CASE REPORT

Acute painful paraplegia in a 49-year-old man with allergic asthma

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SUMMARY

We present a case of a 49-year-old man, with a 10-year history of bronchial asthma and nasal polyposis, who developed acutely painful paraplegia and paresthesias. Laboratory data showed elevated blood creatine kinase levels and myoglobinuria, which were diagnostic for rhabdomyolysis but only partially explained the neurological deficit. Electrophysiological studies revealed a sensorimotor neuropathy of multiple mononeuritis type. The patient also had leucocytosis with marked eosinophilia and antineutrophil cytoplasmic autoantibodies. Bronchial biopsies showed inflammatory infiltrates with a prevalence of eosinophils. All these findings led us to diagnose eosinophilic granulomatosis with polyangiitis, a systemic vasculitis with almost constant respiratory tract involvement and good response to corticosteroid treatment. This can also affect other organs including the nervous system, while muscular involvement is unusual. Some diseases deserve attention in differential diagnosis. Histology can support the diagnosis which remains essentially clinical. Steroid sparing agents/immunosuppressants are suggested for extensive disease.

BACKGROUND

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare small-vessel vasculitic disease, previously called Churg-Strauss syndrome or allergic granulomatosis angiitis.^{1 2} The most frequent clinical manifestations are respiratory tract involvement (75%) such as bronchial asthma (which is an almost universal feature), allergic rhinitis and pulmonary infiltrates, associated with marked peripheral hyper-eosinophilia. EGPA is histologically characterised by a necrotising vasculitis with eosinophilic infiltration and extravascular granuloma formation in tissues. It may be present with multiple mononeuritis (65–75%), gastrointestinal, cardiac, dermatological and renal involvement, while muscular involvement is unusual.¹

CASE PRESENTATION

A 49-year-old man experienced a fever (38°C) with intense myalgia and weakness of both lower limbs. After a couple of days these symptoms also affected the right upper limb and included paresthesias, so he presented to the emergency room. He had never smoked and had a 10-year history of asthma treated with local and systemic steroids plus antileukotriene agents (Montelukast 10 mg/day for several years), and nasal polyposis treated with surgery. Blood tests dating back several years before admission showed the presence of eosinophilia

up to 4000 cells/ μ L (normal <500 cells/ μ L). On admission the patient had a global muscle weakness predominant on the proximal muscle groups of lower limbs, associated with diffuse myalgia, paresthesias in the right median nerve territory and hypoaesthesia in glove to pinprick in his right hand. Chest examination revealed slightly decreased breath sounds to auscultation bilaterally. Vital signs and the remainder of the examination were normal.

INVESTIGATIONS

Blood tests showed high white cell count (WBC: 40.680 cells/ μ L), elevated serum creatine kinase (CPK: 1226 UI/L, normal <170), marked peripheral eosinophilia (23.510 cells/ μ L), elevated serum IgE: 1397 KU/L, normal <25 KU/L) and high inflammatory indices with C reactive protein (CRP) 180.5 mg/L, normal <5 mg/L. The remaining haematological and biochemical profiles were normal.

His chest X-ray showed bilateral areas of hazy increased opacities, mainly in the lower lung fields (figure 1A). Cardiac and mediastinal silhouettes were normal. A chest CT revealed bilateral pulmonary infiltrations and cystic bronchiectasis with diffusely thickened walls in the lower lung lobes, partly occupied by dense content without contrast enhancement (figure 2). ECG and echocardiogram were entirely normal.

A video bronchoscopy was performed and cytological findings of the bronchial aspirate from the left main bronchus showed numerous leucocytes and eosinophils, as well as cylindrical cells, alveolar macrophages and erythrocytes.

Bronchial mucosa biopsies showed several mixed inflammatory infiltrates, with prevalence of eosinophils, some of which assembled in intraepithelial microabscesses. The endoscopic sinus examination showed nasal polyps, hyperplasia, inflammatory changes and oedema of the mucosa, which supported the previous diagnosed sinusitis. A histological examination of the nasal mucosa was not available because technical difficulties did not allow the execution of biopsy in time (before the start of therapy).

Lung function tests showed mild airway obstruction (FEV₁/VC 68%; FEV₁ 85%), with a positive response to the bronchodilator reversibility test: FEV₁ increase of 413 mL (13%) after administration of salbutamol 200 mcg by metered-dose index.

The elevated blood CPK levels and myoglobinuria were diagnostic for rhabdomyolysis, but only partially explained the neuromuscular defect.

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Figure 1 Chest X-ray showed bilateral parenchymal hazy opacities, mainly at the lower lung fields (A), partially regressed in the control after 2 weeks (B).

Electroneuromyography showed sensorimotor axonal polyneuropathy. ANCA with a perinuclear staining pattern (p-ANCA), the main autoantibodies in EGPA, were positive; in particular MPO-ANCA (p-ANCA with anti-myeloperoxidase specificity) were 176.2 UR/mL (normal <18 UR/mL). The screening for parasitic infections was negative.

DIFFERENTIAL DIAGNOSIS

Possible causes of non-traumatic acute or subacute paraplegia include: (1) spinal diseases (vascular, inflammatory, neoplastic); (2) non-spinal disorders, such as polyradiculitis (Guillain-Barré syndrome), hyperkalaemic and hypokalaemic paralysis and psychogenic paraplegia.

In our case neuroimaging with MRI of the spinal cord was unremarkable, whereas the collection of clinical data was highly suggestive of the diagnosis of EGPA. In particular, the patient met all of the six criteria proposed by the American College of Rheumatology: asthma, eosinophilia >10%, neuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormality and extravascular eosinophils (the presence of any four or more of them yields a sensitivity of 85% and a specificity of 99.7%).³ Thus, a specific treatment was started. Because of the complete reversibility of muscle symptoms no further investigations were undertaken; in particular, muscle biopsy was not carried out.

Figure 2 CT of chest showing diffuse bilateral infiltrates.

TREATMENT

A broad-spectrum antibiotic (levofloxacin 500 mg once daily) was initiated on admission since the patient presented with fever and leucocytosis. Faced with the highly probable EGPA vasculitis, 3 days after admission we added 1 g/day of methylprednisolone intravenously. The patient experienced a progressive improvement of myalgia and muscle weakness; the disappearance of fever and a reduction in the blood eosinophilic count and in markers of systemic inflammatory response were observed in a few days, as well as the normalisation of CPK. Chest X-ray control showed partial regression of parenchymal consolidations (figure 1B). Forced diuresis was used to decrease the risk of myoglobin-induced renal damage.

OUTCOME AND FOLLOW-UP

The patient was discharged taking prednisone 1 mg/kg/day orally and 2 weeks later he begun tapering it. He was also prescribed a bisphosphonate to prevent corticosteroid-induced osteoporosis and a proton-pump inhibitor (PPI) as prophylaxis for oesophageal-gastric pathology. Montelukast was discontinued. A chest CT performed 3 months after discharge showed the complete disappearance of pulmonary cloudiness, while spirometric parameters were stable. However, 8 months after discharge a relapse of disease occurred with asthma exacerbation and recurrence of paresthesias at the lower limbs. A therapy with cyclophosphamide was consequently undertaken and corticosteroid again increased to 1 mg/kg/day. A new remission was obtained within 4 weeks, Prednisone was tapered to 10 mg/day and intravenous pulse cyclophosphamide (15 mg/kg every 3 weeks) was continued for 6 months.

DISCUSSION

Eosinophilic granulomatosis with polyangiitis is a potentially fatal disease, affecting small-sized and medium-sized vessels. Its prevalence ranges from 10.7 to 13 per million in adults; annual incidence is lower than 10 new cases per million inhabitants in the general population, but it is about 10 times higher in asthmatic subjects.⁴

EGPA diagnosis is essentially carried out on a clinical basis and can be confirmed by histology.⁵ The American College of Rheumatology criteria for diagnosis of EGPA include bronchial asthma, blood eosinophilia >10%, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates, paranasal sinus abnormalities and histological evidence of extravascular

eosinophils. The presence of any four or more of these six criteria indicates that a patient has EGPA with a sensitivity of 85% and a specificity of 99.7%.³ Other frequent systemic manifestations include fever, weight loss, cutaneous lesions such as purpura and subcutaneous nodules. Moreover, patients can experience: gastrointestinal system involvement with abdominal pain, diarrhoea or bleeding; heart involvement with congestive heart failure, cardiomyopathy and pericardial effusion; and/or kidney involvement with focal segmental glomerulonephritis, usually of mild relevance.⁶ Blood eosinophilia is present in every patient with EGPA and is usually extremely high, averaging greater than 1000 cells/ μ L. A proportion that goes from half to two thirds of patients have a positive p-ANCA test result,⁷ whereas a positivity for PR3-ANCA or more generically cytoplasmic staining pattern (c-ANCA) is more common in Wegener's granulomatosis.

According to some authors, the disease often develops through three stages: a prodromal phase characterised by allergic rhinitis that may be present for several years and that is followed by asthma; a second phase with blood and tissue eosinophilia and eosinophilic pneumonia or gastroenteritis; and a third phase characterised by systemic vasculitis.⁵

Our case suggests that the occurrence of myalgia, weakness and paresthesias of limbs in the context of systemic inflammation with hypereosinophilia should lead to considering the diagnosis of EGPA and to prompt corticosteroid treatment. Muscle involvement in EGPA is rare⁸ but can be the first manifestation of a systemic vasculitis. The transient muscle weakness and pains observed in our patient in association with the elevated CPK and the response to corticosteroid treatment were considered likely to reflect such a process. Rhabdomyolysis is a condition in which damaged skeletal muscle tissue breaks down rapidly. Breakdown products of damaged muscle cells are released into the bloodstream; some of these, such as the myoglobin, are harmful to the kidneys and may lead to acute renal failure (for the prevention of which we administered hydration and diuretics).

The most common chest radiographic findings of EGPA comprise transient patchy alveolar opacities, whereas rarely a diffuse interstitial infiltrates or nodular densities can be observed.⁹ In our case, the execution of chest CT allowed us to better define the radiographic abnormalities present on admission; it probably would not have been necessary if the patient had presented only the symptoms of an asthma exacerbation without systemic manifestations suggesting EGPA.

Some diseases share various aspects of EGPA and deserve attention in the differential diagnosis of lung disorders with

blood eosinophilia (table 1). Idiopathic chronic eosinophilic pneumonia (ICEP) is most likely the leading condition to distinguish from EGPA, since it is relatively common and often has less severe clinical consequences. It usually occurs in subjects with asthma, but the level of eosinophilia is generally not as high as in EGPA.¹⁰ Even if there may be eosinophil infiltration of blood vessel walls, this aspect is modest, whereas necrotising vasculitis and necrotising granulomas are absent. Extrathoracic features are absent in ICEP. When the symptoms and signs of extra-pulmonary involvement are present, a diagnosis of EGPA or idiopathic hypereosinophilic syndrome (IHS) should be considered. It is likely that in some patients a continuum exists between ICEP and EGPA.

Hypereosinophilic syndrome (HES) is a myeloproliferative disorder characterised by persistent blood and bone marrow eosinophilia, and is associated with tissue infiltration by eosinophils and damage to multiple organs (heart, skin, nervous system, lungs, gastrointestinal tract, liver and spleen).¹¹ There may be some overlap with EGPA, but commonly HES differs from EGPA clinically by the absence of asthma and histopathologically by the absence of vasculitis and granulomas.

Bronchocentric granulomatosis (BCG) is a rare disease characterised by a destructive granulomatous lesion of the bronchi and bronchioles that is supposed to represent a non-specific response to several types of airway injury. The cause is unknown in approximately half the cases, while the other half is associated with allergic bronchopulmonary aspergillosis.¹² As in EGPA, patients generally have asthma, eosinophilia, pulmonary infiltrates and systemic symptoms. Lung biopsy also shows necrotising granulomatous inflammation that differs from EGPA because of its typically bronchocentric location. Blood eosinophilia in BCG is usually not as great as in EGPA, and extrapulmonary involvement is not a feature.

Five factors are classically recognised as important for prognosis: proteinuria >1 g/24 h, serum creatinine >1.58 mg/dL, gastrointestinal tract involvement, cardiomyopathy and CNS involvement. The treatment of EGPA without any poor-prognosis factors traditionally consists of corticosteroid monotherapy.¹³ People with severe disease may require an adjuvant immunosuppressive drug such as cyclophosphamide, azathioprine or methotrexate to reduce the body's immune reaction still further.¹⁴⁻¹⁶ Such drugs may also be used as steroid-sparing agents in order to reduce corticosteroids with their side effects. Even if muscle disease is not specifically contained within the classical scoring system, its presence could justify a therapeutic regimen including an immunosuppressant since diagnosis. Once EGPA was almost always a fatal disease; corticosteroids and

Table 1 Features helpful in the differential diagnosis of CSS

	EGPA (CSS)	ICEP	HES	BCG
Extrapulmonary involvement	Yes, (neurological, gastrointestinal, cardiac, dermatological, renal)	No	Yes	No
Asthma	Yes	Frequent	No	Frequent
Blood eosinophilia	Marked	Frequent	Marked	Yes
ANCA positivity	50-70% of cases	No	No	No
Eosinophilic pneumonia	Yes	Yes	No	Yes
Necrotising vasculitis	Yes	No	No	No
Necrotising granuloma	Yes	No	No	Yes (lesions centre on and replace bronchioles)

BCG, bronchocentric granulomatosis; EGPA (CSS), eosinophilic granulomatosis with polyangitis (Churg-Strauss syndrome); HES, hypereosinophilic syndrome; ICEP, idiopathic chronic eosinophilic pneumonia.

immunosuppressants have considerably improved the prognoses and overall survival rates. Since our patient was in treatment with leukotriene receptor antagonists (LTRAs), which have been reported to be a possible trigger of EGPA,¹⁷ we discontinued this drug after admission. However, it should be noted that there may be multiple non-causative reasons for an association between LTRAs and EGPA, such as their broad use in patients with asthma and allergic rhinitis (including those who are already in the process of developing EGPA), or the reduction in corticosteroid dosage in patients using LTRAs, which in turn allows the EGPA to be unmasked.

Learning points

- ▶ Paraplegia is a rare but possible presentation of a systemic vasculitis such as eosinophilic granulomatosis with polyangiitis (EGPA).
- ▶ The laboratory and histological data may support the diagnosis of EGPA, but it remains essentially clinical.
- ▶ A diagnosis of EGPA should be suspected in case of bronchial asthma, allergic rhinitis and systemic inflammation with hypereosinophilia.
- ▶ The treatment of EGPA traditionally consists of corticosteroid monotherapy. Other immunosuppressive drugs may be used in people with severe disease or as steroid-sparing agents.

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