Asian Journal of Dental Sciences

3(4): 72-82, 2020; Article no.AJDS.63752

A Review on Pemphigus

U. Prathusha[1*], A. H. Harini Priya[1], R. Sathishmuthukumar[1], Nachiammai[1], Serena Florence[1] and J. Rebecca Elizabeth Susanna[1]

[1]Department of Oral Pathology, Chettinad Dental College and Research Institute, Kelambakkam, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author UP designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AHHP and RS managed the analyses of the study. Author JRES managed the literature searches. All authors read and approved the final manuscript.

Article Information

Editor(s):
(1) Dr. Armando Montesinos Flores, National Autonomous University of Mexico, Mexico.
Reviewers:
(1) Francesco Bellinato, University of Verona, Italy.
(2) Tibin K. Baby, Kerala University of Health Sciences, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/63752

Review Article

Received 06 October 2020
Accepted 10 December 2020
Published 26 December 2020

ABSTRACT

Autoimmune bullous diseases is a heterogeneous group of disorders that is characterized by intraepithelial or sub epithelial blistering caused by formation of autoantibodies targeted against structures essential for integrity of skin and mucous membrane. One such type of autoimmune vesiculobullous disease is Pemphigus, which affects the skin and the mucous membrane. There are different types of pemphigus based on the clinical features, histopathological features and the specific antigens against which autoantibodies have been produced. This review gives an overview on thedifferent types of Pemphigus with its clinical, histopathological and immunopathological characteristics and its treatment.

Keywords: Vesiculobullous lesions; pemphigus; pemphigus variants; histopathology; immunopathology; treatment.

**Corresponding author: Email: prathushaumakhanth@gmail.com;*

1. INTRODUCTION

Vesiculobullous (VB) diseases are a set of oral disorders, which are characterized by the formation of vesicles or bullae [1]. This group includes autoimmune mucocutaneous diseases, viral diseases, diseases with immunologically mediated mechanism, and genetic diseases. The terms most commonly used in Vesiculobullous lesions are vesicle and bulla. Vesicle is defined as a superficial blister, 5 mm or less in diameter, usually containing clear fluid and bulla is defined as a circumscribed collection of free fluid greater than 5 mm in diameter [1,2] [Fig. 1]. In the oral mucosa, usually intact vesicles cannot be seen on clinical examination as these lesions are soon ruptured because of the oral functions to create ulcers with ragged edges [1,2].

2. CLASSIFICATION

According to Fitzpatrick classification, the Vesiculobullous or mucocutaneous diseases are categorized depending on specific separation in line with the anatomical plane [Tables 1 and 2].

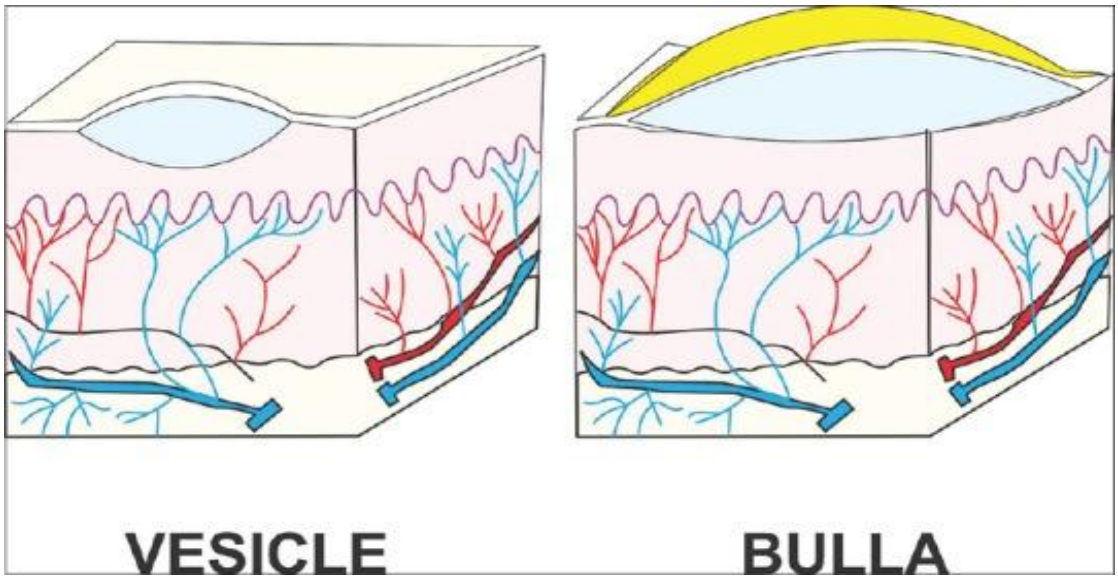


Fig. 1. A diagrammatic representation of Vesicle & Bulla [1]

Table 1. According to separation at intraepithelial level [1,2]

Granular layer	Spinous layer	Suprabasal layer	Basal layer
Pemphigus foliaceous	Herpes simplex virus infection	Pemphigus vulgaris	Erythema multiforme
Pemphigus erythematosus	Familial benign pemphigus	Pemphigus vegetans	Toxic epidermal necrolysis (TEN)
Frictional blisters	Herpes zoster and varicella	Darier's disease	Lichen planus
Bullous impetigo	Eczematous dermatitis		Epidermolysis bullosa simplex
			Lupus erythematous

Table 2. According to separation at dermoepidermal junction [1,2]

Lamina lucida	Below basal lamina (sub lamina densa)
Bullous pemphigoid	Epidermolysis bullosa acquisita
Cicatricial pemphigoid	Epidermolysis bullosa dystrophica
Dermatitis herpetiformis	Bullous systemic lupus erythematous (SLE)
Epidermolysis bullosa junctional	Linear IgA dermatosis

Vesiculobullous lesions can be classified as given below [2,3]:

- Vesiculobullous lesions due to infections (Viral)
- Vesiculobullous lesions due to autoimmune diseases
- Vesiculobullous lesions due to allergy
- Hereditary diseases

3. VESICULOBULLOUS LESIONS DUE TO AUTOIMMUNE DISEASES

In autoimmune diseases, the patient's immune system fails to recognize 'self' and 'foreign' antigens. This may occur due to sensitization of immune cells by the expression of new or modified antigens by some of the patient's cells, resulting in cellular and humoral response [2,3].

Various modified antigens are:

- Enzymatic degradation of cell surface
- Viral infections
- Drug action
- Cellular antigens or Cross-reacting antigens that resemble foreign antigens
- Idiopathic Factors [2,3].

Immunobullous diseases are autoimmune diseases where autoantibodies directed against components of the skin or oral epithelium produce blisters [2,3].

The vesiculobullous lesions with possible autoimmune etiology are:

- Pemphigus vulgaris
- Paraneoplastic pemphigus
- Mucous membrane pemphigoid
- Bullous pemphigoid
- Linear IgA dermatosis
- Epidermolysis bullosa acquisita
- Dermatitis Herpatiformis [2,3]

4. PEMPHIGUS

Pemphigus is a chronic skin disease characterized by the formation of vesicles and bullae, small or large fluid-filled blisters that develop in cycles [4,5,6,7]. It includes a group of autoimmune blistering diseases of the skin and mucous membranes characterized histologically by intradermal blisters. Immunologically they are caused by circulating immunoglobulin G (IgG) antibody directed against the cell surface of keratinocytes [4,5,7].

There are four types of pemphigus. These are the following:

- Pemphigus vulgaris
- Pemphigus vegetans
  1. Pemphigus vegetans of Hallopeau
  2. Pemphigus vegetans of Neumann
- Pemphigus foliaceous
  - Pemphigus erythematosus
  - Endemic pemphigus
- Paraneoplastic pemphigus (PNP)
- Immunoglobulin A pemphigus
  - Submucosal pustular dermatosis
  - Intraepidermal neutrophilic IgA dermatosis

The common form among the four types is pemphigus vulgaris (about 80%) [3,4,5].

5. PEMPHIGUS VULGARIS

Pemphigus vulgaris (PV) is an autoimmune disease causing blister formation in the skin and mucous membranes and is mediated by circulating autoantibodies formed against keratinocyte cell surfaces. Clinical and experimental observations indicate that the pathogenic factor is the circulating autoantibodies [4,5,6,8].

6. ETIOPATHOGENESIS

The binding of IgG autoantibodies to keratinocyte cell surface molecules leads to blister formation in pemphigus vulgaris .The intercellular antibodies bind to keratinocyte desmosomes and to desmosome free areas of the keratinocyte cell membrane [4,7]. The binding of autoantibodies leads to loss of cell-cell adhesion. The antibody binds to keratinocyte cell surface molecules desmoglein 1 and 3. The antibodies bind components of complement to the surface of epidermal cells, which activates complement to release inflammatory mediators and recruitment of activated T-cells [8,9,10] [Fig. 2].

7. CLINICAL FEATURES

Patient's symptoms include persistent painful ulcers and sloughing, that may affect any part of the oral cavity but is commonly seen on the buccal mucosa, palatal mucosa and lips [7,9]. Occasionally blisters are seen [Fig. 3(a)], but these usually rupture quickly and are often unnoticed [8,9,11]. The Nikolsky's test is positive. The ulcerations may be noted in other mucous membranes as well such as the nasal

mucosa,conjunctiva, pharynx, larynx, esophagus and genital mucosa and the skin where intact blisters are more commonly seen [11,10]. Localized lesions in the oral cavity are not life threatening but maybe associated with morbidity if untreated, and patients have to be carefully monitored for spread of the condition to the skin and other mucous membranes [11,10]. [Fig. 3(b)]

Table 3. Antigens targeted by antibodies in vesiculobullous (VB) lesions [1]

Autoimmune VB lesions	Antigen
Pemphigus vulgaris	Desmoglein 1 and 3
Paraneoplastic pemphigus	Desmoglein 1 and 3, plakin proteins
Cicatricial pemphigoid	BP 180, laminin V
Bullous pemphigoid	BP 180 and 230
Epidermolysis bullosa acquisita	Type VII collagen
Dermatitis herpetiformis	Tissue transglutaminase

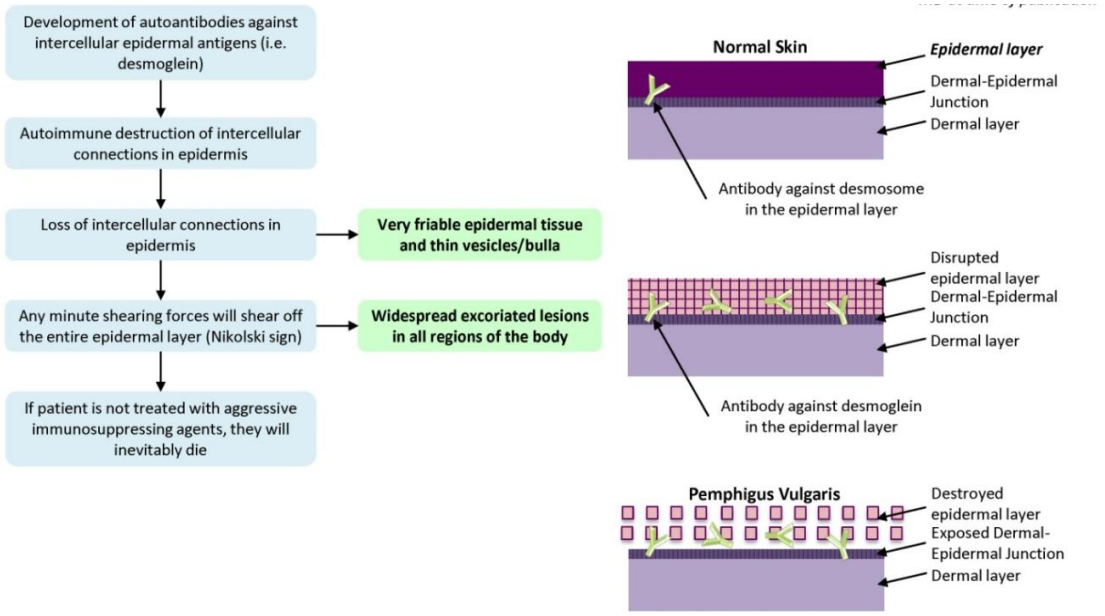
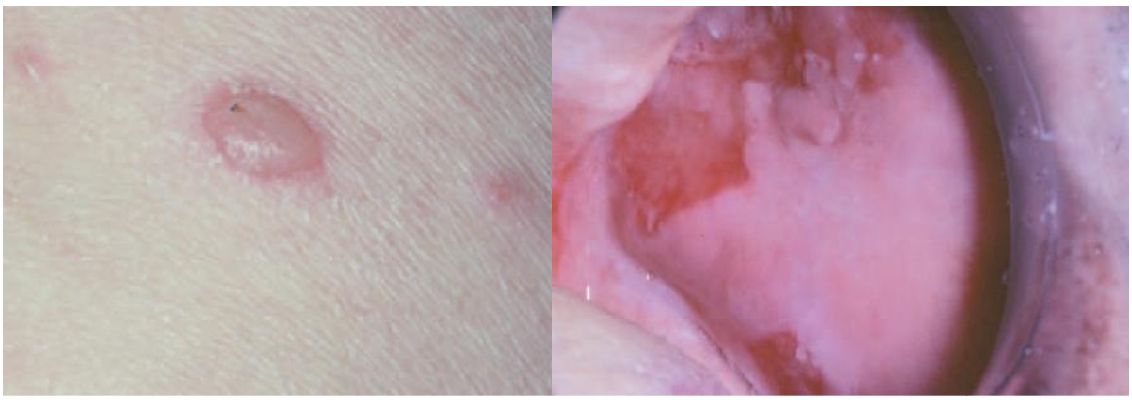


Fig. 2. Pemphigus vulgaris –pathogenesis and clinical findings [12]



(a) **(b)**

Fig. 3 (a). This flaccid cutaneous bulla is characteristic of skin involvement. (b). Multiple erosions of the left buccal mucosa [21]

8. HISTOPATHOLOGICAL AND IMMUNO-PATHOLOGICAL FEATURES

Biopsy of the lesion shows an intraepithelial vesicle containing floating, rounded keratinocytes (Tzanck cells) that has detached from surrounding cells (acantholysis). The basal layer cells are still firmly attached to the connective tissue [4,6,7]. The roof of the blister is tenuous and of variable thickness, or may be absent. Long rete pegs lined by a single layer of basal cells are often present, and there is a mild to moderate chronic inflammatory infiltrate in the adjacent connective tissue [9,11,10].

Under direct immunofluorescence, a “chicken wire” or “fishnet” appearance is seen due to the binding of IgG and C3 between epithelial cells. No staining is noted in the basement membrane zone (BMZ) [13,14,11,10] [Fig. 4(c)].

8.1 Treatment

The primary drugs used in the treatment of pemphigus vulgaris are corticosteroids. In patients with mild localized lesions in the oral cavity having low titer of circulating autoantibodies, the disease may be controlled, at least temporarily, with topical corticosteroid rinses or creams, including agents such as clobetasol propionate. Intralesional triamcinolone may be used for resistant local lesions [14,11,10].

8.2 Pemphigus Foliaceus

Pemphigus foliaceus (PF) is a benign form of pemphigus. It is an autoimmune skin disorder that is characterized by the formation of superficial blisters due to the loss of intercellular adhesion of keratinocytes in the upper parts of the epidermis (acantholysis) [4,15]. It includes six subtypes: pemphigus erythematosus (PE), pemphigus Herpatiformis (PH), endemic pemphigus foliaceus, immunoglobulin A (IgA) pemphigus foliaceus, paraneoplastic pemphigus foliaceus (PNPF), and drug-induced pemphigus foliaceus [4,15].

8.3 Etiopathogenesis

Superficial blisters in PF are caused by immunoglobulin G (IgG) (mainly IgG4 subclass) autoantibodies directed against a cell adhesion molecule, desmoglein 1, that is expressed mainly in the granular layer of the epidermis. Precipitating factors include medications and ultraviolet light radiation. There has been a recent suggestion that both factors enhance autoantibody epidermal binding and preferential neutrophil adhesion to UV-irradiated epidermis which contributes to the acantholysis in photo-induced PF [4,14,15].

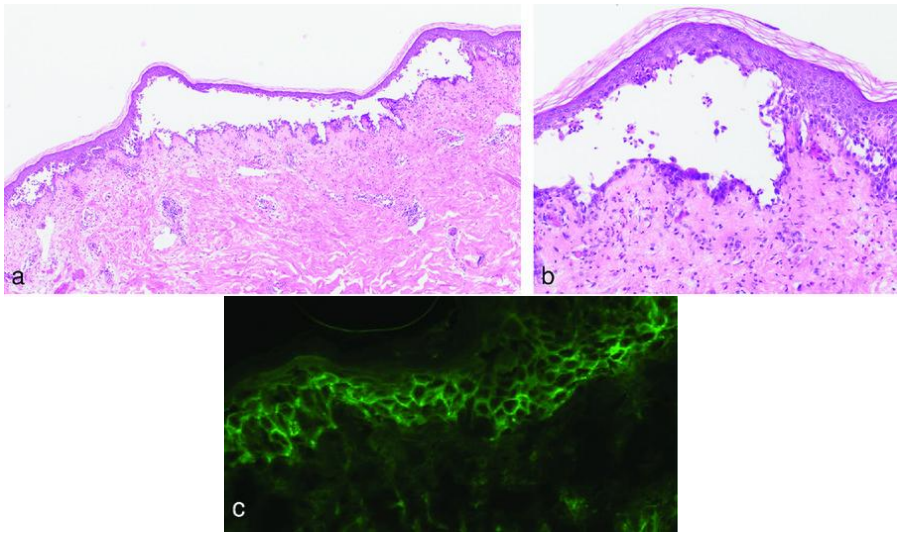


Fig. 4 (a). Histology shows intraepidermal, suprabasal split formation. Numerous eosinophils are found in the dermis (hematoxylin& eosin stain, original magnification x 40). (b) Basal keratinocytes are attached to the basement membrane; a few round, acantholytic keratinocytes are seen within the blister (Tzanck cells) (x 200). (c) Direct immunoflurosence shows tissue bound IgG autoantibodies and C3 complement on the surface of epidermal keratinocytes [18]

8.4 Clinical Features

Pemphigus foliaceus shows characteristic early bullous lesions that rapidly rupture and dry to leave masses of flakes or scales. It is a relatively mild form of pemphigus, which is most common in older adults but may occur in young children as well [4,15,16,17].

Brazilian pemphigus is a mild endemic form of pemphigus foliaceus found in tropical regions, particularly in Brazil, that often occurs in children and frequently in family groups. The course of action of the disease is similar to that of pemphigus foliaceus. Oral lesions in pemphigus foliaceus are rare, according to Perry and Brunsting (1965) in their extensive study of this form of the disease [15,16] [Fig. 5].

9. HISTOPATHOLOGICAL AND IMMUNOPATHOLOGICAL FEATURES

Pemphigus foliaceus initially starts as acantholysis of the upper epidermis. Later it enlarges and detaches without bullae formation, though sometimes a bulla may form showing acantholysis at both the roof and the floor. Established lesions have acanthosis and mild-to-moderate papillomatosis. Hyperkeratosis and parakeratosis is also evident, with Dyskeratosis cells seen within the granular layer. A mild lymphocytic infiltrate occurs, often with the presence of eosinophils [3]. Similar to Pemphigus vulgaris, Direct Immunofluorescence shows intercellular IgG and C3 deposits in the subcorneal layer of the epidermis [18,19,20] [Fig. 6].

9.1 Treatment

The treatment for PF is usually less aggressive than that for pemphigus vulgaris because of its low morbidity and mortality rate. Few studies have stated that nonsteroidal treatment of pemphigus is possible. Mestinon can be used to slow down the progress of the disease and to treat mild cases with chronic lesions on limited areas [4,15].

9.2 Paraneoplastic Pemphigus

Paraneoplastic pemphigus is a rare vesiculobullous disorder that affects patients having a neoplasm like lymphoma or chronic lymphocytic leukemia [21,20,22]. Although the correct pathogenetic mechanisms are unknown, certain evidences have suggested abnormal levels of the cytokine, interleukin 6 (IL-6), could be produced by host lymphocytes in response to the patient's tumor. This IL-6 is accountable for stimulating the abnormal production of antibodies that are directed against the antigens that are related with the desmosomal complex and the basement membrane zone of the epithelium [21,23,24].

9.3 Clinical Features

Patients generally give a history of a malignant lymphoreticular neoplasm, or a benign lymphoproliferative disorder such as angiofollicular lymph node hyperplasia (Castleman's disease) or thymoma [21,23,24]. In approximately one third of reported cases, paraneoplastic pemphigus developed before a malignancy was identified, thus signalling the presence of a tumor. The neoplastic disease may or may not be under control at the time of onset of the paraneoplastic pemphigus [21,23,24]. The signs and symptoms of paraneoplastic pemphigus have a sudden onset and may appear polymorphous. In some instances, multiple vesiculobullous lesions affect the skin and oral mucosa [Fig. 7(a)] [21,24,25]. A feature that is uncommon in pemphigus vulgaris but evident in paraneoplastic pemphigus is palmar or plantar bullae. Multiple areas of erythema and diffuse, irregular ulceration are seen in the oral mucosa. If the lesions are untreated, they persist and worsen. Some patients may develop oropharyngeal lesions, without cutaneous involvement [21,24,26].

10. HISTOPATHOLOGIC AND IMMUNO-PATHOLOGICAL FEATURES

The features of paraneoplastic pemphigus as seen on light microscopy are a lichenoid mucositis with subepithelial clefting (like pemphigoid) or intraepithelial clefting (like pemphigus) [Fig. 7(b)]. Direct immuno-fluorescence shows a weakly positive deposition of immunoreactants (IgG and complement) in the intercellular zones of the epithelium and/or a linear deposition of immunoreactants at the basement membrane zone [21,27] [Fig. 7(c), 7(d)].

10.1 Treatment

As the morbidity and mortality rates are high in paraneoplastic pemphigus, it indicates a poor prognosis for the patient. It is treated by systemic corticosteroids, often combined with other immunosuppressive agents such as

azathioprine, cyclophosphamide and methotrexate [7,11,28].

10.2 IgA Pemphigus

IgA pemphigus is a group of intraepidermal autoimmune blistering diseases that is characterized by vesiculopustular eruption, neutrophil infiltration, acantholysis and tissue-bound and circulating IgA antibodies that target the desmosomal or nondesmosomal cell surface components in the epidermis. It has two clinical types: intraepidermal neutrophilic type (IEN) and subcorneal pustular dermatosis (SPD) [5,28,29].

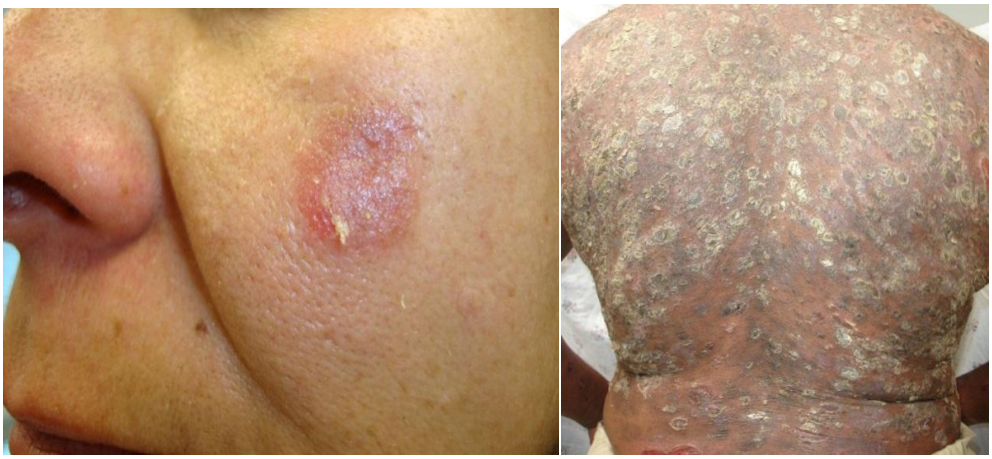


Fig. 5. (a) Isolated scaly, erythematous plaque with peripheral erosion on left cheek. (b) Disseminated papulosquamous eruption on back evolving from the preceding superficial blisters and secondary erosions of PF [15]

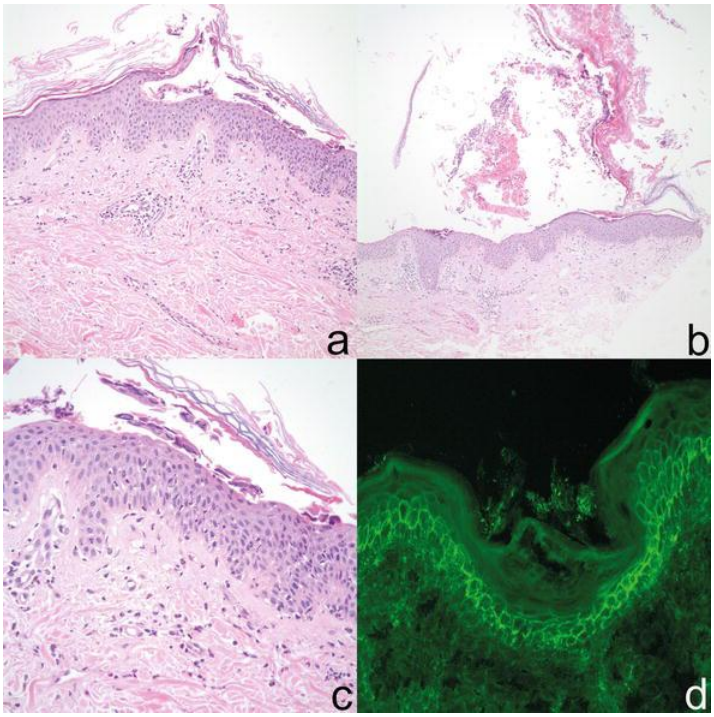


Fig. 6. Pemphigus foliaceus. (a) Upper granular split (40×). (b) Frail bulla is tearing off the upper epidermal layers (40×). (c) Acantholytic granular layer cells (200×). (d) Intraepidermal IgG positivity mainly at the superficial levels of the epidermis (200×) [19]

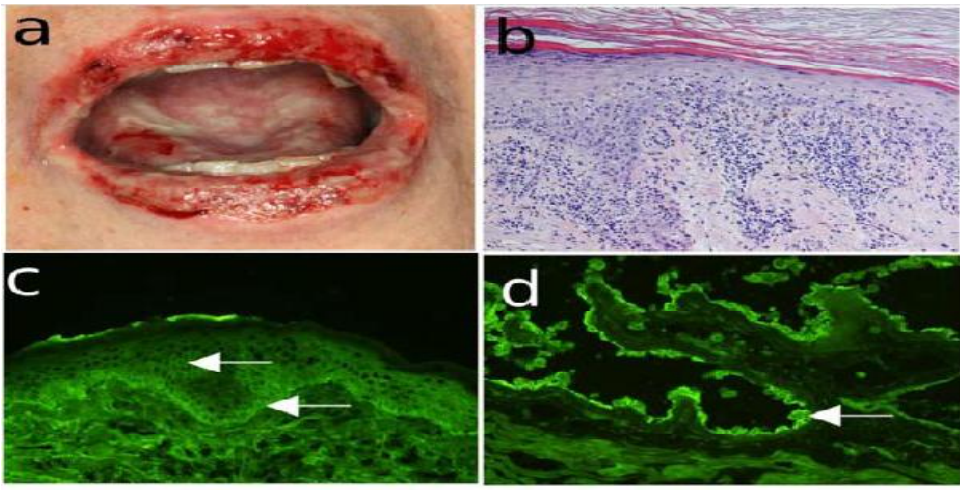


Fig. 7. (a) Hemorrhagic erosions with crusts on the lips and oral cavity seen in a patient with non-Hodgkin lymphoma. (b) Interface dermatitis by histopathology (H&E staining). (c) Immunofluorescence (IF) microscopic analysis of a perilesional biopsy reveals deposits of IgG at the dermal-epidermal junction and at the intercellular spaces of keratinocytes. (d) Further serological testing by indirectIF microscopy shows binding of IgG autoantibodies to rat bladder urothelium [20]

10.3 Etiopathogenesis

IgA pemphigus is a disease in which the reaction of the IgA antibodies to the keratinocyte cell surfaces is thought to be the pathogenic factor. The antigen of the SPD type was identified as Desmocollin-1, whereas the antigen of the IEN type is still unknown, although some rare cases have shown IgA antibodies to either Desmoglein-1 or Desmoglein-3. The IgA autoantibodies bind to the Fc receptor CD89 on monocytes and granulocytes, which results in the accumulation of neutrophils, which eventually leads to proteolytic cleavage of the keratinocyte cell-cell junction [28,29,30].

10.4 Clinical Features

The onset of IgA pemphigus is subacute. Patients with both types of IgA pemphigus clinically present with either flaccid vesicles or pustules on erythematous or normal skin [28,29]. The pustules tend to merge to form an annular pattern with crusts in the central area. The SPD type of IgA pemphigus shows clinical features similar to those of SPD [28,31]. The IEN type demonstrates a characteristic appearance, the so-called "sunflower-like" configuration. The sites most commonly involved are axillary areas, groin areas, trunk and proximal extremities. About half of IgA pemphigus patients suffer from pruritus, and mucous membrane involvement is rare [28,30,32] [Fig. 8].

11. HISTOPATHOLOGY

On histopathologic examination of IgA pemphigus, slight acantholysis and neutrophilic infiltration in the epidermis is seen. Acantholysis in IgA pemphigus is milder than in classic pemphigus. In subcorneal pustular dermatosis type ,the pustules are present in the subcorneal layer in the upper epidermis, whereas in the intraepidermal neutrophilic type, suprabasilar pustules in the lower or entire epidermis are present [28,31,32] [Fig. 9].

12. IMMUNOPATHOLOGY

IgA deposition in the intercellular region of the epidermis is detected in all cases of IgA pemphigus by DIF in a pattern similar to pemphigus IgG deposition. IgG or C3 is also sometimes deposited .In the SPD type of IgA pemphigus, IgA deposition is limited to the upper epidermal cell surfaces [Fig. 10(a), 10(b)], whereas in the IEN type of IgA pemphigus, there is intercellular IgA deposition confined to the lower epidermis [Fig. 10(c), 10(d)] [31,32]. IIF using patient sera and substrates such as healthy human skin show positive result in the cell-cell contact region in the entire epidermis in about 50% of patients [28,29].

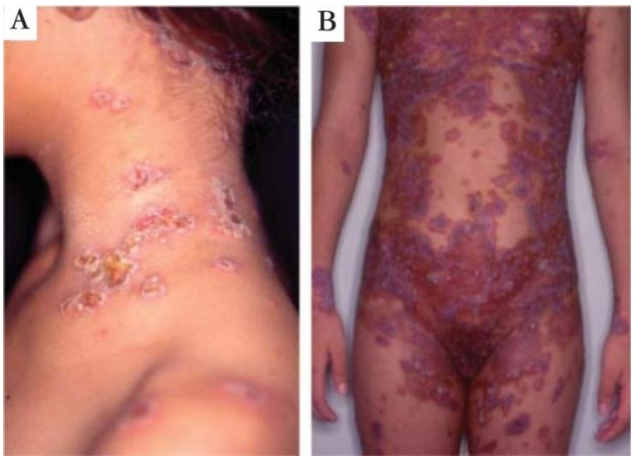


Fig. 8. IgA Pemphigus (Intraepidermal neutrophilic type): (A), (B) show vesicles, blisters and pustules, involving the entire trunk, neck and part of the upper limbs [28]

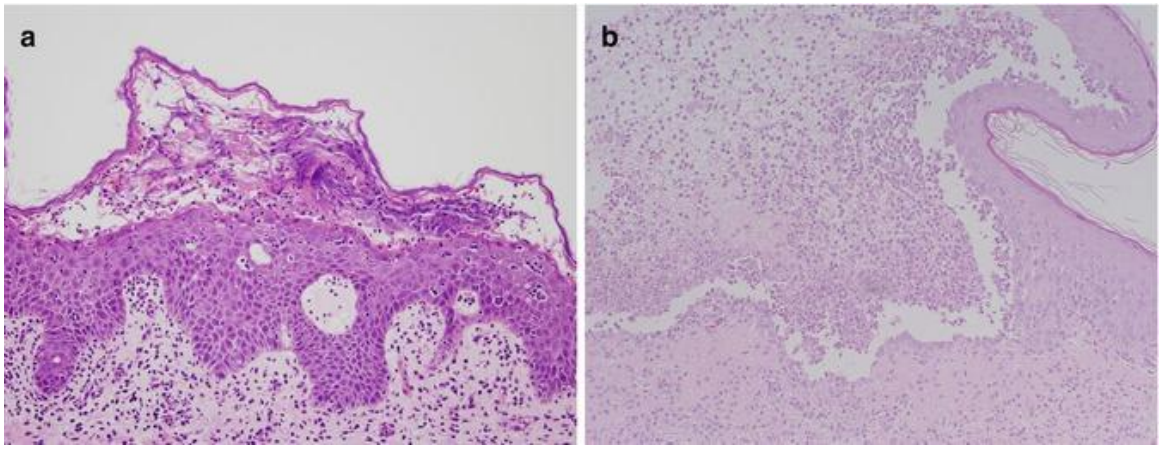


Fig. 9. (a) Histopathological features of SPD-type IgA pemphigus (40 x) and (b) IEN-type IgA pemphigus (10x) [32]

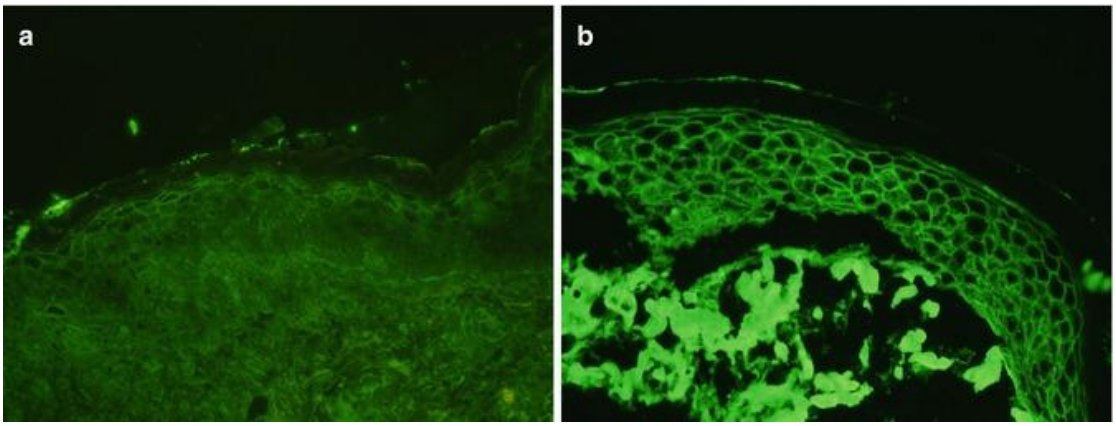


Fig. 10. (a) Direct immunofluorescence features of SPD-type IgA pemphigus. (b) Direct immunofluorescence features of SPD-type IgA pemphigus [32]

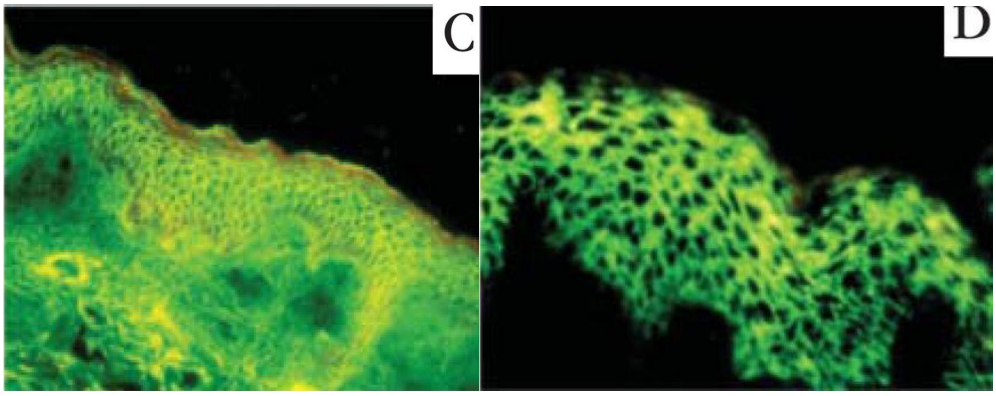


Fig. 10. (c) DIF: IgA deposits intercellular; (d) IIF showing presence of IgA in the patient´s sera (1:640) [28]

12.1 Treatment

The treatment for IgA pemphigus is oral and topical corticosteroids, due to the inflammatory nature of the disease. The suggested dose is 0.5 to 1 mg/kg daily. Dapsone usually at a dose of 100 mg daily can also be used in treating IgA pemphigus because of its effect in suppressing neutrophilic infiltration. As IgA pemphigus is a superficial blistering disease it usually heals without scarring if appropriate treatment is provided [28,31,32].

13. CONCLUSION

Pemphigus, especially certain types, is a life-threatening disease and has a mortality risk. Hence, the diagnosis should be made as soon as possible, and the treatment should be started. This article has reviewed the knowledge about the classical as well as the non classical forms of pemphigus along with its pathophysiology, histopathological and immunopathological features and treatment modalities for better understanding of these diseases so that prompt diagnosis and treatment can be provided. Future research on the patho-physiology and the role of the target antigens may help better elucidate the mechanisms underlying this group of diseases.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Rastogi V, Sharma R, Misra SR, Yadav L. Diagnostic procedures for autoimmune vesiculobullous diseases: A review. Journal of Oral and Maxillofacial Pathology: JOMFP. 2014;18(3):390.
2. Baum S, Sakka N, Artsi O, Trau H, Barzilai A. Diagnosis and classification of autoimmune blistering diseases. Autoimmunity Reviews. 2014;13(4-5):482-9.
3. John P. Textbook of oral medicine. JP Medical Ltd; 2014.
4. Rajendran R. Shafer's textbook of oral pathology. Elsevier India; 2009.
5. Bystryn JC, Rudolph JL. Pemphigus. The Lancet. 2005;366(9479):61-73.
6. Santoro FA, Stoopler ET, Werth VP. Pemphigus. Dental Clinics. 2013;57(4): 597-610.
7. Rashid H, Lamberts A, Diercks GF, Pas HH, Meijer JM, Bolling MC, Horváth B. Oral lesions in autoimmune bullous diseases: An overview of clinical characteristics and diagnostic algorithm. American Journal of Clinical Dermatology. 2019;1-5.
8. Dagistan S, Goregen M, Miloglu O, Çakur B. Oral pemphigus vulgaris: a case report with review of the literature. Journal of oral science. 2008;50(3):359-62.
9. Venugopal SS, Murrell DF. Diagnosis and clinical features of pemphigus vulgaris. Dermatologic clinics. 2011;29(3):373-80.
10. Scully C, Challacombe SJ. Pemphigus vulgaris: update on etiopathogenesis, oral manifestations, and management. Critical Reviews in Oral Biology & Medicine. 2002;13(5):397-408.
11. Darling MR, Daley T. Blistering mucocutaneous diseases of the oral mucosa-a review: Part 2. Pemphigus vulgaris. Journal-Canadian Dental Association. 2006;72(1):63.

12. Yan yu. The Calgary Guide. [Online]; 2020. Available:https://calgaryguide.ucalgary.ca/pemphigus-vulgaris/ [Accessed 18 November 2020]
13. Pohla-Gubo G, Hintner H. Direct and indirect immunofluorescence for the diagnosis of bullous autoimmune diseases. Dermatologic clinics. 2011;29(3):365-72.
14. Fernando SL, Li J, Schifter M. Pemphigus Vulgaris and Pemphigus Foliaceus. Skin Biopsy: Diagnosis and Treatment. 2013; 105.
15. James KA, Culton DA, Diaz LA. Diagnosis and clinical features of pemphigus foliaceus. Dermatologic Clinics. 2011; 29(3):405-12.
16. Perks AC, Farthing PM, Murphy R, Hegarty AM. A case of concomitant pemphigus foliaceus and oral pemphigus vulgaris. Head and Neck Pathology. 2018; 12(4):5927.
17. Kawana S, Hashimoto T, Nishikawa T, Nishiyama S. Changes in clinical features, histologic findings, and antigen profiles with development of pemphigus foliaceus from pemphigus vulgaris. Archives of dermatology. 1994;130(12):1534-8.
18. Hofmann SC, Juratli HA, Eming R. Bullous autoimmune dermatoses. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2018;16(11):1339-58.
19. Ates D. Histomorphologic and Direct Immunofluorescence Findings of Autoimmune Bullous Disease. Autoimmune Bullous Diseases. 2018;155.
20. Otten JV, Hashimoto T, Hertl M, Payne AS, Sitaru C. Molecular diagnosis in autoimmune skin blistering conditions. Current molecular medicine. 2014;14(1): 69-95.
21. Neville BWS. Oral and maxillofacial pathology. 2nd ed. New Delhi: Elsevier; 2002.
22. Laskaris GC, Papavasiliou SS, Bovopoulou OD, Nicolis GD. Association of oral pemphigus with chronic lymphocytic leukemia. Oral Surgery, Oral Medicine, Oral Pathology. 1980;50(3):244-9.
23. Zhu X, Zhang B. Paraneoplastic pemphigus. The Journal of Dermatology. 2007;34(8):503-11.
24. Kartan S, Shi VY, Clark AK, Chan LS. Paraneoplastic pemphigus and autoimmune blistering diseases associated with neoplasm: characteristics, diagnosis, associated neoplasms, proposed pathogenesis, treatment. American Journal of Clinical Dermatology. 2017;18(1):105-26.
25. Tirado-Sánchez A, Bonifaz A. Paraneoplastic pemphigus. A life-threatening autoimmune blistering disease. Actas Dermo-Sifiliograficas. 2017;108(10): 902-10.
26. Anhalt GJ. Paraneoplastic pemphigus. InJournal of Investigative Dermatology Symposium Proceedings. 2004;9(1):29-33. Elsevier.
27. Horn TD, Anhalt GJ. Histologic features of paraneoplastic pemphigus. Archives of Dermatology. 1992 Aug 1;128(8):1091-5.
28. Porro AM, Caetano LD, Maehara LD, Enokihara MM. Non-classical forms of pemphigus: pemphigus herpetiformis, IgA pemphigus, paraneoplastic pemphigus and IgG/IgA pemphigus. Anais Brasileiros de Dermatologia. 2014;89(1):96-106.
29. Kilic A. Pemphigus: Subtypes, Clinical Features, Diagnosis, and Treatment. In Autoimmune Bullous Diseases. Intech Open; 2017.
30. Hashimoto T. Immunopathology of IgA pemphigus. Clinics in Dermatology. 2001; 19(6):683-9.
31. Yasuda H, Kobayashi H, Hashimoto T, Itoh K, Yamane M, Nakamura J. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. British Journal of Dermatology. 2000;143(1):144-8.
32. Tsuruta D, Ishii N, Hamada T, Ohyama B, Fukuda S, Koga H, Imamura K, Kobayashi H, Karashima T, Nakama T, Dainichi T. IgA pemphigus. Clinics in Dermatology. 2011;29(4):437-42.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/63752