Official journal of the Spanish Society of Chemotherapy

Letter to the Editor

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Daptomycin eosinophilic pneumonia: an adverse effect to be aware of

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Article history
Received: 31 July 2017; Revision Requested: 22 January 2018; Revision Received: 23 January 2018; Accepted: 23 January 2018

Dear Sir,

Daptomycin is an antibiotic in the family of glycopeptides that is characterized by its great activity against Gram-positive bacteria. Clinicians are aware of its potential muscle damage (5%) and gastrointestinal manifestations (7%). Eosinophilic acute pneumonia (AEN) is another adverse effect that can be potentially fatal. Early recognition and reasonable exclusion of other causes can make the difference.

We present a case of a 50-year-old female patient with arterial hypertension, dyslipidemia, grade II obesity, and mild extrinsic allergic asthma admitted to our hospital initially for placement of elective knee prosthesis. During the intervention, traumatic rupture of the popliteal artery occurs, so the postoperative was complicated with shock, which ends in supracondylar amputation of the right leg. Treatment with meropenem (1g/8 h) and daptomycin (5 mg/kg/day) was started, obtaining as the only microbiological finding *Klebsiella pneumoniae* BLEE in blood cultures. Urine and bronchial aspirate culture were negative and the surgical wound was not cultured. After 14 days of stay in Reanimation, the patient presented a new febrile peak with no clear focus, so broad-spectrum antibiotics were maintained since all cultures of different sources were negative. On day +23 with daptomycin and meropenem as antibiotic treatment, the patient develops insidious dyspnea, orthopnea and dry cough. Physical examination revealed tachycardia, superficial tachypnea, dry crackles in pulmonary auscultation and 90% pulse oximetry. Chest x-ray show bilateral reticulointerstitial pattern of new appearance. Blood tests show eosinophilia with 4,010 eosinophils/mm^3. High resolution thoracic CT is performed confirming this nonspecific bilateral diffuse interstitial pattern with some areas of tarnished glass of peripheral predominance (figure 1). Daptomycin is withdrawn given the high clinical suspicion of eosinophilic pneumonia secondary to it. Preferential bronchoscopy was requested - without macroscopic findings. Finally, the result of the cytometry of bronchoalveolar lavage shows the presence of 98% of eosinophils. All cultures in conventional and specific media were negative. Given the absence of improvement 3 days after daptomycin withdrawal, Prednisone was started at 0.5 mg/kg/ day. The patient experimented progressive disappearance of dry cough and the tendency to tachypnea in 48 hours. The x-ray also demonstrated the disappearance of bilateral infiltrates (figure 2), so the patient was discharged to an orthopedic rehabilitation center with a short tapering in its rehabilitation center. This case was notified through the usual route to Spanish National Drug Agency.

AEN is a severe syndrome usually associated with drug exposure. Its pathophysiology is related to a recruitment of Th2 lymphocytes and release of IL-5, which promotes the migration of eosinophils to the lung [1]. Daptomycin is a glycolipopeptide with a high bactericidal activity against Gram-positive microorganisms. The drug mechanism undergoes conformational change through interaction with the membrane, increasing its permeability and blocking protein synthesis. However, the pulmonary toxicity mechanism of daptomycin is unknown. It has believed that it can be related to drug accumulation in the pulmonary epithelium that leads to a lipid alteration that stimulate the inflammatory response [2]. There are two diagnostic classifications for AEN related to pneumonia: one from FDA warning [3] and one established by Solomon and Schwartz [4]. Both are similar and are summarized in: 1) exposure to daptomycin; 2) fever, dyspnea and increased oxygen requirements; 3) new onset pulmonary infiltrates; 4) bronchoalveolar lavage with>25% eosinophils; and 5) clinical improvement after daptomycin withdrawal. A recent meta-analysis showed that reports of eosinophilic pneumonia due to daptomycin occurred in patients with a dose range of 4-10mg/kg/day and with generally prolonged exposures to the drug (2.8 ± 1.6 weeks) [5]. Therefore, it has suggested that it is a time de-

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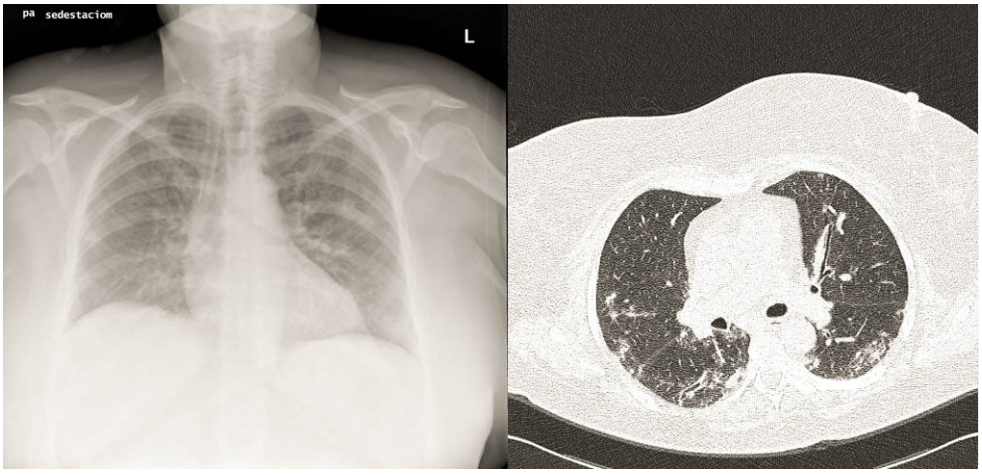

Figure 1 | **Chest x-ray and CT scan at the beginning of symptoms that showed diffuse interstitial infiltration with some ground glass opacities.**

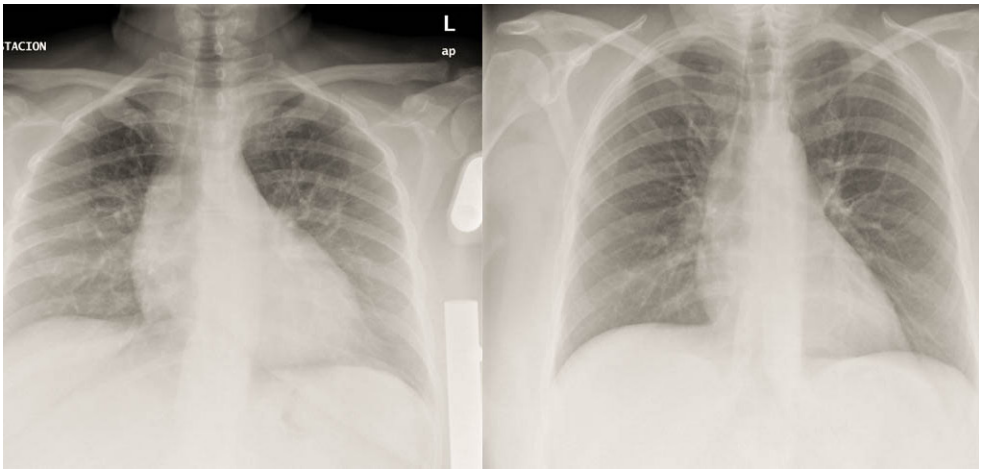

Figure 2 | **Chest x- ray on day +3 and day +7 after daptomycin withdrawal. The second one was done after 4 days of corticosteroids treatment.**

pendent rather a dose dependent effect. Peripheral eosinophilia is the most frequent finding (77%). However, the pharmacokinetics of daptomycin vary with changes in effective volume (sepsis, malnutrition, edema) and tissue concentration depends on the serum concentration of daptomycin. According to this, some authors propose the measurement of daptomycin levels for finer dose adjustment [6]. The clinical spectrum is varied and ranges from interstitial pneumonia with mild symptomatology to pulmonary involvement that leads to severe respiratory insufficiency and mechanical ventilation [7,8,9]. There is no clear consensus, but it seems that corticoids may be a therapeutic option [10]. In fact, the first diagnostic criteria for AEN proposed by Allen [11] included response to corticoid treatment as a criteria. We believe that the present case supports this idea since our patient did not begin to improve substantially until the introduction of corticosteroids 3 days after the daptomycin withdrawal.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

FUNDING

None to declare

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