Wegener’s granulomatosis and multiple cranial neuropathies

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Date accepted for publication 17 February 2010

Abstract

Wegener’s granulomatosis, first described by Friedrich Wegener in 1936, is a systemic vasculitis that characteristically causes necrotizing granulomas of the respiratory tract and necrotizing crescentic glomerulonephritis. This article describes the history and modern treatment of the disease in conjunction with a clinical case.

Keywords

Wegener’s granulomatosis; treatment; neurological involvement.

Clinical case

A 69-year old Caucasian man developed sinusitis and earache in October 2008. A procedure was attempted to insert a grommet, however, because of the severity of inflammation, the tympanic membrane ruptured and the purulent discharge drained naturally.

During the following month he again developed earache and sinusitis in conjunction with a severe chest infection and striking weight loss and was admitted to hospital. On admission he looked cachectic and he had multiple cranial nerve palsies affecting cranial nerves VI to XII. He had lost his cough reflex and had a left facial palsy. Blood tests were positive for anti-neutrophil cytoplasmic antibody (c-ANCA) and anti-proteinase 3 (PR3) antibodies. A diagnosis of Wegener’s granulomatosis was made.

He was started on oral cyclophosphamide 50 mg daily and a marked, albeit short-lived, improvement was seen. He was readmitted less than a month later with the same symptoms and worsening weight loss and he was transferred to our unit.

At St. Thomas’, a magnetic resonance imaging (MRI) scan showed diffuse, non-specific soft tissue abnormality at the base of the skull and sub-cranial region (Fig. 1a,b). Despite corticosteroid therapy he failed to improve and he was started on intravenous cyclophosphamide with some improvement after the first 500 mg infusion. However, he developed an aspiration pneumonia due to the absent cough reflex. He was given antibiotic therapy with some improvement although with a persisting high C-reactive protein (CRP) titre. He was given a second infusion of intravenous cyclophosphamide.

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Initially, he appeared to be doing well after the second infusion. Three days afterwards he became drowsy and very unwell requiring admission to intensive care where he received intravenous antibiotics for a severe chest infection. Computed tomography (CT) chest showed left lower lobe consolidation and small areas of ground glass opacity in both lung fields. The patient showed signs of improvement 2 days after commencing antibiotics. However, he suffered a sudden pulseless electrical activity (PEA) cardiac arrest and could not be resuscitated.

Postmortem examination found infarction in the upper lobe of the left lung with active capillaritis and haemorrhage into the trachea. There was acute tubular necrosis and mild interstitial nephritis, but no active glomerular capillaritis in the kidneys. In the skull, there was necrosis with giant cells in the dura affecting the adjacent cranial nerves (Fig. 2). There was sterile osteomyelitis of the sphenoid bone with medullary necrosis (Fig. 3). The histological findings confirmed a diagnosis of Wegener’s granulomatosis, with pulmonary capillaritis and necrogranulomatous dural involvement of the skull base resulting in multiple cranial neuropathies.

**Discussion**

This case report illustrates how Wegener’s granulomatosis can evolve. The patient’s symptoms began as recurrent earache and sinusitis that later developed into recurrent chest infections,
which in retrospect may have been episodes of pulmonary capillaritis without haemoptysis, and continued severe weight loss with increased acute phase markers and positive c-ANCA antibodies. What is unusual is the involvement of multiple cranial nerves. A study from the Mayo Clinic found that just over 30% of 324 patients had neurological involvement\cite{1}. The cranial nerves most commonly affected were II, VI and VII and only 8 patients had involvement of multiple cranial nerves.

Wegener’s granulomatosis is a systemic vasculitis that characteristically causes necrotizing granulomas of the upper and lower respiratory tract and necrotizing crescentic glomerulonephritis. The disease is strongly associated with c-ANCA antibodies with specificity for PR3, a neutrophil alpha-granule serine protease.

There is some debate as to when the condition was first described. Although Heinz Klinger, a medical student, is credited with the first description of the disorder in 1932, he attributed the findings to a form of periarteritis nodosa\cite{2}. A Scottish surgeon, McBride, is sometimes credited with a description of this disease\cite{3}. However, Friedmann postulated that McBride was in fact describing a different disease known as Stewart’s type idiopathic pleomorphic midfacial granuloma\cite{3}. On closer inspection of this article, this would seem to be the case.

The condition was not formally described until 1936 when a landmark presentation was published in the Proceedings of the German Pathological Society by Dr Friedrich Wegener describing 3 patients with a systemic illness affecting the upper and lower respiratory tract and renal system\cite{4}. These 3 patients all had a disease with very similar features:

1. Preceding septic course
2. Severe necrotizing granulomatous inflammation of the nasal space

**Fig. 2.** Cranial nerve longitudinal section (lower part of picture) adherent to necrotizing inflammation of the dura (arrows); H&E.

**Fig. 3.** Sterile necrotizing osteomyelitis of the sphenoid bone; H&E.
3. Microscopic renal changes, specifically, toxic focal glomerulonephritis
4. Generalized arteritis similar to polyarteritis nodosa.

It was from this paper that the disease became known as Wegener’s granulomatosis, a term used by a Swedish pathologist, Sven Johnson, who distinguished it from periarteritis nodosa. The nomenclature of the disease has come under scrutiny recently. The use of eponyms has always divided opinion and Wegener’s granulomatosis featured heavily in an article advocating that the use of eponyms should be abandoned. This article suggested a link between Friedrich Wegener and the Nazi Party and that he was wanted as a war criminal after World War II. Many of these claims are unsubstantiated but despite this various patient groups have called for the disease to be renamed.

The pathogenesis of Wegener’s granulomatosis is not fully understood. It has been suggested that there is an association between infection by fimbriated bacteria (which includes several types of gram-negative bacteria) that can initiate the auto-immune process. Recent data points towards the involvement of lysosomal associated membrane protein 2 (LAMP-2). LAMP-2 appears to be involved with the activity and maturation of phagosomes. LAMP-2 is an ANCA target and antibodies to LAMP-2 have been found in patients with ANCA-associated vasculitis. These antibodies could be pathogenic and activate neutrophils and cause microvascular endothelial cell injury in vitro. There is recent evidence that interaction between LAMP-2 and fimbriated bacteria produces a human-like ANCA-associated vasculitis in animals through molecular mimicry. This mechanism could provide a novel therapeutic target but this data needs to be confirmed.

**Treatment**

In 1936 when Wegener described this condition there was no treatment and the outcome was universally fatal in generalized disease, especially if there was renal involvement. Even by 1956, a landmark paper by Walton reported that the median time to death was still only 5 months. However, the advent of modern immunosuppression has revolutionized the prognosis for patients with 5- and even 10-year survival over 80% being commonly reported.

Treatment of Wegener’s granulomatosis, and indeed other ANCA-associated vasculitides can be broken down into 4 stages: (1) diagnosis; (2) remission induction; (3) remission maintenance; and (4) long-term follow-up with early recognition and treatment of relapses. Early diagnosis is essential to optimize patient survival and prevent further renal disease. Current treatment uses intravenous or oral cyclophosphamide and glucocorticoids. Cyclophosphamide may be given in 5–6 pulsed intravenous doses over a period of 6 months as this reduces the negative side effects such as neutropenic sepsis and also reduces the overall exposure to the drug by approximately 50%.

The use of other immunosuppressants after 3–6 months of cyclophosphamide treatment has been shown to be beneficial in remission maintenance of the disease. Jayne et al. and Pagnoux et al. found that azathioprine or methotrexate were both effective in remission maintenance. Their use can also reduce the need for long-term glucocorticoid therapy.

Developments in the treatment of Wegener’s granulomatosis include promising data from randomized controlled trials of rituximab versus cyclophosphamide in the induction of remission; this data is still in abstract form. Although anti-tumour necrosis factor agents showed initial promise, a randomized trial of etanercept failed to show additional benefit over standard of care as it was associated with a significant risk of solid malignancies. Randomized controlled trial evidence exists for intravenous immunoglobulin but clinical improvement is not sustained. Stem cell transplantation to support immune reconstitution has also been investigated but there is not enough evidence at present to support its routine use.

**Teaching point**

Cranial nerve involvement is unusual in Wegener’s granulomatosis but may lead to significant morbidity. In this patient, the loss of the cough reflex increased the risk of aspiration pneumonia.
References