RHEUMATOLOGY AND IMMUNOLOGY RESEARCH

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Severe asthma with viral infection can develop into eosinophilic granulomatosis with polyangiitis

Changxing Ou[1,#], Jianjuan Ma[1,2,#], Ning Lai[1,#], You Li[1], Jiaxing Xie[1], Xueyan Zhang[3,*], Qingling Zhang[1,*]

[1]*Pulmonary and Critical Care Medicine, Guangzhou Institute of Respiratory Health, National Clinical Research Center for Respiratory Disease, National Center for Respiratory Medicine, State Key Laboratory of Respiratory Diseases, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong Province, China.*
[2]*Department of Pediatric Hematology, Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou Province, China*
[3]*School of Basic Medical Sciences, The Second Affiliated Hospital, State Key Laboratory of Respiratory Disease, Guangdong Provincial Key Laboratory of Allergy & Clinical Immunology, Guangzhou Medical University, Guangzhou, Guangdong Province, China*

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Abstract

Asthma is common in eosinophilic granulomatosis with polyangiitis (EGPA), and the annual incidence of EGPA in patients with asthma is much higher compared with the general population, and the trigger factor for this is unknown. We report a case of a 19-year-old male with a background of severe asthma who presented with eosinophilic lung infiltration after viral infection, which progressed to clinical EGPA. The diagnosis of EGPA was supported by an initial clinical presentation of recurrent cough and wheezing accompanied by a red rash, followed by peripheral eosinophilia, a high eosinophil percentage in bronchoalveolar lavage fluid (BALF), and migratory pulmonary eosinophilic infiltrates. Lung biopsy showed blood vessels with extravascular eosinophils. The patient responded well to high-dose glucocorticoids and cyclophosphamide, and symptoms and biochemical markers improved. Our literature review identified few reports on the triggers of EGPA, which highlights that viral infection may be a risk factor for asthma that progresses to EGPA.

Keywords

severe asthma • eosinophilic granulomatosis with polyangiitis • clinical presentation • triggers • viral infection

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, previously known as Churg-Strauss syndrome, is characterized by peripheral and tissue eosinophilia.[1–3]

Triggering factors for the progression of asthma to EGPA are unknown. We describe a patient with severe asthma with pulmonary eosinophil infiltration and viral infection during the course of the disease. After antibiotic treatment, the patient developed clinical EGPA manifestations and presented with signs and symptoms suggestive of pulmonary and skin disorders. To our knowledge, this is the first case of asthma with influenza progressing to EGPA.

Case Presentation

A 19-year-old male with a history of rhinitis was admitted to the medical admissions unit at a district general hospital with a 1-year history of recurrent cough and fever and lung infiltrates for over 1 month. The patient received treatment with

Address for correspondence:

*Qingling Zhang, Department of Respiratory and Critical Care Medicine, State Key Laboratory of Respiratory Diseases, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong Province, China. E-mail: zqling68@hotmail.com

*Xueyan Zhang, School of Basic Medical Sciences, The Second Affiliated Hospital, State Key Laboratory of Respiratory Disease, Guangdong Provincial Key Laboratory of Allergy & Clinical Immunology, Guangzhou Medical University, Guangdong Province, China. E-mail: zhangxy@gzhmu.edu.cn

#Changxing Ou, Jianjuan Ma and Ning Lai have contributed equally to this work.

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inhaled beclomethasone dipropionate/formoterol (FOSTER) (two puffs twice/day) and took occasional oral corticosteroids and antibiotics, but asthma was not well-controlled. The patient attended our hospital on July 27th, 2019. He had a significantly elevated eosinophil percentage in peripheral blood, induced sputum, and bronchoalveolar lavage fluid (BALF) with obvious allergic airway inflammation (Table 1). Pulmonary function showed a forced expiratory volume in 1 s (FEV_1) of 2.04 L, a percentage predicted FEV_1 of 51.8%, an FEV_1/forced vital capacity of 75.26%, moderate-to-severe mixed ventilatory dysfunction, and a positive bronchodilator test (Table 1). The urinalysis and urinary sediment results showed that a trace of urinary occult blood, 11/μl bacteria, but other indexes, such as urinary protein, were in the normal range. Lung computed tomography (CT) showed paranasal sinus abnormality, inflammation in both lungs, and thickening of the bronchus wall (Figure 1A). After 5 days of treatment with FOSTER, tiotropium, montelukast, ketotifen, theophylline, mometasone furoate nasal spray (Nasonex), and azelastine, cough improved, and the patient was discharged.

The patient had a fever of up to 40°C on August 6th, 2019, and a cough with yellow phlegm, chills, general pains, sweats, and wheezing occurred. The eosinophil count in peripheral blood was normal, but the patient was positive for influenza viruse A Flu and H1N1 RNA. CT showed inflammation in both lungs, with a high possibility of bronchopneumonia and thickening of the bronchus wall (Figure 1B). The patient was given moxifloxacin with antibiotics infection treatment. After treatment in hospital with antibiotics, FOSTER, tiotropium, montelukast, ketotifen, theophylline, and nebulization, the patient's body temperature returned to normal, and he was discharged.

Table1: Relevant significant results in table format

Relevant Investigations	Results
Full blood count	Eosinophils 11.3%, 830 cells/μL
Induced sputum	Neu 53.5%, Mac 0.5%, Eos 46%, Lym 0%
FeNO	131 ppb
Total IgE	529 kU/l
Specific IgE	House dust mites 0.60, Fungus:0.07
ANA/ANCA	Negative
Spirometry test	Moderate to severe mixed ventilatory dysfunction, bronchodilator test positive

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; IgE, immunoglobulin E.

The patient was followed up at the outpatient clinic on September 5th, 2019. A red skin rash appeared on his right shoulder and back, which gradually enlarged. The color of the rash faded when pressed. CT presented further lesions in the right lung and left upper lobe, the lower lingular segment of the left upper lobe, and the anterior and medial basal segments of the left lower lobe (Figure 1C). The percentage of eosinophils in peripheral blood, induced sputum, and BALF significantly increased. Next-generation sequencing did not reveal any antigens in BALF. ANCA was still negative in serum. No abnormality was found in urinalysis and urinary sediment results. The 24-h urinary protein was within the normal range.

Biopsy of the alveolar cavity of lower right lung tissue showed eosinophil exudation. The interstitial area was widened and showed perivasculitis with eosinophil infiltration. Staining observations of lung biopsy were as follows: Giemsa stain (GMS) (−), periodic Acid-Schiff stain (PAS) (−), antacid (−), gram stain gram's (−), antacid fluorescence (−), fungal fluorescence (−). More eosinophils infiltrated into the submucosa and the wall of small vessels of the lower right lobe mucosa (Figures 2A, 2B). Skin biopsy showed no obvious abnormality in the epidermis. Some lymphocytes infiltrated around small vessels of the dermis, and collagen fibers proliferated (Figure 2C). Biopsy of gastric mucosa showed interstitial edema and occasional eosinophilic infiltration (Figure 2D). To exclude other causes of initial eosinophilia, the patient underwent a bone marrow biopsy, which demonstrated that bone marrow was generally normal with eosinophilic infiltration (Figure 2E). Hypereosinophilia-associated mutant gene test of *BTKD FLT3*, *JAK2 V617F*, *TEL/ABL1*, *ITD FLT3*, *FGFR1*, *PDGF*-α, and *PDGFR*-β

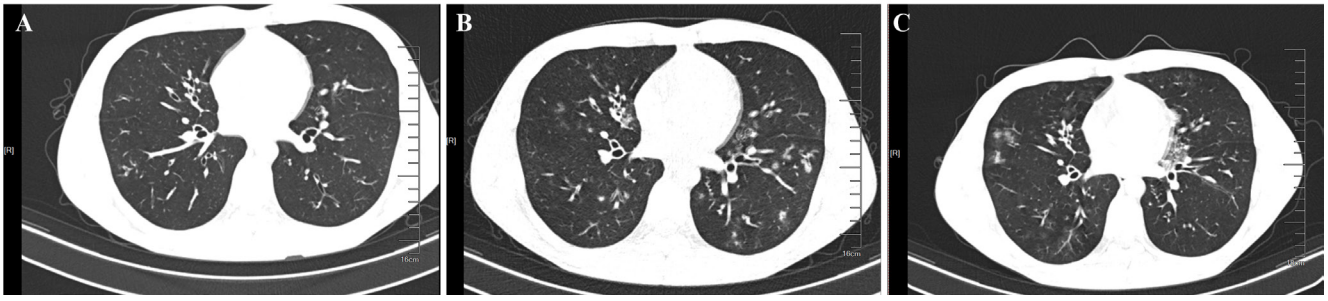

Figure 1: (A) Imaging studies of the chest, obtained during the first admission, showed: multiple inflammations of both lungs and thickening of the wall of the bronchus. (B) 1 month later, there were multiple inflammations in both lungs, with a high possibility of bronchopneumonia and thickening of the wall of the bronchus. (C) 2 months later, there were more lesions in the right lung and left upper lobe, lower lingular segment of left upper lobe and the anterior and medial basal segment of the left lower lobe than before.

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showed negative. No clinical manifestation of nervous system damage was seen on this patient during the course of the disease.

Based on 1984 Lanham criteria[4] and 1990 American College of Rheumatology (ACR) criteria,[2] a diagnosis of EGPA was established. The patient was immediately started on cyclophosphamide and a high-dose steroid regime. The patient's condition improved and the percentage of eosinophils in peripheral blood returned to normal. The patient took treatment at home and attended the outpatient department regularly. He also received treatment with benralizumab six times. Ten months after the initial diagnosis, he remains under the care of respiratory, allergy, pathology, rheumatology, and hematology teams, and his symptoms have remained under control.

Summary of the Course

The course of this patient is summarized in Figure 3, including symptoms, peripheral blood eosinophils, peak expiratory flow (PEF), CT results, and treatment.

Outcome and Follow Up

At writing, 18 months after the patient's discharge, he is still under regular review by different specialists, but his symptoms have been under control and he has not had any vasculitis flare-ups. His respiratory symptoms have significantly improved, and CT results have also improved (Figure 4).

Discussion

EGPA is a systemic necrotizing vasculitis of small- and medium-sized vessels, classified as ANCA-associated vasculitis, even though detection of ANCA is not constant. EGPA is characterized by asthma, blood eosinophilia, and extrapulmonary manifestation.[5, 6] The ACR recommends six diagnostic criteria for EGPA: asthma, extravascular eosinophilia, peripheral blood eosinophilia (>10%), paranasal sinus abnormalities, mononeuropathy/polyneuropathy, and non-fixed pulmonary infiltrates. The existence of any four or more of these criteria has a specificity of 99.7% and a sensitivity of 85%.[2] This patient met five of the six ACR criteria: asthma, eosinophilia, pulmonary infiltrates, paranasal sinus abnormality, and extravascular eosinophilia.

The respiratory system is the most frequently involved site in patients with EGPA. Many patients had refractory asthma as the first symptom, which antedated the onset of the systemic manifestations by a mean ± SD of 11.81 ± 18.18 years.[7] Asthma is usually refractory and glucocorticoid dependent in EGPA. This patient also had asthma as the first symptom, but he was accompanied by severe eosinophilic inflammation. Routine asthma treatment made his condition under control. However, his condition began to get out of control again in a very short time and was accompanied by systematic manifestations quickly. EGPA pathogenesis remains unknown, with many factors contributing to its pathophysiology. Genetic

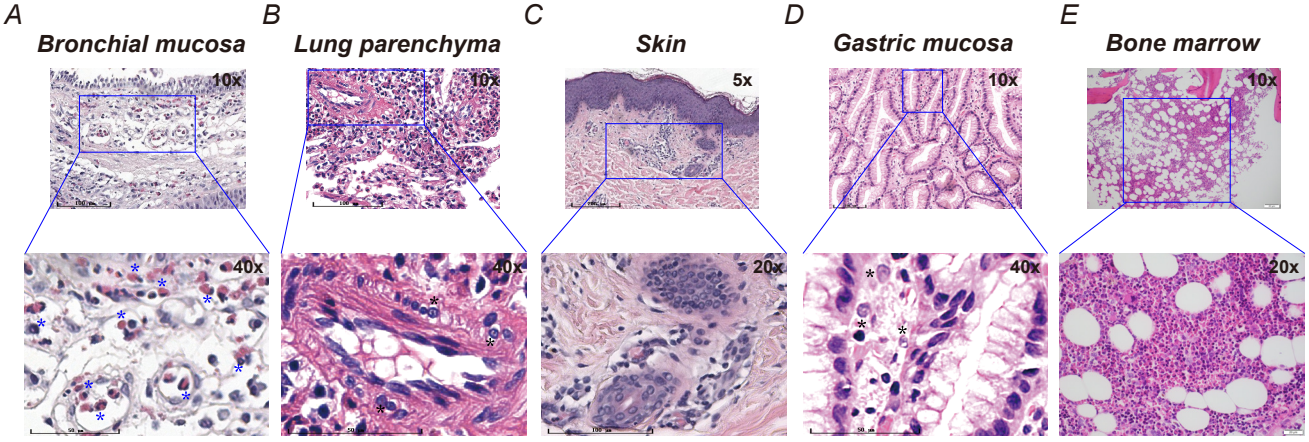

*Figure 2: HE staining for multiply organs pathological detection. (A, B) Bronchial mucosa is squamous, with focal ulceration, cellulose and eosinophil exudation on the surface, and large numbers of eosinophil infiltration under the mucus; also a large number of eosinophils were found in the lung tissue and around the walls of small blood vessels. (C) Skin biopsy: scanning shows no obvious abnormality was found in the epidermis. Some lymphocytes infiltrated around the small vessels of dermis, and collagen fibers proliferated. H and E staining. (D) Gastric mucosa biopsy: scanning shows interstitial edema and occasionally eosinophilic infiltration. (E) Bone marrow biopsy: scanning shows hyperplasia was generally normal, granulocytes, erythrocytes, and megakaryocytes were not abnormal, and eosinophils were significantly increased. *Indicated Eosinophil with blue and black color.*

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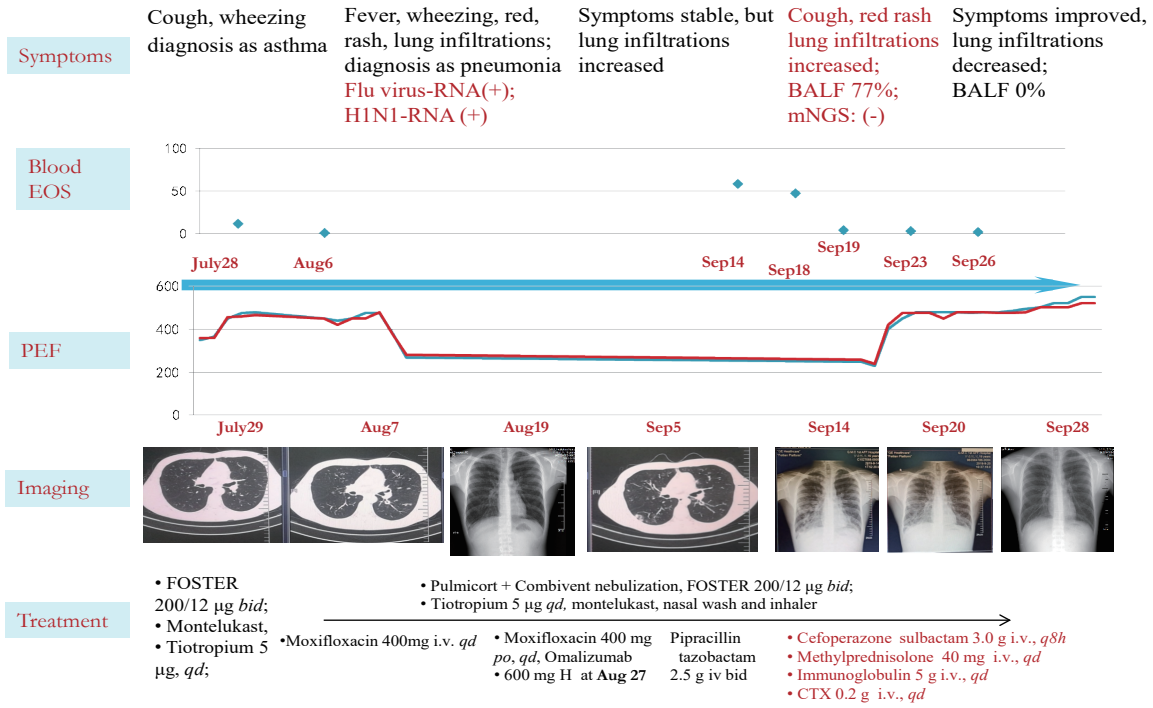

Figure 3: Symptoms, peripheral blood eosinophils, PEF, CT image, and treatment according to day of illness and day of hospitalization, July 28–Sep 28, 2019. CT, computed tomography; EOS, eosinophils; PEF, peak expiratory flow.

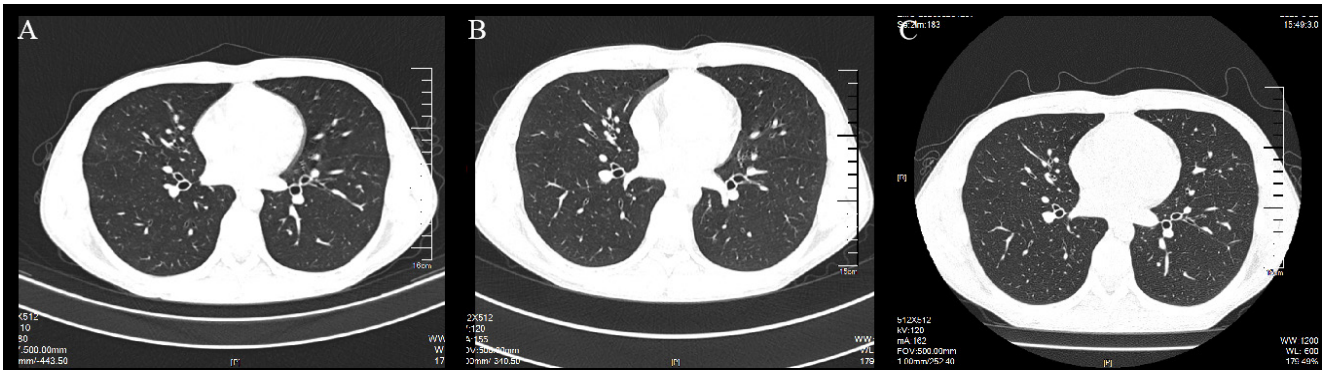

Figure 4: (A) 3 months later, the lesions in the right lung, the left lower tongue segment and the anterior inner basal segment of the left lower lung were less than those before. (B) 6 months later, a CT scan showed, a few small patches of ground-glass density were scattered in both lungs, and the inflammatory thickening of bronchial walls of both lungs was roughly the same as before. (C) A follow-up CT 10 months CT scan showed the lesions in both lungs were absorbed locally. CT: computed tomography.

predisposition and immune dysregulation seem to be implicated. Eosinophils are key players in EGPA pathogenesis with abnormal eosinophilic proliferation, impaired apoptosis, and elevated tissue toxicity attributed to eosinophil products. The presence of ANCA is another aspect of EGPA. ANCA activates neutrophils, and the activated neutrophils attack vessel walls via degranulation and the formation of neutrophil extracellular traps (NETs).[8] It is assumed that ANCA in EGPA also has a pathogenic role at such conditions.

Triggering factors of EGPA are not clear. Many environmental factors have been considered as triggers for EGPA, such as antigen inhalation (dark diesel fumes, grain dust, cereal dust, and dust), desensitization, and immunization.[9, 10] Some drugs, such as leukotriene-receptor antagonists (e.g., montelukast) and anti-immunoglobulin E (IgE) antibodies (e.g., omalizumab), are considered potential triggers, but because they are usually used when glucocorticoids are gradually reduced, their role remains unclear.[11–14] This patient's total IgE was 529 kU/L. The value for house

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dust mites was 0.60 kUA/L, and the value for fungus was 0.07 kUA/L. He did not present with any other environmental triggering factors, but he did demonstrate influenza A and H1N1 RNA. Influenza infection can cause a wide range of pathological complications. The main manifestations of pathological lung damage are pulmonary edema and extensive inflammatory exudation. During this process, a large number of neutrophils, macrophages, lymphocytes, proinflammatory factors, and chemokines are produced, which cause a cytokine storm. [15] This patient took montelukast and was positive for allergens. He was accompanied by a viral infection in the meantime. Thus, these factors if combined may lead to the development of EGPA; however, this requires clarification.

The treatment strategy should be adapted to each EGPA patient's characteristics, such as disease severity, organ involvement, prognosis, age, and comorbidities. The French Vasculitis Study Group identified five prognostic factors (FFS), each accorded 1 point, which is significantly and independently associated with higher 5-year mortality. [16] The FFS was devised to assess disease prognosis; however, using it to adapt the therapeutic regime remains debated, with international recommendations still contradictory. [17] For patients without poor prognosis factors (FFS = 0), we recommend starting treatment with glucocorticoids alone, which is effective and safe to induce and maintain remission. [18] For EGPA patients with poor prognosis factors (i.e., FFS = 1) and/or when other life-threatening manifestations are present, even those not included in the FFS (i.e., possible blindness due to eye involvement, severe alveolar hemorrhage, and/or fulminant mononeuritis multiplex), combining an immunosuppressant with glucocorticoids is recommended. [19, 20] Glucocorticoids and immunosuppressants have revolutionized the prognosis of EGPA, with the 5-year survival rate rising from 10% in the 1950s to approximately 90% currently. This patient's FFS was 1, and he had three infusions of cyclophosphamide for remission induction and an oral maintenance dose of prednisone. Therefore, his clinical symptoms improved significantly, but the patient still requires dynamic follow-up.

In conclusion, EGPA is a rare but severe systemic vasculitis that can affect every organ system. Corticosteroids are the first choice for EGPA therapy, but other immunosuppressive therapies should be considered according to disease severity. Early diagnosis and appropriate treatment can prevent morbidity and mortality. We present a case of a 19-year-old male with asthma co-existent with pneumonia who developed EGPA. Our aim with this case report was to demonstrate how severe asthma with eosinophilic lung infiltration can develop into EGPA and to highlight the possible triggering factors to enable clinicians to identify EGPA early in asthmatic populations. However, the pathogenesis is still unknown. We thus need to identify reliable biomarkers to identify the disease and manage patients.

Declarations

Ethics Approval and Consent to Participate

Ethics approval was obtained from the ethics committee for scientific research project review of the First Affiliated Hospital of Guangzhou Medical University (Ethical Review of Medical Research 2018 No. 35).

Consent to Publish

Written informed consent was obtained from the patient for publication of this case report.

Availability of Data and Materials

All data discussed in the manuscript are included within this published article.

Competing Interests

The authors have declared no conflicts of interest and are responsible for the content of this manuscript.

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Authors' Contributions

JM, NL, and CO analyzed, interpreted the patient data, performed the literature review and drafted the manuscript. JM, NL, YL, and JX were responsible for patient management. QZ and XYZ critically revised the manuscript. All authors read and approved the final manuscript.

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