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Histopathological Features of Recurrent Oral Ulceration Diagnosed as Oral Pemphigus Vulgaris: A Case Report

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Abstract: ***Background: Pemphigus is a rare group of life-threatening muco-cutaneous autoimmune blistering diseases. Frequently, oral lesions precede the cutaneous ones. Sometimes oral clinical features could be misdiagnosed as aphthous ulcer especially when cutaneous lesion could not be found. Histopathology examination is essential to diagnose any vessicobullous diseases. Case report: A case of 44-year-old man with chief complaint recurrent oral ulceration since two years ago, working diagnosed as suspect tuberculosis cutis orificalis was reported. Histopathological examination showed suprabasilar blisters contained of acantholytic cells. Basillary cells remained attached to the basement membrane and lamina propria, arranged like "thombstonesappearance". Lymphocytes and neutrophills were the main inflammatory cells in dermis. Discussion: Clinically, it may be difficult to differentiate recurrence aphthous-like ulcer as oral pemphigus, especially when oral lesion was the main clinical feature. To make diagnose of pemphigus, histopathological examination is necessary and must be done. In some case when both direct and indirect immunofluorescence could not be performed, immunohistochemistry is one of alternative to determine the autoantibodies that involve in disease. Unfortunately this examination is not available in our department and several studies still ongoing in purpose to replace immunofluorescence with immunohistochemistry.***

Keywords: recurrent oral ulceration, oral pemphigus vulgaris, histopathology

1. Introduction

The term *pemphigus* refers to a group of autoimmune blistering diseases of skin and mucous membranes that are characterized histologically by intra-epidermal blisters due to acantholysis (i.e., separation of epidermal cells from each other) and immunopathologically by in vivo bound and circulating immunoglobulin (Ig) directed against the cell surface of keratinocytes.[1,2]Pemphigus vulgaris (PV) is the most common type of pemphigus, approximately 80% of all cases of pemphigus.[3] It affects middle-aged adults, with the peak incidence occurs between fourth and sixth decade of life, without gender predilection and has an incidence varying from 0.76 to 32 per million inhabitants per year in worldwide.[4-5]

Pemphigus vulgaris (PV) is an autoimmune disease caused by antibodies directed against mostly desmoglein 1 (dsg1) and desmoglein 3 (dsg3) resulting in the loss of cohesion between keratinocytes in the epidermis.[1] Desmoglein 1 (dsg1) is mostly seen within epithelium of skin, while dsg3 is commonly seen in mucosal epithelium.[6] The antibodies against both dsg1 and dsg3 have predominant IgG4 subclass specificity.[3,7] The exact etiology of PV remains unclear. There is an increased susceptibility of genetic factor, in particular Human Leucocyte Antigen (HLA) class II.[1,3,4] Along with this genetic factor, certain environmental triggers also seem to be essential for the disease to occur, such as medications (carbamazepine, captopril, antibiotics, rifampicin, etc), chemicals (pesticides), traumas, viruses and diet (thiol, thiocyanates, phenols and tannins).[3]

Pemphigus vulgaris (PV) affects both skin and mucosal epithelium. Skin lesions are common, and it is easy to identify intact blisters on the skin. However, many patients may develop oral lesions exclusively. In circumstances above, early identification of the disease seems to be difficult, as oral lesions might be mistaken for less severe and more common lesions of the oral cavity, such as aphthous ulcers, traumatic ulcers, and oral candidiasis. [4,6]

Histopathological examination become essential in established diagnosis of PV. Direct immunofluorescence can identify the localization of IgG autoantibodies and C3 complement, but extremely care must be taken, since tissue obtained from actual lesion might result in false negative due to internalization of the immune reactants on the cell surface.[6] Recent studies have been conducted to find alternative examination in detecting those autoantibodies, by using immunohistochemistry (IHC).[4,7]

2. Case Report

A 44-year-old man was referred to Dermatology-Venereology outpatient clinic Dr. M. Djamil Hospital Padang with chief complaint there were reddish-blackish crusted in lower lip that felt pain and expanded since 2 months. Patient had a history of recurrent oral ulceration since 2 years. The history revealed that oral ulcer was begun by small blister that broke soon after and healed without scarring. Blisters often reappeared in the same site, caused eroded skin that expanded as it bleed easily. In the first time visit, patient denied history of skin lesion such as flaccid blisters or erosion. Physical examination revealed reddish-

blackish crusted with fissure in the lower lip (Figure 1.A). An incisional biopsy was performed from the edge of eroded area and sent to department of pathology with working diagnosis suspect of tuberculosis cutis orificialis.

Histopathological examination showed vesicobullous reaction pattern, unlikely in tuberculosis cutis orificalis which is belong to granulomatous reaction pattern. The blister was formed in suprabasilar area, acantolytic cells could be seen inside the cleft. Basal cells were arranged as *"thombstone-like"* appearence. Lymphocytes and polymorphonuclear cells infiltrated the dermis predominantly (Figure 1.B&C).

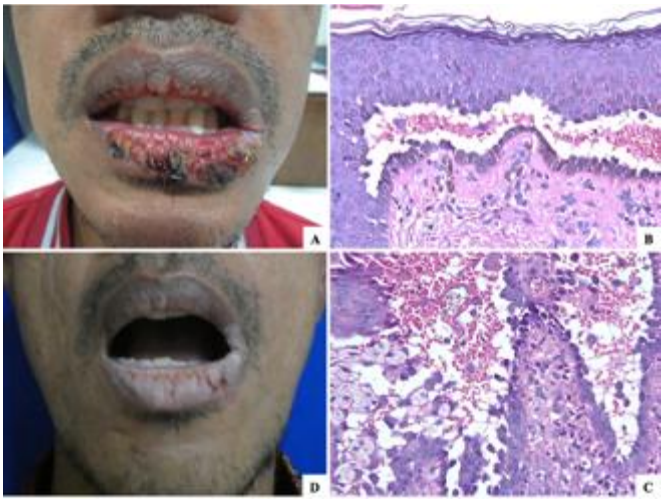

Figure 1: A. Patient's picture at the first time visit; reddish-blackish crusted in lower lip. **B&C.**Histopathology result; suprabasal split contains ofacantholytic cells, basal cellswere arranged as *"row of thombstone"*. (H&E,40x) **D.**Follow up's picture after two weeks of oral corticosteroid administration.

Patient was diagnosed as pemphigus vulgaris, were treated with oral corticosteroid; methylprednisolone 24mg/day. Wet dressing of normal saline was used to reduce the crusted.

3. Discussion

Pemphigus is a group of chronic autoimmune disease characterized by the presence of antibodies against desmosomal protein.[5] Pemphigus vulgaris (PV) is the most common variant,[3,5] that can affect both cutaneous and mucosa as presenting auto-antibodies both dsg1 and dsg3.[1-8] Those auto-antibodies and other immune mechanisms caused damage in adhesion of intercellular of epithelial cells and giving out several clinical and pathological features.

The primary lesion of PV is a flaccid blister, which may occur anywhere on the skin surface, but typically not the palms and soles. Because PV blisters are fragile, the most common skin lesions observed in patients are erosions resulting from broken blisters.[1] Nearly all patients have mucosal lesions and they can be the presenting symptoms in 50-70% cases.[5] Oral lesions present as vesicles or bullae that quickly breaks, leaving painful erosions or ulcers with ill-defined borders. It most often affects buccal mucosa, and heals slowly without scarring.[4]

Dagistan *et al.*, López-Jornet and Bermejo-Fenoll, Javali and Zainab, Ohta *et al.*, Kumar *et al.*, and several others have shown in the past that oral lesions precede skin lesions frequently. However, early identification of the disease seems to be difficult, as oral lesions might be mistaken for less severe and more common lesions of the oral cavity, such as aphthous ulcers, traumatic ulcers, and oral candidiasis.[6] The same holds true in this case, wherein the patient had initially been working diagnosed as tuberculosis cutis orificialis. To ensure the diagnosis histopathological examination was perfomed by incisional biopsy.

Histopathological examination determined the definite diagnosis in this case. Tuberculosis cutis is included to granulomatous reaction pattern, one of major tissue reactions.[3] The preparation showed vesicobullous reaction pattern, which is characterized by blistering formed within epidermis, which could rule out the working diagnosis of tuberculosis cutis from clinician. In vesicobullous reaction pattern, the following three morphological features may need to be assesed in the diagnosis of vesiculobullous lesions; the anatomical level of the split, the mechanism responsible for the split, and the inflammatory cells component.[3,8] Those three morphological features help pathologist to specify the diagnosis.

Overall, anatomical level of the split is divided into; intraepidermal (intracorneal, subcorneal, suprabasilar) and subepidermal blisters.[3,8] In this case, the preparation, under haematoxylin and eosin (H&E) staining, showed blisters right above the basal cells, confirmed as suprabasilar blisters. The underlying mechanism that responsible for the split consist of spongiosis, achantosis, destruction of basement membrane zone and ballooning degenration of keratinocytes.[3,8] In higher magnification of preparation, in cavity of blisters could be seen few keratinocytes had lost the intercelullar bridges, significant sign of achantolysis mechanism. The keratinocytes are rounded and detached within the blisters. The basal keratinocytes, although separated from one another through the lost of attachment, remain firmly attached to the dermis, resulted in "*rowoftombstones*" appearance (Figure 2.B). This feature is patognomonic for PV.[1-3,8] In dermis there were mild infiltration of lymphocytes and polumorphonuclear cells as inflammatory cells that involved in the disease. Interestingly, some areas showed bleeding such as in dermis and inside bullae. This condition might be happened because of traumas (i.e. scracthing, removing the crusted) (Figure 2.A).

Patologically, PV can be differentiated with pemphigus vegetans, a rare variant of PV. Pemphigus vegetans shows not only suprabasilar acantholysis, but also papillomatosis of the dermal papillae and downward growth of epidermal stands into the dermis, with hyperkeratosis and scale-crust formation (Figure 2.D).[1] Pemphigus vulgaris can be potentially confused with other acantholytic disorders, particularly *Hailey–Hailey disease* (familial benign chronic pemphigus), an inherited acantholytic disorder.However, those conditions usually show much more extensive suprabasilar acantholysis, with separation of keratinocytes in the spinous layer producing the appearance of a '*dilapidatedbrickwall'* (Figure 2.C). Paraneoplastic

pemphigus usually has similar clinical presentations; however, it is commonly seen in association with neoplasms such as non-Hodgkin's lymphoma or leukemia.[6]

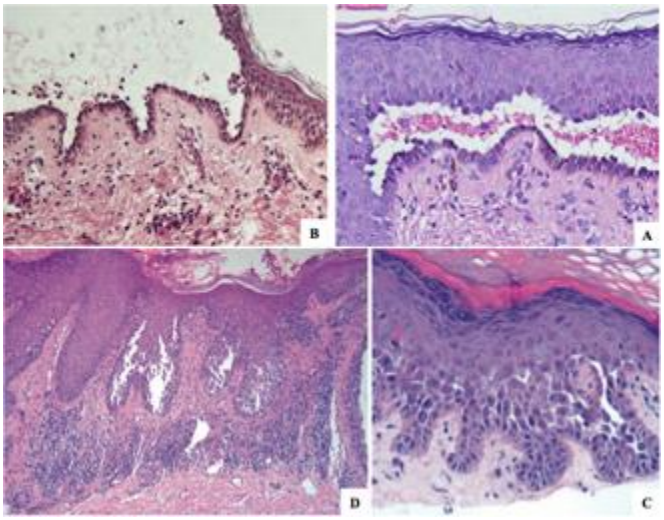

Figure 2: Histopathological examination under H&E stain. **A.**Photomicrograph of our preparation; suprabasilar cleft with a "*row of thombstones*"; the cleft contains of acantholytic cells and bleeding. **B.**Classic PV; suprabasal blister, '*tombstoneappearance'*. **C.***Hailey-haileydisease*; suprabasilar cleft with "*dilapitedbrickwall*". **D.**Pemphigus vegetans; hyperkeratosis, papillomatosis and prominent acanthosis. (B,C&D taken as it is from reference 3).

A diagnosis of pemphigus usually can be established with histopathological examination of an incisional biopsy. However, immunofluorescence is more specific and can help to assess diagnosis. A direct immunofluorescence test aims to identify the localization of IgG autoantibodies and C3 complement within the tissue of the patient. For this technique, care must be taken to examine the perilesional tissue under direct immunofluorescence, since tissue obtained from actual lesion might result in false-negative result due to internalization of the immune reactants on the cell surface.[6] Another limitations, it is costly and thus not affordable for all patients. Besides, not all of health center provide this examination. In situations where immunofluorescence is difficult to perform, immunohistochemistry (IHC) on formalin-fixed tissue samples may be an alternative test to confirm the diagnosis. Suliman, et al (Sudan, 2013) conducted study using IHC staining to detect IgG and C3 and established the diagnosis of PV.[4] Other studies still on going, trying to replace immunofluorescence with IHC. Until now, immunofluorescence is still the best in detecting auto-antibodies in pemphigus disease.

Despite the potentially fatal prognosis, there are currently no FDA-approved treatments.[1]The initial aim of treatment is to induce disease remission, decrease the production of auto-antibodies and stop the eruption of new lesions, followed by a period of maintenance treatment using the minimum drug doses required for disease control in order to minimize their side effects.[9,10]The systemic administration of glucocorticoids, usually prednisone, is the mainstay of therapy for pemphigus.[1] Their introduction in the early 1950s resulted in dramatic fall in mortality to an average of 30% with complete remission rate of 13-20%. Outcomes have continued to improve and in a recent study, the mortality was zero and the complete remission rate was 29% in 17 patients treated with steroids alone and followed for 4–6 years. On average, cessation of blistering takes 2–3 weeks and full healing may take 6–8 weeks.[10,11] In this case, patient received 24mg methylprednisolone daily (prednisone 0.5mg/kg/d) and topical steroids. Patient showed good improvement after 2 weeks therapy (Figure 1.D).

4. Conclusion

Oral pemphigus vulgaris often confusing the clinician especially when it appeared as main lesion or without any cutaneous lession.Histopathological examination is needed to established the diagnose which confirmed by suprabasilar bullae with tombstone appearance.Immunofluorescence is important to determine autoantibodies that involved and to located where the mechanism took place. As the technique is limited in further health centre and difficulties in taken care of samples, immunohistochemistry have been proposed to take place immunofluorescence procedure.

References

[1] Stanley JR. Pemphigus. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffel DJ, editors. Fitzpatrick's dermatology in general medicine. 8th ed; vol.1. New York: McGraw-Hill; 2012. p. 586-599.
[2] Amagai M. Pemphigus. In: Bolognia JL, Jorzzo JL, Rapini RP, Horn TD, Mascaro JM, Mancini JA, et al., editors. Dermatology. 2nd ed; vol.1. Spanyol: Mosby; 2003. p. 449-61.
[3] Weedon D. The vesicobullous reaction pattern. In: Weedon D, editor. Weedon's skin pathology. Fourth edition. China: Churchill Livingstone; 2016: p.135-188.
[4] Suliman NM, Astrom AN, Ali RW, Salman H and Johannessen AC. Clinical and histological characterization of oral pemphigus lesions in patients with skin diseases: a cross sectional study from Sudan. BMC oral health. 2013;13(66):p.1-12.
[5] Mahajan A, Kaur J, Manjari M, Sharma S, Bains P, Awal G, et al. Oral pemphigus vulgaris: clinicopathological study of 35 cases at a tertiary care centre in North India. International journal of research in dermatology. 2017;3(2):p.192-195.
[6] Kala N, Manjeu J, Dominic N, Kirubanidhi SP and Babu K. Oral pemphigus without skin lesions treated with pulse steroid therapy. Journal of indian society of periodontology. 2018;22(6):p.551-554.
[7] Abe T, Maruyama S, Babkair H, Yamazaki M, Cheng J and Saku T. Simultaneous immunolocalization of desmoglein 3 and IgG4 in oral pemphigus vulgaris: IgG4 predominant autoantibodies in its pathogenesis. Journal of oral pathology and medicine. 2014:p.1-7.
[8] Mobini N, Toussaint N, Kamino H. Noninfectious erythematous, papular, and squamous diseases. In: Elder, DE, Elenitsas R, Johnson BL, Murphy, GF, editors. Lever's Histopathology of the Skin. Eleventh edition. Lippincott Williams & Wilkins; 2016: p.174-181.

[9] Borradori L, Bernard P. Pemphigoid group. In: Bolognia JL, Jorzzo JL, Rapini RP, Horn TD, Mascaro JM, Mancini JA, et al., editors. Dermatology. 2nd ed; vol.1. Spanyol: Mosby; 2003. p. 463-70.
[10] Knudson RM, Kalaaji AN, Bruce AJ. The management of mucous membrane pemphigoid and pemphigus. Dermatologic Therapy, 2010; 23: 268-80.
[11] Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. Journal of Dermatology, 2003: 149: 926-37.

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