The production of cerebral polyarteritis by *Mycoplasma gallisepticum* in turkeys, the neurotoxic property of the *Mycoplasma*. *J Exp Med* 123: 897-919, 1966
  - 33) Urich H: Neurosarcoidosis or granulomatous angiitis: A problem of definition. *Mt Sinai J Med NY* 44: 718-725, 1977
  - 34) Valavains A, Friede R, Schubiger O, Hayek J: Cerebral granulomatous angiitis simulating brain tumor. *J Comput Assist Tomogr* 3: 536-538, 1978
  - 35) Vincent FM: Granulomatous angiitis. *N Engl J Med* 296: 452, 1977 (letter)
  - 36) Yankner DS, Skolnik PR, Shoukima GM, Gabuzda DH, Sobel RA, Ho DD: Cerebral granulomatous angiitis associated with isolation of human T-lymphotrophic virus type III from the central nervous system. *Ann Neurol* 20: 362-364, 1986
  - 37) Younger DS, Hays AP, Brust JCM, Rowland LP: Granulomatous angiitis of the brain: An inflammatory reaction of diverse etiology. *Arch Neurol* 45: 514-518, 1988
  - 38) Zimmerman RS, Young HF, Hadfield G: Granulomatous angiitis of the nervous system: A case report of long-term survival. *Surg Neurol* 33: 206-212, 1990

Address reprint requests to: K. Iwata, M.D., Department of Neurosurgery, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi-machi, Kawachi-gun, Tochigi 329-04, Japan.