Crescentic glomerulonephritis and eosinophilic interstitial infiltrates in a patient with hypereosinophilic syndrome

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Summary
Crescentic glomerulonephritis with immune complex deposition and acute eosinophilic interstitial nephritis developed in a patient with the hypereosinophilic syndrome. Acute renal failure ensued but was rapidly reversed by high-dose oral prednisone. Confounding factors and unusual findings are described with a review of recent literature. This mode of presentation has not previously been reported.

Keywords: immune-complex crescentic glomerulonephritis, eosinophilic interstitial nephritis, hypereosinophilic syndrome, neuropathy, prednisone

Introduction

Eosinophilia can be associated with a wide spectrum of organ dysfunction (box).¹ Patients with an elevated eosinophil count persistently greater than $1.5 \times 10^9/l$ for a minimum of six months who develop end-organ damage but have no recognised underlying cause for their eosinophilia, can be considered to have the idiopathic hypereosinophilic syndrome (HES).^{2,3}

Many organs and organ systems may be involved in HES (box).⁴ Acute renal failure and HES are associated only rarely and the relationship is complex.⁵ We report crescentic glomerulonephritis, renal immune complex deposits, interstitial nephritis, and prominent renal eosinophilic infiltrates in a patient with HES in apparent symptomatic and haematologic remission.

Case report

A 67-year-old woman presented in June 1990 with symmetrical sensory polyneuropathy and a persistent peripheral eosinophil count over $5 \times 10^9/l$. Eosinophil counts during the eight years before presentation ranged from 0.2 to $0.7 \times 10^9/l$.

The patient had a seven-year history of asthma which was asymptomatic at the time and well controlled by theophylline preparations and inhaled beta-agonists. She had also been treated for sinusitis but there was no history of allergic rhinitis. Five years previously she had developed infiltrating ductal carcinoma of the right breast, without axillary lymph node involvement, which was

treated by modified radical mastectomy. She had been free of disease since. Two years prior to presentation, an 8 mm $\times$ 8 mm lung nodule was found on routine chest radiograph. Computed tomography (CT) scan appearance was consistent with benign neural or connective tissue tumour. The nodule remained stable and no tissue diagnosis was sought. In May 1989 she presented with chest pain and a subendocardial myocardial infarction was diagnosed. Echocardiogram showed inferior and posterior hypokinesis with overall systolic function in the normal range. Pulsed colour Doppler revealed a mitral valve inflow pattern consistent with mild diastolic dysfunction. A cardiac biopsy was not performed and she has had no further cardiac symptoms.

There were no known drug allergies that might have contributed to the eosinophilia; she had not received tryptophan at any time and there was no clinical evidence of collagen vascular disease. Multiple screens of stool for ova and parasites were negative. Serum IgE

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Blood and tissue eosinophilia
Secondary to: <ul style="list-style-type: none">• vasculitic syndromes• invasive parasitic infection• extrinsic allergic asthma• allergic rhinitis• pulmonary aspergillosis• certain collagen vascular diseases• skin conditions• neoplasia

Organ involvement in HES
Major: <ul style="list-style-type: none">• heart• lungs• upper airways• liver• spleen• skin• nervous system Minor: <ul style="list-style-type: none">• kidneys• gastrointestinal tract• lymph nodes• eyes• muscles

level was 619 mg/l (normal range: 12–240 mg/l). Tuberculosis screen, viral serology, antinuclear antibody, rheumatoid factor and antineutrophil cytoplasmic antibody were negative. Her renal function and other serum chemistries were normal. Specifically, her serum creatinine was 71 $\mu\text{mol/l}$ with her body weight at 62 kg and a height of 151 cm.

Bone marrow aspiration and biopsy demonstrated marked eosinophilic hyperplasia with otherwise normal maturation and no evidence of leukemia. Nerve conduction studies showed sensory polyneuropathy of axonal type characteristic of HES but no nerve biopsy was performed.

A diagnosis of HES was made. The patient received prednisone with resolution of her neuropathy and the eosinophil count fell to below $1 \times 10^9/\text{l}$. One year later, she relapsed with recurrent neurologic symptoms and eosinophilia of $3.5 \times 10^9/\text{l}$. Therapy with hydroxyurea was begun but discontinued because of nausea and dyspepsia. Prednisone was started in late June 1991 and stopped in July when the neurologic symptoms disappeared and the eosinophil count decreased to $0.8 \times 10^9/\text{l}$.

In early August, coliform cystitis developed which was first treated with ampicillin, then trimethoprim and finally cleared by ciprofloxacin. Routine screening of renal function three weeks later detected renal impairment which progressed rapidly to acute renal failure. At the time, the patient felt well and had no complaints. She was normotensive and without rash, arthropathy, myopathy, bony tenderness, adenopathy or organomegaly. There was no evidence of peripheral vascular disease, mass lesion in her left breast or recurrent breast cancer in her right mastectomy scar.

Investigations revealed a peripheral eosinophil count of $0.499 \times 10^9/\text{l}$, an elevated erythrocyte sedimentation rate of 95, antinuclear antibody of 1:160, with negative anti-ds DNA, anti-Sm, ribonucleoprotein, and rheumatoid factor. C3 and C4 were within the normal range. Sinus X-rays were normal and a repeat antineutrophil cytoplasmic antibody was negative. The antinuclear antibody was not considered significant given the low titre and the lack of supporting evidence for lupus. Liver function tests were within normal limits. Serum immunoelectrophoresis was normal and hepatitis B surface antigen was negative. Chest X-ray showed normal heart size, no hilar or mediastinal enlargement and clear lung fields with no change in the appearance or size of the peripheral lung nodule noted on previous studies. Urine analysis and microscopy demonstrated mixed cellular casts (white cells, red cells and renal tubular cells), 3+ protein, 100–300 red cells, and 20–30 white cells (12% eosinophils by Hansel's stain). Serial urine cultures were negative. Spot urine protein:creatinine ratio was 2.0 (normal less than 1.5). A renal ultrasound was unremarkable.

A renal biopsy was done and the specimens were processed for light microscopy and electron microscopy with immunofluorescence studies. A total of 28 glomeruli were present on

two biopsies examined by light microscopy. Most glomeruli showed cellular or fibrocellular crescents, segmental sclerosis and some global sclerosis. The interstitium contained a dense, mixed inflammatory infiltrate with a marked predominance of eosinophils. There was also extensive interstitial fibrosis with tubular atrophy (figure 1). Electron microscopy demonstrated marked thickening of the capillary basement membranes with electron dense deposits both in mesangial and intramembranous locations. Immunofluorescence revealed IgG (++) , IgA (+ to ++), IgM (++) and C3 (++) as focal and segmental granular deposits along the capillary basement membranes and in the mesangium. IgE staining was not done. Focal globular deposits of fibrinogen were also present. The pathology was reported as crescentic glomerulonephritis with immune complex deposits and interstitial nephritis with abundant eosinophils.

Prednisone, 60 mg/day, was started and her renal function improved (figure 2). The urine sediment became benign with only 2–4 red cells, 2–4 white cells and a trace of protein. Spot urine protein:creatinine ratio was 0.83. The eosinophil count fell to $0.1 \times 10^9/\text{l}$ and she had no neurological symptoms. Prednisone was tapered off over 14 weeks and then stopped.

At follow-up one year later, serum creatinine was 110 $\mu\text{mol/l}$, spot urine protein:creatinine ratio was 0.5, and urinalysis was normal. Her peripheral eosinophil count was $0.1 \times 10^9/\text{l}$ and she was clinically asymptomatic.

Discussion

Idiopathic HES is a heterogeneous group of disorders with prolonged eosinophilia and

Figure 1 (A) Renal biopsy showing crescentic glomerulonephritis with extensive glomerulosclerosis and interstitial nephritis with eosinophils (H&E $\times 100$). (B) Glomerulus with cellular crescent (arrows) and mixed interstitial infiltrate with numerous eosinophils (H&E $\times 200$)

Figure 2 Response of serum creatinine and urine protein:creatinine ratio to prednisone therapy over time

organ system dysfunction. In 55 patients evaluated at the National Institute of Health, no cases of renal disease were seen.² Case reports in the medical literature have described membranous glomerulonephritis, immune-complex glomerulonephritis, interstitial nephritis, and renal vasculitis.⁵⁻⁷ Acute renal failure from haemoglobinuria and Charcot-Leyden crystals has also been reported.⁸

The immunopathogenesis of crescentic glomerulonephritis is complex (see box). Churg-Strauss syndrome and polyarteritis nodosa are important considerations in the differential diagnosis of acute renal failure with crescentic glomerulonephritis, interstitial nephritis, and a history of hypereosinophilia.

This patient had no evidence of upper respiratory tract granulomatosis, pulmonary infiltrates, diffuse interstitial lung disease or cutaneous angiitis as is commonly seen in these causes of renal vasculitis.^{9,10} There was a long-standing, very small pulmonary nodule, but this had remained stable and was felt to be benign and unrelated.

Churg-Strauss syndrome is characterised by three phases (see box).^{11,12} This was not the pattern in our patient, although the seven-year history of asthma was a confounding factor in the diagnosis both in terms of Churg-Strauss syndrome *vs* HES and HES *vs* eosinophilia due to asthma. The latter is a reflection of atopic activity and mirrors the progress of the pulmonary process, usually from onset.^{13,14} At presentation, she did not have symptoms or signs of acute asthma, lung function was stable and previous eosinophil counts were normal, so this could not account for her syndrome. Similarly, Churg-Strauss syndrome could be ruled out on the basis of the clinical features which evolved subsequently.¹²

Pathologic features seen by light microscopy may be similar in polyarteritis nodosa, Wegener's granulomatosis, or Churg-Strauss syndrome and may include granulomas with or

Immunopathogenesis of crescentic glomerulonephritis

Hypersensitivity: hypereosinophilic syndrome, allergic vasculitis

Direct antibody mediated: Goodpasture's syndrome (via the anti-glomerular basement membrane antibody)

Immune complex formation: lupus, post-infectious, membranoproliferative, membranous, and IgA nephropathy.

Cell mediated injury: idiopathic crescentic nephritis, antineutrophil cytoplasmic antibody-associated crescentic nephritis (either the anti-myeloperoxidase-type antibody in polyarteritis nodosa and small vessel vasculitis, or the anti-pr3-type in Wegener's granulomatosis)

Churg-Strauss syndrome

Prodromal phase: atopic asthma, allergic rhinitis

Second phase: eosinophilic tissue infiltration, chronic pneumonia, gastroenteritis, Loeffler picture

Vasculitic phase: skin rash, severe constitutional symptoms, mononeuritis multiplex, renal disease (occasional)

without vasculitis.¹⁵ While her renal biopsy showed severe crescentic glomerulonephritis, and widespread glomerular sclerosis, the prominent eosinophilic interstitial infiltrates with extensive fibrosis and tubular atrophy are the distinguishing feature. Marked eosinophilic interstitial infiltrates would be unusual for polyarteritis nodosa, Wegener's granulomatosis or Churg-Strauss syndrome but are typical of organ involvement in HES.¹ Furthermore, electromicroscopy and immunofluorescence identified mesangial and intramembranous immune complexes, which are not found in polyarteritis nodosa, Wegener's granulomatosis or Churg-Strauss syndrome.^{16,17}

The possibility that the onset and severity of her renal disease was influenced by the preceding antibiotic therapy was addressed. Ciprofloxacin and ampicillin rarely cause acute interstitial nephritis and trimethoprim in the absence of a sulfonamide is not recognised as an aetiological agent.^{18,19} Drug-related acute interstitial nephritis typically shows mixed inflammatory cell infiltrates likely to include some neutrophils and eosinophils, together with lymphocytes and plasma cells.²⁰ Eosinophils have commonly been described in biopsies from methicillin-related cases but are less prominent in cases due to other agents.²¹ An allergic reaction to drug therapy is possible but cannot explain the severity of the crescentic glomerulonephritis, nor the markedly prominent eosinophilic interstitial infiltrate.

The subendocardial infarction one year prior to the diagnosis of HES is of interest. In cardiac disease associated with HES, the primary site of damage is the endocardium.²² Echocardiographic findings in the heart affected by HES

include increased left ventricular wall thickness and impaired mitral valve leaflet motion secondary to fibrosis of papillary muscles, chordae and valves.²³ None of these features was described in our patient, plus the eosinophil count was normal at the time and she has had no further cardiac symptoms or signs. Hence, the likelihood of the subendocardial infarct being a prodrome of her HES would seem small but, in the absence of a tissue diagnosis, cardiac involvement cannot be ruled out with certainty.²⁴

Adenocarcinoma is associated with secondary eosinophilia,²⁵ and the history of breast cancer five years prior to diagnosis might be considered contributory. However, she had no evidence of recurrent malignancy at the time she presented with HES. Furthermore, she was over six years after mastectomy with no suggestion of relapse when her renal disease occurred. A causal role would be unlikely given the paraneoplastic mechanism of tumour-derived eosinophilopoiesis.²⁶ Further, crescentic glomerulonephritis and eosinophilic interstitial infiltrates as paraneoplastic, renal, manifestations of breast cancer have not been described²⁷; the associated glomerulopathy typically seen being membranous glomerulonephritis.²⁸

It is difficult to explain the eosinophilic infiltration of the renal interstitium in light of the normal peripheral eosinophil count. This discordance confirms that other organ system involvement may occur in the face of haematologic remission.² Careful monitoring of cardiac, pulmonary, neurologic, renal, and

liver function should be considered in patients with HES who are asymptomatic and are in apparent remission.

Immune complex deposition in the kidneys is unusual in HES.⁸ Staining for IgE was not done but renal deposition of IgE has been associated with secondary peripheral eosinophilia, immune complex glomerulonephritis and eosinophilic interstitial nephritis;²⁹ therefore, it is possible that this immunoglobulin was involved in the process.

Cytotoxic drugs and plasma exchange have been recommended as first-line therapy in other causes of vasculitis and progressive glomerulonephritis.³⁰ The rapid, sustained improvement in renal function and decrease in proteinuria after a course of prednisone suggests that acute progressive glomerulonephritis secondary to HES may not require initial, aggressive treatment.

In conclusion, this patient represents, to the best of our knowledge, the first recorded case of HES, eosinophilic interstitial nephritis, and crescentic glomerulonephritis with immune complex deposits resulting in acute renal failure rapidly resolved by steroid therapy. Our report illustrates the complexity surrounding the diagnosis, management and complications of HES, and the importance of close follow-up of patients with this condition.

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