Teaching Point
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ANCA-positive rapidly progressive glomerulonephritis: there may be more to the diagnosis than you think!

Th. Messiaen, Ch. Lefebvre, F. Zech, J. P. Cosyns and M. Jadoul

Departments of Nephrology, General Internal Medicine and Pathology, Cliniques Universitaires Saint-Luc, University of Louvain Medical School, B-1200 Brussels, Belgium

Case report

A previously healthy 56-year-old woman was referred for evaluation of fatigue, skin lesions and renal failure. She had noticed for several months progressive asthenia, nocturnal sweats, intermittent fever (38°C), anorexia and a 3 kg weight loss. Two weeks before admission, red spots appeared on the legs. At that time, erythrocyte sedimentation rate reached 60 mm/h, while serum creatinine had risen to 154 μmol/l from 88 μmol/l 1 month earlier.

On admission, cardiopulmonary auscultation was normal. Blood pressure was 120/80 mmHg. Noticeable findings were palpable purpura on the legs and mild spleen enlargement. Serum C-reactive protein (CRP); (5 mg/l) and plasma fibrinogen (212 mg/dl) were normal. Serum creatinine was elevated (181 μmol/l). Additional tests included: haemoglobin 8.2 g/dl with microcytosis (71.6 μm3), iron 17 μg/dl, TIBC 224 μg/dl, ferritin 269 μg/ml, white cell count 3.69 × 109/l (neutrophils 56%), platelets 150 × 109/l, total protein serum level 90 g/l (albumin 32 g/l, gamma-globulins 42 g/l (IgM 0.41 g/l, IgG 3.59 g/l, without evidence of monoclonal component)). Urinalysis disclosed 80–90 red blood cells/hpf with red cell casts; proteinuria was 1.8 g/24 h. Several autoantibodies were detected: antinuclear antibodies (ANA) at a titre of 1/320 (nucleolar and speckled patterns), anticiardioliopin antibodies 61 U.GPL (normal < 10), perinuclear ANCA at a titre of 1/2560 without reactivity, by ELISA, for myeloperoxidase, elastase, cathepsin or lactoferrin extracts. C3 serum level was 0.6 g/l (normal 0.7–1.3). A mixed type III cryoglobulin (IgM–IgG) was detected (0.7 mg/ml, normal < 0.08). Serological tests for hepatitis B and C viruses were negative. Bone marrow biopsy, chest and abdominal computerized tomographies were normal except for splenic enlargement.

Kidney biopsy showed six obsolescent glomeruli, 14 glomeruli with cellular crescents associated with segmental capillary wall necrosis in seven (Fig. 1), and acute interstitial nephritis. Granular mesangial and endomembranous deposits of IgM and C3 were observed by immunofluorescence microscopy (Fig. 2). A diagnosis of necrotizing glomerulonephritis associ-
Fig. 3. Dark masses of bacteria (arrows) embedded in fibrin. Valve leaflet (below) diffusely infiltrated by fibroblasts. H&E (×320).

ated with type III mixed cryoglobulinaemia was made. Methylprednisolone 500 mg i.v. was given for 3 consecutive days, followed by prednisolone 0.5 mg/kg daily orally and cyclophosphamide 750 mg i.v. monthly. Within 1 month, skin lesions and fever subsided and serum creatinine stabilized.

Two weeks later the patient was readmitted for acute heart failure with pulmonary oedema requiring mechanical ventilation. She was febrile (38.3 °C). Echocardiography revealed a grade IV aortic insufficiency with a large aortic valvular vegetation. Oxacillin, gentamicin and amphotericin B were administered. The haemodynamic status remaining unstable, aortic valvular replacement (mechanical valve) was performed the next day. At surgery, the aortic valve appeared massively destroyed (perforation of one cuspid and large vegetation on another). Microscopic examination of the valve showed few bacterial colonies without significant inflammatory reaction (Fig. 3). Blood and valve cultures remained sterile. The immunosuppressive treatment was stopped and ampicillin and gentamycin administered for 6 weeks.

The patient recovered uneventfully. Seven months later she is asymptomatic; serum creatinine is 88 μmol/l. Autoantibodies (ANA, anticardiolipin antibodies, ANCA) and cryoglobulins have disappeared.

This second hypothesis did not account unequivocally for the spleen enlargement. The latter has indeed been frequently observed in so-called essential mixed cryoglobulinaemia [1,2] but this may reflect the major role of hepatitis C virus as a cause of both so-called essential mixed cryoglobulinaemia and chronic liver disease with an attendant spleen enlargement [2]. No evidence of hepatitis was present in our patient.

After the patient subsequently presented with endocarditis, we again revised our diagnosis: subacute bacterial endocarditis accounted for both the valvular destruction and the mixed cryoglobulinaemia (no longer essential) with immune glomerulonephritis. Subacute bacterial endocarditis fits with the clinical course of several months, the spleen enlargement, the marked polyclonal B-cell activation with various autoantibodies and cryoglobulins, all of which (including anticardiolipin antibodies and ANCA) resolved after curing the endocarditis without further immunosuppressive treatment [3,4].

The absence of a heart murmur as well as of an acute phase response (normal CRP level) initially led us astray. In fact, a cardiac murmur may be initially absent and develop only in the course of endocarditis in up to 24% of the patients [5]. Rare cases of endocarditis and septicaemia with normal levels of CRP have also been reported [6].

**Discussion**

Our initial diagnostic hypothesis in this patient with a nephritic syndrome and circulating ANCAs was a primary renal vasculitis. Subsequently, however, the presence of glomerular immune deposits (Fig. 2) together with the detection of circulating cryoglobulins led us to a revision of this hypothesis and to the conclusion that this patient had a type III essential mixed cryoglobulinaemia with glomerular involvement. Immunosuppressive treatment was therefore initiated [1].

**Teaching points**

1. ANCA are not fully specific for primary vasculitis and may be detected in other (e.g. bacterial) diseases as a result of polyclonal B-cell activation (with secondary renal vasculitis).
2. Essential mixed cryoglobulinaemia is not an aetiological diagnosis. In the absence of evidence for HCV infection, other causes should be thoroughly searched for, including subacute bacterial endocarditis.
3. Subacute bacterial endocarditis may develop in the absence of a cardiac murmur and without elevation of acute phase reactants such as serum CRP level.

References