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Wegener's granulomatosis presenting as otomastoiditis. A case report

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Abstract. *Wegener's granulomatosis presenting as otomastoiditis. A case report.* A 55-year-old male presented with left-sided otorrhoea, hearing loss and tinnitus of 3 months duration. On clinical examination polypoid tissue was seen prolapsing in the external ear canal. A CT scan of the mastoid cells and middle ear showed otomastoiditis with osteolysis. Oral antibiotic therapy and eardrops were started.
When a facial nerve paresis appeared one month later, a mastoidectomy was performed. The mastoid cells and middle ear were filled with a connective tissue-like substance. Postoperative corticosteroids were administered. Despite the therapy the facial nerve problem aggravated and the patient developed severe parietotemporal headache, meningeal irritation and somnolence. The diagnosis of neurosarcoidosis was hypothesised.
Blood analysis, including c-ANCA's, culture of the otorrhoea and biopsies of the connective tissue were inconclusive. A CT scan of the brain showed thickening of the left tentorium. A biopsy of the dura indicated a diagnosis of Wegener's granulomatosis. The patient was treated with immunosuppressive medication with satisfactory results.

Introduction

A common and aspecific chronic otitis can occasionally turn out to be the first symptom of Wegener's granulomatosis. Objective findings on CT or MRI may be very marked and suspicious but don't give a clear diagnosis. A few different granulomatous diseases show some similarities but also have some important differences. Unfortunately, the typical laboratory or imaging findings are not always present, and if so, the diagnosis may have to be found by exclusion.

Case Report

A male patient of 55 years presented with left earache and otorrhoea since a few months. He had already been started on a short course of corticotherapy without improvement.

Probably because of the irradiating character of the earache, a CT scan of the brain was carried out and found to be normal. An atypical infection with otorrhoea was present and oral antibiotics (amoxicillin-clavulanic acid), antibiotic eardrops and non-steroidal anti-inflammatory drugs were prescribed. A culture of the otorrhoea taken at the first consult showed coagulase negative *Staphylococcus*.

A CT scan of the temporal bone showed a soft-tissue mass in the outer and middle ear extending into the mastoid cells. The mass was suspicious for a malignant process, with osteolytic destruction of the tegmen and mastoid cells (Figure 1).

Two weeks later the patient developed a sudden facial nerve paresis. An urgent mastoidectomy was performed. Multiple biopsies were taken from the granulation tissue that filled the outer and middle ear and the mastoid cells. The facial nerve canal was intact.

Postoperative corticotherapy led to rapid improvement of the symptoms.

Anatomopathology examination showed an atypical inflammation with reactive fibrosis and no signs of malignancy.

Two months later the patient developed a severe headache and an increase loss of conductive hearing. A repeat CT scan of the temporal bone showed filling of the middle ear with bulging of the eardrum in spite of previous surgery and extension of the soft-tissue mass into the mastoid cells. An MRI of the brain showed intracranial extension of the inflammatory process into the base of the skull and the posterior fossa (Figure 2).

After one month the facial palsy had aggravated and there

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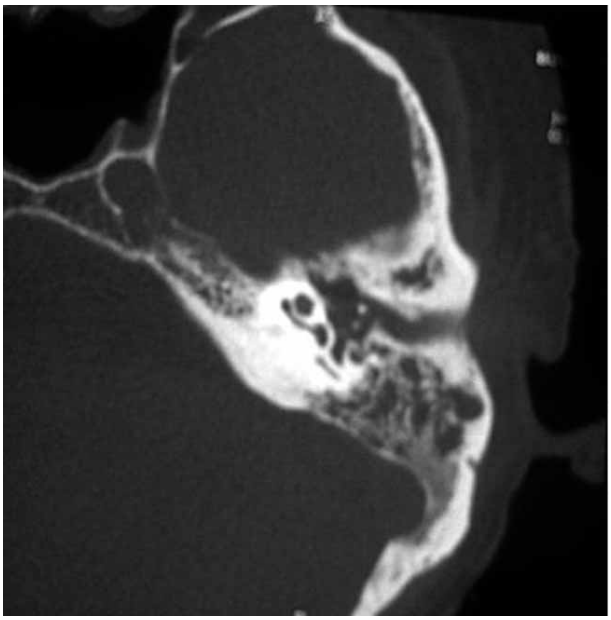

Figure 1
Otomastoiditis with osteolytic destruction of the tegmen and mastoid cells.

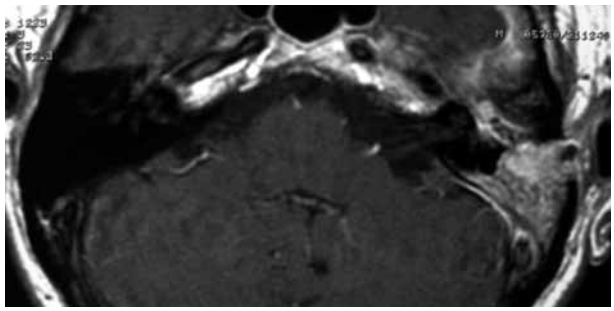

Figure 2
Filling of the middle ear and expansion into the mastoid cells

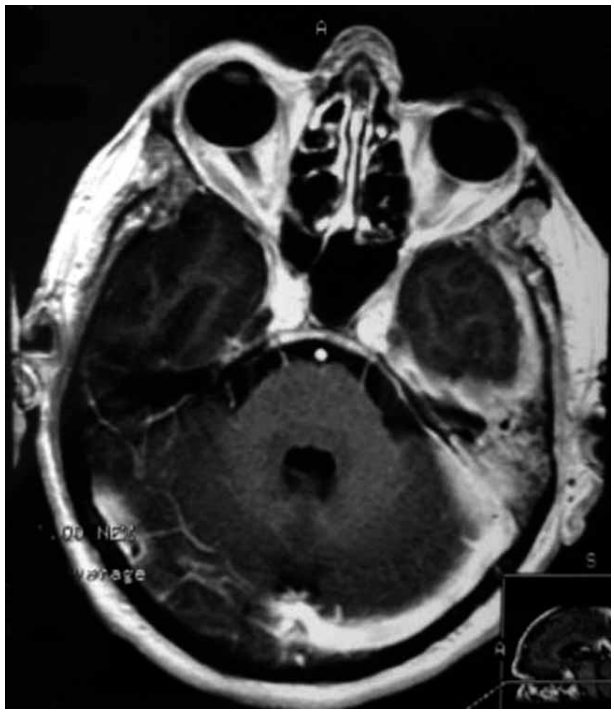

Figure 3
Involvement of the tentorium and meninges of the posterior and middle fossa.

was increase of the temporoparietal headache. A revision mastoidectomy was performed and the histology of the biopsies now also showed some giant cells and a more obvious inflammatory component. A trigeminal neuropathy developed and the parietotemporal headache continued.

Clinical neurological examination confirmed the peripheral facial palsy and hyperesthesia in the left maxillary and mandibular nerves. A repeat MRI of the brain showed an inflammation of the left ear extending into the surrounding muscles and involvement of the tentorium and meninges of the posterior and middle fossa (Figure 3).

Imaging

A CT scan of the thorax showed no abnormalities and no arguments for sarcoidosis. A gallium scan did show pathological contrast captation at the salivary and lachrymal glands, which may have been suggestive for sarcoidosis. A PET scan was negative.

Laboratory findings

Blood examination was normal except for the CRP (4.1 mg/dl) and the sedimentation rate (47 mm/h) that were slightly elevated. Cerebrospinal fluid examination showed clear, colourless fluid with 6 WBC/mm^3, a protein level of 62 mg/dl, and no signs of malignancy. The CSF culture was negative and on microscopy, lymphocytosis and monocytosis were seen. PCR for the bacillus of Koch as well as the anti-neutrophil cytoplasmatic auto-antibodies (ANCA's) were negative. A biopsy of the mediastinal lymph nodes showed anthracosis. Bronchial aspiration was normal.

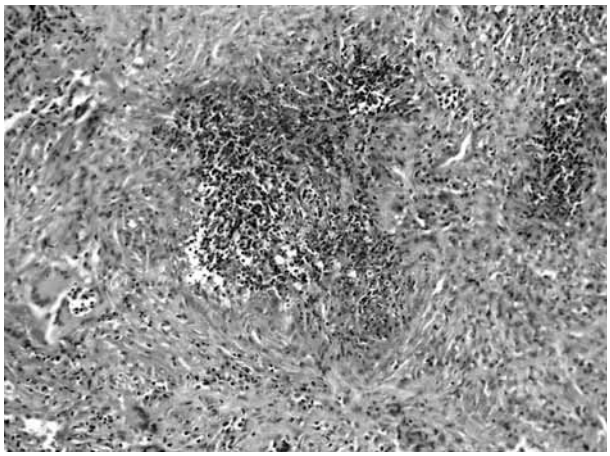

Figure 4
Haematoxylin/eosin colouring: granuloma with giant cells

Figure 5
Contrastcaptation at the temporal bone is the only residual sign of the disease.

The diagnosis of neurosarcoidosis was contemplated. In favour of this diagnosis was the clinical picture with the inflammatory mass of the left tentorium, the presence of giant cells in the biopsies and the very suggestive gallium scan. Against this diagnosis was the negative mediastinoscopy, which would reveal hilar adenopathy in cases of sarcoidosis.

Under corticotherapy there was a slight but significant decrease of contrast captation on MRI.

Because of the development of a Cushing syndrome, the dose of corticoids was gradually reduced. One month later the patient again developed severe, unsupportable pain attacks. Increasing the corticotherapy led to a decrease of the pain. A repeat MRI of the brain showed an increase in meningeal and tentorial contrastcaptation. A biopsy of the temporal artery was normal. A repeat PCR analysis for the bacillus of Koch and a culture for over 3 months were negative.

In view of a lack of a diagnosis, a meningeal biopsy was performed. On histology chronic inflammation with foci of necrosis as well as perivascular inflammation and necrosis were seen. Giant cells and granulomatosis, two findings typical of Wegener's granulomatosis were now detected (Figure 4).

As soon as the patient was treated with a combination of methylprednisone and cyclophosphamide, his complaints and the radiological findings improved (Figure 5).

Discussion

This case illustrates that even very aspecific, atypical symptoms may lead to a very specific diagnosis. Although Wegener's granulomatosis is defined as a systemic granulomatous, necrotizing vasculitis with a predilection for the upper and lower respiratory tract and the kidneys, it often might be limited. The ENT-localisation is not rare in these cases, which places the otorhinolaryngologist in an important position to diagnose the disease before it has become systemic and before irreversible harm to the vital organs has occurred.[1] The clinical presentation can be diverse. The differential diagnosis ranges from infections (syphilis, Lyme disease, fungal infections) to neoplasms, to other vasculitides or connective tissue diseases, like sarcoidosis, Behçet's and Sjögren disease.[2]

In 1990, the American College of Rheumatology developed diagnostic criteria in order to distinguish patients with Wegener's granulomatosis from patients with other forms of vasculitis.[3] For classification as having Wegener's granulomatosis, at least 2 of the 4 criteria need to be present, this giving a sensitivity of 88% and a specificity of 92% (Table 1).

Table 1
Diagnostic Criteria for the classification of Wegener's graulomatosis and distinguish it from other forms of vasculitis

Criterion	Definition
1. Nasal or oral inflammation	Development of painful or painless oral ulcers or purulent or bloody nasal discharge
2. Abnormal chest radiography	Showing the presence of nodules, fixed infiltrates or cavities
3. Urinary sediment	Microhaematuria (> 5 RBC/field)
4. Granulomatous inflammation on biopsy	Histological changes presenting granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area.

Epidemiology

Most patients are Caucasian and in the fourth or fifth decade of life. There is an equal sex distribution and the genetic predisposition is complex. The estimated prevalence in the USA is 3/100000.[2,4,5]

Clinical presentation

Fever and weight loss may be reported at the onset of the disease. The respiratory tract is the most common location of the disease with cough, haemoptysis and pleuritis as the most frequent symptoms. The radiographic findings include pulmonary infiltrates and nodules.

Renal involvement may lead to glomerulonephritis and even renal failure.[2] ENT-involvement often occurs at an early stage with sinonasal manifestations being the most common.[6-8] These include sinusitis, nasal discharge, nasal stuffiness, pain, crusting, epistaxis, polyposis with hyposmia, ulcers leading to septal perforation and chondritis leading ultimately to the typical saddle-nose. Wegener's granulomatosis in childhood is more frequently complicated by nasal deformity.[3]

Otological symptoms include otorrhoea, conductive hearing loss, pain and facial palsy. Even sensorineural hearing loss may occur as a result of bone formation in the labyrinth and haemorrhage in the endo- or peri-lymphatic space, probably due to vasculitis. Laryngopharyngeal involvement includes pain, ulcers and even subglottic stenosis, which is a life-threatening complication more frequently seen in childhood and may require a tracheostomy.[3,5]

Other rarer localisations are the Eustachian tube and the base of the skull[3], the pterygopalatine fossa causing a trigeminal neuropathy,[9] the fourth ventricle[10] and the eye due to retinal artery occlusion.[11]

Aetiology

The cause of Wegener's granulomatosis is not yet clear. It is proposed that Wegener's granulomatosis is an auto-immune disease, in which the presence of antineutrophil cytoplasmic autoantibodies (c-ANCA's) lead to tissue injury.[12] Circulating c-ANCA's producing a granular cytoplasmic staining pattern on fixed neutrophils by binding to human proteinase 3 (PR3) of cytoplasmic granules are diagnostic markers for the idiopathic auto-immune vasculitis, Wegener's granulomatosis. On the other hand, p-ANCA's have a perinuclear staining pattern and are typical for peri-arteritis nodosa.

Usually, the levels of PR3-c-ANCA's correlate with the activity and the severity of the disease, decreasing when the disease improves. Significant rises of the PR3- c-ANCA-titres are predictors of clinical relapses while relapses have rarely been observed in the absence of PR3- c-ANCA's.

In vitro experiments indicate that many of the pro-inflammatory effects require binding of the c-ANCA's to target antigens expressed on the surface of primed effector cells. It is therefore thought that if patients with c-ANCA's are exposed to an inflammatory stimulus such as an infection, c-ANCA's may interact with their target antigen expressed on the surface of primed neutrophils and monocytes. Several clinical findings suggest that microbial infections may provide a primary stimulus necessary for disease induction in Wegener's granulomatosis.

Several studies consider *Staphylococcus aureus* responsible for inducing the disease or triggering relapses.[5,13,14] *S. aureus* colonizes the upper airways in about 20% of healthy persons. Most patients with serious sinus or nasal disease due to Wegener's granulomatosis develop secondary infections in which *S. aureus* is predominantly involved. Activation of Wegener's granulomatosis might be precipitated by infection with *S. aureus*, which initiates a cascade of immunological events caused by bacterial toxins. This hypothesis is supported by the observation that chronic nasal carriage of *S. aureus* is related to

exacerbations of Wegener's granulomatosis. The bacterial toxins can induce interleukin-8 expression, which plays an important role in neutrophil proliferation in the pulmonary tract. Antigens in purulent sputum react strongly with IgG isolated from sera in patients with Wegener's granulomatosis, indicating a possible mechanism by which *S. aureus* might trigger relapses. Whether it is the agent that induces the presence of the auto-antibodies is speculative.

Another explanation is that the damaged tissue impairs mucosal immunity, thus favouring secondary infection. However, in that case, other pathogens would be expected to be present. The relationship with *S. aureus* supports the beneficial effect of trimethoprim/sulphamethoxazole in the treatment of the disease and in the prevention of relapses.

Diagnosis

Although the c-ANCA's may occasionally occur in other inflammatory conditions, they are highly specific for Wegener's granulomatosis.[15] Nevertheless, absence of c-ANCA's doesn't exclude the diagnosis of Wegener's granulomatosis. The clinical picture is therefore important. The sensitivity ranges from 34% to 92%, the specificity is more than 90%.[15] When c-ANCA's are negative they should be repeated for up to 4 years.

The typical histological findings on biopsy are a necrotizing vasculitis, perivascular granulomas and multinuclear giant cells in a highly inflammatory background. Micro-abscesses might be present. Rasmussen[16] recommends diagnostic biopsies be obtained from active lesions in the nose and paranasal sinuses. Del Buono *et al*.[17] found that nasal biopsies should be taken from abnormal as well as from normal tissue. Nasal biopsy in his study was diagnostic in 53% of patients with proven Wegener's granulomatosis. Samples larger than 5 mm are more likely to be diagnostic than smaller samples.[5]

Granulomas can be identified on MRI as low-signal lesions on T1- and T2-weighted images but only in a later stage. As in this case, MRI shows the inflammatory process when there is extension into the surrounding tissue.

Treatment

Before immunosuppressive treatment was known, the prognosis of Wegener's graulomatosis was poor with a median survival time of 5 months. Corticotherapy alone cannot control pulmonary or renal disease sufficiently and chronic use may lead to a severe Cushing syndrome. A combined treatment of cyclophosphamide (2 mg/kg/d) and methylprednisolone is effective. In case of relapse, a short pulse therapy of methylprednisolone can be given in high dose (1 g/d for 3 days). Cotrimoxazole in the prevention of relapse is given successfully (800 mg sulphamethoxazole and 160 mg thrimethoprim).

Conclusions

When confronted with chronic, progressive inflammatory middle ear disease, Wegener's granulomatosis should be considered and appropriate tests should be done.

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