Dynamically changing antineutrophil cytoplasmic antibodies in granulomatous with polyangiitis: a case report

Yan Z et al. Dynamically changing ANCA in GPA

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Abstract

BACKGROUND
Granulomatosis with polyangiitis (GPA) is one of the most prevalent forms of the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). GPA is characterized histologically by necrotizing granulomatous inflammation in addition to vasculitis. The diagnosis of GPA depends on clinical presentation, serological evidence of a positive ANCA, and/or histological evidence of necrotizing vasculitis or granulomatous destructive parenchymal inflammation. Cytoplasmic ANCA (c-ANCA) is positive in 65-75% of GPA patients, accompanied by Proteinase 3 (PR3), the main target antigen of c-ANCA, another 5% of GPA patients had negative ANCA.

CASE SUMMARY
The patient, a 52-year-old male, presented with unexplained nasal congestion, tinnitus, and hearing loss. After a duration of four months experiencing these symptoms, the patient subsequently developed fever and headache. The imaging examination revealed the presence of bilateral auricular mastoiditis and partial paranasal sinusitis, and the ANCA results were negative. The anti-infective therapy proved to be ineffective, but the patient's symptoms and fever were quickly relieved after one week of treatment
with methylprednisolone 40 mg once a day. However, after continuous use of methylprednisolone tablets for three months, the patient experienced a recurrence of fever accompanied by right-sided migraine, positive c-ANCA and PR3, and increased total protein in cerebrospinal fluid (CSF). The patient was diagnosed with granulomatosis with polyangiitis (GPA). After receiving a treatment regimen of daily methylprednisolone a dosage of 40 mg and monthly cyclophosphamide (CYC) at a dose of 0.8 g, the patient experienced alleviation of fever and headache. Additionally, the ANCA levels became negative and there has been no recurrence.

CONCLUSION
For GPA patients with negative ANCA, there is a potential for early missed diagnosis. The integration of histopathological results and multidisciplinary communication plays a crucial role in facilitating ANCA-negative GPA.

Key Words: Anti-neutrophil cytoplasmic antibodies; Granulomatosis with polyangiitis; Antineutrophil cytoplasmic antibody-associated vasculitis; Immunosuppressive therapy; Case report


Core Tip: In this case, otomastoiditis was the initial clinical manifestation, and then the clinical manifestations of central system involvement gradually appeared. Laboratory examination showed that c-ANCA and PR3 changed from negative to positive 3 months later. Therefore, for patients with clinical suspicion of GPA, repeated examination of ANCA should be considered, and obtained pathological evidence whenever possible. Meanwhile, the importance of early participation of the rheumatological immunology team is emphasized. Through multidisciplinary communication, the probability of early
diagnosis of GPA can be improved, and timely drug intervention can be carried out to prevent disease progression and reduce the risk of local and systemic sequelae.

INTRODUCTION

The antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an autoimmune disease characterized by necrotizing vasculitis of small and medium-sized vessels, comprising granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[1]

GPA is characterized histologically by necrotizing granulomatous inflammation in addition to vasculitis. Clinical features typically include destructive sinonasal lesions, lower respiratory tract involvement with pulmonary haemorrhage and granulomatous inflammation, and necrotizing glomerulonephritis.[2] The diagnosis of GPA depends on clinical presentation, serological evidence of a positive ANCA, and/or histological evidence of necrotizing vasculitis or granulomatous destructive parenchymal inflammation. Cytoplasmic ANCA (c-ANCA) is positive in 65-75% of GPA patients, accompanied by Proteinase 3 (PR3), the main target antigen of c-ANCA, and perinuclear ANCA (p-ANCA) and its target antigenic myeloperoxidase (MPO) are positive in 20-30% of GPA patients. Another 5% of GPA patients had negative ANCA,[3] which is more common in GPA patients with respiratory tract involvement.[4]

We present a case of GPA with bilateral otomastoiditis and recurrent fever as the initial presentation. ANCA was negative in the first determination. The ANCA profile was re-examined 3 months later, and c-ANCA was positive and PR3 had a high titer. Meanwhile, right-sided migraine, increased cerebrospinal fluid protein, and other manifestations of central nervous system vasculitis were found.

CASE PRESENTATION

Chief complaints
A 52-year-old male patient with symptoms of chronic nasal congestion, tinnitus, hearing loss lasting for over 8 months, and recurrent fever persisting for more than 4 months.

**History of present illness**

A 52-year-old male presented with nasal congestion and tinnitus, accompanied by bilateral conduction and sensorineural hearing loss in both ears. After enduring these symptoms for a duration of 4 months, the patient subsequently developed a fever, which was accompanied by an excessive weight loss exceeding 8 kg. A tympanic puncture was performed and dexamethasone was injected into the tympanic membrane. Two days later, tympanic catheter drainage was performed. The results of the pathogen culture of the tympanic hydrops showed Staphylococcus aureus, and the patient was given an intravenous injection of linezolid glucose 0.6 g once every 12 h. After 1 wk of anti-infection treatment, the patient continued to experience fever. Consider that Staphylococcus aureus may be a contaminating bacterium rather than a causative factor in fever and otomastoiditis, and given the insufficient diagnostic evidence for fungal or active tuberculosis infection, a trial of intravenous methylprednisolone at a dose of 40 mg once daily was initiated for 1 wk. Following treatment, there was a significant reduction in hs-CRP and ESR levels, accompanied by resolution of fever. The symptoms of ear tightness and tinnitus were also alleviated. Following discharge, the patient commenced oral administration of methylprednisolone tablets at a dosage of 8 mg twice daily, gradually tapering down by 4 mg per week until reaching a maintenance dose of 2 mg twice daily.

After 3 months of glucocorticoid maintenance treatment, the patient developed a fever again, with body temperature fluctuating between 36.9 °C to 38.0°C accompanied by right-sided migraine, stuffiness in the right ear, poor ventilation in the right nostril. Otorhinolaryngology examination showed a clear tympanic catheter and a negative meningeal stimulation sign. The ENT department referred the patient to the rheumatology department.
**History of past illness**

The patient was diagnosed with chronic nephritis 20 years ago based on positive occult blood in urine, however, biopsy to determine the pathological type of the kidney was not performed. Additionally, it should be noted that the patient had a history of raising parrots 1 year ago.

**Personal and family history**

The personal and family history did not reveal any notable features.

**Physical examination**

Temperature: 37.5 °C, pulse rate: 112 beats/min, respiratory rate: 18 beats/min, blood pressure: 121/85 mmHg. The ear canal was clear and unobstructed. There was no tenderness observed in the sinuses, and both lungs showed no abnormalities upon auscultation, and there was no edema observed in both lower limbs.

**Laboratory examinations**

First stage of disease, laboratory examination results showed that hypersensitive C-reactive protein (hs-CRP) was 55 mg/L, erythrocyte sedimentation rate (ESR) was 58 mm/h. The results of active urinary sediment examination revealed a urinary protein level of 1+, a urinary erythrocyte count of 66.7/μl, and a 24-hour total protein excretion rate of 284mg/L. Additionally, the urinary pathogen culture and renal ultrasonography showed no abnormalities. The results of p-ANCA, c-ANCA, antinuclear antibody (ANA) detected by indirect immunofluorescent assay and PR3, MPO detected by enzyme-linked immunosorbent assay were all negative as confirmed by two medical agencies.

After relapse, laboratory examination results showed that hs-CRP was 55mg/L, ESR was 71 mm/h, a urinary protein level of 1+, a urinary erythrocyte count of 89.0/μl, and a 24-hour total protein excretion rate of 373mg/L, c-ANCA was positive, PR3 was 100.8
RU/mL, p-ANCA and MPO were negative. The cerebrospinal fluid (CSF) pressure was 130mmH₂O, the Pandy test was positive, and the total number of nucleated cells was 6.0 × 10⁴/μL. Total protein in CSF was 89.4 mg/dL, chlorine and sugar were normal. ANCA of CSF was negative. The cryptococcus antigen and Xpert MTB/RIF detection of tuberculosis in CSF were normal. No clinically significant pathogenic microorganisms were detected by next-generation sequencing technology (NGS) in the blood.

Imaging examinations
First stage of disease, computed tomography (CT) showed bilateral otomastoiditis with auditory ossicles and partial paranasal sinusitis (Figure 1). Nasopharyngeal enhanced magnetic resonance imaging (MRI) showed bilateral otomastoiditis and right maxillary sinus inflammation (Figure 2).

After relapse, the head enhanced MRI and CT angiography (CTA) revealed no significant abnormalities, except for the presence of bilateral otomastoiditis and right maxillary sinusitis.

Otolaryngology examination
First stage of disease, the otolaryngology examination revealed a deviated nasal septum, purulent discharge in the right middle nasal passage, and absence of any masses in the nasopharynx. Otoscope showed bilateral tympanic membrane invagination and bilateral tympanic effusion.

After relapse, the otolaryngology examination revealed a clear ear canal with no presence of pus or fluid discharge.

Final Diagnosis
Combined with the patient's medical history, the final diagnosis was GPA with bilateral mastoiditis, active glomerulonephritis and suspected central nervous system vasculitis.

Treatment
According to the patient's condition, the Birmingham Vasculitis Activity Score (BVAS) was 23.[5] The patient received intravenous methylprednisolone at a dosage of 40 mg per day, while rituximab was not administered due to cost considerations. Additionally, a combination of intravenous cyclophosphamide (CYC) and 0.8 g/m induced remission was given. To maintain continuous disease remission, cyclophosphamide injections at a dosage of 0.8g were continued every 2 months for a total of 3 consecutive treatment cycles. After treatment, the patient's ear blockage was resolved, hearing function was restored, symptoms of headache and fever subsided, and urine protein and occult blood became undetectable.

OUTCOME AND FOLLOW-UP
At present, the patient is taking methylprednisolone tablets 4 mg once a day, and the cumulative dose of CYC is 7.2 g (Until July 2023). The c-ANCA and PR3 have turned negative, and there has been no recurrence.

DISCUSSION
The patient did not exhibit purulent or bloody nasal discharge, and the presence of right maxillary sinusitis on imaging does not necessarily indicate granulomatous sinusitis. Furthermore, there was no clinical evidence of lung invasion or pathological evidence of granulomatous inflammation. Therefore, due to the challenges associated with procuring pathological specimens and obtaining negative ANCA results, early-stage diagnosis disease can be easily overlooked, particularly in cases where it is not the initial assessment within the rheumatology department. However, considering the patient's otomastoiditis, increased albuminuria, microscopic hematuria, positive response to glucocorticoid therapy, as well as conversion to positive c-ANCA/PR3, there is substantial evidence supporting the diagnosis of GPA in this patient. The patient's "chronic nephritis" condition was stable for a long time, only a small number of red blood cells in urine, and there was no significant clinical significance. In the course of this patient’s disease, progressive increases in urinary erythrocytic cells and urinary
proteins were observed, as well as fever, otomastoiditis, suspected central vasculitis, and PR3-ANCA positivity. Therefore, it was considered that the patient's kidney damage was related to GPA. Although MPA can also involve the respiratory system and kidney, more than 80% of patients are p-ANCA positive, and there is no classification standard for this disease, which is an exclusive disease. This patient has the characteristic clinical manifestations of GPA, and PR3-ANCA turns positive during the course of the disease, so it is still identified as GPA despite the lack of pathological support.

Up to 90% of GPA patients can be involved in the ears and nose, with sinus involvement being the most common.\textsuperscript{[5]} Local involvement in the above respiratory tract and ears is generally more likely to occur in young patients.\textsuperscript{[7]} Literature reports have shown that GPA patients with c-ANCA negative may have a positive result after 4 years,\textsuperscript{[8]} and it is more commonly seen in patients with lesions limited to the upper and/or lower respiratory tract that do not affect renal GPA,\textsuperscript{[9]} but there are also cases of ANCA negative GPA patients with renal biopsy showing necrotizing inflammation with crescent formation.\textsuperscript{[10]} A study summarizing the data of WGET and RAVE found that ANCA negative patients with GPA more commonly had relapsing disease at trial entry (87% vs 57%, \(p = 0.02\)),\textsuperscript{[11,12]} but the rate of relapse during follow-up was similar in the 2 groups.\textsuperscript{[13]} Disease damage did not differ between the 2 groups.

The patient's serum ANCA spectrum showed "cANCA-PR3 positive" in the reexamination after a 3-months interval, accompanied by right migraine, and there was no abnormal neurological examination. The patient had a history of raising birds, so in order to detect infectious diseases such as cryptococcus and chlamydia, blood NGS and cerebrospinal fluid puncture were performed to eliminate infectious diseases. Although the patient's cranial enhanced MRI and intracranial vascular CTA did not suggest the presence of hypertrophic cranial pachymeningitis, cranial nerve involvement, hypophysitis, and cerebral ischemia/hemorrhage lesions, the presence of headache and significantly elevated cerebrospinal fluid protein levels suggests a potential diagnosis of central nervous system vasculitis. Among GPA patients with central involvement,
ANCA positive was found in 89% of patients, of which PR3 positive patients accounted for 84%, and most patients presented with clinical manifestations of headache and hearing loss.\cite{14} CSF analysis may demonstrate nonspecific abnormalities such as elevated protein and pleocytosis, but it can help to rule out infectious, neoplastic, or other diseases in the differential diagnosis. One study reported 3 young patients with biopsy-proven active generalized GPA who were consistently ANCA negative over observation times ranging from 58 to 114 months, indicating that severe CNS manifestations could represent a clinical hallmark of ANCA negative GPA.\cite{15} Although treatment with glucocorticoids and immunosuppressants may affect ANCA results, ANCA titers/Levels may not be parallel to important organ involvement in GPA.\cite{16} For GPA patients with unexplained headaches, sensory and/or movement disorders, diabetes insipidus, cranial enhanced MRI and/or intracranial vascular CTA should be performed in a timely manner to assess central nervous system involvement.

**CONCLUSION**

In this case, otomastoiditis was the initial clinical manifestation, and then the clinical manifestations of central system involvement gradually appeared. Laboratory examination showed that c-ANCA and PR3 changed from negative to positive 3 months later. Therefore, for patients with clinical suspicion of GPA, repeated examination of ANCA should be considered, and obtained pathological evidence whenever possible. Meanwhile, the importance of early participation of the rheumatological immunology team is emphasized. Through multidisciplinary communication, the probability of early diagnosis of GPA can be improved, and timely drug intervention can be carried out to prevent disease progression and reduce the risk of local and systemic sequelae.
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