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Drug-Induced Pemphigus

12

Sylvia H. Kardaun
and Laura de Sena Nogueira Maehara

Short Introduction in Layman Terms

Pemphigus can be induced or triggered by drugs. In drug-induced pemphigus (DIP) the disease was not present before exposure to the putative drug, whereas in drug-triggered pemphigus (DTP) the autoimmune process was already programmed by a predisposed genetic background, and only facilitated by the drug. Contrary to the latency time in most other cutaneous adverse drug reactions, latency between start of new medication and onset of the reaction can sometimes be long, up to several months. This can easily lead to a missed diagnosis. Timely withdrawal of the culprit drug regularly results in full resolution in DIP, whereas in DTP this is generally not the case. Because both DIP/DTP and idiopathic pemphigus mainly occur in the elderly, often using polypharmacy, establishing the culprit can be challenging.

Learning Objectives

After reading this chapter you should be aware that:

- Some drugs can induce or trigger pemphigus; in every patient with pemphigus, and in particular in new cases, a meticulous drug history should be taken to identify and withdraw potential culprits to achieve a potential remission.
- Although clinical and immunopathological features in DIP are rather similar to those in idiopathic pemphigus, itching or absence of mucosal involvement can be clues for the differentiation.
- Different subtypes of pemphigus can preferentially be provoked by different drugs or groups of drugs, sometimes with a different prognosis.

Case Study: Part 1

A 57-year-old woman presented with pruritic, painful erosions and crusts on the upper trunk since 2 weeks. She denied fever and the use of new medication. Careful history learned that captopril had been prescribed for hypertension since 6 months. Moreover, penicillin i.v. had been used for 10 days for erysipelas, 2 weeks before the onset of trunk lesions.

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Facts and Figures

To date, more than 100 drugs have been associated with pemphigus, classified in three different functional groups (Table 12.1): (1) thiol-associated drugs (drugs containing a thiol (-SH) group or a disulphide bond that releases SH groups or "masked thiols": non-thiol drugs containing sulphur that metabolizes to an active thiol group), (2) phenol drugs, and (3) non-thiol/non-phenol drugs [1–6]. Next to systemic drugs, some cases of "contact pemphigus" have been ascribed to topical application of e.g. ophthalmic drops or cutaneous ointments such as imiquimod or cantharidin [4].

Although cases of DIP have been regularly published, it is a rare condition occurring in probably 10% of pemphigus, with a slight male predominance, except for penicillamine in which females outnumber males. However, because e.g. penicillins are regularly prescribed and probably often overlooked as a culprit, pemphigus might be more often drug related than previously substantiated.

Clinical presentations of DIP comprise pemphigus vulgaris (PV, most cases), closely followed by pemphigus foliaceus (PF), and few cases of pemphigus erythematosus (PE), pemphigus herpetiformis (PH), IgA pemphigus, polymorphic pemphigus, combined features of pemphigus and pemphigoid, paraneoplastic pemphigus, and unclassified cases [1].

Contrary to idiopathic pemphigus, DIP is often associated with pruritus and has a prodromal stage with nonspecific lesions resembling common drug eruptions, preceding the genuine pemphigus lesions, or e.g. pharyngitis. Full-blown DIP often shows scaling and crusting (PF, Fig. 12.1), seborrheic lesions with a butterfly distribution predominantly on the face (PE), or small vesicles with crusted erosions grouped to annular or gyrate lesions (PH) [2].

It is estimated that up to 7% of patients treated with penicillamine for at least 6 months might acquire pemphigus [2]. Thiol-drugs probably account for the majority of cases of DIP [6]. In a systematic review of 170 reported patients with the reported outcomes, thiol-associated drugs,

Table 12.1 Drugs involved in inducing or triggering pemphigus, grouped according to their chemical structure

Thiol-associated drugs
Penicillamine
Captopril
Bucillamine
Penicillins and its derivatives (aminopenicillins)
Cephalosporins[a]
Piroxicam
Gold sodium thiomalate
Imatinib
Thiamazole
Thiopronin
Pyritinol[a]
5-thiopyridoxine[a]
Phenols (drugs containing a phenol ring)
Cephalosporins[a]
Aspirin
Rifampicin
Levodopa
Heroin
Pentachlorophenol
Phenobarbital
Pyritinol[a]
5-thiopyridoxine[a]
Non-thiol, non-phenol drugs
ACE inhibitors other than captopril
Ca channel blockers
Most NSAIDs
Nifedipine
Biological modifiers of the immune response[b]
Glibenclamide
Psoralens
Imiquimod
Others

ACE: angiotensin-converting enzyme, *NSAID:* nonsteroidal anti-inflammatory drug

[a]Both thiol and phenol drugs

[b]Including rituximab, interferon-α, interleukin-2, vaccins

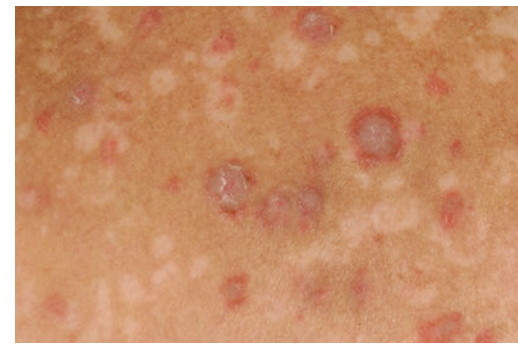

Fig. 12.1 Drug-induced pemphigus foliaceus in a female who received penicillamine for seronegative rheumatoid arthritis

especially penicillamine (33.1%), captopril (7.7%) and bucillamine (6.5%) were the three most reported drugs related to DIP, in which PF was the most common clinical presentation. The mean age was about 57 years, and most cases were less severe and had a better prognosis. Cutaneous, mucocutaneous and mucosal involvement were reported in 68.6, 30.1 resp. 1.3% with a mean latency of 154 days [1].

Where lesions can appear from days to several months after drug initiation with a median latency of 60 days, thiol drugs have a longer latency time compared to non-thiol drugs.

DIP caused by thiol drugs will often subside after drug withdrawal, in contrast to pemphigus due to non-thiol drugs [2]. In a systematic review of 170 reported patients, about 30% of thiol-associated pemphigus did resolve spontaneously after only drug withdrawal, others needed additional or maintenance therapy, while only about 12% did not heal [1]. The median time to remission was significantly longer for penicillamine-induced pemphigus (90 days) compared to captopril (60 days) or bucillamine or other drugs (30 days) [1].

Features of PV are most often seen in DIP and DTP in users of non-thiol drugs. Mucosal involvement is mainly restricted to the PV subtype and is otherwise rare. In the majority of DIP cases, tissue bound antibodies (93%) and less often circulating antibodies (Dsg 3: 34.9% and Dsg 1: 72.7%), although often with low titres are in accordance with idiopathic pemphigus, complicating differentiation [1, 3].

Notably, exacerbations or flares, mainly of PV, most likely caused by drugs. have also been reported, though never ascribed to thiol drugs.

Pathogenesis is not completely known, but probably comprises endogenous (e.g. predisposing genetic background or underlying comorbidities, especially of autoimmune origin, such as rheumatoid arthritis) and exogenous factors (e.g. drugs), acting as a trigger to unmask the disease. Immunologic acantholysis may start with biochemical events resulting in neoantigen formation and autoantibody production. Thiol-associated drugs and immune modulators could also directly interfere with the immune system resulting in release of forbidden B-cell clones. Moreover, autoantibodies could be mediated by enzymes promoting plasminogen activators. Phenol drugs may cause cytokine release, promoting acantholysis and effecting regulation and synthesis of complement and proteases. The non-thiol/non-phenol drugs may promote immune acantholysis in several ways: by overexpression of target antigens, overactivation of the immune system, amplification of the local immune response and release of plasminogen activators [3, 5].

Diagnosis Paths

Apart from idiopathic pemphigus, DIP and DTP should be differentiated from other bullous eruptions, such as bullous pemphigoid, erythema multiforme, Stevens-Johnson syndrome, impetigo, and varicella zoster. Every new case or flare up of pemphigus should be thoroughly investigated for a potential drug-relation. Cases of DIP may present with nonspecific cutaneous manifestations or e.g. pharyngytis before genuine lesions of pemphigus occur [3]. Pruritus or absence of mucosal involvement are important hints for DIP. History including in particular last year's drug use, nonspecific prodromal skin lesions and pruritus, is followed by a thorough dermatological examination of skin and mucosae. Histopathology may reveal eosinophilic spongiosis, epithelial necrosis, irregular acantholysis, variability of the epidermal splitting level, even in a single biopsy, and rather dense dermal infiltrates [3]. Intercellular antibodies are generally found in the skin, similar to in idiopathic pemphigus, but antibodies in the serum are more rare and, if present, of a low titre.

Drug causality in some cases has been strengthened e.g. by a positive patch test and/or lymphocyte transformation test with the suspected drug. Because the gold standard of dechallenge, followed by rechallenge with the suspected culprit is complicated due to the inherent risk, a stepwise dechallenge can be a useful alternative.

Case Study: Part 2

The patient had pruritus, scaling and small erosions on the face and upper body, while mucosal involvement was absent. Histology revealed cleavage of the epidermis at several levels and dermal mixed infiltrates containing many eosinophils. DIF identified intercellular epidermal staining, mainly confined to the upper layers. The ELISA test detected antibodies to desmoglein 1.

Treatment Tricks

Withdrawal of the suspected culprit drug is mandatory and, sometimes temporarily sustained by additional therapy, will lead to remission in approximately 50% of cases of DIP caused by thiol-associated drugs, opposed to only 15% in those due to non-thiol drugs [3]. However, sometimes maintenance therapy is needed. In DTP, despite elimination of the drug, the disease often continues with all the characteristics of idiopathic pemphigus, in particular when presenting as PV.

Case Study: Part 3

Captopril was withdrawn, while penicillin had already been stopped a few days earlier. Prednisolone 0.5 mg/kg resulted in remission within a few weeks. The preferred diagnosis was DIP, caused by captopril and/or penicillin. The patient was informed about the diagnosis, possible causes, the need for a careful follow up, and the advice to avoid certain drugs, especially those with "thiol groups" (see Table 12.1).

Review Questions

1. Choose the correct statement about drug-induced pemphigus:
   (a) In drug-induced pemphigus (DIP) the autoimmune disease was not programmed before the drug exposure.
   (b) In drug-triggered pemphigus (DTP) the autoimmune disease was not present before the drug exposure.
   (c) In drug-triggered pemphigus (DTP) the autoimmune process will be stopped after suspension of the culprit drug.
2. In DIP, lesions may appear from days to several months after drug initiation. Which drug is more likely to induce pemphigus with a longer time-latency?
   (a) enalapril
   (b) penicillamine
   (c) none
3. Drug withdrawal, sometimes temporarily sustained by additionally therapy will lead to remission of pemphigus in approximately:
   (a) 50% of cases due to non-thiol drugs
   (b) 50% of cases of DIP caused by thiol drugs
   (c) none of above

Answers

1. (a)
2. (b)
3. (b)

On the Web

Litt's Drug Eruption & Reaction Database. http://www.drugeruptiondata.com

References

1. Ghaedi F, Etesami I, Aryanian Z, Kalantari Y, Goodarzi A, Teymourpour S, Mahmoudi H, Daneshpazhooh M. Drug-induced pemphigus: a systematic review of 170 patients. Int Immunopharmacol. 2021;92:107299.
2. Brenner S, Wolf R, Ruocco V. Drug-induced pemphigus. Clin Dermatol. 1993;11:501–5.
3. Brenner S, Bialy-Golan A, Ruocco V. Drug-induced pemphigus. Clin Dermatol. 1998;16:393–7.
4. Brenner S, Goldberg I. Drug-induced pemphigus. Clin Dermatol. 2011;29:455–7.
5. Ruocco V, Ruocco E, Lo Schiavo A, Brunetti G, Guerrera LP, Wolf R. Pemphigus: etiology, pathogenesis, and inducing or triggering factors: facts and controversies. Clin Dermatol. 2013;31:374–81.
6. Goldberg I, Kashman Y, Brenner S. The induction of pemphigus by phenol drugs. Int J Dermatol. 1999;38:888–92.