

Renal Involvement in Antimyeloperoxidase Antineutrophil Cytoplasmic Antibody-positive Granulomatosis with Polyangiitis with Chronic Hypertrophic Pachymeningitis

To the Editor:

Granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis) is a small to medium-size vessel vasculitis involving various organs, with the classic triad of upper airway, lung, and kidney involvement. GPA can be accompanied by chronic hypertrophic pachymeningitis (CHP), characterized by inflammatory thickening of the cerebral or spinal dura mater¹. Although the pathology of CHP does not depend on the contiguous spread of granulomatous lesions from the nasal or paranasal sinuses, GPA with CHP has been reported to present mostly with limited organ involvement^{2,3}. Specifically, antimyeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA)-positive GPA with CHP has been reported to lack renal involvement^{1,2,4}. We describe a case of MPO-ANCA-positive GPA, which presented with CHP-related central nervous system (CNS) symptoms and with renal abnormalities, with a discussion of the incidence of renal involvement in MPO-ANCA-positive GPA accompanied by CHP.

A previously healthy 48-year-old Japanese man presented to the otolaryngology department with a 3-month history of fever, bilateral temporal headaches, left facial nerve paralysis, dysphagia, and hoarseness, which occurred sequentially. Otolaryngeal examination identified bilateral exudative otitis media, left nasal septal ulceration, pharyngitis, and an elevated C-reactive protein of 67 mg/l. Cytology of the left ear aspirate and the epipharyngeal mucous membrane showed no malignant cells, and biopsy of the nasal septal ulcers revealed neutrophilic and lymphocytic infiltration without neoplastic changes. Granulomatous lesions and vasculitic changes were not found. Thickened dura mater of the bilateral basal temporal lobes and the tentorial cerebelli were observed on cranial contrast magnetic resonance imaging (MRI), indicating the presence of CHP (Figure 1A, 1B).

MPO-ANCA was elevated at 48 ELISA units (EU; normal < 20 EU), while antiproteinase 3 (PR3) ANCA was negative.

The patient was then referred to our department. The physical examination showed cranial nerve dysfunctions including left lower lip droop, combined deafness, impaired left palatal movement and oropharyngeal constriction, and slight tongue atrophy without fasciculation. Urinalysis showed proteinuria 1 g/day and hematuria 50–99 red blood cells/HPF with red blood cell casts. Other significant laboratory findings included a high white cell count of 10,900/ μ l, low hemoglobin level of 8.5 g/dl, increased erythrocyte sedimentation rate of 139 mm/h, and hypoalbuminemia (2.5 g/dl). Serum creatinine was normal with the value of 0.88 mg/dl but creatinine clearance from 24-h urine collection was slightly decreased at 65 ml/min. Antinuclear antibody was negative, as well as serologic tests for *Syphilis*, *Aspergillus*, *Candida*, and *Cryptococcus*. Cerebrospinal fluid (CSF) showed a slight protein elevation of 57 mg/dl but the fluid was clear and watery with normal fluid pressure, cell count, glucose, and adenosine deaminase. The CSF culture yielded no microbes and no malignant cells. Chest radiographs showed no abnormal findings. Renal and meningeal biopsies were not performed considering the patient's poor general medical condition. The diagnosis of GPA was established using the combination of upper airway and renal symptoms (the surrogate markers in the European Medicines Agency algorithm) and MPO-ANCA positivity⁵.

Treatment was initiated with oral prednisolone 50 mg/day (1 mg/kg/day) and oral cyclophosphamide 50 mg/day, with the patient seeing gradual symptomatic improvement. Resolution of CNS and upper airway symptoms were clinically consistent with the imaging studies confirming the improvement of CHP and otitis media (Figures 1, 2). MPO-ANCA decreased to within normal limits after 2 weeks of treatment. Although there was no change in the slightly decreased creatinine clearance, proteinuria and hematuria normalized after 2 months. Cyclophosphamide was switched to azathioprine for maintenance therapy and prednisolone was tapered to 2 mg/day during the following 3.5 years.

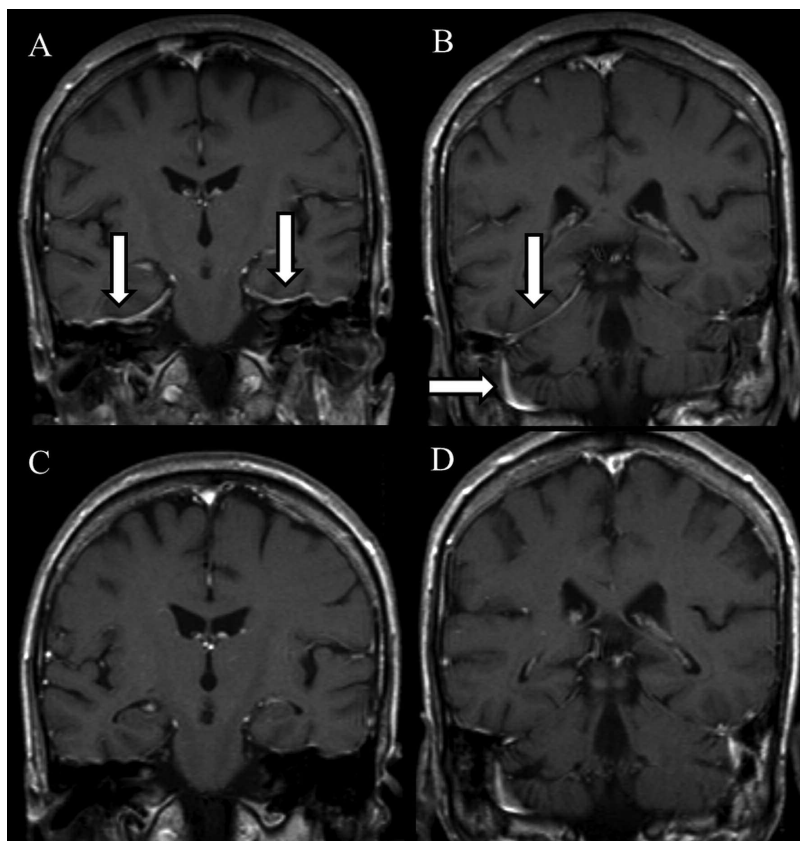


Figure 1. Gadolinium contrast T1-weighted cranial MRI before and after the treatment. Pretreatment MRI reveals enhancement of the thickened dura mater (arrow) around the bilateral basal temporal lobes (A) and the tentorial cerebelli (B). Posttreatment MRI reveals improvement of the thickened dura mater significantly around the bilateral basal temporal lobes (C) and partially around the tentorial cerebelli (D).

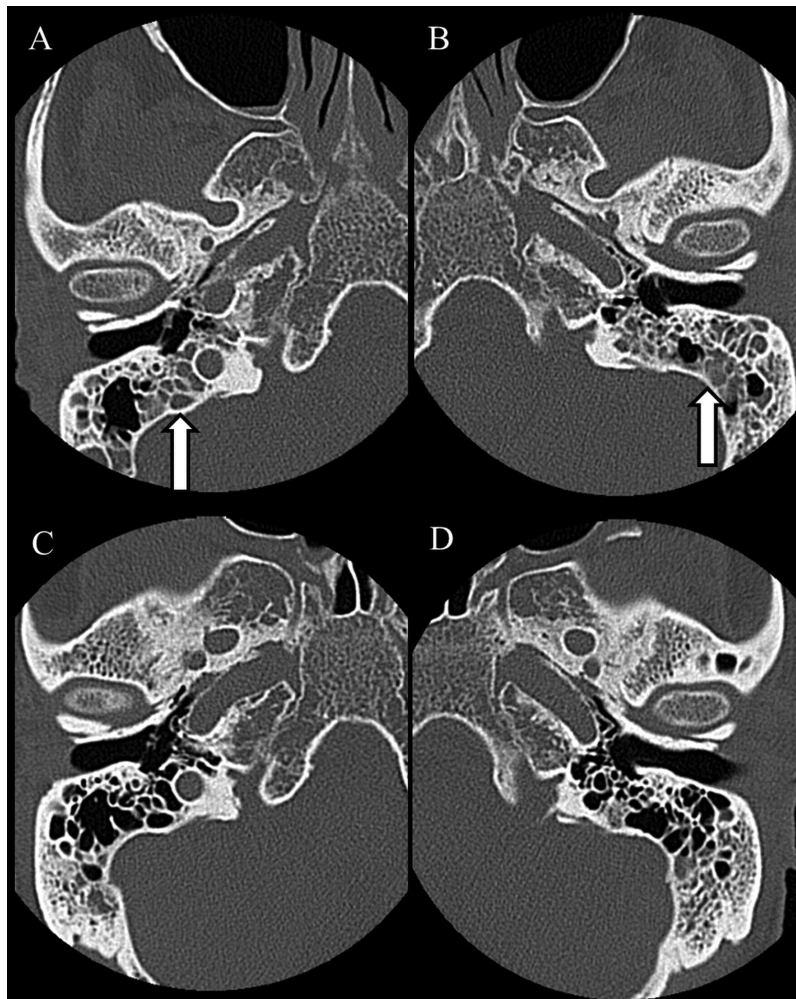


Figure 2. Computed tomography (CT) images of the bilateral middle ear before and after treatment. Pretreatment CT reveals multiple iso-density areas (arrow) that present fluid accumulation in bilateral middle ear cavities with no bone destruction (A: right ear, B: left ear). Posttreatment CT reveals a decrease of fluid accumulation and an increase of air inclusion in bilateral middle ear cavities (C: right ear, D: left ear).

GPA with CHP, especially with positive MPO-ANCA, has been reported to present with upper and lower airway disease, and possible eye involvement, but without renal abnormality^{1,2,3,4}. However, our case of MPO-ANCA-positive GPA with CHP presented with proteinuria and hematuria that resolved on immunosuppressive therapy. Among this case and the previously reported 8 cases of GPA with CHP (positive for perinuclear ANCA and/or MPO-ANCA), 2 had renal involvement (22%)^{1,2,4,6,7,8,9,10}. In comparison, there are reports of 5 cases of renal involvement out of 21 cytoplasmic and/or PR3-ANCA-positive GPA with CHP in the literature (24%). The majority of GPA with CHP are independent of nasal/paranasal sinus lesions³, and many cases of CHP reveal vasculitic lesions histologically^{1,2,4,6}. Thus, we believe it is reasonable that cases of MPO- and PR3-ANCA-positive GPA with CHP develop vasculitic renal abnormalities at similar frequencies.

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ACKNOWLEDGMENT

The authors thank Dr. Peter Shane for helpful comments on this report.

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- J Rheumatol 2012;39:10; doi:10.3899/jrheum.120473