Eosinophilic Pleural Effusion due to Cloxacillin and Piperacillin/Tazobactum

Ibrahim A.S., Allangawi M.H., Ghadban W.K., Arrayes M.
Department of Medicine, Hamad Medical Corporation
Doha, Qatar

Abstract:
A young male was treated for right-sided pneumonia with cloxacillin and piperacillin/tazobactam. As he was recovering from the pneumonia he developed left-sided pleuritic pain and pleural effusion. At thoracocentesis an exudative pleural effusion contained 16% eosinophils with a simultaneous 28% peripheral eosinophilia. An allergic reaction to penicillins was thought to be the cause. After withdrawal of those medications and institution of prednisolone a rapid resolution was seen of symptoms, signs, peripheral eosinophilia and radiological abnormalities.

Key words: Piperacillin/tazobactum, cloxacillin, penicillins, eosinophilic pleural effusion, allergic reaction

Introduction:
Drug-induced pleural disease is uncommon compared to drug-induced parenchymal lung disease (1). An increasing number of drugs are implicated in the development of pleural disease and may incite a pleural reaction alone or in conjunction with parenchymal disease. In the course of treatment with antibiotics several reactions can occur; a detailed history of drug intake and a high index of suspicion are crucial to a diagnosis. Any drug should be considered a potential cause of an undiagnosed exudative effusion before pursuing an extensive diagnostic evaluation that might lead to unnecessarily expensive tests and patient discomfort (2). We report a case of an eosinophilic pleural effusion caused by a combination of cloxacillin and piperacillin/tazobactam and we review etiologic considerations in eosinophilic pleural effusion, especially drug-induced pleural disease.

Material and Method:
A 20-year-old Qatari male was admitted with a four-day history of high-grade fever, rigors, cough productive of yellowish sputum and right-sided pleuritic chest pain. He had no history of chronic illnesses or drug allergies. His temperature was 38°C and he was mildly dyspneic. There was dullness to percussion, bronchial breath sounds and inspiratory crepitations in the right posterior thorax. Chest x-ray showed homogenous consolidation in the right mid and lower zones. A complete blood count showed leucocytosis with neutrophilia and a normal eosinophil count (Table 1). Blood sugars, BUN, creatinine and liver function tests were normal.

He was started empirically on ceftriaxone 2 gm intravenously once daily plus azithromycin 500 mg orally once daily. A CT chest scan showed extensive pneumonic consolidation in the right lower zone with evidence of loculated right-sided pleural effusion (Figure 1). The patient did not consent to thoracocentesis of the right-sided pleural effusion.

Table 1: Serial complete blood count with differential and the antibiotic used.

<table>
<thead>
<tr>
<th></th>
<th>DAY 1</th>
<th>DAY 7</th>
<th>DAY 25</th>
<th>DAY 29</th>
<th>DAY 32</th>
<th>DAY 35</th>
</tr>
</thead>
<tbody>
<tr>
<td>White Blood Cell</td>
<td>29X10⁹/ul</td>
<td>15.2X10⁹/ul</td>
<td>13.4X10⁹/ul</td>
<td>14.4X10⁹/ul</td>
<td>11 X10⁹/ul</td>
<td>10.5 X10⁹/ul</td>
</tr>
<tr>
<td>Differential</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>88%</td>
<td>75.5%</td>
<td>36.8%</td>
<td>48.7%</td>
<td>43.5%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>6%</td>
<td>16%</td>
<td>26.6%</td>
<td>21.2%</td>
<td>30.9%</td>
<td>39.6%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>5%</td>
<td>5%</td>
<td>7.3%</td>
<td>6%</td>
<td>6.1%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.5%</td>
<td>2.7%</td>
<td>28.9%</td>
<td>23.6%</td>
<td>18%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Ceftiraxone</td>
<td>Cloxacillin</td>
<td>Pipracillin-Tazobactum</td>
<td>Antibiotics stopped</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 - 5</td>
<td>Day 6 - 24</td>
<td>Day 25 - 28</td>
<td>stopped</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Refer to the text for doses and route.

Address for correspondence:
Abdulsalam Saif Ibrahim, MD, CABM
Pulmonary and Intensive Care Section, Department of Medicine
Hamad Medical Corporation, P. O. Box 3050, Doha, Qatar
Fax: (+974) 4392273; E-mail: salam145@yahoo.com

Blood cultures were negative but his sputum produced a Staphylococcus aureus sensitive to cloxacillin and so, on the sixth day, the antibiotic treatment was changed to intravenous cloxacillin, 2 grams every 6 hours. On the seventh day the white
cell count was $15.2 \times 10^3/\mu l$ with 2.7% eosinophils (Table 1). By eighth day he was afebrile and a chest x-ray on day 14 showed improvement of the right-sided infiltrate with a clear left lung field. He was discharged on cloxacillin 1 gm orally every 6 hours and the decision was taken to extend the treatment for another two weeks, for possible empyema based on CT chest findings of loculated parapneumonic pleural effusion.

A complete blood count showed a peripheral eosinophilia of 28.9% (Table 1). A diagnostic thoracocentesis removed 50 mL of straw-colored exudative eosinophilic pleural effusion containing: white blood cells 3400/\mu l, 35% neutrophils, 39% lymphocytes, 9% monocytes, 16% eosinophils, 1%, mesothelial cells, total protein 63 gm/L, albumin 31 gm/L, lactate dehydrogenase 1456 mu/mL, glucose 4.8 mmol/L, pH 7.48. Gram stain, acid-fast smear and cytology were negative. Repeated tests for sepsis were negative.

His chest pain was increasing and so was the pleural effusion on serial chest x-rays. As a drug reaction was suspected, piperacillin/tazobactam was stopped and replaced with prednisolone 30 mg once daily for one week. Two days later CBC showed a lower eosinophil count of 18.9% and pleural effusion on chest radiographs had diminished by 50%. Six days after stopping the piperacillin/tazobactam the eosinophil count was normal and chest x-ray showed only minimal pleural effusion. Another chest x-ray two weeks after discharge showed complete resolution of the left pleural effusion and the eosinophil count was normal.

Discussion:

A large number of drugs are associated with the development of pleural inflammation. The presentation of drug-induced pleural disease may vary from an asymptomatic pleural effusion to acute pleuritis and symptomatic pleural thickening. Except in some cases of drug induced lupus pleuritis, the pathogenic mechanism for most drug induced pleural disease remains speculative. These mechanism include: 1) hypersensitivity or allergic reaction; 2) direct toxic effect; 3) increased oxygen free radical production; 4) suppression of the antioxidant defences and 5) chemical induced inflammation. Approximately 30 drugs are believed to cause pleural disease, while pleural fluid eosinophilia has been reported in therapy with the following drugs: dantrolene, nitrofurantoin, fluoxetine, warfarin, gliclazide, propylthioracil, isotretinoin, mesalamine, bromocriptine, valproic acid, tinazidine and antibiotics (penicillin, ceftriaxone, streptomycin). The presence of pleural fluid eosinophilia may provide a clinical clue to the presence of drug-induced pleural disease but its presence or absence is not specific. Pleural fluid eosinophilia (PFE) is defined as pleural eosinophils comprising greater than ten percent of total nucleated cells in the pleural fluid. It accounts for about 5 to 8% of exudative pleural effusions. PFE, although not diagnostic by itself, helps to narrow the differential diagnosis of an exudative effusion. The important causes of pleural fluid eosinophilia include pneumothorax, hemothorax, benign asbestos pleural effusion, fungal disease, malignancy, pulmonary emboli with pulmonary infarction, parasitic infection, infection (including tuberculosis), congestive heart failure, connective tissue diseases, and hypersensitivity reactions. It is important to exclude
these diseases before considering the diagnosis of drug-induced pleural disease. Eosinophilic pleural effusion remains undiagnosed in 30% of cases.

Our patient had been admitted with right-sided pneumonia with loculated parapneumonic effusion that necessitated a long duration of treatment with cloxacillin but he developed left-sided pleurisy eight days later. Eosinophilic pleural effusion was recorded later after thoracocentesis. Despite a change to piperacillin/tazobactam, his pleural effusion increased. The presence of peripheral eosinophilia, eosinophilic pleural effusion, the temporal relationship of the presentation with the use of penicillin group of antibiotics, and the lack of an alternative explanation for his acute presentation after being treated for pneumonia, supported the possibility of an allergy to penicillins (cloxacillin and piperacillin/tazobactam) causing the pleural effusion. Both cloxacillin and piperacillin/tazobactam are reported to cause peripheral eosinophilia in less than one per cent of cases but a review of the literature revealed one study describing eosinophilic pleural effusion to several antibiotics (penicillin, claphoran, streptomycin) it cannot be decided for certainty whether the drug reaction in our patient was related to all B-lactam antibiotics or only to penicillins; he had taken ceftriaxone for six days only and it had been stopped before the development of the eosinophilic pleural effusion. Drug reactions may be related to the duration of therapy and/or the dose, as our patient started to have pleurisy on the 9th day on a total daily dose of Cloxacillin 8 gm intravenously, and was progressing while on oral cloxacillin 4 gm daily. Pleural effusion was documented 11 days later and was even increasing on being shifted to piperacillin/tazobactam. This suggests that the patient was allergic to both cloxacillin and piperacillin/tazobactam. Discontinuation of the drug was associated with a rapid and dramatic resolution of the pleural effusion within days with a marked decrease in the patient’s symptoms. Interestingly, his chest pain subsided abruptly even before the next scheduled dose of the offending drug. He was given prednisolone 30 mg once daily for one week. Peripheral eosinophilia and pleural effusion disappeared by day 6 of stopping the offending drug. The duration of resolution of drug induced pleural disease may take up to 6 months; adjunctive corticosteroids can hasten resolution of symptoms if they are severe at presentation. Improvement of symptoms was reported within two days and of the effusion within three weeks in a case of EPP due to dantrolene treated with steroids. The favorable response to steroids may suggest further that inflammation underlies the pathogenesis of drug induced pleural disease. This case report documents that though penicillins are rare causes of peripheral eosinophilia, they may cause drug-induced eosinophilic pleural effusion. It should be emphasized that any drug must be considered as a potential cause for an undiagnosed exudative effusion, before pursuing an extensive diagnostic evaluation that may lead to patient discomfort and unnecessary expensive tests.

References: