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Beta-lactam (BL) antibiotics are the most common cause of drug-induced hypersensitivity reactions (DHR).

Clinical Implications:

We present two clinical cases of patients with suspected immediate BL DHR who underwent drug allergy work-up according to standardized diagnostic procedures, including skin tests (ST: prick, SPT and intradermal tests, IDT) and drug provocation tests (DPT)[1]. ST became positive after the first DPT dose. The patients gave their consent to the diagnostic allergy work-up and use of their de-identified data for research purposes.

A 68-year-old man placed on the liver transplantation waitlist for cirrhosis due to hepatitis C viral infection in August 2017 was admitted to the hospital for cholangitis. The patient was empirically treated with piperacilline/tazobactam (piperacillin 4g/t.i.d) intravenously. He had previously tolerated this drug. About 45 minutes after the first dose, he developed pruritus and urticaria on the neck and trunk without other associated symptoms. He rapidly recovered with cetirizine (10 mg) by oral route. In December 2018 the patient reported a similar episode, treated with intravenous dexchlorpheniramine. In June 2019, the patient underwent ST with several penicillin and cephalosporin reagents. Histamine was used as a positive control. As SPT and IDT at the highest recommended concentrations were negative when read after 15 minutes and 20 minutes respectively (according to current recommendations), we proceeded to DPT (the first dose was given 60 minutes after the IDT reading). Single-blind challenge with intravenous piperacilline/tazobactam was performed, with 30 minutes increments, starting with 5%[2] (200 mg) of the therapeutic dose (4000 mg) that elicited his initial reaction. A few minutes before the administration of the second dose the patient reported itching on the arms and scalp, in the absence of objective clinical signs. Therefore, we decided to interrupt the test and monitor the patient for 15 minutes. A few minutes later the patient presented a localized itchy erythema at the site of the ST corresponding to pure IDT to piperacillin/ tazobactam and piperacillin, with ascending lymphangitic infiltration (Figure 1). No wheal was observed. The ST was nonetheless considered positive, the DPT was interrupted and cetirizine (10 mg) was administered.

Two hours after the administration of the first dose of the drug, the patient presented localized urticaria on the arms and the abdomen, with resolution in 90 minutes (see Figure E1 in the Online Repository).

A 62-year-old male patient, mentioned an episode of potential DHR in October 2012, with generalized urticaria, preceded by pruritus of palms and soles. This reaction started five minutes after the ingestion of 1000 mg amoxicillin for sinusitis, and during a meal containing shrimps. The allergy work-up was performed six weeks after the initial reaction. Skin tests (read at 20 min for IDT) were negative at the maximum recommended concentrations. As the patient had a history of immediate reaction, DPT with amoxicillin was started immediately after reading the skin tests. The began with 1 mg of amoxicillin (this was the first dose of the empirical DPT protocols that have been used in our unit till 2016). Thirty minutes after the first dose of amoxicillin, the patient presented a positive ST (> 3mm increase in the diameter compared to the injected wheal, surrounded by erythema) in IDT only at the site of amoxicillin injection, with a linear shape form and ascending lymphangitis 7.5 cm upward from the injection site (Figure 2). All the other ST were negative. The DPT was stopped immediately, he was treated with cetirizine (10 mg) and monitored for 90 minutes. No other symptoms appeared.

When negative immediate-reading ST occur in patients with a clinical history compatible with an immediate reaction (i.e., potentially IgE-mediated), a DPT is usually performed, in absence of contra-indications[1]. In the two cases we present, the first dose of the oral DPT was followed by ST positivity, associated in Case 1 with a systemic reaction (dose administered, 5% of initial eliciting dose). The peculiarity of the second case is that the patient developed a positive ST at 60 minutes, as opposed to 20 minutes following their performance and 30 minutes after the start of DPT without systemic symptoms (dose administered 0.1% of the initial eliciting dose). The absence of any systemic reaction in Case 2 may be due to the low initial dose.

ST reversal in these patients is likely due to a flare-up phenomenon. Flare-up reactions refer to the reactivation of previous positive ST or the switch from negative to positive ST, usually after a systemic challenge. This phenomenon is classically described in delayed-type allergy[3]. To the best of our knowledge, such rapid flare-up reactions have not been described for BL (published cases include delayed reactions)[3,4], but case reports suggestive of a flare-up-like reactivity suggesting IgE-mediated allergy have been described for other drugs (e.g., ibuprofen[5], paracetamol[6]).

In the two cases we present we observed localized superficial inflammation processes that induced linear in superficial lymphangitis from the site of the IDT of piperacillin and piperacillin/tazobactam (Case 1) and amoxicillin (Case 2), extending toward the arm. Lymphangitis is an inflammation of one or more lymphatic channels mostly induced by infections (mostly bacterial infections) occurring at the distal site of vessels. Many other causes could induce linear supralymphatic eruptions with superficial lymphangitis and some of these are viral and fungal

infections, insect or spider bites, and iatrogenic etiologies like vaccinations, purified protein derivative placement7. In a case series reported by Kano et al, three different cases which focus on the theme of superficial lymphangitis were discussed and the idea of the effect of contact allergens as a co-factor in this pathology was put forward. In their report, ST were negative for the alleged contact allergens and this is why they were merely considered as co-factors8. In our cases, the drugs are not contact allergens in the clinical history but injecting them by IDT may render them similar to a contact allergen. Most described cases of allergic lymphangitis concern delayed hypersensitivity reactions. Because dendritic cells are known to migrate from the sites of allergen exposure to draining lymph nodes during the inflammatory response, this hypothesis could explain why the linear lesions begin within the sites of IDTs and extend proximally to the draining lymph nodes, in delayed DHR. The two cases we presented revealed acute superficial lymphangitis, which raises the hypothesis of a local immunologic reaction to an allergen along lymphatic vessels, establishing a linear lesion overlying the skin. The promptness in onset and resolution of the lesions supports the assumption of this local reaction being elicited by mast cell mediator release, as connective tissue mast cells are located by nerve endings and alongside the blood and lymphatic vasculature[9]. Late-phase IgE-associated inflammatory responses to allergens cannot be excluded, considering that the reaction occurred later than classically observed in ST for immediate type reactions.

Although in Case 1, the reactive IDTs did not match the recommended positivity criteria (no wheal was detected, only surrounding erythema), in Case 2, the IDT became positive according to recommended reading criteria. In our experience, in more than 4000 patients tested for a suspicion of DHR to BL, these are the only two cases of their kind.

As clinicians working in the drug allergy field and operating with iatrogenic procedures (especially with BL antibiotics), we should be aware of rare cases. In these examples, monitoring the site of a negative ST (despite clinical histories of immediate reactions) even after reading the ST result within recommended lapses of time and when starting DPT prevented us from exposing our patients to higher doses of allergens and potentially a more severe reaction.

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Figure Legends

FIGURE 1: The following reagents were tested at the maximal non-irritant concentrations ("pure"): penicillin G (10 000 UI/ml, PG), amoxicillin/clavulanic acid (20 mg/ml for amoxicillin, Ag), ampicillin (20 mg/ml, Ap), piperacillin (20 mg/ml), piperacillin/tazobactam (20 mg/ml for piperacillin), cefuroxime (20 mg/ml, Z), ceftriaxone (20 mg/ml, C4).

FIGURE 2: Positive skin test to amoxicillin (20 mg/ml); the injected wheal is circled at the time of the performance of IDT; the increased wheal, erythema and lymphangitis occurred after 1 mg amoxicillin by oral route.

FIGURE 1

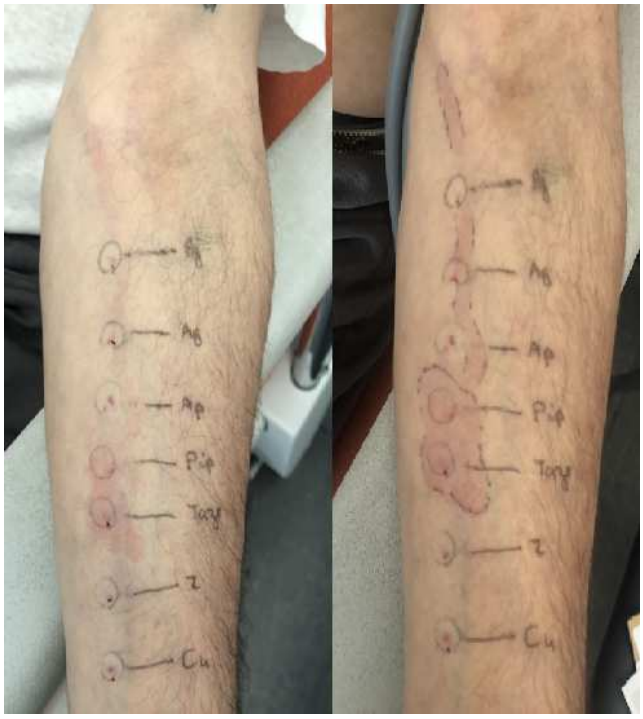

FIGURE 2