Case Report

Meningeal Involvement in Wegener's Granulomatosis

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ABSTRACT. We describe a patient with Wegener's granulomatosis (WG) who developed neurological symptoms attributed to meningeal involvement. The diagnosis of WG was complicated by persistently negative antineutrophil cytoplasmic antibodies (ANCA) and lack of specificity in the histopathological findings from multiple anatomical sites. This rare neurological manifestation of WG was treated successfully with oral cyclophosphamide and the patient has continued remission for 3 years taking oral methotrexate. (J Rheumatol 2006;33:364–7)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS MENINGEAL INVOLVEMENT NERVOUS SYSTEM

Wegener's granulomatosis (WG) is a multisystem autoimmune disorder characterized by necrotizing granulomatous vasculitis predominantly in the upper and lower respiratory tract and kidneys[1-3]. It was first reported by Klinger in 1931. Five years later, Wegener described the clinical manifestations and pathological features in 3 patients. Although neurological involvement is well described, this is most frequently manifested in peripheral nervous system disease, especially neuropathy[4-7]. We describe a patient with unusual and striking meningeal disease attributed to WG who responded dramatically to standard therapy and has been maintained in remission taking methotrexate (MTX) for a 3 year period.

CASE REPORT

A 41-year-old man with no significant medical history was assessed initially in August 1998 for a left ear infection that had been unresponsive to multiple courses of antibiotic therapy. Additional clinical features included headache, neck stiffness, dyspnea, cough, fever, night sweats, fatigue, and blurred vision, but no myalgia or arthralgia. Examination revealed submandibular lymphadenopathy and erythema and white exudates in the left external auditory canal. Chest, cardiovascular, and neurological examinations were unremarkable.

Peripheral blood white cell count was 18,000/mm^3 and C-reactive protein (CRP) was 147 (normal 0–8) mg/l. The erythrocyte sediment rate (ESR) was 84 mm/h, antineutrophil cytoplasmic antibody (ANCA) determined by indirect immunofluorescence was negative, and serum complement concentrations were normal. Urinalysis was also normal. A chest radiograph showed a right upper lobe mass. This was confirmed on computed tomography (CT), which also showed bony destruction of the left mastoid.

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An open-lung biopsy of the right lung mass showed an area of organizing pneumonia, associated with an inflammatory infiltrate composed of lymphocytes, plasma cells, and foamy histiocytes. There was no evidence of vasculitis, granuloma formation, tuberculosis (TB), or malignancy. A left mastoid biopsy revealed fibrotic tissue with aggregates of lymphocytes and foamy macrophages. There was no evidence of granuloma formation or vasculitis.

Around this time he developed bilateral uveitis, for which he was given 40 mg prednisone daily. Four weeks later he reported a substantial improvement in his systemic complaints. The ESR had fallen to 15 mm/h, CRP was 6 mg/l, and ANCA again was negative. A repeat chest radiograph showed a reduction in the right lung mass.

In November 2000, he was admitted to hospital with right-side headache associated with dizziness, unsteady gait, and distortion of his sense of taste and smell. This was associated with blurred vision in the right eye and nausea. He denied any fever, slurred speech, limb weakness, numbness, or paresthesias. The neurological examination was normal, apart from difficulty walking a straight line. His white blood cell count, hemoglobin, electrolytes, and creatinine were normal. His ESR was 20 mm/h and CRP 19 mg/l. Repeat autoantibody testing that included ANCA (indirect immunofluorescence and ELISA for anti-proteinase 3 (PR-3) and anti-myeloperoxidase) was again negative. He had a normal chest radiograph. A CT scan of the head showed substantial vasogenic edema in the right temporal and parietal area extending into the basal ganglia and internal capsule. There was a modest midline shift from right to left, with very early hydrocephalus involving the left temporal horn. Magnetic resonance imaging (MRI) showed a mass effect in the right temporoparietal region, involving white and grey matter extending into the internal capsule and cerebellum. There was thick leptomeningeal enhancement and loss of venous/sinus flow due to sinus thrombosis (Figure 1). A craniotomy revealed a thickened white dura (5–6 mm) that was adherent to the underlying brain, which was soft and grey. There was no purulent material. Meningeal biopsy showed a brisk pachy- and leptomeningitis, characterized by a microangiopathy with fibrin deposition and infiltration by lymphocytes and plasma cells. The subdural and subarachnoid spaces were obliterated. Several small arteries lay unperturbed within the inflammatory mass. There was extension into the adjacent cerebral cortex, marked by conspicuous aggregation of lymphocytes around reactive endothelial cells. There were rare multinucleate giant cells in the leptomeninges. No necrotizing vasculitis was found, but widespread vascular destruction was present (Figure 2). There was no evidence of granuloma formation or lymphoma. The biopsy material did not grow any organisms, including TB. DNA and RNA analysis showed no evidence of clonal proliferation of B or T cells to indicate the presence of lymphoma.

On the basis of these clinical, radiographic, and pathologic findings a diagnosis of WG was made and the patient was started on prednisone 60 mg/day, oral cyclophosphamide 3 mg/kg/day, and cyclical didronel 400

mg/day for 2 weeks followed by calcium 500 mg/day for the ensuing 10 weeks. The dose of prednisone was continued at 60 mg/day for 4 weeks and then tapered by 5 mg/week thereafter.

Six months after discharge he had a full recovery of his vision, olfactory symptoms, and sense of taste, and most of the abnormalities on the initial MRI scan had resolved (Figure 3). In January 2002 prednisone was discontinued and in March he was switched from oral cyclophosphamide to oral MTX 15 mg/week and folic acid 1 mg/day. The total duration of cyclophosphamide therapy was 15 months.

At his most recent clinic visit in April 2005, the disease remains well controlled with MTX and he has been normotensive throughout his disease course. Five repeat MRI scans of the brain have been normal.

DISCUSSION

Neurological involvement in WG is uncommon at the onset of disease[1,2], but may develop in 22% to 54% of cases over time[1,2,4-6]. The most frequent nervous system manifestation is peripheral neuropathy, which occurs in 15% to 43% of cases[1,3,5,7]. The most common form of peripheral neuropathy is mononeuritis multiplex, followed by distal symmetric sensorimotor polyneuropathy. Involvement of the central nervous system (CNS) is infrequent. Among 249 cases of WG reported by Anderson, *et al*, there were 12 patients with CNS vasculitis, and 32 had evidence of CNS granuloma[6]. CNS involvement occurred in 8% of 158 patients followed at the US National Institutes of Health[1] and in 11% in a more recent European series[3]. The spectrum of CNS involvement includes stroke, cranial nerve abnormalities, cerebrovascular events, seizures, and meningeal involvement.

Meningeal involvement, illustrated in our patient by contiguous pachymeningitis and leptomeningitis, is rare in WG. Among 324 consecutive patients seen at the Mayo Clinic there were only 2 reported cases of meningeal involvement[5]. Drachman found 7% of 104 patients with WG had brain and meningeal lesions[4]. The most common symptom was headache, followed by cranial nerve involvement causing visual loss and diplopia.

Our case highlights some of the difficulties encountered in confirming a diagnosis of WG even with the availability of recent serologic tests and adequate tissue for histopathological examination. In particular, the persistently negative ANCA and nonspecific findings on biopsied lung and mastoid tissue delayed confirmation of the diagnosis by 2 years. In a study of 701 patients, 68% were diagnosed within 6 months of the onset of the disease, but up to 25% were diagnosed at least one year after the start of their symptoms[8]. The identification of cytoplasmic ANCA (cANCA) by indirect immunofluoresence and anti-proteinase 3 (PR-3) by ELISA has proven to be useful in the diagnosis of WG[9]. However, it is important to recognize the limitations of these assays as indicated by their sensitivity and positive predictive value[10]. In a recent metaanalysis, the sensitivity of cANCA for the diagnosis of WG varied from 34% to 90%, and specificity ranged from 88% to 100%[11]. In another study the positive predictive value of cANCA was 60% and the negative predictive value was 97%[12]. The combination of immunofluorescence and ELISA results further increases the specificity to 99%[13]. In our patients the limited form of the disease and in particular the absence of renal involvement probably increased the likelihood of a negative ANCA. The finding of negative ANCA was also reported to be common in patients developing meningeal involvement in WG[14].

The diagnostic value of biopsy varies depending on the source of the tissue. In a study of 126 biopsies, the triad of vasculitis, necrosis, and granulomatous inflammation was seen in only 16% of cases[15]. Diagnostic information may be obtained in up to 53% of nasal biopsies[16], in less than 7% of tracheobronchial biopsies[1], in 3%–8% of renal biopsies[1], and in up to 90% of lung biopsies[1,17]. Skin involvement in the form of leukocytoclastic vasculitis or granulomatous angiitis was found in 12.4% of one series[18]. Very few patients with WG have had histologically confirmed CNS vasculitis. The findings in previously biopsied meningeal tissue from patients with WG[4,5] have varied from a nonspecific inflammatory infiltrate to the presence of necrotizing granulomatous inflammation with lymphocytes, histiocytes, plasma cells, epithelioid macrophages, and multinucleated giant cells, as in our case.

A systemic disease process that involves the upper and lower respiratory tract as well as the brain has a broad differential diagnosis that includes lymphoma, sarcoidosis, and infections such as TB. All these possibilities were considered in our patient, but repeated histological, molecular biological, and microbiological studies were negative.

About 21% of patients with WG of less than 5 years' duration develop hypertension, and the percentage increases to 31% when the disease duration reaches 10 years[8]. This may be attributed to both the underlying vasculitis and its therapy[19]. In our case, after almost 7 years of disease, the patient continues to have normal blood pressure.

Before the introduction of effective treatment for WG the mortality rate at one year was 82%[20] compared to 13% over 8 years following the introduction of cyclophosphamide[1]. However, due to the significant toxicity associated with longterm use of cyclophosphamide, recent studies have examined alternative strategies for maintaining remission after induction with cyclophosphamide. To date, both MTX and azathioprine have shown significant promise in this regard[21,22]. There have been 4 deaths in reported cases of meningeal involvement in WG (2 due to interstitial pneumonia[23,24], one septicemia[14], and the fourth due to progressive neurological dysfunction[25]). Our patient was treated with cyclophosphamide for 15 months with no evidence of toxicity, and he remains in remission taking MTX for the past 3 years.

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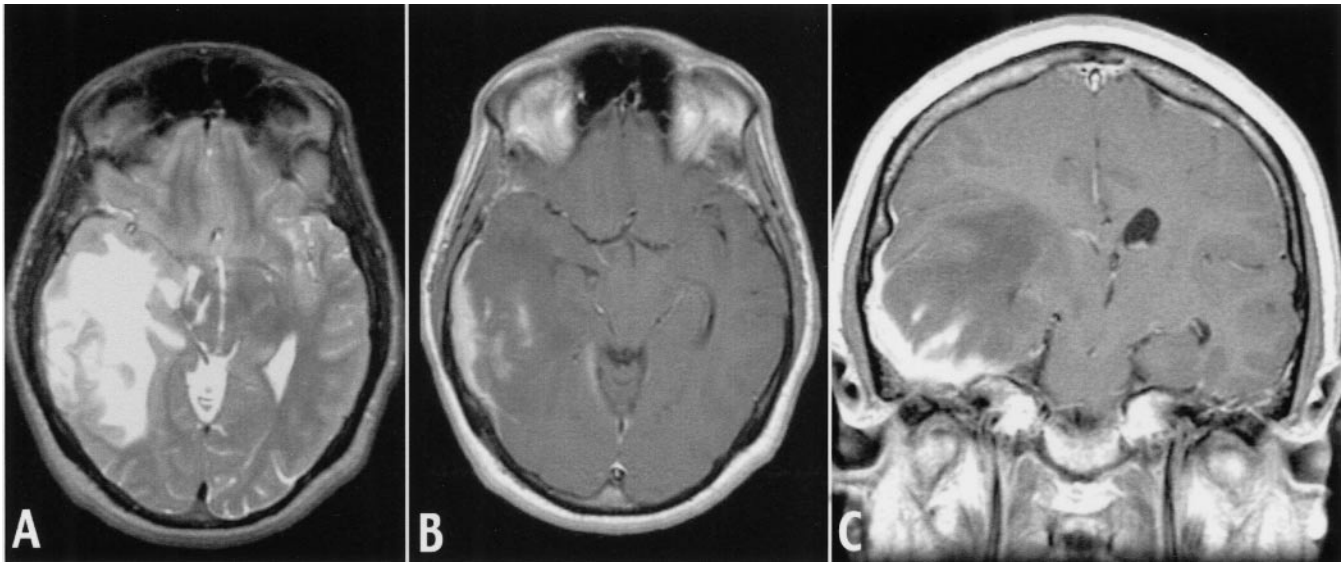

Figure 1. MRI scan prior to treatment. A. Axial T2 weighted image showing vasogenic edema throughout the temporal lobe and into the right cerebral peduncle and midbrain. The third ventricle is shifted across the midline from the mass effect. B. Axial T1 weighted post-contrast scan with dural and pial arachnoid enhancement. The right temporal horn is pushed forward and medially with midbrain compression. C. Coronal T1 weighted post-contrast scan showing pachymeningeal, pial-arachnoid, and parenchymal enhancement (bright high signal) and parenchymal edema (low signal) with subfalcine shift.

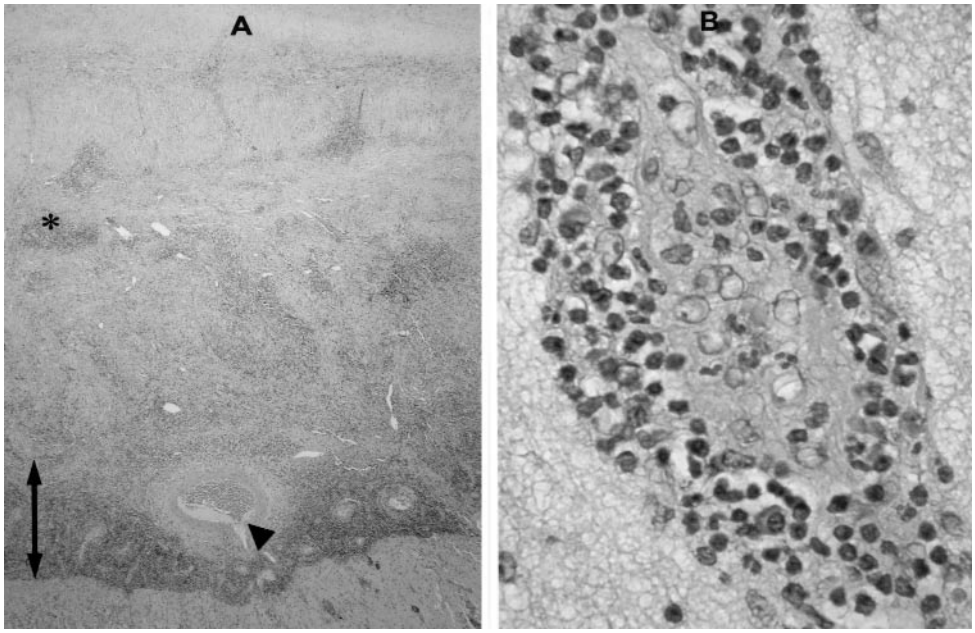

Figure 2. Histopathology of intracranial biopsy. A. Leptomeningeal infiltrate that obliterates the subarachnoid space (arrows), surrounds a small artery (arrowhead), and extends into superficial cortex (below). Note the marked dural thickening (*) (H&E, original magnification ×20). B. Cortical microvessel showing endothelial proliferation and perivascular inflammation with surrounding edema (H&E, ×400).

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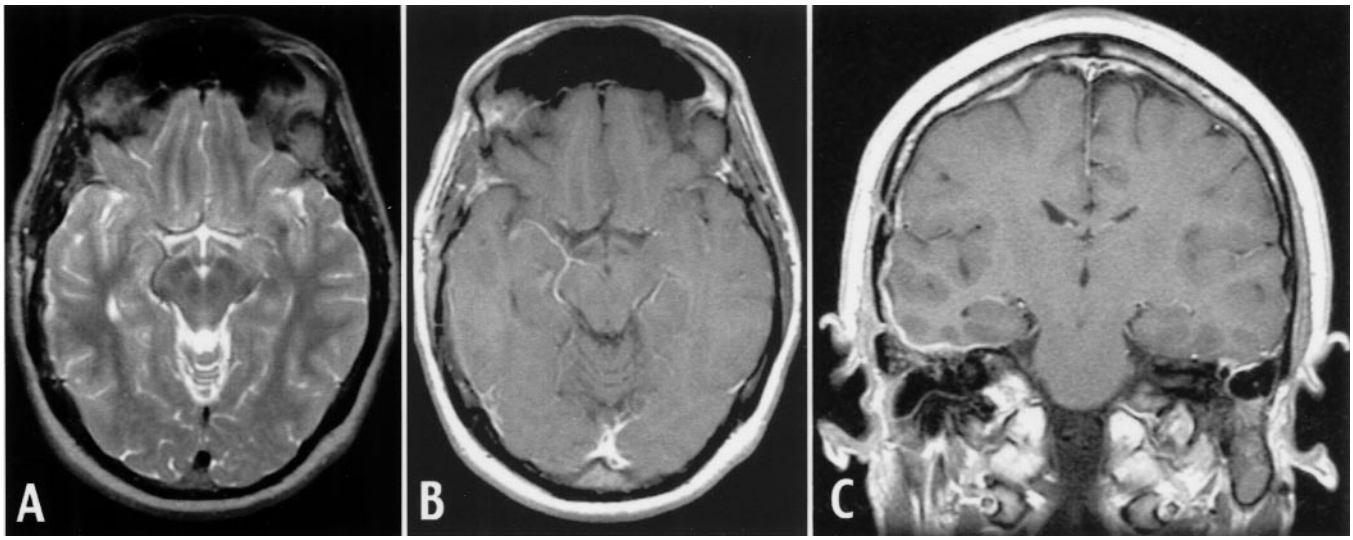

Figure 3. MRI scan after 4 months of treatment. A. Axial T2 weighted image showing normal white matter and grey matter with resolution of pretreatment vasogenic edema. B. Axial T1 weighted image showing slight residual right-side dural enhancement. C. Coronal T1 weighted image showing a significant reduction in dural, pial arachnoid, and parenchymal enhancement. Subsequent scans (not shown) also revealed gradual clearing of dural enhancement.

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