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Case Report



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Imipenem/cilastatin–induced acute eosinophilic pneumonia: A case report

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ABSTRACT

Rationale: Acute eosinophilic pneumonia (AEP) is an acute pulmonary illness caused by eosinophilic infiltration of the lung parenchyma. It can happen after using drugs such as daptomycin and minocycline. AEP induced by imipenem/cilastatin is a rare condition.

Patient's Concern: A 45-year-old male patient, who previously suffered from a urinary tract infection and treated with imipenem/cilastatin antibiotic, was presented to us with acute respiratory distress, soon after the initiation of the antibiotic. Computed tomography identified pulmonary infiltrates in the upper and middle lung fields and eosinophils were found to account for 36% of differential count of the broncho-alveolar lavage fluid. He also developed peripheral eosinophilia as the disease progressed.

Diagnosis: AEP, secondary to imipenem/cilastatin therapy.

Interventions: Steroid therapy was administered and imipenem/cilastatin antibiotic was discontinued.

Outcomes: The patient improved completely following the therapy and had clear lung fields on follow-up.

Lessons: Imipenem/cilastatin is an uncommon cause of AEP and requires close monitoring during therapy.

KEYWORDS: Acute eosinophilic pneumonia; Broncho-alveolar lavage; Imipenem/cilastatin, Pulmonary infiltrate; Peripheral eosinophilia

1. Introduction

Antibiotics constitute the cornerstone of treatment for infectious diseases, however, they are not free of adverse effects. One such

complication is acute eosinophilic pneumonia (AEP), which is an acute lung parenchymal eosinophilic syndrome, secondary to drug or toxin exposure. Smoking is an important cause of AEP with a reported incidence of 9-11 per 100 000 person-year[1]. This disease predominantly affects the male population in the 20-40 age group and is more prevalent in the summer season[1]. Numerous other causes, for example, parasitic diseases like ascariasis and schistosomiasis, chemicals that are found in tobacco and gasoline, medicines such as acetaminophen and non-steroidal anti-inflammatory drugs, and antibiotics like daptomycin and minocycline, have also been associated with AEP[1,2]. The carbapenem antibiotic group rarely contributes to this complication, and we are describing one such report.

2. Case report

A written consent is present, duly signed by the patient. The authors obtained the consent after explaining that no information related to the patient's identity will be disclosed and the case report, including the pictures, will be used for education purposes only. The patient gave positive consent and the authors certify that written consent is present, and procured for publication.

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A 45-year-old male patient, a clerk by occupation, presented to our emergency department with breathlessness for 2 days and a fever. The fever was intermittent and relieved with medication, but the patient continued to experience breathlessness. Five days before coming to us, he was diagnosed with a urinary tract infection at his previous medical facility and was prescribed imipenem/cilastatin 500 mg every 6 hours as per the culture growth of *Escherichia coli* and subsequent sensitivity pattern. The patient was dyspnoeic at presentation, with a respiratory rate of 28/min (normal: 12-16/min), capillary oxygen saturation of 82% (normal: 95%-100%) at room air. His oxygen saturation improved to 93% with oxygen supplementation at 12 L/min on a venturi mask. Blood pressure was 124/68 mmHg (normal: 120/80 mmHg) and the capillary glucose levels were 90 mg/dL (normal: 70-100 mg/dL).

On auscultation, the chest findings revealed bilateral crepitations and localized wheezing in the upper and middle parts of the chest. Examination of the cardiovascular system, including measurement of the jugular venous pressure and abdominal examination, revealed no abnormality, and there was no pedal edema in this patient. Sinus tachycardia was observed in the electrocardiogram and chest X-ray had consolidation in bilateral upper and middle lung fields (Figure 1A). High-resolution computed tomography (CT) corroborated with the chest X-ray findings and was suggestive of diffuse ground glass opacities and areas of patchy consolidation involving the bilateral upper and middle lung fields (Figure 1B). Based on the above radiological findings, the patient was administered treatment for pneumonia and an injection of azithromycin was added to his ongoing antibiotic regime. Reverse transcriptase polymerase chain reaction test for coronavirus disease 19 was inconclusive. Meanwhile, sputum culture did not show growth of any organism and two times Ziehl-Neelsen stains for acid-fast bacilli were both

negative. The patient had leukocytosis with a count of $19.2 \times 10^9/L$ (normal: $4 \times 10^9 - 11 \times 10^9/L$) with 82% neutrophils, 14% lymphocytes, 3% monocytes, and 1% eosinophils. Blood and urine cultures were sterile and his renal function test results were within the normal range.

Oxygen requirement decreased to 4 L/min with the ongoing treatment and azithromycin was discontinued after 3 days. Imipenem/cilastatin, along with oxygen supplementation was continued and the patient was observed for further improvement. Unfortunately, the patient deteriorated as oxygen requirement increased and repeat investigations demonstrated a leukocyte count of $17.8 \times 10^9/L$ with 18% eosinophils. This raised the suspicion of eosinophilic pneumonia and a broncho-alveolar lavage (BAL) was planned for this patient. A careful lavage was done and the obtained fluid sample was tested and found 560 cells/mm^3 with 36% eosinophils. Lavage fluid did not grow any organism and the malignant cytology evaluation was negative. Injection of methylprednisolone 60 mg twice a day was started in view of AEP, which led to an improvement in his vital parameters, as well as peripheral eosinophilia. In the absence of any identifiable etiology, imipenem/cilastatin was considered the culprit for the patient's AEP, as his symptoms developed after the initiation of this antibiotic. The antibiotic was stopped immediately, and the patient showed progressive recovery thereafter with gradual resolution of the symptoms and the peripheral eosinophilia. His oxygen support was weaned off over the next 7 days after discontinuation of the antibiotic, and the patient was discharged after 14 days of in-patient management on oral prednisone 40 mg once a day. On follow-up after one month, his repeated chest X-ray showed normal lung parenchyma and complete clearance of the previous lesions (Figure 1C).

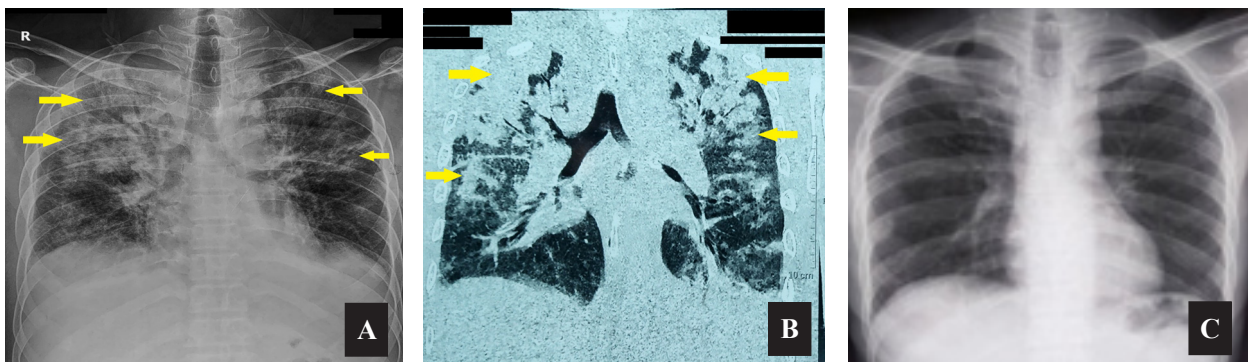


Figure 1. The chest X-rays and high-resolution computed tomography of a 45-year-old male patient. (A) The initial chest X-ray demonstrating pulmonary consolidation, predominantly in the upper and middle lung fields (right > left) (arrows). (B) High-resolution computed tomography demonstrating ground glass opacities and consolidation in bilateral upper and middle lung parts (arrows). (C) Repeat chest X-ray demonstrating normal lung parenchyma on follow-up after one month.

3. Discussion

Antibiotic use has previously been associated with eosinophilic syndromes such as AEP and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. DRESS syndrome comprises cutaneous manifestations like rash, which differentiates it from AEP, however peripheral eosinophilia is observed in both these conditions (predominantly in DRESS). Distinctly, eosinophilia in AEP occurs late in the disease course[1]. Documented antibiotics causing AEP include ceftaroline, clarithromycin, colistin, dapson, levofloxacin, and roxithromycin[1]. Recently, case reports have mentioned the use of imipenem/cilastatin and meropenem as an etiological agent for AEP[2,3]. The pathogenesis of this complication is poorly understood, but type I hypersensitivity immune reaction plays a major role. Due to this reaction, interleukin-33 and thymic stromal lymphopoietin are secreted from alveolar epithelium, leading to eosinophil recruitment[1].

AEP presents as an acute respiratory illness with fever and hypoxia, rapidly after exposure to the culprit agent, but it can develop after 2 months to 5 years post-insult[4,5]. A patient can also present with mild symptoms like dry cough, dyspnoea, myalgia, malaise, pleuritic chest pain, and night sweats[1]. X-ray and CT chest may demonstrate pulmonary infiltrates, which are non-specific, mimicking bronchopneumonia in mild or acute respiratory distress syndrome in dire cases[1]. Thus, vague clinical presentation and imaging patterns give rise to diagnostic difficulties in most cases. BAL is a crucial investigation, as it identifies the presence of eosinophilic infiltration, an essential component for AEP diagnosis, and can rule out other infective etiologies as well[3]. Lung biopsy is usually not required, but performed in the milieu of diagnostic dilemma or atypical clinical presentation[1]. Histopathological features in biopsy include preserved alveolar architecture, eosinophilic abscesses, fibrinous exudates, perivascular inflammation, and type II pneumocyte hyperplasia[6].

To overcome the diagnostic hitch, Phillips *et al.* proposed a criterion for the diagnosis of antibiotic-induced AEP, as the conventional eosinophilic count of >25% in BAL fluid is not readily applicable[7]. The criterion included concurrent identified agent exposure, hypoxemia with fever, cough and dyspnoea, diffuse bilateral pulmonary infiltrates in imaging, any value of eosinophilic count in BAL sample or lung biopsy consistent with eosinophilic pneumonia, exclusion of other possible etiologies and clinical improvement after removing the offending agent. Originally, the criterion was developed for daptomycin-induced AEP, but Solomon *et al.* suggested that the diagnosis of drug- or toxin-induced AEP can be also made using this criterion, if the same guideline is fulfilled, in addition to the recurrence of the symptoms after re-exposure[8].

Identifying the cause is essential for the diagnosis of AEP, and removing the cause is a crucial step in the management.

Administration of systemic glucocorticoid therapy suppresses the ongoing inflammatory damage and constitutes the mainstay of treatment[1]. Methyl-prednisolone at a dose of 60 mg to 125 mg 6 hourly has been described as the most commonly used regimen for a total of 4 weeks[1]. Objectively, corticosteroids lead to resolution of pulmonary infiltrates within one week and complete recovery within 3-4 weeks[1]. Spontaneous resolution, even without steroidal therapy, has been documented in mild cases, but supportive measures like oxygen supplementation, and invasive and non-invasive ventilation may be required in more complicated scenarios. Once initiated, steroids can be tapered according to clinical and radiological improvement and Rhee *et al.* found that 2 weeks of therapy is equally effective as a 4-week course[9]. The prognosis of AEP is favorable in most cases if dealt with timely with the removal of the offending agent, and steroid remedy as it can fasten the recovery[1]. Complete radiographic improvement can be observed in 1 month and long-term sequelae are rare, but relapse is common if there is re-exposure to the causative agent[1].

Although rare, an association of imipenem/cilastatin with APE should be considered in patients for whom this antibiotic has been started recently. The etiological spectrum of this disease is progressively rising and hence, uncommon agents should be considered in the absence of typical causes. This report narrates the confronted diagnostic difficulties, due to the novelty of the prime etiology, and clinicians should be thoughtful about these unusual scenarios. Further, prompt discontinuation of the offending agent along with the institution of steroid therapy is crucial in AEP management and has a documented benefit. The disease is usually reversible with timely intervention but can have grim outcomes if left unrecognized for long.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

GJ and SG: case presentation, management, data collection, investigations, and writing of the original draft. ASL, SA, and MG: writing of the original draft including discussion, literature review, conclusion, references, and formatting.

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