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CASE REPORT

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The first description of mucous membrane pemphigoid induced by enalapril maleate: a case report

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Abstract

Background Mucous membrane pemphigoid (MMP) is an autoimmune blistering disease (AIBD). Some reports suggest that it has a drug-related pathogenesis especially anti-hypertensive drug.

Case presentation A 67-year-old man with a 7-year history of essential hypertension was prescribed enalapril maleate for 5 months. He presented at our department with pain, ulcers, and blisters on the oral mucosa. We performed clinical, histopathology, and direct immunofluorescence examinations, and findings were consistent with the diagnostic criteria for MMP. Consequently, we consulted with the cardiovascular physician and agreed to discontinue the enalapril maleate replacing it with irbesartan/hydrochlorothiazide tablets and topical corticosteroid therapies instead. The lesions healed without recurrence.

Conclusions ABID induced by antihypertensive drugs have been reported, and enalapril maleate has been implicated as an antihypertensive agent that may trigger AIBDs, such as MMP. This case highlights the potential relationship between antihypertensive drugs and MMP, of which clinicians should be aware to accurately diagnose and promptly relieve patients' pain.

Keywords Hypertension, Enalapril, Mucous membrane pemphigoid, Diagnosis, Drug-related

Background

Mucous membrane pemphigoid (MMP) is an immune-mediated, vesiculobullous disease, characterised by mucosal subepithelial or subepidermal blistering primarily in the oral mucosa and conjunctiva [1, 2]. As one of several subepithelial blistering diseases, autoantibodies are directed against structural proteins of the hemidesmosome in the basement membrane zone [1–4]. The main target in MMP is structural protein BP180 (or type XVII collagen) [5]. However, the mechanisms underlying its pathogenesis have not been elucidated [5]. Some reports indicate that medications trigger MMP, such as antirheumatic drugs, clonidine (a central antihypertensive drug), and practolol (for treating angina pectoris) [6]. Recently, an emerging drug class of anti-programmed death-1 antibodies has been increasingly associated with MMP [7, 8]. The diagnosis of MMP is based on clinical examination, medical history, histopathologic analysis and serology [9], in which direct immunofluorescence (DIF) is the cornerstone diagnostic procedure [10].

Routine histology reveals subepithelial split with mixed inflammatory infiltration of eosinophils and neutrophils

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[11]. DIF reveals linear immunoglobin (Ig) A, IgG, or C3 along the basement membrane zone [11]. DIF serves as the most accurate diagnostic test for MMP, with a sensitivity between 60% and 90% [12]. If there is a concern for a false negative DIF and high clinical suspicion of MMP, repeat biopsies may be warranted. Based on current diagnostic guidelines, repeat biopsies for DIF increase sensitivity from 70–95% [12]. Indirect immunofluorescence microscopy may also be used for diagnosis [3, 13]. Autoantibodies against BP180 and BP230 may be detected via enzyme-linked immunosorbent assay (ELISA) testing [9].

Case presentation

A 67-year-old man presented to our department with pain, ulcers, and blisters in the oral mucosa for 3 months. The patient had no specific disease or familial medical history, except for a history of essential hypertension for 7 years and kidney stones for 5 years. The patient had been taking enalapril maleate for 5 months. Oral examination revealed full mouth edentulism. The alveolar ridge, suboral, and vestibular sulcus mucosae exhibited generalized erythema and desquamation, and there were multiple large ulcers covered with yellowish slough tissue and blisters (Fig. 1a, b). No other cutaneous or mucosal sites were involved, such as the conjunctiva or genital or nasopharyngeal mucosae.

We biopsied the patient's alveolar ridge mucosal erosion lesions and nearby normal mucosa tissue. Histopathological examination revealed local atrophy of the mucosal epithelium, subepithelial blister formation, plasma cell and lymphocyte infiltration into the lamina propria, lymphoid follicle formation, capillary proliferation, and dense neutrophil infiltration in the focal area (Fig. 2a, b). DIF revealed a linear deposition of IgG and IgA along the basement membrane (Fig. 2c, d). BP180-NC16A, desmoglein (DSG) 1, and DSG 3 ELISA did not detect circulating autoantibodies. Therefore, we diagnosed the patient with MMP based on these combined results.

Firstly, we administered topical corticosteroid therapies (Apply locally after diluting 0.5% dexamethasone at a 1:10 ratio, and locally seal after diluting 0.5% betamethasone at a 1:1 ratio), but it was ineffective, and the lesions recurred during treatment. We identified other cases of MMP caused by antihypertensive drugs in the literature [14] and speculated that enalapril maleate might be a trigger for AIBD due to its short-term use. Then, we consulted with the cardiovascular physician and agreed to discontinue enalapril maleate for three weeks, replacing it with irbesartan/hydrochlorothiazide tablets. Simultaneous topical corticosteroid therapies (Apply 0.1% triamcinolone acetonide oral paste locally, seal locally

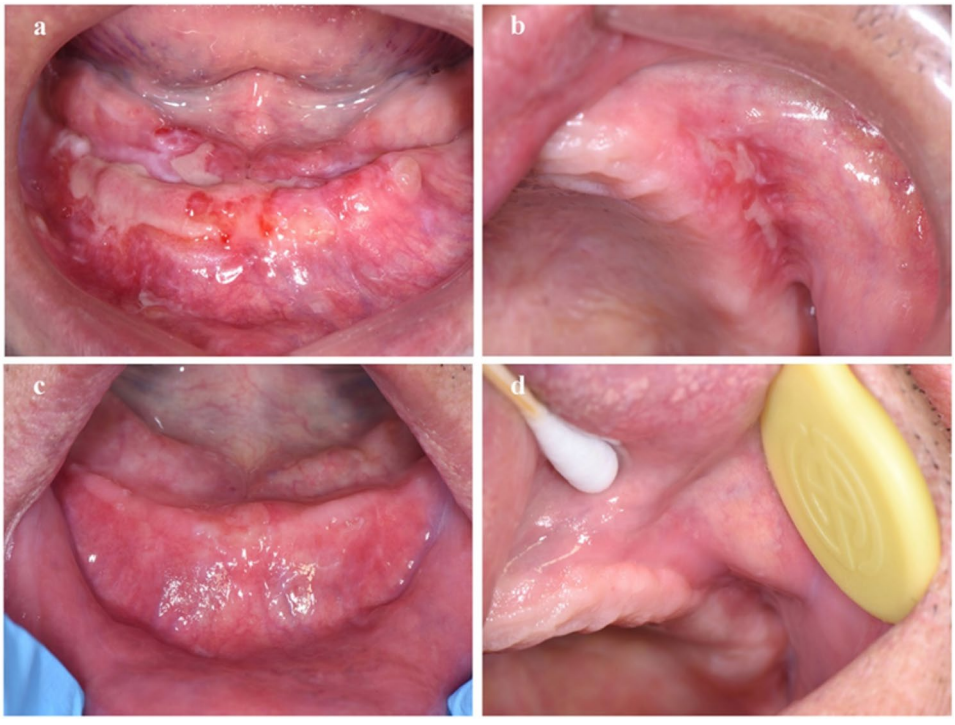

Fig. 1 The clinical manifestations of a 67-year-old man presenting with oral mucosa pain, ulcers, and blisters. (**a**, **b**) The clinical findings at the patient's first visit. The alveolar ridge mucosa and vestibular sulcus mucosa showed generalized erythema, desquamation, multiple large ulcers covered with yellowish slough tissue, and multiple blisters. (**c**, **d**) The clinical findings at the patient's final visit. Most erosions resolved after discontinuing the enalapril maleate. Erosions on the alveolar ridge mucosa and the vestibular sulcus mucosa remained but were healing

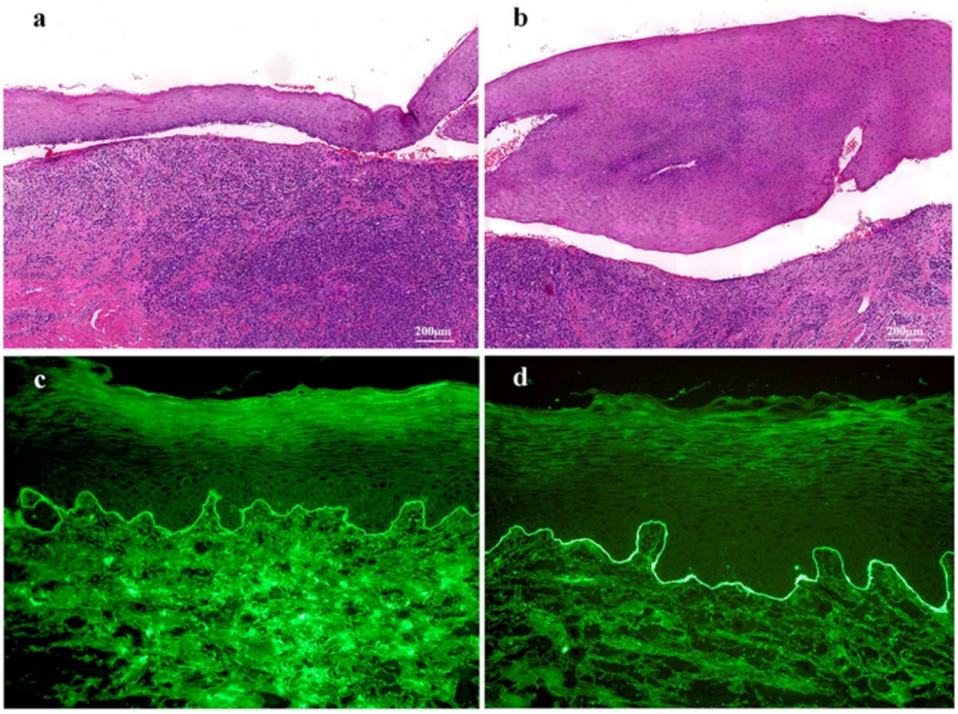

Fig. 2 A supplementary examination of a biopsy sample from the patient's alveolar ridge mucosal erosion lesions. (**a**, **b**) Light microscopy images of a biopsy specimen of the alveolar ridge mucosa showing subepithelial blister formation, plasma cell and lymphocyte infiltration in the lamina propria, lymphoid follicle formation, capillary proliferation, and dense neutrophil infiltration in the focal area (hematoxylin and eosin staining, original magnification ×10). Direct immunofluorescence microscopy images show linear (**c**) immunoglobin (Ig) G and (**d**) IgA deposits along the epithelial basement membrane zone

after diluting 0.5% betamethasone at a 1:1 ratio) gradually healed the oral mucosa erosion and blisters (Fig. 1c, d). The patient's oral lesions had not recurred at the most recent follow-up (11 months).

Discussion

Enalapril maleate is an angiotensin-converting enzyme inhibitor commonly used to treat essential hypertension, stable chronic heart failure, myocardial infarction, and diabetic nephropathy [15, 16]. Enalapril maleate can also cause angioedema [17] and is a suspected trigger of autoimmune blistering diseases (AIBDs) of the skin and mucosa, such as pemphigus [18] and bullous pemphigoid (BP) [19]. A report described a patient who used enalapril maleate for 6 months for primary pulmonary hypertension and arrhythmia, presented with a large area of pustular lesions and erythema on the face and back. Histopathology and DIF confirmed pemphigus vegetans, and the patient was treated with prednisone. Furthermore, the lesions gradually disappeared over 1 month after discontinuing enalapril maleate [20].

Our second treatment attempt discontinued the use of enalapril maleate, a potential MMP inducing factor. The patient's lesions gradually healed with no sign of recurrence, further supporting that enalapril maleate triggers MMP. There is no literature regarding the relationship between enalapril maleate and MMP, and the specific pathogenesis is unclear. BP is one of the most common AIBDs, characterized by autoantibody production against hemidesmosomal proteins of the skin and mucosa, mainly affecting older adults [21]. Drug-induced bullous pemphigoid is common, and here we have summarized the relevant case reports of drug-related bullous pemphigoid in the past five years (Table 1) [22–26].

Table 1 Case reports of drug-induced bullous pemphigoid over the past 5 years

Drug	Number of case/gender	Prognosis
Vildagliptin	1/1F	Complete healing
Dulaglutide	1/1F	Gradually recovering without new lesions
Empagliflozin	1/1F	Gradually recovering without new lesions
Gliptin	10/7M3F	Gradually recovering without new lesions
Rivaroxaban	1/1 M	Stable condition

To address this issue, Stavropoulos [27] proposed four possible pathogenetic mechanisms of drug-induced BP: (1) the drug affects the immune regulation of T-regulatory cells and releases autoantibodies against the BMZ, (2) the drugs are perceived as pathogenic antigens

leading to autoantibody formation, (3) some drugs act as antigenic haptens, which bind and modify protein molecules on the basement membrane, producing specific autoantibodies, and (4) drugs containing sulfhydryl groups directly destroy the dermal-epidermal junction, thereby exposing autoantigens. Since BP and MMP are both AIBDs, we propose that the pathogenetic mechanisms of enalapril maleate-induced MMP are similar to that of drug-induced BP.

In conclusion, we advise to closely monitor to patients presenting with repeated erosion and blisters in the oral mucosa. Furthermore, histopathology, DIF, IIF, and ELISA should be used to assess the patient's condition and make a diagnosis. The patient's medical history can also be beneficial for identifying the causative factors, as in our case, where we identified and excluded the inducing factor during treatment. This idea is especially true given the mounting evidence regarding a correlation between specific medications and MMP.

Abbreviations

AIBD	Autoimmune blistering disease
BP	Bullous pemphigoid
DIF	Direct immunofluorescence
MMP	Mucous membrane pemphigoid
Ig	Immunoglobin
DSG	Desmoglein
ELISA	Enzyme¬-linked immunosorbent assay
HCTZ	Hydrochlorothiazide
C3	Complement factor 3
BMZ	Basement membrane zone
COL17	Type XVII collagen
COL7	Type VII collagen
IIF	Indirect immunofluorescence

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Author contributions
XFZ and XZ: Administrative, technical, and material support; study supervision; conceptualization and design of the manuscript.YHX, QYZ, LY, JKW: Data acquisition.YHX, QYZ, XFZ, and XZ: Manuscript writing, reviewing, and revision. All authors approved the final manuscript and agreed to be accountable for all aspects of the work. Furthermore, all authors ensured that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
The ethics committee of West China Hospital of Stomatology, Sichuan University, approved this study. The patient in this manuscript provided written informed consent for participation.

Consent for publication
The patient in this manuscript provided written informed consent for publishing this case.

Competing interests
The authors declare no competing interests.

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