



Wegener's granulomatosis with multiple pulmonary nodules – diagnostic difficulties

Ricardo Jorge José¹ • John Paul Dilworth¹ • Joanne Cleverley²
• Martin Young³ • Richard Stratton⁴ • Marc Lipman¹

¹Department of Respiratory Medicine, Royal Free Hospital, London, UK

²Department of Radiology, Royal Free Hospital, London, UK

³Department of Histocytopathology, Royal Free Hospital, London, UK

⁴Department of Rheumatology, Royal Free Hospital, London, UK

Correspondence to: Ricardo Jorge Paixão José. E-mail: r.jose@ucl.ac.uk

DECLARATIONS

Competing interests

None

Funding

None

Ethical approval

Written informed consent to publication has been obtained from the patient or next of kin

Guarantor

RJ

Contributorship

RJ undertook the literature review and drafting of the manuscript; ML critically reviewed and edited the draft; JD, JC and RS reviewed and edited the final draft; all authors were involved in the diagnosis and care of the patient and have read and

We describe the case of a 65-year-old woman with multiple pulmonary nodules on a chest radiograph where subsequent investigations led to diagnostic difficulties.

Case history

The patient, a Caucasian woman, was referred for further assessment following a chest radiograph (Figure 1) suggestive of pulmonary metastases. She had a one-week history of increasing fatigue and cough productive of clear sputum. Not improving on a course of amoxicillin, she developed subjective fevers, and reduced appetite. She was an ex-smoker with a 1-pack/year history. She previously worked as a carer, had no tuberculosis contact and had a cat. Prior to this she had always been well except for episodes of nasal congestion.

On examination, she looked well. Her pulse was 70, blood pressure 120/57 mmHg, respiratory rate of 20, oxygen saturations of 94% at rest on air and temperature 38.2°C. Examination of the cardiovascular, gastrointestinal, neurological systems, skin and breasts was normal. On auscultation of the chest she had bilateral inspiratory crackles at the bases extending up to the midzones.

The chest radiograph showed multiple pulmonary nodules (Figure 1) and computed tomography (CT) scan of the thorax revealed multiple lung nodules with the presence of air bronchograms particularly in the lower zones with no cavitation or lobar collapse.

Her blood tests were: haemoglobin 9.6 g/dl (11.5–17.0), white cell count 8.13×10^9 (3.5–11.0),

platelets 433×10^9 (140–400), C-reactive protein 258 mg/L (0–5), erythrocyte sedimentation rate 126 mm/h (0–30). Renal function, immunoglobulins, liver function tests and thyroid function tests were normal. HIV, hepatitis B and C viral screens were negative. Urine dipstick was negative as well as urine and blood bacterial cultures. Autoimmune screen showed ANA positive 1:100, P-ANCA (anti-myeloperoxidase) and C-ANCA (anti-proteinase 3) negative, and atypical P-ANCA was positive.

Bronchoscopy demonstrated normal anatomy. All microbiological investigations on bronchoalveolar lavage fluid were normal, including tuberculosis nucleic acid amplification tests; though cytology showed clusters of macrophages raising the possibility of tuberculosis. CT-guided biopsy of a lung lesion revealed multiple small necrotizing granulomas highly suggestive of tuberculosis (Figure 2).

By day seven, she was clinically deteriorating and as investigations repeatedly suggested a high probability of tuberculosis, weight-dosed anti-tuberculosis quadruple therapy was started together with oral prednisolone 30 mg. She responded rapidly to this and within days was feeling better, however, developed a non-specific erythematous rash on her right ankle and biopsy revealed a leukocytoclastic vasculitis. The lung biopsy was re-assessed and the appearance was felt to be consistent with that of an active vasculitic process with granulomas, suggesting Wegener's granulomatosis. The anti-tuberculosis medication was stopped and treatment was commenced with pulsed intra-venous methylprednisolone

approved the final
manuscript

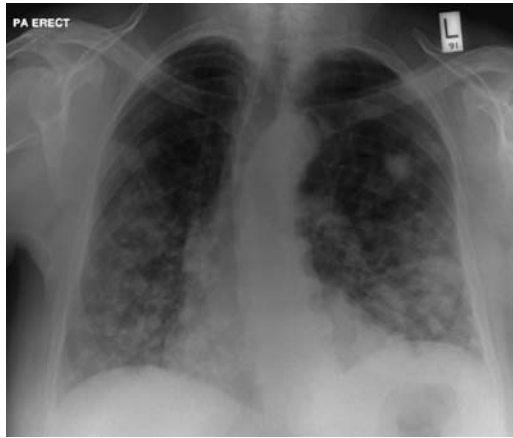
Acknowledgements

None

Reviewer

Simon Taggart

Figure 1
Chest radiograph showing multiple bilateral nodules sparing the apices

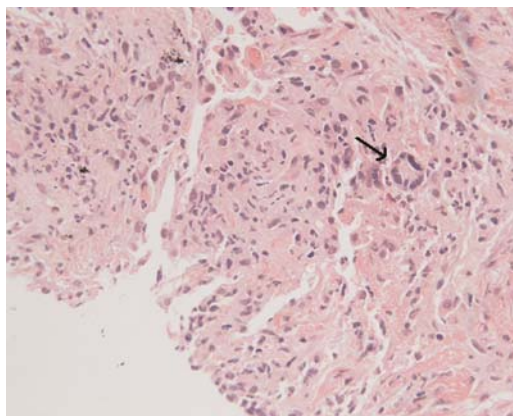


500 mg/day for three days followed by prednisolone 60 mg orally per day together with intravenous pulsed cyclophosphamide 750 mg planned to be given at monthly interval for six months. A chest X-ray performed after one month of treatment showed marked improvement in the previous nodularity.

Discussion

Wegener's granulomatosis also known as necrotizing granulomatous vasculitis is a multi-system

Figure 2
Needle core biopsy of lung (H&E): Necrotising granulomatous inflammation with multinucleate giant cells



small vessel vasculitis. Together with microscopic polyangiitis and Churg-Strauss Syndrome it forms part of a group of disorders known as anti-neutrophil cytoplasmic antibody (ANCA) associated systemic vasculitis (AASV).

In Wegener's granulomatosis the classical clinical triad is disease of upper respiratory tract (sinuses, ears, nasopharynx and oropharynx), lower respiratory tract (trachea, bronchi and lung parenchyma) and kidneys. There is involvement of either the upper or lower respiratory tract or both in 90% of cases and renal involvement in 80%.¹ Other affected systems include skin, musculoskeletal, neurological and gastrointestinal. Approximately 25% of patients will have limited Wegener's granulomatosis without renal involvement and 9% may pulmonary involvement alone.²

The presentation is usually with constitutional symptoms of fever, fatigue and weight loss accompanied by organ specific manifestations. Involvement of the upper respiratory tract includes chronic sinusitis, otitis media and hearing loss. Patients can report headaches, rhinorrhea, nasal congestion, epistaxis, crusts, and collapse of nasal bridge. Lower respiratory tract disease may present with hoarseness, dyspnoea, cough, haemoptysis, wheeze or stridor; although in a cohort of patients with Wegener's granulomatosis, 34% of patients had asymptomatic pulmonary involvement (nodules or infiltrates).² Our patient presented with fever, cough and reduced appetite and a history of episodes of nasal congestion in the preceding months. She had no impairment of renal function or signs of glomerulonephritis on urine dipstick and microscopy. She had pulmonary nodules on chest radiograph and CT. Only in her second week of hospital admission did she clinically deteriorate and develop the rash on her ankle.

ANCA are neutrophil specific antibodies that when detected raise suspicion of systemic vasculitis. These antibodies have two characteristic staining patterns on indirect immunofluorescence – termed 'C-ANCA' and 'P-ANCA'. C-ANCA has a coarse granular cytoplasmic staining pattern and is directed against proteinase 3 (PR3). P-ANCA stains the area around the nuclei (perinuclear) and is directed against myeloperoxidase (MPO). ANCA are detected at varying frequencies in Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome.³ Fluorescent patterns that are neither cytoplasmic

nor perinuclear are termed 'atypical' and are found in conditions such as rheumatoid arthritis and inflammatory bowel disease.⁴ Our patient had an atypical P-ANCA which was anti-PR3 and anti-MPO negative. Although not the usual pattern in Wegener's granulomatosis, it is reported in approximately 10% of cases.

Patients with pulmonary Wegener's granulomatosis commonly have discrete focal radiographic lung opacities varying from diffuse consolidation to nodular masses usually of 2–4 cm in diameter, though occasionally they may be as large as 10 cm. The nodules are often bilateral and generally tend to spare the apices.⁵ These radiographic abnormalities can be mistaken for metastases, as occurred in this case, or lung abscess and septic infarcts.

A biopsy is usually needed to confirm clinical suspicion. Tissue can be obtained from affected organs such as the skin (rash), kidneys (presence of glomerulonephritis) or lung (presence of nodules or consolidation). Skin biopsy is usually the most accessible and least invasive procedure; though the skin pathology (leukocytoclastic vasculitis) of Wegener's granulomatosis can also be found in other diseases, e.g. amyloidosis, behcet's, antiphospholipid syndrome, immune thrombocytopenic purpura, meningococcaemia and cryoglobulinaemia.

Our case highlights the importance of the pathologist being aware of the clinical suspicion of small vessel vasculitis and Wegener's granulomatosis when they review pulmonary tissue samples. The differential diagnosis of necrotizing granulomas includes chronic infections due to mycobacteria, fungi, as well as foreign body type granulomatous inflammation and Wegener's granulomatosis.

The mainstay of current treatment of AASV is immunosuppression with glucocorticoids and cytotoxic agents such as methotrexate, azathioprine and cyclophosphamide.⁶ Our patient responded well to steroids and pulsed cyclophosphamide with resolution of symptoms and chest radiograph changes.

Conclusion

Wegener's granulomatosis is a rare disorder, though is one of the more frequently-seen small vessel vasculitides. Patients do not always have a typical 'triad' presentation and investigations may be non-specific – including the ANCA, which can be negative. Making a prompt diagnosis is important, as, without treatment, the mortality is high. Our case highlights the importance of the pathologist being aware of the clinical suspicion of small vessel vasculitis and Wegener's granulomatosis when they review pulmonary tissue samples and a multidisciplinary approach is useful for the correct and rapid diagnosis.

References

- 1 Jennette JC, Falk RJ. Small-vessel vasculitis. *N Engl J Med* 1997;**337**:1512–23
- 2 Hoffman GS, Kerr GS, Leavitt RY, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;**116**:488–98
- 3 Wiik A. Clinical and pathophysiological significance of anti-neutrophil cytoplasmic autoantibodies in vasculitis syndromes. *Mod Rheumatol* 2009;**19**:590–9
- 4 Peter HH, Metzger D, Rump A, Rother E. ANCA in diseases other than systemic vasculitis. *Clin Exp Immunol* 1993;**93**:12–14
- 5 Allen SD, Harvey CJ. Imaging of Wegener's granulomatosis. *Br J Radiol* 2007;**80**:757–65
- 6 Jayne D. Treatment of ANCA-associated systemic small-vessel vasculitis. *APMIS Suppl* 2009:3–9

© 2010 Royal Society of Medicine Press

This is an open-access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by-nc/2.0/>), which permits non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited.