Granulomatous Angiitis of the Central Nervous System
—Case Report—

Isao FUKASAWA, Shigeru MITSUKA, Hideaki NUKUI, Youji YOSHIDA*, Hidehito KOIZUMI**, Hiromichi YAMAZAKI**, Tetsuo WAKAO** and Hiromu SEGAWA***

Departments of Neurosurgery and *Pathology, Yamanashi Medical College, Yamanashi; **Department of Neurosurgery, Yamanashi Prefectural Central Hospital, Kofu; ***Department of Neurosurgery, Fuji Brain Institute and Hospital, Fujinomiya, Shizuoka

Abstract

A 22-year-old male presented with granulomatous angiitis manifesting as headache. Computed tomography (CT) demonstrated a low-density area and ring-like enhancement in the right frontoparietal region. Steroid therapy caused rapid improvement in the signs and symptoms. Withdrawal of steroid was followed by recurrence of the headache and low-density area. The steroid treatment was resumed until he became asymptomatic 3 months after admission. He was followed up as an outpatient once every 2 weeks. One month after discharge, he complained of mild headache, and CT again demonstrated a mild increase in the low-density area. He was followed up continuously without steroid treatment. Two months after discharge, he suddenly lost consciousness, and CT demonstrated multiple intracerebral hematomas in the bilateral parietal regions. Removal of an intracerebral hematoma in the right parietal region and external decompression were carried out, but he died 3 days later. Histological examination of tissues from the right parietal cortex and leptomeninges demonstrated granulomatous inflammation with several giant cells in the vessels of the cerebral cortex and leptomeninges.

Key words: granulomatous angiitis, giant cell, steroids

Introduction

Granulomatous angiitis of the central nervous system (CNS) is a rare disease characterized by granulomatous inflammation with giant cell infiltration around the medium and small vessels in the brain parenchyma and meninges. The character of the disease requires histological examination for diagnosis. Fifty-five cases with the definitive histological diagnosis1-16 have been reported, two in Japan17,18 both associated with cerebral amyloid angiopathy.

We report a patient with uncomplicated granulomatous angiitis, and discuss the correlations between steroid therapy, clinical symptoms, and computed tomographic (CT) appearance.

Case Report

A 22-year-old male was referred by a local clinic to our hospital on February 15, 1988, with an abnormal CT scan in the right frontoparietal region. He had suffered dull headache in the right frontal region since early January, 1988. His history included generalized convulsion in January, 1987, ulcerative colitis since age 16 years, and administration of salazosulfapyridine for a long time. However, he was in remission at the present admission. There was no contributory familial history.

On admission, his temperature was 37.5°C, and he was mildly emaciated. His consciousness was clear, but papilledema was observed. Laboratory examinations showed a slightly increased C-reactive protein (CRP) level at 2.18 mg/dl, but blood cell counts, erythrocyte sedimentation rate, and immunoglobulin levels were normal. Tests for serum *Treponema
pallidum hemagglutination, rheumatoid factors, and autoantibodies were negative. However, the serum complement titer (CH50) was reduced to 44.4 (normal 70–110). Plain chest x-ray films, electrocardiograms, and general urinary and fecal analyses found no abnormalities.

Precontrast CT scans of the head on February 15 revealed an elliptical low-density area in the right frontoparietal region about 60 mm in diameter with an irregular border. Another low-density mass about 15 mm in diameter suggestive of a cystic lesion was present between the low-density area and the brain surface. Postcontrast CT scans showed ring-shaped enhancement with a smooth internal surface and slightly irregular thickness around the cystic lesion (Fig. 1). Right carotid angiograms showed dissociation in the ascending branches of the middle cerebral artery, but no vascular anomalies, irregularities of the arterial wall, or stenotic lesions. Cerebrospinal fluid (CSF) analysis showed the opening pressure of 190 mmH₂O, cell count 61/mm³ (mononuclear cells 58, segmented leukocytes 3), protein content 134 mg/dl, and glucose content 46 mg/dl. The results of smear staining, culture, and cytological tests were all negative.

A brain tumor was suspected, but his family rejected surgery. Conservative therapy containing steroid (betamethasone 16 mg/dl) and glycerol (600 ml/day) was begun, resulting in immediate relief of fever and headache. CT scans on February 25, 9 days after beginning the treatment, showed reduction in the lesion size (Fig. 2 upper). Administration of steroid in gradually reduced doses was temporarily suspended. Fever and headache recurred 3 days after discontinuation of steroid treatment, and CT scans showed mild enlargement of the low-density area.

Fig. 1 Pre- (left) and postcontrast (right) CT scans on February 15, showing a diffuse low-density area with small ring-like enhancement in the right frontoparietal region.

Fig. 2 Serial pre- (left) and postcontrast (right) CT scans on February 25 (upper), April 28 (middle), and June 9 (lower), showing the decrease in the low-density area and disappearance of the ring-like enhancement, but the later enlargement of the low-density area.
The steroid therapy was therefore resumed, with clinical symptoms and CT findings again showing a good response. On April 28, CT scans revealed only a small residual lesion (Fig. 2 middle). He was discharged on May 13 without symptoms and was followed up at the outpatient clinic.

About 1 month later, fever and headache recurred, and CT scans showed that the same low-density area had enlarged again as at initial hospitalization (Fig. 2 lower). However, observation on an outpatient basis was continued without steroid therapy because of the absence of neurological abnormalities. On July 8, he suddenly lost consciousness and was taken to a local hospital. Neurological examination revealed that his level of consciousness was 100 on the Japan Coma Scale (Glasgow Coma Scale: 6). His right pupil was dilated and his eyes were deviated to the right. CT scans 3 hours postictus showed an enlarged low-density area in the right frontoparietal region and a high-density area with an irregular low-density center in the parietal subcortical area. Similar changes were also noted in the left parietal region (Fig. 3). Removal of the hematoma in the right parietal region and external decompression were carried out immediately. The postoperative course was disastrous because of severe brain edema, and he died on July 12.

Light microscopy examination of tissues from the right parietal lobe revealed multiple granulomatous angiitis mainly in the venules and capillaries of the subarachnoid space and cerebral cortex (Fig. 4). Both effusion and granulation phases of angiitis, and the transitional type between these two phases were observed. The effusion phase demonstrated infiltration of large and small mononuclear cells combined with neutrophils, and fibrinoid degeneration. The granulation phase showed histiocytes and Langhans-type giant cells proliferating nodularly around the vessels with lymphocyte infiltration. Amyloid staining showed no deposition of amyloid in the vascular wall or granuloma. Gram, periodic acid-Schiff, Ziehl-Neelsen, and Warthin-Starry staining detected no bacteria, fungi, tubercle bacillus, or Spirochaeta pallida. The final cause of death was cerebral hemorrhage secondary to granulomatous angiitis.

**Discussion**

Histological examination is essential for the definitive diagnosis of granulomatous angiitis of the CNS. The characteristic histological findings are granulomatous inflammation with infiltration of...
multinucleated giant cells into the walls of medium or small arteries and veins of the brain parenchyma and meninges. The inflammation involves nearly the entire thickness and circumference of the vessel wall. Most infiltrated cells are lymphocytes, histiocytes, and epithelioid cells, although neutrophils are occasionally observed, and eosinophils are uncommon. The inflammation is more intense in the meninges than in the brain parenchyma, and in arteries than in veins or capillaries. These typical histological features were observed in our case.

The etiology of granulomatous angiitis remains unknown. Previous reports have often suggested a relationship with infection or malignant hematological neoplasm, but no confirmation is available. Herpes zoster and mycoplasma-like particles in giant cells have occurred as combined infections. Immunosuppressive states after intensive chemotherapy for leukemia have also been associated, suggesting involvement of immunological disorders. Our case showed no hematological infection or malignancy, including bacteria, fungi, tubercle bacillus, or syphilis spirochete. The possibility of immunological abnormalities was excluded because of normal immunoglobulin and autoantibody levels, and no deposits of amyloid in the affected vascular wall. Autoimmune disease or ulcerative colitis, which is considered analogous to autoimmune disease, have not occurred with granulomatous angiitis, and the relationship with autoimmune disease is unclear. However, the reduced serum complement level and the effectiveness of steroid therapy in this case may suggest that the autoimmune process has an etiological role in this disease.

Review of 56 reported cases including ours indicates that onset occurs from 15 to 96 years (mean 50.5 yrs), and males are more often affected than females (male:female 37:19 cases). The cerebrum (53 cases, 95%) is the most frequently involved site, followed by the pons or medulla oblongata (18, 32%), cerebellum (10, 18%), and spinal cord (9, 16%). The initial symptom was headache in 27 cases, consciousness disturbance in 11, and convulsive attacks and psychiatric symptoms in five. Two major clinical symptoms appearing during the course are signs of increased intracranial pressure such as headache or papilledema and focal neurological signs which vary widely depending on the affected site. However, no symptoms are specific for this disease. Non-specific signs of inflammation such as increased white blood cell count, enhanced erythrocyte sedimentation rate, and positive CRP are occasionally observed, but are not characteristic of the disease. CSF analysis in 44 cases frequently indicated increased protein concentration (43 cases) and mononuclear cells (42), as in our case. Increased CSF pressure (17 cases) is a relatively common sign.

CT in 20 cases demonstrated abnormal low-density areas in 13 cases and high-density areas in five. In our case, CT showed a subcortical low-density area with cystic lesion showing ring-like enhancement postcontrast. Since the subcortical low-density area shrank and disappeared relatively quickly after the beginning of steroid and glycerol treatment, this was probably brain edema caused by increased vascular permeability associated with angiitis, i.e. vasogenic edema. However, since the wall of the cystic lesion was enhanced, this was an old hemorrhage. In our case, the remission and recurrence of the CT findings and clinical symptoms were clearly correlated with steroid administration (Fig. 5), as in other cases reported.

Cerebral angiography revealed abnormalities in 18 of 26 patients previously reported, nine showing only signs of the mass lesions such as an avascular area as associated with vascular deviation as in our case. Vascular wall abnormalities such as caliber change or stenotic lesion, which may suggest this disease, occurred in only 11 cases.

Granulomatous angiitis is difficult to diagnose clinically, because there are no specific clinical features or laboratory findings as described above. Previous diagnosis was antemortem in 10 patients undergoing biopsy, four undergoing operation for suspected brain tumor, and one undergoing operation for the cerebral hemorrhage as in our case, out of 56 reported cases. One characteristic of this disease is rapid response of clinical symptoms and CT findings to steroid therapy. Steroids were effec-
Cerebral infarction due to multiple stenoses and obstruction of medium to small vessels of the brain was responsible for the death of 35 of 43 patients. Only five patients including ours died of cerebral hemorrhage, but the mechanism of bleeding is obscure. Even in those who died, steroid therapy clearly prolonged the mean period from onset to death, 43.4 weeks in 13 patients receiving steroids and 17.7 weeks in 29 who did not. Therefore, the administration of steroids should be initiated whenever this disease is suspected and maintained, indicating granulomatous angiitis when there is a relatively quick response of clinical symptoms and CT findings, even if no abnormalities are detected by cerebral angiography or biopsy. Meticulous observation is mandatory during withdrawal of steroids, which should be resumed if deterioration of clinical symptoms and/or CT findings occurs as in our case. Our patient died of bleeding into the bilateral parietal lobes during the period without steroid therapy, which may have been prevented by immediate resumption when the low-density area on CT again enlarged.

References

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Address reprint requests to: I. Fukasawa, M.D., Department of Neurosurgery, Yamanashi Medical College, 1110 Shimokato, Tamaho-machi, Nakakoma-gun, Yamanashi 409-38, Japan.