Pemphigus Vulgaris: Oral Pathologist as Sentinal

Alkananda Sahoo[1], Swagatika Panda[2], Santosh Subudhi[3], Neeta Mohanty[4], Debkant Jena[5]

[1]Senior Lecturer, [2] Professor, Department of Oral and Maxillofacial Pathology and Microbiology, [3]Professor, Department of Oral and Maxillofacial Surgery, [4]Professor & Head, Department of Oral and Maxillofacial Pathology and Microbiology, [5]Professor, Department of Conservative Dentistry and Endodontics, Institute of Dental Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India

Abstract

The word 'Pemphigus' has been derived from a Greek term meaning "blister". Pemphigus vulgaris is a chronic autoimmune vesiculobullous lesion primarily manifesting as intraoral blisters, gradually involving other parts of the mucous membrane and skin. Though the exact etiology is unknown the lesion is characterized by the production of autoantibodies directed against the intercellular substances thus categorizing it as an autoimmune disorder. Early diagnosis and management determine the course of the lesion hence dental practitioners should be well aware of the clinical features of pemphigus vulgaris as early diagnosis is of considerable value since therapy is simplified when the lesion is confined to the mouth. Here we are reporting a case of a 40 year old female presenting with pain and burning sensation in the left retromolar area along with an overview of the disease.

Keywords: *Pemphigus, autoimmune, corticosteroids, immunosuppressants, oral, vesiculobullous, skin.*

Introduction

Pemphigus is a group of potentially life-threatening autoimmune mucocutaneous disorder which is characterized by epithelial blistering affecting the cutaneous and/or mucosal surfaces. Pemphigus vulgaris is an autoimmune disorder with blister formation on the skin and mucous membrane. It has multiple clinical variants. It has a strong immunological and genetic etiology. Generally,the elderly population is affected and in 50% cases oral mucosal lesions are the initial manifestations.[1] 1 to 5 persons per million populations are affected every year. It has a female predilection with female to male ratio being 2:1 and peaks between the 4th to 6th decades of life.[2] Clinically, oral lesions are recognized by the formation of blisters,which ruptures within no time leaving behind painful ulcerations. Predominantly involves the buccal mucosa, lips and soft palate but can also occur in other areas of the oral cavity.[3] Intra-epithelial vesicles, acantholysis and Tzanck cells are the key histopathological features that confirm the diagnosis.[2] We are reporting a case of pemphigus vulgaris diagnosed with oral vesicles as the most initial sign.

Corresponding Author:
Dr. Alkananda Sahoo
Senior Lecturer, Department of Oral and Maxillofacial Pathology and Microbiology, Institute of Dental Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha, India
e-mail: alkanandasahoo@soa.ac.in

Case report: A female patient aged 40 years resident of Nayagarh, Odisha, came to the Department of Oral Pathology and Microbiology with the chief complaint of pain in the lower left back teeth region for the past 20 days. She had pain during swallowing and also burning sensation on taking food and water. There were no other findings neither on the skin nor on any other mucosal sites. The patient's medical and family history was not significant and non-contributory. The patient had poor oral hygiene.

On general examination, all vital parameters of the patient were normal. There were no extra-oral findings and lymph nodes were not palpable. Intra-oral examination revealed ulceration present on the

oral mucosa extending from left retromolar trigone posteriorly till the anterior faucial pillars (Figure 1).

Figure 1. Erythematous ulcerated areas with ragged border in the left retromolar area.

The lesion extended upwards and backward from the distal of the third molar,ill-defined in shape and covered by pseudomembrane with erythematous surroundings. On manipulation, bleeding from the lesion was positive. There was generalized attrition of teeth and gingival inflammation.

Based on the clinical features differential diagnosis were pemphigus vulgaris, bullous lichen planus, mucous membrane pemphigoid, erythema multiforme, pyostomatitis vegetans, recurrent herpes lesions in immunocompromised patients and pemphigus associated with inflammatory bowel disease.

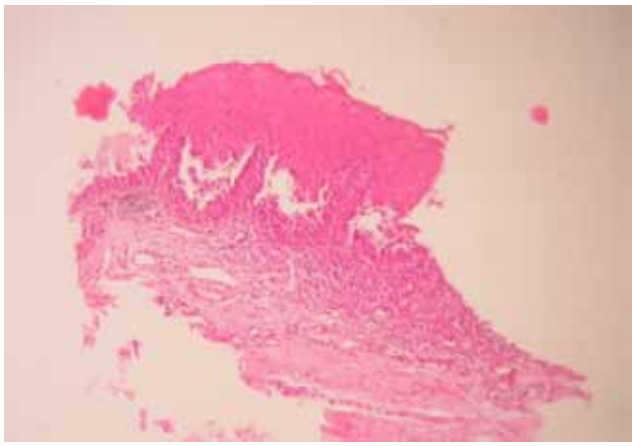

Figure 2. Photomicrograph (4x) shows intraepithelial vesicles and Tzanck cells.

A diagnosis of Pemphigus vulgaris was done after evaluation of the incisional biopsy performed on the perilesional site. The specimens were submitted for direct immunofluorescence study and conventional histopathology. Histopathological examination revealed parakeratinized stratified squamous epithelium beneath which is a moderately collagenous connective tissue stroma. Juxtaepithelial collection of chronic inflammatory cells can be seen in the stroma (Figure 2). Epithelium shows intraepithelial vesicles and clumps of epithelial cells (Tzanck cells) in the vesicular spaces. Tzanck cells exhibit hyperchromatic nuclei (Figure 3).

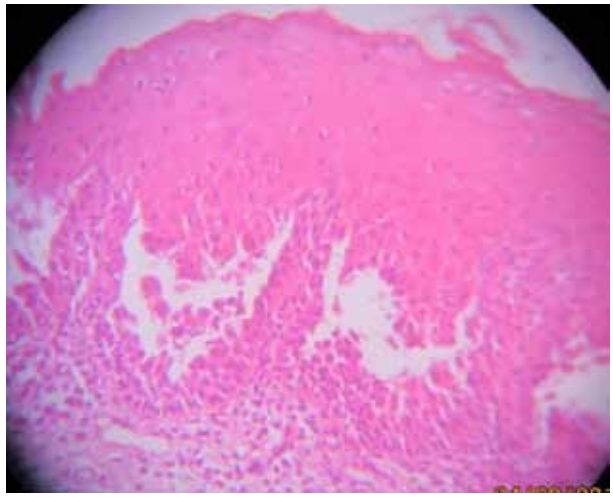

Figure 3: Photomicrograph (10x) shows vesiculation with suprabasilar cleavage and acantholysis and numerous Tzanck cells exhibiting hyperchromatic nuclei.

Direct immunofluorescence (IgG) reveals an immunoglobulin deposit in intercellular areas in a fishnet pattern (Figure 4).

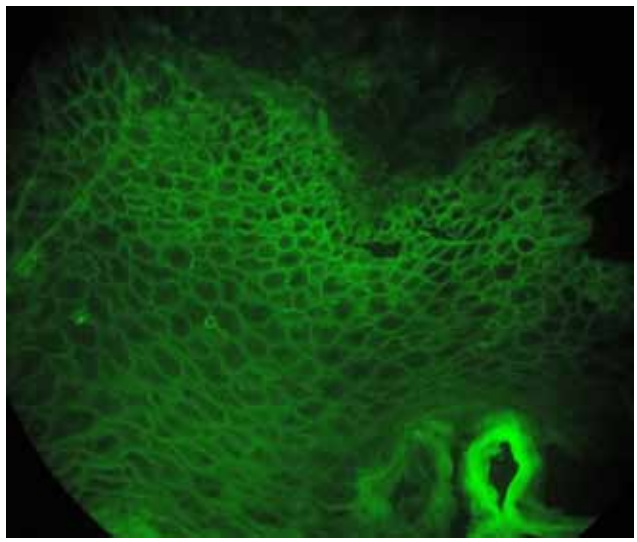

Figure 4. Direct immunofluorescence (IGg): Immunoglobulin deposit in intercellular areas in a fishnet pattern.

Based on histopathological and direct immunofluorescence findings final diagnosis of Pemphigus Vulgaris was given. The patient was immediately put on a combination of immunosuppressive and corticosteroid therapy. Unfortunately the patient was lost for follow up.

Discussion

Pemphigus Vulgaris (Latin: Common) the most common and severest form of pemphigus is a life-threatening vesiculobullous disorder. It is widely recognized that the incidence of pemphigus is higher in Ashkenazi Jews than in any other ethnic group.[4] The estimated incidence is 1 - 5 cases per million people in a year.

The peak age of occurrence is primarily between 4^{th} to 6^{th} decades of life, rarely before puberty. The classical sign is the epithelial blisters/bullae with a very frail wall appearing on cutaneous and/or mucosal surfaces. The bullae rapidly rupture and expand peripherally eventually causing large areas of denuded skin and/or epithelium with ragged edges. The lesions are usually painful. Buccal mucosa is the most common site especially areas of trauma along the occlusal plane. Gingiva and palate are the other common sites of involvement. A characteristic sign of this disorder is this phenomenon called Nikolsky's sign where when lateral pressure is applied to a normal-looking skin, results in the formation of a new lesion.[5,6]

In this case report the patient is a female and is 40 years old presenting with the chief complaint of pain and burning sensation in the left retromolar area. Moreover the patient has the initial intra-oral manifestations first as minute vesicles which rapidly ulcerated. Apart from the left retromolar area there was no involvement of skin or any other parts of the oral cavity. All the above manifestations were in accordance with a provisional diagnosis of pemphigus vulgaris. Histopathological evaluation and by the virtue of direct immunofluorescence the lesion was diagnosed to be pemphigus vulgaris. Because of the vigilance of the oral pathologist and with correct diagnosis immediate therapy was instituted.[7]

The oral lesions are often the first sign (First to Show and the Last to Go) of the disease (in 60 % or more) and they are most difficult to resolve with therapy. Hashimoto and Lever studied the microscopic features of the oral mucosa from patients with pemphigus vulgaris and theorized that initial lesions of pemphigus vulgaris most frequently occur in the oral mucosa because the epithelia demonstrate less intercellular junctions, thus making the area more susceptible to acantholysis.[5,6]

In the pathogenesis of pemphigus vulgaris there is a strong association between genetic and inducing factors. Genetic factors (soil) include HLA class 11 alleles. Predisposing individual factors (seed) that trigger disease initiation include diet, drugs, viruses in association with other diseases and others like smoking, hormone, irradiation and pesticides. The apoptosis theory is a multistep pathogenetic mechanism, first the autoantibodies target keratinocyte membrane acetylcholine receptors leading to activation of apoptosis(cell shrinkage). This is early acantholysis. Anti Dsg Ab targets Dsg 3 and Dsg 1 leading to cell-cell dishesion. This is advanced acantholysis.[4,8]

The ideal site for biopsy is an intact bulla which is rarely encountered and hence biopsies are best taken from the active border of the denuded area. Early changes in this disease consist of intercellular edema and the disappearance of intercellular bridges in the lower part, especially just above the basal cell layer. As the fluid increases the space is increased and a bulla is formed. After the formation of the suprabasal cleft, the intact basal layer remains attached to the lamina propria producing a pattern that resembles a row of tombstones.[9]

The characteristic histopathologic feature is the demonstration of acantholysis, i.e. separation of epithelial cells in the lower stratum spinosum. The separating cells (Tzank cells) present degenerative changes, the cell outlines are round, loss of intercellular bridges and large hyperchromatic nuclei. The underlying connective tissue is densely infiltrated with chronic inflammatory cells. A smear is prepared by unroofing the vesicle and gently scraping the base of the lesion. The smear is dried, fixed and stained with a polychrome stain such as Giemsa. On microscopic examination, a positive smear shows a large number of characteristic acantholytic epithelial cells.[7,8]

Electron microscopy studies indicate that breakdown of the epithelial intercellular substance is the first stage in the development of acantholysis followed by an increase of intercellular space, desmosomal lysis and finally degeneration of the cells. The gradual disintegration of desmosomes and clumping of tonofilaments occurs. As the desmosomal attachment disappears, the cell separates and the cell surface develops numerous microvilli.[6,7]

Direct immunofluorescence technique utilizes the patient's biopsy to demonstrate autoantibodies already fixed to the tissue and in indirect immunofluorescence technique patient's serum is reacted with normal control tissue to demonstrate the presence and concentration of the circulating autoantibodies.[10]

All the vesiculobullous lesions should be considered for differential diagnosis which include bullous pemphigoid, erythema multiforme, bullous lichen planus, dermatitis herpetiformis, aphthous ulcer (when pemphigus vulgaris lesion is small) and herpetic gingivostomatitis. The feature that differentiates pemphigus vulgaris from other lesions in the presence of suprabasillar split whereas pemphigus vulgaris can be differentiated from herpetic gingivostomatitis from the prodromal signs.[11]

Pemphigus Vulgaris was frequently a lethal disease, with most deaths occurring due to electrolyte loss and wound infection. With the advent of immunosuppressive therapy treatment consists primarily of systemic corticosteroids often in combination with immunosuppressive drugs. Pemphigus rarely undergoes complete resolution although remission and exacerbations are common.[1,8]

Conclusion

Some patients with pemphigus vulgaris develop acute fulminating disease, but most cases develop slowly. As oral lesions are first to appear, the oral pathologist should act as a sentinel to keep a check on disease progression before it flares up to give rise to dermatological manifestations.

Conflict of Interests: None

Ethical Permission: Approved

Funding: Nil

References

1. Becker BA, Gaspari AA. Pemphigus vulgaris and vegetans. Dermatol Clin. 1993;11(3):429-52.
2. Shamim T, Varghese VI, Shameena PM, Sudha S. Pemphigus vulgaris in oral cavity: clinical analysis of 71 cases. Med Oral Patol Oral Cir Bucal 2008;13(10):E622-6.
3. Neville BW. Oral and maxillofacial pathology. Saunders/Elsevier. 2009.
4. Scully C. Pemphigus vulgaris: Update on Etiopathogenesis, Oral manifestations, and Management. Crit rev oral biol med 2002; 13(5): 397-408 (2002)
5. Hashimoto K, Memphis T, Lever WF. An Ultrastructural Study of Cell Junctions in Pemphigus Vulgaris. Archives Dermatol 1970; 101(3): 287.
6. Popescu IA, Statescu L, Vata D, et al. Pemphigus vulgaris - approach and management (Review). Experimental Therapeutic Med 2019;18, 5056-5060.
7. Robinson JC, Lozada-Nur F, Frieden I. Oral pemphigus vulgaris: a review of the literature and a report on the management of 12 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84(4):349–355.
8. Yamagami J. Recent advances in the understanding and treatment of pemphigus and pemphigoid. F1000Res. 2018;7:F1000 Faculty Rev-1360. Published 2018 Aug 30.
9. Tamgadge S, Tamgadge A, Bhatt DM, Bhalerao S, Pereira T. Pemphigus vulgaris. Contemp Clin Dent. 2011;2(2):134–137.
10. Dagistan S, Goregen M, Miloglu O, Cakur B. Oral pemphigus vulgaris: a case report with review of the literature. J Oral Sci. 2008;50(3):359–362.
11. Gregoriou S, Efthymiou O, Stefanski C, Rigopoulos D. Management of pemphigus vulgaris: challenges and solutions. Clin Cosmet Investig Dermatol. 2015;8:521–527.