Wegener's granulomatosis: unusual presentations

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Wegener's granulomatosis is a necrotizing vasculitis characterized by respiratory tract involvement and focal glomerulonephritis. Rare presentations include abdominal pain as a result of gut involvement, pericarditis, cardiac arteritis and blindness. Detection of antineutrophil cytoplasmic antibodies should not be used as a substitute for a histological diagnosis.

Wegener's granulomatosis is a necrotizing granulomatous vasculitis of small to medium sized vessels, characterized by upper and lower respiratory tract involvement, necrotizing vasculitis and focal glomerulonephritis. However, virtually any organ system can be involved. A more limited form, with lesions limited to the upper and lower respiratory tract, can occur. The condition is rare with an estimated annual incidence of approximately 10 per million (Watts et al, 2000), thus atypical presentations may not be readily recognized. This article reviews the more unusual presentations of Wegener's granulomatosis.

The development of recognized classification criteria for Wegener's granulomatosis by the American College of Rheumatology (ACR) in 1990 (Leavitt et al, 1990) and the definition produced by the Chapel Hill Consensus conference (CHCC) in 1994 (Jennette et al, 1994) has resulted in clearer understanding of the essential clinical features of Wegener's granulomatosis and better differentiation from other related forms of vasculitis such as Churg–Strauss syndrome, microscopic polyangiitis and classical polyarteritis nodosa. The CHCC defined Wegener's granulomatosis as:

> **'granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium sized vessels (e.g. capillaries, venules, arterioles and arteries). Necrotizing glomerulonephritis is common' (Jennette et al, 1994).**

The ACR (1990) criteria required two out of four criteria: nasal or oral inflammation, abnormal chest radiograph, urinary sediment and granulomatous inflammation on biopsy (Leavitt et al, 1990). It should be remembered that neither were developed for the diagnosis of individual patients; patients with atypical presentations may not be readily classifiable.

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ROLE OF ANTIBODIES

The discovery of the association between antineutrophil cytoplasmic antibodies (ANCA) and systemic vasculitis in the 1980s resulted in increased recognition. Antibodies with a cytoplasmic staining pattern (cANCA) with a specificity against proteinase 3 (PR3) are predominantly found in patients with Wegener's granulomatosis. The presence of such antibodies is a strong pointer to a diagnosis of Wegener's granulomatosis, but should not be used in place of a tissue diagnosis. ANCA of other specificities are not so strongly associated with vasculitis and can occur in non-vasculitic diseases including infection and inflammatory bowel disease (Rao et al, 1995). The presence of ANCA is not required by either the ACR or the CHCC definition.

PRESENTATION

Hoffman and colleagues (1992) reviewed 158 patients seen at the National Institutes of Health (NIH) over a 24-year period. Of these, 90% presented with upper or lower airway symptoms, with nasal, sinus, tracheal or ear abnormalities being initial symptoms in 73% of patients. In patients without concomitant systemic illness, these early symptoms are often ascribed to allergy or infection. However, development of progressive disease or lack of response to symptomatic treatment leads to further assessment.

Pulmonary disease is present in 45% of patients at presentation, the most common

symptoms being cough, haemoptysis and pleurisy, with radiographical findings of pulmonary infiltrates, granulomata and nodules (*Figures 1* and *2*). Mediastinal masses and hilar lymphadenopathy are rare, but must be differentiated from infection and malignancy (George et al, 1997). Cutaneous lesions occur in 25% of patients at presentation with ulcers, palpable purpura, subcutaneous nodules, papules and vesicles reflecting typical small vessel involvement (*Figure 3*).

Renal involvement

Renal disease is only present in 18% of patients at presentation (Hoffman et al, 1992), although it is a typical feature of Wegener's granulomatosis, occurring in 77% of patients at some stage during their illness. Studies from the UK suggest a higher frequency of renal involvement at presentation (56–86%) (Carruthers et al, 1996). Patients may present with life-threatening renal failure as a result of rapidly progressive glomerulonephritis requiring urgent dialysis and immunosuppression. At the opposite end of the spectrum are patients with proteinuria and/or haematuria without evidence of renal impairment.

The presence or absence of renal disease defines the subsets of generalized or limited Wegener's granulomatosis respectively (Carrington and Liebow, 1966). Renal masses are an unusual presentation and raise the possibility of an associated renal cell carcinoma (Villa-Forte and Hoffman, 1999). Gastrointestinal, neurological and cardiac manifestations are rare at presentation (*Table 1*).

Gastrointestinal involvement

Gastrointestinal involvement is uncommon, occurring in 10–12% of patients at presentation or during the course of the illness (Haworth and Pusey, 1984). In a post-mortem study Walton (1958) observed focal necrotizing arteriolitis in 24% of cases, but no clinical data are available on this series and it is possible that some cases would now be considered to have other forms of vasculitis.

Gut involvement is much more common in other forms of vasculitis occurring, for example, in 60–80% of patients with

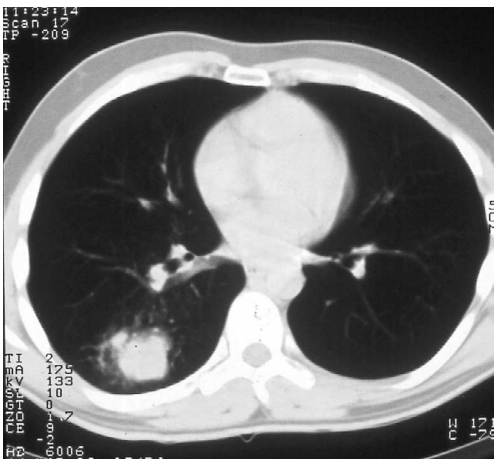

Figure 1. Computed tomography scan of thorax showing a pulmonary nodule in a patient with Wegener's granulomatosis. Biopsy showed a necrotizing vasculitis.

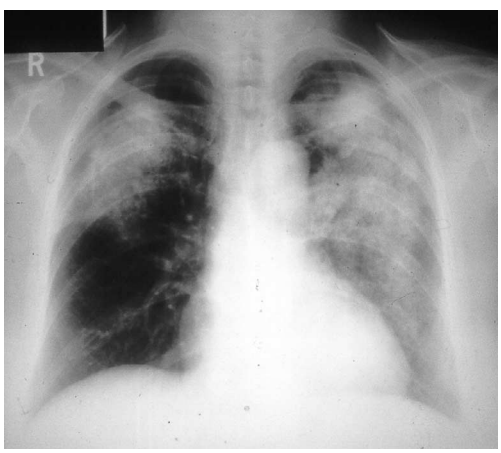

Figure 2. Chest radiograph showing pulmonary haemorrhage in a patient with Wegener's granulomatosis.

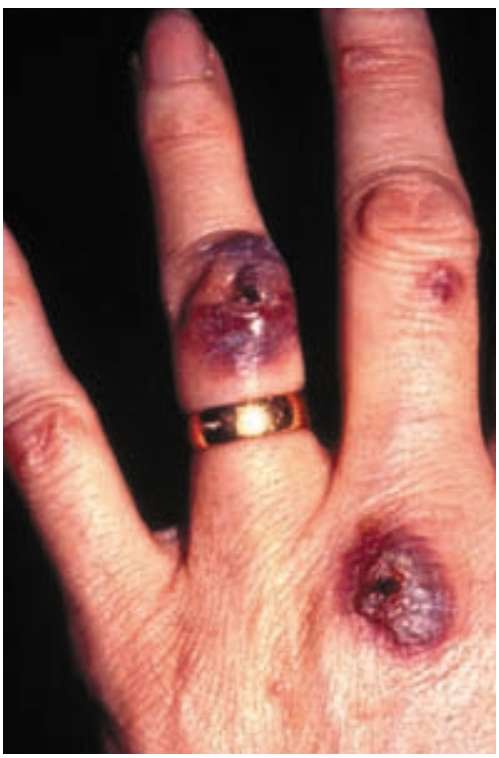

Figure 3. Rash in patient with Wegener's granulomatosis. Biopsy confirmed a necrotizing vasculitis.

Henoch–Schönlein purpura. The severity of gut involvement varies from mild ischaemia, causing intermittent postprandial abdominal pain (abdominal angina), to severe ischaemia leading to infarction, perforation and peritonitis. Development of abdominal symptoms in a patient with multisystem disease including arthralgia and rash would be suggestive of Henoch–Schönlein purpura rather than Wegener's granulomatosis. The distinction can be made on the presence of other features typical for Wegener's granulomatosis, PR3-ANCA and biopsy (immunoglobulin A deposition is typically seen in Henoch–Schönlein purpura).

Storesund et al (1998) reported two cases and reviewed the literature and noted that the majority of cases occurred in the first 2 years after diagnosis and affected both the large and small bowel. In this issue (p. 286), Skaife et al (2000) describe a previously well patient presenting with abdominal pain and distension resulting from intestinal ischaemia and perforation. During the course of his illness he developed cutaneous, neurological and renal involvement. The case highlights the difficulty of making the diagnosis of gastrointestinal vasculitis in a previously undiagnosed patient. The diagnosis is typically made at laparotomy.

Cardiac involvement

Cardiac involvement occurred in 6% of the NIH study (Hoffman et al, 1992). Wegener (1936) reported cardiovascular involvement in his original report of three patients. Cardiac involvement may include the valves, pericardium, myocardium and the conducting system. Symptoms will depend on the site of lesions.

TABLE 1.
Clinical features at presentation in two series of patients with Wegener's granulomatosis

System/symptom	Carruthers et al (1996) (%)	Hoffman et al (1992) (%)
Renal	86	77
Ear, nose and throat	71	92*
Pulmonary	67	85*
Malaise	62	–
Arthralgia	57	67
Cutaneous	43	46
Ophthalmic	33	52
Gastrointestinal	10	–
Neurological	5	15 (PNS)
		8 (CNS)

PNS = peripheral nervous system; CNS = central nervous system.
* = $P<0.01$ using Chi-squared test

Primary pericardial disease will produce pericardial and/or pleuritic pain with a friction rub; pericardial effusion of sufficient size to cause pulsus paradoxus or tamponade is rare. Coronary arteritis may cause myocardial ischaemia and infarction. Granulomata on valves may cause valvular insufficiency while those near or in the conducting system may cause conduction defects (Handa et al, 1997). Fauci et al (1983) reported cardiac involvement in 30% of post-mortem examinations. Parry et al (2000), in this issue (p. 284), describe a patient with fulminant vasculitis in whom the immediate cause of death was diffuse coronary arteritis.

Myocardial infarction is rare in patients with Wegener's granulomatosis. The authors correctly note that coronary arteritis should be considered in patients known to have vasculitis or who develop chest pain or cardiac failure. By contrast cardiac involvement is more common in Churg–Strauss syndrome, with a reported frequency of 12.5% at presentation and up to 40% at some stage of the illness, and is a significant cause of mortality (Reid et al, 1998; Guillevin et al, 1999).

Bacterial endocarditis presenting with a systemic illness has long been recognized to mimic systemic vasculitis, however, the converse does rarely occur. Anthony et al (1999) recently reported a case presenting with culture negative endocarditis with aortic valve vegetations. In patients with a systemic illness resembling bacterial endocarditis who are persistently culture negative or fail to respond appropriately to antibiotics, an alternative diagnosis such as systemic vasculitis must be considered.

Neurological involvement

Neurological involvement at presentation is rare, occurring in 5% of patients presenting to a district hospital (Carruthers et al, 1996), but occurs eventually in 15% (Hoffman et al, 1992). The most typical manifestation is mononeuritis multiplex. Peripheral neuropathy is a more typical feature of classical polyarteritis nodosa and Churg–Strauss syndrome. The diagnosis can be made either on nerve conduction studies or nerve biopsy. Central nervous system involvement is much less common in Wegener's granulomatosis, manifestations include stroke, cranial nerve palsies (Magliulo et al, 1999; Dagum et al, 1998), diabetes insipidus (Hajj-Ali et al, 1999), myelopathy and cerebritis (Nishino et al, 1993).

Ocular involvement is the presenting feature in 16% of cases (Sneller, 1995). Sight-threatening complications are rare, occurring in

those with orbital disease, central retinal vein occlusion and corneoscleral disease. Central retinal artery occlusion is a rare presenting feature and despite prompt immunosuppressive therapy visual acuity may not recover (O'Gradaigh et al, 1999).

Other rare sites of involvement include the parotid gland, breast (Jordan et al, 1987), urethra, cervix and vagina. Symptomatic urogenital disease is uncommon and manifestations include prostatitis, orchitis, ureteral stenosis, bladder pseudotumour and penile ulceration, these may occur as the sole manifestation of Wegener's granulomatosis (Huong et al, 1995). Mastoiditis is a rare presenting feature and is unresponsive to conventional therapy for mastoiditis (Moussa and Abou-Elhmd, 1998).

CONCLUSIONS

Uncommon presentations of Wegener's granulomatosis present a diagnostic challenge. ANCA is a useful adjunct to the diagnosis, but should not be used to replace a histological diagnosis, particularly in atypical cases. HM

Conflict of interest: none.

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KEY POINTS

- Wegener's granulomatosis may involve any organ system.
- Infection, in particular bacterial endocarditis, may mimic vasculitis.
- Cardiac involvement is rare at presentation.
- Gastrointestinal involvement, while uncommon, carries a significant mortality.
- Antineutrophil cytoplasmic antibodies testing should not be used as a substitute for histological diagnosis.