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Wegener's granulomatosis and autoantibodies to neutrophil antigens

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SUMMARY

We report five cases of Wegener's granulomatosis all of whom had clinical and histological evidence of disease activity at presentation and in whom autoantibodies to neutrophil antigens were detected. This test may prove useful for the diagnosis of this serious condition and help to monitor disease activity during treatment.

INTRODUCTION

Wegener's granulomatosis is a necrotising granulomatous arteritis[1] which preferentially involves the kidney and upper and lower respiratory tracts.[2,3] Its aetiology is unknown and its pathogenesis not entirely characterised.[4] Despite the lack of understanding of the immune mechanisms involved in the disease, it can be successfully treated with immunosuppressive agents.[2,5] Diagnosis is usually based on clinical and histological data.[2,5,6] There are a variety of clinical manifestations which include proteinuria, microscopic haematuria, impaired renal function, fever without evidence of infection, ocular inflammation, otitis, sinusitis, tracheitis, haemoptysis, pulmonary infiltrates and evidence of granulomatous vasculitis usually on nasal, lung or renal biopsy.

A number of non-specific immunological abnormalities have been reported including circulating immune complexes,[7,8] rheumatoid factor and IgG and IgA autoantibodies. These have not proved helpful in diagnosis or monitoring disease activity and are present in relatively few patients. Laboratory monitoring of disease activity has relied on non-specific markers such as the erythrocyte sedimentation rate and C-reactive protein.[9]

Van der Woude et al reported the presence of IgG autoantibodies to neutrophil antigens in patients with active Wegener's granulomatosis.[10] More recently Lockwood et al have described a radioimmunoassay method to quantitate the level of these autoantibodies and have shown that they are detectable in certain types of vasculitis including Wegener's granulomatosis.[16]

PATIENTS AND METHODS

Five patients (three female, two male) were studied. Serum samples were tested for the presence of antineutrophil antibodies by the indirect immunofluorescent

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and radioimmunoassay methods described by Lockwood et al.[16] In all patients the diagnosis of Wegener's granulomatosis was confirmed by histological examination of tissue biopsy and the pre-treatment serum samples showed the presence of antineutrophil antibodies (Table).

TABLE

Case	*Age*	*Sex*	*Neutrophil autoantibody*	*Renal impairment*	*Positive biopsy*
1	53	F	+ve	No	Nasal
2	28	M	+ve	No	Lung Nasal
3	41	M	+ve	Yes	Nasal Renal
4	33	F	+ve	Yes	Nasal Skin
5	62	F	+ve	Yes	Skin (Postmortem)

CASE 1

A 53-year-old woman presented with epistaxis, nasal congestion, deafness and a painful swollen left calf. On examination, her temperature was 39°C. She had rhinitis and otitis media. There were signs of consolidation at the apex of the left lung. Venography confirmed the clinical impression of an extensive left leg venous thrombosis. A chest X-ray demonstrated cavitating lesions in both lung fields. A nasal biopsy was reported as showing necrotising arteritis. Urinalysis and microscopy were negative. Treatment with 80mg prednisolone and 2mg/kg cyclophosphamide daily induced clinical remission. Pre-treatment serum samples showed the presence of antineutrophil antibodies both by indirect immunofluorescence and radioimmunoassay. Unfortunately, she died three months after diagnosis from a cerebrovascular accident.

CASE 2

A 28-year-old man presented with earache, deafness, nasal congestion, epistaxis, cough and pleuritic chest pain. On examination, his temperature was 39·2°C. He had episcleritis, rhinitis and a serous effusion in the right middle ear. Signs of consolidation were present in the left lung apex. A chest X-ray revealed the presence of circular opacities in both lung fields. Biopsy of the nasal septum and percutaneous needle biopsy of lung confirmed the diagnosis. Serum samples showed the presence of antibodies to neutrophil antigens. Treatment with 60mg prednisolone and 2mg/kg cyclophosphamide induced clinical remission. Repeat serum samples showed no evidence of antineutrophil antibodies either by indirect immunofluorescence or the radioimmunoassay.

CASE 3

A 41-year-old man presented with facial pain, recurrent epistaxis and jaundice. On examination, his temperature was 38·5°C. Apart from jaundice, he had no other stigmata of liver disease. Biochemical investigations included bilirubin

102 umol/l, alkaline phosphatase 45 U/l, gamma GT 771 U/l, ALT 1295 U/l and AST 365 U/l. Viral hepatitis, leptospiral and toxiplasma screening was negative. Initial urinalysis was negative except for bilirubinuria. Facial X-rays showed opacification of both maxillary antra which were subsequently drained. He developed right hypochondrial pain two weeks after admission and ultrasound scan and percutaneous cholangiogram showed a dilated gallbladder and dilated common hepatic duct. He developed pleuritic chest pain, cough and haemophysis and on examination there was a left-sided pleural rub. Investigations revealed microscopic haematuria, pulmonary infiltrates on chest X-ray and multiple perfusion defects on isotope lung scan. He developed rapidly progressive origuric renal failure. Renal biopsy demonstrated crescentic glomerulonephritis. He was treated with 60 mg prednisolone and 2 mg/kg cyclophosphamide daily but there was no recovery of renal function despite remission of other clinical features. He was subsequently maintained on twice weekly haemodialysis until receiving a cadaveric renal allograft in November 1985. Repeat assay for antineutrophil antibodies are consistently negative.

CASE 4

A 33-year-old woman presented with general malaise and weight loss for three months. She developed arthralgia, skin rash, cough, haemoptysis and sinusitus in the two weeks prior to admission. On examination her temperature was 37·8°C. She had tender nodular erythematous swellings on the right ankle and left wrist and a florid haemorrhagic rash. Investigations revealed rapidly progressive renal failure with proteinuria and haematuria on urinalysis and haemogranular casts and microscopic haematuria on microscopy. A chest X-ray showed pulmonary infiltrates. Nasal biopsy was consistent with the diagnosis. Treatment with 60 mg prednisolone and 2 mg/kg cyclophosphamide induced clinical remission with recovery of renal function. Significant proteinuria 2–5 g/24 hours persists at follow up.

CASE 5

A 62-year-old woman presented with a three week history of a flu-like illness, cough and sputum. On examination, her temperature was 38·4°C. She was anaemic and in congestive cardiac failure. Consolidation was present at the left lung base. Investigations revealed rapidly progressive renal failure. A skin biopsy was reported as vasculitis. Renal arteriography was suggestive of multiple micro-aneurysms. Peritoneal dialysis was instituted but was complicated by peritonitis. She died from cardiac arrest during haemodialysis. Post mortem demonstrated a myocardial infarct secondary to haemorrhage into an atheromatous plaque occluding the right coronary artery. The diagnosis was confirmed by the finding of necrotising granulomatous arteries in lungs and spleen. The renal lesion was crescentic glomerulonephritis.

DISCUSSION

Wegener's granulomatosis is a serious and life-threatening condition in which a rapid and accurate diagnosis may improve the clinical outcome.[11] Untreated, the one year survival in patients with renal disease is 20 per cent.[2, 5] It can be effectively treated with immunosuppressive drugs, usually a combination of steroids and cyclophosphamide.[12, 13, 14] Azathioprine and plasma exchange may also have a role in treatment.[15]

Autoantibodies against neutrophils and monocytes in Wegener's granulomatosis have been described by Van der Woude et al[10] and were reported as being specific for this disease. Lockwood et al have confirmed the presence of autoantibodies to neutrophil antigens in this condition, but have shown that they may also be detected in other forms of vasculitis.[16] We report five patients with clinical and histopathological evidence of Wegener's granulomatosis in whom neutrophil autoantibodies were present at time of diagnosis and in whom the antibody test became negative when clinical remission was achieved. Testing for neutrophil autoantibodies may soon become part of the screening investigations in vasculitic disorders and testing for these immunoglobulins may be of benefit when biopsy material is inconclusive or unobtainable. Rapid serological diagnosis would enable earlier treatment to be initiated in an attempt to reduce overall morbidity and mortality of this disease. This assay would also appear to be a more reliable and sensitive method for monitoring disease activity than the non-specific markers such as ESR or C-reactive protein.

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