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Two cases of MPO-ANCA-positive hypertrophic pachymeningitis mimicking as intracranial infection

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Abstract

Hypertrophic pachymeningitis (HP) is a rare disorder marked by thickening of the dura mater due to diverse etiologies. MPO-ANCA-positive HP represents a variant of AAV confined to the central nervous system, distinguished by the presence of serum MPO antibodies. Distinguishing HP triggered by MPO-ANCA from other causes can be challenging.

In this study, we present two cases of MPO-ANCA-positive HP initially misdiagnosed as intracranial infections. Case 1 underwent surgery for chronic suppurative otitis media, with histopathological findings revealing inflammatory changes without definitive suppuration. He was presumed to have a secondary intracranial infection resulting from the surgery. However, his condition deteriorated despite two weeks of antibiotic and antiviral treatment. Case 2 presented with headache and was initially suspected of having intracranial Brucellosis given his serum Brucella positivity. Despite treatment for brucellosis, his symptoms persisted, and he developed visual and hearing impairments. Both patients were ultimately diagnosed with MPO-ANCA-positive HP, exhibiting serum MPO antibody positivity. Their symptoms showed improvement with glucocorticoid and immunosuppressive therapy.

Based on these observations, we propose that MPO-ANCA-positive HP may initially present as intracranial infection. For HP patients presenting with headache, mastoiditis, otitis media, and visual loss, it is imperative to conduct ANCA antibody-related tests to enhance diagnostic precision.

Keywords Hypertrophic pachymeningitis, Myeloperoxidase-ANCA-positive, Mastoiditis, Otitis media, Brucellosis

Background

Hypertrophic pachymeningitis (HP) is a rare condition identified by a fibrosing inflammatory process that leads to the thickening of the dura mater, causing a range of neurological symptoms such as headache, cranial neuropathies, seizures, hydrocephalus, and sensorimotor disorders [1, 2]. It can have multiple causes, including inflammation, tumors, autoimmune diseases, or it can be idiopathic [3]. Among these, HP patients with myeloperoxidase-antineutrophil cytoplasmic antibody-positive (MPO-ANCA-positive) are relatively rare and there is difficulty in distinguishing it from infection [1, 4]. In this study, we present two cases initially diagnosed with intracranial infection – one following otitis media surgery and another due to Brucella infection. Despite relevant anti-infection treatment, both patients experienced escalating headaches, decreasing mental states, and visual loss. Further examination confirmed the diagnosis of MPO-ANCA-positive HP. This serves as a valuable reminder to not only neurologists but also for

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otolaryngologists and rheumatologists that early identification of MPO-ANCA-positive HP is imperative for effective management and avoiding misdiagnosis.

Case presentation

Case 1

A 61-year-old man presented with progressive hearing impairment in his left ear. Over 30 years ago, he was diagnosed with "acute mastoiditis" in a local hospital due to sudden hearing loss in his left ear, but there was no improvement despite anti-inflammatory treatment. One month ago, he experienced a throbbing headache in the left front-parietal region, intermittent purulent discharge from both ears, tinnitus, and left peripheral facial paralysis without fever, respiratory symptoms or rash. His feces and urine were normal recently, without hematochezia, melena, or hematuria. He doesn't have unexplained weight loss in the past few months or any relevant family history of previous diseases.

Routine laboratory tests, including complete blood count (measuring white and red blood cells and platelets), liver and kidney function, ions, tumor markers such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), prostate-specific antigen (PSA), neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), carbohydrate antigen 153 (CA153), and carbohydrate antigen 199 (CA199), as well as screening for hepatitis, HIV, and syphilis, were normal. Neurological examination indicated severe peripheral facial paralysis on the left side. An audiologic test revealed that the left ear exhibits mixed hearing loss, characterized primarily by sensorineural hearing loss (Fig. 1a). The otoscopy examination revealed that the left external auditory canal was patent, with a small amount of purulent discharge visible. Middle ear CT showed chronic mastoiditis in both ears (Fig. 1b). He was diagnosed with left chronic suppurative otitis media, left severe sensorineural hearing loss, and then underwent left tympanoplasty type I, left mastoidectomy, left ossicular resection, and left external auditory meatoplasty under general anesthesia at the same time. The Pathology results showed inflammation without definite suppurative changes (Fig. 1c).

After the operation, his hearing, tinnitus, and left peripheral facial paralysis improved, but the headache still persisted without fever.

Lumbar puncture revealed colorless and transparent cerebrospinal fluid (CSF) with an opening pressure of 100 mmH_2O, an elevated protein level of 1594 mg/L (normal range, 120 to 600 mg/L), elevated cells at 28*10^6/L (normal range, 0 to 8 *10^6/L, monocytes=96%), normal glucose and chloride levels without tumor cells.

Brain MRI revealed thickening of the dura mater in the left middle cranial fossa (Fig. 2) and enhancement in the left middle cranial fossa and tentorium cerebelli (Fig. 3d), consistent with hypertrophic pachymeningitis. MRV with contrast and diffusion-weighted imaging were normal. Chest computed tomography showed no evidence of silicosis, sarcoidosis or recent tuberculosis.

Suspecting an intracranial infection secondary to the operation and considering his lumbar puncture results, the patient was administered empirical treatment consisting of intravenous Ceftriaxone 2.0 g daily due to its excellent blood-brain barrier permeability, as well as Ganciclovir (5 mg/kg) twice daily. However, after two weeks, the patient's headache intensified, accompanied by the development of a fever with a peak body temperature of 38.2 ℃. Consequently, his mental state deteriorated, resulting in a loss of appetite and confining him to bed.

A repeat lumbar puncture revealed an elevated protein level of 2067 mg/L, cells at 36*10^6/L (monocytes=96%), normal glucose and chloride levels without any tumor cells, indicating ineffective anti-inflammatory and antiviral treatments. Further immunological investigation showed positive pANCA, an elevated serum MPO-ANCA of 233.7CU (normal range, 0 to 20CU), an erythrocyte sedimentation rate (ESR) of 49 mm/hour (normal range, 0 to 15 mm/hour), a C-reactive protein (CRP) level up to 109.80 mg/L (normal range, 0 to 6 mg/L), and a urinary protein of 1.42 g/24 h (normal range, 0.028–0.141 g/24 h). Anticardiolipin antibody was negative, and both serum IgG4 and rheumatoid factor were within the normal range.

A diagnosis of hypertrophic pachymeningitis associated with a high serum level of MPO-ANCA (MPO-ANCA-positive HP) was made. Empirical treatment was started with intravenous methylprednisolone at 80 mg daily for 5 days, followed by oral prednisone (50 mg/d), with a gradual tapering of the dose by 5 mg every 15 days, until reaching a maintenance therapy of 20 mg/d. During the administration of steroids, his headache gradually subsided and fever released.

Over a 4-month treatment period with steroids, his headache was relieved, but he was unable to communicate with others due to his hearing loss. A follow-up MRI showed reduced thickness of the dura mater and diffuse regression of dural enhancement (Fig. 3e). A repeat CRP level test showed 45.1 mg/L, while the pANCA was negative, and CSF appeared normal. Given the persistence of symptoms and elevated CRP levels, the patient was prescribed Mycophenolate Mofetil 0.75 g orally twice a day, along with prednisone 50 mg/d. Throughout the 1-year follow-up period, there was a gradual improvement in his hearing, enabling him to answer phone calls without difficulty.

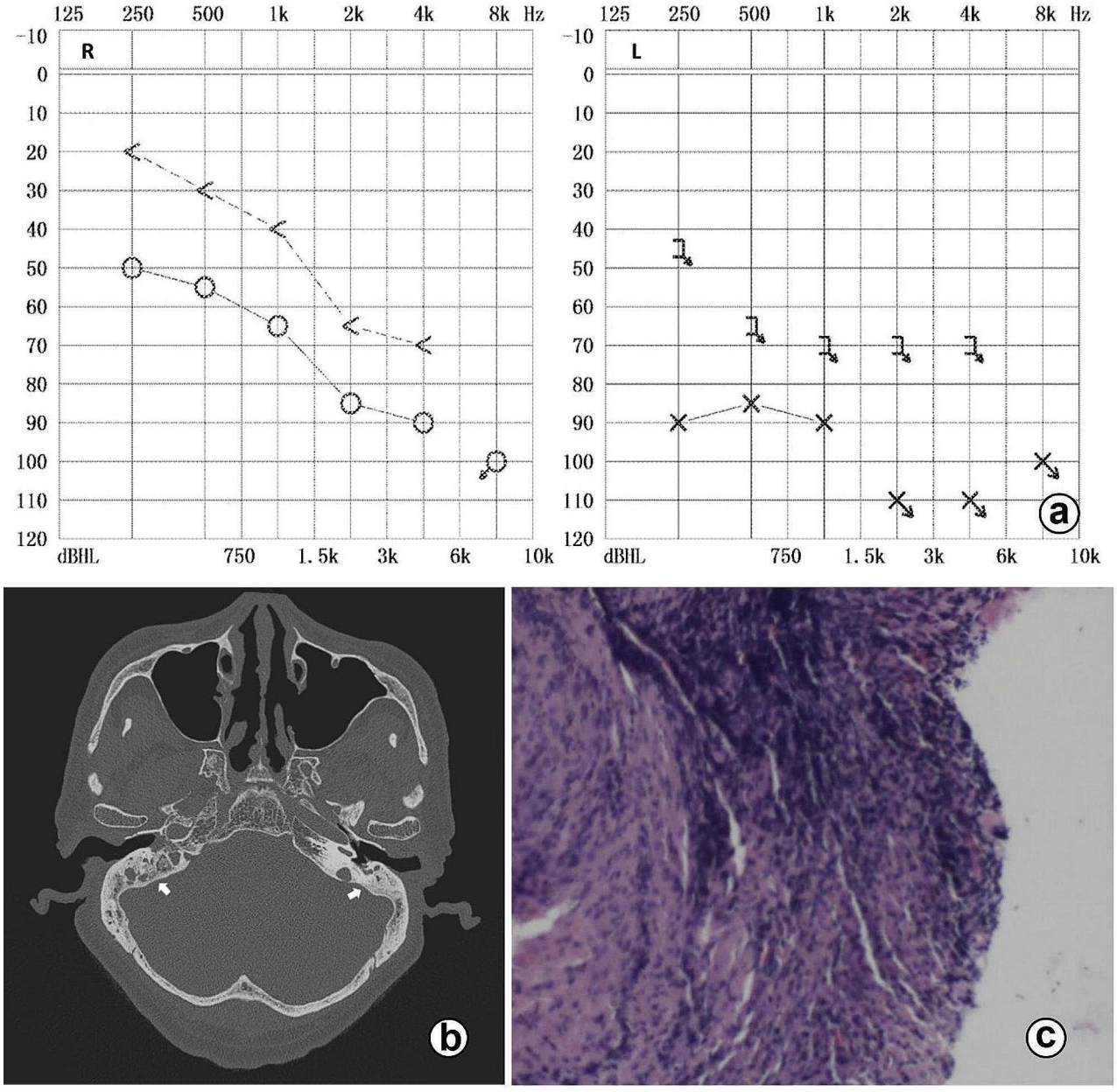

Fig. 1 The audiologic test in case 1 revealed left ear hearing loss with a bone conduction of 61 dB and air conduction of 98 dB on the pure tone audiogram (**a**). Middle ear CT (**b**) in case 1 showed increased density in the bilateral tympanic and mastoid compartments (arrow). Histopathological image by hematoxylin-eosin staining showed the left upper tympanic granulation tissue at 100×magnification (**c**)

Case 2

A 49-year-old farmer was admitted to the hospital with a 5-month history of intermittent throbbing pain in both temporal regions of his brain, which had intensified in the previous 20 days. He hasn't had a fever in the past 5 months, nor respiratory symptoms, rash, hematochezia, melena, or hematuria. He had no relevant family history or unexplained weight loss recently. A Brain MRI conducted after his admission revealed significant thickening and enhancement of the dura mater following contrast administration (Fig. 4a). However, no notable abnormalities were detected within the brain parenchyma.

Routine laboratory tests, including complete blood count (measuring white and red blood cells and platelets), liver and kidney function, ions, tumor markers such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), prostate-specific antigen (PSA), neuron-specific enolase (NSE), carbohydrate antigen 125 (CA125), carbohydrate antigen 153 (CA153), and carbohydrate antigen 199 (CA199), as well as screening for hepatitis, HIV, and syphilis, were normal. The CSF was colorless and

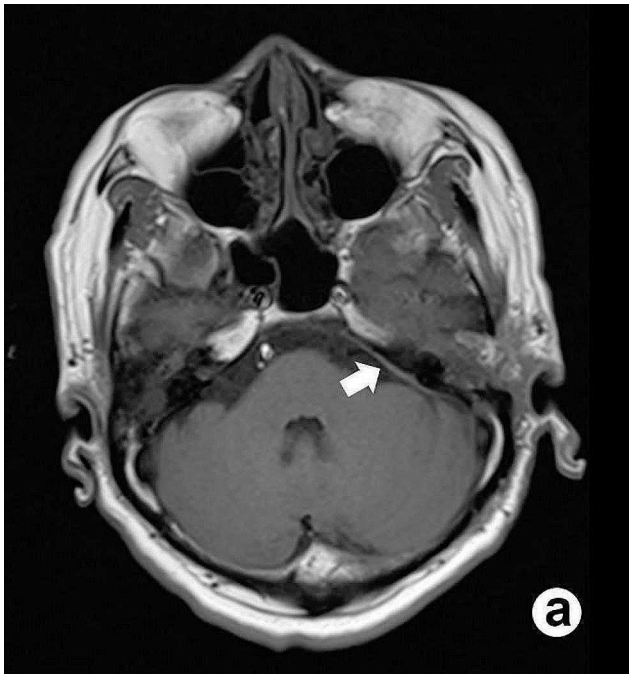

Fig. 2 Brain MRI in Case 1. Axial T1-weighted sequence (**a**) showed hypodense thickening of meninges (arrow) in the left middle cranial fossa

transparent, with an opening pressure of 130 mmH_2O, an elevated protein level of 835 mg/L, cells at 48*10^6/L (monocytes=100%), normal glucose and chloride levels, and no tumor cells were found. The CSF Next Generation Sequencing (NGS, carried out by Vision Medicals Co. Ltd, Guangzhou, Guangdong, China) revealed a negative result, indicating the absence of bacteria, fungi, DNA or RNA viruses, or parasites. Enhanced CT scans of the lungs and entire abdomen were normal.

Given the patient's occupation in cattle breeding, a specific test for Serum Brucella was conducted, revealing the presence of Brucella antibodies in both the Brucellosis Tiger Red Plate Agglutination Test (positive) and the Brucella Tube agglutination test (1:50). Suspecting an intracranial infection caused by Brucellosis, the patient was prescribed a regimen of oral doxycycline 100 mg twice daily and rifampicin 600 mg once daily for 4–6 months, and intravenous Ceftriaxone 2.0 g twice daily for a duration of four weeks. He was also given intravenous methylprednisolone at 80 mg daily for 7 days as experimental treatment, followed by oral methylprednisolone (24 mg/d), with a rapid tapering of the dose by 4 mg every 2 days, until complete reduction. Following 7 days of this treatment, his headache showed improvement, and he was subsequently discharged.

Six months after his initial discharge, the patient was readmitted due to a recurrent headache. He reported that his headache had returned two months after his initial discharge, gradually worsening over time, although it could be temporarily alleviated with oral NSAIDs. However, one month prior to his readmission, the headache became unbearable, and he also experienced decreased hearing in both ears and decreased vision in his right eye. His family noticed that only when they raised their voice could he perceive their words. He also found that when he covered his left eye, his right eye could only perceive light and was unable to discern the number of fingers in front of him. The patient underwent a lumbar puncture at a specialized infectious disease hospital, and the CSF was colorless and transparent, with an opening pressure of 100 mmH_2O. The CSF analysis revealed an elevated protein level of 1400 mg/L and a cell count of 120*10^6/L (monocytes=82.7%). Additionally, the Brucellosis Tiger Red Plate Agglutination Test remained positive, while the Brucella Tube agglutination test yielded a titer of 1:50. Despite reinitiating antibacterial treatment for Brucellosis, the patient's symptoms did not show any improvement.

Upon reexamination, the brain MRI displayed significant thickening and contrast enhancement of the dura mater (Fig. 4b), while the brain parenchyma appeared normal. Additional immunological tests yielded positive results for pANCA, an elevated serum MPO-ANCA level of 246.3CU (normal range, 0 to 20CU), an ESR of 26 mm/hour, and a high CRP level of 72.10 mg/L. However, the serum IgG4 and rheumatoid factor were within the normal range, and the anticardiolipin antibody test was negative.

Based on these findings, a diagnosis of MPO-ANCA-positive HP was established. The patient's treatment plan consisted of an initial 3-day course of intravenous methylprednisolone at 500 mg daily, followed by oral methylprednisolone 40 mg daily and cyclophosphamide 0.4 g administered intravenously once every two weeks. Over the course of steroid and cyclophosphamide treatment, the patient's headache gradually subsided, and both his hearing and vision showed improvement, making brucellosis infection unlikely. A follow-up MRI conducted after a 2-month treatment period revealed a reduction in dural thickness and a diffuse regression of dural enhancement (Fig. 4c). Repeat CRP and ESR tests showed levels of 12.0 mg/L and 26 mm/hour, respectively.

Discussion

We present two cases initially diagnosed with intracranial infections secondary to ear surgery and Brucella, respectively. The first patient underwent surgery for chronic suppurative otitis media, however, no suppurative changes were identified upon pathology. The second patient underwent treatment for brucellosis for six months, however, his headache intensified and symptoms developed in the eyes and ears, indicating that the anti-Brucella treatment was ineffective and the diagnosis of intracranial infection was incorrect. Ultimately, they

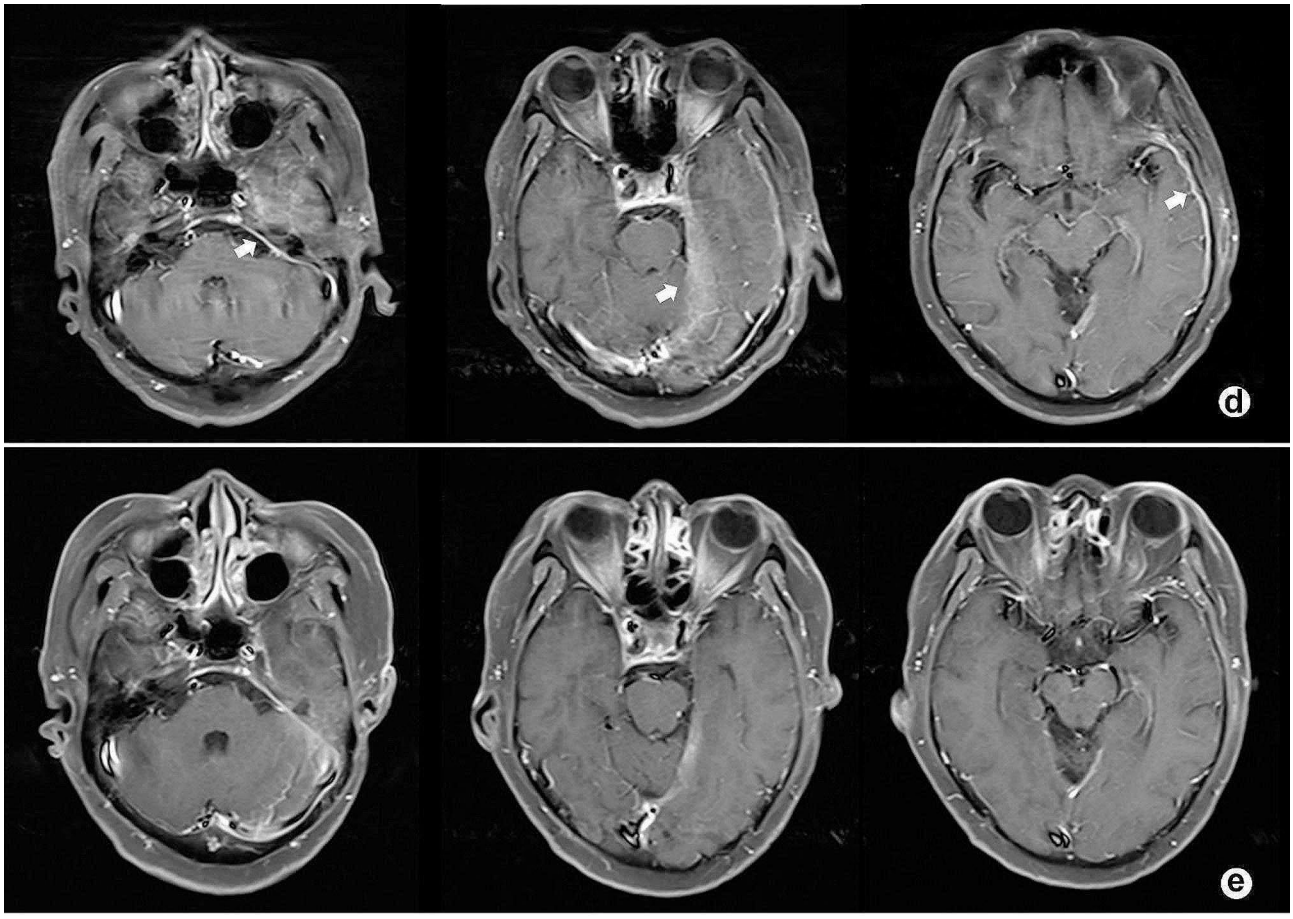

Fig. 3 The gadolinium enhanced T1-weighted axial images in Case 1 showed markedly enhanced meninges in the left middle cranial fossa and tentorium cerebelli (**d**, arrow). After 4-month steroid treatment, a control MRI showed a significant reduction in enhancement (**e**)

were diagnosed with MPO-ANCA-positive HP, and their symptoms showed improvement following steroids and immunosuppressant treatment.

HP was initially characterized by Charcot et al. [5] in 1869 as a progressive disease that leads to widespread thickening of the dura mater. It can either be idiopathic or secondary to a range of underlying conditions, including infections (such as neurosyphilis or fungal meningitis), inflammatory disorders (such as rheumatoid arthritis or neuro sarcoidosis), and neoplasms (such as dural carcinomatosis and meningioma) [6]. ANCAs are classified as either cytoplasmic (c-ANCA) or perinuclear (p-ANCA), based on their distinct immunofluorescence patterns. The antigens responsible for these patterns are proteinase 3 (PR3) for c-ANCA and MPO for p-ANCA [7]. Some patients with idiopathic meningitis have been found to have positive serum MPO-ANCA antibodies in recent years, hinting at a possible link between idiopathic HP and ANCA-related diseases.

Among the neurological symptoms associated with MPO-ANCA-related HP, headache is the most prevalent, affecting over 90% of patients with HP [8]. The cranial nerves II, VI, and VII are most commonly affected, leading to eye involvement, such as sudden visual loss in these patients [9, 10], as seen in case 1. Other typical clinical manifestations of MPO-ANCA-positive HP include otitis media, sinusitis, and mastoiditis, which often result in conductive hearing loss [10, 11]. The close proximity of the mastoid and sinus to the dura mater may account for the coexistence of HP and ear/nose complications [12]. Our case 1 presented with headache, hearing loss, festering, tinnitus, and left peripheral facial paralysis, while case 2 exhibited headache, hearing, and visual impairment, aligning with the typical manifestations mentioned above. Choi HA et al. [13] have proposed that the presence of an unexplained headache, particularly with paranasal inflammation, should be considered as a criterion for the early recognition and accurate diagnosis of MPO-ANCA-related HP, alongside neuroimaging findings.

Elevated ESR (87.5%) and CRP (79.0%) are the most prevalent abnormalities in laboratory tests for ANCA-related HP, with WBC elevation (57.1%) and neutrophil elevation (85.7%) also commonly observed [14], as demonstrated in our cases. Initially, both of our patients were

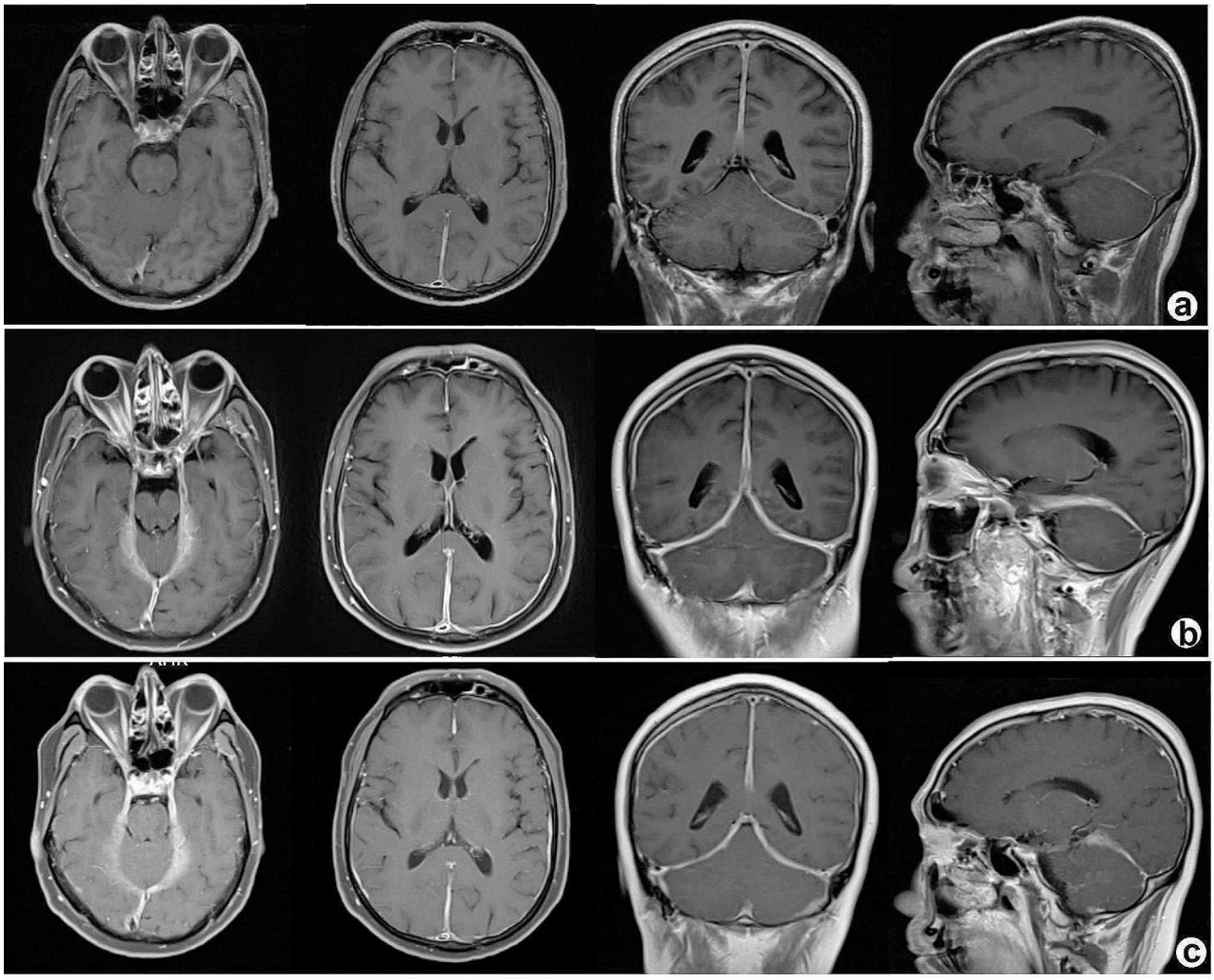

Fig. 4 The gadolinium enhanced T1-weighted axial, coronal and sagittal images in Case 2. Initial images demonstrate diffusely enhanced thick dura mater (**a**). 6 months after discharge marked enhancement (**b**). After 2-month steroid and cyclophosphamide treatment (**c**). Note that diseased dura mater became more thickened (**b**) compared to initial MR image (**a**), and less thickened as treatment was maintained (**c**)

diagnosed with intracranial infection due to increased CSF protein and cell counts. A retrospective study has indicated that CSF pressure may increase with protein elevation in HP patients, similar to intracranial infection [14]. Further ANCA-related tests, such as MPO-ANCA antibodies in CSF, have exhibited specificity, and research suggests that 58% of ANCA-related HP patients have ANCA in the CSF [8]. In terms of histology, the typical finding is thickened dura mater tissues that show extensive fibrotic changes and infiltration of various immunocompetent cells, which is consistent with the observations in case 1.

In our results, the patients showed a "diffuse" enhancement pattern on MRI. Contrast-enhanced MRI stands out as the most sensitive diagnostic imaging technique for HP, hallmarked by dura mater enhancement that is most prominently observed in the frontal parietal and occipital lobes [15]. On MRI T1-weighted images, low-to-iso intensity is also visible. The T1-weighted contrast-enhanced coronal images typically exhibit brilliant enhancement of the falx cerebri and tentorium cerebelli, resembling the appearance of the Benz sign or the illuminated Eiffel Tower at night, and are described as the "Benz sign" [14, 16] or "Eiffel Tower sign" [17, 18].

A case series of fifteen ANCA-associated HP patients pointed out that HP can result from a wide range of inflammatory and infectious diseases, making it challenging to differentiate solely based on imaging [12]. In case 1, the thickened dura mater was initially thought to be caused by intracranial infection following surgery due to the definite surgical history. However, the underlying cause remained elusive until the infection treatment proved ineffective, highlighting the limitations of relying solely on imaging for diagnosing the true cause

of HP. While in case 2, the Brucella antibody titer was only 1:50, which was lower than the diagnostic criterion for brucellosis (1:160 or greater) [19]. Considering his occupation involving long-term contact with cattle and sheep, and his having a 5-month history of headache at the first visit, we suspected that he had chronic intracranial infection caused by Brucella, and he was also given an experimental small-dose methylprednisolone therapy. The steroids treatment improved his symptoms, but we mistakenly believed that the anti-Brucella treatment was effective, and we did not retest the antibody within 2 to 4 weeks. This may have delayed re-examining the diagnosis sooner and further investigations that could have led to the ANCA diagnosis. It was until the patient's headache became unbearable, along with decreased hearing and vision, that we rechecked the Brucella antibody titer and further confirmed the diagnosis of MPO-ANCA-positive HP. This not only reminds clinicians to be cautious in diagnosing brucellosis when the antibody titer is less than 1:160 and to recheck it in time, but also indicates that when the infectious diagnosis cannot be confirmed, we should have a high index of suspicion for an inflammatory disorder, especially if the patient is not improving on antibiotics.

Both of our patients achieved successful treatment outcomes with the administration of corticosteroids and immunosuppressive agents. Research has demonstrated that adequate steroid therapy, in combination with other immunosuppressive agents such as cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, and rituximab, constitutes the standard treatment approach for MPO-ANCA-positive HP [1, 9, 14, 20]. Corticosteroids are considered the first-line therapy, and the addition of immunosuppressive agents represents an effective strategy for achieving remission [1]. The consensus on the course and dose of glucocorticoid treatment has not yet been achieved. The majority of recommended corticosteroid dosages in relevant studies involve prednisolone at 0.5–1 mg/kg/day or dexamethasone, along with intravenous infusion of methylprednisolone at 0.5–1.0 g/day for 3 days [14]. The dosage is then gradually tapered down, with maintenance therapy involving a smaller dose of 20-30 mg prednisolone. However, in Case 1 of our article, his hearing impairment developed over a four-month period of treatment with steroids alone. The symptoms were alleviated again after increasing the dosage of prednisone and introducing Mycophenolate Mofetil. The patient in Case 2, on the other hand, received short small-dose steroids from the onset, and his symptoms recurred again after a brief relief. Six months later, he received cyclophosphamide in combination with methylprednisolone, and then the symptoms and imaging findings improved gradually. Therefore, we propose that the application of low-dose steroids alone may not effectively control the patient's symptoms. Instead, we recommend the use of high-dose steroids (methylprednisolone at 0.5–1.0 g/day for 3 days) or the simultaneous application of small-dose steroids maintenance and immunosuppressants.

In conclusion, when patients present with atypical sensorineural hearing or visual loss accompanied by headache, and MRI reveals dural enhancement, particularly in cases where anti-infection treatment has been proven ineffective, MPO-ANCA-positive HP should be considered as a potential diagnosis. The presence of ANCA in the CSF can aid in diagnosing ANCA-related HP. Treatment for ANCA-related HP typically begins with the administration of corticosteroids, and the addition of immunosuppressive agents is often necessary to achieve remission.

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Author contributions
JW wrote the main manuscript text, SW and ML completed the collection of clinical data, XS guided the completion of this paper. All authors have read and approved the final version of this manuscript for submission.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients provided their written informed consent to participate in this study.

Consent for publication
Written informed consent for publication was obtained from all participants.

Competing interests
The authors declare no competing interests.

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