



ENDGAMES

CASE REVIEW

A 77 year old man with asthma and renal impairment

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A 77 year old man presented after a collapse at home with a three week history of dyspnoea, malaise, and myalgia. He reported a 10 year history of hypertension, and that he had undergone a nasal polypectomy seven years earlier and had recently been diagnosed as having asthma. Prescribed drugs included candesartan 4 mg daily, enalapril 20 mg daily, beclometasone dipropionate 200 µg twice daily, and salbutamol as needed. He had not recently changed his drugs or used non-steroidal anti-inflammatory agents or herbal remedies. On examination his blood pressure was 156/88 mm Hg; temperature was 36.8°C; and he had generalised polyphonic wheeze, raised jugular venous pressure (5 cm above the sternal angle), and mild bilateral ankle oedema.

Blood tests showed impaired renal function, with creatinine 691 µmol/L (reference range 60-110), urea 46.2 mmol/L (3.0-6.2), compared with creatinine 102 µmol/L and urea 3.0 mmol/L two months earlier. Other results showed haemoglobin 99 g/L (135-180), mean corpuscular volume 89.9 fL (78-100), white cell count $11.52 \times 10^9/L$ (4.0-11.0), neutrophils $9.38 \times 10^9/L$ ($2.0-7.5 \times 10^9/L$; 81.4%,), lymphocytes $0.37 \times 10^9/L$ (1.0-4.5; 3.2%), monocytes $0.29 \times 10^9/L$ (range 0.2-0.8; 2.5%), eosinophils $1.46 \times 10^9/L$ (0.04-0.4; 12.7%), basophils $0.00 \times 10^9/L$ (<0.1; 0%), platelets $228 \times 10^9/L$ (150-400), C reactive protein 857.16 nmol/L (<47.62), and erythrocyte sedimentation rate 115 mm in the first hour (<30).

No paraprotein was detected on serum or urine electrophoresis. Serology was negative for hepatitis B, hepatitis C, and HIV. Urine was positive for protein (urine protein:creatinine ratio 170 mg/mmol, <30), and blood (3+ on dipstick testing). A plain chest film showed clear lung fields and normal cardiac outline. Normal sized, unobstructed kidneys with preserved corticomedullary differentiation were seen on renal tract ultrasound.

He was started on haemodialysis before further investigations to establish a diagnosis.

Questions

1. What is the likely diagnosis?
2. What further assessments and tests are indicated?

3. What treatments are used?

4. What is the prognosis?

Answers

1. What is the likely diagnosis?

Answer

In view of the history of asthma and nasal polyposis, eosinophilia, and severe renal impairment, the likely diagnosis is eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome) with renal involvement.

Discussion

EGPA is a systemic small vessel necrotising vasculitis, characterised by eosinophilia, reactive airway disease, and nasal polyposis, with neurological (typically mononeuritis multiplex), gastrointestinal, myocardial, and renal manifestations well recognised.¹

EGPA is defined by the Chapel Hill consensus of 2012 as an eosinophil-rich and necrotising granulomatous inflammation, mainly affecting small and medium sized vessels, which is associated with asthma and eosinophilia.² The American Rheumatology Association diagnostic criteria stipulate the presence of four of the following: asthma, greater than 10% eosinophilia, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophils. These criteria have a sensitivity of 85% and specificity of 99.7%.³

Most patients present with non-specific symptoms of malaise and fever. A history of reactive airway disease is essentially universal, with late onset asthma common,⁴ and 70% of patients have a history of allergic rhinitis or nasal polyposis.⁵

Typical laboratory findings include a normocytic anaemia, marked circulating eosinophilia, and an acute phase response with raised erythrocyte sedimentation rate and C reactive protein.⁵

Renal involvement is rare. A prospective study of 383 patients reported that only 49 patients developed proteinuria greater than 1 g/day and 11 developed renal insufficiency (defined as creatinine >140 µmol/L).⁶

2. What further assessments and tests are indicated?

Answer

EGPA is a multisystem disorder and assessment for neurological, gastrointestinal, and cardiac involvement is required. An autoimmune screen, including anti-neutrophil cytoplasmic antibodies (ANCA), is indicated. Diagnosis requires renal biopsy. Histology showed crescentic glomerulonephritis, segmental necrosis, and interstitial inflammation with an eosinophilic infiltrate, characteristic of EGPA renal disease.

Discussion

EGPA is a multisystem disorder and evidence of cardiac, gastrointestinal, cutaneous, or nervous system involvement should be sought. Further investigation by means of electrocardiography, echocardiography, endoscopy, and nerve conduction studies should be considered if clinically indicated.⁷

EGPA is classified by the Chapel Hill consensus of 2012 as an ANCA associated vasculitis (AAV). ANCA are typically IgG autoantibodies directed against intracellular autoantigens in neutrophils and monocytes. ANCA are subdivided on the basis of immunofluorescent staining into cytoplasmic (typically targeting serine proteinase 3) and perinuclear (typically targeting myeloperoxidase). A positive ANCA test is neither sensitive nor specific for EGPA and is not a requisite for diagnosis. About 30–40% of patients with EGPA are ANCA positive, typically with a perinuclear pattern of staining (but not specifically to myeloperoxidase), on enzyme linked immunosorbent assay (ELISA).⁸ Other AAVs include granulomatosis with polyangiitis (formerly Wegener's granulomatosis), 85% of which are positive for cytoplasmic ANCA and microscopic polyangiitis, which is associated with perinuclear ANCA.

It has been suggested that ANCA status influences the clinical expression of EGPA.⁹ A case series of 93 patients found a significant correlation between perinuclear ANCA status and renal involvement, with 51% of perinuclear ANCA positive cases having renal involvement compared with only 12% of ANCA negative cases ($P<0.001$).¹⁰ The association between positive ANCA status and glomerulonephritis is recognised by the Chapel Hill consensus definition of EGPA.² ANCA negative disease is more typically associated with cardiac manifestations. In a retrospective analysis of 49 patients with EGPA, none of the 22 patients with cardiac involvement were positive for ANCA, whereas seven of the 27 patients without cardiac involvement were ANCA positive ($P<0.05$).¹¹

ANCA are used as serological markers of disease, although their predictive value for disease relapse is poor. The pathogenic role of ANCA in clinical disease has not been determined.¹²

The histological findings of crescentic glomerulonephritis with segmental necrosis and interstitial inflammation are typically found in ANCA associated vasculitis. In a series of 19 patients presenting with EGPA with renal involvement, renal biopsy showed a focal segmental glomerulonephritis in 85% of cases, with segmental necrosis and crescents being common.¹³ In a further series of 16 biopsies, necrotising crescentic glomerulonephritis was seen in 11 patients,¹⁴ and eosinophilic interstitial nephritis was documented in both studies.

It is not possible to differentiate EGPA from microscopic polyangiitis or granulomatosis with polyangiitis on the basis of renal biopsy, but EGPA is more often associated with an eosinophilic interstitial infiltrate.

3. What treatments are used?

Answer

EGPA typically responds well to steroids but more severe cases may require cyclophosphamide. Steroid sparing agents such as azathioprine and methotrexate can be used to maintain remission. Small scale studies suggest a role for the novel agents, rituximab and mepolizumab, in the management of refractory disease.

Discussion

EGPA is a rare condition and randomised trial data are lacking. A prospective study of 342 patients with polyarteritis nodosa or EGPA identified five factors that were poor prognostic indicators—the five factor score (FFS). These factors comprised renal insufficiency (serum creatinine >140 µmol/L), proteinuria (>1 g/day), involvement of the gastrointestinal tract, involvement of the central nervous system, and cardiomyopathy. A relative risk of death of 3.6 ($P=0.0001$) was reported for proteinuria greater than 1 g per day, and 1.86 ($P<0.02$) for renal insufficiency.¹⁵ Furthermore, analysis of the outcomes of 1108 patients with systemic necrotising vasculitides has also implicated age over 65 years as a poor prognostic factor (hazard ratio 3.3; $P=0.001$).¹⁶

Similar to that for other autoimmune conditions, the management of EGPA aims to induce and maintain remission, assess for relapse, and treat any relapses that occur. Treatment of EGPA starts with intensive (induction) therapy with high dose systemic corticosteroids. Patients without poor prognostic indicators (FFS=0), can be treated with steroids alone. A prospective study of 72 such patients showed 93% remission with steroid monotherapy; however, relapse was common but responded to further immunosuppression with azathioprine or cyclophosphamide.¹⁷

Cyclophosphamide is also warranted for EGPA that presents with poor prognostic indicators (FFS ≥1).¹⁸ The aim of treatment is to move away from the use of cyclophosphamide, with carefully monitored weaning away from steroids over a prolonged period, typically with ongoing low dose steroid requirement. Medium potency steroid sparing agents such as azathioprine, methotrexate, or leflunomide may be considered for patients who need prolonged high doses of steroids for adequate disease control.¹⁹

Additional treatment strategies have been explored for the management of severe or refractory disease. Plasma exchange has been advocated by some for the management of severe disease, although trial evidence for its use is lacking. A single randomised trial that compared prednisolone and cyclophosphamide versus prednisolone, cyclophosphamide, and plasma exchange as first line treatment of EGPA with poor prognostic indicators found no significant difference in five year mortality.²⁰ However, a meta-analysis of plasma exchange as an addition to immunosuppression demonstrated improved renal prognosis in patients with other renal AAVs, and by analogy plasma exchange has been supported by some experts.²¹

Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed by B cells. Several case reports and small scale studies have suggested its efficacy in the management of refractory EGPA.^{22–24}

Mepolizumab is a humanised monoclonal antibody to interleukin 5, a cytokine associated with eosinophil release and maturation.²⁵ Small scale studies have shown that patients with EGPA who are treated with mepolizumab have reduced eosinophil counts and steroid requirements.²⁶

4. What is the prognosis?

Answer

Overall prognosis in EGPA is favourable, with remission in 90% of patients, and five year survival exceeding 90%.

Discussion

In a series of 96 patients with EGPA, 86 achieved clinical remission when treated with high dose steroids, with or without cyclophosphamide. Twenty two patients relapsed, with three patients experiencing multiple relapses.²⁷

Poor prognostic indicators include renal insufficiency (serum creatinine >140 µmol/L), proteinuria (>1 g/day), involvement of the gastrointestinal tract, involvement of the central nervous system, cardiomyopathy,¹⁵ and age greater than 65 years.¹⁶ Cardiac involvement is the most common cause of death in EGPA. In a retrospective analysis of 133 patients who died within one year of starting treatment for EGPA, cardiac involvement was the cause of death in 83% of cases.²⁸ Furthermore, a retrospective analysis of 150 patients showed that, compared with the general population, patients with EGPA associated heart failure have an increased standardised mortality rate (3.09, 95% confidence interval 1.10 to 6.00).¹⁹

Data on the outcomes of patients presenting with severe renal involvement are limited. In one case series, three of four patients presenting with uraemia regained independent renal function.⁸ In another, four patients with myeloperoxidase positive EGPA and crescentic glomerulonephritis at biopsy were all discharged with independent renal function.²⁹

Patient outcome

Our patient was positive for perinuclear ANCA (anti-myeloperoxidase antibody titre 90 IU/mL, reference range 1-10). Crescentic necrotising glomerulonephritis with a diffuse interstitial eosinophilic infiltrate was seen on renal biopsy.

He was treated with three pulses of intravenous methylprednisolone then high dose oral steroids. Because of the renal involvement he was started on pulsed intravenous cyclophosphamide with a steroid wean. He required haemodialysis for two weeks before regaining independent renal function. He was discharged from hospital after 22 days.

In the three months since discharge renal function has continued to improve (creatinine 178 µmol/L, urea 12.1 mmol/L), proteinuria has resolved (urine protein:creatinine ratio fell to 17 mg/mmol), and his eosinophil count and anti-myeloperoxidase titre have normalised (7 IU/mL).

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Patient consent obtained.

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