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Pemphigus Vulgaris : Oral and Skin Manifestations

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Abstract
Pemphigus vulgaris is the most common blistering disease of oral mucosa and skin. Itcomprises of group of autoimmune diseases where antibodies are targeted towards self-antigen particularly of desmoglein family (Dsg 3 and Dsg1) of desmosomal junctions.
Autoantibodies of IgG class are targeted against these desmosomal junctions. Thisreview gives an overview of important characteristic features of Pemphigus vulgaris withits various oral and skin manifestations.

1. Introduction

Pemphigus vulgaris(PV) is derived from:

1. *pemphigus*, a greek word meaning *blister or a bubble*
2. *vulgaris*, comes from latin word vulgare meaning *common*.

It means that Pemphigus vulgaris is the most common blistering disease of oral mucosa and skin[1].

A blister is generally described as a swelling on surface of skin that is filled with liquid[2] which can be further classified into 2 types[3]:

1. vesicle, 5mm or less in diameter
2. bulla, greater than 5 mm in diameter

PV can thus be characterized as:

1. Autoimmune disease: Antibodies are produced against self antigens (intercellular junctions)
2. Most common vesiculobullous lesion: PV makes 70% of all reported cases of pemphigus[4] with 80% of reported cases in Europe[5].
3. Rare: United States prevalence rates of 0.1% to 0.5% per 100,000 people[6]. Due to a correlation with certain human leukocyte antigen haplotypes, the disorder is more prevalent among Ashkenazi Jews and persons of Mediterranean heritage. [7] possibly genetic predisposition linked to HLA class II alleles[8] including HLA DRβ1*0402, β1*1401, β1*0503.

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4. Chronic: The blisters rupture rapidly leading to formation of chronic erosions and ulcers which progress to increased clinical severity.
5. Intraepithelial blistering disease: a blister is confined to the inside of epithelium as opposed to the subepithelial dermatoses where the separation occurs below the epithelium.
6. Potentially life threatening disease:
   Prompt corticosteroid medication decreases the risk of death. High morbidity and even mortality in 5-10% of untreated cases[9] highlight the urgency with which this illness must be addressed. Due to dehydration, protein loss, and opportunistic infections, the first-year death rate was as high as 75% before the development of corticosteroid treatment. [10,11].

2. Pathogenesis

PV is a group of autoimmune disease where antibodies are targeted towards self antigen.

Self antigen

This self antigen is epithelial cell adhesion molecule, Desmosome. Desmosome consists of cellularglycoproteins of cadherinsupergene family, desmoglein and desmocollins. In PV, desmoglein family particularly desmoglein3 and 1 is attacked. The transmembrane domain formed by desmogleins consists of an external domain that attaches to neighboring cells in a calcium-dependent manner and an intracellular domain that binds to catenins and, in turn, to actin. [12].

3. Autoantibody

T cells are involved in aberrant antigen recognition leading to initiation and perpetuation of B cell response4possibly through cytokine TNF-α.

Autoantibodies are of IgG class against the desmosomal junctions. In active PV are predominantly Th2 dependent IgG4 subtype polyclonal antibodies but Th1 dependent IgG1 subtype are present in remission[13,14]. The Th2 response predominates in PV which then initiates the antibody production by B cells.

4. Mode of action of antibodies causing loss of cell adhesions[5]

1. Indirectly through disruption of calcium dependent interactions between extracellular domains
2. Direct lysis of desmogleins

5. Effect of antigen-antibody reaction

Desmogleins can be eliminated and the actin cytoskeleton reorganized if you aim for them. Apoptotic cell death and acantholysis ensue from a subsequent cascade of signaling processes, the details of which remain unknown. [15].Acantholysis is an active process resulting from binding of IgG to keratinocyte receptor in receptor ligand fashion[16]. Acantholysis (disintegration of cellular adherence) causes blister formation due accumulation of fluid.

Desmoglein 3 is predominantly expressed in lower layers of oral mucosa while desmoglein 1 is predominantly expressed in upper layers ofskin[17]. Hence oral lesions appear first followed by skin lesions.

PV is classified into 2 variants:

1. Mucosal dominant which affects only oral mucosa (Antibodies against Dsg 3)
2. Muco-cutaneous which affects both oral mucosa and skin (Antibodies against Dsg 3 followed by Dsg1)

6. Oral manifestations

Oral lesions caused by PV develop early in 75% to 80% of cases[18]. Lesion of the mouth caused by PV is uncommon in kids. [19]. The initial lesions are often insidious and localized or sometimes diffuse. An intact flaccid thin walled vesicle or a single hemorrhagic bulla is difficult to find in oral cavity. These soon rupture to leave an area of denudation manifested as a shallow, ill defined, irregular, persistent, highly painful, bleedingerosion or ulcer with associated burning sensation especially on consuming hot and spicy food which affects the appetite[15, 6].These

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lesions usually remain for about 2-6 months until the appearance of cutaneous lesions.

Reasons for rupture of vesicle or bulla are[20,21]:

1. Oral mucosa is friable in nature
2. Oral mucosa is constantly exposed to mechanical irritation due to mastication
3. Intra epithelial blister is more prone to rupture due to superficial position compared to the subepithelial dermatoses
4. Oral blisters have very thin roof and hence readily rupture

Whitish superficial covering with collapsed roof of a thin walled bulla, several centimeters in diameter developing in both normal and erythematous areas is consistent and characteristic finding[22]. Other subjective symptoms like sialorrhea, halitosis and difficulty in chewing and swallowing are seen associated with PV[11].

Location according to the decreasing order of occurenece[23,24]:

Buccal mucosa, soft palate, ventral surface of tongue, lips and gingiva.

PV affecting gingiva especially free gingiva is considered to be an advanced sign of the disease presenting as severe desquamativegingivitis[25] while PV affecting lip can manifest as a superficial crusting.

7. Manifestations on skin

Skin lesions arise later and occasionally concurrently to the mouth lesions. Cutaneous lesions are identified within 6 months in 99% of instances [18].

In a few weeks or months, the mucosal lesions spread to the skin, where they manifest as individual or widespread blisters filled with a clear fluid. These blisters are so delicate that if they break, erosions surrounded by epidermal rings are left behind. [9,1].

The primary lesion consists of a thin walled bulla, several centimeters in diameter developing in both normal and erythematous skin which are asymptomatic, slow healing and are not usually pruritic[21,11,7].

Location[26]:

Skin lesions have a predilection for the trunk, groins, axillae, scalp, face, and pressure points.

8. Conclusion

Pemphigus vulgaris is an autoimmune blistering illness that mostly affects the oral mucosa and skin. Prior to the development of corticosteroid medication, the condition was very lethal and debilitating. A clinician must be familiar to the oral and skin manifestations for early and prompt diagnosis.

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