Case Report

Negative anti-neutrophil cytoplasmic antibodies and eosinophilic granulomatosis with polyangiitis accompanied by cough variant asthma: a case report

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Abstract: Eosinophilic granulomatosis with polyangiitis (EGPA), formerly called Churg-Strauss syndrome, is a rare chronic necrotizing eosinophilic granulomatous inflammatory disease characterized by eosinophil-rich granulomatous inflammation and small- to medium-size vessel vasculitis associated with bronchial asthma and eosinophilia, which is positive for anti-neutrophil cytoplasmic antibody (ANCA) in approximately 50–70% of cases. We report a case of a 23-year-old woman was admitted to our hospital because of a of small vesicles on both lower limbs and a 4-month history of small scattered skin rash with pruritus V6 on both lower limbs four-month history of scattered skin rash with pruritus. Laboratory data from peripheral blood revealed leukocytosis, eosinophilia, thrombocytosis, hyperfibrinolysis, and mild renal injury. Her ANCA was negative, and the skin pathological examination showed granuloma lesions with eosinophils, while elevated eosinophils were also found in the bone marrow. EGPA was diagnosed. On the other hand, the patient had 2-year-long rhinosinusitis, 9-month-long nephrotic syndrome, and 1-month-long dry cough, which might be a type of asthma. With steroid therapy followed by systemic immunomodulatory therapy, the patient's symptoms were relieved. Our case report and literature review highlight the importance of recognizing cough variant asthma as an initial presenting symptom of EGPA, providing an opportunity for early diagnosis and treatment to reduce the risk of further disease progression and morbidity.

Keywords: Eosinophilic granulomatosis with polyangiitis (EGPA); cough variant asthma; anti-neutrophil cytoplasm antibody (ANCA); case report; herpes simplex virus (HSV)

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Introduction

According to the 2012 Chapel Hill Consensus Conference, eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome, is defined as eosinophil-rich necrotizing vasculitis and extravascular granuloma formation of small-to-medium size blood vessels (1). However, the exact pathogenesis is still unknown. It is generally agreed that EGPA is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), which is positive for ANCA in approximately 50–70% of cases (2,3), especially in patients with glomerulonephritis (4). The time from disease activity to diagnosis was shorter in ANCA positive patients than in ANCA negative patients, and the inflammatory response was more severe. EGPA

is associated with asthma, eosinophilia, allergic rhinitis, eosinophil-rich vasculitis, polyneuropathy, purpura, gastrointestinal ulcer, cerebral infarction, and myocardial infarction (5). Cough variant asthma refers to chronic cough as the only or the main clinical manifestations of a special type of asthma, is the first cause of chronic cough in adults. Therefore, EGPA is difficult to diagnose due to the diversity of its manifestations. Up to now, the diagnosis is still based on classification criteria proposed by the American College of Rheumatology in 1990 (6).

Here, we describe a case of EGPA that presented with cough variant asthma and negative ANCA. A literature review of similar cases was completed and is summarized. We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2236).

Case presentation

A 23-year-old Chinese female with a history of 4-month purplish red itching rash all over the body without any clear causes was admitted to the rheumatology department of our hospital. She took part in the routine vaccination schedule, as she was growing up. She did not report any history of surgical operations or injury or allergies to foods or medicines. She had a history of nephrotic syndrome for 9 months, and chronic rhinosinusitis for the last 2 years. She was medically maintained by another hospital on ciclosporin, methylprednisolone acetate, and leflunomide. Rashes, itching, and edema of the face, double eyelids, and two lower limbs had appeared 4 months previously. One month ago, she reported more serious itching rashes, including an increasing number of vesicles on both lower extremities, with a dry cough. Recently there was no noticeable improvement of her condition, even though she had been taking medicines continuously.

Physical examination on admission revealed scattered red rashes all over her skin and vesicles on her two lower limbs. Her blood pressure was 89/67 mmHg, her pulse rate was 134/min, and her body temperature was 37.0 ℃. She had a dry cough. The patient did not have a swollen throat or tonsils. Her respiratory sounds were normal, and no heart murmur was heard. Her abdomen was soft, without tenderness or rebound tenderness, and her liver and spleen were impalpable. Her muscle response was normal. No joint swelling and pain were present. However, she had mild pitting edema in both extremities. The neurological findings did not reveal any obvious sensory or movement disorder.

On admission, the laboratory findings revealed an elevated white blood cell count (14.10×10^9/L) and neutrophil count (9.10×10^9/L), an elevated eosinophil proportion (18.5%) and count (2.60×10^9/L), an elevated platelet (Plt) count (505×10^9/L), and there were no atypical lymphocytes. The erythrocyte sedimentation rate (ESR) was normal (1 mm/h). Her serum lactate dehydrogenase (LDH) (548.0 U/L), creatine kinase (CK) (234.0 U/L), CK-MB (165.0 U/L), and C-reactive protein (CRP) (15.39 mg/L) were increased, while the serum total protein (TP) (56.9 g/L) and albumin (Alb) (31.8 g/L) were decreased.

In addition, her plasma D-dimer (DD) (2.87 mg/L) and fibrin(ogen) degradation product (FgDP) (5.22 mg/L) were higher, while her activated partial thromboplastin time (aPTT) was 27.4 s close to the lower reference limit. The lupus anticoagulant ratio (1.09) was within reference limits. Positive serum anti-herpes simplex virus (HSV) type 1+2 immunoglobulin (IgG) and anti-rubella virus (RV) IgG were 14.46 and 15.10 AU/mL, respectively. Various auto-antibodies including ANCA were negative.

Peripheral blood lymphocyte subsets with Flow Cytometer (Beckman Coulter Navios, Sydney, Australia) showed elevated T cells, $CD4^+$ T cells, an elevated $CD4^+$ T/$CD8^+$ T ratio, a lower $CD8^+$ T cells count, decreased B cells, decreased natural killer (NK) cells and decreased natural killer-like T cells (NKT) in terms of both percentage and count. The $CD4^+$ T count was close to the low reference limit. Her regulatory T cells (Treg) was within the reference range. Peripheral cytokines showed elevated interleukin (IL)-6, IL-10, and interferon γ (γ-IFN), and decreased tumor necrosis factor α (TNF-α). Serum complement tests showed decreased complement 1q (C1q) and complement 3 (C3) (See *Table 1*).

On admission, bone marrow cytomorphology revealed three cell line proliferation and elevated eosinophils (see *Figure 1*). Her skin biopsy specimens also showed a lot of eosinophils (see *Figure 2*).

Computed tomography (CT) scans showed: bilateral ethmoid sinusitis at admission, multiple small patchy and high-density nodules in the lungs (see *Figure 3*), multiple small lymph node enlargement in the mediastinum and bilateral axillary fossa, and some pericardial effusion.

Based on findings of eosinophil-infiltrating granulomatous vasculitis of the skin accompanied by notable peripheral blood eosinophilia, sinusitis, intractable cough, and pulmonary nodules on radiographic evaluation, she met the American College of Rheumatology criteria (6)

Table 1 Laboratory findings on admission

Project	Results
Lymphocyte subsets	
T%	89.60%
$CD4^+$ T%	56.93%
$CD8^+$ T%	27.13%
CD4/CD8	2.10
B%	5.97%
NK%	2.37%
NKT%	2.13%
Regulatory T cell (Treg) %	2.25%
T count	1,523 cells/μL
$CD4^+$ count	968 cells/μL
$CD8^+$ T count	461 cells/μL
B count	101 cells/μL
NK count	40 cells/μL
NKT count	36 cells/μL
Treg count	38 cells/μL
Plasma cytokines	
IL-2	1.96 pg/mL
IL-4	2.03 pg/mL
Il-6	15.26 pg/mL
IL-10	12.93 pg/mL
IL-17A	1.41 pg/mL
IFN-γ	2.17 pg/mL
TNF-α	1.12 pg/mL
Serum immunoglobulin and complements	
IgA	2.32 g/L
IgG	9.94 g/L
IgM	0.86 g/L
Factor B	221.2 g/L
C1q	118 mg/L
C3	0.80 g/L
C4	0.13 g/L

T, T lymphocyte; B, B lymphocyte; NK, natural killer; NKT, NK-like T cell; Treg, regulatory T lymphocyte; IL, interleukin; IFN-γ, interferon γ; TNF-α, tumor necrosis factor α; Ig, immunoglobulin; C, complement.

for EGPA. She was diagnosed with EGPA with cough variant asthma. With steroid therapy (methylprednisolone sodium succinate, 40 mg, ivgtt, ONCE) followed by systemic immunomodulatory therapy, the patient's peripheral blood eosinophil proportion and count from the first 18.5% (2.60×10^9/L) to 33.9% (9.30×10^9/L), 24.3% (3.87×10^9/L), 0.8% (0.08×10^9/L) one week interval, her symptoms obviously improved, although her asthma was improved only slightly. One month later, she was discharged with a prescription of a regular steroid and cyclosporine A.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Our patient had a cough variant asthma phenotype with peripheral eosinophilia and elevated eosinophils in bone marrow besides eosinophil-infiltrated skin lesions, and she also had a history of nephrotic syndrome for 9 months and chronic rhinosinusitis for 2 years.

The patient was a 23-year-old woman. Patients have typical age demographics for this disease, with few cases occurring during childhood and in those over 70 years (7). We also noticed that female adults are more likely to get EGPA based on case reports published in recent years (8-14), while about 38% of children with EGPA are female (15).

Some studies suggest that cutaneous manifestations are present in 40% to 81% of EGPA patients (16). It has been reported that the most common presenting features of EGPA in children are: pulmonary (69%), skin (61–64%), gastrointestinal (46%), and cardiac manifestations (46%); paranasal sinus abnormality (38%); arthritis/arthralgia (38%); neurological involvement (15%); and even vasculitis (15,17-19). In another study of children, the respiratory system was found to be mostly involved, mainly the upper airways (85%), while other frequently involved organ systems were the skin (71%), digestive tract (64%), and heart (57%) (20).

However, regardless of whether children or adult patients are affected, some manifestations are rare, with some case

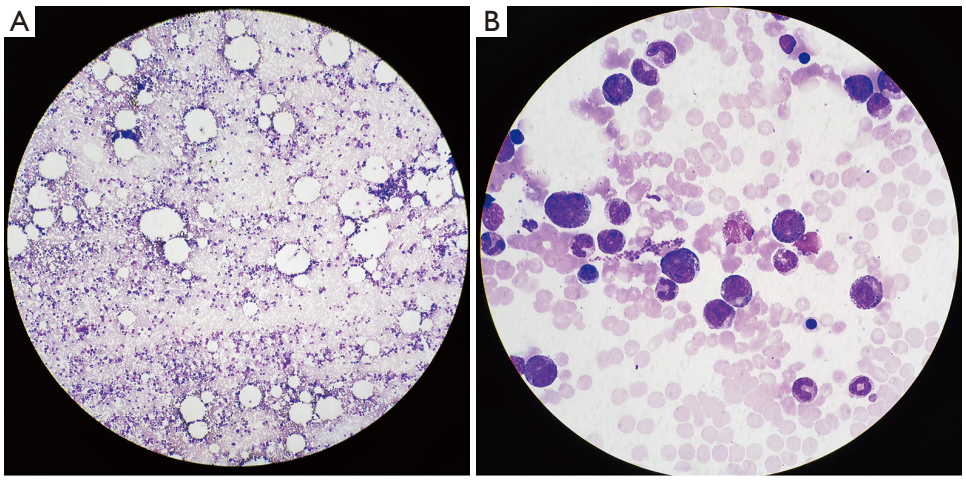

Figure 1 Bone marrow cytomorphology showing elevated eosinophils at different stages [Wright and Giemsa staining, (A) ×100 and (B) ×1,000].

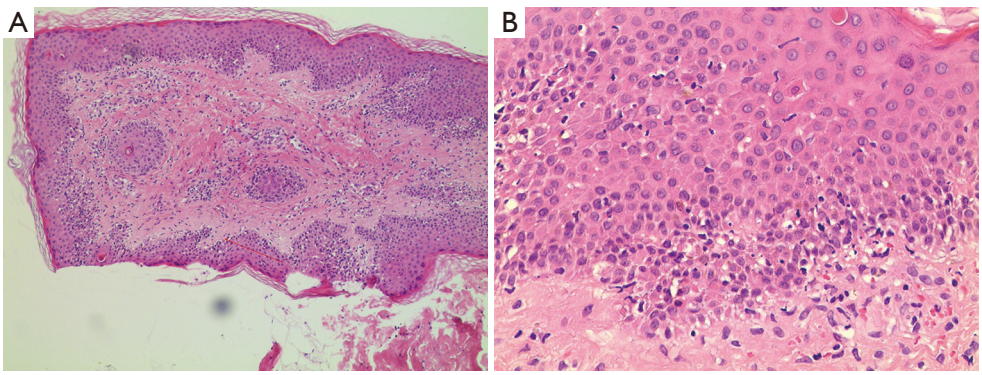

Figure 2 Skin biopsy showing tissue eosinophilia [hematoxylin and eosin staining, (A) ×100 and (B) ×400].

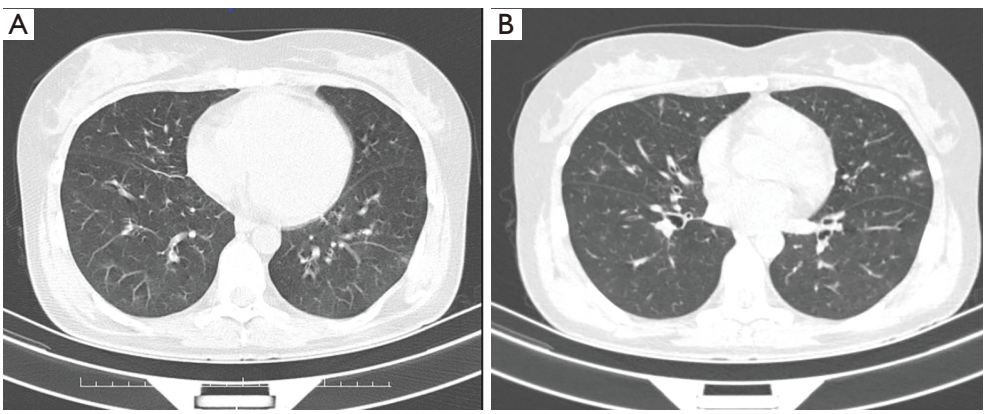

Figure 3 Two different levels of chest computed tomography scanning on admission for obvious diminution of small multiple small patchy and high-density nodules.

reports showing the occurrence of vulvar granuloma, neuropathic ulcer, and corneal melt in EGPA (21-23).

In adult patients, additional respiratory manifestations are also very common. A study involving 62 people showed that peripheral neuropathy was noted in 55% and cardiac manifestations in 41% of cases. About 54% (38/71) were ANCA-positive, with a perinuclear-labeling pattern and/or anti-MPO specificity. The central nervous system (CNS) was involved in 86% (76 cases), 52% (46 cases) had ischemic cerebrovascular lesions, 24% (21 cases) had intracerebral hemorrhage and/or subarachnoid hemorrhage, 33% (28 cases) had loss of visual acuity (15 with optic neuritis, 9 with central retinal artery occlusion, and 4 with cortical blindness), and 21% (18 cases) had cranial nerve palsies, with 25 patients having more than one clinical CNS manifestation (24).

Asthma is one of the respiratory symptoms of EGPA. Severe/uncontrolled asthma was observed in 42.7% of patients at diagnosis (25). There are several types of asthma: allergic asthma mediated by IgE; nonallergic asthma often triggered by viral upper respiratory tract infections or no apparent cause; occupational asthma; aspirin-exacerbated respiratory disease; potentially fatal, exercise-induced asthma; and cough variant asthma. The latter type of asthma is the differential diagnosis of chronic cough. Our case was also a patient with cough variant asthma. Patients with cough variant asthma usually have a nonproductive cough, which only responds to treatment for asthma, but not to treatment with antibiotics, expectorants, mucolytics, antitussives, or beta-adrenergic agonists, and not to treatments for acid reflux and rhinosinusitis (26).

ANCA is one of kind of anti-neutrophil cytoplasmic antibodies, which is negative in most EGPA patients (15). In all, 40–70% of cases are ANCA negative. ANCA positive cases are usually accompanied by elevated eosinophils, which might mediate organ damage (27). Our patient was ANCA negative and had high levels of eosinophils in the bone marrow and peripheral blood accompanying her renal, heart, skin, nasal, and lung injuries. The possible mechanism of organ injury is eosinophil-associated vascular occlusion leading to ischemia and eosinophil-associated tissue damage (28).

The exact pathogenesis of EGPA is not fully understood but probably results from the mutual effects of T and B cells besides eosinophils (29). The present case showed a higher percentage of T cells, $CD4^+$ T cells, and $CD4^+$ T/$CD8^+$ T ratio; a lower percentage of $CD8^+$ T cells, B cells, NK cells, and NKT; and a lower count of $CD8^+$ T cells, B cells, NK cells, and NKT cells. Her Treg were within the reference range. These results suggest that this patient has higher cellular immunity, lower humoral immunity, and lower natural killer ability. Among cytokines produced by various immune cells, proinflammatoryIL-6, IFN-γ and TNF-α and anti-inflammatory IL-10 were higher while the others, such as proinflammatory IL-2 and IL-17A and anti-inflammatory IL-4, were in the reference range. Serum C1q and C3 level were lower, which might have resulted from immune exhaustion of a high autoimmune response. All of the above suggests that both the imbalance of the immune system and the inflammatory response play an important role in EGPA pathogenesis. Another proof of this is that the recently developed monoclonal antibodies targeting B cells and eosinophilopoietic cytokines such as IL-5, which is the major driver of eosinophilic inflammation and related high disease activity in EGPA, are emerging as valid alternatives to conventional immunosuppressive therapies (29,30).

The present case revealed positive anti-HSV type 1+2 IgG. HSV may cause tissue necrosis in EGPA. Shintaku *et al.* found that a 59-year-old woman with EGPA had HSV type 1 infection. Also, disseminated eosinophils and HSV were detected in her pancreatic tissue (31). We also found that this patient had positive anti-RV IgG. Whether RV plays role in EGPA has not been reported in the available literature. It is disappointing that we did not detect HSV and RV in her tissue.

The genetic basis of EGPA may contribute to EGPA. A previous study found that genes were mutated in four affected siblings suggesting genetic involvement in susceptibility to EGPA (32). This study found three EGPA cases in four members of a Saudi family affected by asthma. Another report from Japan relates to a sister and brother with EGPA (33). The HLA-DRB1 (34), HLA-DRB4 (35), and IL-10genes have been reported to play a role in EGPA pathogenesis (36).

Here we reported an EGPA case with a rare type of cough variant asthma. High-dose corticosteroids and immunomodulatory therapy were effective for EGPA. We highlighted cough variant asthma, which is easy to overlook as an initial presenting symptom of EGPA. The presence of eosinophilia and dry cough provided an opportunity for early diagnosis and treatment to reduce the risk of further disease progression and morbidity. More data are needed in relation to EGPA.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2236). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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