INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

PEMPHIGUS AND THE ORAL CAVITY: A NARRATIVE REVIEW

Trabalho submetido por
Paulo Ricardo Nunes da Risca Curado
para a obtenção do grau de Mestre em Medicina Dentária

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Trabalho orientado por
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outubro de 2022

"그런 게 인생인 거지...
살아만 있다면 뭐든 별거 아니야. 정말이지."

Itaewon Class (이태원 클라쓰), episode 15

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Resumo

Pênfigo constitui um conjunto de doenças auto-imunes bolhosas nas quais autoanticorpos, principalmente da isoforma IgG, atacam proteínas estruturais dos desmossomas, desmogleína 1 e desmogleína 3. Estes desmosomas são estruturas de adesão que, juntamente com as desmogleinas, são essenciais para a adesão celular entre queratinócitos e têm um papel importante na integridade estrutural entre células do epitélio pavimento estratificado, tanto na pele como na mucosa oral. O pênfigo compreende três apresentações clínicas principais, pênfigo vulgar, que frequentemente cursa com erosões/bolhas orais dolorosas, pênfigo foliáceo, que apresenta lesões exclusivamente cutâneas, e pênfigo paraneoplásico, que apresenta dois tipos de resposta autoimune, humoral e celular, e que está normalmente associado a malignidades do foro hematológico. Formas raras de pênfigo incluem o pênfigo herpetiforme, pênfigo IgA e pênfigo induzido por medicação. O diagnóstico diferencial das doenças de pênfigo baseia-se numa combinação da interpretação de achados clínicos, como o sinal de Nikolsky, em conjunto com microscopia de imunofluorescência direta e indireta, análise histopatológica e testes serológicos. As modalidades de tratamento para o pênfigo incluem principalmente terapêutica com corticosteróides, isolada ou associada a medicamentos imunossupressores, azatioprina e mofetil micofenolato, que actuam como agentes poupadores de corticosteróides (steroid-sparing agents), e terapias de depleção de células B, incluindo anticorpos anti-CD20, tais como o rituximab. Novas terapias para o tratamento do pênfigo incluem antagonistas neonatais dos receptores Fc e inibidores da tirosina quinase de bruton. Uma vez que o pênfigo se apresenta frequentemente com lesões orais, e em muitos casos é a primeira manifestação da doença, esta revisão pretende servir como um guia prático para dentistas e especialistas em medicina oral compreenderem a doença pênfigo, e para diagnosticarem e tratarem adequadamente tais doenças, correlacionando-as com a cavidade oral.

Palavras-chave: pênfigo, cavidade oral, doenças autoimunes vesiculo-bolhosas, tratamento

Abstract

Pemphigus is a group of autoimmune bullous diseases in which autoantibodies of mainly IgG isoform target structural proteins of desmosomes, desmoglein 1 and desmoglein 3. These desmosomes are adhesion structures that, alongside desmogleins, are essential for cell-cell adhesion between keratinocytes and have an important role in structural intercellular integrity in stratified squamous epithelia, such as skin and oral mucosa. Pemphigus comprises three main clinical presentations, pemphigus vulgaris, which often presents with painful oral erosions/blisters, pemphigus foliaceus, that presents exclusively cutaneous lesions, and paraneoplastic pemphigus, that presents with both humoral and cellular autoimmune responses and is frequently associated with hematologic malignancies. Rare forms of pemphigus include pemphigus herpetiformis, IgA pemphigus and drug-induced pemphigus. Differential diagnosis of pemphigus diseases is based on a combination of interpretation of clinical findings, such as Nikolsky´s sign, direct immunofluorescence microscopy (DIF), and histopathological presentation, and serological tests. Treatment modalities include mainly corticosteroids, alone or associated with immunosuppressive drugs, azathioprine, and mycophenolate mofetil, that act as steroid-sparing agents, and B-cell depleting therapies including anti-CD20 antibodies such as Rituximab. Novel therapies for pemphigus treatment include neonatal Fc receptor antagonists and bruton tyrosine kinase inhibitors. Since pemphigus presents frequently with oral lesions, and in many cases is the first manifestation of the disease, this review pretends to serve as a practical guide for dentists and oral medicine specialist to understand pemphigus diseases, and to properly diagnose and treat such diseases, correlating them with the oral cavity.

Keywords: pemphigus, oral cavity, autoimmune bullous diseases, treatment

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List of Abbreviations

AIBD	Autoimmune Blistering Diseases
ASMSG	Association of the Scientific Medical Societies in Germany
AZA	Azathioprine
BAD	British Association of Dermatologists
BTK	Bruton Tyrosine Kinase
DIF	Direct Immunofluorescence (Microscopy)
DIP	Drug-Induced Pemphigus
Dsg	Desmogleins
EADV	European Association of Dermatology and Venereology
ELISA	Enzyme-linked Immunoabsorbent Assay
FcRn	Neonatal Fc receptor
IIF	Indirect Immunofluorescence (Microscopy)
KC	Keratinocytes
KIF	Keratin Intermediate Filaments
MMF	Mycophenolate Mofetil
MMP	Mucous Membrane Pemphigoid
PDAI	Pemphigus Disease and Area Index
PF	Pemphigus Foliaceus
PH	Pemphigus Herpetiformis
PNP	Paraneoplastic pemphigus
PV	Pemphigus Vulgaris
RTX	Rituximab

I. INTRODUCTION

The term pemphigus stems from the Greek *pemphis*, meaning blister or bubble, and it designates a group of chronic blistering diseases in which autoantibodies target the cell surface of keratinocytes, therefore leading to the loss of cell-cell adhesion of keratinocytes through a process called acantholysis.[1]

These autoantibodies are mainly of the IgG isoform and target mainly against two structural proteins of epidermal desmosomes, referred to as desmogleins (Dsg), Dsg 1 and Dsg3.[2] Desmosomes consist of cell-to-cell adhesion structures that connect neighboring keratinocytes and are important for tissue integrity. Dsg (1 and 3) molecules of the cadherin family are predominantly in charge of preserving intercellular adhesion in stratified squamous epithelia, such as the skin and oral mucosa.[3] The functional inhibition of Dsg by IgG autoantibodies results in blister formation, a phenomenon that is the main trigger factor in pemphigus.[1]

Pemphigus has three main clinical presentations: pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PNP).[2]

Pemphigus vulgaris typically manifests with oral mucosal lesions such as painful, persistent erosions that impair with eating, as well as skin involvement that may show up weeks or months after the initial manifestation of mucosal lesions.[4] Pemphigus foliaceus is characterized by cutaneous transitory, flaccid bullae or exfoliation resembling puff pastry in areas of seborrheic skin (chest, scalp, face, and interscapular region).[4] PF endemic varieties, such as seen in South America and Africa, may have more extensive cutaneous involvement.[4] PNP also has mucosal involvement, with patients first presenting with limited cheilitis and/or ulcerative stomatitis, as well as painful erosions that lead to severe dysphagia.[4] Cicatricial conjunctivitis, keratitis, and vaginal involvement are also common, as is pharyngeal involvement, and the nasal cavity and esophagus can also be affected leading to phagodynia.[4]

Non-classical, rarer variants of pemphigus comprise pemphigus herpetiformis (PH), drug-induced pemphigus (DIP) and IgA pemphigus, and endemic forms (similar to PF but with epidemiological *foci*).

Mucous membrane pemphigoid, the most common autoimmune blistering condition occurring in the mouth, is a differential diagnosis for erosive mucosal lesions of pemphigus.[5]

Diagnosis of pemphigus is usually confirmed through direct immunofluorescence microscopy (DIF) of a perilesional biopsy, which detects IgG antibodies or complement component 3 deposits (or both) at the keratinocyte membrane. Serum anti-Dsg1 or anti-Dsg3 antibodies (or both) are identified using ELISA.[2] IgG antibodies against Dsg 3 and Dsg 1 are found in patients with pemphigus vulgaris and pemphigus foliaceus, respectively. Patients with paraneoplastic pemphigus present additional IgG antibodies against plakin molecules and a T-cell-mediated autoimmune response that results in an interface dermatitis.[1.] Pemphigus and pemphigoid disorders can be distinguished by DIF, and paraneoplastic pemphigus must be diagnosed with additional serological tests.[6]

The epithelial cell surface staining for in vivo IgG deposition is generally granular or linear in DIF evaluation.[4] Epithelial cell surface deposits are occasionally coupled with linear IgG or C3 deposits at the dermal-epidermal junction, indicating PNP or pemphigus erythematosus, or the coexistence of pemphigus and pemphigoid.[4]

Treatment modalities include systemically administered corticosteroids, immunosuppressant drugs (azathioprine, methotrexate, mofetil mycophenolate) that are associated with steroids acting as sparing agents, and biologic therapies such as rituximab and intravenous immunoglobulins.[7]

Considering that oral signs are frequently present in these autoimmune diseases (except pemphigus foliaceus), dentists are of utmost importance in the early detection of such pathologies. This review is aimed at correlating pemphigus as a systemic disease and the oral cavity, presenting a guide for dentists and stomatologists on the correct diagnosis and management of these pathologies, using a solid theoretical basis with practical application. Pathophysiology, clinical features, histopathology, differential

diagnosis, and current treatment options will be presented, as well as other features regarding pemphigus and the oral cavity environment.

II. DEVELOPMENT

1. Epidemiology

Regarding the epidemiology of pemphigus and its different forms, there is a heterogeneous distribution among different geographic regions, showing an ethnic predisposition for PV in Ashkenazi Jews and those of the Mediterranean region, believed to be strongly associated with the presence of several HLA class II genes, such as HLA-DRB1*04 and HLA-A*10 I.[8] 90% to 95% of pemphigus diagnoses are of pemphigus vulgaris and pemphigus foliaceus.[2]

A study conducted in Israel demonstrated an incidence of PV 3.5 times higher in the Jewish population compared to an Arab population, with PF not showing a predisposition related to ethnicity.[9]

Interestingly, in a group of racial minorities in North America, higher PV prevalence was seen in individuals of Hispanic and Caucasian ancestry (52.63% and 27.63%, respectively) compared to those of African American and Asian (19.3% and 4.5%) groups, demonstrating a possible higher prevalence in the skin of color ethnic groups bigger than what is traditionally reported in the literature.[10]

A recent study conducted in Germany on a pediatric group identified PV as being the most prevalent AIBD (30.5/million patients), followed by linear IgA disease and bullous pemphigoid (24.5 and 4.9/million children each), with the lowest prevalence for mucous membrane pemphigoid (1.6/million) and pemphigus foliaceus (PF) (0.6/million).[11]

The term "Endemic PF" refers to a condition where PF incidence is significantly greater than PV in well-defined locations, such as South America and North Africa.[12] The epidemiological correlation between an increase in PF in places like South America, North Africa, Brazil, and Tunisia, as reviewed in Kasperkiewicz[3], may indicate that an environmental agent can cause some genetically vulnerable people to develop a

pathogenic low-level autoantibody response against Dsg 1.

Pemphigus may occur in all age groups, nonetheless, onset is diagnosed more frequently between ages 40 and 60, with a mean age in Europe being around ages 50 and 60 and in remaining countries between 30 and 50, with a higher prevalence more frequently reported in females and a female-male ratio varying between 0,45 and 5.[12]

2. Pathophysiology

2.1 Autoimmune Blistering Diseases

The term "autoimmune blistering diseases" (AIBD) refers to a class of conditions in which patients generate autoantibodies against structural proteins of the epidermis and/or dermal-epidermal junction, resulting in the development of cutaneous and/or mucosal blisters and erosions.[14] Among these targeted structural proteins, desmosomes play an important role in pemphigus pathophysiology.

2.2 Desmosomes

Desmosomes consist of cell-to-cell adhesion transmembrane glycoproteins that connect neighboring keratinocytes and are essential for structural maintenance and barrier function in the epidermis and mucous epithelia. Keratinocyte-keratinocyte adhesion is mediated by these desmosomes, which are responsible for the linkage of keratin intermediate filaments (KIFs) to the plasma membrane region, and structurally consist of a central electron-dense midline between two plasma membranes (desmoglea) and intracellular dense plaques - the outer and inner dense plaques.[15] Intracellularly, their extremities interact with plakoglobin (Pg) and plakophilins (Pkps) thus forming the outer dense plaque. These molecules then attach to desmoplakin (Dp), plectin, envoplakin (EVP), and periplakin (PPL), which are elements of the inner dense plaque (IDP) that play a role in desmosome stabilization and KIF anchorage.[15] The extracellular portion that originates the desmoglea comprises desmogleins (Dsg 1-4) and desmocollins (Dsc1-3) - see figure 1.

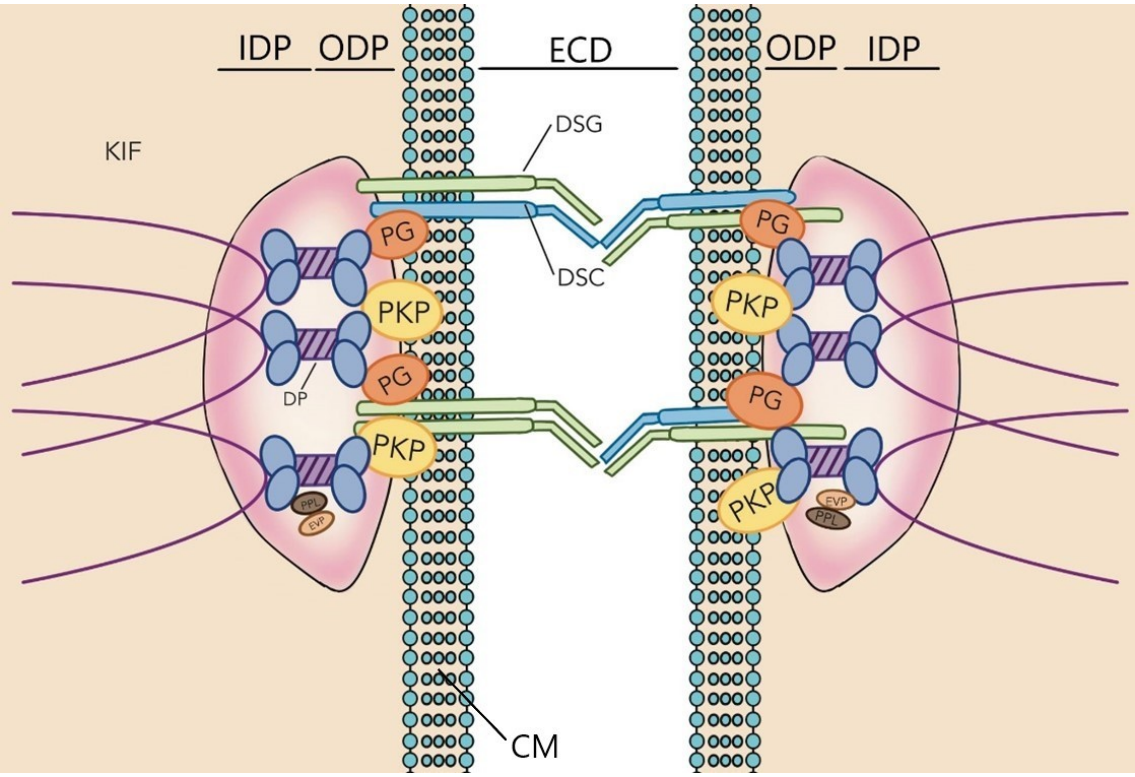

Figure 1– **Molecular Schema of the desmosome**. CM = Cellular Membrane; DSC = Desmocollin; DSG = Desmoglein; DP = Desmophilin, ECD = Extracellular Domain (Desmoglea); EVP = Envoplakin; IDP = Inner Dense Plaque; KIF = keratin intermediate filament; ODP = Outer Dense Plaque; PKP = plakophilin; PG = plakoglobin; PPL = Periplakin. Adapted from Kitajima, Y. New insights into desmosome regulation and pemphigus blistering as a desmosome-remodeling disease. The Kaohsiung Journal of Medical Sciences. 2013 Jan;29(1):1–13.[15]

2.3 Theories on pemphigus pathophysiology

For better understanding, the pathophysiology of pemphigus can essentially be divided into two different pathological theories: monopathogenic and multipathogenic.

Regarding the monopathogenic theory, it focuses on the hypothesis of "Dsg compensation" to explain intra-epidermal blistering, where Dsg 1-and/or Dsg 3-mediated cell-cell attachment of keratinocytes (KCs) is disabled through antibody activity, which suffices to compromise epidermal integrity and result in blistering.[16]

Pemphigus diseases are mucocutaneous intra-epithelial blistering diseases where there is targeting of desmosomal proteins, which results in KCs losing their ability to adhere to one another. The two main variants comprise PV which presents with autoantibodies targeting Dsg3 and sometimes Dsg1, and PF with autoantibodies reactive to Dsg1 only.[6]

While patients with the mucocutaneous type of PV present with both mucosal and skin lesions and autoantibodies against both Dsg1 and Dsg3 are found, the mucosal-dominant type of PV shows a preference for anti-Dsg3 autoantibodies.[17] Lesions are limited to the skin in patients presenting with pemphigus foliaceus, and autoantibodies exclusively recognize Dsg1.[17]

This correlation between clinical phenotype and autoantibody specificity is reflected in the different expressions of Dsg1 and Dsg3 in the epidermis and surface-close mucosal epithelia.[2] Dsg molecules seem to be able to compensate each other (Dsg compensation theory) when expressed together in the same cell layer if the adhesive property is compromised in one of the two, and either Dsg 1 or Dsg 3 alone are sufficient to maintain keratinocyte adhesion in the upper and lower epidermal compartment, respectively.[2,16] This is of special relevance in what concerns the maintenance of epidermal integrity.

2.4 Non-Dsg Antibodies

In patients with PV, besides classically described anti-Dsg antibody activity, proteomic studies have demonstrated the roles of numerous other autoantibodies in the physiology and cell adhesion of keratinocytes, including desmocollins 1 and 3 (Dsc1/Dsc3), mitochondrial antigens, human secretory pathway Ca2+/Mn2+ ATPase (hSPCA1,) thyroid peroxidase (TPO), several muscarinic and nicotinic acetylcholine receptor (nAChR) subtypes, plakoglobin, E-cadherin and plakophilin 3. [18] Although anti-desmoglein autoantibodies are typically necessary and sufficient to generate the pathogenic way of pemphigus, several of these non-desmoglein autoantibodies have been confirmed to have a pathogenic role in pemphigus, whether by altering the desmosomal plaque, working in a synergetic and complementary way with classic anti-Dsg autoantibody action, or even altering mitochondrial physiology.[18]

A recent review demonstrated that in addition to classically described anti-Dsg autoantibodies, twenty-five molecules were found to play a pathogenic role in PV, including Urokinase-type plasminogen activator (uPA), ADAM Metallopeptidase Domain 10 (ADAM10), Epidermal growth factor receptor (EGFR), Proto-oncogene tyrosine-protein kinase (Src), protein kinase C (PKC), Cyclin-dependent kinase 2 (cdk2), ERK (type of serine/threonine protein kinase), Phospholipase C (PLC), calmodulin, Nitric oxide synthases (NOS), p38 mitogen-activated protein kinases (p38MAPK), and caspase-3, with selective inhibition of these molecules resulting in varying degrees of reduction in acantholysis and blistering.[19]

All this suggests the idea of a multipathogenic theory regarding pemphigus pathophysiology: when a unique type of autoantibody is present, only reversible changes are induced, and targeted KC have the capability of self-repair, however, when the salvage pathway and/or other cell functions are compromised by a partnering autoantibody and/or another pathogenic factor, and synergistic action of antibodies - to different adhesion molecules, mitochondrial proteins, self-antigens such as acetylcholine receptors, as well as humoral factors like FasL, TNF-α, cytokines, serine proteases, and nitric oxide - are present, natural resistance can be overcome and both extrinsic and intrinsic cell death pathways in KCs can be activated, leading to irreversible changes.[16] When several physiological mechanisms regulating and mediating KCs' intercellular adhesion are simultaneously and synchronically deactivated, maintenance of epidermal integrity is subsequently irreversibly compromised.[16]

2.5 Paraneoplastic Pemphigus

Considering atypical forms of pemphigus (Paraneoplastic Pemphigus, IgA Pemphigus, Drug-Induced Pemphigus, Herpetiform Pemphigus, etc.), PNP is particularly relevant to the oral cavity.

PNP is an uncommon but possibly fatal mucocutaneous disease caused by paraneoplastic autoimmunity.[20] It is genetically linked to the human leukocyte antigens (HLA)-Cw*14 and HLA-DRB1*03, and tumors associated with it are primarily hematologic malignancies such as lymphoma, leukemia, and Castleman's disease.[20]

PV and PF are both the result of a humoral autoimmune reaction, whereas PNP is the result of combined humoral and cellular autoimmune responses.

Patients with PNP develop IgG autoantibodies to multiple antigens, including Dsg3 and/or Dsg1 (resulting in mucosal and cutaneous blisters), as well as IgG autoantibodies to multiple plakin family members (plectin, epiplakin, desmoplakins I and II, bullous pemphigoid antigen 1, envoplakin, and periplakin), and the protease inhibitor alpha-2-macroglobulinlike-1.[21]

2.5.1 Role of T-cells in PNP pathophysiology

Besides mucosal and cutaneous blistering, PNP presents with combined interface dermatitis (vacuolization of basal cells, apoptosis of keratinocytes, dyskeratotic cells (cells with early keratinization), and band-like lymphocytic inflammation at the dermal-epidermal junction) or severe oral lichenoid reaction (chronic inflammation of the oral mucosa) owing to self-reacting T cells.[3]

In addition to humoral autoimmunity, cell-mediated cytotoxicity plays a role in the pathogenesis of paraneoplastic pemphigus, which is distinguished by more severe and refractory oral erosions and stomatitis, as well as more polymorphic skin eruptions, when compared to classic forms of pemphigus.[21]

Autoreactive T cells exhibit cytotoxic activity in PNP, which is mediated by autoimmune CD4+ and CD8+ T cell infiltration.[22] A study in PNP model mice found prominent bronchial inflammation of CD4+ and CD8+ T cells, as well as ectopic Dsg3 expression in the lungs of PNP mice, mirroring the observation that squamous metaplasia is frequently found in the lungs of PNP patients. [22] Furthermore, after pulmonary injuries induced by naphthalene, Dsg3 and other epidermal antigens were ectopically expressed in the lungs, which was sufficient for the recruitment of Dsg3-specific CD4+ T cells, implying that Dsg3-specific CD4+ T cells could induce pulmonary inflammation, most likely due to ectopic expression of Dsg3.[22] Ectopic expression of epidermal autoantigens may help to explain the involvement of multiple organs in PNP.[3]

In patients presenting with PNP, CD8+ T lymphocyte infiltrate can be seen in bronchiolitis obliterans (an inflammation and fibrotic change that causes bronchial obstruction).[23] Thus, autoreactive T-cell activity has a role in autoimmune response regulation in PNP pathogenesis.

3. Clinical Findings

3.1. Pemphigus Vulgaris

In most patients presenting with PV, and in over 50% of cases, the first signs of the disease arise in the oral mucosa, with nearly all patients presenting with PV developing oral lesions at some stage of the disease.[2,24] Oral mucosal involvement encompasses flaccid blisters that easily rupture, resulting in painful erosions that produce a burning sensation, especially in the inner cheek region (buccal area) as well as eroding blisters on the palate, tongue, inner side of the lips, and gingival affection – less frequent - presenting with enanthema in addition to blistering. [2,3,24]

Other mucous membranes aside from oropharyngeal mucosa can be affected, such as the larynx, esophagus, conjunctiva, nose, genitalia, and anus, with less frequency.[3]

Associated with the mucocutaneous variant of PV cutaneous involvement is likely, and patients present with flaccid blisters and erosions on the skin that appear concurrently with mucosal lesions or develop during the disease.[2,25] Predilection sites of these skin lesions are the scalp, neck, axillae, upper trunk, and groin which tend to induce mechanical friction. Nonetheless, any site of the body can be affected. [2,25]

Fingernail involvement in PV has been reported in up to 33,7% of cases, with a correlation between fingernail changes in PV and overall disease severity being shown.[26]

3.2. Pemphigus Foliaceus (PF)

In patients presenting with PF, mucosal surfaces are unaffected, due to the absence of Dsg3 antibodies. Blister formation level is high in the subcorneal region of the epidermis with blisters being even more fragile than those seen in PV, with the scarce presence of intact blisters.[27] Upon examination, skin blisters or erosions can be seen, commonly accompanied by scaly or crusty erythematous patches.[24,27] Since there is no mucosal involvement, oral manifestations are not expected in PF.

3.3 Paraneoplastic Pemphigus (PNP)

The most distinguishing aspect of PNP is severe and painful stomatitis, which is frequently the first symptom and lasts throughout the disease. This stomatitis manifests itself orally as erosions and ulcerations involving the vermilion border of the lips, the lateral borders of the tongue, as well as oropharynx involvement. In addition to stomatitis, mucositis can be present in the pharynx, larynx, esophagus, and anogenital and conjunctival mucosal regions.[20,25] Ulceration of the entire oral mucosal surface is possible and may represent the sole manifestation of this condition.[28]

Cutaneous lesions typically arise after mucosal lesions have developed.[28] Albeit lesions are polymorphic and may show different features in the same patient, blisters and erosions are prevalent and are often identical to those found in PV, PF, or bullous pemphigoid, affecting any portion of the body.[20]

3.4 Nikolsky´s Sign

A clinical hallmark of AIBDs, particularly the pemphigus group of diseases, is the presence of the Nikolsky´s sign. Dr. Pyotr Vasilyevich Nikolsky initially characterized this widely known clinical and pathological sign in 1896, as a symptom of a weakening relationship of contact between corneal and granular layers on all surfaces, including in locations between lesions on seemingly undamaged skin. The underlying pathophysiology of this sign is acantholysis, which is defined as a loss of coherence between epidermal cells caused by the breakdown of their intercellular bridges [29,30] – see figure 2b.

Nikolsky´s sign is elicited by applying firm tangential/lateral sliding pressure with the thumb or a finger into perilesional skin, affected skin, or seemingly unaffected skin, particularly over a bony prominence, resulting in dislodging of the upper layer of the epidermis (stratum corneum) from the lower layers (granular layer) – see figures 2a and 2b - leaving behind an erythematous, moist, and denuded dermis, which can be not only painful as well as increase the risk of developing secondary infection. [29,30]

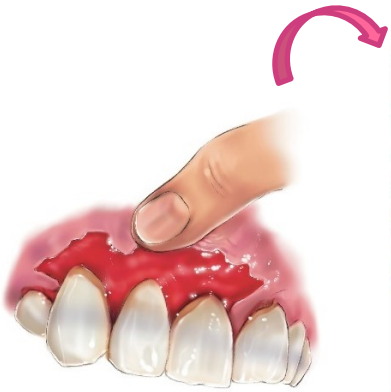

Figure 2a

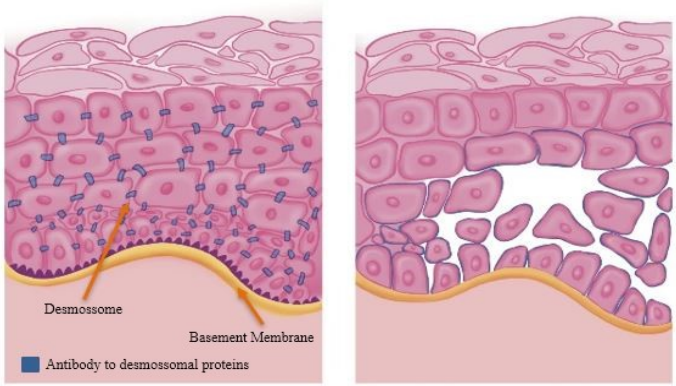

Figure 2b

Figure 2a – **Elicited Nikolsky´s sign on oral mucosa** (Author: Ana Silva)

Figure 2b **- Secondary acantholysis (epithelial cell splitting) after eliciting Nikolsky´s sign**. Adapted from Oiseth, S., Jones, L., Maza, E. Bullous Pemphigoid and Pemphigus Vulgaris | Concise Medical Knowledge [Internet]. [cited 2022 Oct 11]. Available from: https://www.lecturio.com/concepts/bullous-pemphigoid-and-pemphigus-vulgaris/[31]

A positive Nikolsky´s sign is usually pathognomonic for pemphigus, toxic epidermal necrolysis, and staphylococcal scalded skin syndrome (SSSS).[30] Practitioners need to be careful to further assess whether they are in the presence of a "positive" Nikolsky´s sign, where there is true acantholysis - or a "false"/" pseudo" Nikolsky´s sign, such as seen in bullous pemphigoid, epidermolysis bullosa ("false" Nikolsky´s sign) and Stevens-Johnson syndrome (pseudo-Nikolsky´s sign), where the cause for dermo-epidermal separation is not acantholysis, but necrosis of keratinocytes.[30]

A previous study demonstrated that Nikolsky´s sign has a high specificity (96.3%) (although much higher that the sensitivity – 46.7%) for preliminary detection of AIBDs.[32] This high specificity value difference suggests that eliciting Nikolsky´s sign can be used as a simple and effective rule-out test, particularly when the clinician's index of suspicion is high for blistering disease, while low sensitivity indicates that, while Nikolsky's test can aid in the diagnosis of autoimmune oral blistering disease, additional diagnostic tests such as biopsy, immunofluorescence, and blood autoimmunity tests may be required for confirmation.[32,33]

Nikolsky´s sign is, therefore, a useful clinical sign that can guide practitioners in the preliminary diagnosis of the pemphigus group of disorders and other AIBDs, acting as a simple but helpful clinical diagnostic tool with value in lesion recognition in this group of diseases, reducing the risk of misdiagnosed or undiagnosed cases.[33]

3.5 Non-Classical Forms of Pemphigus

Non-classical, rarer forms of pemphigus have been described since 1975, and they differ from the described classic PV and PF presentations in clinical, histological, and pathophysiological aspects.[34.] It is possible to consider the following non-classical forms of pemphigus: pemphigus herpetiformis (PH), endemic forms of pemphigus foliaceus (Brazilian and Tunisian variants), IgA pemphigus and drug-induced pemphigus.

3.5.1 Pemphigus Herpetiformis (PH)

PH is a distinct and uncommon form of pemphigus. It accounts for 6–7% of all pemphigus cases, with an average onset age of 65 years old and no sex preference.[35] In PH, Dsg1 is the most often targeted antigen, but both Dsg1 and Dsg3 have been demonstrated as target cell surface antigens for PH. Given that some patients presenting with PH show features of either PV or PF at some time in the course of the disease, PH can be clinical and histologically viewed as a variant of PF or PV.[36]

Clinical manifestations of PH are atypical, with lesions being primarily associated with various other bullous diseases, such as dermatitis herpetiformis, linear IgA bullous dermatosis, pemphigus foliaceus, and even bullous pemphigoid due to the presence of erythematous and urticarial plaques perilesional to bullae or vesicles with herpetiform disposition. [34-37] Prominent itching can be seen, a characteristic not common in classical forms of pemphigus. Nikolsky´s sign is not constant, as well as mucosal affection. [34-37]

3.5.2 IgA Pemphigus

IgA Pemphigus is a characterized group of AIBD first described in 1982 by Wallach, Foldes, and Cottenot under the designation *subcorneal pustular dermatosis and monoclonal IgA.*[38] It presents with vesiculopustular eruption, neutrophil infiltration, acantholysis, and circulating and tissue-bound IgA antibodies that target desmosomal or non-desmosomal surface components in the epidermis.[39] Several cases have been reported with other designations, such *as intraepidermal neutrophilic IgA dermatosis, intercellular IgA dermatosis, IgA pemphigus foliaceus, IgA herpetiform pemphigus, intraepidermal IgA pustulosis, and intercellular IgA vesiculopustular dermatosis.*[39-46]

IgA Pemphigus can be divided into two distinct types: *subcorneal pustular dermatosis* (SPD) type, commonly referred to as the "IgA Pemphigus Foliaceus"; and the *intraepidermal neutrophilic* (IEN) type, also referred to as the "IgA pemphigus vulgaris.[40]

Patients with either type of IgA pemphigus exhibit flaccid vesicles or pustules on erythematous or normal skin, that are likely to generate an annular or circinate pattern with crusts in the center.[34] IgA SPD type frequently displays clinical features like those of SPD, with the IEN type presenting with a characteristic "sunflower-like" configuration.[47] Sites of predilection include axillary and groin areas, but common involvement of the trunk, proximal extremities and lower aspect of the abdomen is possible. Mucous membrane involvement is rare.[34,47]

3.5.3 Endemic Forms of Pemphigus

Several possible EPF foci have been reported in South and Central American regions, as well as in Tunisia.[48] Nonetheless, the most extensive and well-characterized variant is referred to as "Fogo Selvagem" (FS), meaning "Wildfire" in Portuguese.[48] Brazil has the world's largest number of patients with FS, with patients being mostly young people and adults who have been exposed to rural areas, with the occurrence of familial cases.[48] Environmental, genetic, and immunological factors may trigger the disease. Among the

environmental factors, exposure to mercury, mineral, dust and *Simulium nigrimanum* mosquito bite should be considered.[49] FS affects both sexes equally and demonstrates a high incidence of onset at around 10-30 years of age.[50]

FS shares clinical, histopathological, and immunological characteristics like those of classic PF, being distinguished from it primarily through epidemiological aspects, mainly higher frequency in children and young adults living in rural areas where a high incidence of FS is known.[50]

Clinically, patients present with primary cutaneous lesions, such as superficial vesicles/blisters that can be filled with light or yellowish-hue liquid that resemble impetigo lesions.[50] Lesions are flaccid and burst easily resulting in erosive and/or erosive-crusted areas.[50] Seborrheic areas are the main target (scalp, face, neck, and upper central region of trunk with distal spreading tendency).[50,51] Similar to classical PF, it never presents in the oral mucosa. Nikolsky´s sign is positive in all patients with active diseases.[51]

3.5.4 Drug-Induced Pemphigus

Drug use has been linked to disease flare-ups or exacerbations in pemphigus patients. Although precise mechanisms through which they induce/exacerbate pemphigus are unknown, three categories of medicines have been associated with the occurrence of drug-induced pemphigus: Non-thiol/non-phenols, phenols, and thiols.[52,53]

Clinically, DIP features nonspecific manifestations like those that are characteristic of common drug eruptions that may precede the appearance of genuine pemphigus lesions.[54] In the "full-blown disease, drug-induced pemphigus presents features of either PF, erythematous, and more often PV features, which demonstrates a reality contrary to what was initially postulated.[53-55]

Commonly prescribed anti-hypertensive, anti-convulsant, anti-microbial, and anti-inflammatory drugs have been proven to induce pemphigus, with the most reported being penicillamine, captopril, and bucillamine in decreasing order; all belonging to the thiol

group. However, none of these three common agents has been linked to pemphigus exacerbation.[55]

4. Differential Diagnosis

Differential diagnosis of pemphigus diseases is based on a combination of interpretation of clinical findings, direct immunofluorescence microscopy (DIF), and histopathological presentation - through means of perilesional and lesional biopsy, respectively - as well as serological tests through serum sampling. [2,4,6,25,56]

Biopsies from ulcerated and blistering regions should be carried out differently: on blisters, biopsies carried out for histological evaluation purposes should be taken at the edge of the blister to determine the level of split in AIBD, while ulcerated region biopsies should be taken from perilesional erythema.[6]

In addition to routine diagnosis methods, cytology, a method that evaluates individual cells, known as the "Tzanck smear", has shown considerable sensitivity and specificity for rapid diagnosis of PV lesions.[57]

4.1 Histopathology

Acantholysis is present in lesional biopsy specimens of all types of pemphigus.[3]

In PV, intraepithelial cleft spaces, rounded acantholytic cells with eosinophilic cytoplasm, and pyknotic nuclei are present. Moderate mixed inflammatory infiltrate can be present in subjacent connective tissue.[58] Basal cell shrinkage is typically superior in comparison to suprabasal keratinocytes, hence why suprabasal acantholysis occurs. As acantholysis advances, secondary antiantibodies production is stimulated, and retained basal cells exhibit a "rounded" aspect, also called the *tombstone* effect[59]- see figure 3.

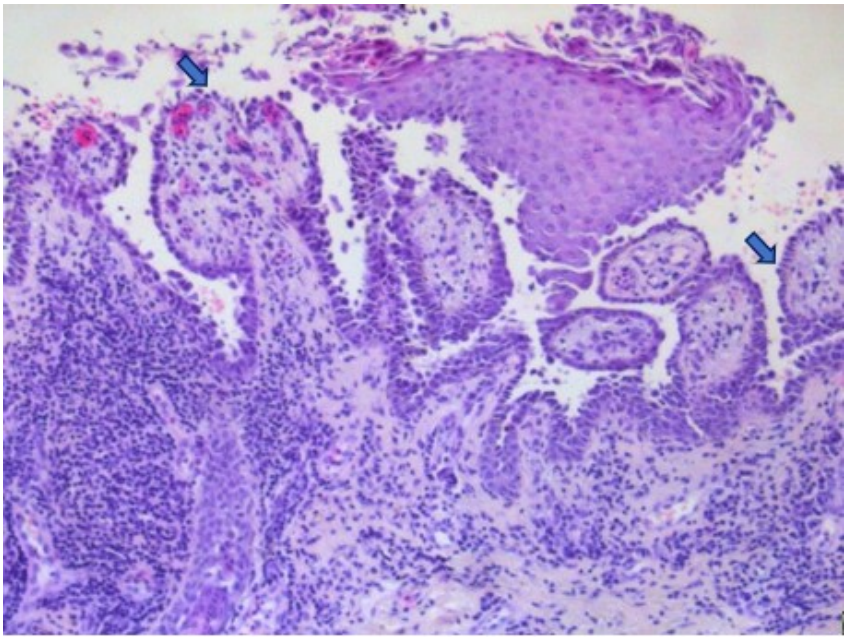

Figure 3- **Histological appearance of PV** – Distinctive suprabasal clefting, rounded acantholytic cells with eosinophilic cytoplasm, and intraepithelial clefting. Retention of a single layer of basal cells that display tombstone appearance (arrows) (x100, H&E stain) (Source: Laboratório de Histopatologia Cutânea do Serviço de Dermatologia do Hospital de Santa Maria - CHLN)

Epidermal blisters are usually non-inflammatory for both PV and PF, nonetheless, in the upper dermis and epidermis, eosinophilic or neutrophilic infiltration can sometimes be found.[3]

In PNP, histological findings show variable morphological changes, that span from bullous lesions that display lower levels of inflammation up to dense lichenoid reactions.[60] PNP presents a combination of both humoral and cellular mediated phenomena: Humoral – suprabasal epithelial acantholysis with clefting and dyskeratosis; Cellular autoimmune – Interface dermatitis and lichenoid changes (thick lichenoid infiltrate that can be seen along the dermal-epidermal junction).[60] Dyskeratosis in the setting of suprabasal acantholysis is a distinctive feature and clue to paraneoplastic pemphigus[60].

4.2 Direct Immunofluorescence Microscopy (DIF)

Alongside clinical and histopathological findings, DIF is needed for the differentiation of AIBD diseases and remains the gold standard for the effect. Biopsied

sections of perilesional skin or mucosa around 1mm (with mucous membrane biopsies around at least 3mm) are taken and placed into cryotubes for transportation in either liquid nitrogen, saline solution (delivery < 36 h), or Michel's medium.[4,6] Autoantibodies bound in the samples are then visualized by targeting with fluorescent-labeled antibodies against human IgG.[4,6]

4.2.1 Pemphigus Vulgaris

In DIF of PV, immunoglobulin G (IgG) and C3 deposits are observed on the keratinocyte plasma membrane, with intercellular staining frequently involving the whole epidermis and more rarely only the basal layer.[61] DIF aspect should demonstrate an intercellular IgG and C3 deposition in a netlike or honeycomb-like pattern within the stratified squamous epithelium[58, 61] – see Figures 4a and 4b.

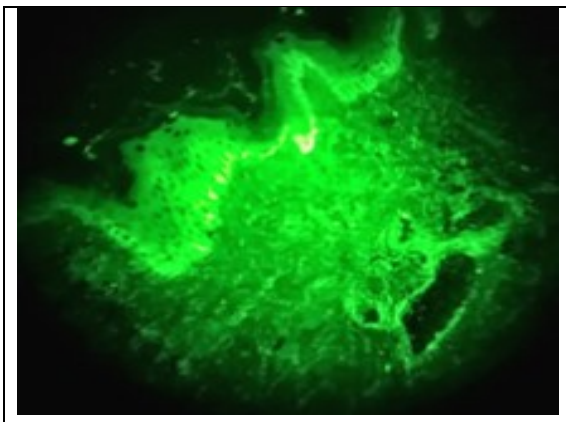

Figure 4a- DIF appearance of PV, demonstrating strong intercellular deposition of IgG alongside the basal layers of the epidermis. (Source: Laboratório de Histopatologia Cutânea do Serviço de Dermatologia do Hospital de Santa Maria – CHLN)

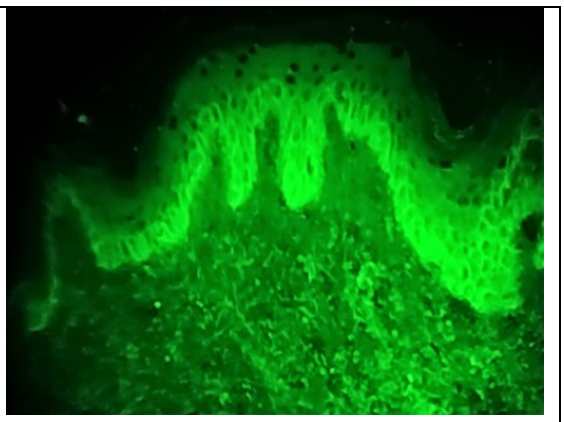

Figure 4b- DIF appearance of PV, demonstrating strong intercellular deposition of C3 alongside the basal layers of the epidermis. (Source: Laboratório de Histopatologia Cutânea do Serviço de Dermatologia do Hospital de Santa Maria – CHLN)

4.2.2 Pemphigus Foliaceus

DIF for PF shows IgG and C3 deposits most often located on the whole epidermis and less frequently predominating in the upper layers of the epidermis, presenting with a honeycomb pattern like that of PV. [3,61]

4.2.3 Paraneoplastic Pemphigus

Epithelial cell surface deposits combined with linear IgG or C3 along the dermal-epidermal junction are suggestive of PNP, pemphigus erythematosus, or the coexistence of pemphigus and pemphigoid. DIF for PNP can sometimes demonstrate false negatives owing to the presence of necrotic tissue and lichenoid infiltrate.[60,62]

4.3 Serological Tests

Various immunoserological assays are performed to identify circulating autoantibodies targeting Dsg proteins, which may be useful for diagnosing and differentiating AIBDs.[6] Serology has the advantage of being non-invasive, which is especially useful when biopsy specimens are unavailable (children, uncooperative adults).[63] Clinical findings and serology, when combined, are usually sufficient to establish a diagnosis.[64]

Within the available tests, indirect immunofluorescence microscopy (IIF) and ELISA are of special relevance for the differential diagnosis of pemphigus diseases.

4.3.1 Indirect Immunofluorescence Microscopy (IIF)

IIF is regarded as a reliable method for pemphigus diagnosis and monitoring.[63] It is a simple, sensitive, and fast approach for autoantibody identification in pemphigus sera, and it is essentially a two-stage assay[65], in which firstly, the patient's serum is applied to a specific tissue substrate where antibodies attach to antigens, followed by washing of unbound antigens; secondly, secondary fluorescent-labeled antibodies visualize the tissue-bound antibodies under a fluorescent microscope, making possible the visualization of autoantibodies bound to the substrate.[6,64] Because it is widely available commercially, monkey esophagus is frequently used as a substrate.[6]

A significant limitation of IIF, similar to DIF, is its inability to differentiate between PV and PF, as well as immunofluorescence studies not being able to distinguish between drug-induced and idiopathic PV.[65] Indirect immunofluorescence on rat bladder substrate, is one of the few serological tests that can diagnose PNP and is thus critical for that purpose.[6]

4.3.2 Enzyme-linked immunoabsorbent assay (ELISA)

Enzyme-linked immunosorbent assays (ELISA) and immunoblots are frequently used for specifying targeted antigens.[6] ELISA is a reliable and sensitive technique that allows the detection of biological molecules at very low concentrations and quantities, such as minimal amounts of antibodies. It is a biochemical assay that acts detecting the presence of antigen (proteins, peptides, hormones, etc.) or antibody in a given sample, using antibodies and an enzyme-mediated color change.[66] It is also a commercial technology for detecting Dsg1 and Dsg3 circulating antibodies, providing objective, quantifiable, and reproducible results.[63] ELISA testing presents several perks: detection of anti-Dsg3 and anti-BP180 ELISA during routine clinical practice might influence the diagnostic process and aid in identifying PV from pemphigoid at first glance; because of its minimal invasiveness and cheap cost, ELISA is an economical and rapid test that is widely available in clinics and clinical laboratories.[66] In this approach, the patient's road to diagnosis and therapy would be reduced, with histological examination and DIF being reserved exclusively for the most doubtful instances, limiting the need for surgical biopsy

in many oral pemphigus patients, and thus being a shorter, more effective diagnostic path.[66]

4.4 Differential diagnosis – Other pathologies

The differential diagnosis of erosive oral lesions comprises several diseases that can be classified based on their etiology, whether it be autoimmune, related to systemic diseases, inflammatory conditions, genetic or metabolic impairment, drug-induced reactions, viral and bacterial infections [3,6], as well as neoplastic conditions. Because these conditions have distinct morphological features as well as overlapping clinical features, additional testing in concurrence with clinical examination is required, such as histological examination, for correct diagnosis.[6]

Conditions of the oral mucosa associated with autoimmune diseases, included in the differential diagnosis of pemphigus lesions are pemphigoid diseases and their subtypes, particularly mucous membrane pemphigoid (MMP), epidermolysis bullosa, linear IgA dermatosis and lupus erythematosus. [2,3,6] Related to infectious diseases, staphylococcal scalded skin syndrome, bullous impetigo, herpes simplex, and varicella-zoster virus infections can be considered for differential diagnosis.[2,3,6] Genetic-associated conditions such as Hailey-Hailey disease (benign chronic familial pemphigus) are also considered.[3] Other conditions that are considered in the differential diagnosis of pemphigus lesions include aphthous stomatitis, erythema multiforme and Stevens-Johnson syndrome (differential diagnosis with PV mucosal variant lesions), toxic epidermal necrolysis, severe drug eruption, lichen planus, graft-versus-host disease, Grover disease (transient acantholytic dermatosis), seborrheic dermatitis and subcorneal pustular dermatosis[2,3]

Pemphigoid lesions, particularly mucous membrane pemphigoid (MMP) - the most prevalent oral autoimmune blistering disease presenting in the oral cavity – differ from pemphigus in terms of location where splitting occurs. While in pemphigus, splitting occurs at the epithelial level (in between epithelial cells), in MMP splitting occurs at a subepithelial level.[5] MMP is, therefore, a subepithelial blistering disorder. In MMP, 60% of the patients present solely oral involvement, and in 48–96% of cases, oral cavity symptoms are the first manifestation of the disease.[5] Because it frequently represents the

only site of involvement, oral mucous membranoid pemphigoid may be considered a subset of MMP.[5] Patients with MMP present with painful erosions, erythema, and ulceration, and collapsed blisters may present as a membrane-like shape with a yellow-white coloration, that peels off the mucosa with ease.[5]

5. Treatment

5.1 General Considerations

Treatment of pemphigus is of utmost importance, given that there is high mortality of pemphigus secondary to sepsis, which mainly occurs due to delaying or non-treatment of cutaneous erosions.

Several guidelines exist in the literature for the treatment of pemphigus diseases, such as those presented by the British Association of Dermatologists (BAD), Japanese Dermatological Association (JDA), German guidelines by the Association of the Scientific Medical Societies in Germany (ASMSG), European Academy of Dermatology and Venereology (EADV), as well as recommendations by a body of international experts following the American Academy of Dermatology conference. [67-71]

Although several guidelines exist, most of them contemplate corticosteroids as the most widely used drugs for pemphigus treatment, typically prescribed as first-line therapy for patients with mild and moderate-to-severe disease.[72] However, there are variations in the initial dose, tapering timing, and relapse care between various guidelines.[72] Regarding corticosteroid therapy, methylprednisolone and dexamethasone are mostly utilized in pulse therapy, while prednisone and prednisolone are typically supplied orally.[73]

For severe cases of pemphigus, the classical basis of treatment is a combination of high doses of systemic corticosteroids, intravenously or by topical application directly onto blisters/erosions, concurrently with immunosuppressive drugs.[74] Mainly prescribed immunosuppressive drugs are azathioprine and mycophenolate mofetil, which act as steroid-sparing agents.[74]

Corticosteroids is a general term that refers to all steroid hormones, which are synthesized and secreted by adrenal glands.[75] They are absorbed in the gastrointestinal tract and undergo hepatic metabolism and renal excretion. In broad terms, corticosteroids possess anti-inflammatory and immunosuppressive properties (mainly glucocorticoids), as well as bodily potassium and water regulation (mineralocorticoids).[75] Corticosteroid-

associated adverse events commonly include hypertension, bone fracture or osteoporosis, cardiac conditions, type-2 diabetes and hyperglycemia, cataract, nausea/vomiting, and other gastrointestinal conditions[76].

Azathioprine (AZA) acts in purine metabolism downregulation, blocking the synthesis of DNA, RNA, and proteins, reduces Langerhans and monocyte cells, as well as diminishes T- and B- lymphocyte activity.[77] It also blocks T-helper-cell-dependent responses of B-cells.[77] Adjuvant therapy with AZA for pemphigus often presents adverse effects including diarrhea, liver function test abnormalities, myelosuppression (leukopenia, pancytopenia, thrombocytopenia), pharyngitis, and vomiting.[78] Since thiopurine (purine) metabolism is mediated by the thiopurine methyltransferase enzyme (TPMT), TPMT level testing might be of aid to determining AZA toxicity levels and achieving proper dosing.[79]

Mycophenolate mofetil (MMF) acts in suppression of the immune system through the downregulation of purine synthesis in T- and B- cells and represents a safer corticosteroid-sparing drug in comparison to other immunosuppressant drugs due to its mode of action.[77] Adverse effects of MMF use include fatigue, hypokalemia, liver function test abnormalities, and myelosuppression (lymphopenia, neutropenia).[78]

Patients with pemphigus require a multidisciplinary approach due to the disease's chronic relapsing nature. To avoid further complications, it is crucial to consider prophylactic medications.[4] Due to the use of long-term corticosteroids, it is recommended to start osteoporosis preventive treatment as soon as possible, consider histamine-2 blockers and/or proton pump inhibitors for digestive hemorrhage prevention[80], as well as a hyposaline and hypoglycemic diet to prevent hypertension and iatrogenic type-2 diabetes.

Nowadays, the introduction of B-cell depleting therapies including anti-CD20 antibodies alongside corticosteroid therapy, for pemphigus treatment, such as the use of Rituximab, has been accepted for onset and remission stages of treatment.[67-72,74] Rituximab (RTX) is a human/murine chimeric monoclonal antibody that specifically targets the protein CD20, presenting with a human Fc portion and a murine variable region that serves as a CD20 binding site on its large extracellular loop.[81,82] CD20 is a

transmembrane protein involved in the generation of T-cell independent antibody responses and expressed on the surface of B cell lineage cells at different stages of B-cell differentiation, from naïve to memory B cells.[83] Thus, CD20 is expressed by autoreactive B-cells that are in charge of creating pathogenic auto-antibodies against Dsg.[82]

RTX as a first-line treatment combined with short-term prednisone versus prednisone alone for the treatment of pemphigus, has been demonstrated to be more effective than the use of prednisone alone, presenting with fewer adverse events.[74] Special care should be taken in patients undergoing treatment with RTX that may require plasmapheresis (ex-vivo blood component separation through blood sampling), in which dose adjustment of RTX may be required due to possible pharmacokinetic alterations.[84] Frequent adverse effects associated with RTX therapy include *de novo* infections, false-negative serologic tests for viral infections, reactivation of chronic infections, interference with the effectiveness of vaccinations, and the emergence of *de novo* psoriasis[85]. Less frequent adverse effects include reaction upon infusion, nervous system disorders, and gastrointestinal disorders.[85] Heart rhythm disturbances have also been shown as a possible side effect of RTX infusion, although risk-benefit determines treatment is preferable to non-treatment, and eligible patients should receive RTX infusion when needed.[86]

5.2 Therapeutic management of Pemphigus

The primary objective of treatment is to heal and control new bullous skin lesions and/or mucous lesions while reducing the risk of serious side effects associated with the treatment.[4] Other aims comprise the disappearance of functional impairment of the diseases, prevention, and limitation of recurrences.[4]

Several clinical scores measure pemphigus activity, such as the Pemphigus Disease and Area Index (PDAI) and the Autoimmune Bullous Skin Intensity and Severity Score (ABSIS)[87], which serve as an aid for clinicians when choosing an appropriate treatment scheme for their patients. Guidelines differ in standard methods for grading severity, presenting different values within the same clinical scores.[72] Mild, moderate, and severe are frequently used classifications for illness severity.[72] EADV presents a PDAI score of

≤ 15 or BSA <5% for mild pemphigus, and a PDAI score > 15 or BSA > 5% for moderate-to-severe pemphigus, which provides a comparison between guideline standards.[4]

Treatment of pemphigus encompasses essentially three main phases, being them remission induction, remission maintenance and tapering in remission maintenance. With special relevance, EADV[4], ASMSG[69] and BAD[67] therapeutic recommendations for pemphigus are expressed in Tables 1,2 and 3. Since PF doesn´t have mucosal manifestation, treatment options for PF were not included.

Mild PV treatment

	First line	*Second line*	*Third line*
EADV (2020)	PV: ① RTX ② RTX + PDN 0.5 mg/kg/d ③ PDN 0.5–1.0 mg/kg/d ④ PDN 0.5–1.0 mg/kg/d + adjuvants	PV: *CS alone as firstline*: PDN 0.5–1.0 mg/kg/d + RTX *CS + RTX as firstline*: RTX + PDN 1.0 mg/kg/d	
ASMSG (2019)	PV: PSL1.0–1.5 mg/kg/d + adjuvants	PV: Pulsed IV CS, PSL up to 2.0 mg/kg/d	
BAD (2017)	PV: PSL 0.5–1.0 mg/kg/d + adjuvants (including RTX)	PV: PSL 0.5–1.0 mg/kg/d + alternate adjuvants (including RTX)	IVIG, PE, IA

Table 1 - Therapeutic schema of remission induction therapy concerning mild PV, according to guidelines[4,67,69]; ASMSG Association of the Scientific Medical Societies in Germany, BAD British Association of Dermatologists, CS corticosteroids, EADV European Academy of Dermatology and Venereology, IA immunoadsorption, IVIG intravenous immunoglobulin, PDN prednisone, PSL prednisolone, PE plasma exchange, RTX rituximab.

Moderate-to-severe Pemphigus treatment

	First line	*Second line*	*Third line*
EADV (2020)	*CS + RTX as firstline*: ① RTX + PDN 1.0 mg/kg/d ② PDN 1.0–1.5 mg/kg/d ③ PDN 1.0–1.5 mg/kg/d + adjuvants	*CS + RTX as firstline*: ① RTX + PDN 1.5 mg/kg/d at most ② Pulsed IV CS *CS alone as firstline*: ① RTX + PDN 1.5 mg/kg/d at most ② PDN 1.5 mg/ kg/d + adjuvants	
ASMSG (2019)	① PSL 1.0–1.5 mg/ kg/d + adjuvants ② RTX + PSL 1.0 mg/kg/d ③ Pulsed IV CS	PSL up to 2.0 mg/kg/d	Immunoapheresis, IVIG
BAD (2017)	① PSL 1.0 mg/ kg/d + adjuvants (including RTX) ② Pulsed IV CS (if > 1 mg kg/d oral prednisolone required)	PSL 1.0–1.5 mg/ kg/d + alternate adjuvants (including RTX)	IVIG, PE, IA

Table 2 – Therapeutic schema of remission induction therapy concerning moderate-to-severe pemphigus, according to guidelines[4,67,69]; ASMSG Association of the Scientific Medical Societies in Germany, BAD British Association of Dermatologists, CS corticosteroids, EADV European Academy of Dermatology and Venereology, CS corticosteroids, IA immunoadsorption, IVIG intravenous immunoglobulin, PDN prednisone, PSL prednisolone, PE plasma exchange, RTX rituximab.

Maintenance therapy and relapse of pemphigus – treatment recommendations

	Maintenance	Remission
EADV (2020)	With RTX: Timetable dictates CS tapering: - Mild: Month/dose scheme: (month 1–2–3–4) (dose 0.5–0.3–0.2 ± 0.1 mg/kg/d) - Moderate/severe: Month/dose scheme: (month 1–2–3–4–5–6) (dose 1–0.75–0.5–0.3–0.2–0.1 mg/kg/d) Without RTX: Depends on CS dose: - The dose of CS when tapering begins:> 15−25 mg/d: taper by 10−25% every 2−3 weeks; ≤ 15−25 mg/d: 1/5 mg every 3 to 4 weeks)	With RTX: Depends on the *time of relapse*: ① If relapse occurs during tapering of PDN between *month 0 and month 4*: re-increase oral CS doses; ② If relapse occurs during tapering of PDN between *month 4 and month 6*: an additional cycle of 2 g of RTX (with month 6 canceled); ③ If relapse occurs after stopping PDN: re-evaluation Without RTX: apply RTX or re-increase CS dose and add immunosuppressants
ASMSG (2019)	With RTX: Gradual CS tapering Without RTX: Depends on CS dose: The dose of CS when tapering begins: ≥ 20 mg/d: taper by approximately 25% every 7−14 days; < 20 mg/d: taper by approximately 25% every 2−4 weeks); Minimal therapy: ≤ 7.5 mg/d	With RTX: - Reintroduction of RTX, CS optional Without RTX: re-increase CS dose: - Resume dose given at two reduction intervals prior and resume taper after 14 days of disease control
BAD (2017)	Depends on CS dose: The dose of CS when tapering begins: ≥ 20 mg/d: taper by 5−10 mg every 2 weeks; 10−20 mg/d: taper by 2.5 mg every 2−4 weeks); Minimal therapy: ≤ 7.5 mg/d	① Lower CS doses ② Prescribe CS dose for the initial presentation

Table 3 - Therapeutic schema of maintenance therapy and relapse of pemphigus, according to guidelines[4,67,69]; ASMSG Association of the Scientific Medical Societies in Germany, BAD British Association of Dermatologists, CS corticosteroids, EADV European Academy of Dermatology and Venereology, PDN prednisone, RTX rituximab.

5.3 Future Therapies

5.3.1 Neonatal Fc receptor Antagonists

Recently, newer therapies for pemphigus treatment are being discovered, and the use of neonatal Fc receptor (FcRn) antagonists is currently being contemplated as a possible treatment. Being that FcRn is implied in endogenous IgG binding and protects it from lysosomal degradation by transporting it back to the cell surface to re-enter the circulation, it is directly linked to serum IgG life span extension.[88] Since inhibiting the FcRn causes IgG catabolism and lower levels of both pathological autoantibodies and total IgG are seen, FcRn targeting with FcRn antagonists may provide a novel therapeutical approach for pemphigus.[88]

Efgartigimod (efgartigimod alfa-fcab, Vyvgart™) is a pioneering neonatal Fc receptor antagonist being developed by argenx for the treatment of autoimmune diseases including myasthenia gravis, which has already obtained approval in countries such as USA and Japan for myasthenia gravis treatment, under specific conditions.[89] Studies regarding intravenous and subcutaneous formulations of efgartigimod are being conducted to determine this drug as a possible treatment for other autoimmune diseases such as bullous pemphigoid, chronic inflammatory demyelinating polyradiculoneuropathy, immune thrombocytopenia, autoimmune myositis, and pemphigus.[89] Efgartigimod has demonstrated a reduction of serum levels of IgG of 50% in humans, upon single administration, with multiple dosing lowering IgGs on average by 75% of baseline levels, with serum IgG levels returning to baseline approximately 8 weeks after, with no registered serious adverse events following efgartigimod infusion.[90] This specific, significant, and long-lasting decrease in serum IgG levels calls for additional research as to introducing this therapy as a strategy for IgG-driven autoimmune diseases.[90]

5.3.2 Bruton Tyrosine Kinase Inhibitors

Bruton tyrosine kinase (BTK) is an important enzyme in both innate and adaptive immune responses.[91] Apart from T cells and plasma cells, it is a component of the signaling pathway used by the majority of white blood cells, with special relevance in the growth and differentiation of B-cells.[91] It also contributes to the inflammatory cytokine production of myeloid cells. Although BTK inhibitors have been demonstrated effective for canine pemphigus, further studies are necessary to assess them as a formal treatment for pemphigus.[91] Since they may act more quickly than rituximab through the innate immune system, BTK inhibitors may present a new paradigm for the treatment of autoimmune diseases and AIBD in particular, with pemphigus having the most compelling unmet need.[91]

6. Oral Cavity and Pemphigus – Take Home Messages

PV, within pemphigus subtypes previously addressed, is a chronic AIBD that primarily involves the oral cavity and can be a life-threatening condition. For that reason, it is imperative that clinicians can recognize the primary oral findings associated with PV at an early stage, so that appropriate treatment and/or referral can be conducted. Dentists and oral medicine professionals are, therefore, in a privileged position for the detection of these pathologies since access to the oral cavity is more frequent in comparison to other medical fields.

It makes sense to hypothesize that PV patients may be impacted by the long-term use of corticosteroids and/or other immunosuppressive medications and may have a compromised capacity to carry out efficient and effective oral hygiene activities.[92] Pain and discomfort associated with PV-related lesions (gingival blisters and erosions) may not only refrain patients with such conditions from attending dental routine examinations and professional hygiene procedures but also induce plaque buildup as a result of the incapacity of performing personal oral hygiene due to sore blisters/erosions that make it difficult to perform these tasks effectively.[92] All of this can put patients with PV at an increased risk for carious lesions and an increased risk of periodontal disease.

Pemphigus was discovered to be linked to several validated measures of poor periodontal health, such as the Community Periodontal Index of Treatment Needs (CPITN).[93] Additionally, PV patients have demonstrated worse Clinical Severity Score (CSS), with a significant difference in comparison to healthy groups.[94] In the CSS, probing depth (PD) and clinical attachment loss (CAL) were increased.[94] Poor periodontal status in PV patients may link PV involvement to the onset or progression of periodontitis.[94] In addition, patients with PV present with a higher number of carious teeth than that in healthy groups.[92]

It has been suggested that a decrease in periodontal care is linked to higher gingival tissue involvement in pemphigus, lichen planus, pemphigoid, and epidermolysis bullosa acquisita.[95]

In a small sample of pemphigus patients, it has been demonstrated that one week of professional oral hygiene therapy, including supragingival scaling and polishing, oral hygiene instructions, prescription of chlorhexidine mouth rinses (0,20%/1min), and toothbrushing with appropriate techniques, improved the overall gingival status.[96]

It is possible to think that, since many patients with PV present with blisters/erosions and clinical settings of desquamative gingivitis, conditions such as bad tooth positioning, and poor occlusion might cause friction upon gingival areas, acting as trauma-inducing factors, worsening the patient's condition. Poor restorations with no respect to dental anatomy might also constitute additional trauma factors. For that reason, dentists need to not only be aware of systemic conditions but also carefully assess dental issues that might worsen the disease´s current scenario.

III. CONCLUSION

Clinicians should be aware that AIBDs frequently present with oral manifestations, and in some cases, it is either the first or sole manifestation of the disease, and for that reason, dentists must be the first to diagnose it.

Pemphigus is an AIBD associated with either mucosal or cutaneous damage, presenting in the form of painful blisters or erosions that, left untreated, might be potentially fatal.

Associated functional limitations due to pain and itching may have psychological impacts on the patient and worsen his oral health conditions due to the inability to conduct proper oral hygiene.

Patients with pemphigus frequently present with oral blistering, which can delay in months the diagnosis, and having privileged access to the oral cavity, dentists should be aware of such disease when considering the differential diagnosis of AIBDs.

Alongside clinical examination, histological examination, and direct immunofluorescence on a biopsy from skin or mucosa combined with indirect immunofluorescence and additional serological tests, are the foundation for diagnosing AIBDs with pemphigus being no exception.

Treatment of pemphigus relies mainly on corticosteroids as the first line, either associated with steroid-sparing agents, such as azathioprine and mycophenolate mofetil, or B-cell depleting therapies, such as rituximab. Nonetheless, other novel therapies for pemphigus treatment, such as neonatal Fc receptors and bruton tyrosine kinase inhibitors are currently being tested as options for pemphigus treatment.

Dentists have a key role in the early detection of pemphigus diseases, and with the described diagnostic and treatment algorithms, they should be able to quickly and properly diagnose pemphigus diseases. Moreover, dentists and oral medicine practitioners should seek to work within a multidisciplinary frame with other medical

fields, such as Dermatology and Otorhinolaryngology (ENT doctors), Oncology, Ophthalmology, and Surgery, to fully comprehend the patient´s disease and properly diagnose and treat his medical conditions.

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