CASE REPORT

Rare case of eosinophilic granulomatosis with polyangiitis in two patients with α -1-antitrypsin deficiency (PiSZ)

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SUMMARY

We present two cases of eosinophilic granulomatosis with polyangiitis occurring with α -1-antitrypsin deficiency, both PiSZ phenotype. The simultaneous occurrence of these two conditions has seldom been described in the literature, despite evidence of an association between α -1-antitrypsin deficiency and other forms of vasculitis. Both patients had pulmonary involvement and reported intermittent exacerbations of vasculitic symptoms. Both patients were managed on low-dose oral steroids and azathioprine remaining well with occasional exacerbations. It is important to consider whether there is an association between eosinophilic granulomatosis with polyangiitis and α -1-antitrypsin deficiency, as this may lead to more severe pulmonary symptoms during exacerbations. If a genetic association between the two conditions is found, clinicians should be aware of the possible need to screen for α -1-antitrypsin deficiency in appropriate patients.

BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic inflammatory disease of small-sized and medium-sized blood vessels. It is associated with eosinophilia, asthma and damage to the skin, nerves, lungs, kidneys and heart due to vasculitis.^{1 2} No widely accepted diagnostic criteria currently exist for EGPA, though a number of classification criteria are available.^{3 4} A common but underdiagnosed genetic disorder, α -1-antitrypsin deficiency (AATD) causes relative shortage of the liver enzyme antitrypsin, which protects the lung against proteinases. AATD is caused by mutations in the SERPINA1 gene located on the long arm of chromosome 14 (14q31-32.3) that are inherited in an autosomal co-dominant manner.^{5 6} The highly polymorphic nature of this gene has resulted in over 90 protein variants (known as Pi* types) being identified.⁷

The deficiency phenotypes Pi*SZ and Pi*ZZ are associated with greater severity of disease in AATD.⁸ An association between AATD phenotype and a number of forms of vasculitis has been outlined in the literature. Mahr *et al*⁹ and Morris *et al*¹⁰ identified an association between carriage of the Z deficiency allele, and granulomatosis with polyangiitis (GPA), also known as Wegener's granulomatosis. Mahr *et al*⁹ concluded that SZ and ZZ phenotypes increased the risk of GPA in AATD. Both alleles are over-represented in patients with antineutrophil

cytoplasmic antibodies (ANCA)-associated vasculitis compared with normal populations.^{9 11} ANCA positive status is found in many vasculitic syndromes, including EGPA.² Therefore, it is possible that a number of patients with EGPA may express S and Z deficiency alleles, as part of undiagnosed AATD. We present two such cases, with both patients expressing Pi*SZ AATD phenotypes in conjunction with EGPA.

CASE PRESENTATION

Patient 1

An 82-year-old Caucasian woman presented to hospital, with a 2-week history of lethargy, shortness of breath, anorexia, back pain, myalgia and paraesthesia in the arms and legs. She had noticed a mottled, red rash on the medial aspect of her left leg a week previously, which had resolved prior to presentation. The patient had been diagnosed with asthma 30 years previously, later being diagnosed with chronic bronchitis and AATD (Pi*SZ type). She was a lifelong non-smoker. On inspection, there were no skin changes identified, the chest was clear on auscultation and heart sounds were normal with no added sounds. On abdominal examination, there was mild tenderness in the epigastric and umbilical regions. On examination of the peripheral nervous system, there was normal tone, power, sensation, reflexes and coordination, in the upper and lower limbs. After initial assessment, the clinical suspicion was of an underlying malignancy.

Patient 2

A 36-year-old Caucasian woman was admitted to hospital, with a 6-week history of increasing dyspnoea, cough, fatigue, palpitations, back pain and night sweats. Recently, she had suffered with persistent nausea and had lost weight. There was pain in her elbow joints, and there were no other changes to her joints or skin. She had a medical history of postnatal jaundice, juvenile arthritis, perennial rhinitis, chronic sinusitis, hay fever, endometriosis and late-onset asthma. She had a paternal second cousin with haemochromatosis and maternal second cousin with Wegener's granulomatosis. The patient took salbutamol as required and beclomethasone inhalers for her asthma. She was a non-smoker. On examination, she was tachycardic and appeared considerably short of breath at rest. Auscultation of the chest was clear and general examination was normal apart from a low-grade fever.

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INVESTIGATIONS

Patient 1

Blood tests revealed an unusually high eosinophil count of $24.4 \times 10^9/L$, deranged liver function tests; alkaline phosphatase (ALP) 255 U/L, alanine transaminase (ALT) 45 U/L, raised inflammatory markers; white cell count (WCC) $37.4 \times 10^9/L$, C reactive protein (CRP) 105 mg/L. Creatine kinase was 330 U/L. Serology showed positive antinuclear antibodies (ANA), positive ANCA, titre 1/50, (pANCA or cANCA pattern unknown), negative myeloperoxidase (MPO) antibodies and negative proteinase 3 (PR3) antibodies. The patient's α -1-antitrypsin (AAT) level was 0.83 μM . A CT of the thorax, abdomen and pelvis showed bilateral apical scarring, and small hilar and mediastinal calcified lymph nodes but no other obvious abnormalities.

Patient 2

Resting saturation was 93–96%, peak flow was 450 L/min and forced expiratory volume in 1 s/forced vital capacity ratio had reduced from 2.6/2.7 L to 2.15/2.2 L. Serum testing demonstrated raised WCC; $15.9 \times 10^9/L$ and raised eosinophils; $5.6 \times 10^9/L$ with neutrophils of $7.6 \times 10^9/L$. Liver function was mildly deranged ALP 121 U/L, ALT 42 U/L and erythrocyte sedimentation rate (ESR) was markedly raised at 103 mm/h. Serology showed negative ANCA. Sputum cultures, thyroid function tests, urea and electrolytes were normal.

Urinalysis showed a trace of blood and protein but no haematuria. A chest X-ray showed significant bilateral patchy infiltrates, particularly of the upper lobes, with a slightly prominent left hilum. Bronchoscopy and transbronchial biopsy were inconclusive.

TREATMENT

Patient 1

The patient was treated with three doses of intravenous methylprednisolone 500 mg and a prolonged reducing course of oral prednisolone, with the option of introducing intravenous cyclophosphamide if symptoms did not resolve. On review in clinic 2 weeks after discharge, the majority of her symptoms had resolved, aside from mild residual paraesthesia in the fingers and toes. Her Birmingham Vasculitis Activity Score had improved from 15 to 0 and the eosinophil count had normalised from 24.4 to 0.2. Intravenous cyclophosphamide was therefore not required and the patient was started on azathioprine at a dose of 2–3 mg/kg, for up to 5 years.

Patient 2

The patient was managed with oral prednisolone. This led to a rapid improvement in symptoms, serum tests normalised, aside from liver function, which remained slightly deranged. The patient was started on long-term, low-dose prednisolone 5 mg once daily and azathioprine 75 mg once daily. On review in clinic 2 weeks later, a diagnosis of EGPA with pulmonary and sinus involvement was made.

OUTCOME AND FOLLOW-UP

Patient 1

Eighteen months on from her initial presentation, the patient reported marked symptomatic improvement. Prednisolone was continued for 18 months and gradually stopped. She remains on azathioprine alone, at a dose of 100 mg once daily. On review, the patient reports regular exacerbations of her respiratory symptoms, occurring approximately every 2 months, with worsening cough, production of white sputum, worsening shortness

of breath and reduced exercise tolerance from 300 yards to 100 yards on the flat. She is managed by her general practitioner (GP) for the mainstay, and exacerbation of symptoms are generally treated with antibiotics, which have appeared to improve but not fully resolve her symptoms.

Patient 2

Twenty years following her first presentation of vasculitis, the patient presented to the specialist AATD clinic with a diagnosis of PI*SZ AATD, identified through family screening. At the time of review, the patient was well and had unremarkable examination findings. The most recent serology showed an eosinophil count of $0.3 \times 10^9/L$ and normal inflammatory markers, IgE 9 kU/L, negative ANA, negative ANCA, weakly positive smooth muscle antibodies and normal liver function. The most recent imaging showed no evidence of emphysema on CT of the thorax.

Patient 2 remains under the care of a specialist rheumatology team, which she sees regularly and during exacerbations. She reports a baseline of persistent fatigue with mild exacerbation of the vasculitis once yearly on average. Exacerbations are typified by gradually increasing fatigue followed by cough with minimal white sputum and increasing shortness of breath. Low-grade fever, nausea, joint and back pain, and palpitations also feature commonly. Sinus symptoms include pain, headache and serous yellow discharge with occasional bloody discharge. Patient 2 adopts a supervised self-management strategy. During mild exacerbations, she checks for reversibility in peak flow to salbutamol, and tests her urine for blood and protein. If peak flow demonstrates no reversibility and her urine dip is positive for blood and protein, she manages this as a vasculitis flare up and increases prednisolone to 20 or 30 mg for up to 3 days and then continues or titrates down depending on response. She also seeks advice from her GP or rheumatologist.

DISCUSSION

We describe the rare occurrence of EGPA in two patients with PI*SZ α -1-antitrypsin deficiency. In this case series, both patients presented with distinctive clinical features of EGPA. Both met four out of six criteria for classification of EGPA according to the American College of Rheumatology (ACR): asthma, eosinophilia $>10\%$, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities and extravascular eosinophil infiltration on biopsy.³ The ACR classification is not designed for the purpose of diagnosis,⁴ but is useful for the consideration of essential characteristics for EGPA in the absence of validated diagnostic criteria. Given that our patients exhibited the majority of classification criteria and were, in both cases, assigned their diagnosis by an appropriate specialist (rheumatologist), we believe the diagnosis of EGPA is accurate. Histological investigation would be desirable, however, this was not available for patient one and the only available sample for patient two, collected at initial presentation, was inconclusive.

Investigations demonstrated markedly high eosinophils with raised inflammatory markers in both cases. Both patients have been treated successfully with high-dose steroids and azathioprine, though exacerbation symptoms manifest intermittently in both. As a rare and complex condition, it is important to highlight the importance of specialist input into the management of patients with EGPA. Patient 1 is largely managed by the GP and patient 2 has, over time, adopted a supervised self-management approach. The role of the specialist team is fundamental to safe and expert management of this complex chronic disease. Failure

to involve specialists in the ongoing care of such patients is expressly discouraged.

The coexistence of AATD and vasculitis is shown to be strongly associated with expression of the Z deficiency allele.^{11 12} In such cases, patients are often positive for anti-PR3 antibodies and cANCA, a characteristic feature of GPA.^{11 12} Evidence has also shown that expression of the S deficiency allele may be associated with other forms of vasculitis.⁷ PI*SS or PI*SZ patients demonstrate a tendency to be pANCA positive.⁷ pANCA positive status is often found in conjunction with positive anti-MPO antibodies; this occurs in approximately 40% of EGPA cases,^{2-4 13} such that the majority of patients with EGPA, as in our presented cases, do not exhibit anti-MPO antibodies. Nevertheless, an association between EGPA and AATD may exist and the occurrence of EGPA in the two PI*SZ AATD patients described raises two questions: Is there an association between the PI*SZ phenotype and vasculitis? And, Is this distinct from the association already established between ANCA positive vasculitis (GPA) and PI*ZZ? The generalised nature of vasculitis symptoms, and indeed of AATD, may mean that diagnosis is missed initially so biochemical investigations are required; these eventually led to diagnosis in our presented cases. Clinicians should therefore consider the possibility of AATD as a causative or exacerbating factor in EGPA, particularly when the vasculitic presentation is severe or accompanied by additional signs of AATD. Given the strength of evidence for an association between AATD and other forms of vasculitis, mainly GPA, further investigation into the association between AATD and EGPA is warranted. If additional evidence were to emerge in support of an association between AATD and EGPA, it would strengthen the argument for early screening.

It is also interesting to speculate whether AATD would alter the management of vasculitis. Specific therapy for AATD does exist, in the form of intravenous supplementation of AAT, known as augmentation therapy. This treatment may slow the progression of emphysema¹⁴ and is also an accepted way to manage episodes of panniculitis.¹⁵ A single case of concurrent vasculitis and PiZZ AATD has also been reported where the vasculitis responded to augmentation therapy,¹⁶ though this did not appear to be a case of EGPA. The role of augmentation in vasculitis unrelated to AATD is unclear; theoretically it might

limit the damage from neutrophil elastase release in the inflamed vasculitic areas. Indeed, AAT activity has been shown to be low in vessel walls of patients with GPA,¹⁷ thus giving a rationale for use of AAT augmentation in this condition. However, there have been no reports of such management in the literature, to our knowledge, thus this also remains an area for future research.

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Contributors AMT identified the research question, approached the patients for inclusion and reviewed the manuscript. JM conducted the literature search, and drafted and revised the manuscript; this process was supervised by EVL, who also extracted the data, obtained consent, and drafted and revised the manuscript. JM and EVL equally contributed to the project and therefore share joint first authorship. EVL is guarantor.

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Learning points

- ▶ Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic inflammatory condition that affects multiple organs.
- ▶ Eosinophilia and asthma are both associated with EGPA.
- ▶ Presenting symptoms may be non-specific but marked eosinophilia and raised inflammatory markers should raise the suspicion of EGPA.
- ▶ Deficiency of α -1-antitrypsin has previously shown an association with vasculitis.
- ▶ More research is required to determine whether there is an association between the PI*SZ phenotype and EGPA.

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