Wegener's granulomatosis in primary care

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Wegener's granulomatosis is a potentially devastating disorder that warrants prompt recognition, referral and initiation of treatment to improve patient prognosis.

Introduction

Wegener's granulomatosis is an uncommon yet potentially devastating multisystem vasculitis. Early recognition of active disease is challenging in the primary care setting due to the initial presentation of non-specific symptoms, ultimately resulting in a delayed diagnosis. We report the initial presentation of a cough leading to the eventual diagnosis of Wegener's granulomatosis.

Case history

A 49-year-old Caucasian male warehouse worker presented to his general practitioner (GP) with a 4-week history of a productive cough that was worse at night and hacking in nature. He denied any fever or night sweats. Past medical history is relevant for focal segmental glomerulosclerosis (FSGS), confirmed by renal biopsy in 2004, and a 16-pack year history of smoking. Respiratory examination was unremarkable. Initial impression was of an upper respiratory tract infection and amoxicillin was prescribed. The patient was asked to return if the cough did not abate. One week later, the patient returned, describing the cough as 'mainly dry'. The patient was feeling increasingly fatigued and unwell, denying any shortness of breath on exertion. Respiratory examination was again unremarkable. Pulse oximetry undertaken in the practice revealed an oxygen saturation level of 94% on room air: the GP prescribed erythromycin for atypical cover. An urgent chest X-ray ordered by the GP revealed multiple ill-defined opacities throughout both lung fields, the largest of which was apparent within the left mid-zone. In addition, there was bilateral blunting of the costophrenic angles: features suspicious of multiple pulmonary metastases (Figure 1). The reporting radiologist fast-tracked the patient to the respiratory physicians for further assessment.

The respiratory physicians subsequently ordered a computed tomography (CT) scan and serum immunological testing. CT confirmed multiple pulmonary nodules in the peripheral and basal lung zones, demonstrating signs of early cavitation, most suggestive of squamous cell carcinoma with no definite primary lesion identified. Immunological testing highlighted an erythrocyte sedimentation rate (ESR) of 86 mm/hr, positive perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA) and a significantly elevated myeloperoxidase (MPO) titre of 209 units. Neither pulmonary nodule biopsy via bronchoscopy nor CT-guided biopsies were possible, resulting in a left-sided video-assisted thoracoscopy which progressed to a minithoracotamy. Lung biopsy revealed no evidence of malignant cells. However, fibrotic interstitial lung disease changes with elements of necrosis and granulomata were identified, indicative of Wegener's granulomatosis. The patient was referred to the nephrologists, to whom the patient was already well-known given his past history of FSGS and subsequently referred to a physician with a special interest in Wegener's granulomatosis. In light of the patient's stable renal function, a renal biopsy was not performed at this time. The patient has since started immunosuppressive therapy and is progressing well. He is aware that further CT investigation will be necessary over the coming months to monitor disease progression.

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Reviewer

Frank Cross

Discussion

Wegener's granulomatosis, an aggressive vasculitic disorder with an initial presentation of non-specific symptoms, can be difficult to recognize in primary care. The mean delay between the onset of symptoms and the eventual diagnosis ranges from 2–20 months.[1] Wegener's granulomatosis is more prevalent in men; more than 90% of cases primarily affects Caucasian men in their fifth decade[2] at a median age of 59 years.[3] Although reported in middle age, cases have been reported in the literature of both much younger (13 years)[4] and older patients (71 years)[2] at initial presentation.

The pattern of symptom progression can range from gradual to rapid life-threatening multisystem organ failure. Although any organ system may be affected, Wegener's granulomatosis has a predilection for the upper airways disease (87%)[3] and symptoms may include rhinorrhoea, sinusitis and epistaxis,[5] in addition to pulmonary symptoms such as cough, pleuritis and haemoptysis.[2] The pulmonary and renal systems may be affected to a lesser extent, 69% and 48% at presentation, respectively.[3] Complaints of fatigue, lethargy and weight loss indicate further systemic involvement. Morphological evidence of renal involvement at initial presentation, such as rapidly progressing glomerulonephritis, can be found in up to 80% of patients and is associated with a more severe prognosis.[6] Established disease may also present with a classic 'saddle nose deformity' which may be particularly distressing given the aesthetic implications. Other important causes of this deformity include septal haematoma, congenital syphilis and relapsing polychondritis.[5]

Vasculitic disorders are strongly associated with antineutrophil cytoplasmic autoantibodies (ANCA) and depending upon their staining pattern can be grouped as cytoplasmic (c-ANCA) or perinuclear (p-ANCA). Proteinase 3 (PR3) and myeloperoxidase (MPO) have been identified as the main antigens for c-ANCA and p-ANCA, resulting in the production of anti-PR3 and anti-MPO, respectively.[7] Although Wegener's granulomatosis is classically associated with c-ANCA in approximately 85% of patients, it can present with a positive p-ANCA and elevated MPO level in approximately 10% of patients, such as in the case of our patient. ANCA titres are reflective of the extent and severity of disease and become clinically useful in distinguishing between acute exacerbations of Wegener's granulomatosis and acute infections, with the former heralding an increase in ANCA titres.[8] Biopsy reveals characteristic histopathological changes consistent with Wegener's granulomatosis: necrotizing granulomatous vasculitis with neutrophilic infiltrates (Figure 2).[3]

Immunosuppression is the hallmark of treatment in active disease: Wegener's granulomatosis can be fatal without prompt and appropriate intervention.[1] With the correct therapeutic dosing, response to treatment is almost immediate and is aimed at inducing remission; tapering of cyclophosphamide and prednisolone therapy at a later stage, however, may precede a relapse.[2] Side-effects of immunosuppressive therapy are dose-dependent and may include haemorrhagic cystitis, myelodysplastic syndrome and severe infections.[2] Pulsed or intermittent intravenous therapy can be utilized to limit the extent of adverse effects, which although known to be as effective as oral therapy,[9] is associated with an increased incidence of relapse.[2]

Figure 1

Chest radiograph report. The heart is not enlarged. There are multiple ill-defined opacities throughout both lungs. The largest is noted within the left mid-zone. There is blunting of both costophrenic angles. Comment: The features are suspicious of multiple pulmonary metastases

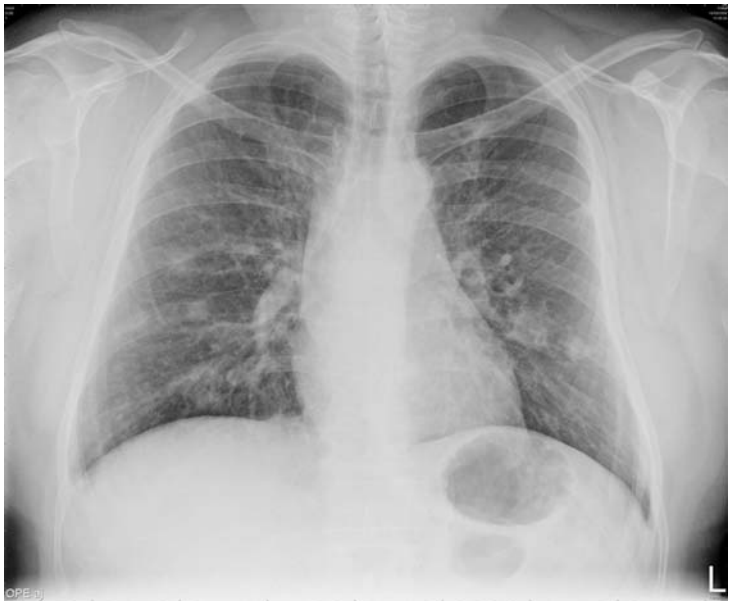
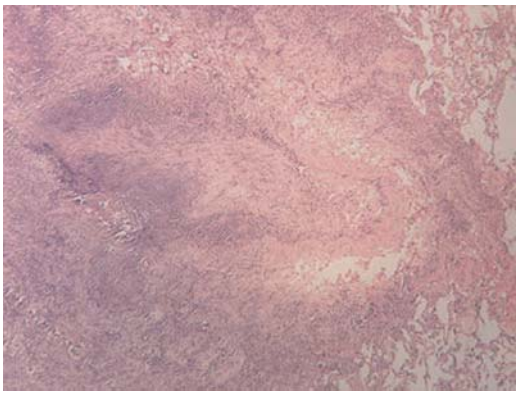


Figure 2
Histology of lung tissue on eosin and hematoxylin staining showing necrotizing vasculitis in low power field[3]



The use of co-trimoxazole as antibiotic prophylaxis has been shown to prevent the rate of relapse through a decreased incidence of respiratory and non-respiratory opportunistic infections.[10] A low threshold for the treatment of community-acquired infections should be adopted. Particular care should be taken when prescribing antimicrobials and non-steroidal anti-inflammatory drugs, in addition to other nephrotoxic medications, particularly in the presence of pre-existing renal impairment. Given that deterioration of renal function is the main determinant of survival,[2] we recommend that a timetable be negotiated with the patient in order to monitor this periodically in the community. Reported mortality of Wegener's granulomatosis remains considerably high at 14.6%;[3] however, with strict adherence to treatment regimes and regular monitoring of disease progression, five-year survival rate is reported to be 76%.[1]

Conclusion

The current guidelines for the management of vasculitis aim to increase awareness among primary care physicians and encourage referral to a consultant with a special interest in vasculitis.[11] In addition, close contact between both parties is recommended for detailed advice and continuity of patient care. The prolonged duration of non-specific symptoms and associated disease advancement results in a graver morbidity, mortality and prognosis. Therefore, the need for an increased awareness among primary care physicians is strongly advocated. Primary care physicians should be aware of presentation, treatment protocols and provide a supportive role in helping patients cope with the psychosocial ramifications of systemic immunosuppressive therapy and their subsequent adverse effects.

References

1 Ponniah I, Shaheen A, Shankar KA, Kumaran MG. Wegener's granulomatosis: The current understanding. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;**100**:265–9

2 Watts RA, Al-Taiar A, Scott DGI, Macgregor AJ. Prevalence and incidence of Wegener's granulomatosis in the UK General Practice Research Database. *Arthritis Rheum* 2009;**61**:1412–16

3 Danda D, Mathew AJ, Mathew J. Wegener's granulomatosis – a rare presentation. *Clin Rheumatol* 2008;**27**:273–5

4 Halstead LA, Karmondy CS, Wolff SM. Presentation of Wegener's granulomatosis in young patients. *Otolaryngol Head Neck Surg* 1986;**94**:368–71

5 Longmore M, Wilkinson I, Turmezei T, Cheung CK. Eponymous syndromes. In: *Oxford Handbook of Clinical Medicine*. 7th edn. Oxford: Oxford University Press; 2008

6 Aasarod K, Iversen BM, Hammerstrom J, Bostad L, Vatten L, Jorstad S. Wegener's granulomatosis: clinical course in 108 patients with renal involvement. *Nephrol Dial Transplant* 2000;**15**:611–18

7 Franssen CFM, Stegemen CA, Kallenberg CGM, *et al.* Antiproteinase 3- and antimyeloperoxidase associated vasculitis. *Kidney Int* 2000;**57**:2195–206

8 West S. Wegener's granulomatosis and other ANCA-associated disease. In: *Rheumatology secrets*. 2nd ed. Philadelphia, PA: Hanley & Belfus Inc/Elselvier Health Sciences; 2002:226–7

9 Vasculitis – aims of therapy. An overview. *J Rheumatol* 2000;**39**:229–37

10 Stegman CA, Cohen Tervaert JW, De Jong PE, Kallenberg CGM. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevalence of relapses of Wegener's granulomatosis. *N Eng J Med* 1996;**335**:16–20

11 Lapraik C, Watts R, Bacon P, *et al.*; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guidelines for the management of adults with ANCA associated vasculitis. *Rheumatology (Oxford)* 2007;**46**:1–11