

## **Bullous Pemphigoid of the Oral Cavity -2 Case Reports With Review of Literature**

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**Abstract:** Bullous pemphigoid (BP) is a autoimmune blistering disease encountered in India. It is a subepidermal bullous disorder commonly seen in the older generations. It manifests as blisters on a rash and may be pruritic at times. Diagnosis is based on the histopathological confirmation and can also be assessed by direct and indirect immunofluorescence. Treatment is based on the extent and severity of the lesion. Mostly the first line of treatment is topical and systemic anti-inflammatory and immunosuppressive agents.

**Keywords:** Bullous pemphigoid, Oral cavity, Subepithelial blister formation, Steroids, Vesiculobullous lesion

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### **I. Introduction**

Bullous pemphigoid (BP) is a subepidermal blistering skin disease usually affecting the elderly population and is characterized by large tense blisters[1] with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone[2]. Oral mucosal lesions occur only in a few individuals and vary from 10-40 % [3].

Here we are also presenting two case reports of bullous pemphigoid lesions that had occurred in the oral cavity.

### **II. Case Reports**

A 37 year old female patient came to the department of oral medicine & radiology with a chief complaint of peeling of the skin [Figure – 1] . This patient has been noticing this for the past one year. She said that the lesions first appeared as small nodules which later burst and this period was quite painful. She has a medical history of UTI and hypercholesteremia but is currently not under medication.

On examination, there was presence of a vesicle in relation to the gingiva of 32. Surrounding gingival was erythematous and marginal desquamation was also present. Recession of the gingiva with respect to the lower anteriors was also noted. On palpation the lesion was tender.

In case 2, a 63 year old female patient came with a chief complaint of burning sensation to hot and spicy food since one year [Figure – 3]. Here also patient gave a history of vesicle formation on gingival and on the buccal mucosa which ruptured to form an ulcer. Medical history revealed that she had hypertension and was under medication. On examination she had generalized desquamation of the gingival and was tender on palpation.

In both our cases, we advised biopsy under local anaesthesia and the histopathology report came as pemphigoid. Hence we arrived at a final diagnosis of bullous pemphigoid in the oral cavity.

### **III. Discussion**

Bullous pemphigoid is an autoimmune vesiculobullous disease [1]. Blisters are formed which are firm, fluid-filled eruptions which occur on the skin and the oral cavity. This disease commonly affects the skin only, but the other mucosal areas like the eyes, mouth, and genitals can also be affected. In most cases, the disease develops by immune mediated responses but certain medications can also cause the lesion to develop [2].

The epidemiology of BP varies between 0.2 and 3 per 100,000 people per year. A regional study in UK estimated an incidence of 1.4 per 100,000 people per year. However BP is also found in parts of India but as a bullous lesion pemphigus vulgaris is more common [4].

Bullous pemphigoid commonly affects people among the 5<sup>th</sup> – 7<sup>th</sup> decade of life but can even occur in younger generations. Average age was found to be 65 years [5]. Once someone is diagnosed as having this disease, they can have it for many years. BP in children has been reported from various countries including India in certain studies. [3] There is no known ethnic or racial predilection. Treatment helps to control the symptoms of the disease, but there is no permanent cure. In our case, both patients were females.

There are no obvious precipitating factors for BP. However, there are several reports of precipitation of BP by ultraviolet (UV) light, either UVB or PUVA , percutaneous endoscopic gastrostomy, thermal burn and incisional hernia scar[2]. In such cases, BP either remained localized to traumatized site or became a generalized condition. BP has also been reported in association with other autoimmune diseases like diabetes

mellitus, pernicious anemia, chronic inflammatory skin diseases such as lichen planus and psoriasis and various other malignancies[4]. Medications that have been associated with BP-causing disease include NSAIDs like ibuprofen and systemic antibiotics. Tibolone (a selective tissue estrogenic activity regulator that has progestogenic, some androgenic and estrogenic effects) induced BP and this has been reported in a case report from India[3]. In our case, one of the patient was under medication.

The pathogenesis of BP is characterized by circulating IgG autoantibodies against two components of the hemidesmosome associated proteins of stratified epithelium - BPAg1 and BPAg2[5]. BPAg1 is a cytoplasmic protein involved in the anchorage of intermediate filaments to the cytoskeleton. This protein only has a secondary role and does not play a major role in the pathogenesis of the disease. BPAg2 is a transmembrane adhesion molecule with several collagenous extracellular domains. This can also be aggravated by expression of plasminogen by the keratinocytes. [2] Autoantibodies against two other skin basement membrane components, alpha 6 integrin and laminin-5, have also been identified in BP. IgG autoantibodies bind to the basement membrane which activates complement and inflammatory mediators. This activation plays a critical role in attracting inflammatory cells to the basement membrane which release proteases like elastases and collagenases from neutrophils and eosinophils degrading hemidesmosomal proteins causing a split of the dermal and epidermal layers leading to blister formation [3].

The symptoms in almost all patients are severe itching and blister formation. In the early course of the disease, the lesions may present itself with distinct clinical presentations[1]. Initially some patients may not have blisters but instead have rashes similar to hives present all over the body. Later blister formation occurs over this erythematous rash and sometimes over normal skin [4] . The individual bullae are usually fluid filled but may even be hemorrhagic. Pruritis is frequently present. When these rupture, the exposed skin becomes raw and painful. Scars usually do not develop, and the skin can return back to its normal texture, although darker pigmented spots may remain.

Oral and ocular mucosal involvement rarely occurs (Bagan, 2005)[5]. However when it occurs patients complain of occurrence of chronic painful ulcers in the mouth which hamper their daily oral functions. The bullae usually heal with post-inflammatory pigmentary changes and there is no scarring or milia formation [3]. The vesicular form manifests as groups of small tense blisters, often on a erythematous base[1]. This form of BP closely resembles pemphigus vegetans. Rare nodular form termed as pemphigoid nodularis has clinical features where blisters arise on normal-appearing or nodular skin[2]. BP in childhood is rare, with approximately 50 reported cases worldwide, 15 of which were infants aged <1 year. The age of onset in childhood BP varied from 2.5 months to 14 years. This disease followed a benign course and the duration was found to be less than 1 year[3]. In our patients also similar clinical features were seen. Both patients gave a history of vesicle formation which ruptured leaving behind a painful ulcer.

The diagnosis of BP is confirmed by histologic and immunopathologic investigations[1]. Routine blood investigations are taken, and skin biopsies are performed which requires a small needle injection of local anesthesia and then removal of a small piece of skin. Histopathology from lesional skin demonstrates a subepidermal blister. The inflammatory infiltrate has a eosinophilic predominance[4]. Mast cells and basophils are prominent early in the disease course. Biopsy of the intraoral lesion in both patients were done which showed similar histopathological findings [Figure – 2,4].

Direct immunofluorescence studies on perilesional skin within 2 cm of a lesion demonstrate in vivo deposits of IgG antibodies C3 in most cases at the basement membrane zone[5]. This pattern of immunoreactants is not specific to BP and may be seen in cicatricial pemphigoid and epidermolysis bullosa acquisita. BP can be differentiated from these conditions by the salt-split technique in which patient's sample of biopsied skin is incubated in 1 mol/l salt solution prior to performing DIF [2]. This process induces cleavage through the lamina lucida. DIF on salt-split skin reveals IgG on the roof of the blister. IIF studies document IgG circulating autoantibodies in the patient's serum that target the skin basement membrane component [2]. Daneshpazhooch et al compared the antibody titers of blister fluid and serum in patients with subepidermal immunobullous diseases and concluded that IIF sensitivity on blister fluid is almost equal to that of serum. Zhou et al. concluded that blister fluid can be used as an alternative to serum for IIF in subepidermal immunobullous diseases [4].

Immunoblotting or Western blotting demonstrates reactivity of IgG in the sera of BP patients. Immunoprecipitation has also been suggested as a diagnostic tool by some authors. ELISA analyzes the BP antigen-specific IgG autoantibodies in the patients' sera[5] . In several reports, ELISA has been demonstrated to be highly sensitive and specific. Immunohistochemistry on formalin-fixed skin sections in BP has been used to examine C3 deposition along the epidermal basement membrane zone. Pfaltz et al and Chandler et al. proved in two different studies the linear deposition of C3 on the basement membrane .In India, histopathology and immunofluorescence (DIF and IIF) studies are routinely used for the diagnosis of BP. The other tests have not yet been used.

The treatment will depend on the extend of skin involvement. If only a small area is affected, topical application to the skin is sufficient. If a large area is involved, then oral steroids, and other supporting medicines are necessary [1]. Oral steroids help the skin but can have a number of adverse effects. The goal of therapy is to decrease blister formation, promote healing of blisters and erosions, and achieve the minimal dose necessary to control the disease process [4]. Therapy must be individualized for each patient, keeping in mind the pre-existing conditions and other patient-specific factors.

Localized BP often can be treated successfully with topical steroids alone. More extensive disease, which is often more difficult to control, is usually treated with systemic anti-inflammatory and immunosuppressive agents along with topical agents also[3]. Studies have shown that oral prednisone doses range from 0.3 to 1.25 mg/kg body weight/day, which usually controls disease within 1–2 weeks. When the lesions subside the dose is then tapered progressively. Longer the doses higher were the side effects.

Pulsed corticosteroids including methylprednisolone (0.5–1 g i.v. over 2 hours daily for 5 days), dexamethasone (100 mg in 500 ml 5% dextrose i.v. over 2–3 hours for 3 consecutive days) and triamcetonolone acetonide 5-10mg/ml are also used [4]. In India, dexamethasone is the preferred steroid for pulse therapy. It is either administered alone (DP) or combined with cyclophosphamide (DCP) [2].

Several studies have suggested the use of concomitant immunosuppressive agents to achieve a corticosteroid-sparing effect [5]. The most frequently used agent is azathioprine (0.5–2.5 mg/kg body weight/day). Other studies have reported successful use of cyclophosphamide, methotrexate, cyclosporine A, combination tetracycline/minocycline along with nicotinamide and, more recently, mycophenolate mofetil (MMF) have been tried.

Some authors concluded that methotrexate was the most effective treatment with only few adverse effects and patients with moderate to severe disease had a better life span[4]. The overall response rate to dapsone, when given either alone or in combination with corticosteroids or immunosuppressive agents, is about 81% in BP. [3] After prescribing a combination of 500 mg of nicotinamide 3 times daily and 500 mg of tetracycline 4 times daily most patients had remission of the disease & remained disease free during a 10 month follow-up period than with prednisone therapy used alone.

For those not responding to conventional therapy and for those who are at risk of developing potentially fatal side effects from use of the immunosuppressive drugs IVIg appears to be effective especially if started early[5]. A dose of 1–2 g/kg is recommended and it usually delivered at a 5-day cycle of 0.4 g/ kg/day. The initial frequency is generally 1 cycle every 3–4 weeks. High dose IVIg is tapered maintaining the same dose but increasing the time interval between infusions.

Clobetasol was also found to be effective in controlling the disease and mortality rates were also found to be less [3]. Topical and systemic corticosteroids were given in our patients. There was regression of the lesion when both patients were reviewed after one month. The most frequently used treatment modality in India is still steroids either in the oral form or by pulse therapy. Non-steroidal immunosuppressive drugs are added as adjuvants to increase the efficacy and to have a steroid sparing effect.

A few studies suggested that there is no relationship between BP malignancy [2]. However, there have been contradictory findings from other countries, especially in Asia. Ogawa et al. reported in a study that in Japan population, there was higher incidence of malignancy among BP patients [3]. But there are also reports suggesting the absence of any clinical or immunological signs that can be used to predict the development of a neoplasm.

Bernard et al found that there was relapse of the lesions in the first year after cessation of therapy and concluded that a positive DIF finding is a good indicator for monitoring the further relapse of BP [2]. Treatments are undertaken to make the patient symptom free but it can be life- threatening if left untreated.

#### **IV. Conclusion**

BP is therefore a self-limiting disease, which may last from several months to many years if left untreated. Almost one-half of the treated patients attain remission within 2.5–6 years and in a few individuals the disease may continue for 10 years or more

Since these diseases have a high morbidity and mortality, it is extremely challenging to achieve a definitive diagnosis and refer the patient for further medical care. Blistering diseases are challenging to diagnose and require management by a multispecialty team consisting of the dentist, primary care physician, dermatologist, and ophthalmologist.

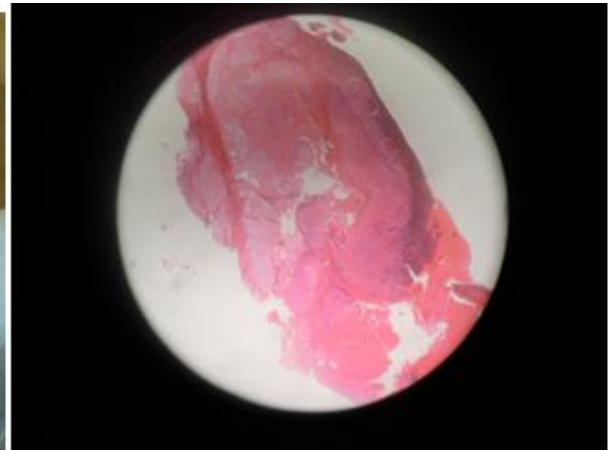
So dentists play a key role in recognizing the early oral manifestations of autoimmune blistering disorders and contribute to timely diagnosis and therapeutic intervention and improve the overall prognosis of the disease and aid in the quality of life.

**References**

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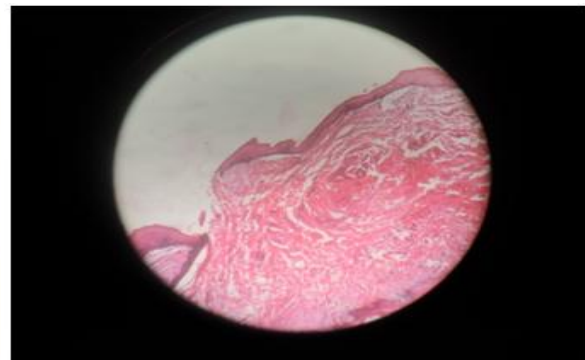
**Figure – 1** A vesicle in relation to 32



**Figure -2** Histopathological report of case 1



**Figure -3** Desquamation of gingiva



**Figure-4** Histopathological report of case 2