Positive Cytoplasmic Antineutrophil Cytoplasmic Antigen with PR3 Specificity Glomerulonephritis in a Patient with Subacute Bacterial Endocarditis

To the Editor:

A 28-year-old man presented with 4 weeks of malaise, 1 week of progressive bilateral leg edema, hematuria, and 2 days of dyspnea and orthopnea. There were no other symptoms. He had chronic hepatitis C and a remote history of asthma. He smoked crack cocaine, marijuana, and cigarettes, but denied intravenous drug or alcohol use. His medical history was otherwise unremarkable and he was not taking any medications. He denied recent dental work.

The patient appeared weak and ill. His initial temperature was 36°C and he remained afebrile. Pulse was 115 beats per minute. Significant physical findings included clubbing, bilateral pitting edema past the knees, jugular venous distension, ascites, and bilateral pulmonary crackles. Cardiac auscultation demonstrated an S3, a diastolic murmur along the left sternal border, and a systolic murmur at the apex. There were no dermatologic manifestations, nasopharyngeal abnormalities, or inflamed joints.

Laboratory data revealed a leukocyte count of $25.3 \times 10^3/mm^3$, neutrophils $20.7 \times 10^3/mm^3$, lymphocytes $1.3 \times 10^3/mm^3$, eosinophils $0.3 \times 10^3/mm^3$, hemoglobin 80 g/l, platelets $360 \times 10^3/mm^3$, creatinine 344 μmol/l, urea 19 mmol/l, and bicarbonate 18 mmol/l. Liver enzymes were normal. Urinalysis demonstrated > 3 g/l protein, dysmorphic red cells, and cellular casts. Chest radiograph showed bilateral pulmonary infiltrates.

Antibiotics were instituted immediately. Blood cultures grew *Enterococcus faecalis*. With diuresis and antimicrobial therapy, the patient improved. Cytoplasmic antineutrophil cytoplasmic antigen (c-ANCA) was positive on immunofluorescence and proteinase 3 (PR3) positive by ELISA. Additionally, C3 was 0.49 g/l (normal 0.88–2.01 g/l), C4 0.26 g/l (normal 0.16–0.47 g/l); antinuclear antibody, rheumatoid factor, cryoglobulins, hepatitis B, and HIV serologies were negative.

Renal biopsy demonstrated immune complex-mediated acute diffuse proliferative glomerulonephritis (GN). Echocardiography revealed 19×10 mm and 15×12 mm vegetations on a bicuspid aortic valve, an 18×13 vegetation on the mitral valve, and an interventricular septum abscess. Aortic and mitral regurgitations were severe.

Urgent bivalvular replacement was performed. At 1 month there was recurrent paravalvular abscess and regurgitation requiring repeat valve replacement. The patient recovered, finished an appropriate course of antibiotics, and was discharged. He was lost to followup and later found dead at home.

This patient presented with a systemic inflammatory response, congestive heart failure, and renal failure due to GN. Positive c-ANCA with PR3 specificity confounded the diagnosis of subacute bacterial endocarditis (SBE). The presentation prompted the immediate search for an infectious etiology, with vasculitis investigations being completed because of the GN. Immune complex-mediated GN on renal biopsy supported the diagnosis of SBE. Cocaine use was an alternative but less likely explanation for the ANCA. Similarly, hepatitis C can be associated with immune complex-mediated GN, but was unlikely with normal liver enzymes and function, negative rheumatoid factor and cryoglobulins. His improvement with antibiotics and without specific hepatitis C virus (HCV) therapy also makes HCV-related GN unlikely.

ANCA has a strong association with small-vessel vasculitis. In particular, c-ANCA on immunofluorescence with specificity for PR3 on ELISA is up to 99% specific for Wegener's granulomatosis[1]. Other causes of c-ANCA/PR3 positivity are rare (Table 1). Among these are a small but growing number of cases of SBE. A literature search revealed 19 such cases, including this one[2,3,4,5,6,7,8,9,10,11]. Eleven were *Streptococcus* species, 3 *Staphylococcus*, 2 *Enterococcus*, and 3 culture-negative. SBE can mimic vasculitis when presenting with constitutional symptoms, GN, and pulmonary infiltrates such as in this case.

The differentiation between ANCA-associated SBE and ANCA-associated vasculitis (AAV) may be difficult. Chirinos, *et al*[12] described some pertinent differentiating features. These characteristics were found to be more indicative of SBE than AAV: splenomegaly, extracardiac manifestations of SBE limited to skin and kidneys, positive blood cultures, hypocomplementemia, rheumatoid factor, cryoglobulins, and antinuclear and anticardiolipin antibodies. Age, sex, subacute presentation, constitutional symptoms, leukocytosis, and erythrocyte sedimentation rate were not differentiating[12].

Table 1. Causes of PR3-specific c-ANCA other than Wegener's granulomatosis.

Connective tissue disease
Cocaine-induced midline destructive lesions
Subacute bacterial endocarditis
Tuberculosis
Chronic hepatitis B virus infection
Chronic hepatitis C virus infection
Amoebic liver abscess
Phlegmon
Cystic fibrosis
Ventriculoperitoneal shunt nephritis
Parvovirus B19

PR3: proteinase 3; c-ANCA: cytoplasmic antineutrophil cytoplasmic antigen.

In cases of GN, a renal biopsy is warranted to differentiate between immune complex-mediated and pauciimmune GN. SBE is associated with immune complex-mediated GN but there have been 2 cases of pauciimmune GN associated with SBE[2,6]. One of these progressed to terminal renal failure with c-ANCA titers remaining elevated 2.5 years after SBE treatment, suggesting true vasculitis superimposed on SBE[2].

Haseyama, *et al* suggested that patients with high PR3 titers in association with SBE be initially treated with immunosuppression[13]. There have been 6 cases of c-ANCA/PR3-associated SBE treated initially with immunosuppression or simultaneously with antibiotics because of delayed or equivocal diagnosis[2,3,5,6,10]. Two of these patients eventually died[2,6]. One of these received only 1 day of corticosteroids, unlikely to have had a major effect[6]. This compares to 2 mortalities (including this patient) of 13 patients with an initial diagnosis of SBE and treated only with antibiotics[8]. In this group of patients, a diagnosis should be pursued without delay. Without convincing evidence of primary vasculitis and ruling out SBE, there is no strong evidence to support immunosuppression.

Of 15 cases with good longterm outcome following SBE treatment, 13 had followup ANCA titers, 10 of which returned to normal. The significance is unknown; the reduction in inflammation with treatment of SBE likely contributed.

There are a small but growing number of cases of c-ANCA/PR3-associated GN due to SBE. Reported bacterial species include *Streptococcus*, *Staphylococcus*, and *Enterococcus*. Distinguishing these cases from true AAV presents an important challenge for clinicians.

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