Case Report

Wegener's Granulomatosis: Are We Still Missing It?

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Abstract

We report the case of an 18-year-old female who was mis-diagnosed as a smear-negative pulmonary tuberculosis and advised standard antituberculosis treatment. She later presented with clinio-radiological worsening and thrombosis of superficial veins of the lower extremity. Cytoplasmic anti-neutrophil cytoplasmic antibody and computed tomography-guided lung biopsy confirmed the diagnosis of Wegener's granulomatosis. The rare association of superficial vein thrombosis with lung manifestation is highlighted here as also the need for a high index of clinical suspicion to avoid a missed or delayed diagnosis. **[Indian J Chest Dis Allied Sci 2015;57:129-131]**

Key words: C-ANCA, TB, ATT, ANCA.

Introduction

Granulomatosis with polyangitis (GPA), earlier known as Wegener's granulomatosis, is a rare, auto-immune vasculitis that affects the nose, lungs, kidneys and other organs.[1] It is characterised by an auto-immune attack by anti-neutrophil cytoplasmic antibody (ANCA) against small- and medium-sized blood vessels. The clinical presentation may be so diverse that the differential diagnosis is vast, ranging from infectious diseases, like tuberculosis to vasculitic diseases as well as malignancies. In 1954, Godman and Churg described the following criteria for this condition: (i) necrotising granulomatous inflammation of the upper and/or lower respiratory tracts; (ii) generalised focal necrotising vasculitis involving both arteries and veins; and (iii) focal necrotising glomerulonephritis. These three criteria became known as the 'Wegener's triad'.[2]

Some physicians insist on the need for all three criteria to be present to diagnose Wegener's granulomatosis. However, it has been recognised that some patients present with typical symptoms and histologic findings in the upper or lower respiratory tracts yet failed to have systemic vasculitis or glomerulonephritis.[3] These individuals respond to the same treatment as for the fully expressed Wegener's granulomatosis and occasionally these evolved into the complete syndrome. This experience resulted in the formulation of the ELK classification system wherein E stands for the ears, nose and throat or upper respiratory tract, L for the lung and K for the kidney. This concept suggested that within the spectrum of Wegener's granulomatosis are patients who may have involvement at any of the ELK sites, singularly or in combination. The so-called limited Wegener's granulomatosis denotes the absence of kidney disease and has a more favourable prognosis.[4] Under the ELK system, any typical manifestation in E, L or K suggested by typical histopathology or a positive cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA) test qualifies for the diagnosis of Wegener's granulomatosis.

Any organ system may be affected and the clinical course is very variable. The C-ANCA is a serological marker for Wegener's granulomatosis and its titres mirror the disease activity. Early detection of ANCA is important because current treatment protocols may achieve remission in a large number of patients; however it is difficult to establish a diagnosis of Wegener's granulomatosis, especially in the early stages or in the limited forms where kidney involvement is not seen.[5]

Here we report a case of Wegener's granulomatosis presenting with thrombosis of superficial veins of lower extremity, an uncommon manifestation.

Case Report

An 18-year-old student presented with fever, cough of 10 days duration and streaky haemoptysis of one day duration. Fever was low-grade, intermittent and associated with weight loss. There was no other significant medical history. On general physical examination, she was febrile, had pallor, a respiratory rate of 28/min. Examination of the respiratory system revealed reduced breath sounds on the right side. Examination of other systems was within normal limits. Laboratory investigations revealed haemoglobin 7.8 g/dL; total leucocyte count 12,900/mm^3 with a differential leucocycte count of polymorphs 78%,

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lymphocytes 10%, eosinophils 10%, and monocytes 2%; erythrocyte sedimentation rate (ESR) was 91mm at the end of the 1st hour. Serum biochemistry was within normal limits. Serological testing for human immunodeficiency virus (HIV) was non-reactive, Mantoux test (5 tuberculin units) was not reactive. Sputum smear was twice negative for acid-fast bacilli (AFB).

Chest radiograph (postero-anterior view) showing a homogeneous opacity in the right upper zone (Figure 1). A high resolution computed tomography (HRCT) of thorax showed consolidation in the right upper lobe with cavitation in the right upper and lower lobes (Figure 2).

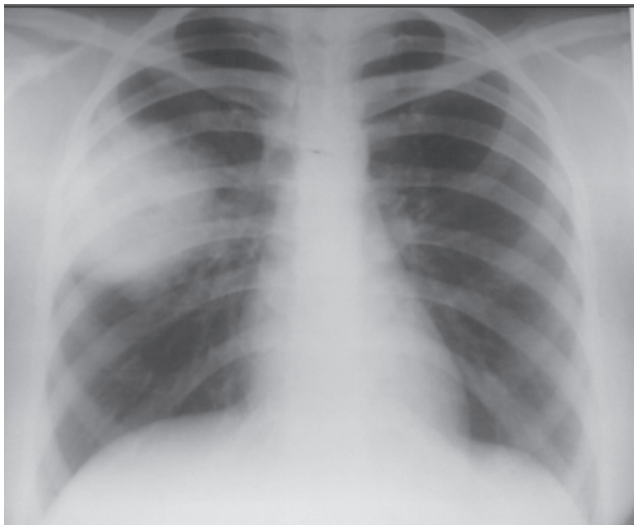

Figure 1. Chest radiograph (postero-anterior view) showing a non-homogeneous opacity in the right upper zone.

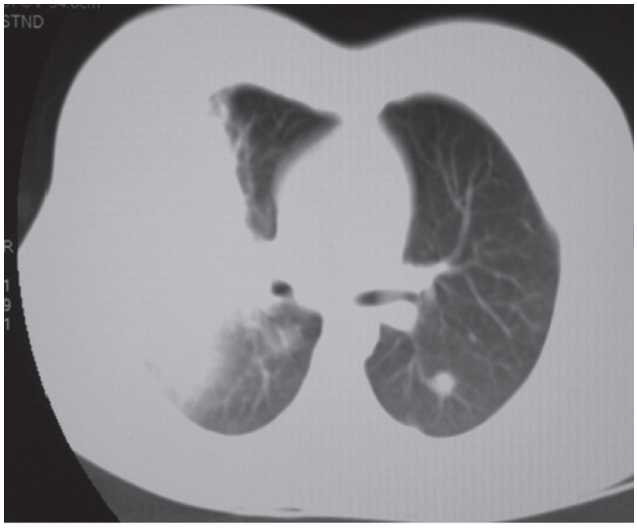

Figure 2. HRCT thorax showing consolidation in the right upper lobe with cavitation and multiple centrilobular nodules in the right upper and left lower lobes.

Based on symptoms and imaging features, a diagnosis of pulmonary tuberculosis was made and she was empirically started on intermittent, thrice weekly category I DOTS regimen after one week and gradually improved with complete remission of fever and haemoptysis. She was discharged on antituberculosis treatment (ATT) and asked to follow-up in the out-patient service.

She, however, reported back after 12 days with recurrence of fever, cough, haemoptysis and right lower limb swelling. Repeat chest radiograph showed further increase in the lesions.

Repeat laboratory testing revealed: haemoglobin 7.7 g/dL; total leucocyte count 11,400/mm^3; ESR was 91mm at the end of the 1st hour. Serum biochemistry and ultrasonography of abdomen were within normal limits. Sputum fungal culture was negative. Urine examination showed microscopic haematuria. Venous doppler revealed thrombosis of right superficial femoral, popliteal and calf veins. Echocardiography was normal. Computed tomography (CT) guided lung biopsy revealed necrotic and inflammatory changes with scattered multi-nucleated giant cells. Few atypical granulomas were seen with evidence of vasculitis and necrosis (Figure 3).

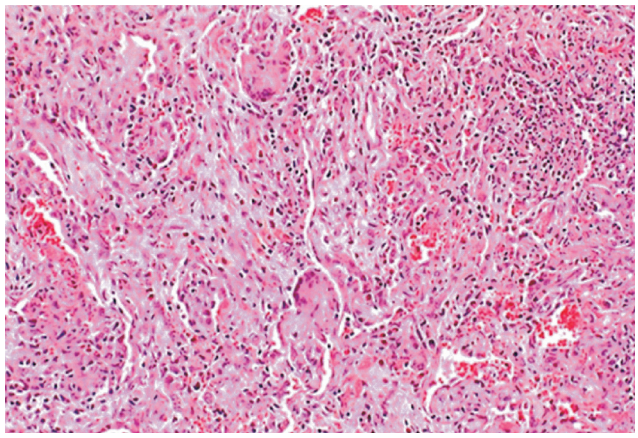

Figure 3. Photomicrograph showing necrotic and inflammatory changes with scattered multi-nucleated giant cells; a few atypical granulomas are also seen with evidence of vasculitis and necrosis (Haematoxylin and Eosin stain × 100).

The C-ANCA tested positive. A diagnosis of Wegener's granulomatosis was made and she was advised oral prednisolone (1 mg/Kg). Oral cyclophosphamide (2 mg/Kg) was added later. The patient was also administered low-molecular weight heparin (enoxaprin) and later switched to warfarin (2 mg) on day 3. Warfarin was increased to 5 mg. She improved clinically and ATT was stopped. Chest radiograph obtained after addition of immunosuppressive treatment two weeks later showed resolution of lesions.

Discussion

Wegener's granulomatosis is a rare, multi-system, autoimmune disease characterised by necrotising granulomatous vasculitic inflammation of the upper

and lower respiratory tracts and the kidneys. Globally, the incidence is estimated to be 10.2 cases per million population.[6] In addition to the classically described involvement of upper respiratory tract, lungs and kidneys, the disease also affects the oral cavity, eyes, musculo-skeletal system, the central nervous system (CNS), and gastrointestinal tract (GIT). Lung involvement is in the form of pulmonary nodules, cavitation mimicking TB, as was seen in our case, pulmonary haemorrhage causing haemoptysis and rarely broncho-ststenosis.

Although it is well known that ANCA-associated vasculitis can affect large vessels of both arterial and venous type, studies dealing with morphological analysis of medium and large vessels involvement in Wegener's have mainly focused on the arterial side. Whereas venulitis is a well known phenomenon of active ANCA-associated vasculities, phlebitis of medium and large size veins has not been convincingly demonstrated.[7] Even in two of the large Indian series[8,9] on Wegener's granulomatosis, thrombosis of superficial veins of lower extremities has not been reported. This may be the first documented case on Wegner's granulomatosis presenting with superficial venous thrombosis documented from India.

The ANCA are considered to be diagnostic for 'pauci-immune' small vessel vasculitis associated disorders like Wegener's granulomatosis, microscopic polyangitis (MPA) and Churg-Strauss syndrome (CSS). There are two main ANCA target antigens in these disorders, namely, myeloperoxidase (MPO) and proteinase 3 (PR3), which have diagnostic utility, though other cytoplasmic antigens like lactoferrin (LF), cathepsin G (CG), elastase and A_3 urocidin are being investigated as possible targets for antibody mediated tissue destruction leading to vasculitis.[10]

In tropical countries, TB, leprosy and occasionally, malaria can produce clinical features similar to a vasculitic illness and all the three infections are known to be associated with autoantibodies.[11] Hence, TB must be actively sought and excluded in ANCA positive patients and treatment decisions should be focused on the clinical presentation of the patient (pre-test probability) and histological findings and not on the result on ANCA testing alone.[12]

In conclusion, we wish to emphasise that a high index of suspicion is required to make a diagnosis of Wegener's, especially in TB endemic areas, several clinical, radiological features and laboratory criteria overlap during some stage of the disease course. Alternate diagnosis should be sought in patients not responding to or deteriorating on ATT as early diagnosis and management has significant positive impact on outcome and prognosis in Wegener's granulomatosis.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, FerrRIO f, *et al*. 2012 REVISED International Chapel Hill Consensus conference nomenclature of vasculitis. *Arthritis Rheum* 2013;65:1–11.
2. Godman GC, Churg J. Wegener's granulomatosis: pathology and review of the literature. *Arch Pathol Lab Med* 1954;58:533–53.
3. Richard A, De Remee. Pulmonary vasclitis. *In: Fishman's Pulmonary Diseases and Disorders*; 3rd edition, 1357–133.
4. Carrington CB, Leibow AA. Limited forms of angitis and granulomatosis of Wegener's type. *Am J Med* 1966;41:497–527.
5. Pradhan VD, Badakere SS, Ghosh K, Almeida A. ANCA: serology in Wegener's granulomatosis. *Indian J Med Sci* 2005;59:292–300.
6. Alam ABMS, Dastider R, Ahmed Z, Rabbani R. Wegener's granulomatosis mimicking pulmonary tuberculosis. *J Bangladesh Coll Physicians Surg* 2012;30:98–104.
7. Lamprecht P, Holl-ulrich K, Wieczorek S. Venous thromboembolism in Wegener's granulomatosis. *J Rheumatol* 2007;34:2323–5.
8. Kumar A, Padhi A, Menon A, Sharma SK, Pande JN, Malaviya AN. Wegener's granulomatosis in India: clinical features, treatment and outcome of twenty-five patients. *Indian J Chest Dis Allied Sci* 2001;43:197–204.
9. Bambery P, Sakhuja V, Bhusnurmath SR, Jindal SK, Deodhar SD, Chugh KS. Wegener's granulomatosis: clinical experience with eighteen patients. *J Assoc Physicians India* 1992;40:597–600.
10. Pradhan VD, Badakere SS, Ghosh K, Pawar AR. Spectrum of anti-neutrophil cytoplasmic antibodies in patients with pulmonary tuberculosis overlaps with that of Wegener's granulomatosis. *Indian J Med Sci* 2004;58:283–8.
11. Ghosh K, Pradhan V, Ghosh K. Background noice of infection for using ANCA as a diagnostic tool for vasculitis in tropical and developing countries. *Parasitol Res* 2008; 102:1093–5.
12. Sherkat R, Mostafavizadeh K, Zeydabadi L, Shoaei P. Rostami S. Antineurtrophil cyctoplasmic antibodies in patients with pulmonary tuberculoiss. *Iran J Immunol* 2011;8:52–7.