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Case report

P-ANCA negative eosinophilic granulomatosis with polyangiitis

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A B S T R A C T

Vasculitis refers to inflammation of the systemic vessels. Eosinophilic granulomatosis with polyangiitis (EGPA) is a medium and small vessel vasculitis characterized by hypereosinophilia, pulmonary infiltrates, difficult to treat asthma and polyneuropathies. Diagnosis can often be challenging. In this article, we present a case of a young lady who was diagnosed ANCA negative EGPA.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a systemic vasculitis characterized by peripheral eosinophilia, asthma, pulmonary infiltrates, and necrotizing medium and small vessel vasculitis. Annual incidence is approximately to be 2.4 cases per million [1]. Radiographic appearance is variable, ranging from transient pulmonary infiltrates to ground glass and tree-in-bud opacities. Considering multisystem involvement and lack of pathognomonic radiographic findings, timely diagnosis remains a challenge.

2. Case presentation

A 35-year-old Caucasian female with a past medical history of hepatitis C virus, thalassemia minor and ankylosing spondylitis presented to the hospital with worsening dyspnea on exertion accompanied by occasional wheezing for the past month. Her symptoms included substernal pleuritic chest pain, heartburn, recurrent epigastric pain, night sweats, and subjective fevers. She also reported weight loss of 30 pounds over the past 4 months. Review of systems was positive for fatigue, headaches, back pain, recurrent sinusitis, and lower extremity weakness.

Complete blood count (CBC) showed hemoglobin 10.5 g/dL with mean corpuscular volume (MCV) 63, white blood cell (WBC) count 24.4 K/mm^3, 75% eosinophils, absolute eosinophil count 18.3 K/mm^3, platelets 256 K/mm^3. Basic metabolic panel showed sodium 135 mmol/L (136–145 mmol/L), potassium 4.2 mmol/L (3.5–5.1 mmol/L), chloride 99 mmol/L (98–107 mmol/L), bicarbonate 27 mmol/L (21–31 mmol/L), blood urea nitrogen (BUN) 5 mg/dL (7–25 mg/dL), creatinine 0.5 mg/dL (0.6–1.3 mg/dL), glucose 87 mg/dL (70–110 mg/dL). Liver function tests were within normal limits. Urinalysis was unremarkable. Procalcitonin was normal at 0.07 ng/mL (< 0.49 ng/mL). Erythrocyte sedimentation rate was elevated at 34 mm/hr (0–20 mm/hr). Serum antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA) panel, serum fungal and parasite serologies were all negative as well. Computed tomography (CT) with angiography of the chest revealed ground-glass tree-in-bud opacities within the upper lobes bilaterally, concerning for respiratory bronchiolitis, interstitial lung disease, or atypical pneumonia. Bone marrow biopsy confirmed hypercellular marrow with trilineage hyperplasia and associated moderate eosinophilia.

Pulmonary function testing (PFT) revealed FEV1 1.97 L (63% of predicted), FVC 3.77 L (74% of predicted), FEV1/FVC 85% of predicted; methacholine challenge test was positive. A follow-up high-resolution CT chest showed subtle centrilobular ground-glass nodules along the bronchovascular structures most pronounced within the bilateral mid and upper lungs (Fig. 1). Bronchoscopy with bronchoalveolar lavage showed marked eosinophilia (47%) on cytology, however, bacterial and fungal cultures were negative. Transthoracic lung biopsy was pursued and subsequent histopathological analysis showed prominent eosinophilic infiltrate, granulomatous reaction around small arterioles with occasional multinucleated giant cells and eosinophilic microabscesses, consistent with granulomatosis with polyangiitis and eosinophilia (Fig. 2A and B). She was started on prednisone 60 mg daily for 8 weeks and was found to have improvement in her symptoms.

3. Discussion

EGPA is a unique clinicopathologic entity bridging the spectrum of both hypereosinophilic syndromes as well as ANCA-associated systemic

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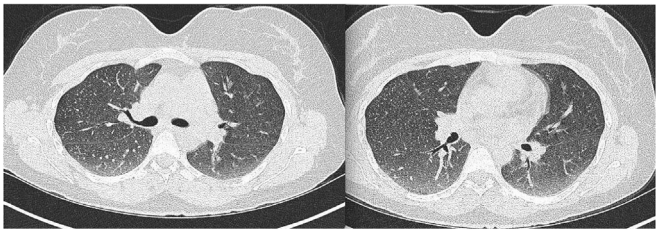

Fig. 1. Diffuse centrilobular ground-glass nodules along the bronchovascular structures in apical and mid lung distribution.

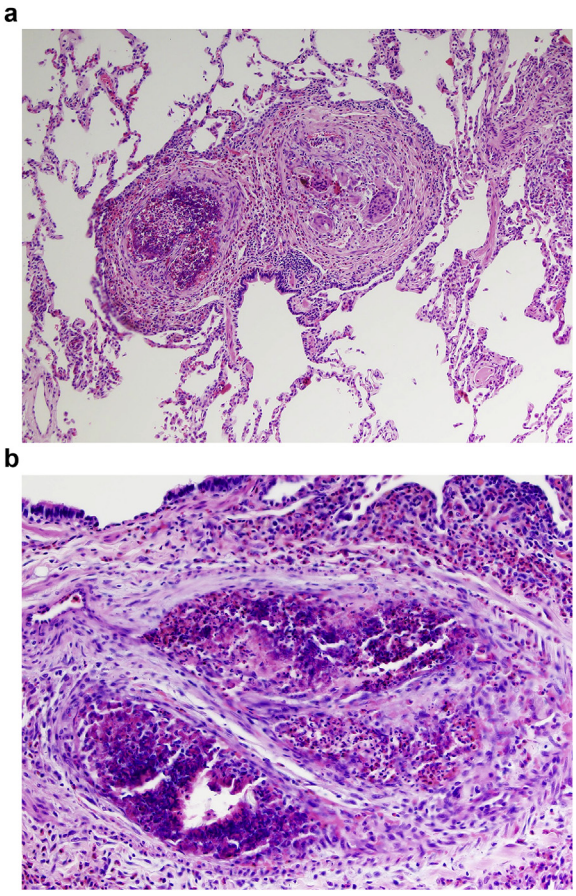

Fig. 2. A (on top) and Fig. 2 B (on bottom): This histology shows prominent eosinophilic infiltrate, granulomatous reaction within and around small arteries or arterioles, so called eosinophilic vasculitis (A, 40X), eosinophilic micro-abscesses (B, 200X).

vasculitides. Annual incidence is estimated to be 0.11–2.66 new cases per 1 million people and overall prevalence is estimated at 10.7 to 14 per 1 million adults [2,3]. The average age of onset is 38–54 years [4,5]. It appears to affect both males and females equally and no racial predisposition has been noted [6]. ANCA is positive in roughly 40% of EGPA cases and the predominant immunofluorescent pattern is perinuclear with antibodies to myeloperoxidase (MPO) [7].

The exact etiology and pathogenesis of EGPA are still unknown, however, it is hypothesized that environmental factors in combination with immunogenetic susceptibility may serve as the trigger for EGPA. Notably, the HLADRB4 gene and HLA-DRB1*04 and *07 alleles have been found to be associated with an increased risk of developing EGPA [8,9]. Lanham et al. hypothesized that EGPA occurs in three distinct phases: prodromal, eosinophilic, and vasculitic [10]. In the initial phase, localized inflammation is triggered by an unknown antigen in a genetically susceptible individual and is manifested as asthma or allergic rhinosinusitis. Subsequent activation of the inflammatory cytokines results in eosinophil proliferation and activation. Vasculitis and end-organ damage soon follow due to neutrophil and eosinophil degranulation.

EGPA is considered to be a Th-2 mediated disease process. As such, patients with EGPA have been found to have elevated levels of interleukins (IL) associated with the Th2 immunophenotype such as IL-4, IL-5, and IL-13 [11]. IL-5 is especially important as it mediates proliferation, terminal differentiation, and release of eosinophils in the bone marrow. Both IL-4 and IL-13 act synergistically to promote synthesis of eotaxin-3 which allows for extravasation of eosinophils into the tissues [12,13]. Within the target tissues, eosinophils degranulation results in the release of pro-inflammatory proteins such as eosinophil peroxidase (EPX), major basic protein (MBP), eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein (ECP). Although serum levels of IL-5 are elevated in EGPA and are closely associated with disease activity, the Th2 response alone does not fully explain the pathophysiology behind EGPA [14,15]. In vivo studies in animal models suggest that p-ANCA induces activation and subsequent degranulation of neutrophils [16]. Interestingly, ANCA-positive patients are more likely to present with the typical small-vessel vasculitis manifestations such as glomerulonephritis, peripheral neuropathy, and purpura [7,17,18].

Given multiorgan system involvement and the wide spectrum of pathology exhibited by EGPA, the diagnosis can be challenging. The American College of Rheumatology (ACR) requires four of the following criteria for the diagnosis of EGPA: peripheral eosinophilia (more than 10%), asthma, pulmonary infiltrates, paranasal abnormalities, neuropathy, and extravascular eosinophilia on biopsy. The sensitivity and specificity for the ACR criteria are 85% and 99.7% respectively [19]. Our patient met the ACR criteria for EGPA. ANCA antibodies are positive in approximately 40% of cases and are associated with more aggressive renal and pulmonary involvement. On the other hand, ANCA negative patients have younger age at diagnosis, refractory asthma, and cardiac involvement [17].

The prognosis for EGPA is variable but certain features portend worse outcomes. The French Vasculitis Study Group identified five prognostic factors associated with worse mortality rates. Collectively these are referred to as the Five-Factor Score (FFS) and are as follows: 1) high serum creatinine (> 1.58 mg/dL); 2) proteinuria (> 1 gm per day); 3) gastrointestinal involvement; 4) cardiomyopathy; and, 5) CNS involvement [20].

The initial therapy of choice is based upon these prognostic factors. Patients without any of these factors achieve clinical remission with corticosteroid therapy alone in approximately 93% of all cases (Table 1) [21]. Although corticosteroids are considered first-line therapy, methotrexate or azathioprine can be used as adjunctive agents if remission is not achieved or if relapse occurs [22,23]. For patients with 1 or more of these negative prognostic factors (i.e. those with renal, gastrointestinal, cardiac, or CNS manifestations), pulse-dose cyclophosphamide can be added to steroid therapy [24].

Although EGPA is usually considered a milder form of vasculitis, the mortality of untreated EGPA approaches 50% which is similar to untreated granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) [31]. Yet with appropriate and timely therapy, long-term outcomes have shown that overall remission rates are quite positive, regardless of the presence of negative prognostic factors. Ribi et al. found that survival rates for patients without any negative prognostic factors were 100% at one year and 97% at five years [21]. For patients with at least one negative prognostic factor, the survival rate at five years was 97% and 89% at ten years. Relapse is relatively uncommon; overall remission rates are about 25% and the mortality rate among those who do relapse is only 3.1% [32].

Table 1
Selected Case Studies of p-ANCA negative EGPA.

Study	# of ANCA-negative Patients	Method of Diagnosis	Treatment	Outcome
Comarmond et al. [25]	240	ACR criteria	FFS-guided[a]	Five-year survival rate: 88% Five-year relapse-free survival rate: 68% Ten-year survival rate: 76% Ten-year relapse-free survival rate: 55%
Sokolowska et al. [26]	35	ACR criteria	FFS-guided	Five-year survival rate: 96%
Samson et al. [27] [b]	70	ACR criteria	FFS-guided	Five-year survival rate: 92%
Cohen et al. [28] [b]	27	ACR criteria; all cases met histologic criteria	FFS ≥ 1: Corticosteroids + either 6 week or 12 week regimen of cyclophosphamide	6 week regimen: 91% in remission, 74% had relapse 12 week regimen: 84% in remission, 62% had relapse
Mahrhold et al. [29]	49	ACR criteria	FFS-guided	37% relapse rate at mean follow-up of 32 months
Thiel et al. [30]	3	ACR criteria	FFS-guided + Rituximab	0% relapse rate at 3 year follow-up

*ACR criteria: Presence of four or more of the following: 1) peripheral eosinophilia (more than 10%), 2) asthma, 3) pulmonary infiltrates, 4) paranasal abnormalities, 5) neuropathy, and 6) extravascular eosinophilia on biopsy.

[a] Five-Factor Score-guided: Individuals with FFS of 0 are treated with corticosteroids alone. Those with FFS ≥1 are treated with corticosteroids plus cyclophosphamide or another immunosuppressive agent.

[b] The study did not compare outcomes between ANCA-positive and ANCA-negative patients directly.

4. Conclusion

EGPA is a rare multisystem disease associated with significant morbidity. Early recognition and appropriate management are critical and failure to do so may result in devastating long-term consequences.

Conflicts of interest

The author(s) declare that there is no conflict of interest regarding the publication of this paper. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100830.

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