Single Case

Eosinophilic Granulomatosis with Polyangiitis Manifesting as Recurrent Nasal Polyps and Hemorrhagic Necrotic Bullae: A Rare Disease Successfully Treated with Azathioprine

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Keywords

Eosinophilic granulomatosis with polyangiitis · Antineutrophil cytoplasmic antibody-associated vasculitis · Azathioprine

Abstract

Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare multisystemic vasculitis which was previously called Churg-Strauss syndrome or allergic granulomatosis. It has an unknown pathogenesis, possibly autoimmune in nature. As it has a low incidence, there is only scant published literature. This case report is valuable to dermatologists, since skin involvement is one of the most common features of the vasculitic phase. This report represents one of the possible presentations of EGPA according to the antineutrophil cytoplasmic antibody status – which in our case was negative, with a low prognostic Five-Factor Score – that was successfully treated with oral steroids and azathioprine as a steroid-sparing agent. Our objective was to add a case report to the scarce existing literature in order to learn more about therapeutic options for EGPA. This case report demonstrates that oral steroids, as induction treatment, and

azathioprine, as maintenance treatment, are effective in elderly patients with EGPA without involvement of any other organs. Nevertheless, additional studies are necessary to achieve appropriate management.

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) was initially described in 1951 by Dr. Churg and Dr. Strauss as a disease composed of necrotizing vasculitis of many organs, as well as eosinophilic and granulomatous infiltration accompanied by asthma. Later, it was named Churg-Strauss syndrome after them [1]. Recently, the name has been changed to EGPA [2]. EGPA is classified under antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and has the lowest incidence rate [2, 3]. It can affect any organ with a high percentage of skin involvement and great variation in clinical manifestations [4]. It is a lethal disease and should be treated with systemic steroids and immunosuppressant drugs if it has a poor prognosis [5].

Case Report

A 72-year-old male was admitted to the hospital due to chronic rhinosinusitis and recurrent nasal polyps. Additionally, numerous hemorrhagic bullae, palpable purpura, and necrotic maculae on the face and upper and lower limbs were found, as well as oral ulcers (Fig. 1). Red skin lesions on his face had appeared during the last two outbreaks of nasal polyps too. These lesions had disappeared spontaneously after treatment of the nasal polyps by surgery and steroid nasal spray treatment. Furthermore, late-onset treatment-refractory asthma had recently been diagnosed. Moreover, he complained of numbness in his left leg and weight loss of 5 kg in the previous 2 weeks. He denied fever, headache, abdominal pain, diarrhea, hematuria, and arthralgia.

A biopsy of the nasal mucosa revealed eosinophilic infiltration. Further, a skin biopsy demonstrated perivascular eosinophilic infiltrate and necrotizing vasculitis, as well as a granulomatous reaction (Fig. 2). Direct immunofluorescence showed slight deposition of complement component C3 in blood vessels. Laboratory studies demonstrated leukocytosis ($20.6 \times 10^9/L$) with distinct eosinophilia (4,280 eosinophils/ μL , 59% of the total leukocyte count), a high erythrocyte sedimentation rate (52 mm in the first hour), elevated immunoglobulin E (568 kU/L), and a slightly elevated antinuclear antibody level (1:320 titer). The other blood tests, p-ANCA, c-ANCA, ENA titer, rheumatoid factor, and hepatitis serology, were negative.

Subsequently, EGPA pursuant to the American College of Rheumatology (ACR) 1990 criteria was diagnosed. A chest X-ray and lung function tests, electrocardiography, transthoracic echocardiography (echo), and a stool culture were normal. After ruling out the involvement of other organs, 100 mg per day of oral methylprednisolone (1.5 mg/kg/day) was administered, which was gradually tapered afterwards. Upon observing clinical improvements under methylprednisolone, oral azathioprine at 50 mg daily was administered as an immunosuppressive agent. The dosage was later increased to 150 mg daily. Seven weeks later, the patient

showed up in our clinic with complete clinical and laboratory remission (Fig. 3). By then, he was taking methylprednisolone 20 mg daily and azathioprine 150 mg daily (2 mg/kg).

Discussion

EGPA is a small- to medium-sized vessel-necrotizing vasculitis within multiple organs characterized by markedly increased blood and tissue eosinophils and a late onset of severe allergic rhinitis or asthma [2, 6]. EGPA is the scarcest type of AAV, which also includes microscopic polyangiitis and granulomatosis with polyangiitis [2, 7]. These other AAV, as well as hypereosinophilic syndrome, are important differential diagnoses [4, 7]. The annual incidence of EGPA differs from country to country, ranging approximately from 0.5 to 3.7 cases per million [7–10]. Most patients are middle-aged, and there is no obvious gender predominance [7].

EGPA has three clear phases as the disease progresses [8]. These phases can occur in no particular order. The prodromal allergic phase mainly consists of asthma, nasal polyps, and allergic rhinitis [8]. The hypereosinophilic phase presents as blood and tissue eosinophilia. One of the characteristic features of EGPA here are Löffler infiltrates [8]. The vasculitic phase is usually accompanied by constitutional symptoms [8]. Skin lesions occur in 40–70% of patients and can manifest as palpable purpura, nodules, urticaria, livedo racemosa, or vesicles with necrosis [11]. Our patient presented with hemorrhagic bullae and necrosis on the extremities and had a history of late-onset asthma and recurrent nasal polyps.

In addition, increased inflammatory parameters, blood eosinophilia, anemia, and high immunoglobulin E (especially during the active vascular phase) are recognized as laboratory findings [4]. ANCA (usually p-ANCA antimyeloperoxidase) has been found in 40–60% of cases [8]. Therefore, the presence or absence of ANCA may play a major role in the clinical presentation and treatment of EGPA, which divides patients into two subgroups [12]. The ANCA-positive phenotype has a high risk of renal involvement, whereas the ANCA-negative phenotype has a high risk of cardiac involvement, which we could exclude in our patient [12].

In 1990, 6 diagnostic criteria for EGPA were determined by the ACR, and 4 of these 6 criteria need to be fulfilled to establish the diagnosis with 85% sensitivity and 99.7% specificity (Table 1). These criteria include asthma, blood eosinophilia greater than 10%, extravascular eosinophilia, neuropathy, migratory pulmonary infiltrates, and paranasal sinus abnormality [13]. A new study published in 2017 showed a decline in sensitivity to 57%, but specificity remained high at 99.8%. Also, this study showed an increase in the sensitivity of ACR criteria when ANCA was positive [14]. Our case fulfilled 5 ACR criteria of the 6, with negative ANCA.

In 2011, a revised Five-Factor Score (FFS) was defined to predict the prognosis for each patient separately and to select the appropriate therapy accordingly to avoid overtreatment (Table 2) [5]. This revised FFS consists of age above 65 years, cardiac involvement, gastrointestinal involvement, renal insufficiency (serum creatinine ≥ 1.5 mg/dL), and absence of ENT symptoms [5]. The first 4 factors have a poor prognosis, and each of them adds 1 point to the score [5]. The presence of ENT symptoms has a good prognosis, whereas their absence has a poor prognostic value and also adds 1 point to the score [5]. Cardiac involvement is the leading cause of death [5]. A 5-year mortality rate of 9, 21, and 40% has been expected for scores of 0, 1, and 2 or more, respectively [5].

Patients with a score of 0 require only steroids as first-line treatment. However, as patients with an FFS of 1 or more have a higher relapse rate, an additional immunosuppressant agent should be prescribed as first-line treatment (azathioprine, cyclophosphamide, and methotrexate) [5, 6, 15]. Alternatively, rituximab, mycophenolate mofetil, plasmapheresis, intravenous immunoglobulin, and mepolizumab (anti-interleukin-5 monoclonal antibody; off-label use) can be used as second-line therapy [6].

Conclusions

In this case report, the patient had an FFS of 1 with ENT symptoms, which is a good prognostic parameter, without cardiac, renal, or visceral involvement. Therefore, we started with an oral steroid for remission induction, which was rapidly achieved, as well as azathioprine as a steroid-sparing agent for maintenance treatment. Our plan is to continue steroid tapering gradually to the minimal effective dose. Simultaneously, we will continue the treatment with daily azathioprine (2 mg/kg/day) for approximately 18–24 months as steroid-sparing therapy for maintenance treatment to avoid relapses and allow glucocorticoid tapering.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.A. and S.W.S. both contributed to writing of the manuscript. Both authors critically revised the manuscript and gave their final approval before submission.

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Fig. 1. **a–c** Hemorrhagic bullae and palpable purpura on both the lower extremities and the sole of the foot. **d** Necrotic lesions on the hands.

Fig. 2. Necrotizing vasculitis with massive eosinophilic infiltration and a granulomatous reaction.

Fig. 3. a–c Remission of the clinical manifestations after 7 weeks of treatment.

Table 1. American College of Rheumatology 1990 criteria for the classification of eosinophilic granulomatosis with polyangiitis

Asthma
Blood eosinophilia greater than 10%
Extravascular eosinophilia
Neuropathy
Migratory or transitory pulmonary infiltrates
Paranasal sinus abnormality

Table 2. Revised Five-Factor Score

Age above 65 years
Cardiac involvement
Gastrointestinal involvement
Renal insufficiency (serum creatinine ≥ 1.5 mg/dL)
Absence of ENT symptoms