Immune-mediated Leukopenia due to Chlamyaphila pneumoniae Pneumonia* 

Leucopenia inmunomediatda secundaria a neumonia por Chlamyaphila pneumoniae 

To the Editor,

Chlamyaphila pneumoniae is known to affect the immune response of hosts, but this bacteria has not been described as a cause of autoimmune leukopenia. To our knowledge, this is the first report of a patient with C. pneumoniae pneumonia who developed antineutrophil IgG antibodies.

A 37-year-old woman presented with a 1-week history of cough, bloody sputum and fever. Physical examination showed temperature of 38 °C and crackles in right lung field. Chest X-ray showed bilateral alveolar infiltrates, corresponding with computed tomography findings of right lower lobe consolidation, and ground glass opacities in left upper lobe and both lower lobes (Fig. 1). ECG was normal. Arterial blood gases: pH: 7.52, PaCO2 34 mmHg, PaO2 67 mmHg. Clinical laboratory tests: blood glucose 95 mg/dl, urea 18 mg/dl, creatinine 0.77 mg/dl, sodium 139 mmol/l, potassium 2.8 mmol/l, chloride 98 mmol/l, GOT 44 U/l, GPT 44 U/l, LDH 510 U/l, C-reactive protein 287 mg/l, procalcitonin 0.18 ng/ml, leukocytes 3080 μl, neutrophils (76.7%), hemoglobin 10.1 g/dl, platelets 222,000 μl. Quick time 68%. Microbiology: sputum, blood culture, and pneumococcal and Legionella urinary antigen tests negative. C. pneumoniae serology was positive in acute-phase serum, with elevated antibody titer with seroconversion (1/4/2013 IgG negative [0.157], IgM negative [0.307]; 2/5/2013 IgG indeterminate [0.992], IgM positive [1.428]) on micro-immunofluorescence. During hospitalization, leukopenia worsened to 1770/μl with neutrophil count of 850/μl in the presence of IgG-positive antineutrophil antibodies. Antineutrophil antibodies were detected with fluorescence-labeled polycyal rabbit anti-human IgM and IgG antibodies (fluorescein isothiocyanate [FITT] (DAKO). Cell suspension was analyzed using flow cytometry (FACS®, Becton Dickinson). The patient received levofloxacin for 3 weeks, resulting in radiological resolution of the pneumonia and normalization of blood panels.

C. pneumoniae is a Gram-negative bacteria, previously known as Taiwan acute respiratory agent (TWAR). It causes 10% of community-acquired pneumonias (CAP) in Europe (12% of CAPs that do not require hospitalization and 3% of those that do).1,2 It may be responsible for immunological phenomena related to coronary atherosclerosis,3 but it is unusual for it to cause autoimmune leukopenia associated with antineutrophil IgG antibodies, as occurred in our case.

In autoimmune neutropenia, antibodies develop that act directly against cell membrane antigens, causing peripheral destruction of neutrophils. These antineutrophil antibodies promote phagocytosis of neutrophils opsonized by splenic macrophages.4 Autoimmune neutropenia may be primary or secondary and is more common in adults. It is often related to autoimmune diseases (primary biliary cirrhosis, Sjögren syndrome, lupus erythematosus, and rheumatoid arthritis), as well as to exposure to medication (fluorurabine, rituximab), solid tumors and blood cancers, neurological diseases, such as multiple sclerosis, or infections. Viral infections, such as human immunodeficiency virus, es Parvovirus, or Epstein–Barr virus, bacteria, such as Helicobacter pylori, Escherichia coli, Neisseria meningitidis, Brucella spp., Salmonella spp. and Mycobacterium tuberculosis, and other pathogens, including Toxoplasma gondii, Leishmania spp. and malaria, have also been implicated. However, a review of the literature did not yield any report of autoimmune neutropenia developing as a result of C. pneumoniae infection.5

References

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Cystic Fibrosis and Piperacillin/Tazobactam: Adverse Reactions

Fibrosis quística y piperacilina tazobactam: reacciones adversas

To the Editor,

Cystic fibrosis (CF) patients commonly have chronic lung infections and frequent exacerbations caused by a range of bacteria, including Pseudomonas aeruginosa (P. aeruginosa) and Achromobacter xylosoxidans, requiring multiple cycles of antibiotics such as piperacillin/tazobactam. This combination has been associated in the literature with increased bone marrow toxicity, and it should be used with caution.\(^1\)

We report 2 cases of CF patients, presenting with fever and myelotoxicity caused by piperacillin/tazobactam administered for P. aeruginosa infection, who required a switch to another antibiotic.

The first patient was a 20-year-old man with CF genotype F508del/F508, colonized with methicillin-resistant Staphylococcus aureus and P. aeruginosa. He was admitted for a respiratory exacerbation, with increased cough, greenish expectoration, weight loss, and worsening lung function, manifesting as forced vital capacity (FVC) 2950 ml (53%), forced expiratory volume in 1 second (FEV\(_1\)) 1885 ml (42%), and FEV\(_1\)/FVC 63.90. Treatment was started with intravenous piperacillin/tazobactam 4/0.5 g every 8 hours, and tobramycin 400 mg/24 h. The patient was discharged after 10 days to complete treatment at home. He was readmitted 7 days later with fever, myalgia, and epigastralgia. Clinical laboratory tests showed anemia (hemoglobin 11.3 g/dl) and leukopenia (2940/mm\(^3\)), with a normal blood smear. Piperacillin/tazobactam was switched to ceftazidime, while the aminoglycoside was maintained, leading to an improvement in laboratory parameters.

Our second case was a 23-year-old man with CF genotype F508del/unknown mutation with the following lung function status: FVC 2950 ml (60%); FEV\(_1\): 1670 ml (42%); and FEV\(_1\)/FVC (56.56%); along with chronic P. aeruginosa bronchial infection. In view of symptoms of respiratory infection and functional decline, treatment was started with piperacillin/tazobactam 4/0.5 g/8 h and tobramycin 400 mg/24 h. On day 17 of treatment, he developed fever (39.5 \(^{\circ}\) C) with no other accompanying signs. Clinical laboratory tests revealed anemia (hemoglobin 12.5 g/dl), thrombocytopenia (96,000/mm\(^3\)) (Table 1), coagulation changes (prothrombin activity 56% and cephalin time 41.6 s), and hepatic involvement (GOT 170 U/L, GPT 51 U/L, GGTT 24 U/L, and LDH 1462 U/L). Piperacillin/tazobactam was switched to levofloxacin. On day 4 after admission, the patient’s platelet count (165,000/mm\(^3\)) increased, coagulation parameters (prothrombin activity 102% and cephalin time 29.6 s), and liver function (GOT 18 U/L, GPT 27 U/L, GGT 19 U/L, LDH 285 U/L) improved.

Several papers have been published on the adverse effects of piperacillin/tazobactam in CF patients. For reasons that are still unclear, these events seem to be more common in CF than in the general population.\(^2\) Risk factors include a high accumulative dose of antibiotics in a short period of time and prolonged treatments (>10 days).\(^3\)\(^4\) Haptene-induced hemolytic anemia\(^5\) has been reported to respond well to intravenous immunoglobulin.\(^2\) Leukopenia, thrombocytopenia, fever, and hypersensitivity reactions that range from pruritus and skin rash to anaphylactic shock\(^5\)

### Table 1
Adverse Reactions Associated With Piperacillin/Tazobactam in Cystic Fibrosis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Number of Patients</th>
<th>Age/Sex</th>
<th>Dose</th>
<th>Onset of Symptoms (days)</th>
<th>Adverse Effects (%)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichardt P.(^1)</td>
<td>1996–1998</td>
<td>32</td>
<td>NR</td>
<td>Accumulated dose over 14 days 4.9 g/kg</td>
<td>11</td>
<td>Fever, general malaise, and headache</td>
<td>PTZ discontinuation</td>
</tr>
<tr>
<td>Bandara M.(^3)</td>
<td>2010</td>
<td>1</td>
<td>39/F</td>
<td>4.5 g iv every 6 h</td>
<td>7</td>
<td>Hemolytic anemia</td>
<td>Transfusion, steroids, iv immunoglobulin, PTZ discontinuation</td>
</tr>
<tr>
<td>Zanetti R.C.(^2)</td>
<td>2013</td>
<td>1</td>
<td>19/F</td>
<td>NR</td>
<td>13</td>
<td>Hemolytic anemia</td>
<td>Transfusion, immunoglobulina iv, PTZ discontinuation</td>
</tr>
<tr>
<td>Marik P.E.(^4)</td>
<td>2013</td>
<td>1</td>
<td>24/M</td>
<td>NR</td>
<td>15</td>
<td>Hemolytic anemia</td>
<td>Transfusion, steroids, immunoglobulina iv, PTZ discontinuation</td>
</tr>
</tbody>
</table>

F: female; iv: intravenous; M: male; NR: not reported; PTZ: piperacillin/tazobactam.

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