CASE REPORT

Childhood-onset eosinophilic granulomatosis with polyangiitis: a rare childhood vasculitis mimicking anthrax and eosinophilic leukaemia

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SUMMARY

A 14-year-old boy previously misdiagnosed as having cutaneous anthrax was referred with a 2-month history of multiple wide and deep ulceronecrotic lesions in the lower extremities, which occurred after contact with animals. Skin biopsy was compatible with vasculitis. Further examination at our hospital elicited eosinophilia and a history of asthma. On the second day of hospitalisation, he developed deep vein thrombosis. A diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was established and intravenous methylprednisolone was administered. The patient showed remarkable improvement of the cutaneous lesions. Diagnosis of EGPA is challenging in the vasculitic phase and necessitates a detailed history that specifically questions the patient for an asthma background. This case illustrates a severe cutaneous presentation of EGPA and emphasises the difficulty of diagnosis as a result of overlapped signs and symptoms with cutaneous anthrax and leukaemia. EGPA should be kept in mind in the differential diagnosis of cutaneous lesions associated with eosinophilia.

BACKGROUND

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is composed of three subtypes, namely, granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (EGPA), with the latter being the rarest. EGPA is a rare small-vessel vasculitis most commonly presenting in adults, with the average age of diagnosis being 50 years. The disease typically follows three sequential phases (prodromal, eosinophilic and vasculitic). After the long-standing prodromal phase (asthma, allergic rhinitis and nasal polyposis), patients progress to the eosinophilic phase, which is marked by eosinophilia and pulmonary infiltrates, and then to the vasculitic phase.^{1–7} We present a case of a child in the vasculitic phase of EGPA, with severe skin involvement, who was initially diagnosed and treated for cutaneous anthrax.

CASE PRESENTATION

A 14-year-old boy was referred to our paediatric rheumatology clinic after documentation of small-to-medium sized vasculitis on skin biopsy from itchy but painless ulceronecrotic lesions that had first appeared in the right lateral malleolus 2 months prior and spread to the left leg and left elbow. A history of contact with animals led to a

differential diagnosis of anthrax, so antibiotic treatment was started. Detailed investigation revealed a history of asthma from when the patient was 3 years of age; however, the asthma had been well controlled for 5 years without the use of drugs. On physical examination, painless ulceronecrotic lesions with a diameter of 12×8 cm on the right lateral malleolus and older necrotic lesions around the left lateral malleolus, appearing to be the black eschar of cutaneous anthrax, were noticed (figure 1A and C). Physical examination was otherwise unremarkable.

INVESTIGATIONS

Complete blood count (CBC) revealed iron deficiency anaemia (haemoglobin: 8.5 g/dL, haematocrit: 26.9%, mean corpuscular volume (MCV): 60.4 fL, serum iron: 10 µg/dL, total iron binding capacity: 470 mcg/dL, transferrin saturation: 2.2%, ferritin: 12 µg/L), eosinophilia (4100/mm³) and thrombocytopaenia (34 000/mm³). A peripheral blood smear also revealed marked eosinophilia (42%).

Elevated immunoglobulin E (351 IU/mL), erythrocyte sedimentation rate (32 mm/h) and C reactive protein level (6.1 mg/dL) (nephelometry; normal <0.5 mg/dL) were present. While prothrombin and activated partial thromboplastin time were in normal limits, d-dimer was increased to 12.1 mg/L (normal <0.5 mg/L).

DIFFERENTIAL DIAGNOSIS

Bone marrow aspiration was performed owing to the prominent eosinophilia, anaemia and thrombocytopaenia in CBC and peripheral blood smear. However, the result also pointed to eosinophilia without signs of eosinophilic leukaemia.

Infectious aetiologies such as cutaneous anthrax, leishmaniasis, aspergillosis and non-specific agents were excluded by Gram staining, wound-blood-bone marrow cultures and serological investigations.

The patient developed deep vein thrombosis (DVT) in the left, and then in the right leg, on the second and eighth days of hospitalisation, respectively. This manifestation clarified the underlying reason for the previously recorded d-dimer elevation. Clinical (for recurrent oral or genital ulcers and uveitis) and laboratory characteristics (for HLA-B51 and pathergy tests) were not compatible with Behçet's disease, despite the venous thrombosis and biopsy-proven vasculitis.

Although ANCA were negative, the robust clinical manifestations concordant with EGPA (eg, eosinophilia, increased Ig E level, history of

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Figure 1 (A) Wide and deep ulcerative and necrotic lesion with a diameter of 12 cm×8 cm on the right lateral malleolus. (B) Size and depth of the lesion in [figure 1A](#) was markedly decreased by the end of the 3rd month with immunosuppressive treatment. (C) Older necrotic lesions around the left lateral malleolus on admission, which appear to be the black eschar of cutaneous anthrax.

asthma, vasculitic lesions) led us to repeat the skin biopsy and search for lung involvement. Pulmonary high-resolution CT (HRCT) demonstrated bilateral ground glass opacity in a mosaic pattern and millimetric subpleural nodules surrounded by a ground glass appearance, particularly in the middle and lower lobes of the lung ([figure 2](#)). Skin biopsy revealed necrotising inflammation without apparent granulomas. However, marked eosinophilic and histiocytic infiltrations in the extravascular areas and their spread to the interstitial spaces were compatible with the diagnosis of EGPA.

TREATMENT

Low-molecular weight heparin (LMWH) was started for acute thrombosis, on the second day. Although not routine therapy in DVT, aspirin prophylaxis was introduced into the treatment for the possible presence of a thrombophilic state. Besides, intravenous methylprednisolone 'pulse' therapy (30 mg/kg/dose) for 5 days to treat this active disease and then systemic glucocorticoid (1 mg/kg/day) orally for maintenance treatment, were administered.

OUTCOME AND FOLLOW-UP

Subsequently, the size of the vasculitic lesions gradually decreased ([figure 1B](#)) and the thrombosis recovered using only the steroid and LMWH therapy. The aspirin treatment was withdrawn once an inherited thrombophilic state was excluded. Thrombocytopenia in our patient was thought to be antibiotic-related and so we terminated the cefazolin treatment. Following this, the platelet level improved to normal. We were only able to follow-up the patient for 6 months, however,

during that period, the treatment response was good, and he responded well to the corticosteroid therapy and did not experience any flare.

DISCUSSION

Over a 3-year period, in 30 paediatric referral centres in the USA and Canada, only 2 of 117 newly diagnosed AAV cases were reported as EGPA.³ To the best of our knowledge, less than 50 childhood-onset EGPA (cEGPA) cases have been described in the literature to date.²

According to the American College of Rheumatology (ACR) 1990 classification criteria, four of the following six clinical findings are necessary for diagnosis of EGPA (with a sensitivity of 85%): asthma, eosinophilia, mononeuropathy or polyneuropathy, pulmonary infiltrates, paranasal sinus abnormality and biopsy including artery, arteriole, or venule, showing accumulation of eosinophils in extravascular areas.⁴

Similarly, according to Lanham, patients should fulfil the three following criteria for EGPA diagnosis: asthma, peak peripheral blood eosinophil counts $>1.5 \times 10^9/L$ and systemic vasculitis involving two or more extrapulmonary organs.⁵

Our patient met four of six ACR criteria (asthma, eosinophilia, pulmonary infiltrates and accumulation of eosinophils in extravascular areas), however, he met only two of the Lanham criteria for EGPA diagnosis.

In the literature, anti-myeloperoxidase-ANCA is not present in 75% of cEGPA cases.^{6,7} Cardiac involvement is more commonly seen in ANCA-negative cases while renal disease, pulmonary haemorrhage, ear-nose-throat and peripheral nerve involvement, and biopsy-proven vasculitis, are more frequent in

Figure 2 High resolution CT of the chest. (A) Bilateral ground glass opacity of the lung parenchyma in a mosaic pattern, more prominent on the left. (B) Subpleural nodules surrounded by a ground glass-like parenchyma particularly in the middle and lower lobes of the lung.

ANCA-positive cases.^{2 8–10} There was no cardiac involvement in our patient, despite ANCA negativity.

Respiratory (asthma in 91%, pulmonary involvement with non-fixed infiltrates in 83%, sinusitis in 75%) and skin involvement (67%) were the most frequent clinical findings of the 47 cEGPA cases that were reviewed until May 2011. This review of cEGPA cases also reveals the presence of cardiac involvement in 45% of patients (cardiomyopathy, 34%; pericarditis, 26%); gastrointestinal involvement in 47%, peripheral neuropathy (mononeuritis multiplex) in 40%, arthralgia in 27%, myalgia in 22% and kidney disease in 13% of patients, respectively.^{6 7}

The studies differ in mortality rates. While Zwerina reported an 18% mortality rate for cEGPA patients, Gendelman reported it as 0%. The main cause of death was related to the underlying disease, the majority of cases having cardiac involvement.^{6 7}

Petechia and purpura are the most frequent cutaneous manifestations, but ulcerative and necrotic lesions may be seen as well.¹¹

Manifestations may vary between children and adults. More frequent renal involvement, myalgia and peripheral neuropathy were reported more in adults than in the cEGPA cases. Besides, cEGPA patients are more likely to develop cardiorespiratory manifestations with a more severe disease course. Asthma and arthralgia rates have been similar in children and adults.^{2 6 7}

Histological characteristics of the vasculitis include extravascular eosinophils, granuloma formation, and necrotising changes in the small and medium-sized vessels.⁶

Peripheral blood eosinophilia over 10%, increased IgE levels with transient pulmonary infiltrates on chest CT and reduced diffusing capacity of the lung, are associated with EGPA. Echocardiography is required to detect cardiac involvement.¹²

DVT was a noteworthy and interesting manifestation in our case. Venous thromboembolism is a well-defined entity of AAV in adults, but there are only limited case reports in cEGPA. Eosinophils are believed to contribute to coagulation by direct damage to the endothelial cells with subsequent exposure of the underlying tissues of the heart and vessels.^{13 14}

The thrombocytopenia in our patient was thought to be related to previously administered cefazolin treatment due to cutaneous anthrax, however, this was not confirmed. There are several case reports that have encountered this association.¹⁵ Unfortunately, we could not analyse the serum of the patient for presence of drug-dependent platelet antibodies to cefazolin. As soon as we had ceased cefazolin treatment, the platelet level improved to normal.

High-dose early systemic glucocorticoid therapy is the mainstay of treatment. According to the severity of disease, additional immunosuppressive treatment may be required.^{6 7} Kidney involvement, nephrotic range proteinuria, cardiomyopathy, neurological and gastrointestinal involvement represent severe disease and necessitate additional cyclophosphamide therapy.¹⁶

In our case, cutaneous anthrax had initially been suspected in the differential diagnosis of the lesions. However, though its incidence has decreased over the years, anthrax is still a serious endemic zoonosis in the eastern part of Turkey. Between 1990 and 2006, 6730 anthrax cases were seen in Turkey and 13.4% of the reported cases in 2009 were from the Kars province—where our patient lived.¹⁷

The literature analysis of cEGPA is considerably limited, as the rarity of the disease has resulted in scant reporting. With this case report, we aimed to increase the number of published cEGPA reports, thus making clinicians more familiar with the different presentations of the disease.

Learning points

- ▶ Lack of awareness of eosinophilic granulomatosis with polyangiitis (EGPA) among paediatricians as a consequence of limited childhood cases, results in diagnostic delay.
- ▶ Coexistence of vasculitic lesions and eosinophilia, associated with a prior history of asthma, should lead to the consideration of EGPA in the differential diagnosis.
- ▶ Skin involvement of EGPA can be misdiagnosed as infection, because of its diverse presentation.
- ▶ Clinicians should be aware of the signs and symptoms of deep vein thrombosis in a patient diagnosed with any type of vasculitis.

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Contributors SS, AA, KB and OK participated in the management of the patient, obtained clinical data, reviewed the literature and drafted the manuscript. OK was the principal clinician involved in the clinical management of the case, helped to draft the manuscript and critically revised the final manuscript. All the authors have read and given final approval to the manuscript submitted.

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