Reminder of important clinical lesson

Wegener's granulomatosis – another challenging case

Henricus van den Heuvel

BFG HS, Gutersloh, Germany

Correspondence to Dr Henricus van den Heuvel, rickvandenheuvel@doctors.org.uk**Summary**

A 54-year-old lady initially presented with mild dyspnoea, left-sided flank pain and bilateral leg swelling. She was diagnosed as having single vessel coronary heart disease. Subsequently, this lady developed malaise, joint aches, an aspecific skin rash and limbal conjunctivitis. She was thought to have Löfgren's syndrome. The patient then developed sore throats and petechiae, later severe dyspnoea with sanguineous expectoration and light nasal bleeds. Cytoplasm-antineutrophil cytoplasmic autoantibodies and proteinase 3-ANCA were determined, found positive and she was diagnosed as having Wegener's granulomatosis. This was at 3 months after her initial presentation. She was treated with pulsed intravenous Cyclophosphamide and oral prednisolone. The patient improved quickly and the medication was changed to oral methotrexate and prednisolone. Currently, the patient is doing well and is in remission.

BACKGROUND

Wegener's granulomatosis is one of the pauci-immune small vessel vasculitides which classically presents with upper and lower respiratory tract granulomas and necrotising focal segmental glomerulonephritis.¹ Several case reports have been written about atypical presentations and related difficulties of diagnosing the disease at an early stage.^{1–3} Due to the high variety of presenting symptoms, these cases remain highly educational. This case has been particularly interesting due to the aspecific symptoms, the range of specialists involved and the genuine diagnosis of single vessel coronary heart disease and Wegener's granulomatosis. Also, it shows the importance of the involvement of a generalist to coordinate care and the relevance of cytoplasm-antineutrophil cytoplasmic autoantibodies (C-ANCA) and proteinase 3-ANCA (pr3-ANCA) to aid early diagnosis.

CASE PRESENTATION

This case presentation is about a non-smoking and non-drinking 54-year-old lady, with a medical history of goitre (no malignancy, no toxicity) and a family history of cardiovascular disease and deep venous thrombosis (DVT).

This lady was sent to hospital early August 2010 with a 6-week history of mild dyspnoea on exertion, left sided flank pain and bilateral leg swelling. On admission, the patient indicated that she had noticed an insect bite in the left foot about 4 weeks ago, yet did not know what kind of insect this had been. As the left leg was more swollen than the right, she was admitted to exclude a DVT. On clinical examination, no significant abnormalities were found apart from bilaterally swollen lower legs, left more than the right. Most routine blood tests were normal apart from raised D-dimers 1.76 µg/ml (normal <0.5 µg/ml), a raised C reactive protein (CRP) 22.9 mg/l (< 5 mg/l) and a borderline haemoglobin (Hb) 11.6 g/dl (12.0–16.0 g/dl). A chest x-ray showed a borderline large heart with otherwise normal cardiopulmonary findings. ECG was normal, yet echocardiography showed a slightly limited ventricular function (ejection fraction 50%), and hypokinesia in the

anterior and posterior basal regions. Therefore a coronary angiogram was performed which indicated a 75–80% stenosis of the circumflex branch in the region of the ostium. A Doppler ultrasound of the left leg veins was done and a DVT excluded. The patient was diagnosed as having single vessel coronary heart disease and she was started on bisoprolol, ramipril, aspirin and simvastatin.

At the end of August 2010, the patient had irritation of both eyes. She was seen by the ophthalmologist, diagnosed as having bilateral limbal conjunctivitis and treated with maxitrol (neomycin, polymyxin, dexamethasone) eye drops.

In September 2010, the patient was seen by the general practitioner (GP) regarding increasing tiredness, neck, shoulder and generalised joint aches and skin rash. On clinical examination, no major structural abnormalities were detected apart from an aspecific erythematous skin rash on the lower legs. Blood tests indicated erythrocyte sedimentation rate (ESR) 49 mm/h (< 20 mm/h), CRP 19.9 mg/l, rheumatoid factor (RF) 26 IE/ml (<14 IE/ml) with normal anti-cyclic citrullinated peptide (anti-CCP), antinuclear antibody (ANA), extractable nuclear antigen (ENA) and double stranded DNA (ds-DNA). *Borrelia burgdorferi* infection was excluded. The patient was referred to the rheumatologist who diagnosed Löfgren's syndrome and advised the patient to use a non-steroidal anti inflammatory drug (NSAID), alternatively prednisolone 20 mg a day if the NSAID would not work.

Symptoms did not improve and the patient developed new symptoms, like sore throats and petechiae on the lower legs. The GP was not convinced of the Löfgren's syndrome diagnosis and therefore a review with general medicine was arranged. In the mid-October 2010, the patient also developed severe dyspnoea with sanguineous expectoration, light nasal bleeds and was readmitted to the hospital. On clinical examination, no substantial abnormalities were documented. Blood tests showed ESR 80 mm/h, Hb 9.9 g/dl, leucocytes $13.0 \times 10^9/l$ ($4.6\text{--}10.2 \times 10^9/l$), thrombocytes $446 \times 10^9/l$ ($142\text{--}424 \times 10^9/l$), C-ANCA positive (1:2560), perinuclear-ANCA negative (p-ANCA), pr3-

ANCA positive (>200) MPO (myeloperoxidase)-ANCA negative. A chest x-ray showed patchy deposits, infiltration and bleeding. CT of the chest showed bleeding, suspected either due to an infection or malignancy, yet no typical Wegener's granulomas.

Based on the positive C-ANCA and pr3-ANCA, a diagnosis of Wegener's granulomatosis was made.

INVESTIGATIONS

The patient underwent a great many investigations, including blood tests, ECG, echocardiogram, coronary angiogram, chest x-ray and CT chest.

Blood tests included Hb, liver and kidney function tests, electrolytes, ESR, CRP, RF, anti-CCP, ANA, ENA, ds-DNA, D-dimers, *Borrelia burgdorferi*. Eventually also C-ANCA, p-ANCA, pr3-ANCA and MPO-ANCA were determined.

DIFFERENTIAL DIAGNOSIS

Single vessel coronary heart disease was considered and confirmed. Initially, a *B burgdorferi* infection was contemplated, yet soon after excluded.

The rheumatologist thought of Löfgren's syndrome, later the patient was diagnosed with Wegener's granulomatosis.

TREATMENT

The Wegener's disease was treated with pulsed intravenous cyclophosphamide (1500 mg every 3 weeks) with uromitexan as bladder protection and combined with oral prednisolone (35 mg, reduction of dose by 5 mg per week). She received co-trimoxazole (960 mg 3 days a week) as *Pneumocystis carinii* prophylaxis.

She made a good recovery and after three cycles of cyclophosphamide, the medication was changed to oral methotrexate (15 mg once a week) and low-dose prednisolone (5 mg/day). On this regime the patient's liver enzymes raised. In response, the dose of the methotrexate was halved and the liver enzymes normalised. Currently, the patient is on methotrexate 10 mg once a week and prednisolone 5 mg a day.

OUTCOME AND FOLLOW-UP

Immediately after the first dose of cyclophosphamide, the patient's symptoms improved and she felt a lot better. There were no longer any chest problems and also the tiredness and joint aches disappeared, allowing a return to work.

The patient is currently doing well and in remission.

DISCUSSION

Various case reports have highlighted the challenge of diagnosing early Wegener's granulomatosis due to atypical presenting symptoms and the involvement of different organ systems. For example, patients initially presented with pleural effusion, with recurrent otitis media or with pulmonary infiltrates. As a result, it often took a long time to set the diagnosis, yet early diagnosis and treatment is important as progression of the disease can lead to permanent organ damage and can be life threatening. Early checking of C-ANCA and pr3-ANCA aids to set an early diagnosis.¹⁻³ The finding of a positive C-ANCA on its own

is by no means diagnostic of Wegener's disease and the gold standard for diagnosis remains tissue biopsy.⁴ However, biopsy is not always feasible and must be balanced by the possibility of iatrogenic risk. As such it is important to interpret C-ANCA with the clinical presentation.

In this case, the patient initially presented with dyspnoea symptoms, flank pain and swollen legs. A genuine diagnosis of single vessel coronary heart disease was made and a DVT and *Borrelia burgdorferi* infection disease were excluded. The patient then presented with diverse symptoms to various doctors (ophthalmologist, rheumatologist, general physician), yet the correct diagnosis could only be made due to the suspicion of the GP, new symptoms like coughing up blood and nasal bleeds, and the measurement of C-ANCA and pr3-ANCA.

As mentioned, the patient had indicated an insect bite in the medical history. It is not possible to say whether this insect bite was a trigger for Wegener's disease onset. However, in Wegener's granulomatosis there is often a bacterial infection in the medical history, which potentially could cause an immunological response.⁵

In this case it took 3 months to make the diagnosis and in the described case reports it took longer to achieve this. Even so the diagnosis could have been made sooner if C-ANCA and pr3-ANCA would have been assessed at an earlier stage, for example by the rheumatologist or the cardiologist.

Finally the disease often presents in an atypical way, frequently affects various organ systems and as such usually involves a range of different specialists. Therefore the involvement of a generalist (general physician or GP) with an open mind is important to maintain an overview and to play a coordinating role.

Learning points

- ▶ The diagnosis of Wegener's granulomatosis can be challenging due to atypical presentation and in this case the presence of genuine single vessel coronary heart disease.
- ▶ Assessing C-ANCA and pr3-ANCA at an early stage will aid early diagnosis and as such the prognosis.
- ▶ Involvement of a generalist with an open mind and holistic approach helps making the diagnosis.

Acknowledgements The author would like to thank the patient for her consent to send the case report for publication. The author also thanks Col David Williams and Col Trevor Jones for their support for publication.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Blundell AG**, Roe S. Wegener's granulomatosis presenting as a pleural effusion. *BMJ* 2003;**327**:95-6.
2. **Ridley MG**, Wolfe CS, Asherson RA, *et al*. Recurrent otitis media and pulmonary infiltrates as presenting features in Wegener's granulomatosis. *BMJ* 1998;**297**:352-3.
3. **Uppal S**, Saravanappa N, Davis JP, *et al*. Pulmonary Wegener's granulomatosis misdiagnosed as malignancy. *BMJ* 2001;**322**:89-90.
4. **Karim M**, Masood A. ANCA testing in the diagnosis of vasculitis. *BMJ* 2001;**322**:89-90(reply).
5. Deutsche Rheuma Liga. 3.6 Die Wegener'sche Granulomatose. www.rheuma-liga.de (accessed 15 April 2011).

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

van den Heuvel H. Wegener's granulomatosis – another challenging case. *BMJ Case Reports* 2011;10.1136/bcr.05.2011.4284, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow