Acute Generalized Exanthematous Pustulosis Due to Teicoplanin

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Acute generalized exanthematous pustulosis (AGEP) is a severe, drug-related reaction, characterized by acute onset of nonfollicular sterile pustules on an erythematous skin, fever (>38ºC) and neutrophilic leukocytosis [1]. It generally appears within 48-72 hours after the administration of the drug, although in some cases, the onset of symptoms may be delayed for up to three weeks [2]. The list of different drugs that have been associated with AGEP is increasing, however very few cases related to glycopeptides have been reported.

We report a case of a 60-year-old woman without personal history of psoriasis or other skin affections, who was admitted at the hospital for a total knee arthroplasty using a cemented prosthesis with gentamicin and clindamycin. Intraoperatively, she received antibiotic treatment with meropenem, with maintenance for up to 6 days associated with teicoplanin for the first 4 days, paracetamol and metamizole. One week after hospital admission, she presented an erythematous rash in axillary and inguinal folds, initially treated with fluconazole 50 mg/24h suspecting a candidiasic intertrigous. However, the lesions evolved unfavorably extending to the thorax, abdomen and lower limbs with, groups of non-follicular pustules on an erythematous desquamation base and fever (38ºC) appeared without mucosal affection. The surgical wound showed no inflammatory signs and traumatology ruled out possible

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postoperative complications. Blood tests showed leukocytosis with neutrophilia (28.000/uL; 91% neutrophils), elevated acute-phase reactants (fibrinogen 506 mg/dl, CPR 6.8mg/dl), and normal renal and hepatic function. Despite treatment with topical and systemic corticosteroids and antihistamines, the patient continued worsening. Two weeks later, treatment with cyclosporine was started, observing improvement in the two following weeks. A skin biopsy revealed frequent spongiform pustules without fungal elements in the spinous layer of the epidermis and a perivascular lymphocytic inflammatory infiltrate with moderate eosinophilia in the dermis, consistent with AGEP. Six months after resolution of AGEP, patch tests (PT) were performed using Finn Chambers AQUA Epicutaneous Patch Test Strips with clindamycin 5% dimetilsulfoxide (DMSO), gentamicin 20% petrolatum (pet), benzylpenicillin 1% (pet), meropenem 5% (DMSO), teicoplanin 10% (DMSO), paracetamol 10% (pet), metamizol 1% (pet) and DMSO control. Readings were done at Day 2 (D2) and D4 with negative results. In addition, intradermal tests (IDT) were performed with benzylpenicilloyl poly-L-lysine as the major determinant at a concentration of 0.04 mg/mL and a minor determinant mixture (benzylpenicillin sodium, benzylpeniciloic acid, and sodium benzylpenicilloate), amoxicillin, meropenem, vancomycin, teicoplanin, gentamicin and metamizole with negative readings at 24 hours. A single blind challenge test (SBCT) with meropenem, clindamycin and paracetamol was performed being negative. Due to our high clinical suspicion of AGEP associated to gentamicin or metamizole, a SBCT with teicoplanin was performed in consecutive several days, increasing doses up to therapeutical dose (table 1). On the second day of the teicoplanin infusion, after 6 hours of administration (200 mg dose), the patient began an erythematous exanthema on folds, neck, upper limbs, trunk, auricular pavilions and scalp with non-follicular pustules on

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occipital region, neck and back accompanied with fever (39º) (Picture A and B). She was treated with topical and systemic corticosteroids at high doses during 10 days, but despite treatment, no improvement was observed. The reaction end up affecting the 90% of the total body surface, reason why she was again admitted to the hospital for intravenous treatment. Despite the high dosage of systemic steroids the skin involvement persisted for 1-2 weeks, reason why a differential diagnosis with generalized pustular psoriasis (GPP) was considered and a weekly treatment with Etanercept 50 mgr was initiated with slight improvement. In this case, due to the long duration of the clinical course, we decide to perform a skin biopsy, which reflected frequent pustules in the spiny stratum of the spongiform-type epidermis. The supraadjacent cornea layer was properly constituted without microabscess or obvious fungal elements and the epidermis showed a thickness preserved without other significant alterations. In the underlying dermis, inflammatory perivascular lymphocyte infiltrate was observed withmoderate eosinophilia, confirming AGEP.

Teicoplanin is a glycopeptide antibiotic, indicated in infections due gram-positive bacteria. Its use has increased in recent years, as it is now first line in the perioperative setting [3]. Immediate allergic reactions to teicoplanin have previously been considered extremely rare, but they are more frequent than delayed reactions [4]. Chu et al [5] reported in 2001 the first case of teicoplanin inducing AGEP. PT with teicoplanin was performed 1 month later. Readings were made 3 days later with negative results. No challenge tests were carried out. Turrentine et al [6] described in 2011 a case of AGEP induced by telavancin, but no skin test were performed. Mawri et al [2] described in 2015 a case of AGEP due to vancomycin with an atypical presentation, however, no allergy workout were carried out. Sideroff et al [7]

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proposed a useful algorithm for the diagnosis of AGEP. Applying the AGEP validation score in our patient resulted in 8, confirming the diagnosis.

In order to diagnose the culprit agent causing the reaction, PT with reading at D2 and D4 is considered useful with sensitivity up to 58% [8]. Nevertheless, IDT with late reading is potentially useful. Both test were performed with negative results.

Typically self-limiting in nature, AGEP tends to resolve spontaneously with cessation of the offending drug. In this case, differential diagnosis between AGEP and GPP was considered. GPP is a rare variant of psoriasis of unknown etiology that usually causes generalized erythematous and pustular rash associated with occasional severe systemic reactions. It can develop in patients with or without previous personal history of psoriasis and it can be triggered by factors, such as infection or drugs. The rash of GPP appears morphologically identical to that of AGEP but the distribution pattern is wider spread and the rash and fever persist longer (9, 10). AGEP and GPP have been suggested as disorders on the same spectrum and they can appear overlapping. In this case GPP was ruled out by skin biopsy.

Teicoplanin is a recognized but very rare cause of AGEP. This case is unique not only in the fact that teicoplanin was confirmed to be the culprit medication with an oral challenge test, but also because the atypically not self-limiting evolution of the cutaneous eruption that required elevated dosage of systemic steroids, cyclosporine and etanercept. In all cases, is important to take into account other entities that could simulate an AGEP but also the possibility of a long course and severity of the AGEP.

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Conflicts of interest

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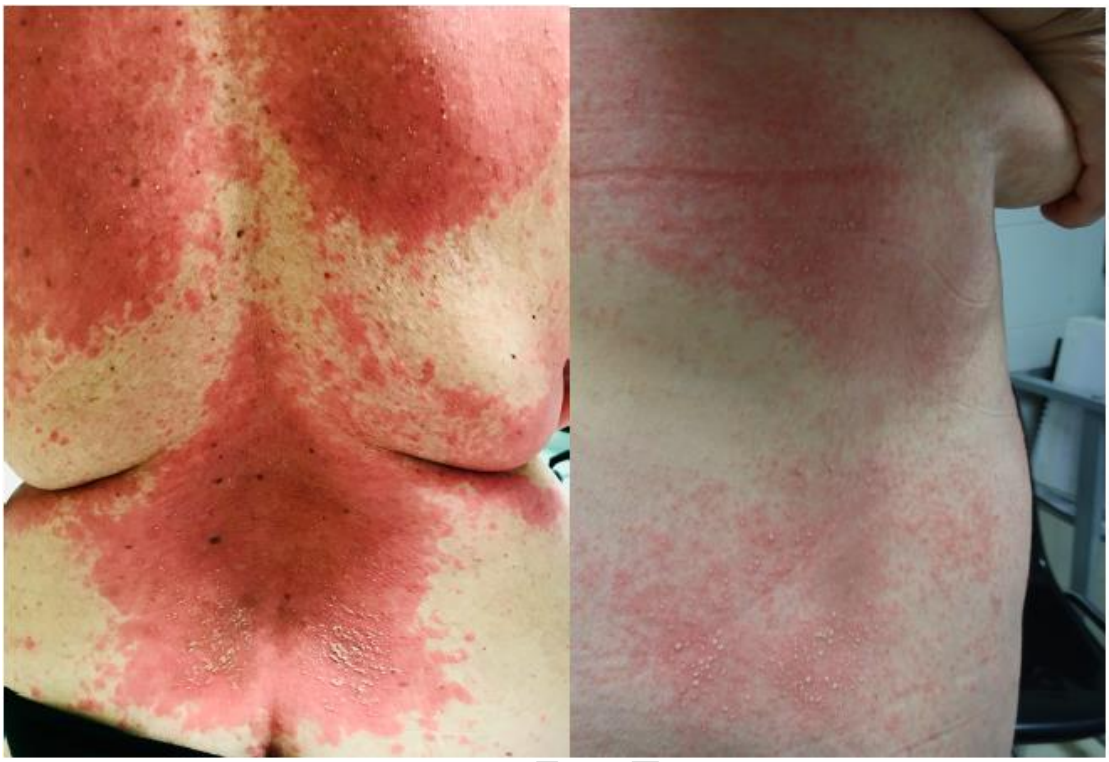
Figure legend: Erythematous exanthema on folds and trunk with non-follicular pustules after single blind challenge test (SBCT) with teicoplanin (200 mgr).



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