Pachymeningitis in microscopic polyangiitis (MPA): A case report and a review of central nervous system involvement in MPA

H. Kono, S. Inokuma, H. Nakayama, J. Yamazaki

Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, Tokyo, Japan.
Hajime Kono, MD; Shigeko Inokuma, MD; Hisanori Nakayama, MD; Junko Yamazaki, MD.

Please address correspondence and reprint requests to: Shigeko Inokuma, MD, Department of Allergy and Immunological Diseases, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2000.

Key words: Pachymeningitis, microscopic polyangiitis, antineutrophil cytoplasmic antibody for myeloperoxidase (MPO-ANCA).

ABSTRACT

A case of microscopic polyangiitis (MPA) with pachymeningitis is described. The patient had renal, skin, gallbladder and peripheral nervous system involvement, simultaneously with pachymeningitis. Necrotizing glomerulonephritis with crescent formation, and necrotizing small vessel vasculitis in the kidney and skin were confirmed by biopsy. A highly elevated titer of antineutrophil cytoplasmic antibody for myeloperoxidase (MPO-ANCA) was observed. All of the clinical and laboratory abnormalities improved with high-dose pulse and conventional steroid therapy. The literature on central nervous system involvement in MPA and perinuclear-ANCA (p-ANCA)-related vasculitis is reviewed. This case serves to emphasize that pachymeningitis can occur as one of the features of MPA.

Introduction

Microscopic polyangiitis (MPA) is a systemic disorder characterized by necrotizing vasculitis with few or no immune deposits, affecting the small vessels (1). Most patients with MPA have antineutrophil cytoplasmic antibodies for myeloperoxidase (MPO-ANCA) (2). Necrotizing glomerulonephritis has been known to occur commonly, and pulmonary capillaritis and peripheral nervous system involvement occur often (2). However, central nervous system involvement has not yet been clearly documented. We describe a case of histologically confirmed MPA with a rare neurological manifestation, pachymeningitis, which responded to high-dose pulse and conventional steroid treatment.

Case report

A 56-year-old woman was admitted to our hospital with a 2-month history of myalgia of both legs and left-sided temporal headache. She had no history of asthma or sinusitis. On admission, physical examination revealed a fever of 39°C, multiple spotty papular erythematos lesions on both legs, and sensory disturbances in both feet. She had no meningeal signs, papilledema, visual field defects, cranial nerve palsies, pyramidal signs, ataxia or involuntary movements. Deep tendon reflexes were normal in the upper extremities and less brisk in both lower extremities. Urinalysis was normal. Hematological examination revealed a white cell count of 10.8 x 10^9/L (77.5% segmented neutrophils, 1% eosinophils, 0.5% basophils, 6.5% monocytes and 14.5% lymphocytes), a hemoglobin level of 9.6 g/dL, and a platelet count of 430 x 10^9/L. The erythrocyte sedimentation rate (ESR) was 124 mm/hr, and the serum C-reactive protein (CRP) concentration was 17.1 mg/dL. Liver enzymes levels and renal function tests were normal. Tests for antinuclear and anti-double stranded DNA antibodies were negative. A highly elevated titer of MPO-ANCA was found (321 EU; normal range < 10 EU). The test for the cytoplasmic ANCA was negative. Repeated blood cultures were negative. Lumbar puncture revealed an opening pressure of 22 cm H2O, and examination of the cerebrospinal fluid revealed a white cell count of 4 / mm^3 (3 lymphocytes) and a protein level of 6 mg/dL. Cytologic examination revealed no malignant or atypical cells. Cultures for bacteria, mycobacteria and fungi were negative. An electroencephalogram showed generalized slowing without focal abnormalities or epileptiform activity. Nerve conduction studies on the sural nerves of both sides showed low-amplitude sensory responses with normal velocities that were consistent with mononeuritis multiplex. A chest roentgenogram and lung function tests were normal. Abdominal echography and computed tomography revealed thickening of the wall of the gallbladder neck. Biopsy of the erythematous papules revealed necrotizing vasculitis affecting the small arteries in subcutaneous fat tissue. The architecture of the arteries was destroyed by fibrinoid necrosis with neutrophilic and lymphocytic infiltrates with leukocytoclasis that extended into the perivascular tissue (Fig. 1). Magnetic resonance imaging (MRI) revealed diffuse thickening of the dura mater and cerebral swelling on the left side. The thickened dura was isointense in T1-weighted images and hypotense in T2-weighted images. T1-weighted post-contrast MRI demonstrated diffuse du-
Pachymeningitis in microscopic polyangiitis / H. Kono et al.

CASE REPORT

ral enhancement only on the left side (Fig. 2a). A biopsy of the dura mater was not performed.

Two weeks after admission, urinalysis showed 6 to 10 erythrocytes per high-power field, and the serum creatinine level increased to 1.9 mg/dL. Renal biopsy showed necrotizing vasculitis of the small arteries, necrotizing glomerulonephritis with crescent formation, and negative immunofluorescence staining for immunoglobulins or complement.

The patient was diagnosed as having MPA with hypertrophic cranial pachymeningitis, and was treated with 5 courses of high-dose steroid pulse (each course consisted of intravenous (IV) methylprednisolone, 1 gram per day for 3 days) every 2 weeks and oral prednisolone, 1.2 mg/kg (65 mg) daily, followed by gradual tapering of the dose. The patient refused treatment with immunosuppressors. Immediately after the initiation of treatment, fever, myalgia, papules and headache subsided. With further treatment, the serum levels of creatinine, CRP, ESR, MPO-ANCA all returned to normal. The wall thickness at the neck of the gallbladder decreased, and MRI scans of the dura revealed marked improvement 2 weeks after the initiation of the therapy (Fig. 2b). The sensory disturbances in both feet persisted in spite of the therapy. The patient has had no evidence of a relapse after 12 months of follow-up.

Fig. 1. Biopsy of the erythematous papules showed vasculitis with fibrinoid degeneration of small arteries in subcutaneous fat tissue. The architecture of the arteries is destroyed and elastic fibers are broken by fibrinoid necrosis with neutrophilic and lymphocytic infiltrates with leukocytoclasis, which extends into the perivascular tissue (a: elastica-van Gieson’s 25x; b: hematoxylin-eosin 100x).

Fig. 2. (a) T1-weighted axial post-contrast MRI before steroid therapy shows left-sided diffuse dural thickening and enhancement, and left-sided cerebral swelling. (b) T1-weighted axial post-contrast MRI shows neither dural enhancement nor thickening, nor cerebral swelling 2 weeks after steroid treatment, when the patient’s headache had already subsided.
The patient had severe left-sided headache, and thickening and enhancement of the dura mater were observed on the MRI. These features were suggestive of pachymeningitis. The patient had multi-organ involvement including mononeuritis multiplex, necrotizing glomerulonephritis, necrotizing vasculitis of the kidney and skin, and thickening of the gallbladder wall, in addition to pachymeningitis. The diagnosis of MPA was confirmed by the pathological findings of necrotizing vasculitis of the small vessels of the kidney and skin, and positive MPO-ANCA.

Pachymeningitis is characterized by inflammation, thickening and fibrosis of the dura mater. It may occur in association with several underlying disorders, including infections, autoimmune disorders, and malignancies. However, most cases have been reported as idiopathic.

Table 1. Central nervous system involvements in patients with microscopic polyangiitis and p-ANCA related vasculitis.

<table>
<thead>
<tr>
<th>No.</th>
<th>Authors year (ref.)</th>
<th>Age (yrs.)</th>
<th>Sex</th>
<th>Neurologic features</th>
<th>Other organ involvement</th>
<th>Neuroimaging (MRI)</th>
<th>Cerebrospinal fluid Opening pressure (cmH2O)</th>
<th>WBC (10^3/μL)</th>
<th>Protein (mg/dL)</th>
<th>EEG</th>
<th>ANCA</th>
<th>Pathology</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T. Ishikura et al. 1994 (12)</td>
<td>63</td>
<td>F</td>
<td>Headache</td>
<td>PNS, skin, kidney, gall bladder</td>
<td>Meningeal thickening, enhancement on gadolinium</td>
<td>22</td>
<td>14</td>
<td>119</td>
<td>N.A.</td>
<td>positive (p-ANCA, IIF)</td>
<td>N.A.</td>
<td>PSL. 50 mg/day</td>
<td>AzP</td>
</tr>
<tr>
<td>2</td>
<td>R. Sasaki et al. 1995 (13)</td>
<td>77</td>
<td>F</td>
<td>Cranial neuropathy (II), transverse myelopathy</td>
<td>N.A.</td>
<td>Meningeal thickening and enhancement on gadolinium</td>
<td>N.A.</td>
<td>10</td>
<td>45</td>
<td>N.A.</td>
<td>positive (p-ANCA, IIF)</td>
<td>N.A.</td>
<td>S-Pulse</td>
<td>N.A.</td>
</tr>
<tr>
<td>3</td>
<td>K Takahashi et al. 1998 (14)</td>
<td>47</td>
<td>M</td>
<td>Headache</td>
<td>Episcleritis</td>
<td>Meningeal thickening and enhancement on gadolinium</td>
<td>20</td>
<td>48</td>
<td>49</td>
<td>Normal</td>
<td>518 EU (MPO-ANCA)</td>
<td>N.A.</td>
<td>S-Pulse, PSL 1 mg/kg/day</td>
<td>Improved</td>
</tr>
<tr>
<td>4</td>
<td>Present case</td>
<td>56</td>
<td>F</td>
<td>Headache</td>
<td>PNS, skin, kidney, gall bladder</td>
<td>Meningeal thickness, enhancement on gadolinium and cerebral swelling</td>
<td>22</td>
<td>4</td>
<td>6</td>
<td>Slow</td>
<td>321 EU (MPO-ANCA)</td>
<td>CGN, MPA (skin, kidney)</td>
<td>S-Pulse, PSL 1.2 mg/kg/day</td>
<td>Improved</td>
</tr>
<tr>
<td>5</td>
<td>H. Honda et al. 1996 (10)</td>
<td>56</td>
<td>F</td>
<td>Seizures, hemiplegia, unilateral blindness, encephalopathy.</td>
<td>PNS, kidney, small intestine</td>
<td>Transient leukoencephalopathy, multiple cerebral hemorrhage</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>Slow</td>
<td>&gt;1000 EU (MPO-ANCA)</td>
<td>CGN</td>
<td>S-Pulse, PSL 40 mg/day, plasma exchange</td>
<td>No change</td>
</tr>
<tr>
<td>6</td>
<td>T. Harada et al. 1997 (15)</td>
<td>52</td>
<td>M</td>
<td>Cranial neuropathy (II), transverse myelopathy</td>
<td>Spinal cord swelling</td>
<td>N.A.</td>
<td>10</td>
<td>116</td>
<td>N.A.</td>
<td>positive (p-ANCA, IIF)</td>
<td>N.A.</td>
<td>S-Pulse, PSL 60 mg/day</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>A. Sasaki et al. 1998 (9)</td>
<td>78</td>
<td>M</td>
<td>Hemiplegia</td>
<td>Kidney, lung, stomach</td>
<td>Multiple cerebral hemorrhagic infarction</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>637 EU (MPO-ANCA)</td>
<td>MPA (cerebral none)</td>
<td>N.A.</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>A. Asahi et al. 1999 (11)</td>
<td>28</td>
<td>M</td>
<td>Schizophrenia</td>
<td>Kidney</td>
<td>normal</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>positive (p-ANCA, IIF)</td>
<td>CGN</td>
<td>PSL 50 mg/day</td>
<td>CY pulse</td>
<td>Improved</td>
</tr>
</tbody>
</table>

Opening pressure in cmH2O: N.A.: not available; EEG: electroencephalography; PNS: peripheral nervous system; ANCA: antineutrophil cytoplasmic antibody; IIF: indirect immunofluorescence; P-ANCA: perinuclear ANCA; MPO-ANCA: ANCA for myeloperoxidase; CGN: Crescentic glomerulonephritis; S-Pulse: steroid pulse therapy; PSL: prednisolone; AzP: azathioprine; CY pulse: cyclophosphamide pulse therapy.
signs such as stiff neck and photophobia were almost absent. An elevated opening pressure of the CSF, lymphocytic pleocytosis and increased protein levels were documented in about half of the cases. MRI with gadolinium enhancement appeared to be the most sensitive imaging method. Central nervous system (CNS) involvement is common during the course of classical polyarteritis nodosa, and its major manifestations are diffuse encephalopathy, focal neurological deficits and seizures (8).

In MPA, peripheral nervous system involvement occurs commonly (2), but CNS involvement has rarely been reported. Three cases of histologically confirmed MPA with CNS involvement were found in the English and Japanese literature: an autopsy case with multiple cerebral hemorrhagic infarctions (9), a case with transient leukoencephalopathy and multiple cerebral hemorrhages (10), and a case with schizophrenia (11) (Table 1). In addition, we found 3 perinuclear-ANCA (p-ANCA)-positive cases with hypertrophic pachymeningitis (12-14), and one p-ANCA positive case with optic neuritis and transverse myelopathy (15), among Japanese patients. The 4 cases were diagnosed only as having p-ANCA-related vasculitis, and not MPA, due to the lack of histopathological confirmation. Table I summarizes the features of these cases of MPA or p-ANCA-related vasculitis with CNS involvement based on reports in the English and Japanese literature.

Among the 4 cases with pachymeningitis, clinically headache was common, but other usual meningeal signs such as stiff neck or photophobia were not observed. Laboratory evaluation frequently revealed abnormalities of the cerebrospinal fluid. The opening pressure was mildly elevated (range, 20-22 cmH2O) in 3 out of the 4 patients in whom the pressure was described. A lymphocytic pleocytosis (10-48 cells/mm3) was documented in 3 cases. The cerebrospinal fluid protein level was increased in 3 cases. MRI revealed meningeal thickening and contrast enhancement in all cases. Three cases responded well to conventional doses of steroids, administered with or without pulse therapy. In contrast to the 3 cases with pachymeningitis and the case with transverse myelopathy without hemorrhagic or ischemic findings on MRI, which responded well to steroid therapy, one case with cerebral hemorrhage did not respond to steroid therapy, and another case with hemorrhagic infarction died soon (18 days) after the onset of the disease. It is likely that cases with cerebral hemorrhage or infarction have a more unfavorable outcome than the other cases.

This report, a first documentation of pachymeningitis in histologically confirmed MPA, serves to emphasize that pachymeningitis in histologically confirmed MPA with CNS involvement has rarely been reported. Three cases of histologically confirmed MPA, in addition to the well-known renal or pulmonary involvement.

References
4. GUILLIEV H, DURAND-GASSELIN B, CE-

Pachymeningitis in microscopic polyangiitis / H. Kono et al.

400