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Case Report

Is it atopic asthma, chronic eosinophilic pneumonia, or eosinophilic granulomatosis with polyangiitis?

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Abstract

A 45-year-old man, used to work in a cement factory, presented to us with a history of adult-onset sub-optimally controlled asthma and was initially managed as a case of acute exacerbation of allergic asthma. However, his repeated evaluation revealed raised eosinophil count, raised serum total IgE and persistent chest infiltrates on imaging. He was provisionally managed empirically with a short course of oral steroids and advised follow-up on an out-patient basis to rule out the possibility of idiopathic eosinophilic pulmonary syndromes. The patient was then lost to follow-up, and after four years, he presented with a vasculitic presentation and was diagnosed with Eosinophilic Granulomatosis with Polyangiitis (EGPA). He improved with corticosteroids and cyclophosphamide pulse therapy. This case depicts the importance of evolving nature of EGPA wherein the eosinophilic phase of the disease can mimic other pulmonary eosinophilic diseases and vasculitic symptoms can be delayed as much as by four years.

Keywords: Atopic asthma, CSS, EGPA

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) or Chrug–Strauss syndrome (CSS) is a rare disease (worldwide incidence 10.7–14 per million people per year).[1] EGPA classically presents with severe asthma, allergic rhino-sinus disease, peripheral eosinophilia, and antineutrophilic cytoplasmic antibody (ANCA) positivity. EGPA can only be diagnosed with regular follow-up and a high index of clinical suspicion. We wish to address this case to emphasize the point that an adult-onset, poorly controlled asthma with eosinophilia even without vasculitic symptoms should be followed up regularly, and differentials other than atopic asthma should be kept at the back of mind. We also want to emphasize the adage that "not every wheeze is because of asthma."

Case Presentation

A 45-year-old gentleman, a worker in a cement factory for the past 28 years, presented to us with a history of adult-onset, controlled asthma for 5 months duration. In 2016, he had visited us with acute worsening of dry cough and shortness of breath for 5 days with a background history of 5 months duration insidious onset, progressive breathlessness associated with wheezing, and dry cough. There was no history of fever, expectoration, hemoptysis, arthralgia/polyarthritis, weight loss, allergies, or atopy in the past. His family history was not significant for asthma or any other allergic condition. He was a lifetime non-smoker and did not

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consume alcohol or recreational drugs. The patient rejected having birds, cats, or any pet at home or workplace, also no history of a basement flood or mold. On examination, there was an absence of sinus tenderness or nasal polyps. On auscultation, a bilateral wheeze was heard. The examination of other systems was unremarkable. He was managed as a case of acute exacerbation of asthma and received antibiotics, a short course of oral steroids with inhaled steroids. On discharge, he was given inhaled steroids twice daily, inhaled salbutamol PRN, and intranasal fluticasone drops, as well as advised outpatient follow-up. Since then, he has been on regular outpatient follow-up and has had moderate persistent asthma with nocturnal awakening once per week despite adequate therapy escalation, good medication adherence, good inhaler technique, and reassignment to a different workplace. There was no seasonal variations or work-time-related variation in his symptoms. During routine outpatient workup, he was found to have persistent eosinophilia (>2000/μL), persistent increased total serum IgE (500–938 IU/mL). However, because of personal issues, he was lost to the follow-up and kept taking over-the-counter medications. The major investigatory findings are shown in [Table 1].

Three years later, in the year 2019, he was hospitalized again for similar complaints. He had a very high absolute eosinophil count (3400/uL) and an elevated serum IgE (546 IU/mL) on routine laboratory workup. He exhibited a positive allergic response to multiple allergens on allergic sensitivity tests using intradermal antigens. High-resolution computed tomography (HRCT) of the thorax had multiple peri-bronchovascular tree-in-bud nodules and ground-glass opacities in both lung fields [Figures 1-4]. His aspergillus-specific IgE was negative. Even after repeated efforts to convince him, he was not willing to undergo bronchoscopy, hence, the possibility of allergic asthma, EGPA, and chronic eosinophilic pneumonia (CEP) was kept open, and after explaining the benefits and harms related to the empirical use of steroids, he was initiated on oral steroids with a plan to continue for 12 weeks on tapering doses. He started feeling better with oral steroids but when the steroids were being tapered off, he experienced worsening of asthma with nocturnal awakenings five times a month and he had to increase the frequency of rescue salbutamol inhaler use to twice a day. He then subsequently required three hospitalizations for exacerbation over the next year which were managed conservatively. We kept the possibility of allergic asthma, EGPA, and CEP open. Since the patient could not afford omalizumab, he was started on a tapering course of oral steroids. Then, when he was weaned off the steroids, he suffered from repeated asthma exacerbations for which he had to get hospital admission on a few occasions.

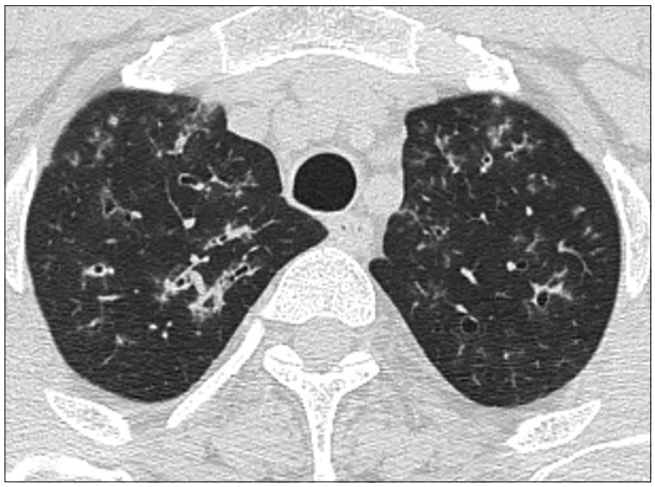

Figure 1: CT chest axial section shows ground-glass opacities in the peripheral and peri-bronchovascular distribution associated with bronchial dilatation. CT: computed tomography, arrow: ground-glass opacities, arrowhead: tree-in-bud sign

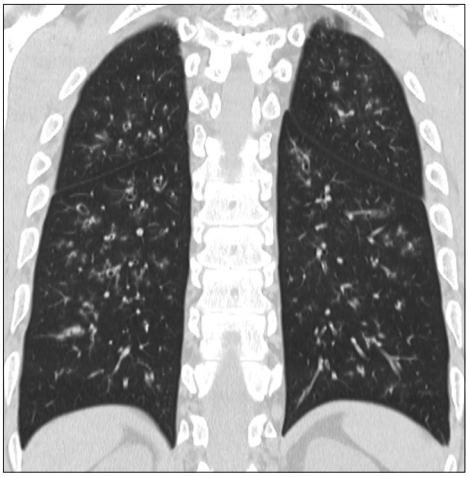

Figure 2: CT chest axial section shows ground-glass opacities, centrilobular nodules, and the tree-in-bud sign. CT: computed tomography, arrow: tree-in-bud sign, arrowhead: centrilobular nodules

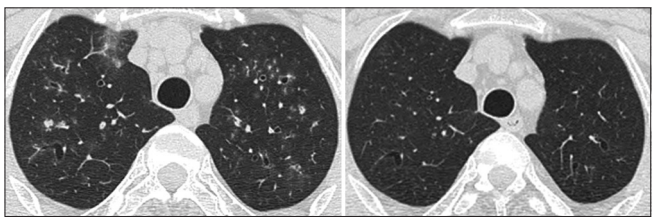

Figure 3: Axial images of CT chest taken a year apart shows resolving ground-glass opacities and centrilobular nodules in the follow-up CT images. The bronchial dilatation persists. (a) Image in 2019, (b) Image in 2020. CT: computed tomography, arrow: centrilobular nodules, arrowhead ground-glass opacities

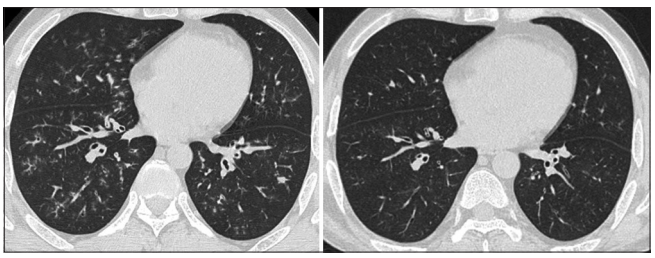

Figure 4: Axial images taken a year apart show resolving ground-glass opacities and centrilobular nodules in the follow-up CT images (a) image in 2019, (b) image in 2020. CT: computed tomography, arrow: tree-in-bud sign, arrowhead: centrilobular nodules

Table 1: Major investigations

In 2016
Absolute eosinophil count (AEC)-3180 cells/μL (reference value - <500 cells/μL)
Serum total IgE-938 UI/mL (reference value - <100 UI/mL)
The erythrocyte sedimentation rate (ESR) was 75 mm at the end of the 1st h
C-reactive protein (CRP) was 28 mg/dL (reference range 0-6 mg/dL)
Stool samples for the presence of ova and parasite (repeated thrice) were negative
Induced sputum (with 3% NaCl) culture and microscopy for acid-fast bacilli, cartridge-based nucleic acid amplification test (CB-NAAT) was negative
Skin purified protein derivative (PPD) test showed 5 mm induration
Enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus was negative
In 2019
Absolute eosinophil count (AEC)-3400 cells/μL
Serum total IgE-548 UI/mL
ANA by immunofluorescence-Negative
ANCA (anti-neutrophilic cytoplasmic antibody) serology including pANCA (perinuclear ANCA), cANCA (cytoplasmic ANCA) by indirect immunofluorescence-Negative
Aspergillus-specific IgE was negative
Allergic sensitivity test using intradermal antigens was performed and the patient was found to be sensitive to multiple allergens, pollens like Parthenium Hysterophorus +++, Cocos Nucifera +++, mite-like d-Farinae ++, dog epithelia, and cat dander ++, insects like mosquito ++, foods like salmon, mushroom, soybean, drumstick, tomato, almond, and peanut +++
In 2020
Absolute eosinophil count (AEC)-3500 cells/μL
Serum total IgE-642 UI/mL
ESR-135 mm at the end of 1st h
CRP-50 mg/dL (0-6 mg/dL)
p-ANCA by indirect immunofluorescence-positive
Urine protein creatinine ratio-160 mg/g (normal <200 mg/g)
24-h urinary protein-150 mg/24 h. (normal ≤150 mg/24 h)
2D Echo-ejection fraction of 60% with no diastolic dysfunction
Plasma N-terminal brain natriuretic peptide (NT-ProBNP)-100 pg/mL. (normal - <125 pg/mL)
Nerve conduction study-predominantly axonal, sensory-motor polyneuropathy affecting upper limbs more than lower limbs
Skin biopsy (from the edge of the ulcer) showed leukocytoclastic vasculitis with eosinophilic infiltration in the walls of medium-sized vessels.

Finally, in August 2020, the patient was admitted with a month-old history of a purpuric rash and bullous eruptions involving both lower limbs with an intense burning sensation for which he had tried herbal decoctions at home. After which, the bullae ruptured spontaneously leaving multiple superficial ulcers [Figure 5]. The patient reported a history of fever, malaise, and lassitude in this period. Soon, after 10 days of the onset of the rash, the patient started experiencing sensory symptoms like tingling sensation over the right upper limb from the elbow to wrist and pin-pricking sensation of both feet extending up to the knee. Gradually leading to difficulty in holding objects, buttoning/unbuttoning his shirt followed by right-sided wrist drop for 5 days. There

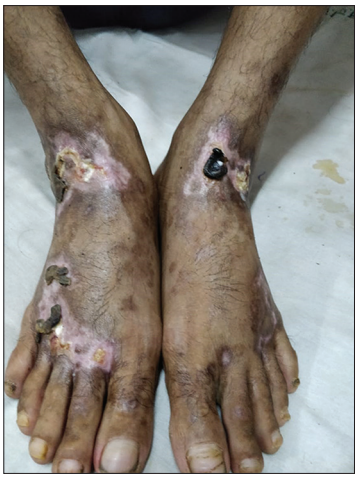

Figure 5: Photograph showing skin ulcer (photograph was taken while patient presented to us in August 2020)

was no history suggestive of weakness in the other limbs, bowel bladder complaints, or autonomic involvement. There was no history suggestive of seizure activity, cranial nerve, or cerebellar involvement. His body mass index (BMI) was 19.5 kg/m^2. Clinically, he had a wrist drop. The auscultation of the lungs indicated bilateral wheezing. During this visit, he emerged with signs of vasculitis with skin and peripheral nerve involvement, allowing us to make the diagnosis of EGPA, which was later validated with a skin biopsy [Figures 6-9].

He was administered methylprednisolone pulse therapy 1 g once a day for 3 days and cyclophosphamide 15 mg/kg, initially once fortnightly (three doses), then once a month (four doses) were advised. Cock-up splint and physiotherapy were provided for wrist drop. The patient was discharged on 1 mg/kg/day oral prednisolone with planned to taper after 12 weeks.

He was being followed up monthly, at 6-month follow-up improvement in the handgrip was noticed. With his right hand, he could button and unbutton clothes, grasp things, and create food morsels. His sensory symptoms improved. His eosinophilia was resolved. At 6 months, he was initiated with a maintenance dose of azathioprine 50 mg twice a day and prednisolone 10 mg daily.

Discussion

EGPA was first reported by Churg and Strauss in the year 1951.[2] It is a small to medium vessel vasculitis that has multisystem involvement. EGPA usually progresses through three stages, viz. prodromal, eosinophilic, and vasculitic.[3] The prodromal phase occurs in the second or third decade of life and is characterized by atopic diseases like allergic rhinitis and asthma. The eosinophilic phase follows and is characterized by peripheral blood eosinophilia and eosinophilic infiltration of organs like the lung and gastrointestinal tract. Finally, the vasculitic phase presents with systemic vasculitis of medium and small vessels often associated with granulomatosis. However, these phases are not easy to tell apart.

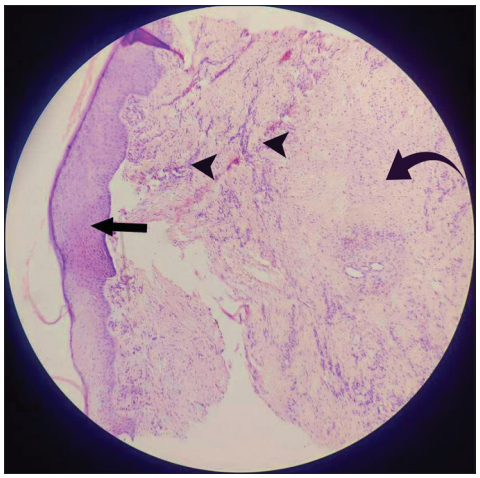

Figure 6: Skin biopsy showing lymphocytic infiltrate (a) 10X, Epidermis (arrow), lymphocytic infiltrate (arrowhead), dermis (curved arrow)

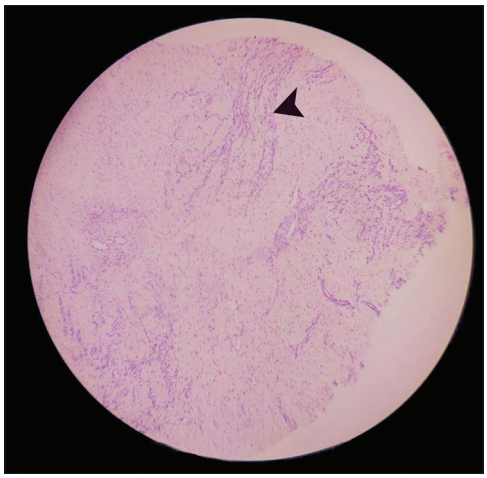

Figure 7: Skin biopsy showing lymphocytic infiltrate (100X), lymphocytic infiltrate (arrowhead)

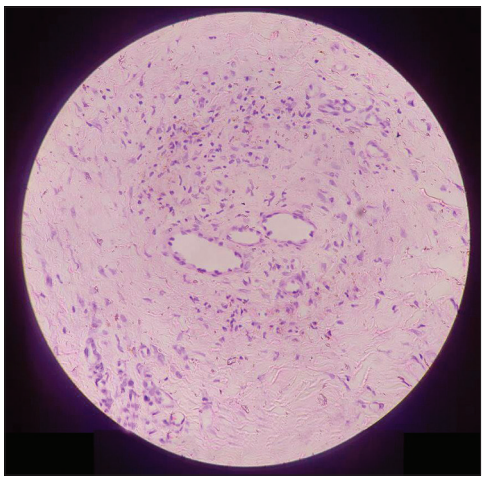

Figure 8: Inflammatory infiltrate around the vessel 10X

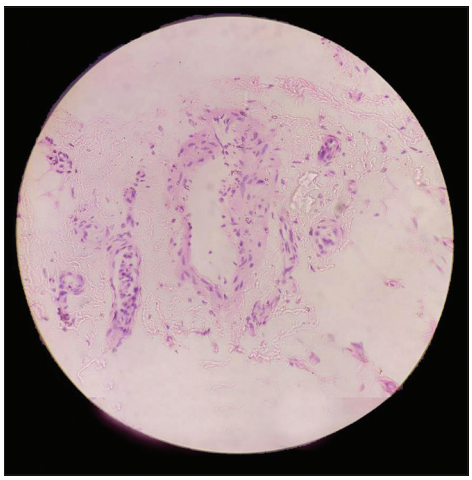

Figure 9: Inflammatory infiltrate around the vessel 100X

We are discussing the case chronologically to demonstrate the difficulties in the diagnostic process and therapeutic decision-making that occurred. In 2016, initial differential diagnoses were considered as occupational asthma secondary to cement dust, allergic asthma, Löeffler's syndrome, drugs and toxins (as the patient received macrolide antibiotic for acute exacerbation of asthma) related eosinophilic pulmonary infiltration, pulmonary tuberculosis, sarcoidosis, hypersensitivity pneumonitis (HSP) and allergic bronchopulmonary aspergillosis (ABPA). During a follow-up visit, due to the chronic nature of his disease, acute illnesses such as Löeffler's syndrome, drugs, and toxins related to eosinophilic lung infiltration were less likely.

Cement dust exposure is known to decrease peak expiratory flow (PEF) and is also found to cause chronic asthma. Coughing, wheezing, and dyspnea are other typical signs of cement dust contact. Since our patient worked in a cement factory for 28 years, the risk of occupational asthma was taken into consideration, and it is well known that occupational asthma has a variable latency after exposure. However, the patient didn't have experienced any difference in the frequency or severity of asthma during work hours or on holidays. Also, he didn't recover despite being reassigned to a new position at work, decreasing the possibility of this differential.

Primary pulmonary tuberculosis can have pulmonary infiltrate, mediastinal lymphadenopathy, and eosinophilia in less than 10% of the cases but, his sputum microscopy, and CB-NAAT were negative for Mycobacterium tuberculosis neither his clinical profile was suggestive of tuberculosis.

In sarcoidosis, 25% of patients have peripheral eosinophilia in addition to hilar lymphadenopathy. But in our patient-associated asthma, elevated IgE levels and clinical profile cannot be explained by sarcoidosis. This possibility, though, cannot be completely ruled out without a lymph node or lung biopsy.

Possibility of chronic HSP was considered, because of continuous exposure of irritant (most of the time organic type irritant is responsible but in our patient history of cement dust exposure was present), patchy infiltrates, ground-glass opacities, and small nodules on imaging along with raised inflammatory markers. But in HSP, on chest CT scans the opacities are primarily found in the

middle lobe. Also clinically for diagnosis of HSP at least six major clauses must be satisfied which include offending allergen exposure, precipitating antibodies against allergen, recurrent episode, crackles on chest auscultation, latency for the manifestation of symptoms 4 to 6 hours after allergen exposure and weight loss. Our patient only had recurring symptoms and exposure to an irritant which decreases the probability of HSP. Presence of bronchodilator reversibility, absence of a history of animal/bird exposure, no history suggestive of precipitation of episode after exposure to a known allergen, elevated total serum IgE, and raised AEC evidence against the possibility of chronic HSP.

However, in 2019, because of chronic sub optimally controlled, adult-onset asthma, peripheral eosinophilia with elevated IgE levels narrowed down the possibilities, which includes allergic asthma and primary pulmonary eosinophilic syndromes like EGPA, ABPA, and hyper eosinophilic syndrome (HES).

History of underlying asthma, elevated total IgE levels, peripheral eosinophilia, and infiltrates on chest imaging during acute exacerbation increase the clinical presumption of ABPA. However, on HRCT there was an absence of central bronchiectasis or impacted mucus plugs. As well as the absence of elevated Aspergillus specific IgE ruled out this diagnosis.

A diagnosis of HES requires the satisfaction of three criteria which include, peripheral eosinophilia (> 500 cells/μL) for >6 months, signs/symptoms indicative of eosinophilic organ infiltration, and absence of another known cause. Organ dysfunction from HES, in contrast to EGPA, is caused only by eosinophilic tissue infiltration, and small-vessel vasculitis is never present. Like EGPA, sensorimotor peripheral neuropathies are common in HES. Despite the fact that HES is suspected to induce pulmonary eosinophilic infiltrate, it is less prone to manifest with wheeze and has little correlation with asthma. In addition, a prolonged course for HES is very unlikely.

The possibility of allergic asthma was supported by repeatedly elevated serum levels of total IgE, peripheral eosinophilia, and his clinical presentation. However, the patient had no history of atopy or asthma as a child which was odd. But this possibility can't be ruled out fully.

In chronic eosinophilic pneumonia (CEP) the peak incidence occurs in the fifth decade of life, is associated with asthma in 2/3rdpatients, with female preponderance (2:1). On HRCT, chest CEP typically shows peripheral, often bilateral, alveolar opacities and has been referred to as the "photographic negative of pulmonary edema," but this is more pathognomic yet less sensitive. CEP Patients respond to corticosteroids but may relapse during taper. bronchoalveolar lavage (BAL) is most diagnostic for CEP, typically the eosinophil count in bronchoalveolar lavage will be more than 40%. Unfortunately, our patient denied consent for bronchoalveolar lavage. Although he had underlying asthma, persistent IgE elevation, and peripheral eosinophilia, he did not have systemic symptoms, which favored CEP.

As a result, we kept the possibility of allergic asthma, EGPA, and CEP open. Since the patient could not afford omalizumab, he was started on a tapering course of oral steroids. Then, when he was weaned off steroids, he suffered from repeated asthma exacerbations, for which he had to get hospital admission on a few occasions. Finally, during his most recent visit to us, he emerged with signs of vasculitis with skin and peripheral nerve involvement, allowing us to make the diagnosis of EGPA, which was later validated with a skin biopsy. Considering these presenting attributes, as well as the patient's financial constraints, the patient was eventually diagnosed with EGPA.

Asthma is the most commonly associated feature of EGPA. It occurs in almost every patient.[4] The median time of an EGPA case from the presentation of asthma to the diagnosis of EGPA is reported as 4 years. In our case, the vasculitic and extra-pulmonary involvement are seen approximately 4 years after the onset of asthma.[5] The appearance of vasculitic symptoms can be delayed as much as by 10 years after the onset of pulmonary symptoms.[6] Surprisingly, several cases have indicated improved asthma control after the onset of vasculitis.[7] Our patient had the same encounter.

Learning points for primary care physicians

- Regular follow-up, a high index of suspicion, and adequate workup in middle-aged patients presenting with a history of poorly controlled adult-onset asthma are the key points to making the diagnosis of EGPA.
- Before the onset of vasculitis and especially in ANCA negative patients, EGPA may mimic CEP, HES (hyper-eosinophilic syndrome), and ABPA (allergic bropulmonary aspergillosis).
- In our case, the patient was diagnosed with a case of eosinophilic pneumonia earlier and with the development of vasculitis manifestations, EGPA was suspected.
- An extensive search for the causes of eosinophilia with lung opacities should be considered in patients presenting with the same, as inappropriate therapeutic decisions impact the prognosis of the EGPA patients.

Ehitcal consideration

Ethical Approval was not required. Appropriate consent was obtained from the patient for publishing this case report.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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