

Drug-Induced Cicatricial Pemphigoid and Acquired Epidermolysis Bullosa

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Autoimmune diseases probably have a multitude of causes. It is obvious that exogenous agents, particularly drugs, may trigger the development of autoimmune responses leading to bullous eruptions. In the literature several cases of drug-induced (disseminated) bullous pemphigoid (BP) have been reported (see article by Fellner in this issue); however, localized variants of pemphigoid and acquired epidermolysis bullosa, although to a lesser extent, apparently can also be induced by drugs.

Important localized variants of pemphigoid are cicatricial pemphigoid (CP) (synonyms: mucous membrane pemphigoid [MMP], ocular pemphigoid) and two non-mucosal localized variants: the non-mucosal scarring type pemphigoid (Brunsting-Perry type) and the non-scarring localized-type pemphigoid (LBP).

Cicatricial pemphigoid is a rather rare disease of late middle age that occurs particularly on the mucous membranes of the eyes, oropharynx, genitalia, or anus. The characteristic skin picture is that of localized recurrent blisters with the development of scarring.¹ The cicatricial process can cause serious adhesions, strictures, and depending on the localization, on the long-term loss of function. Histologically, in contrast to BP, eosinophils in LBP and CP are usually present in significantly small numbers. Particularly in CP lesions, a fairly dense, sometimes predominant lymphocytic inflammatory infiltrate is observed in the dermis.

Immunofluorescence (IF) studies in CP show a linear deposition of IgG and complement along the basement

membrane of lesional and perilesional skin, but circulating serum autoantibodies with affinity for the basement membrane are detectable in only a minority of the patients.²

Several authors have reported cases classified as CP or MMP, apparently triggered by drugs³⁻¹¹ (Table 1). Two cases of drug-induced CP^{3,6} are discussed here in more detail.

Case Report 1

A man, aged 46 years, who had been treated long-term with practolol (Eraldin) (daily oral dose 600 mg) for angina developed, after 2.5 years of usage, a chronic bilateral inflammatory blistering eruption on the ocular mucous membranes of the eyes leading to fibrosis and cicatrization with histologic and immunologic features compatible with CP (Figure 1). Small papules and vesicles were observed in infiltrated erythematous areas on the conjunctivae together with focal scarring and shrinkage. At that time, the patient also had a psoriasiform rash localized on the chest and the extremities. Five weeks after stopping practolol no new active lesions on the conjunctivae were noted, but the old lesions remained unresolved. Epicutaneous and intracutaneous skin tests with practolol at that time (1975) were negative.

Histopathologic examination of the lesional ocular mucous membrane adjacent to a blister showed subepithelial cleavage at the basement membrane. An infiltrate composed largely of lymphocytes with some eosinophils and plasmacytes and a large number of dilated blood vessels was observed in the submucosa.

Immunofluorescence studies on sections of the lesional mucosa adjacent to a blister showed a linear band-like fluorescence in the subepithelial regions with antisera against IgG and complement, but because of tissue degeneration of the epithelium at these sites, the interpretation of the staining was less significant for a definite

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Table 1. Data in the Literature on Drug-Induced Cicatricial Pemphigoid: Localization of the Lesions and Systemic or Topical Drugs Considered to Be Responsible for Eliciting the Syndrome*

Authors	N†	IF‡	Localization	Drug Responsible
Van Joost et al ³	1	Positive	Ocular	Oral practolol
Pattern et al ⁴	2	§	Ocular (2)¶	Topical echothiophate iodide (2)
Pegum and Pembroke ⁵	1	§(?)	Ocular and oral	Oral D-penicillamine
Van Joost et al ⁶	1	Positive	Vulval, anal, and perianal	Oral clonidine
Hirst et al ⁷	2	§(?)	Ocular (2)	Topical pilocarpine (1) Topical demecarium Bromide (1)
Shuttleworth and Graham-Brown ⁸	1	Positive	Ocular, oral, cutaneous	Oral D-penicillamine
Harrington and Messenger ⁹	2	Positive	Oral and cutaneous (1) Ocular, oral, and cutaneous (1)	Oral indomethacin (2)
Fiore et al ¹⁰	5	Negative	Ocular (5)	Topical glaucoma medication (5)
Thiel et al ¹¹	1	Negative	Ocular**	Oral sulfadoxine

* Synonyms: BMM, ocular pemphigoid.

† N = number of patients classified as drug-induced cicatricial pemphigoid, as drug-induced mucous membrane pemphigoid, or as drug-induced ocular pemphigoid. In some of the cases a definite clinical cicatrization was observed.

‡ IF = immunofluorescence examination of the skin.

§ IF not done or not available.

¶ Number of patients in parentheses.

** This patient also had erythema exudativum multiforme lesions of other mucous membranes and of the skin.

classification. A conspicuous linear deposition of IgG and complement, however, was observed along the basement membrane of the buccal mucous membrane. There were no clinical signs of CP at this site.

On IF examination, the serum samples did not contain basement membrane autoantibodies, but did contain an-

tinuclear antibodies in the absence of anti-DNA antibodies. Intercellular pemphigoid-like antibodies (titer 1:40) were also detected using guinea pig lip as the substrate, but 2 months after stopping the practolol treatment, these autoantibodies had disappeared.³ Practolol was withdrawn from the market in 1975 because of a high inci-

Figure 1. Drug-induced cicatricial pemphigoid of the ocular mucous membrane caused by oral practolol (Eraldin).



Figure 2. Drug-induced cicatricial pemphigoid of the anal and perianal regions caused by clonidine (Catapresan).

dence of serious side effects on the skin and several other organs, including sclerosing peritonitis.

Case Report 2

A woman, aged 59 years, treated for systemic hypertension with clonidine (Catapresan) (daily oral dose two or three 0.250-mg capsules) for 2 years, developed a blistering cicatricial eruption with primary localization on the mucosal surfaces of the vulva and the anus with perianal extension (Figure 2).

Histopathologic examination of the perilesional skin adjacent to a blister on perianal skin showed subepidermal blister formation at the basement membrane (Figure 3). A cellular infiltrate consisting predominantly of lymphocytes and neutrophils and, to a lesser extent, eosinophils was seen diffusely in the upper dermis and around the blood vessels. No clear fibrosis of dermal tissue was observed in the biopsy that was examined.

Immunofluorescence studies on sections of perianal skin adjacent to the blister formation showed predominantly a linear deposition of IgG and complement along the basement membrane (Fig 4). Basement membrane autoantibodies were not detected in the serum.

Reappearance of skin lesions localized at the anal and perianal regions, this time accompanied by erythematous nonblistering eruptions on the breast, and abdomen, after reexposure to clonidine was highly suggestive of a relationship between the drug and the development of a syndrome that was classified as CP.⁶

In addition to the cardiovascular drugs implicated in these two cases of CP, nonsteroidal anti-inflammatory drugs (NSAIDs) and D-penicillamine have also been implicated in the development of CP.

Two cases classified as MMP were apparently induced by a NSAID.⁹ Both patients had received indomethacin for rheumatoid arthritis. MMP developed in both patients 6 and 8 weeks respectively after treatment with this drug. In the same report, the authors stated that in a retrospective study it appeared that five other patients with MMP observed previously had all taken NSAIDs in the 6 months prior to the onset of the skin lesions.

Patients with rheumatoid arthritis who developed CP after the introduction of D-penicillamine (D- β_1, β_2 -dimethyl cysteine) have been reported^{5,8} (see Table 1). Although a direct link between the two conditions (CP and rheumatoid arthritis) may exist independently of the use of drugs, the possibility that CP was a complication of D-penicillamine treatment was considered more likely.⁸

Furthermore, ocular mucosal alterations classified as "ocular pemphigoid" have been reported to result from various topical treatments (see Table 1). In none of five patients with ocular pemphigoid induced by topical glaucoma medications were linear immunoglobulin and/or complement deposition along the basement membrane of lesional skin observed using IF techniques.¹⁰ In four patients, the lesions were self-limiting and nonprogressive after stopping the topical treatment. One patient, however, developed progressive scarring even though the offending medication had been discontinued. Because the IF examination was negative it is uncertain whether these cases represent true CP. The term *cicatricial pemphigoid-like* or *ocular pemphigoid-like drug reaction* is probably more appropriate on clinical and histologic grounds.

Of interest is a detailed report on a patient who developed exudative erythema multiforme major with massive involvement of the skin, oral mucous membranes, and mucous membranes of both eyes as a result of sulfadoxine, present as one of the constituents in the antimalaria drug Fansidar (sulfadoxine and pyrimethamine).¹¹ The chronic inflammation of the eyes led to proliferation in the conjunctivae. The final clinical picture was compara-

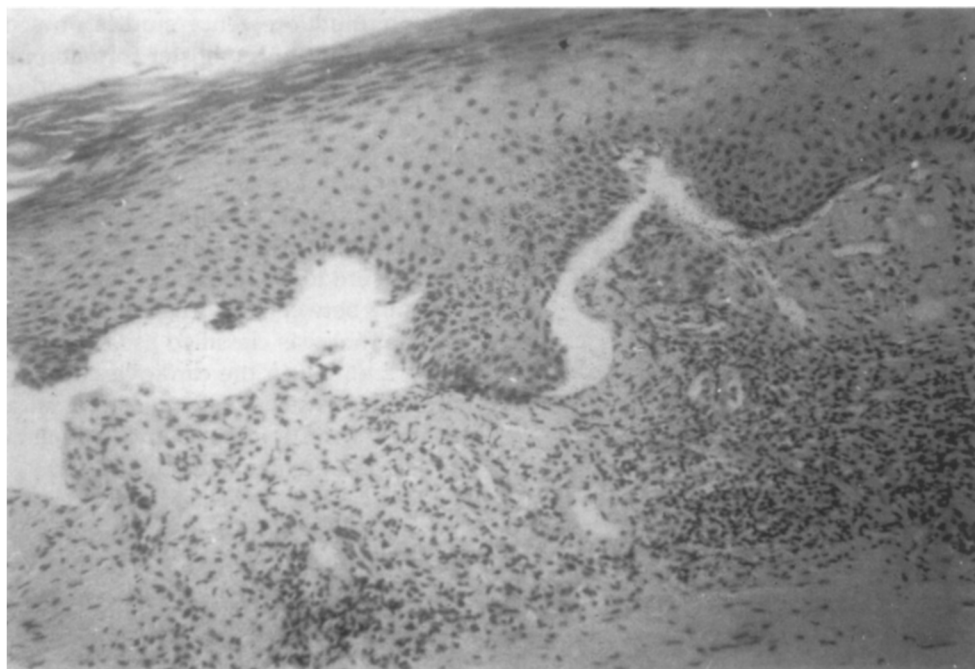


Figure 3. Subepidermal blister formation in drug-induced (clonidine) cicatricial pemphigoid (HE, $\times 250$).

ble to that of severe (ocular) CP, including the development of scarring and blindness in both eyes.

Discussion

Drug-induced MMP, particularly in the eyes, may be thought of as a spectrum of diseases. It may occur as a localized, nonprogressive, "toxic" reaction that remains self-limited once the offending topical medication is withdrawn; or it can progress relentlessly with scarring having the characteristic immunologic (IF) features of true CP; or it can occur as a concomitant manifestation of other syndromes such as exudative erythema multiforme.^{10,11}

In the two cases of drug-induced CP described here, the underlying pathomechanisms of the side effects remained unelucidated. A previous study indicated that during long-term topical ocular treatment with β -adrenergic receptor blocking agents, sensitization can occur as a result of delayed-type hypersensitivity.¹² Interaction of β -adrenergic receptor blocking agents (practolol) or α -adrenergic receptor stimulating agents (clonidine) with the cyclic AMP system in the epidermal (mucosal epithelial) cells may be operative. In view of the concept that at least a part of the basement membrane is of epidermal origin, it is tempting to assume that the underlying factors involved in these cases of drug-induced CP are related to local metabolic disturbances (cyclic AMP sys-

tem?) in the germinal cells. This could lead to the deposition of immunogens in the basement membrane and may subsequently lead to the induction of cellular immunity and/or to the formation of autoantibodies and of immunocomplexes in situ. Other drugs might also play a role in such metabolic disturbances. In this respect, it is interesting that serum autoantibodies with affinity for the cytoplasm of epithelial basal cells have been observed in patients on different drugs and with different clinical adverse effects (eg, exudative erythema multiforme and vasculitis).^{13,14}

Another possible explanation for the elicitation of autoantibodies comes from the experience that prostaglandins of the E series inhibit the expression of major histocompatibility class II antigens (Ia antigens) by murine macrophages and human Langerhans cells.¹⁵ Drugs like indomethacin (see Table 1), that inhibit prostaglandin synthesis have been shown to increase the expression of Ia antigens by these cells, mimicking the action of Ia-inducing lymphokines such as gamma interferon. It has been suggested that increased Ia expression enhances humoral immune responses.¹⁶ Thus, indomethacin and other cyclooxygenase inhibitors might exacerbate autoimmune disease through such mechanisms.

Drugs may have alternating effects on both the humoral and the cellular limbs of the autoimmune response. A mononuclear inflammatory infiltrate may be present in the skin lesions of (disseminated) bullous pemphigoid

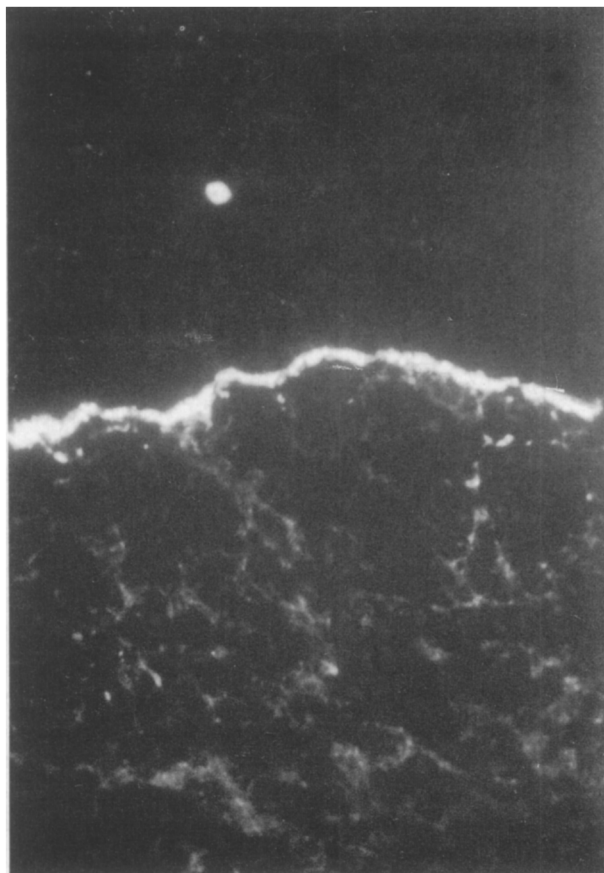


Figure 4. Immunofluorescence study. Border of a subepidermal blister. Predominantly linear fluorescence (IgG/FITC staining) along the basement membrane in drug-induced (clonidine) cicatricial pemphigoid ($\times 500$).

(BP), but usually mononuclear infiltrates are predominant in the lesions of the chronic localized variants of the disease (CP and LBP). This observation may favor a possible role of T cell-mediated immunity in terms of antigen-processing (including immunogens precipitated by drugs) in the early events of this disease complex and probably also in the perpetuation of the disease.^{17,18}

Important observations have been reported in active BP in favor of "in situ" presentation of antigens located in the basement membrane to T cells.^{17,19} A redistribution of Langerhans cells toward the basement membrane and an increase in the total number of Langerhans cells in the lesional skin have been observed.¹⁷ Furthermore, in BP significantly increased numbers of helper-T cells and of HLA-DR-positive T cells in the peripheral blood were observed.¹⁸ These data may suggest that helper-T cell activation may be involved in the acute phase of the disease.¹⁸ In addition, in BP, a decreased level of interleukin-2 (IL-2), assumed to be caused by the consumption of IL-2, has been reported.¹⁹ Thus, T cell-mediated reactions

may be an important link in the inductive phase of immunity leading finally to subepidermal bullous autoimmune disorders. Particularly in BP, the formation of "antigen (BM)-antibody-complement complexes" is thought to play a key role in the chemotaxis of eosinophilic granulocytes and in blister formation.²⁰ Tissue injury based on circulating autoantibodies may be understood better in cases of BP than in the localized chronic variants of the disease (LBP and CP).

In LBP, the predominance of activated helper/inducer T cells in the dermoepidermal regions as well as the expression of IL-2 receptor (IL-2R) on eosinophils in the dermal infiltrate have been observed.²¹ IL-2R can be expressed not only by T cells, but apparently also by non-lymphoid cells. Subsets of activated T cells may possibly produce precursors of eosinophils. This may favor antigen processing at the local level, leading to T cell-mediated recruitment of eosinophils.²¹ LBP resembling fixed drug eruption has been reported.²² Processes mediated by T cells similar to those described earlier might also play a role in the different drug-induced variants of pemphigoid, particularly in drug-induced CP. Future studies are required to establish the exact role of T cells in drug-induced pemphigoid variants. In the case reviewed earlier in this chapter in which drug-induced CP developed together with exudative erythema multiforme lesions, the lymphocyte transformation test with the drug considered as responsible (sulfadoxine) remained positive at least 18 months after the onset of the disease.¹¹

Drug-Induced Acquired Epidermolysis Bullosa

Important clinical criteria for acquired epidermolysis bullosa (AEB) are trauma-induced blisters occurring over the joints of the hands, feet, and elbows; additional atrophic scars; milia; and nail dystrophy. There is no family history and there is postinfancy onset of the disease. On the ultrastructural level the blister formation occurs beneath the basal lamina, with a zone of amorphous material beneath the basal lamina remaining on the epidermal side of the blister.²³

Apart from neutrophils, a mild chronic inflammatory (lymphohistiocytic) perivascular infiltrate may be present in the lesions. In the majority of cases, the immunoreactants in the basement membrane are of the IgG class, but IgM, IgA, and complement deposition at this region may also be present in some patients.²⁴ Circulating IgG antibodies against the basement membrane are usually not detectable in the serum. There is some evidence that AEB is in linkage disequilibrium with the MHC class II allele HLA-DR₂.²⁵ The immune cascade in AEB has yet to be elucidated, but in the inflammatory variant of the disease,

neutrophils are suspected to play an important role in tissue injury.²⁴

The results of previous studies at the ultrastructural level indicate that IgG depositions in both BP and CP are located in the lamina lucida or the lamina basale.^{24,26} In AEB, the ultrastructural location of immunoglobulins has been observed to occur just beneath the lamina densa,^{23,26} which does not support the hypothesis that AEB may be a variant of pemphigoid.²⁷ Drug-induced skin eruptions classified as AEB-like disease have been described apparently as a result of sulfonamides,²⁸ sulfamethoxypyridazine,²⁹ D-penicillamine,³⁰⁻³² and furosemide³³; however, in most of these reports the definite proof for this classification was lacking.

Furosemide, in high doses, is used extensively to treat edematous patients with chronic renal failure. Seven patients developed a skin syndrome classified as AEB while on high-dose furosemide treatment.³³ These cases are described here in more detail. Of the seven patients (five men and two women, aged 17 to 57 years), three had glomerulonephritis; the other diagnoses were pyelonephritis, polycystic disease, secondary amyloidosis, and polyarthritides nodosa. Renal function was seriously impaired in six patients (creatinine clearance 4–10 mL/min) and the remaining patient had refractory edema associated with the nephrotic syndrome. The dose of furosemide ranged from 0.5 to 2.0 g/day and most patients had received a high dose of this drug for several months before the skin lesions appeared. The shortest duration of treatment was 2 months and the longest, 3 years. Superficial bullae, up to 3 cm in diameter, were situated on the dorsum of the fingers or hands and, in two patients, also on the dorsum of the feet. The lesions were itchy, but without systemic manifestations. The bullae were superficial, leaving a raw surface, and filled with clear fluid. Minor trauma had predisposed to the development of the bullae. Porphyrin studies on urine, feces, and blood were carried out in three patients. The results were negative in all three cases. Skin biopsy showed a subepidermal blister with very few inflammatory cells in the blister fluid and minimal inflammatory infiltrate in the dermis. The condition appeared clinically and histologically to be AEB. The lesions persisted for 3 to 9 weeks and then healed, whether or not furosemide was continued.³³

Discussion

Dermatologic complications attributed to the use of furosemide are rare. Furosemide as the cause of drug-induced bullous pemphigoid (BP) has also been reported.^{34,35} The mechanism of blistering in drug-induced AEB-like skin eruptions is obscure. Although its onset in relation to

high-dose furosemide is extremely suggestive, the blistering tendency subsides in weeks or months, whether or not large doses of furosemide are continued. An important primer role for immunologic mechanisms seems to be unlikely in the cases described. It is tempting to speculate that the drug, particularly at high doses, interferes with tissue metabolism in the dermoepidermal region in a manner that depends on light exposure, inducing what is clinically an acquired form of epidermolysis bullosa.

Conclusions

It can be concluded that both cicatricial pemphigoid and acquired epidermolysis bullosa, or patterns closely mimicking these syndromes, may be triggered by the use of certain drugs. Ocular treatment with topical drugs can lead to a syndrome that clinically resembles ocular pemphigoid; however, the results of immunofluorescence studies on the tissue in a number of cases reported in the literature and reviewed in this article were either negative or not available (see Table 1). Therefore, a definite classification cannot be established. Moreover, we think that in the majority of cases with lesions induced by topical drugs, the term *ocular pemphigoid* cannot be considered an appropriate synonym for cicatricial pemphigoid because fibrosis and cicatricial lesions are absent.

Systemic treatment with certain drugs more evidently may trigger a syndrome compatible with true cicatricial pemphigoid in which, besides the mucosal membranes, the skin may also be involved (see Table 1).

Further studies on the interference of drugs with tissue metabolism in the skin and on the aberrant immune responses in cicatricial pemphigoid and acquired epidermolysis bullosa will cast more light on the role of drugs in the pathomechanisms of these blistering disorders.

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