Multifocal Fibrosclerosis with Intracranial Pachymeningitis

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A 29-year-old woman with a 4-year history of multifocal fibrosclerosis showed unique neurologic complications. Episcleritis, orbital pseudotumor, and eosinophilic phlegmon preceded intracranial inflammatory pachymeningitis. The pachymeningitis was associated with disturbance of the visual field, incomplete Gerstmann's syndrome, and pseudotumor cerebri. T₂-weighted magnetic resonance images revealed a high signal intensity lesion in the left temporal and occipital lobes, and gadolinium-enhanced T₁-weighted images revealed the enhancement of the thickened left tentorial leaf. The laboratory data suggested that the etiology might be autoimmune. The disease and MRI abnormalities improved following administration of corticosteroids. (Internal Medicine 34: 267-271, 1995)

Key words: episcleritis, orbital pseudotumor, eosinophilic phlegmon, Gerstmann's syndrome, sensory aphasia, corticosteroids

Introduction

Multifocal fibrosclerosis is the term used to denote a combination of similar fibrous disorders occurring at different anatomical sites. The more common of these disorders include retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis and orbital pseudotumor (1). Other manifestations of multifocal fibrosclerosis include Dupuytren's contractures, Peyronie's disease, fibrosis of the subcutaneous tissues, and vasculitis (2). The disorder is of unknown etiology but may be familial (3), autoimmune (4), associated with alpha-1-antitrypsin deficiency (5), or, rarely, sporadic in nature. Almost all of the cases of this entity are reported to involve intracranial structures presenting orbital pseudotumor and parasellar or intrasellar masses in conjunction with orbital pseudotumor (6, 7). However, to our knowledge, only two cases of multifocal fibrosclerosis with intracranial pachymeningitis have been reported (2, 4). We describe a 29-year-old woman with a 4-year history of multifocal fibrosclerosis that resulted in bizarre, previously undescribed neurological abnormalities.

Case Report

In July 1988, this Japanese woman developed a painful injected left eye when she was 25 years old, about one month after the birth of her second child. In December 1988, she noted increased protrusion of the left eye. The laboratory evaluation was normal except for a 15 mm/hr erythrocyte sedimentation

rate (ESR) and 123 IU/ml RA test (normal range; <20). Computed tomography (CT) scans of the orbits revealed a mass in the left orbit and proptosis (Fig. 1), and biopsy of the mass in the left orbit revealed chronic inflammatory granuloma. Episcleritis and orbital pseudotumor were diagnosed. After betamethasone drops were applied to the eye, the left orbital mass disappeared.

In September 1989, the patient developed a painful swelling of the right ankle. The white blood cell count (WBC) was 12,400/mm³, and eosinophils were increased to 55% of WBC. ESR was 34 mm/hr, and RA test was 1,088 IU/ml. Autoantibody positivity for antinuclear antibody of 40x (<40, homogenous pattern) and anti-DNA antibody of 160x (<80) were noted. Biopsy of the skin revealed eosinophilic phlegmon (Fig. 2), which improved after administration of prednisolone (30 mg daily).

In December 1989, progression of the episcleritis of the left eye was noted. The ESR was 19 mm/hr, and RA test 757 IU/ml. The episcleritis was improved following subconjunctival injection of dexamethasone and oral prednisolone (30 mg daily).

In August 1992, at the age of 29 years, the patient noted a slight fever and left temporal headache, it had been six months since the birth of her third child. She was admitted because of severe headache, which was accompanied by vomiting and photopsia on the right side of the visual field. On admission, blood pressure was 110/60 mmHg, and pulse rate 72/min and regular. The physical examination demonstrated no abnormal signs. The neurological examination revealed incomplete Gerstmann's syndrome, including the symptoms of incomplete

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Fig. 1. Orbital pseudotumor. A CT scan of the orbits discloses a mass in the left orbit and proptosis.

Fig. 2. Eosinophilic phlegmon. Diffuse infiltration of eosinophils is observed in the connective tissue (HE stain, ×100).

alexia, agraphia, acalculia, and slight sensory aphasia. There was neither papilledema nor nuchal rigidity.

The red blood cell count was $3.55 \times 10^4/\text{mm}^3$, Hb 11.0 g/dl, hematocrit 31.3%, and WBC $6100/\text{mm}^3$ (normal differential). ESR was 89 mm/hr, and C-reactive protein 1.00 mg/dl. Biochemical tests of the blood were normal except for elevated gamma globulin (27.5%). Immunoglobulin and complement levels were increased; immunoglobulin (Ig) G was 2,400 mg/dl, IgA 440 mg/dl, IgM 419 mg/dl, C3 87 mg/dl, C4 23.4 mg/dl, and CH50 51.4 U/ml (30.0–40.0). RA test was 15.44 IU/ml.

She was a hepatitis B virus carrier, but her liver function was normal. Lumbar puncture revealed an opening pressure of 160 mmH₂O. In the cerebrospinal fluid (CSF) mononuclear cells were $8/\text{mm}^3$, protein concentration was 41 mg/dl, glucose was 90 mg/dl, and IgG was 9.3 mg/dl. The IgG index of the CSF was 1.01 (<0.5). The CSF cytology was normal, and bacterial, mycobacterial and fungal cultures were negative. CT of the brain revealed a hypodense lesion in the left temporal and occipital lobes and an abnormal thickening of the tentorial leaf on the left side. The thickened left tentorial leaf was enhanced

Fig. 3. CT scans of the brain obtained on admission. A) Axial CT scan reveals a hypodense lesion in the left temporal and occipital lobes. B) Contrast-enhanced coronal CT scan discloses that the thickened left tentorial leaf is enhanced.

after intravenous injection of contrast material (Fig. 3). Magnetic resonance imaging (MRI) disclosed a high signal intensity lesion in the left temporal and occipital lobes on T₂-weighted imaging (Fig. 4A) and enhancement of the thickened left tentorial leaf on coronal gadolinium-enhanced T₁-weighted imaging (Fig. 4B).

Antinuclear antibody and anti-DNA antibody were negative at this admission. Thyroid test, microsome test, anti-RNP antibody and lupus anticoagulant were negative. Alpha-1-antitrypsin and angiotensin converting enzyme levels were normal. LE test was negative. Syphilis serology and tuberculin intradermal reaction were negative. Detailed immunologic studies including analysis of lymphocyte subsets, blastogenesis, mitogenesis assays and immune complexes by Clq binding assay yielded normal results. She was diagnosed as intracranial pachymeningitis based on the symptoms, the slightly elevated CSF pleocytosis, the elevated IgG index of CSF, and CT scans and MRI findings.

The patient was treated with intramuscular dexamethasone (12 mg) with gradual dosage tapering. Her headache, photopsia, incomplete Gerstmann's syndrome and sensory aphasia were temporarily improved but soon progressed again. She was treated with intravenous methylprednisolone (1,000 mg/day) for three days (methylprednisolone pulse therapy). The symptoms improved promptly. After several pulse therapies, symptoms were no longer present in February 1993, and the abnormal laboratory data had normalized (ESR, 5 mm/hr, serum IgG, 787 mg/dl, mononuclear cells in the CSF, 2/mm³, IgG index of the CSF, 0.59) (Fig. 5). CT of the brain revealed a slightly enhanced thickened left tentorial leaf and slightly hypodense

lesion in the left temporal lobe (Fig. 6).

During the clinical course, in November 19, 1992, the patient experienced an episode of drowsiness. Electroencephalogram (EEG) demonstrated irregular alpha rhythm mixed with sharp wave in the left occipital leads and slow wave bursts (about 3 Hz) in the left hemisphere leads. The drowsiness was controlled with phenytoin at the dosage of 300 mg/day.

As of November, 1994, the patient was receiving prednisolone at the dose of 15 mg daily and was free from any symptoms.

Discussion

The combination of neurologic abnormalities observed in our patient with multifocal fibrosclerosis is unique. The illness was heralded by episcleritis with the subsequent development of orbital pseudotumor, eosinophilic phlegmon and pachymeningitis. Neither mediastinal nor retroperitoneal fibrosis, which are frequent features of multifocal fibrosclerosis, were present. The neurologic manifestations included headache, pseudotumor cerebri, seizures, Gerstmann's syndrome, and sensory aphasia. We considered that meningeal inflammation extended to the left temporal and occipital lobes, and that this inflammation caused these neurologic manifestations. This hypothesis was supported by the findings of coronal gadolinium-enhanced MRI which disclosed the enhancement of the left tentorial leaf that extended to the left tentorial lobe (Fig. 4B). The fluctuation in these neurologic symptoms was presumably related to the severity of meningeal inflammation, which was itself affected by the therapeutic intervention.

Fig. 4. MR images of the brain on admission. A) Axial T₂-weighted image discloses a high intensity lesion in the left temporal and occipital lobes. B) Coronal gadolinium-enhanced T₁-weighted image discloses that the thickened left tentorial leaf and left temporal lobe are enhanced.

Fig. 5. The clinical course of the present patient. ESR: erythrocyte sedimentation rate, IgG: immunoglobulin G, p.o.: per os, i.v.: intravenous, i.m.: intramuscular.

Fig. 6. CT scan obtained after the therapy. Coronal CT scan discloses slight enhancement of the left tentorial leaf.

Involvement of intracranial structures has been reported in some cases of this entity, consisting almost always of orbital pseudotumor and parasellar or intrasellar masses occurring in conjunction with orbital pseudotumor (6, 7). To our knowledge, there are only two reports of multifocal fibrosclerosis with pachymeningitis (2, 4). Berger et al (2) described a 34-year-old man with episcleritis, orbital pseudotumor, sclerosing cholangitis and intracranial inflammatory pachymeningitis. The latter was associated with blindness, multiple cranial neuropathies, pseudotumor cerebri, and seizures. Sawada et al (4) described a 78-year-old woman with pericarditis and pachymeningitis, which improved after administration of corticosteroids.

Toda et al (7) reported that idiopathic intracranial pachymeningitis might occur in isolation without any features of multifocal fibrosclerosis. They have reported two patients, who developed progressive headache and multiple cranial neuropathies resulting from hypertrophic pachymeningitis.

The etiology of multifocal fibrosclerosis is unknown. In the present patient, Wegener's granulomatosis, polyarteritis nodosa, and rheumatoid arthritis were all denied. Infectious illness, including treponemal, mycobacterial, and fungal infections, was not found in our patient. Carcinoid syndrome and use of certain drugs, such as methysergide, may result in systemic manifestations that mimic multifocal fibrosclerosis (8). However, there was no evidence that either had affected the nervous system in our patient. The alpha-1-antitrypsin level was normal, and there was no familial history of similar disease. The

symptoms of the disease had become more pronounced after the birth of the patient's second and third children, when the laboratory analysis disclosed inflammation, elevated immunoglobulin and complement levels, and the presence of nucleus and DNA autoantibodies. The CSF showed inflammatory changes including mild pleocytosis and elevated IgG index. Furthermore, normalization of the abnormal laboratory data and improvement of the symptoms and abnormal CT and MRI findings were noted after corticosteroid therapy. These features all suggest that the etiology of this disease involved an autoimmune mechanism.

The treatment of multifocal fibrosclerosis is complex. Some patients show improvement with corticosteroid therapy (4) as did our patient. Although some patients become steroid-dependent, the use of azathioprine permits reduction of the corticosteroid dosage (9). The episcleritis with orbital pseudotumor and eosinophilic phlegmon in our patient initially responded well to oral corticosteroids. Although the pachymeningitis responded to steroid pulse therapy for one month, it thereafter exacerbated. We applied steroid pulse therapy several times, until the disease was no longer exacerbated, and then reduced the dose of oral prednisolone from 60 mg to 15 mg daily. In the present patient, repeated steroid pulse therapy was very effective.

Multifocal fibrosclerosis is a rare disorder that may affect the nervous system in diverse fashion. This syndrome should be considered in the differential diagnosis of any individual with idiopathic pachymeningitis presenting chronic inflammation

and dysfunction of the immune system. Careful evaluation of the history and physical examination together with observation should be sufficient for the recognition of the other fibrotic conditions associated with this syndrome.

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