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Myeloperoxidase Positive Wegener's Granulomatosis with Isolated Otorhinological Involvement

Rebecca Sin Mei Lim, Kim Le Marshall[1], Malcolm Baxter, Michelle Leech[1]
From the Department of Ear, Nose, Throat and Department of Rheumatology, Southern Health, Melbourne, Australia.

Abstract:

Introduction: Granulomatosis with polyangiitis (GPA) is a systemic vasculitis characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract and kidney.
Case Report: We present here the uncommon case of a 71year old Caucasian man with newly diagnosed GPA presenting with isolated otorhinological involvement. The patient described 3 weeks of right-sided otalgia, mastoid pain and right hemifacial pain with associated rhinorrhoea, particularly at night, fevers and sweats. On examination, the right mastoid was tender to palpation but neither erythematous nor swollen. A Computed Tomography (CT) brain scan showed right-sided sinusitis and mastoiditis and right-sided acute on chronic otitis media without bony erosion. A biopsy of the right maxillary sinus found suppurative granulomatous changes, mild active vasculitis with neutrophil polymorphs in vessel walls and healing vasculitis with sclerosed vessels in keeping with a diagnosis GPA. Serology showed that he was p-anti-neutrophil cytoplasmic antibody (p-ANCA) positive, myeloperoxidase (MPO) positive and serine proteinase 3 antigen (PR3) negative. His GPA was treated with prednisolone in the acute phase and azathioprine was later commenced for maintenance therapy.
Conclusion: This case highlights the need to consider GPA in a patient presenting with isolated otorhinological involvement without organ involvement.

Key words: Granulomatosis, Polyangitis, Vasculitis, Aziathrioprine, Sinusitis, Prednisolone.

Introduction

"Wegener's granulomatosis" (WG) is a systemic vasculitis characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract and kidney. It affects small to medium sized vessels, producing a myriad of symptoms that might make it difficult to distinguish clinically from other vasculitides. The term Granulomatosis with polyangiitis (GPA) has recently replaced the eponym "Wegener's Granulomatosis" due to the Nazi affiliations of the latter.

Two patterns of anti-neutrophil cytoplasmic antibodies (ANCA) can be distinguished by indirect immunofluorescence (IIF) - the cytoplasmic staining

Corresponding Author: Dr. Rebecca Sin Mei Lim
Email: rebecca1188@gmail.com
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pattern (c-ANCA) and the perinuclear staining pattern (p-ANCA). The former is seen in 70-90% of patients with GPA, and is usually directed against serine proteinase 3 antigen (PR3-ANCA), which causes the activation of primed neutrophils, leading to production of reactive oxygen species and the release of lytic enzymes that promote tissue damage [1,2]. Of the 5% of all Caucasian patients with GPA who test positive for p-ANCA, most have an ANCA directed against myeloperoxidase (MPO). We describe a 71 year old Caucasian man with newly diagnosed GPA presenting with isolated otorhinological involvement.

Case Report

We present here the uncommon case of a 71-year-old Caucasian man with newly diagnosed p-ANCA positive, myeloperoxidase (MPO) positive and PR3 negative GPA presenting with isolated otorhinological involvement. The patient described 3 weeks of right-sided otalgia and mastoid pain, right hemifacial pain and diffuse scalp tenderness. The pain was constant, sharp and severe. There was associated rhinorrhoea, particularly at night, fevers and sweats. There was no preceding respiratory tract infection, rigors, epistaxis, dysphagia, dysphonia, diplopia nor any other neurological signs or symptoms. He also denied jaw claudication and muscle weakness. On examination, the right mastoid was tender to palpation but neither erythematous nor swollen. The patient had received 3 courses of roxithromycin from his local doctor with no improvement in his symptoms.

On presentation to a regional emergency department, a Computed Tomography (CT) brain scan showed right-sided sinusitis and mastoiditis and right-sided acute on chronic otitis media. No bony erosion was noted on the scan. He was treated with intravenous ticarcillin with clavulanate 3.1grams four times per day and pseudoephedrine 60 mg per oral twice daily and transferred to a tertiary hospital where he was admitted under the Ear, Nose and Throat (ENT) Unit. Prednisolone 50 mg daily and ciprofloxacin 500 mg per oral twice daily were commenced. Prednisolone was used in an attempt to reduce swelling in the sinus ostea area. The patient described a dramatic reduction in pain the following day. His blood tests revealed an MPO ANCA titre of 70 RU/mL (normal range <20 RU/mL). On day 4 of admission, a ventilation tube was inserted into his right tympanic membrane and an examination under anaesthesia was performed, showing a red, dull tympanic membrane with increased vascularity. A week later, an antrostomy and biopsy of the right maxillary sinus was performed. The biopsy demonstrated suppurative granulomatous changes, mild active vasculitis with neutrophil polymorphs in vessel walls and healing vasculitis with sclerosed vessels on the aldehyde fuchsingomori (AFG) elastin stain, in keeping with a diagnosis GPA. As part of the workup for GPA, this patient underwent a chest X-ray and urinalysis which were both normal.

The patient received a total of ten days of intravenous ticarcillin with clavulanate and ciprofloxacin for treatment of sinusitis and mastoiditis. The treatment of his newly diagnosed GPA consisted of 50 mg prednisolone daily for eight days and 30 mg for 15 days. Although the patient's transaminases were normal at baseline, given his age and limited involvement, a low dose of azathioprine 25 mg per oral twice daily was commenced a month into his admission. He was discharged on this and 30 mg of prednisolone.

This gentleman's facial and scalp pain was attributed to sinusitis-induced trigeminal neuralgia and was treated with tramadol, carbamazepine and an intravenous lignocaine (lidocaine) infusion. The symptoms improved and he was discharged on 400 mg carbamazepine per oral twice daily and 10 mg of oxycodone SR per oral twice daily.

After discharge, this gentleman's GPA remained

well controlled with consistently low inflammatory markers. He developed a mild exacerbation 9 months later, which was managed with a temporary increase in prednisolone dose. His prednisolone has been weaned to 5 mg currently. Azathioprine 75 mg daily caused significant gastrointestinal side effects, so the patient's therapy was changed to methotrexate 20 mg per oral weekly. He continued to experience occasional flares of trigeminal neuralgia, which were managed by titrating the carbamazepine dose accordingly.

Discussion

Cases of GPA that are MPO-ANCA positive are far less common than PR3-ANCA positive GPA amongst Caucasians. Literature concerning this subgroup is scarce, possibly due to the small number of patients affected. The two main studies that have investigated this subgroup include a study by Schonermarck *et al*. that compared seven patients with MPO positive GPA with 21 age-and-gender matched PR3 positive ones, and a Chinese study of 89 patients with GPA, of which 54 were MPO positive and the remainder PR3 positive [3,4].

Both studies found MPO positive GPA predominantly affected females. In keeping with our case whose GPA was limited to his paranasal sinuses, this subgroup also had less organ involvement compared to their PR3 positive counterparts. The lower incidence of organ involvement led the authors in the latter study to speculate that MPO positive GPA shared similarities with microscopic polyangiitis (MPA), another ANCA-associated vasculitis, while PR3 positive GPA more commonly manifested as classic GPA.

It is interesting to note that while MPO positive GPA is far less common than PR3 positive GPA amongst Caucasians, the latter study found it to be more common than PR3 positive GPA amongst its sample of Chinese patients. Whether or not this is an epidemiological feature of GPA in the Chinese population remains to be clarified.

The limited form of GPA can be challenging to diagnose, taking an average of 20 months from symptom onset to diagnosis in one study [5]. In the same study, the systemic form of GPA took an average of only 2 months to diagnose. In contrast, the patient we present was diagnosed swiftly, in under 5 weeks. Patients with MPO positive GPA have also been found to present at a later age than their PR3 positive counterparts – median age of 63 versus 56 [6]. This is in keeping with our patient, who was 71 years old at the time of diagnosis.

In contrast to our case, a recent study found that patients older than 60 years when diagnosed with GPA initially presented with renal, pulmonary and other manifestations more so than younger patients [7]. This study also found that the nose and paranasal sinuses in particular, were the sites of presenting symptoms in 50 per cent of patients diagnosed before the age of 60 years, compared with only 27 per cent of those diagnosed when older than 60 years.

Thus far, the reason behind the different clinical and histopathological characteristics of patients with PR3 positive GPA and those with MPO positive GPA is still unclear. The difference may be due to the distinct ways in which anti-PR3 ANCA and anti-MPO ANCA interact with granulocytes and/or endothelial cells, thereby influencing the site and extent of the resulting vascular injury. A difference in T-cell mediated immunity between patients with anti-PR3 and anti-MPO has also been speculated to play a role in the observed higher frequency of granuloma formation in anti-PR3 than anti-MPO patients. This could be due to the fact that PR3 reactive T-cells were observed more frequently in patients with PR3 than in controls, whereas MPO-reactive T-cells were observed at the same frequency in anti-MPO patients and in controls [6].

This case shares some common features with the relatively few case reports of MPO positive GPA in the literature to date. It further illustrates the effective steroid sparing afforded by Azathioprine and Methotrexate in the control of significant otorhinological MPO positive GPA.

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