

Review Article

Vesiculobullous lesions of the oral cavity

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Abstract

Vesiculobullous lesions are a type of mucocutaneous disease that is characterized by vesicles and bullae or blisters. Both vesicles and bullae are fluid-filled lesions, and they are distinguished by size, vesicles being less than 5–10 mm and bulla being larger than 5–10 mm. In the case of vesiculobullous diseases which are also immune disorders the term immunobullous is sometimes used. This review will provide an overview of vesiculobullous lesions involving oral cavity, their characteristic features and recent developments in the diagnosis of these lesions.

Key words

Lichen planus, Herpes simplex, Pemphigus, Bullous pemphigoid, Erythema multiforme, Varicella, Herpangina, Steven-johnson syndrome.

Introduction

Vesiculobullous mucosal disorders, including some life-threatening diseases, manifest in the skin and mucous membranes and are clinically characterized by the appearance of blisters and secondary erosions. Bullous autoimmune dermatoses have a common pathogenic mechanism involving binding of autoantibodies to specific adhesion molecules in epidermal desmosomes and in some cases in the area of the dermo-epidermal basement membrane zone. The binding of circulating autoantibodies and the induction of an inflammatory reaction in the area of target structures lead to loss of adhesion with subsequent intra- or subepidermal blister formation [1].

Lichen planus

Lichen planus is a common disorder of the stratified squamous epithelium that affects oral and genital mucous membranes, skin, nails, and scalp. Oral Lichen Planus (OLP) affects middle-aged women and shows distribution patterns and characteristics such as white striations, white plaques or papules, erythema, blisters and erosions, and may be associated with medication and/or dental materials used by the patient. The clinical diagnosis can only be made if the disease presents classical patterns such as concomitant lesions in the oral mucosa and skin. The laboratory diagnosis is histopathologically characterized by the presence of projections of the epithelium in the form of saw tooth and Civatte. Direct immunofluorescence is used when there is suspicion of other diseases, such as pemphigus and pemphigoid [2].

Bullous lichen planus

It is the most unusual clinical form, exhibiting blisters that increase in size and tend to rupture, leaving the surface ulcerated and painful. The periphery of the lesion is, in general, surrounded

by fine keratinized striae [2]. The incidence of oral lichen planus varies between 0.5 per cent and 2 percent. About 30-70% of patients with skin lesions have oral involvement, while 15% present with only oral involvement. Distinct clinical subtypes such as reticular, erosive, atrophic, hypertrophic and bullous oral lichen planus are well recognized. Of these, the reticular form is the commonest while bullous is the rarest with only few cases reported till date. Presence of cutaneous lesions may be helpful in corroborating the diagnosis of oral lichen planus [3].

Herpes simplex infections

The herpes viruses are a large family of viruses characterized by a DNA core surrounded by a capsid and an envelope. Seven types of herpes viruses are known to be pathogenic for humans, with six of these linked to diseases in the head and neck area. Herpes simplex virus (HSV) infections are common vesicular eruptions of the skin and mucosa. They occur in two forms—systemic or primary—and may be localized or secondary in nature. Both forms are self-limited, but recurrences of the secondary form are common because the virus can be sequestered within ganglionic tissue in a latent state. The incubation period after exposure ranges from several days to 2 weeks. In overt primary disease a vesiculo-ulcerative eruption (primary gingivostomatitis) typically occurs in the oral and perioral tissues. The focus of eruption is expected at the original site of contact [4]. After resolution of primary herpetic gingivostomatitis, the virus is believed to migrate, through some unknown mechanism, along the periaxon sheath of the trigeminal nerve to the trigeminal ganglion, where it is capable of remaining in a latent or sequestered state. Reactivation of virus may follow exposure to sunlight (“fever blisters”), exposure to cold (“cold sores”),

trauma, stress, or immunosuppression causing a secondary or recurrent infection.

Pemphigus

Pemphigus includes a group of autoimmune blistering diseases of the skin and mucous membrane. It is characterized histologically by intradermal blisters and immunologically by circulating autoantibodies directed against the cell surface of keratinocytes. The term Pemphigus is derived from the Greek word "Pempnix", meaning Bubble or Blister. The three primary subsets of pemphigus include Pemphigus Vulgaris(PV), Pemphigus Foliaceus and Paraneoplastic Pemphigus, with PV being the most common and important variant [5]. The oral lesions precede skin lesions in 50% of cases. In cutaneous disease, concomitant oral lesions are encountered in 90% of the cases [6]. Pemphigus can be a life threatening disease and hence its early diagnosis and treatment is essential. The classic histological feature seen in PV is acantholysis which is the loss of cell to cell contact in the epithelial cell layers. Development of intercellular edema within the epithelial layers, dissolution of the intercellular bridges and the widening of intercellular spaces, lead to separation between the cells and the formation of blisters just above the basal cell layer. Hence, the split is characteristically suprabasilar and the basal cells remain tightly attached to the basal lamina producing tombstone appearance [5, 7, 8]. Presence of Tzanck cells which are free floating, rounded acantholytic epithelial cells will be found within the vesicle [7]. They can be demonstrated cytologically by Tzanck test. The vesicular fluid and the connective tissue may show scant inflammatory cell infiltration [5]. Spongiosis and acantholysis of the adjacent epithelium can occur. Pemphigus is a chronic disease with periods of exacerbation and remission, even when patients are on treatment. Thus it becomes opt to define the criteria that aid in measuring the activity of the disease. It has been suggested that the activity in pemphigus can be defined by certain criteria such as presence of

new blisters, spontaneous peripheral extension of existing blisters, positive Nikolsky's sign on lesion, perilesional, or normal appearing skin, demonstration of circulating antibodies against cell adhesion molecules and/or non-desmoglein protein antigen, and presence of IgG antibodies in epidermis demonstrated by DIF, even in clinically normal appearing skin [9]. Prognostic variables for pemphigus vulgaris include localization of the initial lesions as well as diagnosis and treatment of oral lesions before the onset of skin disease [10].

Bullous pemphigoid

Bullous pemphigoid (BP) is a subepidermal blistering skin disease that usually occurs in the elderly population and is characterized by large tense blisters with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone [11]. It primarily affects elderly individuals in the fifth to seventh decade of life, with average age of onset being 65 years. BP in childhood has been reported from various countries including India [12]. There is no known ethnic, racial, or sexual predilection. This bullous disease is seen primarily in the elderly, with the peak incidence in the seventh and eighth decades. Lesions characteristically appear on the skin, although concomitant lesions of mucous membranes occur in approximately one third of patients. Skin lesions are characterized by a trunk and limb distribution. Although tense vesicles and bullae are typically noted, they are often preceded by or associated with an erythematous papular eruption. Oral smucosal lesions of bullous pemphigoid cannot be distinguished from those of MMP. Bullae and erosions may be noted, especially on the attached gingiva, a commonly affected site. Other areas of involvement may include the soft palate, buccal mucosa, and floor of the mouth [4]. The diagnosis of BP is confirmed by histological and immunopathologic investigations. Histopathology from lesional skin demonstrates a subepidermal blister. The inflammatory infiltrate is typically polymorphous, with an eosinophilic

predominance. Mast cells and basophils may be prominent early in the disease course. Tzanck smear shows only inflammatory cells.

Bullous systemic lupus erythematosus

Bullous systemic lupus erythematosus (BSLE) is a rare variant of systemic lupus erythematosus (SLE) which histologically resembles dermatitis herpetiformis (DH) and responds dramatically to dapsone. BSLE is an autoantibody mediated subepidermal blistering disease that occurs in patients with SLE. Not all blistering eruptions that occur in patients with lupus erythematosus represent BSLE. Vesiculo-bullous skin lesions can also develop as a result of extensive damage to the epidermal basal layer (and even suprabasal keratinocytes) due to intense interface dermatitis in the setting of lupus erythematosus specific skin disease. Such patients may present with a severe form of acute or sub acute cutaneous lupus erythematosus (SCLE) that resembles erythema multiforme (Rowell syndrome) or TEN. Because EBA and BSLE share the same target antigen, distinguishing between the two may be difficult [13]. In SLE, skin and mucosal lesions are relatively mild and involvement of the skin result in an erythematous rash, classically seen over the malar process and bridge of the nose. When blisters are a clinical feature in SLE disease is called BSLE. Primarily young black women are affected, often beginning in the second or third decade of life; however, the disease does occur in both sexes, in many races, and in children. BSLE accounts for 2-3% of cases of autoimmune subepidermal blistering disease, with an estimated incidence of fewer than 0.5 cases per million populations per year [13]. Histologically, bullous lupus erythematosus is characterized by neutrophil-rich, subepidermal bulla. There are often neutrophils along the dermal-epidermal junction and papillary microabscess formation. Immunohistologically, it resembles LE with immunoglobulins and complement components deposited in a linear-granular pattern along the dermal-epidermal junction. Bullous lupus erythematosus is often

associated with an autoimmunity to type VII collagen [14].

Varicella-zoster infections

Primary varicella-zoster virus (VZV) infections in seronegative individuals are known as varicella or chickenpox; secondary or reactivated disease is known as herpes zoster or shingles. Structurally, VZV is very similar to HSV, with a DNA core, a protein capsid, and a lipid envelope. Microscopically, striking similarities can also be noted. The ability of the virus to remain quiescent in sensory ganglia for indefinite periods after a primary infection is common to both. A cutaneous oromucosal vesiculo-ulcerative eruption following reactivation of latent virus is also typical of both VZV and HSV infections. A number of signs and symptoms, however, appear to be unique to each infection [4]. Transmission of varicella is believed to be predominantly through the inhalation of contaminated droplets. The condition is very contagious and is known to spread readily from child to child. Much less commonly, direct contact is an alternative way of acquiring the disease. During the 2-week incubation period, virus proliferates within macrophages, with subsequent viraemia and dissemination to the skin and other organs. Host defense mechanisms of nonspecific interferon production and specific humoral and cell-mediated immune responses are also triggered. Overt clinical disease then appears in most individuals. As the viremia overwhelms body defenses, systemic signs and symptoms develop. Eventually, in a normal host the immune response is able to limit and halt the replication of virus, allowing recovery in 2 to 3 weeks. During the disease process the VZV may progress along sensory nerves to the sensory ganglia, where it can reside in a latent, undetectable form [4]. Reactivation of latent VZV is uncommon but characteristically follows such occurrences as immunosuppressive states resulting from malignancy (especially lymphomas and leukemias), drug administration, or HIV infection. Radiation or surgery of the spinal cord or local trauma may also trigger

secondary lesions. Prodromal symptoms of pain or paraesthesia develop and persist for several days as the virus infects the sensory nerve of a dermatome (usually of the trunk or head and neck). A vesicular skin eruption that becomes pustular and eventually ulcerated follows. The disease lasts several weeks and may be followed by a troublesome post-herpetic neuralgia (in approximately 15% of patients) that takes several months to resolve. Local cutaneous hyperpigmentation may also be noted on occasion [4]. Cytological examination of the contents of vesicles is carried out for varicella and herpes zoster in the same way as for herpes simplex. It is a very useful diagnostic test, confirming the diagnosis in 80% to 100% of the cases, whereas viral cultures can confirm in only 60% to 64% [15].

Erythema multiforme

Erythema multiforme (EM) is an acute mucocutaneous hypersensitivity reaction characterized by a skin eruption, with or without oral or other mucous membrane lesions. Occasionally EM may involve the mouth alone. EM has been classified into a number of different variants based on the degree of mucosal involvement and the nature and distribution of the skin lesions. EM minor typically affects no more than one mucosa, is the most common form and may be associated with symmetrical target lesions on the extremities. EM major is more severe, typically involving two or more mucous membranes with more variable skin involvement – which is used to distinguish it from Stevens - Johnson syndrome (SJS), where there is extensive skin involvement, and significant morbidity and a mortality rate of 5-15%. Both EM major and SJS can involve internal organs and typically are associated with systemic symptoms. Toxic epidermal necrolysis (TEN) may be a severe manifestation of EM, but some experts regard it as a discrete disease. EM can be triggered by a number of factors, but the best documented is preceding infection with herpes simplex virus (HSV), the lesions resulting from a cell mediated immune reaction triggered by HSV-DNA. SJS and TEN are usually initiated by drugs [16]. The

basic cause of EM is unknown, although a hypersensitivity reaction is suspected. Some evidence suggests that the disease mechanism may be related to antigen-antibody complexes that are targeted for small vessels in the skin or mucosa. In about half the cases, precipitating or triggering factors can be identified. These generally fall into the two large categories of infections and drugs. Other factors, such as malignancy, vaccination, autoimmune disease, and radiotherapy, are occasionally cited as possible triggers. Infections frequently reported include HSV infection (due to HSV types 1 and 2), tuberculosis, and histoplasmosis. Various types of drugs have precipitated EM, with barbiturates, sulfonamides, and some antiseizure medications such as carbamazepine and phenytoin being among the more frequent offenders. Although these drugs are pharmacologically unrelated, the mechanism by which EM is precipitated is related to similar protein folds that expose regions that are antigenically similar [4].

Measles

Measles is a highly contagious viral infection caused by a member of the paramyxovirus family of viruses. The virus, known simply as measles virus, is a DNA virus and is related structurally and biologically to viruses of the orthomyxovirus family, which cause mumps and influenza. The virus is spread by airborne droplets through the respiratory tract. German measles or rubella is a contagious disease that is caused by an unrelated virus of the togavirus family. It shares some clinical features with measles, such as fever, respiratory symptoms, and rash. These features are, however, very mild and short lived in German measles. In addition, Koplik's spots do not appear in German measles. The significance of the German measles virus lies in its ability to cause congenital defects in a developing fetus. The abnormalities produced are varied and may be severe, especially if the intrauterine infection occurs during the first trimester of pregnancy [4]. The diagnosis of measles is usually made on the basis of clinical signs and symptoms in an individual who has not been vaccinated for the

disease. Prodromal symptoms, Koplik's spots, and rash should provide sufficient evidence of measles. If necessary, laboratory confirmation can be made through virus culture or serologic tests for antibodies to measles virus [4].

Mucous membrane pemphigoid

Mucous membrane pemphigoid (MMP) is a chronic blistering or vesiculo-bullous disease that affects predominantly oral and ocular mucous membranes. It is also known as cicatricial pemphigoid, benign mucous membrane pemphigoid, ocular pemphigus, childhood Pemphigoid, and mucosal pemphigoid; when it affects gingiva exclusively, it is referred to clinically as gingivosis or desquamative gingivitis [4]. MMP is an autoimmune process with an unknown stimulus. Deposits of immunoglobulins and complement components along the basement zone (on DIF testing) are characteristic. The antigenic targets include laminin 5 (epiligrin) and a 180-kd protein that is also known as bullous pemphigoid antigen 180 (BP180). Circulating autoantibodies against the basement membrane zone antigens in MMP are usually difficult to detect, presumably because of relatively low serum levels [4]. This is a disease of adults and the elderly and tends to affect women more than men. MMP has rarely been reported in children. Oral mucosal lesions typically present as superficial ulcers, sometimes limited to attached gingiva. Bullae are rarely seen because the blisters are fragile and short lived. Lesions are chronic and persistent, and may heal with a scar (cicatrix)—particularly lesions of the eye. Here there is the risk of scarring of the canthus (symblepharon), inversion of the eyelashes (entropion), and resultant trauma to the cornea (trichiasis). To prevent corneal damage, many patients with ocular pemphigoid will have their eyelashes permanently removed by electrolysis. Extraoral sites in the order of frequency following oral mucosa are the conjunctiva, larynx, genitalia, esophagus, and skin. Cutaneous lesions are uncommon and usually appear in the head and neck and extremities. Gingival lesions often present as bright red patches or confluent ulcers

extending to unattached gingival mucosa with mild-to-moderate discomfort. Concomitant ulcers may be seen on marginal and attached gingiva. With chronicity, the pain associated with oral MMP typically diminishes in intensity. Intact epithelium, especially adjacent to ulcers, can often be stripped away with ease, leaving denuded submucosa. This is one of several mucocutaneous diseases in which a positive Nikolsky's sign may be elicited. Because of patient discomfort, routine oral hygiene is often compromised. This results in dental plaque accumulation, which in turn superimposes an additional, but nonspecific, inflammatory response [4].

Hand-foot-and-mouth disease

Hand-foot-and-mouth disease is caused by a coxsackievirus, an Enterovirus. In most instances coxsackievirus type A16 has been isolated; only rarely has another type, such as A5 or A9, been found [17]. Hand-foot-and-mouth disease occurs in small epidemics, affecting mainly children and having a mild course that usually lasts less than a week. Transmission is mainly via fecal-oral contact and less commonly by respiratory droplets [18]. Symptoms usually appear 3 to 5 days after exposure. After a 1-to 2-day mild prodrome of low-grade fever, sore throat, and malaise, small red macules present on the oral mucosal and progress to 1- to 3-mm vesicles, where they evolve into small ulcers. Between 25% and 65% of patients may have the classic vesicular lesions on the hand and feet, which presented as scattered small vesicles surrounded by an erythematous halo on the palms of the hands, soles of the feet, and ventral surfaces and sides of the fingers and toes [19]. Similar lesions may develop on the rest of the skin. Viral culture has been the gold standard until recently, when PCR has become the diagnostic test for rapid and accurate enterovirus infection. The coxsackievirus can be cultured from stool and occasionally from skin vesicles. The virus grows well on human epithelial cell and monkey kidney cell culture.

Paraneoplastic pemphigus (Neoplasia induced pemphigus)

Paraneoplastic pemphigus is a recently described rare vesiculo-bullous disorder that affects patients who have a neoplasm, usually lymphoma or chronic lymphocytic leukemia. It is thought that cross-reactivity develops between antibodies produced in response to the tumour and antigens associated with the desmosomal complex and the basement membrane zone of the epithelium. A variety of different antibodies that attack these epithelial adherence structures are produced, resulting in an array of clinical features [4]. Patients typically have a history of a malignant lympho-reticular neoplasm or less commonly a benign lymphoproliferative disorder such as angiofollicular lymph node hyperplasia or thymoma. In some cases, paraneoplastic pemphigus develops before a malignancy is 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 condition. Signs and symptoms of paraneoplastic pemphigus usually begin suddenly and may appear polymorphous. In some instances multiple vesiculo-bullous lesions affect the skin and oral mucosa. Palmar or plantar bullae may be evident, a feature that is uncommon in pemphigus vulgaris. For other patients skin lesions can appear more papular and pruritic, similar to cutaneous lichen planus. The lips often show hemorrhagic crusting similar to that of erythema multiforme [15]. The oral mucosa shows multiple areas of erythema and diffuse irregular ulceration affecting virtually any oral mucosal surface. If the lesions remain untreated, they persist and worsen. In this area, a cicatrizing (scarring) conjunctivitis develops, similar to that seen with cicatricial pemphigoid. The vaginal mucosa and mucosa of the respiratory tract may be involved [20].

Toxic epidermal necrolysis and stevens-johnson syndrome

Toxic epidermal necrolysis (TEN) and Stevens Johnson Syndrome (SJS) are severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. Both

are rare, with TEN and SJS affecting approximately 1 or 2/1,000,000 annually, and are considered medical emergencies as they are potentially fatal. They are characterized by mucocutaneous tenderness and typically hemorrhagic erosions, erythema and more or less severe epidermal detachment presenting as blisters and areas of denuded skin. Currently, TEN and SJS are considered to be two ends of a spectrum of severe epidermolytic adverse cutaneous drug reactions, differing only by their extent of skin detachment. Drugs are assumed or identified as the main cause of SJS/TEN in most cases, but Mycoplasmapneumoniae and Herpes simplex virus infections are well documented causes alongside rare cases in which the aetiology remains unknown. Several drugs are at "high" risk of inducing TEN/SJS including: Allopurinol, Trimethoprim-sulfamethoxazole and other sulfonamide-antibiotics, aminopenicillins, cephalosporins, quinolones, carbamazepine, phenytoin, phenobarbital and NSAID's of the oxicam-type. Genetic susceptibility to SJS and TEN is likely as exemplified by the strong association observed in Han Chinese between a genetic marker, the human leukocyte antigen HLA-B*1502, and SJS induced by carbamazepine. Diagnosis relies mainly on clinical signs together with the histological analysis of a skin biopsy showing typical full-thickness epidermal necrolysis due to extensive keratinocyte apoptosis.

Dermatitis herpetiformis

Dermatitis herpetiformis is a cutaneous vesiculo-bullous disease characterized by intense pruritus. The disease is associated with granular IgA deposits in the papillary dermis that precipitate with an epidermal transglutaminase, an enzyme not normally present in the papillary region of normal skin. Serum IgA in patients with dermatitis herpetiformis also binds epidermal transglutaminase. Dermatitis herpetiformis is frequently associated with the gluten-sensitive enteropathy, celiac disease, which is characterized by IgA type autoantibodies to a closely related enzyme, tissue transglutaminase. It is now widely accepted that dermatitis

herpetiformis is a cutaneous manifestation of celiac disease and affects approximately 25% of patients with celiac disease. Both dermatitis herpetiformis and celiac disease are closely linked to HLA class II locus in chromosome 6 with 90% of patients having HLA DQ2 and almost all the remainder HLA DQ8. Dermatitis herpetiformis is a chronic disease typically seen in young and middle-aged adults, with a slight male predilection. Periods of exacerbation and remission further characterize this disease. Cutaneous lesions are papular, erythematous, vesicular, and often intensely pruritus. Lesions are usually symmetric in their distribution over the extensor surfaces, especially the elbows, shoulders, sacrum, and buttocks. Of diagnostic significance is the frequent involvement of the scalp and face. Lesions are usually aggregated (herpetiformis) but often are individually disposed. In some patients exacerbations may be associated with ingestion of foods or drugs containing iodide compounds. In the oral cavity, dermatitis herpetiformis is very rare, with vesicles and bullae having been described that rupture, leaving superficial nonspecific ulcers with a fibrinous base with erythematous margins. Lesions may involve both keratinized and nonkeratinized mucosa [4].

Herpangina

Herpangina is an acute viral infection caused by another Coxsackie type A virus (types A1-6, A8, A10, A22, B3, and possibly others). It is transmitted by contaminated saliva and occasionally through contaminated feces [4]. Herpangina is usually endemic, with outbreaks occurring typically in summer or early autumn. It is more common in children than in adults. Those infected generally complain of malaise, fever, dysphagia, and sore throat after a short incubation period. Intraorally a vesicular eruption appears on the soft palate, faucial pillars, and tonsils. A diffuse erythematous pharyngitis is also present. The signs and symptoms are usually mild to moderate and generally last less than a week. Diagnosis is usually based on historical and clinical information. The characteristic distribution and

short duration of herpangina separate it from other primary viral infections such as herpetic gingivostomatitis, HFM disease, and varicella. The vesicular eruption, mild symptoms, summer or early autumn presentation, and diffuse pharyngitis also distinguish the condition from streptococcal pharyngitis, and the systemic symptoms distinguish it from aphthous stomatitis. Laboratory confirmation can be made by virus isolation or by detection of serum antibodies [21].

Linear IgA disease

Linear IgA disease is a chronic autoimmune disease of the skin that commonly affects mucous membranes, including gingiva. Unlike dermatitis herpetiformis, it is not associated with gluten-sensitive enteropathy (and may not be responsive to dapsone therapy or dietary gluten restrictions). Skin lesions may be urticarial, annular, targetoid, or bullous. Oral lesions, present in a majority of cases, are ulcerative (preceded by bullae). Ocular lesions, also seen in a majority of cases, are in the form of ulcers. The biological basis of linear IgA disease is not well understood. Central to the disease are autoantibodies to BP180 (collagen XVII), which normally functions as a cell-matrix adhesion molecule through stabilization of the hemidesmosome complex and whose extracellular portion is constitutively shed from the cell surface by ADAMs (proteinases that contain adhesive and metalloprotease domains). Similar to MMP, in vivo and in vitro studies provide experimental evidence for a central pathogenic role of BP180 but that the serum level and epitope specificity of these antibodies influence phenotype and disease severity.

Epidermolysis bullosa

Epidermolysis bullosa is a general term that encompasses one acquired and several genetic varieties (dystrophic, junctional, and simplex) of disease that are basically characterized by the formation of blisters at sites of minor trauma. The several genetic types range from autosomal dominant to autosomal recessive in origin and

are further distinguished by various clinical features, histopathology, and ultra structure [22]. The acquired nonhereditary autoimmune form, known as epidermolysis acquisita, is unrelated to the other types and is often precipitated by exposure to specific drugs. In this type, IgG deposits are commonly found in sub-basement membrane tissue and type VII collagen antibodies located below the lamina densa of the basement membrane. In the hereditary forms of epidermolysis bullosa, circulating antibodies are not evident. Rather, pathogenesis appears to be related to genetic defects in basal cells, hemidesmosomes, or anchoring connective tissue filaments, depending on the disease subtype.

Conclusion

The diagnosis of these blistering disorders should be a highly satisfactory exercise. Despite considerable overlap of clinical features a careful evaluation of combined clinical, histological and immunofluorescence data usually enables a correct diagnosis to be made in majority of cases. Clinicopathological correlation is always an essential prerequisite before coming to any final decision.

References

1. Sitaru C, Zillikens D. Mechanisms of blister induction by autoantibodies. *Exp Dermatol.*, 2005; 14: 861–75.
2. Canto AM, Müller H, Freitas RR, da Silva Santos PS Oral lichen planus (OLP): clinical and complementary diagnosis. *An Bras Dermatol.*, 2010; 85(5): 669-75.
3. Rashmi Jindal, Dipankar De, and Amrinder J. Kanwar Bullous oral lichen planus: An unusual variant Indian *Dermatol Online J.*, 2011; 2(1): 39–40.
4. Regezi. *Oral Pathology: Clinical Pathologic Correlations*, 5th edition, 2008.
5. Rajendran R, Shivapathasundharam. *Shafer's Textbook of Oral Pathology*. 5th edition, Elsevier publications.
6. Eversole LR. Immunopathology of oral mucosal ulcerative, desquamative and bullous diseases. Selective review of the literature *Oral Surg Oral Med Oral Pathol.* 1994; 77: 555-571.
7. Weinberg MA, Insler MS, Campen RB. Mucocutaneous features of autoimmune blistering diseases. *Oral Surg Oral Med Oral Pathol Oral Radio Endod.*, 1997; 84: 517- 534.
8. Ettlin DA. Pemphigus. *Dent Clin N Am.*, 2005; 49: 107-125.
9. Vaishnani JB, Bosamiya SS. Pemphigus. Active or Inactive? *Indian J Dermatol.*, 2009; 54: 186-188.
10. Sciubba JJ. Autoimmune aspects of pemphigus vulgaris and mucosal pemphigoid. *Adv Dent Res.*, 1996; 10: 52-56.
11. Khandpur S, Verma P. Bullous pemphigoid. *Indian J Dermatol Venereol Leprol.*, 2011; 77: 450-5.
12. Sharma R, Nadeem M, Chandra M. Bullous pemphigoid in childhood. *Indian J Dermatol Venereol Leprol.*, 1996; 62: 100-2.
13. Devaraju D, Vijeev Vasudevan, Yashoda Devi B.K, Manjunath V. Autoimmune mucocutaneous blistering diseases. *E-Journal of Dentistry*, 2011; 1(1): 7-13.
14. Freedberg, IM, Eisen, AZ, Klaus, W, Austen, KF, Goldsmith, LA, Katz, Fitzpatrick's *Dermatology in General Medicine*, 2003, p. 1686.
15. Vida M.M., et al. Molecular assays for the diagnosis of minimal residual head-and-neck cancer: Methods, reliability, pitfalls, and solutions, *Clinical cancer research*, 2000; 6: 3803-3816.
16. P Farthing, J-V Bagan, C Scully *Mucosal diseases series. Number IV Erythema multiforme Oral Diseases*, 2005; 11: 261–267.
17. Ellis AW, Kennett ML, Lewis FA, et al. Hand, foot and mouth disease: an outbreak with interesting virological features. *Pathology*, 1973; 5:189.

18. Potbart HA, Kirkegarrd K. Picornavirus pathogenesis: viral access, attachment, and entry into susceptible cells. *Semin Virol.*, 1992; 3: 483.
19. Fields JP, Mihm MC Jr, Hellreich PD, et al. Hand, foot, and mouth disease. *Arch Dermatol.*, 1969; 99:243.
20. Fullerton S, Woodley D, Smoller B, et al. Paraneoplastic pemphigus with autoantibody deposition after autologous bone marrow transplantation. *JAMA*, 1992; 267: 1500-1502.
21. Neville B, Damm D, Allen C, Bouquot J. *Oral and Maxillofacial Pathology*, 2nd edition, WB Saunders Co., 2002; p. 277-230.
22. Wright J, Fine J, Johnson L. Oral soft tissues in hereditary epidermolysis bullosa. *Oral Surg Oral Med Oral Pathol.*, 1991; 71: 440-446.