



## Review of Mucocutaneous Disorders

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The term desquamative gingivitis is a clinical diagnosis encompassing a myriad of vesiculoerosive disorders. The effected gingiva have red to white lesions of varying sizes and can be localized or have generalized involvement of oral soft tissue. The white areas represent a thickening of the keratin, while the red areas represent an ulcerative process. Desquamative gingivitis is rare. However, when present, up to 88% of patients will have one of three disorders; lichen planus, pemphigoid, or pemphigus (Russo 2009) and should, therefore, be included in the differential diagnosis. Desquamative gingivitis can go undiagnosed and, if not properly treated, can lead to severe morbidity and possible mortality. This underscores the importance of early diagnosis and corresponding treatments for these disorders.

### **Pemphigus**

Pemphigus is a group of blistering diseases that can have systemic symptoms or be limited to the oral mucosa. The mean age of onset is 40-60 years old and has an incidence between 0.05-3.2 cases per 100,000 persons (Sagi 2011) with the highest incidence for those of Jewish and Mediterranean ancestry. Subtypes of pemphigus include: pemphigus vulgaris, pemphigus foliaceus, pemphigus erythematosus, pemphigus vegetans and paraneoplastic pemphigus. Classic pemphigus vulgaris presents with oral lesions in 50-70% of the cases. The bullae may not be present as they are prone to early disruption of the thin, friable epithelium.

Histologically, pemphigus is characterized by separation of the deep portions of the epithelium above the basal layer. The separation occurs when antibodies predominantly attack the basal layers causing bulla that often break apart before they are clinically detected (Figure 1). In 1964 pemphigus was identified as an autoimmune disease in which auto antibodies attack desmoglein 1 and 3 (Sciubba 2011). Affecting both the skin and mucosa, pemphigus is believed to be caused by genetic and/or environmental factors such as viruses and bacteria (Sagi 2011). Pemphigus has been associated with certain human leukocyte antigen (HLA) class II loci and environmental factors such as UV light, radiation, infections and stress (Sagi 2011). More recently an association has been found suggesting a contributing role for HBV, HCV, H. pylori, T. gondii and CMV in inducing autoimmune bullous diseases in a genetically susceptible host (Sagi 2011).

### **Pemphigoid**

Bullous pemphigoid is another autoimmune bullous forming disease that may present systemically, be limited orally and may include lesions of the eye. There is equal distribution between men and women with no racial predilection (Sagi 2011). The reported incidence of bullous pemphigoid is between 4.4 and 14 cases per one million people. Of the diagnosed cases, 10-40% have oral mucosa involvement and ocular involvement is seen in 37% of cases (Knudson 2010). Clinically the disease is characterized by subepithelial blistering where, in contrast to pemphigus, the bullae may be seen in this disease because of the thick epidermis that remains intact over the affected tissue. Since ocular involvement can result in symblephron formation and eventual blindness, a referral to an ophthalmologist should be made upon a confirmed diagnosis of pemphigoid (Sciubba 2011). In the United States, mortality from the disease is estimated between 6 and 12% (Sagi 2011).

In contrast to pemphigus, pemphigoid is histologically characterized by separation of the epidermis below the basal layer resulting from autoantibodies attacking the hemidesmosomes of the basement membrane and the basal cell layer (Figure 2). Two collagen transmembrane proteins, bullous pemphigoid antigen 230 (BPAG 1) and bullous pemphigoid antigen 180 (BPAG 2), are part of the cells' anchoring filaments and have been identified as the antigens within the hemidesmosome region of the epithelium (Knudson 2010).

### **Lichen Planus**

Lichen planus (LP) is a cutaneous disease typically affecting squamous epithelium. While LP may affect both the dermis and the mucosa, many cases may be limited to the oral mucosa (Canto 2010). Worldwide it has about 1%-2% prevalence with a slight female predilection (Sciubba 2011). Oral LP has been described as either reticular or erosive. The reticular form is more common and usually presents on the buccal mucosa, gingiva and tongue. Lesions termed "Wickham striae" are pathognomonic of oral LP and are characterized by the presence of numerous interlacing and branching white lines which are typically asymptomatic. The malignant potential of LP has not been fully identified. However, some reports have shown it to have a malignant potential of up to 5.3% when following patients for 20 years (Canto 2010).

Histologic features vary with the clinical types of LP, however the spinous cell layer can be thickened with pointed (sawtooth) rete pegs. Erosive LP may have a complete loss of rete peg formation and a dense band-like infiltrate of lymphocytes juxtaposed to surface epithelium and typically presents with pain due to ulcerations (Figure 3). While its cause is unknown, LP is thought to have a T-cell mediated chronic inflammatory process of autoimmune origin (Canto 2010).

### **Erythema Multiforme, Steven Johnson Syndrome and Toxic Epidermal Necrolysis**

Erythema multiforme (EM) is a rare mucocutaneous disease affecting the skin and mucosa that encompasses multiple forms with a mortality rate of 1-35% (Harr 2012). These forms include EM minor, EM major, Steven Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN). The manifestations of oral EM have large variations ranging from minor superficial lesions to painful hemorrhagic bullae and erosions, which may result in scarring. Although symptoms and their severity vary greatly, they typically share cutaneous target lesions and necrosis of the epithelium (Ayangco 2003).

Histologic presentations often show subepithelial separations at the basement membrane level. The pathoetiology is believed to involve cytotoxic immunologic attack on keratinocytes which are expressing non-self antigens of viral or drug origin (Ayangco 2003). The immune response to these antigens leads to a wide spectrum of sequelae such as bullae, ulcers and epithelial sloughing. Although there is no confirmed pathogenesis, it is believed that EM major and minor are of viral origin, with HSV-1 and HSV-2 being the most common causative agents, while SJS and TEN are of drug origin (Ayangco 2003). The diagnosis of EM is one of exclusion. Therefore, a thorough clinical evaluation is needed before a differential diagnosis can be determined. A biopsy is required to establish a diagnosis.

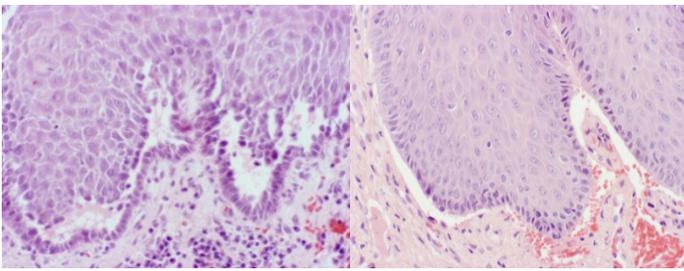


Figure 1. Pemphigus

Figure 2. Pemphigoid

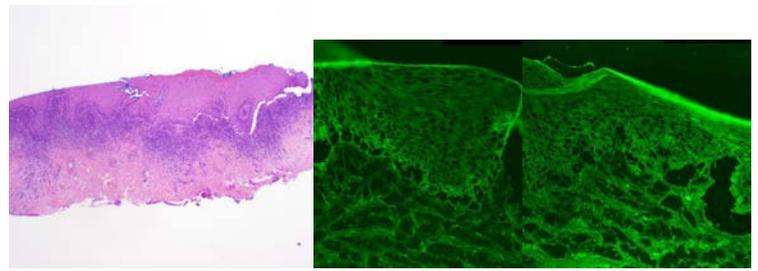


Figure 3. Lichen Planus

Figure 4. DIF (Pemphigus)

### Biopsy and Treatment of Desquamative Gingivitis

After clinical detection and a differential diagnosis is identified, a biopsy of the affected tissue is necessary to establish a definitive diagnosis. The biopsy should be cut in half; with half going into formalin and the other half into Michel's solution for direct immunofluorescence (DIF) histology (Figure 4). After the diagnosis of a desquamative gingivitis disease has been established, the treatment varies with the disease. A referral should be made to dermatology with a diagnosis of these diseases, in addition an ophthalmology referral should be made with a diagnosis of pemphigoid because of the eye lesions that can occur.

The treatment of desquamative gingivitis will depend on the diagnosis, severity and location of the disease. Treatment is typically palliative with a period of time needed to optimize the medication dosing. If the disease is thought to be related to a food or toxin, they must be discontinued.

Mild cases of pemphigoid, pemphigus and erosive lichen planus can be treated with topical steroids (e.g. dapsone) two to three times daily or by a combination of oral medications; such as tetracycline and nicotinamide. Reticular lichen planus is usually observed and not treated unless symptoms develop. More severe pemphigoid, pemphigus and erosive lichen planus cases, or those which do not respond to the first line of treatment, require systemic immunosuppression therapy. Initial treatment is with oral steroids and adjunctive drugs such as: cyclosporine, cyclophosphamide, methotrexate, azathioprine or mycophenolate mofetil. After the symptoms have been controlled, the steroid can be tapered down while continuing the adjunct medications. In refractory cases, immunomodulatory procedures or plasmapheresis may have to be used under a specialist physician's care. Reported treatments of anti-TNF (Tumor Necrosis Factor) alpha drugs, etanercept, infliximab, rituximab, thalidomide, sunconjunctival mitomycin and gold have been reported with some success (Schultz 2011, Pandya 1998).

EM will typically regress spontaneously over a 2 to 4 week period. If manifestations are mild, palliative care is provided (Ayangco 2003). In severe cases of EM, SJS or TEN, these patients are at risk for dehydration and secondary infections; therefore mortality is a serious concern. In severe cases, identifying the etiologic agent is critical so that treatment can begin immediately (Harr 2010). Many times ICU care is indicated and treatment includes: withdrawal of culprit drug, supportive care, systemic steroids, thalidomide, IV immunoglobulins, cyclosporin A, TNF antagonist, plasmapheresis and cyclophosphamide (Harr 2010).

### Conclusions

In conclusion, desquamative gingivitis encompasses many diseases. Even if a desquamative gingivitis is suspected, these diseases have very similar clinical manifestations and cannot be diagnosed without a biopsy. If patients suffering these diseases go undiagnosed or are managed poorly, they can experience severe morbidity or even mortality. However, with palliative treatment and regularly scheduled follow-ups many patients can do well. A

comprehensive oral exam and proper referrals are imperative to suitably treat these patients.

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