CASE REPORT

Granulomatosis with polyangiitis affecting the skull base and manifesting as spontaneous skull base osteomyelitis

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SUMMARY

A 53-year-old woman presented with right-sided otalgia radiating to the temporal region, angle of the mandible and upper neck. Otoscopy was unremarkable on examination and there were no signs of otitis externa. MRI revealed an infiltrative soft tissue mass to the right lateral aspect of the clivus. Transnasal and CT-guided biopsies were performed, however, these showed either inconclusive or benign tissue. Following multidisciplinary team assessment a diagnosis of spontaneous skull base osteomyelitis was made and treatment with intravenous antibiotics started. Failure to respond to antimicrobials and the development of cranial nerve palsies raised the possibility of a vasculitis. Subsequently, a clinical diagnosis of granulomatosis with polyangiitis (GPA) was made. Remission has now been maintained with cyclophosphamide and prednisolone. We discuss the rare presentation of GPA mimicking that of spontaneous skull base osteomyelitis as well as its management and related primary otolaryngological manifestations.

BACKGROUND

Primary otolaryngology manifestations of granulomatosis with polyangiitis (GPA) occur in around 85% of cases,¹ however, GPA affecting the skull base alone, spontaneously, is rare. In this case, MRI findings were in keeping with malignancy or infection and histological analysis was inconclusive. Initial raised inflammatory markers were suggestive of an infective process and a multispecialty team decision was made to treat the case as spontaneous skull base osteomyelitis. Following intravenous antimicrobial treatment, there was an initial response radiologically on MRI, however, pain persisted, and during the treatment a hypoglossal nerve palsy developed.

The diagnosis of GPA affecting the skull base in this case was delayed due to the atypical presentation, however, since initiation of cyclophosphamide and prednisolone, symptoms resolved and MRI appearances improved.

MRI of the skull base, as in this case, does not distinguish between GPA and infective or malignant pathology. Furthermore, GPA is not always associated with the presence of antineutrophilic cytoplasmic antibodies and histological analysis may not show granulomas or vasculitis. Thus GPA is a clinical diagnosis—although involvement of the skull base is rare, it should be considered in patients with clinical features of skull base osteomyelitis. Failure to diagnose GPA can result in systemic

disease progression and also mortality, therefore early diagnosis is important.

CASE PRESENTATION

In March 2014, a 53-year-old Caucasian woman presented to the otolaryngology clinic several times with symptoms of otalgia radiating to the right-sided temporal region, oropharynx, angle of the mandible and upper neck. Medical history included Crohn's disease, hypothyroidism and previous episcleritis. Initially, a diagnosis of trigeminal neuralgia was made, however, following otolaryngological assessment, right-sided conductive hearing loss was found secondary to a middle ear effusion.

Myringotomy was performed for presumed Eustachian tube dysfunction and otitis media with effusion, but there was no symptomatic relief. The clinical impression at this point was a possible skull base malignancy invading the foramen lacerum and therefore MRI was arranged.

MRI revealed an infiltrative soft tissue mass to the right lateral aspect of the clivus ([figure 1](#)). Subsequent transnasal and CT-guided biopsies showed either inconclusive or benign tissue. At this point, a diagnosis of spontaneous skull base osteomyelitis was made and long-term intravenous antibiotics were started. Despite antibiotic treatment, further MRI revealed progression of the disease including more extensive involvement of the clivus, early skull base erosion, and involvement of both, the right and left hypoglossal canals ([figure 2](#)). Clinically, the pain persisted and a right hypoglossal nerve palsy developed.

Subsequently, the patient developed facial cellulitis overlying the nasal bridge, which slowly resolved with intravenous antibiotics.

A biopsy of the cutaneous tissue involved in the cellulitis was taken and this showed chronic inflammation. Further MRI showed recurrent inflammatory changes in the skull base and possible focal dural enhancement in the left middle cranial fossa. Following this, a lower motor neuron facial nerve palsy developed in the absence of associated middle ear pathology.

INVESTIGATIONS

Initial inflammatory markers included a white cell count of $11.2 \times 10^9/L$, C reactive protein (CRP) 100.9 mg/L and erythrocyte sedimentation rate (ESR) of 53 mm/h, these fluctuated throughout the course of the illness, despite an initial response. The patient remained non-feverish throughout.

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Figure 1 MRI showing an infiltrative soft tissue mass to the right lateral aspect of the clivus.

Autoimmune screening was performed during the course of the illness and results included positive antinuclear antibodies (ANAs) ELISA, and negative ANAs, antineutrophilic cytoplasmic antibody (ANCA) immunofluorescence and ENA. Serum creatinine was within normal limits and there was neither proteinuria nor haematuria on urinalysis.

Serial MRI scans showed progression of the soft tissue mass around the clivus, as well as early skull base bony erosion and involvement of both, the right and left hypoglossal canals.

Figure 2 MRI showing more extensive involvement of the clivus, early skull base erosion, and involvement of both the right and left hypoglossal canals.

Furthermore, there was possible focal dural enhancement in the left middle cranial fossa.

Histological analysis of tissue was inconclusive on two separate occasions, no microbiological sensitivities were identified following cultures. There was evidence of neither dysplasia nor malignancy.

Following a diagnosis of GPA and initiation of treatment with cyclophosphamide and prednisolone, remission was maintained.

Positron emission tomography scanning was also performed but no further information was gathered.

DIFFERENTIAL DIAGNOSIS

The underlying differential diagnosis includes skull base malignancy, spontaneous skull base osteomyelitis and eosinophilic vasculitis.

TREATMENT

The patient has been maintained on medical treatment including cyclophosphamide and prednisolone. The excruciating pain, which was the primary presenting symptom has now resolved, along with the hypoglossal palsy. The facial nerve function is now improving and hearing is almost within normal thresholds.

OUTCOME AND FOLLOW-UP

The patient is currently under regular follow-up by the otolaryngology and rheumatology teams.

DISCUSSION

GPA was, until recently, known as Wegener's granulomatosis, from when it was first described by Friedrich Wegener in 1936 and 1939.² In 2011, rheumatology and vasculitis entities decided the condition should be renamed, due to evidence that Dr Friedrich Wegener was linked to the Nazi party prior to the Second World War.³

The incidence of GPA is around 10 cases per million, and it typically presents in Caucasians between 20 and 40 years of age.⁴ GPA is a relatively rare, multisystemic granulomatous disease characterised by vasculitis of small-sized and medium-sized vessels. The exact aetiology is unknown, but it is thought to involve an autoimmune inflammatory process driven by ANCA. The disease typically affects the upper and lower airways and a glomerulonephritis, but any organ can be affected. Typically, the diagnosis of GPA is based on criteria published by the American College of Rheumatology, and in those who meet two of the four following criteria, classic GPA can be diagnosed with a sensitivity and specificity of 88% and 92%, respectively⁵:

- ▶ Oral and nasal inflammation with painful or painless ulcers or purulent bloody nasal discharge;
- ▶ Abnormal chest radiography showing nodules, fixed infiltrates or cavities;
- ▶ Urinary sediment with microhaematuria or red cell casts;
- ▶ Granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area, or haemoptysis if a specimen is unavailable.

In this case report, the above criteria did not apply. This case was an example of limited GPA, which is GPA without glomerulonephritis, however, according to the Vasculitis Foundation, this term has become unpopular because it does not take into account disease severity in those without multisystemic involvement.

Head and neck involvement of GPA occurs in around 85% of cases.¹ Head and neck involvement is associated with improved

survival but higher relapse rates.⁶ Furthermore, it has been shown that those patients with GPA limited to the head and neck have their diagnosis made later than those presenting with systemic disease. Necrotising granulomas are rarely seen in biopsies from the head and neck, which may contribute to delay in diagnosis, furthermore, nasal biopsy specimens are most likely to produce pathognomonic results compared with other head and neck sites if the nasal cavity is involved in the disease process.⁷ Prompt initial immunosuppression is associated with lower relapse rates and, therefore, GPA should be considered by all otolaryngologists in those patients with a presumed infection and refractory response to antimicrobials.

GPA is a diagnostic challenge as it often presents with non-specific symptoms. As in this case, there is a high incidence of those with GPA and hearing loss. Both conductive and sensorineural hearing loss has been shown to indicate presentation and relapse of GPA.⁸ In the literature, the incidence of sensorineural hearing loss in those with GPA varies between 19% and 61%.⁹

Imaging as described in this case report cannot differentiate between infective, inflammatory and malignant processes. Additionally, the autoimmune screening including the sensitivity of ANCA is as low as 60%, and therefore this cannot exclude a diagnosis of GPA. Additionally, negative CRP and ESR results cannot rule out GPA.¹⁰

There are three classifications to aid in the diagnosis of GPA. These are described by the American College of Rheumatology, Chapel Hill Consensus Conference and the European Vasculitis Study Group. The American College of Rheumatism Classification states that a positive test for cytoplasmic ANCA targeted to antiproteinase 3 antibodies or perinuclear (P) ANCA against myeloperoxidase (MPO) has a high sensitivity and specificity for the diagnosis of ANCA-associated vasculitides but a negative test does not exclude a diagnosis. If there is a high index of suspicion of GPA, the test should be repeated every 3–6 months for 24 months.⁵

Although histopathological evidence of vasculitis remains the gold standard for the diagnosis of vasculitis,⁵ biopsy results correlating to a diagnosis of GPA range from 25% to 57%.⁴ Skull base biopsies were taken for analysis as well as cutaneous tissue in this case, but these did not support the diagnosis of GPA. Therefore, this case is not comparable to previous cases of skull base GPA described in the literature that has shown granulomatous inflammation and vasculitis on histology.^{11 12}

More recently, positron emission tomography scanning has been used to evaluate disease activity in those with antineutrophil cytoplasmic antibody-associated vasculitis. Although in this case it did not contribute to making the diagnosis, recent studies have shown positive findings in multiple sites of the body where biochemical markers are inconclusive.¹³

Prompt diagnosis of GPA is particularly important in those with otolaryngological manifestation, as prompt initial immuno-

Learning points

- ▶ In those with presumed infection and refractory outcome to antimicrobial treatment, a high index of suspicion for granulomatosis with polyangiitis (GPA) is needed.
- ▶ Early diagnosis is important in primary otological manifestation, as this prevents systemic disease and lowers relapse rates after remission.
- ▶ Antineutrophil cytoplasmic antibody tests may be negative in the presence of GPA.
- ▶ Furthermore, CT and MRI may not accurately differentiate between infective, inflammatory and malignant processes.
- ▶ Histology is the gold standard for the diagnosis of vasculitis, however, it does not exclude GPA if inconclusive, as in this case.

suppression has been linked to low relapse rates.¹⁰ With regard to treatment of the condition, The European League against rheumatism recommends a combination of cyclophosphamide and glucocorticoids for remission induction in those with generalised primary small and medium vessel vasculitis.⁵ Bactrim, which is a combination of sulfamethoxazole and trimethoprim, has been shown to be used specifically for cytotoxic-resistant GPA and usually for GPA limited to the upper respiratory tract. Bactrim was therefore not used in this case.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient's perspective

As the patient in this case I have had a tough year with the initial uncertainty around my diagnosis and would like to raise awareness among clinicians about GPA affecting the skull base. It is a rare diagnosis but an important one that needs prompt treatment.

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