Case Report

Cranial Pachymeningitis: An Unusual Manifestation of Wegener's Granulomatosis

ADEL G. FAM, ELANA LAVINE, LIESLY LEE, BAYARDO PEREZ-ORDONEZ, and MAYANK GOYAL

ABSTRACT. We describe a patient with limited Wegener's granulomatosis (WG) presenting with saddle-nose deformity, pachymeningitis with prominent visual symptoms due to constriction of ophthalmic arteries at their transdural course, and positive for perinuclear antineutrophil cytoplasmic antibody. Early diagnosis of this rare presentation of WG can facilitate appropriate treatment to avoid irreversible neurologic dysfunction. (J Rheumatol 2003;30:2070–4)

Key Indexing Terms:
WEGENER'S GRANULOMATOSIS PACHYMENINGITIS

Wegener's granulomatosis (WG) is a rare, systemic disease of unknown etiology, characterized by necrotizing granulomatous inflammation and vasculitis, that in its classic form chiefly affects the upper and lower respiratory tracts and kidney[1-3]. In the limited or partial form, the pathological findings are similar but the upper respiratory tract, orbit, or lung are primarily affected, in the absence of renal disease[1-4]. Although neurologic manifestations occur in 23–34% of patients with WG[1,5], granulomatous pachymeningitis is rare, and typically occurs in the setting of early active, limited disease[6-16]. We describe a patient with limited WG with nasal lesions, pachymeningitis, and a positive perinuclear antineutrophil cytoplasmic antibody (pANCA). Early recognition of this rare manifestation of WG is essential for optimal treatment, especially to prevent irreversible neurologic dysfunction.

CASE REPORT

A previously healthy 60-year-old woman presented in September 1996 with a one month history of intermittent rhinorrhea, epistaxis, and nasal obstruction associated with crusting, and progressive swelling. Antihistamines were prescribed for presumed allergic rhinitis. However, by January 1997, she had developed a saddle-nose deformity (Figure 1), and complained of recurrent headaches. A nasal biopsy revealed chronic nonspecific inflammation. In March 1997, she presented with sudden loss of vision in the left eye, and funduscopic examination revealed an edematous pale optic disc with circumpapillary dilated vessels, suggesting anterior ischemic optic neuropathy. The hemoglobin was 141 g/l, white blood cell count 8.4×10^9/l with normal differential, platelets 474×10^9/l, and erythrocyte sedimentation rate (ESR) 45 mm/h. Biochemical profile was normal and urinalysis showed < 5 red cells/high power field with no casts or other abnormalities. Cytoplasmic (c)ANCA/antiproteinase 3 (PR3) ANCA and pANCA/antimyeloperoxidase (MPO) ANCA, by both indirect immunofluorescence (IIF) and antigen-specific ELISA, were 3 times negative for: PR3 < 1 u/ml (normal < 2 units/ml) and MPO < 5 units/ml (normal < 6 units/ml). Hepatitis and syphilis serologies, human immunodeficiency virus, antinuclear antibody, and rheumatoid factor were negative. C3 and C4 complements and serum angiotensin converting enzyme concentration were normal. Radiographs of the nose showed depressed nasal bridge but normal paranasal sinuses. Chest radiographs, a computer tomography (CT) scan of the head, chest and abdomen, and magnetic resonance imaging (MRI) with gadolinium of the orbits were normal. A left temporal artery biopsy was normal. A diagnosis of ANCA-negative WG was considered but a further nasal biopsy, a maxillary sinus specimen, and a skin biopsy of a transient cutaneous rash were nondiagnostic. Prednisone 60 mg daily, gradually tapered over a 6 month period, resulted in a resolution of headache but only slight improvement of vision in the left eye. In November 1998, she underwent nasal reconstruction successfully. Excised nasal tissue showed minor inflammatory changes.

In June 1999, she presented with recurrent headache and transient loss of vision in the right eye, and funduscopic examination revealed occlusion of the right inferotemporal branch of the retinal artery. Prednisone 50 mg daily was restarted and low dose aspirin added. Both cANCA and pANCA were negative, and neck Doppler studies and echocardiography were unrevealing. Brain MRI with gadolinium showed questionable enhancement along the falx cerebri and pachymeninges at the base of the skull. Her right eye visual loss recurred and cerebral angiography revealed bilateral segmental narrowing of the ophthalmic arteries, worse on the right side, in their course through the dura (Figure 2). She was given coumadin.

In July 1999, she developed more severe, persistent bifrontal and occipital headaches. She was alert and both cognitively and neurologically intact. Repeat funduscopic examination was unrevealing, but visual acuity was 20/25 OD and 20/70 OS, with patchy visual field loss attributed to the ischemic optic neuropathy. Repeat cANCA/PR3 ANCA was still negative but pANCA/MPO ANCA had become positive in titers of 10.3 and 14.4 units/ml. Lumbar puncture yielded clear, watery cerebrospinal fluid (CSF) with white cell count of 34×10^6/l (7% neutrophils, 45% lymphocytes, 45% monocytes) with normal cytologic analysis, elevated protein level of 2444 mg/l (normal 250–550 mg/l), normal glucose, and negative tests for syphilis and cryptococcal antigen. Stains and cultures for bacteria, mycobacteria, fungi, and viruses were negative. A repeat gadolinium enhanced T1-weighted brain MRI showed more marked pachymeningeal

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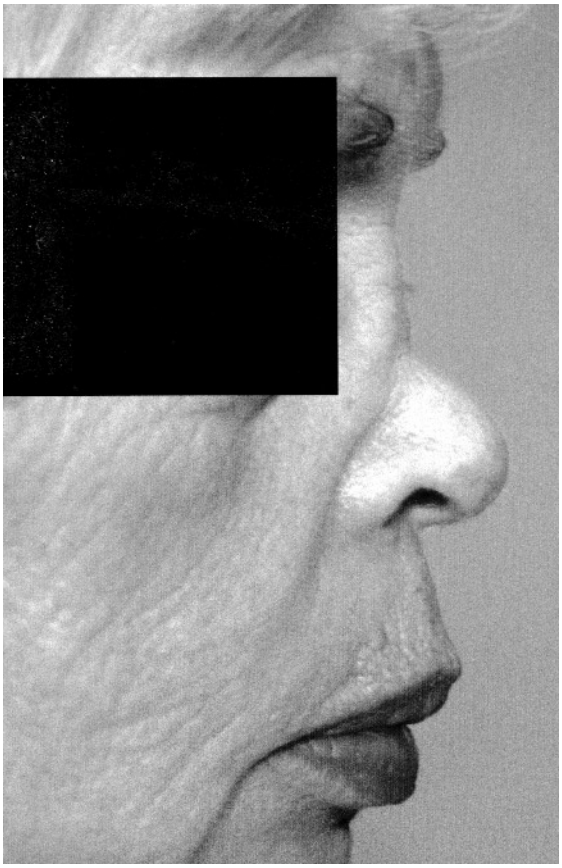


Figure 1. Saddle-nose deformity.

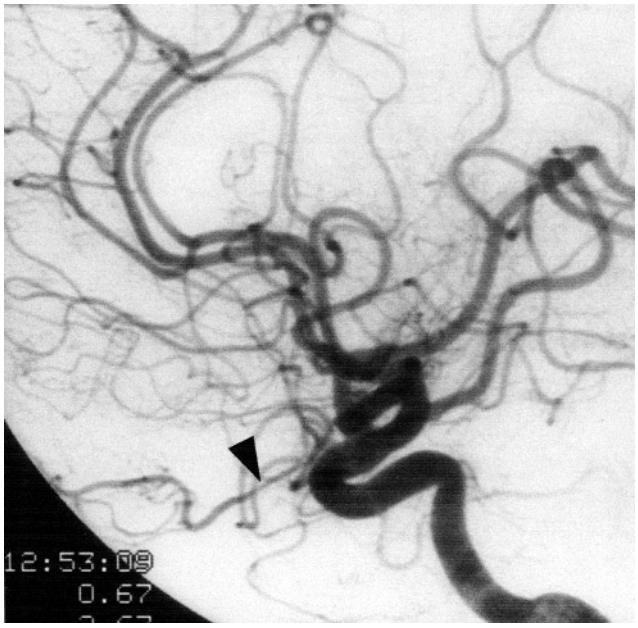
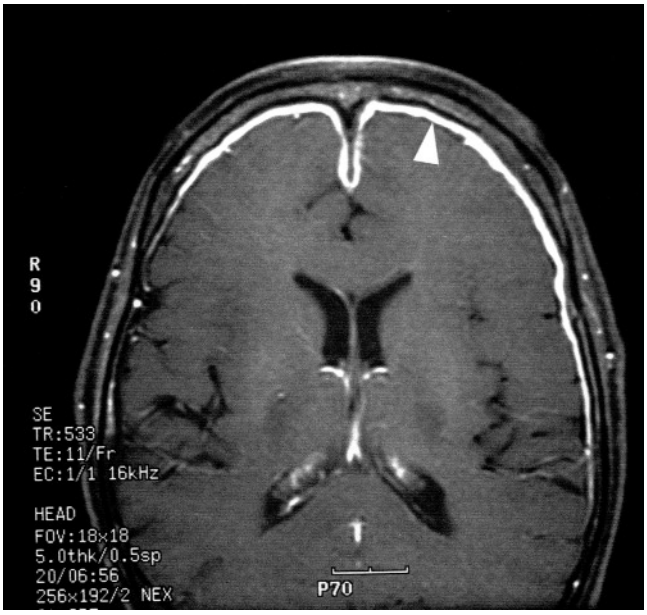


Figure 2. Cerebral angiogram of right common carotid artery shows narrowing of ophthalmic artery in its course through the dura (arrowhead).

enhancement along the skull base, with lesser enhancement over the hemispheres. There were no intracerebral lesions (Figures 3A, 3B). A stereotactic dural biopsy of the right frontal convexity showed necrotizing granulomatous pachymeningitis with small vessel vasculitis (Figure 4). A diagnosis of limited, cANCA-negative, pANCA-positive WG, with nasal lesions and pachymeningitis associated with bilateral ischemic optic neuropathy, was made. There was no evidence of pulmonary or renal lesions characteristic of WG. Cyclophosphamide 100 mg OD and prednisone 50 mg OD were begun. This was followed by gradual resolution of



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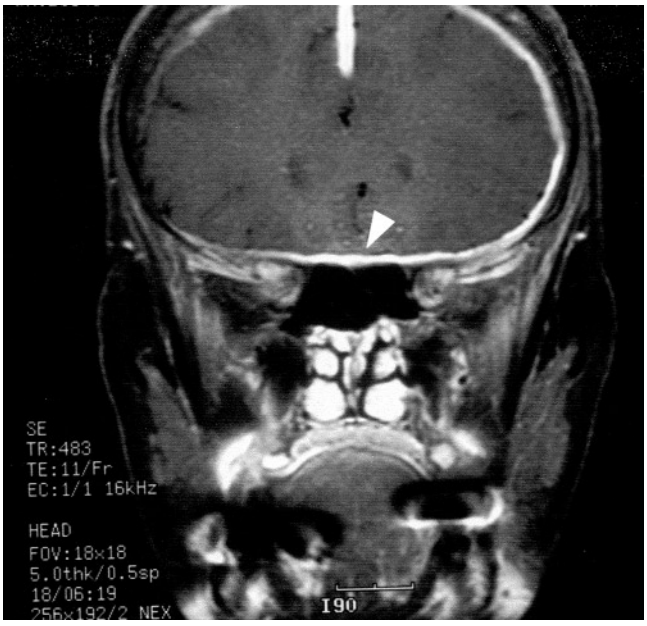

B

Figure 3. A. Gadolinium-enhanced axial T1-weighted MRI scan showing pachymeningeal enhancement over frontal convexities (arrowhead); B. gadolinium-enhanced coronal T1-weighted MRI scan shows pachymeningeal enhancement along skull base (arrowhead).

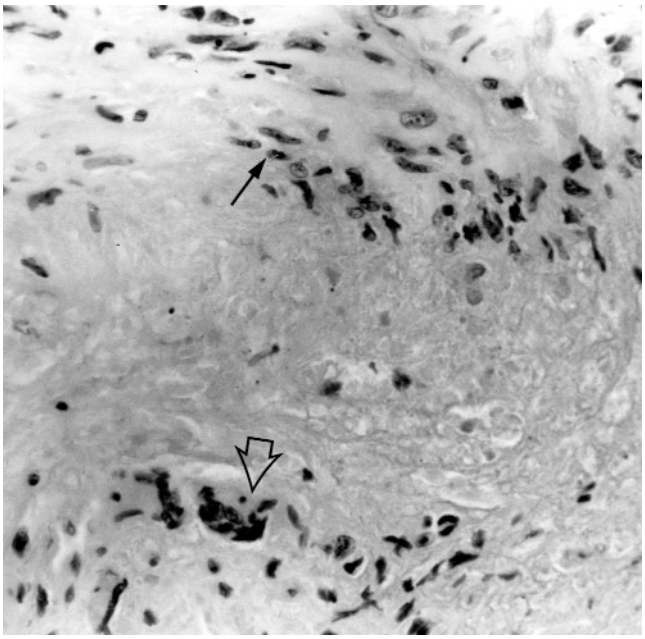

Figure 4. Photomicrograph of the dural biopsy showing necrotizing granulomatous inflammation with multinucleated giant cells (open arrow), palisading histiocytes (small arrow), and focal fibrinoid necrosis (H&E ×400).

her headache, improvement of visual symptoms, and normalization of ESR. Repeat cANCA was still negative, but pANCA had become negative since December 1999. In February 2000, cyclophosphamide was withdrawn and maintenance therapy with oral methotrexate (MTX) 5–10 mg/week, prednisone 2.5–5 mg/day, and coumadin was established. She has since remained clinically stable, and by June 2000, prednisone was withdrawn while MTX 7.5 mg/week was continued.

Pathologic findings. Three nasal biopsies and one from the maxillary sinus showed nonspecific chronic inflammation, with plasma cells, small T cells, macrophages, and neutrophils. There was no evidence of tissue necrosis, granulomatous reaction, vasculitis, lymphoma, or infection. Immunohistology and gene molecular analysis were nondiagnostic.

A right frontal dural biopsy showed thickening of the dura with a necrotizing granulomatous inflammation consisting of a dense infiltrate of small and transformed lymphocytes, plasma cells, occasional macrophages, and giant cells. Several small arterioles showed transmural granulomatous necrotizing inflammation consisting of small and activated transformed lymphocytes, plasma cells, and macrophages. In other areas, the arteriolar walls showed numerous palisading histiocytes and few multinucleated giant cells with focal fibrinoid necrosis (Figure 4). Immunohistochemical studies indicated that the infiltrate was composed of T cells positive for CD3, CD43 and CD45RO, a few CD 20-positive B cells, and CD79-positive plasma cells. Occasional CD56-positive natural killer cells were present. There was no evidence of lymphoma, and stains for acid-fast bacilli, spirochetes, fungi, and protozoa were negative.

DISCUSSION

Meningeal inflammation is a rare manifestation of WG. An early study reported meningitis in 7 of 104 (6.7%) patients with WG[17]. However, in 2 recent large series, meningitis was observed in 0% and 0.6% of those with WG, respectively[1,5]. Review of the English literature uncovered only 15 patients with WG and biopsy-proven cranial pachymeningitis, including our patient (Table 1)[6-16]. Not included in this analysis are a number of histologically unconfirmed "probable" cases[15,18-21]. Reported features of WG-associated pachymeningitis include (Table 1): (1) frequent occurrence early in the course (within 6 mo of onset) of active, limited WG; (2) elevated ESR (range 29–115, mean 83 mm/h) in the majority of cases (Table 1), although a few patients had no apparent signs of extracranial disease activity[13,15]; (3) common presentation with severe headache and cranial neuropathies, in the absence of nuchal rigidity or other meningeal signs. Spinal pachymeningitis is very rare[16]; (4) variable CSF findings with mild, predominantly lymphocytic pleocytosis in about one-third and elevated protein concentration in about one-half the patients; (5) a positive serum ANCA, either c- or pANCA, in about two-thirds of patients; (6) high sensitivity of gadolinium-enhanced brain MRI in the detection of pachymeningitis; (7) a dural biopsy showing granulomatous necrotizing inflammation, giant cells, and often vasculitis. The leptomeninges may show similar abnormalities[10]; (8) exclusion of other forms of granulomatous pachymeningitis including infections, lymphoma, sarcoidosis, and so-called idiopathic hypertrophic pachymeningitis[22]; and (9) a favorable response to standard treatment with prednisone, cyclophosphamide, or other cytotoxic drugs, with early therapy being associated with improved outcome in terms of neurologic recovery. In common with other reported cases, our patient developed pachymeningitis (with severe headache and ischemic optic neuropathy) early in the course (within 6 mo of onset) of clinically active, limited WG. Diagnostic findings included dural enhancement on MRI and a dural biopsy showing necrotizing granulomatous vasculitis (Table 1).

The diagnosis of WG depends upon typical clinical manifestations, biopsy evidence of necrotizing granulomatous inflammation and small vessel vasculitis, and exclusion of infectious, neoplastic and other lesions[1,8,14]. In patients with limited WG, the upper respiratory tract, eye, or lung are primarily affected in the absence of renal disease, the classic histopathologic triad is less frequently seen on biopsy, and the clinical course tends to be relatively benign and protracted[1-4,11]. It is worth noting, however, that head and neck biopsies in patients with WG are not always diagnostic[1,23]. Measurement of serum ANCA, particularly cANCA, has proved valuable in supporting the diagnosis of WG[1,4,12-16,24,25]. cANCA/PR3-ANCA antibodies are highly specific for WG, including the limited form[1,4,24,25]. A recent study also suggests that measurement of cANCA titers in the CSF may be useful in diagnosing and monitoring the activity of WG-associated pachymeningitis[20]. By contrast, pANCA/MPO antibodies, which are present in 10–20% of patients with WG, are less specific and occur in microscopic polyarteritis and a variety of other disorders[1,4,12-16,24,25]. The sensitivity of cANCA is greater than 90% in patients with active generalized WG, but only about 67% in those with

Table 1. Biopsy-proven pachymeningitis in Wegener's granulomatosis[6-16].

Finding	Patients Described in English Literature, n = 14	Present Case	Total/Estimated Frequency (%), n = 15
Wegener's granulomatosis			
Age: mean (range), yrs	53 (31–73)	60	54
Male/female	9/5	F	9/6 (3:2)
Active extracranial WG	12/14	+	13/15 (87)
Elevated ESR	10/11	+	11/12 (92)
Limited WG	13/14	+	14/15 (93)
Upper respiratory tract/orbit	11/14	+	12/15 (80)
Lung	4/14	–	4/15 (27)
Kidney	1/14	–	1/15 (7)
Positive c- or pANCA	7/11	+	8/12 (67)
Positive nasal biopsy	6/8	–	6/9 (67)
Pachymeningitis			
Early onset (within 6 mo)	12/14	+	13/15 (87)
Headache	11/14	+	12/15 (80)
Cranial neuropathies	10/14	+	11/15 (73)
Mental symptoms	5/14	–	5/15 (33)
Seizures	3/14	–	3/15 (20)
CSF			
Pleocytosis	4/13	+	5/14 (36)
Increased protein	7/13	+	8/14 (57)
Abnormal CT*	6/9	–	6/10 (60)
Abnormal MRI**	12/12	+	13/13 (100)
Abnormal cereb. angiography†	2/4	+	3/5 (60)
Positive dural biopsy	14/14	+	15/15 (100)
Granulomatous inflammation	14/14	+	15/15 (100)
Giant cells	13/14	+	14/15 (93)
Tissue necrosis	13/14	+	14/15 (93)
Vasculitis	8/14	+	9/15 (60)
Favorable response to therapy	11/14	+	12/14 (86)

* Thickening and enhancement of dura, falx cerebri, and/or tentorium. ** Dural enhancement. † Transdural narrowing of internal carotid and/or ophthalmic arteries.

active limited disease[4,24,25]. Thus, ANCA is absent in about one-third of patients with limited WG[4,25]. Although our patient developed prominent nasal symptoms with characteristic saddle-nose deformity, confirming the diagnosis of limited WG was delayed for a number of reasons. Included among these are 4 nondiagnostic nasal/sinus biopsies, repeatedly negative initial ANCA test results, an indolent atypical clinical course, and lack of pulmonary or renal lesions. The diagnosis was subsequently made when she developed pachymeningitis with prominent visual symptoms, abnormal brain MRI, and typical histopathologic changes on dural biopsy. The findings on cerebral angiography indicated that her bilateral ischemic optic neuropathy and visual loss were likely due to constriction of the ophthalmic arteries at the point of passage through the thickened dura (Figure 2). The subsequent development of pANCA/MPO antibodies and their disappearance following immunosuppressive therapy is of particular interest in light of recent reports from Japan indicating a possible association between limited WG, pANCA antibodies, and pachymeningitis[16].

The widespread application of MRI has greatly facilitated early recognition and followup of patients with pachymeningitis[8-16,19,22,26]. In those patients, MRI T1-weighted imaging after intravenous injection of gadolinium-DTPA is characterized by dural enhancement (which follows the contours of the cerebral convexities, falx cerebri, and/or tentorium cerebelli), sometimes associated with leptomeningeal enhancement (which follows the convolutions of the gyri)[11-13,19]. Although these findings are nonspecific, and may occur in other disorders associated with meningeal edema (such as malignancy or infection), their sensitivity exceeds that of CT and other neuroimaging modalities (Table 1)[9-16,19,22,26]. In our patient, there was no MRI evidence that pachymeningitis had spread from extradural disease in the nasal cavities. CT abnormalities were less frequent and included thickening and contrast enhancement of dura, falx cerebri, and/or tentorium cerebelli (Table 1)[8,10-12,14]. Cerebral angiography was also less sensitive than MRI; abnormalities including signs of a mass on posterior suprasylvian convexity[7], narrowing or occlusion of transdural portions of internal carotid and/or

ophthalmic arteries[16], were noted in only 3 of 5 (60%) patients (our patient included) who underwent the procedure (Table 1).

A gratifying response to immunosuppressive therapy with resolution of headache, improvement or stabilization of cranial neuropathies and other neurologic symptoms, reduction of ESR, and sometimes reversal of MRI abnormalities was observed in the majority of those with WG-related pachymeningitis, our patient included (Table 1)[7-16]. Most cases, including our patient, initially received standard therapy with prednisone and cyclophosphamide, in doses similar to those used in generalized WG. In order to minimize therapy-related toxicity, we followed a "staged" approach to the treatment of our patient's limited WG: induction of remission with corticosteroids and daily cyclophosphamide, switching to oral MTX for remission maintenance[27,28].

Meningeal inflammation is undoubtedly a rare manifestation of active limited WG. Heightened awareness, early diagnosis, and timely therapy of this atypical presentation of WG are important to prevent permanent neurologic dysfunction and further disease progression. If the clinical findings, ANCA results, MRI abnormalities, and extracranial biopsies are inconclusive or nondiagnostic of WG, a dural biopsy may be necessary to confirm the diagnosis before committing the patient to longterm, potentially toxic immunosuppressive therapy. Although there are no controlled studies, our experience and that of others indicates that most patients with WG-associated pachymeningitis respond favorably to treatment with corticosteroids and cytotoxic drugs (cyclophosphamide, MTX, or azathioprine), particularly when such therapy is initiated early, before irreversible neurologic damage.

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