Amoxicillin/Clavulanic Acid-Induced Pemphigus Vulgaris: Case Report

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SUMMARY Drug-induced pemphigus is a well-established variety of pemphigus, presenting with clinical and histopathologic features identical to idiopathic form. Medical history plays a fundamental role in the diagnosis of drug-induced pemphigus. A large variety of drugs have been implicated in its pathogenesis and they may induce acantholysis via biochemical and/or immune mechanism. We present a case of a 69-year-old woman affected by amoxicillin/clavulanic acid-induced pemphigus and discuss its pathogenetic mechanism.

KEY WORDS: pemphigus, amoxicillin/clavulanic acid, biochemical acantholysis, amoxicillin/clavulanic acid-induced pemphigus, drug-induced pemphigus

INTRODUCTION

Pemphigus is an autoimmune bullous disease that may be influenced by genetic and exogenous factors, among which drugs are considered as the leading cause (1,2). Drug-induced pemphigus is a well-established variety of pemphigus (3). The clinical, histologic and cytologic features are identical to idiopathic pemphigus (4). A large variety of drugs (Table 1) have been implicated in the onset and/or exacerbation of the disease (3). Among them, beta-lactams are rarely reported.

Herein, we report a case of a woman with amoxicillin/clavulanic acid-induced pemphigus, in the absence of autoantibodies.

CASE REPORT

A 69-year-old woman was referred to our Department with a three-week history of skin and painful mucosal lesions. On physical examination, she showed whitish-erythematous erosions of the oral mucosa, and cutaneous blisters affecting abdominal and lumbar regions, pubis and upper limbs (Fig. 1). Nikolsky’s sign was present.

Cytologic and histopathologic examinations supported the diagnosis of pemphigus vulgaris (Fig. 2). Screening laboratory tests did not show the presence of autoantibodies (anti-desmoglein and anti-desmocollin). On epidermal extract immunoblotting, the patient’s serum did not react with Dsg-1 and Dsg-3.

Medical history revealed that the patient had received amoxicillin/clavulanic acid combination (2 g/day for 15 days) for a perimandibular abscess and that 20 days after the first administration, erosive lesions had appeared on the oral mucosa, followed by blisters appearing on the pubis and progressively...
spreading to all the aforementioned cutaneous areas. The patient reported that a similar eruption had appeared a few months earlier, 2 weeks after another amoxicillin/clavulanic acid treatment for the same recalcitrant dental infection. During both events, direct and indirect immunofluorescence did not reveal positivity for autoantibodies.

Based on the clinical, cytologic and histopathologic findings, and on the relationship between the onset of skin eruption and previous drug administration, a diagnosis of drug-induced pemphigus was made. Withdrawal of the culprit drug and short-term systemic corticosteroid therapy led to complete and permanent remission of the disease. After six months, no new lesions appeared.

### DISCUSSION

Pemphigus is a potentially life-threatening autoimmune disease of the skin and mucous membranes, clinically characterized by the formation of blisters and erosions, and histologically by acantholysis (1).

Acantholysis is a morphofunctional change of malpighian epithelia, resulting in the loss of intercellular cohesion and the halt of process of keratinization. It is considered the initial and the main pathogenetic event in pemphigus, provoked by circulating and skin-fixed autoantibodies directed against intercellular desmosomes of epidermal keratinocytes, namely two groups of transmembrane glycoproteins called desmoglein (Dsg) and desmocollin (Dsc). Both proteins belong to the cadherin gene family. The desmogleins most frequently involved in the pathogenesis of pemphigus are Dsg-1 and Dsg-3. Dsg-1 is primarily expressed in the upper layers of the epidermis and weakly in the squamous mucosa, whereas Dsg-3 is strongly expressed in mucosa and weakly in the epidermis. Thus, generally, high levels of anti-Dsg-1 antibodies are present in pemphigus foliaceus, while high levels of anti-Dsg-3 antibodies are detectable in pemphigus vulgaris (1,3).

Pemphigus is considered to stem from a genetic predisposition to the disease, induced and/or aggravated by one or more exogenous factors, summarized by Brenner et al. in the acronym ‘PEMPHIGUS’: PEsticides, Malignancy, Pharmaceuticals, Hormones, Infectious agents and Immunization, Gastronomy, Ultraviolet radiation, and Stress (3).

In drug-induced pemphigus (DIP), acantholysis can be evoked with biochemical and/or immune mechanism. Biochemical acantholysis occurs without antibody mediation, but with a direct interference of the drug with keratogenesis, while immune acantholysis would be caused by elicitation of autoantibody production (3).

According to the literature (5), there are three groups of drugs that can cause pemphigus: thiol drugs, inducing acantholytic changes by inhibition of enzymes that aggregate keratinocytes, activation of keratinocyte-disaggregating enzymes, disturbance of cell-adhesion; phenol drugs, that would be responsible of the release of cytokines, such as tumor necrosis factor alpha and interleukin 1 alpha by keratinocytes; and nonthiol nonphenol drugs.

Beta-lactams are rarely reported to be inducers of pemphigus (6-8). In particular, penicillin has been considered as a masked thiol that contains an S molecule and can be converted in a thiol (6). It has been postulated that, in case of an abortive form of pemphigus induced by protracted penicillin treatment,
the probable trigger is actually penicillamine, which is formed by the metabolic breakdown of the penicillin molecule (9).

The diagnosis of drug-induced pemphigus with biochemical acantholysis is challenging and not consensual because clinical signs are equal to those of autoimmune (idiopathic) forms, and because the interval between the administration of the culprit drug and the onset of cutaneous lesions is not well defined. Moreover, patients often take multiple drugs and some of them have a prolonged latency period between exposure and onset of the disease (5). Recently, the in vitro interferon-gamma release from lymphocytes test has been shown to be of diagnostic value in drug-induced skin reactions based on the resolution of eruption upon cessation of the drug incriminated by the assay (5).

It is well known that drug-induced pemphigus can follow two different courses after withdrawal of drugs. If the disease continues despite drug withdrawal, it is called “drug-triggered pemphigus”, whereas the form that resolves upon discontinuation of the culprit drug is called “drug-induced pemphigus” (10). Permanent recovery from the disease after withdrawal of the culprit drug, also favored by short courses of steroid therapy, suggests that in these patients, the acantholysis is induced by drug with a “biochemical mechanism”, and thus in the absence of autoantibodies (3,10,11). This is what presumably happened in our patient.

Figure 1. (A) Erosions of oral mucosa; (B) blisters and erosions of abdominal regions, pubis and upper limb; (C) blisters and erosions of lumbar regions.

Figure 2. (A) Cytologic examination showing typical acantholytic cells; (B) histopathologic examination showing intraepidermal blistering mostly above the basal layer, numerous acantholytic cells and mixed inflammatory-cell infiltrate. (HE, X10)
CONCLUSION

We describe this case of amoxicillin/clavulanic acid-induced pemphigus vulgaris for its singularity. Moreover, we think that a scrupulous collection of the history of drug administration would be necessary and useful to better clarify the etiology when it is not completely clear for the clinician.

References