



## Letters

## Acute eosinophilic pneumonia due to piperacillin/tazobactam

Eosinophilic pneumonia (EP) is a rare and severe disease that belongs to the group of pulmonary eosinophilias (PE). There are 2 clinical presentations: chronic eosinophilic pneumonia (CEP) and acute eosinophilic pneumonia (AEP). In 1989, Allen et al. described the first case of AEP.<sup>1</sup> Many causes of AEP have been described, although the idiopathic form is the most common.<sup>2</sup> We herein present a case of AEP probably attributable to piperacillin/tazobactam (P/T).

We report the case of a 61-year-old, non-atopic, ex-smoker man with a previous episode of cholecystitis resolved with laparoscopic cholecystectomy, who was admitted 3 months later to undergo surgery of post-cholecystectomy biliary fistula. At that moment, laboratory findings only showed a liver damage with cholestasis (aspartate triphosphatase, 87 U/L; alanine transaminase 126 KU/L, gamma glutamyl transferase 142 KU/L, alkaline phosphatase 146 U/L, and bilirubin 1.2 mg/dL). No abnormalities were detected in the complete blood counts. In the 6 days leading up to the surgery, he received treatment with omeprazole, lorazepam, and single doses of metoclopramide and paracetamol. Immediately after the successful surgery, treatment with P/T, 4 g/0, 5 g was started.

Four days later, he started with cough, fever up to 38.7 °C, and diarrhea. Suspecting a septic intraabdominal complication, metronidazole was added to the previous treatment with P/T. A mild peripheral eosinophilia (1000/mm<sup>3</sup>) was observed, and a thoracoabdominal computed tomography (CT) scan only revealed bilateral ground-glass opacities in lung bases.

The 7th day after surgery, he continued with cough and fever, and he started to report dyspnoea without skin eruption. Physical examination indicated wet crackles on pulmonary auscultation. The oxygen saturation while breathing room air was 69%. Chest radiography showed diffused bilateral pulmonary infiltrates (Fig 1). Laboratory findings demonstrated leukocytosis (16,500/mm<sup>3</sup>) with peripheral eosinophilia (800/mm<sup>3</sup>), elevated C-reactive protein (6.4 mg/dL), and a hypoxemic respiratory failure (pH of 7.45, partial carbon dioxide of 37 mmHg, and partial oxygen of 48 mmHg in arterial blood gas analysis). Renal and liver function test results and autoantibody test results were within normal ranges. Electrocardiogram showed a known right bundle branch block.

He was admitted to the intensive care unit, requiring noninvasive mechanical ventilation. P/T and metronidazole were suspended, and the antibiotic spectrum was escalated to meropenem, ciprofloxacin, fluconazole, and linezolid. Blood, sputum, urine, feces, and drainage secretion cultures for bacteria, virus, fungi, and parasites were negative. A week later a bronchoscopy was performed because the patient did not improve. The

differential cell count in the bronchoalveolar lavage yielded 70% eosinophils without bacteriological findings. Treatment with high-dose methylprednisolone (2 mg/kg/day) was started, with a rapid improvement of the respiratory symptoms and of the oxygenation parameters; therefore, noninvasive mechanical ventilation was removed 2 days later, and fever also came down, peripheral absolute eosinophil count dropped to 0, and chest radiography improved (Fig 1). Broad-spectrum antibiotics were removed 10 days later; omeprazole and metoclopramide were maintained all over the hospitalization period. Corticosteroid doses were progressively reduced, and a dosage of 5 mg oral prednisolone was maintained for 3 months until disappearance of lung infiltrates on the CT scan.

Because of the chronology of symptoms, attending pneumologists suspected an AEP in relation with P/T, so the patient was referred to our outpatient clinic. A detailed medical history was compiled.

The allergologic study revealed the following: a total serum IgE of 2.57 KU/L. Specific IgE (ImmunoCAP ThermoFisher system) to penicillin G, penicillin V, ampicillin, and amoxicillin: 0.00 KU/L. Epicutaneous tests performed with P/T at 20% in petrolatum with readings at 48 and 96 hours were negative. Prick and intradermal tests with immediate and delayed readings, with benzylpenicilloyl polylysine (0.04 mg/mL), sodium benzylpenicilloate (0.5 mg/mL), penicillin G (10 000 IU/mL), and P/T (20/0.25 mg/mL) were performed, with negative results.

According to the clinical history, the laboratory and radiological findings, and the temporary relationship between the symptom onset and the beginning of the treatment with P/T, the diagnosis of P/T-induced AEP was established, and beta-lactams were forbidden.

Pulmonary eosinophilia courses with pulmonary infiltrates, or peripheral eosinophilia, or eosinophilic infiltration on lung biopsy and eosinophilia in bronchoalveolar lavage fluid at any moment of their evolution. The group includes mainly drug- and toxin-associated eosinophilic lung diseases, parasitic and fungal infections, allergic bronchopulmonary aspergillosis, Churg-Strauss syndrome, and acute/chronic eosinophilic pneumonias.<sup>1,3</sup>

The AEP diagnosis is based on laboratory, radiological, and clinical criteria, and any known cause of pulmonary eosinophilia must be discarded. Acute eosinophilic pneumonia must be considered in any patient with a fever, rapid respiratory failure, and blood eosinophilia. Ground-glass opacities and airspace consolidation, together with poorly defined nodules and interlobular septal thickening, are mainly present on CT scan.<sup>1–3</sup> Drug-induced eosinophilic pneumonia is usual, but the idiopathic form is the most common.<sup>1–3</sup> A temporal relationship has been described in a number of patients between the development of AEP and the recent onset of cigarette smoking.<sup>4</sup>

**Disclosures:** The authors report no conflicts of interest.

**Funding Sources:** None.

<https://doi.org/10.1016/j.anai.2018.12.007>

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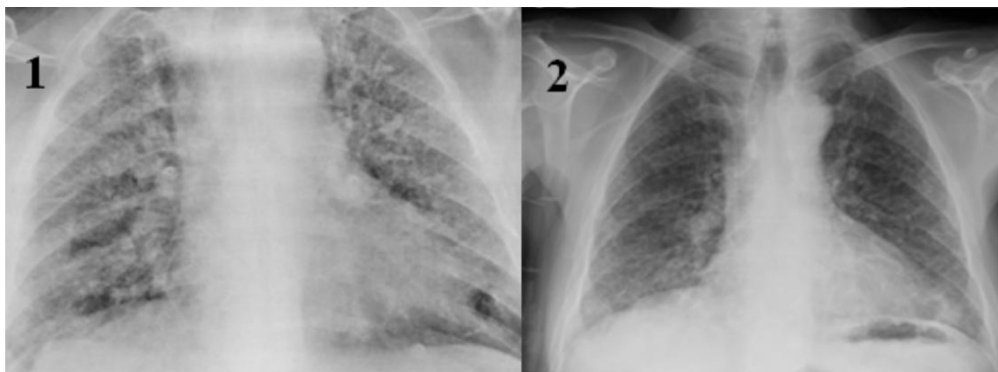


**Figure 1.** Chest X-ray showing bilateral infiltrates before (1) and after corticosteroid treatment (2) in the same patient.

In vitro and cutaneous available tests with the implicated drug are usually negative. New ways to establish drug-induced eosinophilic pneumonia diagnosis and suitable biomarkers of good response to the treatment need to be sought. Several studies associate interleukin (IL)-5, IL-18, and IL-33 with eosinophils recruitment into the lungs, degranulation, and eosinophil survival. Serum levels of these cytokines seem to predict the good response to steroid treatment and the clinical improvement.<sup>5–7</sup>

In the reported case, a temporal relationship was seen between the suspected drug and the onset of the clinical symptoms and of the lung disease. The rest of the involved drugs (omeprazole, metoclopramide, paracetamol, and lorazepam) were tolerated during the entire hospitalization period and after recovery. Infectious diseases and other lung diseases with possible associated eosinophilia, and autoimmune diseases, were ruled out. Based on these findings, the diagnosis of P/T-induced AEP was established.

Only 1 case has been reported of pulmonary infiltrates and eosinophilia related to P/T administration that also was associated with exanthema. In that case, cutaneous tests were positive to penicillin but negative to P/T.<sup>8</sup> To our knowledge, we report the first case of drug-induced AEP, probably caused by piperacillin/tazobactam administration.

### Acknowledgment

We would like to thank Julia Rodriguez Rodriguez for her contribution to the work.

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