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Current dental approaches in autoimmune bullous diseases

Otoimmün bülloz hastalıklarda güncel diş hekimliği yaklaşımları

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Abstract

The first clinical findings of pemphigus vulgaris, paraneoplastic pemphigus and mucous membrane pemphigoid, which are autoimmune bullous diseases, are usually seen in the oral cavity. Questioning the initial lesions by the dentist is very important for the early diagnosis of these diseases. Early diagnosis of lesions in the oral region reduces mortality by providing early treatment. Poor oral hygiene due to lesions also increases the bacterial load in the oral cavity. The prognosis of the disease can be improved by controlling the progression of infections with current periodontal approaches.

Key words: *pemphigus, mucous membrane pemphigoid, paraneoplastic pemphigus, oral health*

Öz

Otoimmün bulloz hastalıklardan olan Pemfigus vulgaris, paraneoplastik pemfigus ve mukoz membran pemfigoidinin ilk klinik bulguları sıklıkla oral kavitede görülmektedir. Diş hekimi tarafından başlangıç lezyonlarının sorgulanması bu hastalıkların erken tanısı için çok önemlidir. Oral bölgedeki lezyonların erken teşhisi, erken tedavi imkanını sağlayarak mortaliteyi düşürür. Lezyonlar sebebiyle bozulan ağız hijyeni oral kavitedeki bakteriyel yükü de arttırmaktadır. Güncel periodontal yaklaşımlarla enfeksiyonların ilerlemesi kontrol altına alınarak, hastalığın prognozu iyileştirilebilir.

Anahtar kelimeler: *pemfigus, mukoz membran pemfigoid, paraneoplastik pemfigus, ağız sağlığı*

Introduction

Desquamative gingivitis (DG) is a clinical term that describes desquamation, erosions, ulcers, vesicles, and bullae in the free and attached gingiva.[1] It is very important to have adequate knowledge about DG-related diseases, because the first manifestation of diseases and the only place of involvement may be the oral cavity.[2] Pemphigus vulgaris (PV), paraneoplastic pemphigus (PNP), mucous membrane pemphigoid (MMP) are the most common autoimmune bullous diseases in the oral region among the conditions that give DG findings.[3] Oral lesions may be the first sign of the disease in many patients, and the disease can be diagnosed early due to examinations made

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in this region. In this way, these diseases with high mortality can be treated more effectively by starting treatment early. Making the first diagnosis of the most common autoimmune bullous diseases in the oral regions in dentistry and then managing oral lesions in coordination with dermatology will enable better results in these persistent lesions. Pemphigus is an autoimmune bullous disease with a potentially life-threatening chronic course, characterized by intradermal vesicles affecting the skin and mucous membranes.[4,5] Autoantibodies cause adhesion loss or acantholysis by targeting the intercellular adhesion molecules of keratinocytes. Among the five main categories of pemphigus (pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, drug-induced pemphigus and IgA pemphigus), only pemphigus vulgaris and paraneoplastic pemphigus (PNP) typically have oral involvement.[6] Pemphigus is a rare disease, and it is seen in the range of 0.5 to 32.0 per 1.000.000 person in different regions and ethnic groups.[7] In a study covering multicenter clinics in Turkey, 220 pemphigus patients were obtained in a year. According to the results of this study, the annual incidence in Turkey is found as 4.7 per million.[8] The incidence of pemphigus in men and women is equal. Although it is more common in individuals between the ages of 50 and 60, pemphigus can also be observed in children and advanced ages.[9]

Pemphigus vulgaris

The most common clinical type of pemphigus is pemphigus vulgaris (PV). This form constitutes approximately 80% of all pemphigus patients.[10] It is more common in South Asian and Jewish races.[11] PV is considered a disease in middle-aged individuals, with the highest incidence between the fourth and sixth decades of life.[12] Although studies show no gender difference in the disease occurrence,[13] it has been reported that it is more common in women.[14] Although very rarely, the disease has been diagnosed in children and adolescents.[15] PV is a life-threatening, chronic disease with high mortality and requires definitive treatment.[11,16] While the mortality of PV was 90% in the absence of treatment, this rate decreased to 10% with effective treatment protocols.[17] In people with genetic predisposition, the use of drugs such as ACE inhibitors or rifampicin, stress, physical agents, diet, cancer, some viruses (especially herpes simplex virus "HSV"), and increased estrogen level are effective in the emergence and exacerbation of the disease.[18,19] In the pathogenesis of this disease, IgG autoantibodies developed against desmoglein 1 (Dsg1) and/or desmoglein 3 (Dsg3), desmosomal adhesion proteins in epidermal keratinocytes, cause the development of intraepithelial bullae.[5]

The concentration of Dsg1 and Dsg3 autoantibodies in the serum determines the severity of the disease. Autoantibodies are formed due to the more intense Dsg3 proteins in the oral mucosal epithelium, including oral lesions.[20]

Diagnosis

Histopathological examination reveals these regions' intraepithelial separations in the basal layer and acantholytic cells (Tzanck cells). The biopsy specimen should be taken from the margin of the bulla or early stage lesion, including the epithelium. In direct immunofluorescence examination, the biopsy sample is taken from the clinically normal perilesional mucosa. In this method, IgG and/or C3 accumulation is observed in the intercellular spaces of the stratified squamous epithelium in the mucosa.[21-23]

Oral Manifestations of PV

The first and early sign of this disease is intraoral lesions seen at a rate of 60%.[16] These lesions are in the form of permanent erosions of the buccal and gingiva that are painful and make it difficult to eat.[23] Oral lesions can be observed clinically, ranging from very superficial ulcers to small vesicles or bullae. The bullae rupture rapidly and turn into painful erosive sores that produce a burning sensation.[14] The size of the ulcers is highly variable. By applying light pressure to the epithelium of these patients, it can be noticed that the formation of bubbles and separation can occur in a large area of the surface. This finding is called the Nikolsky sign.[12] Chronic and ulcerated areas with ir-

regular borders at the site of rapidly ruptured vesicles and bullae are most common in the soft palate (80%), buccal mucosa (40%), ventrum of the tongue (20%) and lips (10%).[11,24] Lesions are usually superficial and are recognized by pain caused by bursting vesicles.[25] They last for a long time due to their slow healing tendency. The patient may experience severe pain, hypersensitivity, dysfunction, increased salivation, and halitosis.[26] While these painful lesions may cause weight loss by making food intake difficult, the process may become more complex when bleeding and swallowing difficulties occur.[27,28] Although gingival lesions of PV (2%) are rare, they can have different clinical manifestations, ranging from isolated small vesicles and their rupture to erosive areas to lesions covered with diffuse white-green pseudomembrane.[11,25,29] Detection of bullous lesions in the free gingiva is not easy.[16] While erosions recur in the early stages of PV, it is seen as severe erosive gingivitis in the later stages.[30] In cases where only the gingiva is affected, clinically as in PV, the initial lesions should be differentiated from diseases such as pemphigoid, psoriasis, lichen planus, chronic ulcerative stomatitis, epidermolysis bullosa, linear Ig A disease, systemic lupus erythematosus, showing the picture of "desquamative gingivitis".[16]

Paraneoplastic Pemphigus

Paraneoplastic Pemphigus (PNP) was first reported by Anhalt et al. It is a rare autoimmune bullous disease characterized by painful mucosal erosions and polymorphic skin lesions with a high mortality rate.[31] They are lesions that occur in the presence of neoplasm and are mostly seen at 60 years and above.[32] PNP is a dermatosis most commonly secondary to diseases such as Non-Hodgkin lymphoma (42%), chronic lymphocytic leukemia (29%), Castleman disease (10%), thymoma (6%), sarcoma (6%), and Waldenstrom's macroglobulinemia (6%). The disease is more common in males.[25,27,33]

Five criteria are valid for defining PNP; [31,34]

1-Painful mucosal erosions and polymorphic skin rashes,

2-Histopathological findings include intraepidermal acantholysis, dyskeratosis, and basal layer vacuolar changes.

3- IgG and complement deposition along the epidermal and basement membrane detected by direct immunofluorescence,

4- Detection of serum autoantibodies against many epithelial types,

5- Complex formation of four antigens 250, 230, 210 and 190 kd by immunoprecipitation.

The clinical features of the disease may resemble drug reaction, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrosis, and may mimic these diseases. There is evidence that the majority of cases are still not properly diagnosed.[33]

Diagnosis

Histopathological findings of PNP are polymorphic. Most of the biopsy specimens detected suprabasal acantholysis, similar to pemphigus vulgaris. Necrosis of epidermal keratinocytes and macular degeneration of basal cells, similar to that seen in erythema multiforme, are common.[35] Direct immunoflourescence examination may reveal linear staining of IgG/C3 at the dermal-epidermal junction in addition to intercellular staining of the epithelium.[23,36-37] Indirect immune fluorescence; It is a precise and sensitive test for PNP and also shows high titers of circulating autoantibodies.[25,32]

Oral Manifestations of PNP

The first and most prominent clinical feature of PNP is the development of severe, painful and persistent stomatitis.[33,38] In some cases, only the oropharynx is affected, while skin lesions do not develop at all.[39] Painful mucous membrane erosions are the first diagnostic sign of the disease, and these lesions are present in all patients with PNP.[25,32] Painful bullae or erosions are most common on the lips, tongue, gingiva and buccal mucosa. It is especially seen on the lateral part of the tongue and on the vermillion line of the lips. It has been reported that ulcerative and erosive areas in the tongue cause very severe pain in patients.[33,40] Lesions

in the oral mucosa can also be located in the uvula, tonsil, oropharynx, and nasopharynx.[41]

Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a chronic, scarring, inflammatory and autoimmune disease primarily characterized by subepithelial vesicles and bullae in the mucous membranes.[42,43] Patients with mild and moderate MMP usually present with lesions confined to the oral mucosa, while patients with severe MMP usually also have additional sites such as the ocular, nasopharynx, laryngeal, esophageal, genital mucosa, or skin.[44] MMP is also called desquamative gingivitis, oral pemphigoid, oral mucous membrane pemphigoid, cicatricial pemphigoid, ocular cicatricial pemphigoid, ocular pemphigoid, benign mucous membrane pemphigoid.[45,46] Its prevalence is 5-7.5 cases per 10,000 adults.[42] MMP often occurs in the 5th and 6th decades.[11,47] Women are more prone to the disease and the female/male ratio is 2/1.[48] This disease rarely occurs in children.[49]

MMP can sometimes be associated with other autoimmune diseases, including pemphigus. Some cases of MMP are associated with B-cell lymphoproliferative disease.[11] It has also been reported that the effects of HIV on the immune system cause the progression of the autoimmune process. In this case, it is influential in developing autoimmune bullous diseases such as MMP.[50] In all locations of the disease, there is atrophy of the epithelium followed by detachment from the connective tissue at the level of the epithelial basement membrane.[43]

It is known that any one or combinations of IgG, IgA, IgM, or C3 autoantibodies against epithelial basement membrane components are effective in the pathogenesis of MMP.[45,51]

Diagnosis

The positivity of the Nikolsky phenomenon in the diagnosis of MMP is not specific. For histopathological study, biopsy should be taken from the vesicle area or perilesional tissue, not from the erosive site. In direct immunofluorescence, a flat, continuous band of IgG and/or C3 and sometimes IgA is observed across the basement membrane.[54] In more than 50% of patients with MMP, anti basement membrane IgG antibodies are detected on the indirect immunofluorescence study, attached to the epidermal part of the mucosa. Vesicle matching with Type 4 collagen is a valuable technique for diagnosing MMP in terms of locating the separation in the basement membrane. Typically, vesicles are located in the lamina lucida in MMP.[55]

Oral Manifestations of MMP

MMP with oral involvement generally affects the Caucasus more frequently between the ages of 54-76.[56,57] In 85% of patients with MMP, the initial site of the lesions and the most frequently affected area is the oral mucosa.[58] However, bullae and ulcers can be seen all over the oral cavity, especially the gingiva (80%), buccal mucosa (58%), palatal (26%), alveolar region (16%), tongue (15%) and lower lip (7%) are affected.[59,60]

Regarding the clinical findings of MMP, it is stated that up to 95% of the cases may have desquamative gingivitis.[59,61] Desquamative gingivitis ranges from localized gingival erythema to generalized inflammation with blisters or ulceration. While the labial gingiva is always affected, the lingual and palatal gingiva are less frequently affected. Lesions in the oral region may appear as surrounding erythematous patches, blisters, and erosions. In the healing phase, white reticular fibrosis mimicking lichen planus may be observed.[62] The predominant symptoms include discomfort, burning, gingival bleeding, mucosal peeling, and difficulty in eating.[57] Inadequate oral hygiene leads to gingival bleeding, marginal gingivitis associated with plaque, and chronic periodontitis occurs.[56]

Treatment Approaches to Autoimmune Bullous Diseases in Dentistry

Today, the first symptoms in many diseases appear with intraoral findings. While the symptoms are limited to the oral tissues, early diagnosis of the dentist is very important in terms of determining the prognosis of the disease. Thus, diseases can be brought under control in a shorter time with the use of lower doses of

drugs.[63] Complications that may occur with high-dose, long-term use of corticosteroids are also prevented. In addition, the systemic corticosteroid dose used can be reduced with topical steroids. However, the risk of topical steroids causing opportunistic candida infections in the mouth should not be forgotten.[64] One of the critical points in these disease groups is that immunosuppressive drugs change the host response and this causes oral health to deteriorate.[65] In this chronic process characterized by bullae and ulcerations, patients may experience severe pain, burning, bleeding, tenderness, difficulties in chewing, swallowing problems, and malnutrition. Sustainability of oral hygiene is very difficult, especially during exacerbations of the disease. Plaque accumulation in this process is an essential irritating factor that increases the bacterial load in the mouth. This situation increases the production of systemic autoantibodies and develops an excessive immune response.[27] Therefore, the lesions of the oral region become more severe, and the healing rate slows down.

Continuation of palliative treatment of oral lesions is the responsibility of dentists. Periodontal approach is very important in controlling the lesions in the oral region, and healing can be accelerated by treating inflammation due to local factors in the periodontium. Non-surgical periodontal approach and optimal oral hygiene, especially in cases with gingival involvement, are essential to control existing lesions and prevent the formation of new lesions.[66]

Thorat et al., evaluated the periodontal status of patients with PV and healthy individuals in their study. As a result of the study, they found that plaque index, pocket depth, and clinical attachment loss were higher in the group of patients with PV. It has been stated that continuously developing mouth lesions increase plaque accumulation and thus exacerbate periodontal disease.[67] A systematic review comparing patients with MMP and healthy individuals stated that the incidence of desquamative gingivitis is increased in patients with periodontitis.[56]

In a study conducted in patients with MMP, it was shown that non-surgical periodontal treatment and oral hygiene practices increased gingival health and significantly reduced gingival pain.[68]

Another study stated that patients diagnosed with MMP have higher gingival and periodontal inflammation levels compared to the healthy group. This result is explained by the differences in oral hygiene levels between the two groups.[69] It should not be forgotten that the first and most prominent clinical symptom in patients with PNP is painful stomatitis. Especially since the mortality rate is very high, initiation of corticosteroid therapy is essential in the early diagnosis of this disease.[70]

Daily care of erosive wounds should be done and topical drugs that accelerate wound healing should be used. Making arrangements in prosthetic materials is recommended to minimize the damage to the environment.[27]

Non-surgical periodontal treatment including scaling and root planing and effective plaque control, reduce gingival problems, thus becoming a complementary treatment to the use of corticosteroids.[68,71]

Maintaining oral hygiene is very important in the treatment of desquamative gingivitis. Soft or extra-soft bristle toothbrush and floss should be used regularly. An initial concentration of 0.2%, followed by 0.12% chlorhexidine oral rinse for 1 to 4 weeks, is recommended.[1]

Current Practices and New Methods in Autoimmune Bullous Diseases

Along with technological applications in dentistry, new palliative approaches are being developed to reduce the side effects of topical or intralesional corticosteroid applications in treating persistent lesions in the oral mucosa. Especially Low Level Laser Therapy (LLLT) accelerate wound healing when applied to oral tissues with the effect of biostimulation.[72] Laser helps to stimulate the regenerative abilities of cells in different intercellular biological reactions without any side effects.[72,74] It can accelerate epithelization by increasing keratinocyte proliferation and motility.[75]

In addition to its regenerative effect on mucosal surfaces, LLLT also shows an important immunomodulatory effect.[76] Tumor necrosis factor-alpha (TNF-α) is thought to play an essential role in the pathogenesis of MMP.[77] It has been shown that LLLT reduces the level of TNF-α depending on the dose applied.[78] Cafaro et al., showed that LLLT applied to oral mucosal surfaces has a rapid pain relief effect in patients with MMP.[79]

Completely autogenous Platelet-rich fibrin (PRF) accelerates wound healing thanks to its many growth factors and leukocytes.[80] In a study on oral ulcers in patients with blistring skin, rapid pain relief and accelerated clinical results of ulcer healing were demonstrated by PRF compared to corticosteroids.[81]

Injectable PRF (i-PRF) is a current biomaterial used in medicine and dentistry.[82] In a study comparing the efficacy of i-PRF and corticosteroids in patients with erosive Oral Lichen Planus (EOLP), both groups found reduced lesions and pain reduction. It has been shown that i-PRF can be as effective as corticosteroid injection, which is considered the gold standard in the treatment of EOLP lesions.[83] There is no clinical study involving i-PRF application in oral lesions of autoimmune bullous diseases.

Conclusion

Early stage findings of some autoimmune bullous diseases are seen especially in the mouth, and this situation imposes a vital responsibility on the dentist in the differential diagnosis. Patients who apply to the dentist provide early diagnosis of many important diseases, especially oral cancer and autoimmune diseases, by examining the oral mucosal tissues (tongue, floor of the mouth, buccal mucosa, hard and soft palate). With the early diagnosis of these diseases, periodontal treatments that reduce the bacterial load in the mouth and the continuity of oral hygiene significantly affect the prognosis. With periodontal treatments in dentistry, current approaches to lesions, and increasing the oral hygiene level of patients, the side effects of these drugs can be minimized by reducing the dose and application times.

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