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“Prick or treat”: a case of systemic reaction during intradermal tests with beta-lactams

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A 58-year-old man with a history of psychiatric disorders (schizophrenia), chronic alcoholism, diabetes and hypertension was referred to our dermatology and allergology department for a history of drug hypersensitivity reaction to beta-lactams. Ten years ago, the patient had experienced malaise after oral penicillin intake. He did not report any other associated symptoms. The precise drug details were unknown. He received no specific medical treatment and the symptoms quickly resolved spontaneously. The exact time between taking a tablet and the onset of symptoms and the time between the start of antibiotic treatment and the reaction were not known. His general practitioner could not provide us with any further details. He has not taken beta-lactam since.

This atypical case did not seem compatible with an allergic mechanism, thus we decided to start skin tests (ST) directly with intradermal tests (IDT) with a 1/10 dilution of the maximum dose for different beta-lactams (amoxicillin, penicillin G, ceftazolin, cefuroxime, cefotaxime, ceftriaxone, cefixime) as the culprit drug was unknown. Ten minutes after IDTs, the patient complained of intense pruritus, atypical flares (~200-mm diameter wheals and >200-mm diameter flares (figure 1A). The other tests were not interpretable due to the diffuse...
erythema. Within five minutes, the patient developed general-ized urticaria with angioedema. His vital signs were stable with no other associated symptoms. The reaction subsided with treatment with intravenous antihistamines only. Symptoms fully resolved within two hours and the patient was discharged home after three hours of monitoring. Tryptase level, one hour after the onset of symptoms, was positive at 15.4 μg/L (with a basal level of 4.5 μg/L, 24 hours later). Amoxicillin-specific IgE was slightly elevated at 0.54 kUa/L. We also performed basophil activation tests that were positive for amoxicillin and penicillin G and negative for ceftriaxone.

The patient was seen again, six weeks later, for further evaluation to determine alternative treatments. This time, we started with skin prick tests (SPT) and then IDTs with 1/1000 dilution of the maximum recommended dose based on the previous negative tests. SPTs were positive with 15-mm and 10-mm-diameter wheals and 30-mm and 20-mm-diameter flares for amoxicillin and penicillin G, respectively (figure 1B). IDTs were positive for piperacillin (0.02 mg/mL), cefazolin (0.2 mg/mL), and cloxacillin and oxacillin (2 mg/mL). ST were negative for cefuroxime, cefotaxime, ceftazidime, imipenem, ceftriaxone and cefixime, up to the maximum dose. We performed provocation tests with ceftriaxone and cefixime with excellent tolerability, and thus authorized these two drugs as therapeutic alternatives in case of future need for beta-lactam use.

Beta-lactam antibiotics, including penicillin, cephalosporins, carbapenem, and monobactam, are the most widely used class of antibiotics, but also the most commonly reported cause of immediate drug allergy, with a prevalence ranging from 5% to up to 15% [1]. However, over 90% of patients labelled as allergic are in fact able to tolerate beta-lactams.

The first approach to diagnose IgE-mediated drug allergy is to establish a plausible history, which implies that symptoms must be compatible and occur within one hour of drug intake [2]. Then, skin testing is unanimously recommended as the first line of diagnosis of allergic sensitization to penicillin and other beta-lactams [3-5]. Indeed, an IgE-mediated reaction can be demonstrated by a positive skin prick and/or intradermal test after 20 minutes [3]. SPT is performed by pricking the skin percutaneously with an allergen solution. It is the safest and easiest test, but only moderately sensitive. Intradermal testing is more sensitive than SPT but results in an increased antigen load to which the body is exposed through the skin, and can therefore cause significant local and, more rarely, systemic reactions. As far as penicillin is concerned, the rate of systemic reactions from skin tests is apparently higher than for common allergens.

It has been shown that the relative risk of systemic reactions from skin testing is proportional to the pre-test probability of a true immediate hypersensitivity reaction to beta lactam antibiotics, i.e., patients with a clinical history of generalized or severe adverse reactions, even if there is a long time interval between the initial reaction and skin testing [6-10]. Nevertheless, the magnitude of the risk is largely variable across studies, with an incidence ranging from 0.02% to 1.4% for patients tested and from 0.7% to 9.4% for patients tested with positive skin [7, 8, 11, 12]. Most of the systemic reactions were skin manifestations of pruritus and urticaria, and local swelling. Very severe reactions or death have only been reported anecdotally [13, 14]. Few reactions appeared after SPT and the majority were described after IDT. In patients reporting previous severe reactions, after negative SPT, IDTs should be carried out, starting with a 1,000-fold dilution, gradually increasing at logarithmic steps, until a positive test is elicited, or the maximum concentration is reached. Moreover, in vitro tests could be performed before ST, such as specific IgE dosage or basophil activation tests, but these show very low sensitivity, at around 50% [15, 16]. In our case, the patient self-reported a history of adverse reaction to penicillin with vague, poorly documented and subjective symptoms (e.g. general malaise). These criteria led us to consider that the patient belongs to the subgroup with a low probability of allergic sensitization to penicillin. Nevertheless, because of his medical history, especially psychiatric disorders, documenting a detailed history of past reactions was difficult and unreliable.

This case illustrates that intradermal testing should be performed with caution in patients with an unreliable clinical history. In this context, SPT should precede IDT in order to ensure the allergological assessment and avoid any risk of systemic reaction. Patients should receive a detailed explanation of the risks of the procedure, and it is essential to have well-trained medical staff who are immediately available in case of emergency, as well as facilities for continuous monitoring of the patient’s condition.

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Pemphigus foliaceus after mRNA COVID-19 vaccine

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Pemphigus foliaceus (PF) is a rare autoimmune bullous disorder. The key target is desmoglein 1 (Dsg1), an impor-
tant component of desmosomes along with Dsg3, which holds keratinocytes within the epithelium [1]. Genetic susceptibility, drugs, malignant disorders, ultraviolet light, and stress have been reported to trigger or exacerbate PF. Here, we report the case of a patient who developed PF following COVID-19 vaccination with the mRNA vaccine, BNT162b2 (Comirnaty, Biontech/Pfizer).

A 35-year-old Caucasian female patient, previously healthy, was referred to our department after developing scaly and crusted plaques associated with erosions over the scalp and upper body. The lesions began approximately two weeks after the second administration of BNT162b2. The lesions initially started on the trunk as small purpuric erythematous plaques with fragile vesicles that evolved to erosions and yellow crusts. Two weeks later, the patient also noticed lesions on the scalp, with extensive erosions and crusts with areas of pseudoalopecia (figure 1A, B). The mucosa was spared. A diagnosis of pemphigus was suspected on clinical presentation. The anatomopathological examination of lesional skin showed mostly ulceration due to excoriation. At the periphery, the residual epidermis had a superficial cleft with few acantholytic keratinocytes and detachment of the stratum corneum. There was a mild perivascular inflammatory infiltrate at the papillary dermis (figure 1C). Direct immunofluorescence of perilesional skin revealed a prominent deposition of IgG and C3 in a honeycomb-like intercellular epidermal pattern (figure 1D).

The titre of autoantibody against Dsg1 in the patient’s serum was 40 RE/mL, and the patient was negative for Dsg3 (Euroimmun, Lübeck, Germany). The indirect immunofluorescence tests also revealed honeycomb-like fluorescence of an intercellular substance in the stratum spinosum and confirmed the presence of autoantibodies against Dsg1 (Dermatology Mosaic 11, Euroimmun, Lübeck, Germany) (figure 1E). These findings confirmed the diagnosis of PF.

The patient initiated treatment with oral prednisolone (0.75 mg/kg) and topical clobetasol with significant improvement. Over the following six months, she developed sporadic flares when oral prednisolone was reduced to less than 0.25 mg/kg. She developed COVID-19 infection at Month 7 of follow-up which again worsened the disease and led to an increase in oral prednisolone to 0.75 mg/kg. At present, Month 8, the disease is stable, she is being followed at our clinic, and we are discussing the possibility of initiating rituximab, which was previously limited due to the COVID-19 pandemic.

Single cases of de novo and flares of pemphigus vulgaris (PV) and bullous pemphigoid have been reported after COVID-19 vaccination [2-5]. However, reports of PF are scarce in the available literature [6, 7]. A direct pathological link between the vaccine and these events has not been established, and the association is based on a clear temporal relationship between the two events. BNT162b2 is a lipid nanoparticle-formulated, nucleosome-modified RNA vaccine that encodes prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein [8]. Antibody response and activation of CD4+ and CD8+ T-cell responses induced by the vaccine are dose-dependent and are particularly significant after the boosting dose [9]. Similar to previous reports, there was a clear temporal relationship between these two events, but the pathological link remains elusive [2]. We know from history that both vaccinations and infections may cause autoimmune reactions in predisposed individuals [10]. The mecha-