

Mucosal-dominant pemphigus vulgaris in a captopril-taking woman with angioedema*

Justyna Gornowicz-Porowska¹
Pawel Pietkiewicz¹

Marian Dmochowski¹
Monika Bowszyc-Dmochowska¹

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Abstract: We describe a 39-year-old woman with an apparent captopril-induced, contact mucosal-dominant pemphigus vulgaris and angioedema, who took captopril during a bout of arterial hypertension. This exposure suggests that captopril and pathophysiology of angioedema stimulated the development of pemphigus vulgaris, which was diagnosed using the novel, indirect immunofluorescence BIOCHIP mosaic, with the modification to detect serum IgG4 autoantibodies. We discuss the patient, who experienced a chain of events leading to the active stage of pemphigus vulgaris, and review concepts of pemphigus vulgaris inducible by drugs and pathological immunity.

Keywords: Angioedema; Captopril; Pemphigus

INTRODUCTION

Autoimmune blistering dermatoses (ABDs), especially pemphigus vulgaris (PV) and mucous membrane pemphigoid, are uncommon causes of chronic oral lesions. Early diagnosis and prompt/correct treatment are essential to prevent serious involvement of other sites and even death. Checks on systemic diseases and previous exposition to drugs are advisable in patients with ABDs.

Chronic PV lesions may develop in patients presenting with arterial hypertension (AH), treated with angiotensin-converting-enzyme inhibitors (ACEI), but they have not been described in relation to angioedema.¹

Here, we describe a case of contact mucosal-dominant PV, probably induced by captopril throughout the course of angioedema and its management.

CASE REPORT

We received a 39-year-old woman with a 4-month history of oral lesions, previously diagnosed as having angioedema without urticaria (at the age of 9) and AH (Figure 1 A, B).

She took captopril *pro re nata* ("as required") sublingually for AH episodes and showed no signs of involvement of cutaneous or other mucosal surfaces. Investigations revealed slight blood eosinophilia (8%). Indirect immunofluorescence (IIF) on monkey esophagus revealed IgG (Fig. 1C) and IgG4 pemphigus-type antibodies (titre: >1/80 and 1/80, respectively). Direct immunofluorescence of oral mucosa showed IgG4 (+) (Fig. 1D) and C3 (++) , but not IgA, IgM, IgG or IgG1, pemphigus deposits. Histopathology H+E staining did not allow for unequivocal evaluation due to a lack of oral epithelium in the specimen sent to the laboratory. Anti-desmoglein 3 (DSG3) IgG and IgG4 (Fig. 1E,F) were detected in the serum using IIF on 6-substrate mosaic (monkey esophagus; primate salt-split skin; dots of tetrameric BP180-NC16A; DSG1/DSG3 – extracellular and transmembrane domains; BP230 C-terminal domain expressed in HEK293 cells).² The ELISA demonstrated elevated serum IgG anti-DSG3, but not anti-DSG1, autoantibodies (>200 RU/ml and 1.514 RU/ml, respectively; manufacturer cut-off 20 RU/ml).

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¹ Poznan University of Medical Sciences – Poznan, Poland.

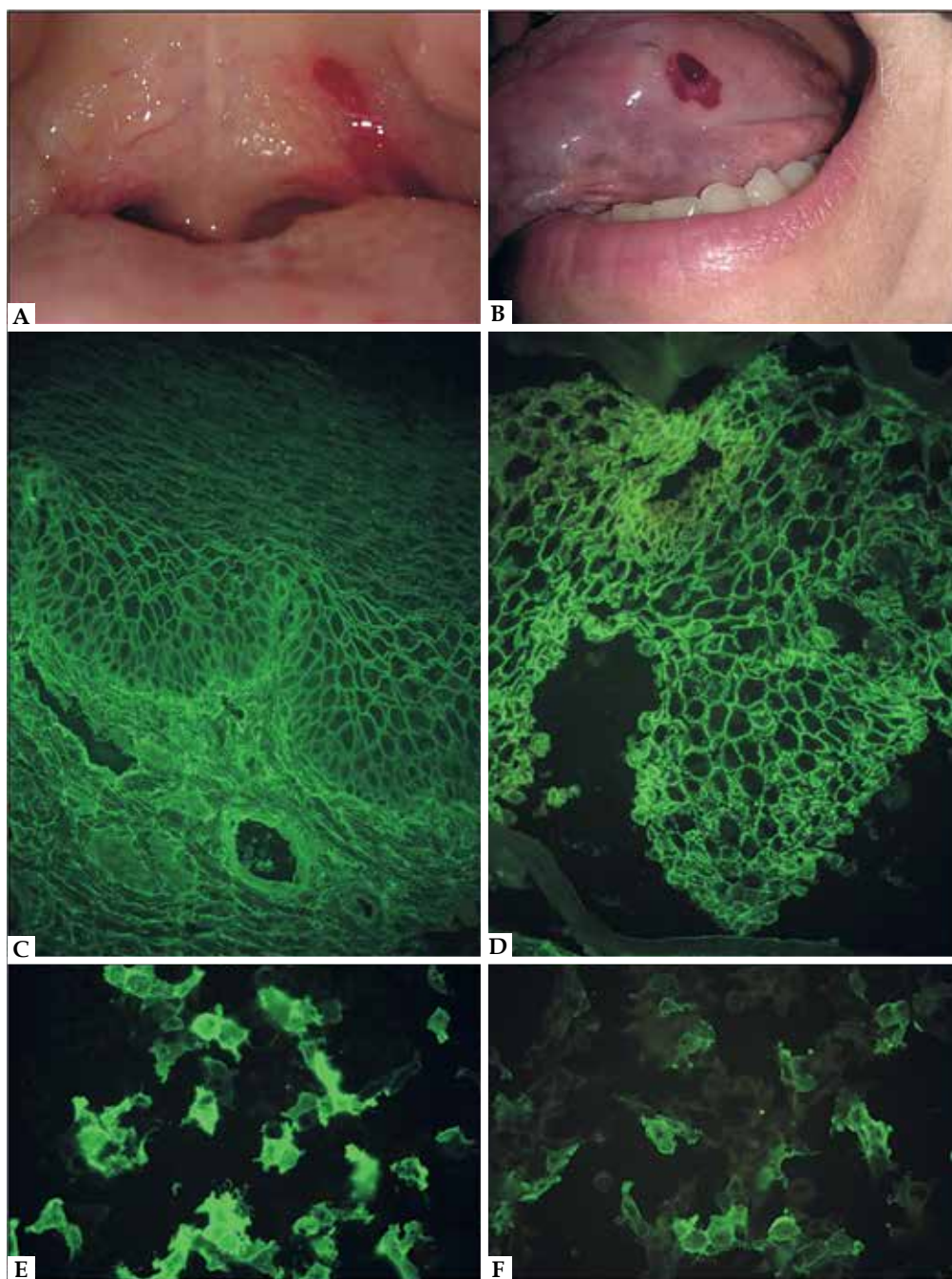


FIGURE 1: Mucosal erosions on the soft palate (A). Blood-filled blister on erythematous base on the side of the tongue (B). Indirect immunofluorescence (IIF) on monkey esophagus: Serum IgG pemphigus antibodies (C). Direct immunofluorescence of perilesional oral mucous membrane: IgG4 pemphigus deposits (D). IIF mosaic for autoimmune blistering dermatoses: IgG (E) and IgG4 (F) autoantibodies to extracellular and transmembrane domains of DSG3 expressed in transfected HEK293 cells

IIF and ELISA kits were produced by the German company Euroimmun.

Based on clinical, immunopathological and biochemical/molecular data, a diagnosis of an apparently captopril-induced, contact mucosal-dominant PV was established.

At the hospital, the patient was advised to refrain from taking pemphigus-triggering drugs and to take the following orally: doxycycline 2x100mg/day, niacinamide 1200mg/day and cetirizine dihydrochloride 2x10mg/day. She also received cy-

closporine solution as a mouthwash (twice a day). The oral lesions initially became less burdensome.

DISCUSSION

The etiology of PV is multifactorial, often resulting from environmental triggers acting on a proper genetic/immunological predisposition.

Commonly, these triggers include drugs, physical/infectious agents, cancers and even pesticides. Thence, 5 subtypes of drug-induced pemphigus (DIP) may be postulated.¹ Our experience suggests that in

suspected DIP cases, *ex vivo* tests with triggering drugs should be performed instead of oral provocation tests to eliminate the unknown organism's influences. The use of provocative tests is also unwise due to the grave nature of pemphigus.

There are data indicating an association between ACEI (e.g. captopril) and pemphigus.¹ However, the pathogenesis of captopril-induced pemphigus is unknown. Perhaps the most relevant mechanism to the reported case herein is contact pemphigus. Brenner *et al.*³ used the sensitization pathophysiology of contact dermatitis to describe the sequence of events in contact pemphigus (induction phase, elicitation phase, phenotypic manifestation). Thus, chronic low-level captopril exposure, in conjunction with the angioedema immunological background, could initiate in our patient the production of anti-DSGs autoantibodies. Interestingly, the patient also had lesions on the soft palate that may have been caused by: (i) indirect spreading of the drug influences to more distant sites, (ii) absorption of the drug.

Sebaratnam *et al.*⁴ reported a pemphigus foliaceus relapse induced by topical imiquimod therapy for basal cell carcinoma (BCC). As it is postulated that DSG3 is involved in both pemphigus and BCC pathogenesis, we cannot exclude the possibility of BCC as a contact pemphigus, co-triggering factor.⁵

Underscoring the importance of the Th2-dependent IgG4 subtype in the active stages of ABDs, we modified the commercial IIF mosaic to detect IgG4 autoantibodies.^{2,6} Hence, we demonstrated the presence of anti-DSG3 IgG4 isotype in the serum, suggesting the active stage of PV. We use stably transfected HEK293 cells, which probably reveal no physiological expression of desmosomal cadherins; however, the interpretation of IF images with transfectants is occasionally too challenging for routine laboratory work.

The history of angioedema since childhood perhaps suggested a hereditary form resulting from deficient production/function of C1 inhibitor.⁷ Therefore, the patient was also advised to undergo diagnostics for hereditary angioedema. Thus, proper diagno-

sis of angioedema revealed the initial factor in pemphigus development. Furthermore, the complement and kinin pathways are recognized as essential in angioedema onset/progression.⁷ Interestingly, they are also important in acantholysis and blister formation during pemphigus development (increased kinin formation in plasma of pemphigus patients).⁸ Hence, the linking factors of angioedema and pemphigus may involve: (i) proteolytic enzymes, (ii) the complement and kinin pathways. Additionally, successful administration of rituximab, the useful monoclonal antibody for treating ABDs, in C1 inhibitor deficiency, suggests overlying immune pathways in these disorders.^{9,10}

Angioedema may be induced/worsen with ACEI acting on the ACE-modulated, entangled kallikrein-kinin system, resulting in increased bradykinin.⁷ Thus, captopril probably linked the angioedema and pemphigus pathophysiologic processes in this particular case. Still, the associations suggested here might be purely fortuitous (based on a single case), especially as there was a 30-year interval between the occurrence of angioedema and clinical manifestation of PV.

The demonstration of IgG4 pemphigus mucosal deposits and serum IgG4 autoantibodies to DSG3 E+TM expressed in HEK293 cells indicates that the patient, following the repetitive chain of events – angioedema episodes treated intravenously with *ad hoc* glucocorticosteroids, leading to AH episodes treated with *ad hoc* sublingual captopril (even though this drug is contraindicated for angioedema) – developed active pemphigus, but no pemphigus-like reaction. □

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MAILING ADDRESS:

*Justyna Gornowicz-Porowska
49 Przybyszewski Street
60-355 Poznan, Poland.
E-mail: justynagornowicz1@poczta.onet.pl*

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