Amit Panjwani[1], Kanchan Gupta[2]

drameetp@gmail.com

[1]Pulmonary Medicine, Sevenhills Hospital, Mumbai, India.
[2]Radiology, Sevenhills Hospital, Mumbai, India.

A 43-year-old patient presenting with marked eosinophilia and multisystem disease

Case report

Cite as: Panjwani A, Gupta K. A 43-year-old patient presenting with marked eosinophilia and multisystem disease. *Breathe* 2016; 12: e77–e82.

A 43-year-old male developed progressive dyspnoea and swelling of both lower limbs over a period of 1 month. He also noticed left foot drop 1 month previously and weakness of both hands and legs over a period of 3 weeks. He had anorexia for the last 6 months and had lost 12 kg of weight over the last 1 year. He had no chest pain, haemoptysis, fever, syncope or palpitations. He had a history of asthma for the last 5 years. There was no history of allergic rhinitis, diabetes, hypertension or ischaemic heart disease and he was a non-smoker.

On examination, his temperature was 36.8°C, pulse was 100 beats·min^{-1}, respiratory rate was 22 breaths·min^{-1}, blood pressure was 140/80 mmHg. He was asthenic and had bilateral pitting pedal oedema. Jugular venous pressure was mildly elevated and he had fine end inspiratory crepitations in both infrascapualar areas. There was no ronchi heard on either side. Heart sounds (S1 and S2) were heard normally and S3 gallop was heard over the cardiac apex. Neurological examination revealed sensorimotor quadriparesis predominantly distal with differential involvement (left more than right). Distribution of weakness was along the distribution of nerves suggestive of mononeuritis multiplex.

Task 1
What investigations would be useful at this point?

@ERSpublications
A middle-aged male presenting with marked eosinophilia and multisystem disease
http://ow.ly/Z7JX301ABjF

Answer 1
Simple blood test for complete blood counts and biochemistry. Chest radiography. Cardiac workup, including electrocardiography, echocardiography, troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP). Nerve conduction studies are also recommended.

Investigations showed a haemoglobin level of 12.8 $g \cdot dL^{-1}$, total leukocyte count of 40 700 $cells \cdot mm^{-3}$, with differential counts of neutrophils: 24%; lymphocytes: 8%; monocytes: 2%; and eosinophils: 66%. Absolute eosinophil counts were 26 860 $cells \cdot mm^{-3}$. The platelet count was 472000 per mm^3 and erythrocyte sedimentation rate (ESR) was 100 mm in the first hour. Peripheral smear showed leukocytosis with eosinophilia. Eosinophils showed trilobed nucleus with irregular distribution of granules. Red cells were microcytic and there were no haemoparasites seen. Frontal chest radiograph revealed ill-defined alveolar opacities in right upper zone along with reticular opacities in left lower zone; the cardiac dimensions were within normal limits (figure 1). There was no history of tryptophan ingestion.

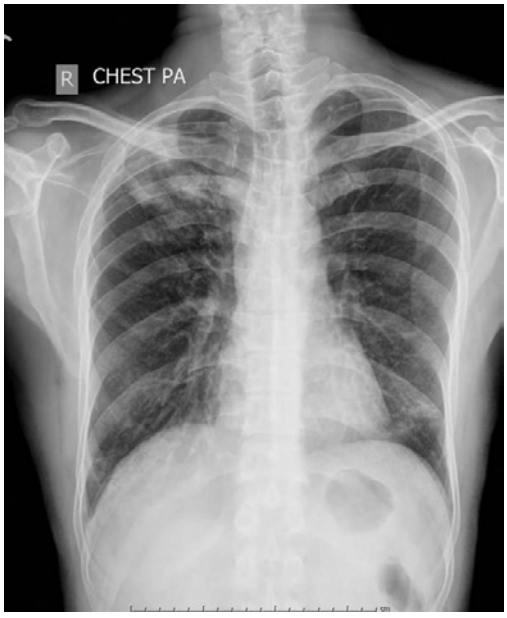

Figure 1 *Frontal chest radiograph.*

Task 2
What are the causes of marked peripheral blood eosinophilia?

Answer 2
The causes of marked peripheral blood eosinophilia include parasitic infections especially with helminthes, fungal infections like allergic bronchopulmonary aspergillosis (ABPA), drug hypersensitivity reactions, atopic diseases, hyper-eosinophilic syndromes, leukaemias including acute myelogenous leukaemia, Hodgkin's lymphoma, immunodeficiency diseases such as hyper-immunoglobulin E (IgE) syndrome, hypoadrenalism and others.

High-resolution computed tomography (HRCT) of the thorax revealed patchy areas of consolidation with surrounding ground-glass opacities and interlobular septal thickening predominantly

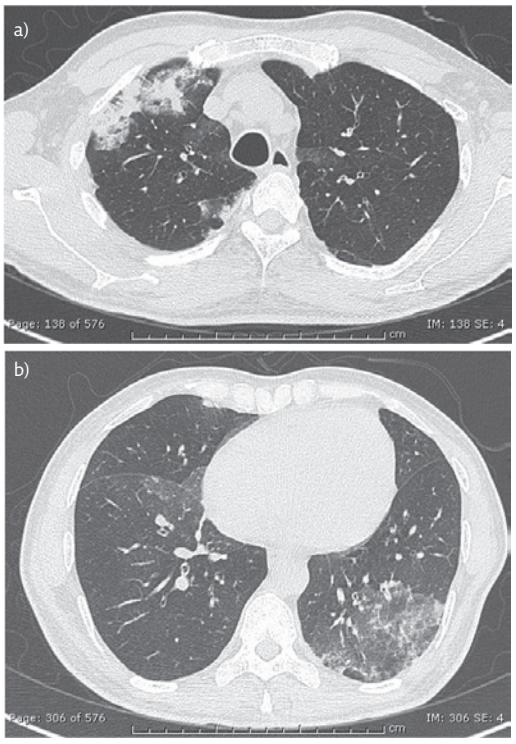

Figure 2 *a and b) HRCT of the thorax reveals patchy areas of consolidation with surrounding ground-glass opacities and interlobular septal thickening predominantly in peripheral distribution involving both lungs.*

Task 3
What disorders account for the HRCT findings?

Answer 3
Chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis (EGPA), bronchiolitis obliterans organising pneumonia, sarcoidosis.

in peripheral distribution involving both lungs (figure 2a and b).

The electrocardiograph showed normal sinus rhythm, prolonged QT interval and no significant ischaemic changes. Urine examination was normal. Creatinine, liver function tests and electrolytes were normal. NT-proBNP was 2208 $pg \cdot mL^{-1}$ (normal value: <125 $pg \cdot mL^{-1}$). Troponin T was 0.09 $ng \cdot mL^{-1}$ (normal value: <0.03 $ng \cdot mL^{-1}$), D-dimer was1.5 $mg \cdot L^{-1}$ (normal ≤0.5 $mg \cdot L^{-1}$). Echocardiography showed a diffuse left ventricular hypokinesia with ejection fraction of 35%. There was no regional motion abnormality. Venous Doppler ultrasound of both lower limbs showed no evidence of deep vein thrombosis. A possibility of congestive cardiac failure very likely due to myocarditis was entertained. To exclude ischaemic heart disease, a myocardial perfusion scan was performed, which showed no regional ischaemic defect.

Cardiac magnetic resonance imaging (MRI) depicted moderate-to-severe hypokinesia of ventricular septum and cardiac apex. Delayed, gadolinium-enhanced cardiac MRI demonstrated circumferential patchy subendocardial and myocardial enhancement; involving anterior, lateral, inferior and septal walls of the left ventricle (figure 3).

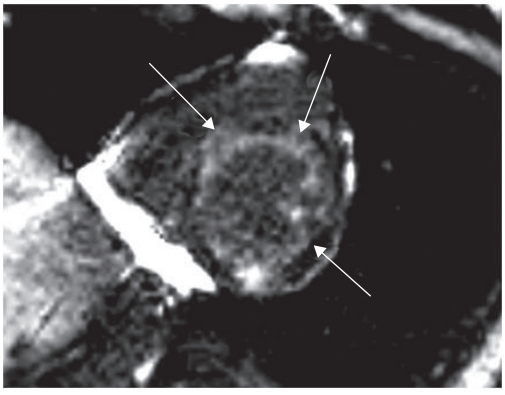

Figure 3 *Short axis delayed enhancement MRI shows circumferential patchy subendocardial enhancement extending into the neighboring myocardium.*

Task 4
What is your differential diagnosis?

Answer 4
Drug reactions, parasitic infections, hyper-eosinophilic syndrome (HES), EGPA, eosinophilic leukamia and lymphomas.

Nerve conduction studies showed sensorimotor axonal nerve involvement in mononeuritis multiplex pattern.

The patient was treated with diuretics, angiotensin-converting enzyme inhibitors and statins. During the hospital stay, the patient developed multiple necrotic vesicles filled with turbid fluid over both hands, feet and legs. A skin biopsy of the lesion showed a subepidermal bulla with a dense infiltration of neutrophils and eosinophils in the underlying superficial dermis along with leukocytoclasia. Small vessels in the superficial dermis showed endothelial swelling, eosinophilic degeneration of their walls, perivascular and intravascular infiltration of neutrophils and eosinophils and extravasation of red cells. There was no evidence of parasitic infection or myeloproliferative disorder.

Task 5
Which tests can be helpful for achieving the diagnosis?

Answer 5
Anti-nuclear antibody (ANA), anti-neutophil cytoplasmic antibody (ANCA), clonal T-cell studies and molecular analyses to detect Fip1-like 1 (*FIP1L1*)–platelet-derived growth factor receptor-a (*PDGFA*) gene fusion.

ANA was found to be positive by indirect immunofluorescence assay (IIFA) and showed a homogenous pattern. Anti-double stranded DNA by IIFA was negative. Antigen-specific myeloperoxidase (MPO) was found to be positive while proteinase-3 was negative by ELISA. *FIP1L1–PDGFA* mutation was not detected. He was diagnosed as having EGPA with a revised five-factor score (FFS) of 2 and was offered treatment with a combination of systemic steroids and cyclophosphamide. Unfortunately, cyclophosphamide administration was deferred, according to the patient's wishes and he was treated with oral corticosteroids at 50 mg·day^{-1} which was gradually tapered off to 10 mg·day^{-1} over a period of 2 months and this dose was continued for a total of 18 months. He showed a remarkable clinical and radiological improvement with therapy. At the time of last follow up (2 years after the diagnosis), the patient was asymptomatic with normal eosinophil counts, ESR of 24 mm in the first hour and there was a complete radiological resolution of the patchy areas of consolidation on the HRCT thorax. (figure 4a and b). Echocardiography showed good left ventricular function with an ejection fraction of 52%.

Discussion

Eosinophilia is defined as eosinophil levels >450 cells·mm^{-3} (or >500 cells·mm^{-3} in some studies). Peripheral blood and tissue eosinophilia occurs in a wide variety of conditions like the parasitic infections, allergies, neoplasms and other less common conditions. Identifying the aetiology for marked eosinophilia is challenging, given the large number of conditions associated with it. The importance of careful history and thorough physical examination cannot be overemphasised. Attempts should be made to look for an underlying organ dysfunction (liver and renal function tests, chest radiography and electrocardiography), assess the inflammatory markers (C-reactive proteins, ESR) and IgE levels to understand the possible cause of eosinophilia. Further diagnostic studies based on the initial evaluation are required to establish the appropriate aetiology for the eosinophilia. These include imaging modalities like computed tomography/MRI, tissue biopsies, bone marrow examination, specific tests like ANCA, serological studies for helminthes and others [1].

Eosinophilic lung diseases are group of disorders associated with lung parenchymal abnormalities which may be accompanied by eosinophilia in the peripheral blood, bronchoalveolar lavage or lung tissue obtained by a biopsy. These include conditions like ABPA, simple pulmonary eosinophilia, acute eosinophilic pneumonia, chronic eosinophilic pneumonia, EGPA, idiopathic HES, parasite-induced pulmonary eosinophilia and drug/toxin-related eosinophilic pneumonia. Other pulmonary conditions that may be accompanied by blood eosinophilia are lung cancer, lymphoma, sarcoidosis and tuberculosis. It is important to correctly diagnose eosinophilic lung disease as most of these conditions are responsive to steroid therapy [2].

HES were the closest differential diagnosis in the present case. HES constitute a group of disorders characterised by persistent and marked eosinophilia (>1.5×10^9 cells·L^{-1} for more than six consecutive months), associated eosinophil-related organ damage, where other causes of eosinophilia like allergic, parasitic and malignant disorders have been excluded. Heart, lungs, skin, nervous system, gastrointestinal tract, liver and spleen are commonly affected. There may be an overlap with EGPA; however, clinically, the absence of asthma and pathologically, the absence of vasculitis as well as granulomas differentiate the two disorders [3]. Detection of *FIP1L1–PDGFA* gene fusion by reverse transcription polymerase chain reaction in the peripheral blood and/or bone

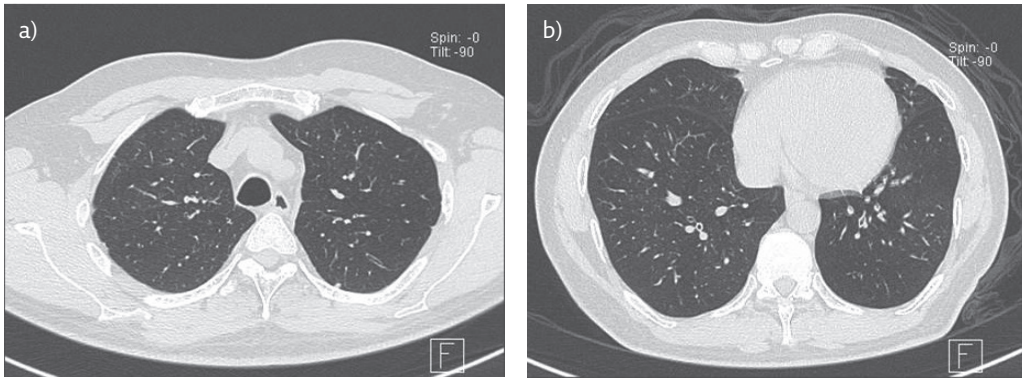

Figure 4 *a and b) HRCT of the thorax showing complete radiological resolution of the patchy areas of consolidation.*

marrow helps in further cementing the diagnosis and identifies the disease variant responsive to tyrosine kinase inhibitor: imatinib [4].

EGPA, previously known as Churg–Strauss syndrome was first described in 1951 as a necrotising vasculitis with extravascular granulomas occurring exclusively among patients with asthma and eosinophilia. EGPA is a part of the spectrum of ANCA-associated vasculitis which also includes granulomatosis with polyangiitis and microscopic polyangiitis. It usually manifests between 7 and 74 years of age with no sex predominance or ethnic predisposition. It is an idiopathic condition which evolves through a prodromic phase characterised by asthma, which occurs in almost all cases and precedes the systemic manifestations of the disease by many years [5], with allergic rhinitis, sinusitis and nasal polyposis are also common during this phase; an eosinophilic phase with peripheral blood eosinophilia and organ involvement (lungs, heart and the gastrointestinal tract); and a vasculitic phase with clinical features of small vessel vasculitis affecting the kidneys and the peripheral nerves. Lung involvement occurs in two-thirds of cases. It is characterised by ground glass opacities and consolidation in peripheral distribution pattern, interlobular septal thickening, bronchial wall thickening and pleural effusion, all of which are better appreciated on HRCT of the thorax compared with chest radiograph [6]. One-quarter to one-half of EGPA cases have a symptomatic cardiac involvement. It may present as eosinophilic myocarditis [7], myocardial infarction due to vasculitis of coronary arteries [8], arrhythmias, pericarditis or valvular defects. Cardiovascular involvement is a major cause of death in these patients and mostly occurs during the first few months after diagnosis [9, 10]. Hyper-eosinophilia, absence of hypertension, infections or toxin exposure, previous cardiopathy related to valvular or coronary abnormalities, elevated troponin T and NT-proBNP, typical echocardiography and cardiac MRI findings favoured the presence of eosinophilic myocarditis in the present case. Peripheral neuropathy is seen in more than two-thirds of cases [11]. They present with mononeuritis multiplex or a mixed sensorimotor peripheral neuropathy. Mononeuritis multiplex typically presents with a wrist drop or foot drop, as was seen in our patient, and can be confirmed with nerve conduction studies or sural nerve biopsy. Gastrointestinal involvement may present with abdominal pain, nausea, vomiting or diarrhoea. Eosinophilic enteritis or vasculitis causing ulcers resulting in intestinal haemorrhages or bowel perforation are the manifestations of gastrointestinal involvement. Less than 25% of EGPA cases have renal involvement, which ranges from isolated urinary abnormalities to chronic renal failure. Cutaneous manifestations include palpable purpura and nodules, commonly located on the limbs and scalp. Other presentations include vesicles, aseptic pustules, urticaria, erythematous rash and dermatitis [12].

Marked peripheral blood eosinophilia (>1500 cells·mm^{-3} or 10%), elevated ESR and C-reactive protein are characteristically seen in the active EGPA cases. Raised IgE and IgG4 levels are also commonly seen. Approximately 50–65% of cases with EGPA are ANCA-positive. Most of these ANCA-positive patients have a perinuclear staining, demonstrable by direct immunofluorescence (P-ANCA) and these correspond to anti-MPO antibodies by ELISA [13]. New biomarkers, like eotaxin-3, an eosinophil-attracting chemokine, are slowly finding their way as an important diagnostic tool for confirming the presence of EGPA. The American College of Rheumatology, in an attempt to distinguish different vasculitides, identified six criteria for EGPA in 1990. They were asthma, eosinophilia >10%, neuropathy, fleeting pulmonary infiltrates, paranasal sinus abnormalities and extravascular eosinophil infiltration on biopsy. With the presence of four or more of these criteria, vasculitis can be classified as EGPA with a sensitivity of 85% and specificity of 99.7%. Our patient fulfilled at least four of these criteria, as well as having ANCA positive for MPO by ELISA.

The patient's prognostic profile determines the choice of initial therapy [14]. The revised FFS helps identify patients requiring aggressive immunosuppressive therapy [15]. The following five criteria, each accorded one point, are associated with a higher 5-year mortality rate: age over 65 years; cardiac symptoms; gastrointestinal involvement; renal insufficiency (serum creatinine >150 µmol·L^{-1}); and absence of any ear, nose and throat manifestations. A 5-year mortality rate of 9%, 21% and 40% is associated with the FFS of 0, 1 and 2, respectively. Corticosteroids remain the hallmark of EGPA treatment and are useful in both induction and maintenance of remission. In patients with at least one poor-prognosis factor (FFS >1), addition of cytotoxic drugs, like cyclophosphamide, is necessary to induce remission. Once remission is achieved, azathioprine is recommended during the maintenance period for at least 18–24 months. In a large French study of EGPA cases, 10% of the study population with FFS of ≥1 was treated only with oral corticosteroids. Relapses occur in almost one-quarter of the cases with EGPA and more commonly in ANCA-positive cases [16]. Our patient refused treatment with cyclophosphamide and therefore was treated only with corticosteroids. Surprisingly, he showed a remarkable response to the single drug and was doing well at the last follow up. Other drugs like interferon-α, mepolizumab (anti-interleukin-5 monoclonal antibody), rituximab, omalizumab, immunoglobulins in combination with plasma exchanges maybe required in difficult situations.

Conclusion

EGPA is a rare systemic vasculitis which has the potential to affect multiple organ systems, as was seen in our case. It should be suspected in patients with asthma presenting with severe eosinophilia, lung infiltrates and vasculitis. Appropriate treatment with steroids and immunosuppressants, where indicated, is associated with good outcome.

Conflict of interest

None declared.

References

1. Nutman T. Evaluation and differential diagnosis of marked, persistent eosinophilia. *Immunol Allergy Clin North Am* 2007; 27: 529–549.
2. Mann B. Eosinophilic lung disease. *Clin Med* 2008; 2: 99–108.
3. Katzenstein A. Diagnostic features and differential diagnosis of Churg-Strauss Syndrome in the lung. A review. *Am J Clin Pathol* 2000; 114: 767–772.
4. Roufosse F, Goldman M, Cogan E. Hypereosinophilic syndromes. *Orphanet J Rare Dis* 2007; 2: 37.
5. Vaglio A, Buzio C, Zwerina J. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): state of the art. *Allergy* 2013; 68: 261–273.
6. Szczeklik W, Sokolowska B, Mastalerz L, *et al*. Pulmonary findings in Churg-Strauss syndrome in chest X-rays and high resolution computed tomography at the time of initial diagnosis. *Clin Rheumatol* 2010; 29: 1127–1134.
7. Hara T, Yamaguchi K, Iwase T, *et al*. Eosinophilic myocarditis due to Churg-Strauss Syndrome with markedly elevated eosinophilic cationic protein. *Int Heart J* 2013; 54: 51–53.
8. Kozak M, Gill E, Green L. The Churg-Strauss Syndrome. A case report with angiographically documented coronary involvement and a review of literature. *Chest* 1995; 107: 578–580.
9. Bourgarit A, Toumelin P, Pagnoux C, *et al*. Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome. A retrospective analysis of causes and factors predictive of mortality based on 595 patients. *Medicine* 2005; 84: 323–330.
10. Guillevin L, Cohen P, Gayraud M, *et al*. Churg-Strauss Syndrome. Clinical study and long term follow up of 96 patients. *Medicine* 1999; 78: 26–37.
11. Lanham J, Elkon K, Pusey C, *et al*. Systemic vasculitis with asthma and eosinophilia: A clinical approach to the Churg-Strauss Syndrome. *Medicine* 1984; 63: 65–81.
12. Kim M, Sohn K, Song W, *et al*. Clinical features and prognostic factors of Churg-Strauss Syndrome. *Korean J Intern Med* 2014; 29: 85–95.
13. Eustace J, Nadasdy T, Choi M. The Churg Strauss syndrome. *J Am Soc Nephrol* 1999; 10: 2048–2055.
14. Greco A, Rizzo M, Virgilio A, *et al*. Churg-Strauss syndrome. *Autoimmunity Rev* 2015; 14: 341–348.
15. Guillevin L, Dunogue B, Pagnoux C. Churg-Strauss syndrome. *In*: Cordier J-F, ed. Orphan Lung Diseases (ERS Monograph). Sheffield, European Respiratory Society 2011; pp. 140–151.
16. Comarmond C, Pagnoux C, Khellaf M, *et al*. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Clinical characteristics and long term follow up of the 383 patients enrolled in the French Vasculitis Study group cohort. *Arthritis Rheum* 2013; 65: 270–281.