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Sulfa-induced acute eosinophilic pneumonia

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ABSTRACT

Acute eosinophilic pneumonia (AEP) is an infrequently seen interstitial lung disease secondary to medications. We report a series of 3 case of severe AEP which developed as a result of sulfa medication. 2 patients had received treatment with sulfamethoxazole for acne and 1 was treated with sulfasalazine for colitis. Patients were on sulfa medication for 1–3 weeks prior to presentation. All patients presented with fever, acute onset bilateral pulmonary infiltrates as well as marked peripheral eosinophilia. Mean eosinophil count was 2.21 $\times$ 10^9/L. There was a lack of response to steroids. One patient required extracorporeal membrane oxygenation and prolonged mechanical ventilation via tracheostomy. 2 patients underwent successful lung transplantation (1 bilateral living-related lobar lung transplant and 1 orthotropic cardiopulmonary allotransplantation). In all cases lung biopsy and explants showed acute and organizing diffuse alveolar damage with increased interstitial and airspace eosinophils. To our knowledge, our series is the first to show the clinical features of sulfa induced AEP in an adolescent population.

1. Introduction

Acute eosinophilic pneumonia (AEP) is a rare disease characterized by fevers, acute onset diffuse bilateral infiltrates and pulmonary eosinophilia in a previously healthy individual. Most cases remain idiopathic but medications are an established identifiable cause [1]. In some cases, the eosinophilic infiltrates are transient and resolve with discontinuation of the offending medication [2]. Other times despite the withdrawal of medication, the disease may pursue a fulminant course. Medications reported to have induced severe AEP include daptomycin, minocycline, imipenem, risperidone, sertraline and amitriptyline [3–8]. There is one recent case report of sulfasalazine induced AEP [9]. Sulfa medications are the second most common allergenic medication with an all-time allergy prevalence rate of approximately 5.4% [10]. We describe our experience with 3 cases of sulfa induced severe AEP. This is the first report to describe the clinical features of sulfa-induced severe AEP in an adolescent population. (see Table 1)

2. Case presentation

2.1. Case 1

A16-year-old previously healthy female presented with symptoms of high grade fever (103.6F), progressive fatigue, sore throat, cough, pleuritic chest pain headaches. She reported a history of acne and had used sulfamethoxazole/trimethoprim (Bactrim ®), 20 days prior to onset of her reported symptoms. She was a never smoker with no prior allergies. Her white cell count was 16.8 with eosinophil count was 1.76 $\times$ 10^9/L. Markedly diffuse and patchy alveolar pulmonary opacities with pneumomediastinum and bilateral pleural effusions were seen on chest-x-ray. Pleural effusion was transudative. No infectious etiology was found. She was suspected to have AEP and treated with high dose solumedrol with no response. She required prolonged mechanical ventilation and extracorporeal membrane oxygenation (ECMO) support. Hospital course was complicated with hemopericardium, right brachial plexopathy secondary to compression from the infraclavicular hematoma and renal failure requiring continuous renal replacement therapy. She made a remarkable recovery after 4 months on ECMO and was discharged to rehabilitation facility. Follow up pulmonary function shows residual mild restrictive lung disease pattern and a 6-min walk

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distance of 1911 feet with an ongoing need for supplemental oxygen.

2.2. Case 2

A13-year-old female with no known comorbid conditions, presented with high grade fever (103.1F), sore throat, cough, headaches and dizziness followed by shortness of breath and myalgias. She reported using sulfamethoxazole/trimethoprim (Bactrim ®) 18 days prior to her onset of respiratory symptoms for treatment of acne like rash. She otherwise had no known medication allergies and history of smoking. CXR showed diffuse pulmonary infiltrates with significant pneumomediastinum consistent with subcutaneous emphysema on physical examination. She was profoundly hypoxemic on admission requiring non-invasive ventilation. WBC count was 14.1 with 0.63 × 10(9)/L eosinophils on admission, which peaked to 1.87 × 10^9/L 8 days later. CT scan chest revealed extensive diffuse bilateral interstitial and alveolar infiltrates with areas of peribronchial consolidation, diffuse bronchiectasis and bilateral pleural effusions. Bronchoscopy with bronchoalveolar lavage (BAL) was positive for a mixed cell population with neutrophils, monocytes/alveolar macrophages, lymphocytes, respiratory epithelial cells and eosinophils. Tracheal secretions were also positive for increased eosinophils. Workup for infectious etiology was negative. Right mini thoracotomy with lung biopsy revealed acute and organizing diffuse alveolar damage with increased interstitial and airspace eosinophils consistent with acute eosinophilic pneumonia (Image 1A-B).

The patient was treated with intravenous methylprednisolone 1 g daily for five days followed by 60 mg three times a day. Despite high dose steroids, her hypoxemia worsened requiring initiation of ECMO therapy. After 4 months on ECMO, she underwent successful orthotopic heart and bilateral lung allo-transplantation.

2.3. Case 3

A17-year-old female with a history of ulcerative colitis presented with fever, dyspnea on exertion, progressively worsening cough and pleuritic chest pain. She was started on treatment with prednisone, mesalamine and sulfasalazine one week prior to her presentation. She had no known drug allergies and past exposure to smoking. Her white cell count was elevated to 19.5 with eosinophilia. Her peak eosinophil count was 3 × 10^9/L. Her chest x-ray was remarkable for interstitial infiltrates predominantly in the upper lobes with a spontaneous pneumomediastinum. Bronchoscopy with biopsy showed acute and organizing diffuse alveolar damage. Work up for infectious etiology remained negative. Patient was treated with intravenous methylprednisolone 60 mg every 6 hours for five days. CT chest showed multiple large bullae bilaterally occupying over 50% of the thoracic cavities with diffuse interstitial disease in the remaining lungs which worsened on interval CT scans despite steroid therapy. Lung biopsy showed subpleural blebs characterized by fibrous walled cysts with chronic inflammation and eosinophils. In the setting of worsening respiratory failure, she underwent urgent bilateral living-related lobar lung transplantation.

3. Discussion

Our study reports a series of AEP secondary to use of sulfa medication in three female adolescent patients. Adolescent and pediatric cases of AEP are extremely rare and difficult to diagnose with a prevalence of <1/1,000,000 [11]. They are often reported mixed in adult case series [12]. True pediatric cases are rare and most case series comprise of adolescents [13]. The clinical presentation of AEP has a striking resemblance with that of acute pneumonias and acute respiratory distress syndrome (ARDS).

Diagnosis is differentiated from ARDS and other infectious etiologies based on peripheral blood eosinophilia (defined as an eosinophilic count > 500 cells x10^9/L), increased eosinophils in bronchoalveolar lavage fluid (defined by >5% of eosinophils in the differential cell count), or eosinophilic infiltration of lung parenchyma demonstrated on lung biopsy specimens [1]. The diagnostic criteria of BAL eosinophilia >25% for AEP may not be readily applicable to medication induced AEP. BAL eosinophilia >25% is only seen in 64.3% (33.6 ± 18%) of daptomycin-induced AEP and 47.1% (25 ± 17%) of minocycline-induced AEP and these are the most commonly implicated medications in AEP [4,14]. All 3 of our patients had peripheral eosinophilia (mean eosinophil count = 2.21 × 10^9/L) and eosinophilic infiltration on lung biopsy and/or explants. Similar to our patients, the eosinophil count is known to rise during the course of the disease [15].

Based on the AEP diagnostic criteria proposed by Philip et al. [12], the 1st two cases do not have any other identifiable inciting events leading to this presentation. There is a possibility of inflammatory bowel disease associated lung involvement in our 3rd case who had a comorbid condition of ulcerative colitis [16].

In each of our three cases, the onset was crescendo over one week duration, and occurred within one month of beginning a daily orally administered sulfa containing medication. Overall antibiotic allergy incidence is highest with sulfa-class antibiotics with an incidence of 3.4% in females and 2.2% in males. The antibiotic allergy prevalence rate rises up to 5.4% to all sulfa antibiotics irrespective of gender [10]. Cytotoxic pulmonary injury by multiple mechanisms including release of reactive oxygen species and cytokines, reduction in deactivation of metabolites of the lung, impairment of alveolar repair mechanisms, and even immune mediated pathways are all implicated in sulfa induced interstitial lung disease [17]. Given the limited number of drug induced AEP cases, why certain drugs cause AEP and not others are unknown. Hence the mechanism of sulfa induced AEP remains unclear.

Although, steroids administration in the background of AEP didn't relieve symptoms or improved clinical outcomes significantly in our patients, steroids have been supported as the treatment of choice [18]. Upwards of 16% of patients require an intubation and mechanical ventilation. Refractory hypoxemia requiring institution of ECMO has been reported in one 15 year old and one 23 year old case with AEP [19,20]. Two of our patients required protracted ECMO support. Severe hypoxemia requiring institution of ECMO with AEP in adults has not been reported. This suggests a rapidly developing aggressive pathology with AEP in adolescents. ECMO while waiting for recovery with high dose corticosteroids or while awaiting lung transplantation is a reasonable approach for patient management in the adolescent, otherwise healthy individuals. There are reports of severe and rapidly

Table 1
Summary of clinical characteristics and inciting sulfa medications.

Case (#)	Age (years)	Sex	Prior Health	Antecedent Medication Indication (days prior to respiratory symptom onset)	Air leak at onset	Eosinophil (10^9/L)	Management
1	16	F	Normal	Sulfamethoxazole Acne (20)	+	1.76	ECMO (days) mechanical ventilation (days)
2	13	F	Normal	Sulfamethoxazole Acne (18)	+	1.87	ECMO Heart-lung transplantation
3	17	F	Mild colitis	Sulphasalazine Mild colitis (7)	+	3.00	Bilateral living-related lobar lung transplantation

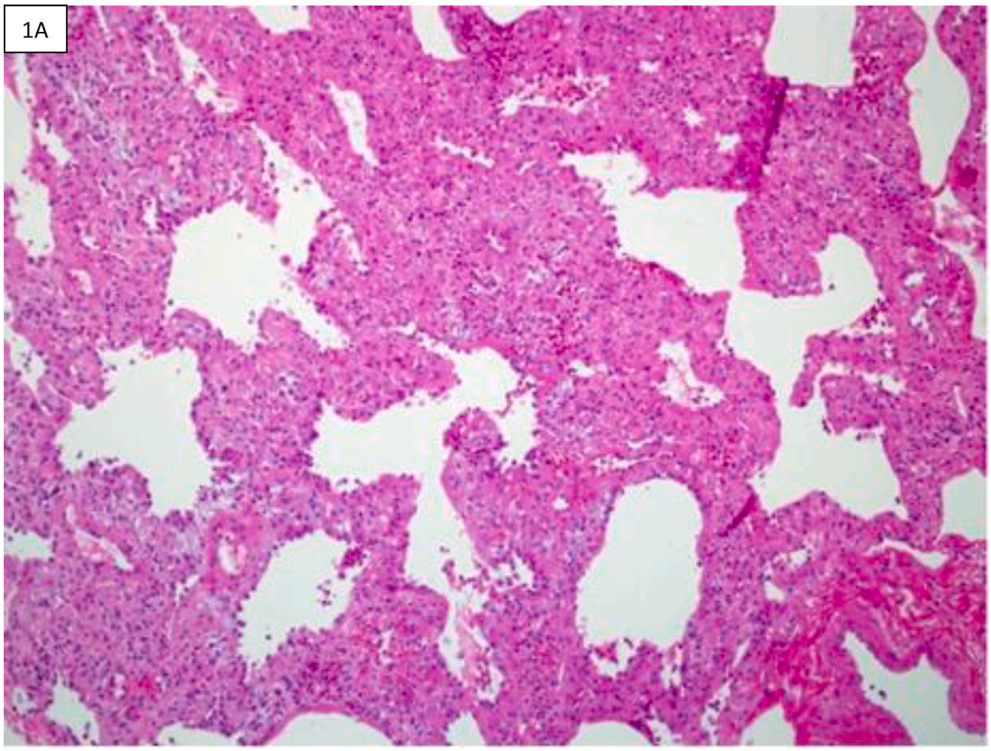

Image 1A. Lung biopsy showing diffuse alveolar septal widening by active fibrosis and scattered chronic inflammation, with scattered hyaline membranes and increased interstitial eosinophils representing acute and organizing diffuse alveolar damage in acute eosinophilic pneumonia.

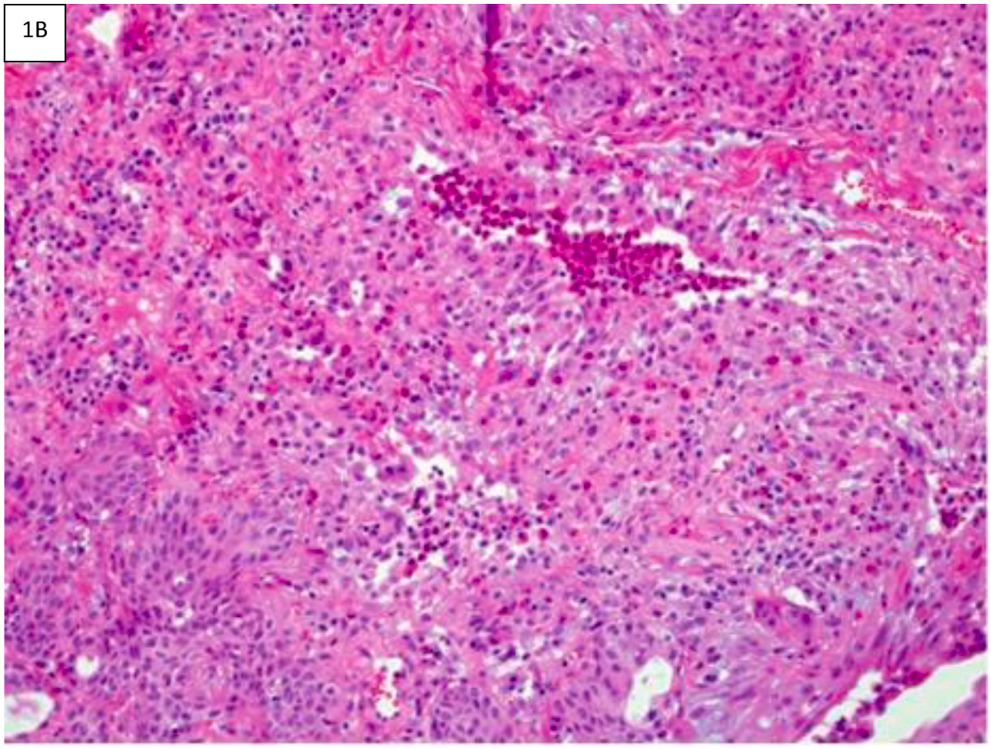

Image 1B. An abundant of airspace eosinophils that focally represent an eosinophilic pneumonia.

progressive AEP leading to fatality [12,21]. To the best of our knowledge, there are no reports of lung transplantation in AEP. Acute eosinophilic pneumonia should be considered early in the differential with acute respiratory distress syndrome in the presence of peripheral eosinophilia. Early suspicion and diagnosis are necessary to discontinue the offending agent and start timely high dose corticosteroids in fulminant refractory hypoxemic respiratory failure.

4. Conclusion

Compared to prior reports of AEP in young adults, sulfa-induced AEP in adolescents may follow brief use, elicit severe respiratory failure and response to corticosteroids may be limited. Sulfa medication is a rare cause of AEP characterized by severe disease manifestations in comparison to idiopathic AEP.

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Author contribution

All authors met the following conditions:

1) Substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data.

2) Drafting the work or revising it critically for important intellectual content.

3) Final approval of the version to be published.

Declaration of competing interest

The authors declare that there are no conflict of interest regarding the publication of this paper.

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