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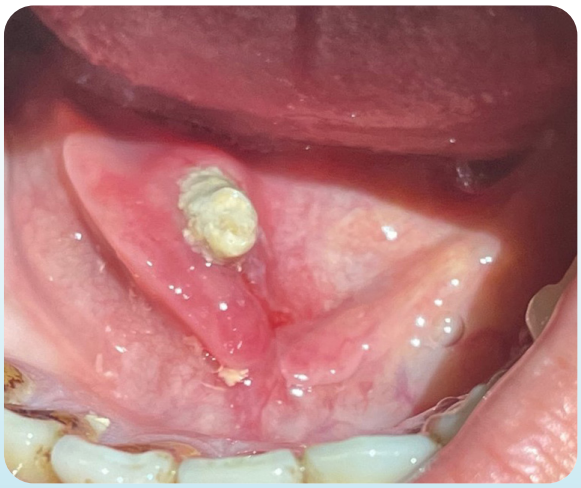

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Contents

Savas Yayli

Murat Cakir

Dear colleagues,

It is pleasure to present the second issue of Mucosa in 2022.

In this issue, we have five scientific articles for you. Uzun Saylan reviewed the current dental approaches to autoimmune bullous diseases in terms of early diagnosis and treatment. In a research article, Demir et al. analyzed the efficacy of olfactory training in patients with persistent anosmia after Covid-19 infection, and they found that olfactory training can be an effective treatment method in these patients.

Varol et al. reported successful diagnosis and treatment strategies of two cases with active tuberculosis and Covid-19 infection. Erdogan reported a case with sialolithiasis that perforated the mouth floor in order to pay attention to differential diagnosis and treatment of submandibular sialolithiasis. Yildirici and Vural reported an interesting case who developed black hairy tongue after Covid-19 infection and successfully treated with topical retinoid.

We want to thank our readers, authors, reviewers, and our publisher for their meritorious contributions. We await your valuable contributions to our forthcoming issues in this new period of Mucosa.

Warm regards,

Murat Cakir
Savas Yayli

Editors-in-Chief

Review

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Current dental approaches in autoimmune bullous diseases

Otoimmün bülloz hastalıklarda güncel diş hekimliği yaklaşımları

Bilge Cansu Uzun Saylan[1]

[1]*Dept. of Periodontology, Dokuz Eylul University Faculty of Dentistry, Izmir,Turkey*

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

Corresponding author: Bilge Cansu Uzun Saylan, Dept. of Periodontology, Dokuz Eylul University Faculty of Dentistry, Izmir, Turkey, Phone: +90 232 412 88 04, E-mail:dtbcuzun@gmail.com
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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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Management of post-COVID olfactory disorder: is olfactory training effective on recovery of olfactory function?

COVID sonrası koku alma bozukluğunun yönetimi: Koku alma eğitimi koku alma fonksiyonunun iyileşmesi üzerinde etkili mi?

Songul Demir[1], Bilal Sizer[2], Enes Sirma[3]

[1]Dept. of Otorhinolaryngology, Mardin Training and Research Hospital, Mardin, Turkey, [2]Dept. of Otorhinolaryngology, Istanbul Arel University, Faculty of Medicine, Istanbul, Turkey, [3]Dept. of Otorhinolaryngology, Dicle University Faculty of Medicine, Diyarbakir, Turkey

Abstract

Background The number of patients presenting with sudden onset and persistant anosmia and other olfactory disorders, which is a finding related to coronavirus disease has increased considerably.

Objective In this study, we aimed to evaluate the efficacy of olfactory training in patients with persistent anosmia after Covid-19 infection.

Methods Forty-six patients who applied for a sudden loss of smell after Covid-19 infection and still had olfactory disorders were included in the study. Odor threshold and odor identification tests were performed on the patients before the treatment. As olfactory training, four scent bottles included the following groups: phenyl ethyl alcohol, eucalyptol group, citronellal group and eugenol group were given to patients, and they were instructed to sniff the odors twice a day, for five seconds each, when they woke up in the morning and before they went to sleep and make a daily check that they applied the treatment. Patients who continued the training for 12 weeks were re-evaluated with the odor threshold test and odor identification test.

Results The pre-training mean olfactory threshold score of the patients was 1.65±1.74, and the post-training mean olfactory threshold score was 3.89±2.73. It was observed that the olfactory threshold scores increased significantly after the olfactory training ($P<0.001$). The pre-training mean odor identification score of the patients before olfactory training was 4.09±3.53 and the post-training mean odor identification score was 8.24±4.53. It was observed that odor identification scores increased significantly after olfactory training ($P<0.001$).

Conclusion The results of this study show that olfactory training can be an effective treatment method for olfactory loss after Covid-19.

Key words: *anosmia, odor threshold, olfactory disorder, covid-19, olfactory training*

Corresponding author: Bilal Sizer, Dept. of Otorhinolaryngology, Istanbul Arel University, Faculty of Medicine, Istanbul, Turkey, Phone:+90 505 957 83 35, E-mail: bilalsizer@hotmail.com
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Öz

Arka plan COVID-19 hastalığına bağlı ani başlangıçlı anosmi ve diğer koku alma bozuklukları ile başvuran hasta sayısı oldukça artmıştır.

Amaç Bu çalışmada Covid-19 enfeksiyonu sonrası inatçı anosmisi olan hastalarda koku alma eğitiminin etkinliğini değerlendirmeyi amaçladık.

Yöntem Çalışmaya COVID-19 enfeksiyonu sonrası ani koku kaybı şikayeti ile başvuran ve koku alma bozuklukları devam eden 46 hasta alındı. Tedavi öncesi hastalara koku eşiği ve koku tanımlama testleri yapıldı. Koku eğitimi olarak hastalara fenil etil alkol, okaliptol grubu, sitronelal grubu ve öjenol grubu olmak üzere 4 koku şişesi verilmiş ve hastalara sabah uyandıklarında kokuları günde iki kez 5'er saniye olmak üzere koklamaları söylenmiştir. Hastaların sabah ve yatmadan önce tedaviyi uyguladıkları günlük olarak kontrol edildi. Eğitime 12 hafta devam eden hastalar koku eşiği testi ve koku tanımlama testi ile yeniden değerlendirildi.

Bulgular Hastaların eğitim öncesi ortalama koku eşik puanı 1.65±1.74, eğitim sonrası ortalama koku eşiği puanı 3.89±2.73 idi. Olfaktör eşik puanlarının olfaktör eğitimden sonra anlamlı olarak arttığı görüldü (P<0,001). Olfaktör eğitim öncesi hastaların eğitim öncesi ortalama koku tanıma puanı 4.09±3.53, eğitim sonrası koku tanımlama puanı ortalama 8.24±4.53 idi. Koku eğitiminden sonra koku tanıma puanlarının anlamlı olarak arttığı gözlendi (P<0,001).

Sonuç Bu çalışmanın sonuçları, koklama eğitiminin Covid-19 sonrası koku kaybı için etkili bir tedavi yöntemi olabileceğini göstermektedir.

Anahtar kelimeler: *anosmi, koku eşiği, koku alma bozukluğu, covid-19, koku alma eğitimi*

Introduction

COVID-19 (coronavirus disease-19), reported for the first time in the Wuhan region of China at the end of 2019, led to the occurrence of pneumonia cases of unknown origin and was declared a pandemic by the World Health Organization in March 2020.[1]

The most common symptoms of the disease were malaise, fever and cough, among other common symptoms such as headache, muscle pain and shortness of breath. Symptoms of the upper respiratory system (runny nose, sore throat and nasal congestion, among others) and gastrointestinal system were less common.[2-4] In the later stages of the pandemic, sudden loss of smell and taste was observed in many patients.[5] Loss of smell was considered to be a symptom of Covid-19 that presents faster than fever, cough and shortness of breath.[6,7] With the disease becoming more common, many researchers thought that sudden loss of smell and taste was one of the important symptoms of Covid-19.[8]

Bacterial and viral upper respiratory tract infections (URTI) are known to play a role in the etiology of sudden loss of smell. It is particularly more common after viral URTI, such as rhinovirus, parainfluenza, coronavirus, and Ebstein-Barr virus, among others.[9] The mechanism underlying the loss of smell after viral infections has not been fully elucidated and many theories have been proposed regarding the mechanism of loss of smell associated with Covid-19. Although some researchers suggest that the virus damages the olfactory epithelium in the nose, some researchers argue that the central pathways are affected and loss of smell is a neurological finding.[10,11]

Loss of smell is a condition that significantly affects a person's quality of life. It can affect the individual in many ways, from personal hygiene problems, loss of appetite and body weight, home security problems to loss of professional workforce and it can consequently lead to psychological problems. For this reason, the treatment of loss of smell can impact the social life of the individual as well as increase the quality of life. Many pharmacological or non-pharmacological treatment methods have been tried for loss of smell after post-URTI, idiopathic and sinonasal olfactory loss. Pharmacologically, agents such as systemic and nasal steroids, oral alpha lipoic acid, oral zinc, vitamin A, and gingko biloba are used.[12-14] Another treatment option is olfactory training. This method can be a preferred treatment method for those who experience loss of smell after Covid-19, owing to its

non-pharmacological and non-invasive nature, low cost, and ease of application.[15-17] The present study aimed to evaluate the efficacy of olfactory training in patients with persistent loss of smell after Covid-19.

Methods

We included 46 patients (25 women, 21 men) who applied to Mardin Public Hospital between April 2021 and June 2021 for sudden loss of smell after Covid-19 infection and still had olfactory disorders. This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval for this prospective study was obtained from Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (No: 270/22-04-2021). The patients included in the study were those who stated that they had a normal sense of smell before Covid-19 infection, who developed sudden loss of smell in the last 1 year, and who were confirmed to have Covid-19 based on polymerase chain reaction (PCR) test performed during the development of loss of smell. Routine anamnesis was taken from the patients, and otolaryngological examination including nasal endoscopy was performed. Those who presented with sudden loss of smell and not confirmed to have had COVID-19 based on the PCR test during the time period loss of smell developed, those with loss of smell for more than 1 year, people with acute URTI, patients with a pathology creating a physiological barrier such as nasal polyposis, pregnant women, and patients aged<18 years were excluded from the study. All patients were informed about other currently recommended treatment options and olfactory training. Participants who selected olfactory training as a treatment option and did not receive any other pharmacological treatment were included in the study. The time between confirmation of Covid-19 by PCR and examination and initiation of treatment ranged from 1 to 6 months. Informed consent was obtained from the subjects who agreed to participate in the study.

Test Procedure

Odor threshold and odor identification tests were performed on the patients before starting the treatment. For the threshold test, 4% n-butanol diluted in geometric series was used. For this purpose, 4% n-butanol was placed in 16, 100 ml bottles with a length of 10 cm and a diameter of 3 cm. The first bottle contained the highest concentration and dilution was made with distilled water at a ratio of 1:2. Starting with the highest concentration, the subjects were asked whether they could smell anything in the bottles. The last threshold where the subjects were able to smell something in three consecutive bottles was noted. A 20-second break was provided between each bottle.

Aromatic oils taken from herbalists were used for the odor identification test (Karden, Karden Agricultural products, Ankara, Turkey). The scents consisted of 16 scents that were previously used as an identification test in our region. The scents were presented with dark colored bottles numbered 1-16 with a length of 5 cm and a diameter of 2 cm. The scents used were as follows: cinnamon, apple, rose, lemon, thyme, garlic, clove, cumin, coffee, black pepper, lavender, orange, banana, mint, fish, and menthol (table 1). The bottles were brought within 2 cm to the nose and the participants sniffed for 3 seconds and were then asked to define the scent from the four options presented (from a list containing three distracters and the correct scent). There was a 20-second break between the presentations, and a break was given when the patients were tired. The correct identification score (0-16) of the subject was recorded according to the result of the test. This two-stage test, in which odor threshold and identification are evaluated, is a modified test like the Sniffin's stick test, which has been used in our region before.[18,19]

As olfactory training, four scent bottles (scents placed in 5 ml black glass bottles) prepared as standard by the researcher were given to the patients. These scents included the following groups: phenyl ethyl alcohol

Table 1. Comparison of olfactory threshold scores and identification scores of patients before and after olfactory training

Groups	n	Median	Mean±SD	Z	*P*
1. Pre-TOTS	46	1.00	1.65±1.74		
2. Post-TOTS	46	3.00	3.89±2.73	5.483	<0.001
1. Pre-TIS	46	4.50	4.09±3.53	5.589	<0.001
2. Post-TIS	46	9.00	8.24±4.53		

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistics significance value

(rose), eucalyptol group (eucalyptus), citronellal group (lemon), and eugenol group (clove). These scents were not randomly selected but represented the main odor groups defined by Henning in the odor prism.[20] The patients were instructed to sniff the bottles given for therapy twice a day, for fiveseconds each, when they woke up in the morning and before they went to sleep and make a daily check that they applied the treatment and evaluate their sniffing status between a range of 1 to 10. The patients were interviewed by the researcher every four weeks, their questions about the treatment were answered, and the olfactory training bottles were renewed. Patients who continued the training for 12 weeks were re-evaluated at the end of the 12th week with the odor threshold test and odor identification test. Participants whose findings were evaluated at the end of the study were those who continued the 12-week training and stated that they applied the procedure regularly.

Statistical Analysis

IBM SPSS 21.0 for windows statistical software package was used for the statistical analysis of the research data. Quantitative variables were presented as mean±standard deviation (SD), and categorical variables were presented as number and percentage (%). The data was checked for conformity to normal distribution. Wilcoxon Test was used to compare pre- and post-therapy data for non-normally distributed variables. Independent t-test was used to compare two independent groups with normal distribution. All hypotheses were two tailed, and $P \leq 0.05$ indicated statistical significance.

Results

Of the 46 patients included in the study, 25 (54.3%) were women, 21 (45.7%) were men. The mean age was 29.80±10.18 years in women and 28.29±8.56 years in men. There was no significant difference between the patients in terms of age and gender (P=0.592).

The pre-training mean olfactory threshold score (pre-TOTS) of the patients was 1.65±1.74, and the post-training mean olfactory threshold score (post-TOTS) was 3.89±2.73. It was observed that the olfactory threshold scores increased significantly after the olfactory training (P<0.001) (Table 1).

The pre-training mean odor identification score (pre-TIS) of the patients before scent therapy was 4.09±3.53 and post-training mean odor identification score (post-TIS) after scent therapy was 8.24±4.53. It was observed that odor identification scores increased significantly after olfactory training (P<0.001) (Table 1).

The patients were divided into three groups in terms of age. Patients aged <20, 20-30, and >30 years were categorized into the 1st, 2nd, and 3rd groups, respectively. Intra- and intergroup evaluations revealed that the difference in the pre-training and post-training evaluation scores was statistically significant in terms of both the olfactory threshold and the odor identification score (Table 2, 3).

Patients were divided into three groups in terms of the duration of olfactory loss. Patients with loss of smell for <2, 2-4, and >4 months were classified into the 1st, 2nd, and 3rd groups, respectively. In terms of duration of loss of smell, the difference between pre- and post-training scores was statistically significant for all three groups (Table 4).

In the evaluation made in terms of sex, the increase in odor scores after olfactory training was statistically significant for both sexes (Table 5).

Table 2. Comparison of olfactory thresholds of patients before and after training with respect to age groups

Groups	n	Pre-TOTS Median	Pre-TOTS Mean±SD	Post-TOTS Median	Post-TOTS Mean±SD	Z	*P*
Group 1: <20 years	13	1.00	1.46±1.33	4.00	4.08±2.56	3.089	0.002
Group 2: 21-30 years	16	1.00	1.63±1.78	3.00	3.56±2.56	3.219	0.001
Group 3: >30 years	17	1.00	1.82±2.04	3.00	4.06±3.13	3.324	0.001

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Table 3. Comparison of odor identification scores of patients before and after training with respect to age groups

Groups	n	Pre-TIS Median	Pre-TIS Mean±SD	Post-TIS Median	Post-TIS Mean±SD	Z	*P*
Group 1: <20 years	13	3.00	3.85±3.24	9.00	8.38±4.21	3.190	0.001
Group 2: 21-30 years	16	4.00	4.00±3.74	8.50	7.50±4.55	3.192	0.001
Group 3: >30 years	17	5.00	4.35±3.74	9.00	8.82±4.91	3.419	0.001

Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Table 4. Comparison of olfactory thresholds and odor identification scores of patients before and after training in terms of duration of olfactory loss

Groups	n	Pre-TOTS Median	Pre-TOTS Mean±SD	Post-TOTS Median	Post-TOTS Mean±SD	Z	*P*
Group 1: <2 months	14	1.00	1.79±1.72	3.50	4.07±2.30	3.208	0.001
Group 2: 2-4 months	16	1.00	1.19±1.52	2.00	3.13±2.63	3.201	0.001
Group 3: >4 months	16	1.50	2.00±1.97	4.50	4.5±3.14	3.203	0.001
	n	**Pre-TIS Median**	**Pre-TIS Mean±SD**	**Post-TIS Median**	**Post-TIS Mean±SD**	**Z**	***P***
Group 1: <2 months	14	5.00	4.93±3.54	9.50	9.00±4.04	3.187	0.001
Group 2: 2-4 months	16	2.00	3.15±3.54	7.00	6.81±4.32	3.302	0.002
Group 3: >4 months	16	4.50	4.31±3.52	10.5	9.00±5.05	3.306	0.001

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Table 5. Comparison of olfactory thresholds and odor identification scores of patients before and after training in terms of gender

Groups	n	Pre-TOTS Median	Pre-TOTS Mean±SD	Post-TOTS Median	Post-TOTS Mean±SD	Z	*P*
Group 1: women	25	1.00	1.56±1.87	3.00	3.68±2.88	3.955	0.001
Group 2: men	21	1.00	1.76±1.61	4.00	4.14±2.59	3.850	0.001
	n	**Pre-TIS Median**	**Pre-TIS Mean±SD**	**Post-TIS Median**	**Post-TIS Mean±SD**	**Z**	***P***
Group 1: women	25	4.00	3.68±3.4	8.00	7.88±4.60	4.122	0.001
Group 2: men	21	5.00	4.57±3.71	10.0	8.67±4.52	3.832	0.001

Pre-TOTS, pre-training olfactory threshold score; Post-TOTS, post-training olfactory threshold score; Pre-TIS, pre-training identification score; Post-TIS, post-training identification score; n, number; SD, standard deviation; Z, Wilcoxon Test test value; *P*, statistical significance value

Discussion

Based on the results of this study, it was our understanding that olfactory training can be effective in treating loss of smell due to Covid-19. In the present study, significant increases were observed in both olfactory thresholds and odor identification scores of patients who regularly applied olfactory training. In addition to the olfactory evaluation, most of the patients stated that there was a significant improvement in their quality of life related to olfactory disorder after the therapy.

Although the prevalence of post-infectious loss of smell due to Covid 19 is 85% in the mild form of the disease, it is less common in the more severe forms of the disease (4.5%).[21] Spontaneous remission is observed in 85%-90% of the patients within an average of 3-4 weeks, whereas some patients develop persistent loss of smell and do not show spontaneous remission. Severe, resistant loss of smell due to Covid 19 is seen in 5% of the patients and it is more common in certain risk groups.[22]

Persistent olfactory dysfunction seems likely after the Covid-19 pandemic. As a result, the number of applications to otolaryngologists will increase. Evidence of treatment options for recovery will be crucial when guiding our patients in this regard.

Olfactory training is non-invasive and non-pharmacological, easy to apply and low cost, and it can be applied after the loss of smell due to any etiology; this is the reason why it has recently been frequently recommended as a treatment option after olfactory loss. Hummel et al. administered olfactory training consisting of four scents for 12 weeks to 56 subjects with post-infectious, posttraumatic and idiopathic loss of smell and found a significant improvement in the training group to the control group.[23] Konstantinidis et al. applied classical olfactory training for 16 weeks to 119 subjects with post-infectious and posttraumatic loss of smell and found a significant improvement in both groups compared to the control group (with a higher difference in the post-infectious group).[24] In the present study, we applied classical scent therapy with four scents for 12 weeks and observed a significant improvement in all scores after training.

Geissler et al. and Damm et al. applied olfactory training on 39 subjects for 32 weeks and on 144 subjects for 16 weeks, respectively, and observed significant improvement in the training groups compared with the control group.[25,26] Pekala et al. in their meta-analysis of

10 studies including 639 patients, thought that olfactory training could be an effective treatment for olfactory dysfunction due to various etiologies.[27] Altundag et al. divided 85 subjects with post-infectious loss of smell into 3 groups. They applied classical olfactory training for 36 weeks to one group and modified scent therapy with three changing sets of 12 odors to one group and observed significant improvement in both groups compared with the control group.[28] Although there are many researchers recommending long-term olfactory training (between 12 and 36 weeks), researchers who think that olfactory improvement after training may be temporary (the duration of well-being is around 6 months) especially recommend keeping the therapy period long.[28] Kattar et al. in their meta-analysis which was focused on the efficacy of olfactory training due to post viral olfactory disorders, stated that this treatment provided clinically significant improvement although there is not a standard olfactory training protocol.[29] Our recommendation is to apply olfactory training for a longer period. However, owing to the ongoing struggles with the Covid-19 pandemic, olfactory training in the present study was planned as 12 weeks in order to provide quicker literature support for the treatment options for loss of smell after Covid-19. Altundag et al. stated that changing the scents used in training at periodic intervals prevents patients from getting bored with the training. The study lasted 36 weeks. Since the present study lasted for 12 weeks, there was no treatment non-compliance.

In the present study, the etiology of the patients who experienced loss of smell was post-infectious olfactory loss after Covid-19. Although the mechanism underlying the development of post-infectious olfactory loss after Covid-19 remains unclear, the theory of neuroepithelial injury through the olfactory cleft, and viral damage after infiltration of the olfactory bulb and central nervous system as a result of viral spread through this route is gaining traction.[30,31] However, there is no definitive data explaining the olfactory dysfunction caused by the virus yet.

In their study, Altundag et al. did not see any improvements in odor thresholds in the patient group that received olfactory training but observed an improvement in odor identification scores.[28] Researchers explained this situation by the fact that the odor threshold is more related to the peripheral olfactory system while odor identification is more related to the upper cognitive pathways. They argued that repetitive olfactory training causes cognitive changes that increase odor perception. Gudziol et al. in their study mentioned that the patient's subjective opinion of an increase in odor perception affected the continuation of the treatment more than the improvement of applied odor tests.[32]

As olfactory training, patients were given four scents, i.e., clove, rose, eucalyptus, and lemon. In the test battery where the odor identification assessment of the subjects was performed, three of these scents were included as descriptive odors. Since the eucalyptus scent is not well known in our region both verbally and as a scent, it was not included in the test battery, but was used in olfactory training. When we look at the odor identification rates before and after the training, the identification rates of the scents used in the the training after the treatment were considerably higher than the others. Therefore, as previously suggested by Altundağ et al., it was thought that extended olfactory training procedures with a larger number of scents can be more beneficial in the treatment of post-infectious loss of smell after Covid-19.[28]

In a latest study, Altundag et al. investigated effect of olfactory training in Covid-19 related parosmia patients, using their modified olfactory training method. They founded both olfactory training and spontan recovery groups were better after a time period, but they also say that olfactory training group had a better improvement than the other group.[33] Post-Covid long-term anosmi-parosmia (over 1 year) can be seen as a long-term effect of Covid.[34] For the proper management of this condition, the literature needs

more participatory studies in which extended scent therapy protocols are applied.

Conclusions

In conclusion, although do not include a control group, results of this study show that olfactory training could be an effective treatment method for olfactory loss after Covid-19. The limitation of these study is the absence of a control group. It is our understanding that this treatment can be further improved with olfactory training including a larger number of scents. Multicenter, double blinded studies with larger samples will provide more precise data to elucidate this issue.

Ethics committee approval: This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval for this prospective study was obtained from Non-Interventional Clinical Research Ethics Committee (No: 270/ 22-04-2021).

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Drafting the manuscript or revising the content: SD, BS, ES

Final approval of the version to be published: SD, BS, ES

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Case report

mucosa

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Prognosis and treatment of COVID-19 infection while receiving treatment for comorbid active tuberculosis: report of two cases

Aktif tüberküloz tedavisi sırasında gelişen COVID-19 enfeksiyonunun tedavi ve prognozu: İki olgu sunumu

Yelda Varol[1], Hilal Ozdemir Demirci[1], Onur Karaman[1], Tulay Akarca[1], Didem Ozbakir[1]

[1]*Tuberculosis Service, University of Health Sciences, Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Izmir, Turkey*

Abstract

Tuberculosis is still a serious public health issue in underdeveloped countries. There is presently little clinical experience with the co-existence of tuberculosis and COVID-19 infection, presented as the severe acute respiratory syndrome coronavirus 2 infection, which was first observed in China in December 2019. This case report details the diagnostic and treatment stages of two patients who had active tuberculosis and COVID-19 infection, as well as the outcomes of their therapies, both of which were effective.

Key words: *tuberculosis, covid-19, co-infection*

Öz

Tüberküloz, az gelişmiş ülkelerde hala ciddi bir halk sağlığı sorunudur. Tüberküloz ve COVID-19 enfeksiyonunun birlikteliği ile ilgili çok az sayıda klinik deneyim mevcuttur. COVID-19 enfeksiyonu ilk kez şiddetli akut solunum sendromu tablosu olarak Çin'de Aralık 2019'da görülmüştür. Bu raporda aktif tüberkülozu ve COVID-19 enfeksiyonu olan iki hastanın tanı ve başarılı olan tedavi aşamaları detaylı olarak sunulmuştur.

Anahtar kelimeler: *tüberküloz, covid-19, koenfeksiyon*

Introduction

More than 1.7 billion individuals (about 25% of the global population) are thought to be infected with *mycobacterium tuberculosis*.[1] Since the first COVID-19 case was detected in late 2019 in Wuhan, China's Hubei region, more than 55 million cases and over 1 million fatalities have been documented globally.[2] The first COVID-19 case was discovered in our nation on March 11th, 2020, and more than 16.500.000 cases and over 100.000 deaths have been documented since then.[3]

Corresponding author: Hilal Ozdemir Demirci, Tuberculosis Service, University of Health Sciences, Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Izmir, Turkey, Phone: +90 232 4333333, Fax: +90 232 4587262, E-mail: hilalozdemr76@gmail.com
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There is presently little information on the prognosis and management of COVID-19 infection in individuals receiving active pulmonary tuberculosis (TB) therapy. As a result, we sought to present two of our cases, who had TB and COVID-19, both of which are infectious illnesses that can be fatal.

Case-1

A 25-year-old male patient was admitted to our hospital complaining of a cough, fever, and fatigue. It was discovered that the patient was involved in a motorbike accident approximately a month ago, which resulted in fractures in his left hand and left shoulder, and that he underwent surgery for the same reason. On respiratory auscultation, rales were heard in the right upper zone. His neurological evaluation also confirmed the existence of flaccid paralysis. Other systematic examinations revealed nothing else out of the ordinary. White blood cell count: 14.200/mm^3, lymphocyte count: 800/mm^3, neutrophil count: 12.500/mm^3, hemoglobin concentration: 11.4 mg/dL, sedimentation rate: 62 mm/hour, and C-reactive protein concentration: 3.19 mg/dL were his laboratory test findings. His liver and renal function tests were in a normal range. During his hospitalization on his postero-anterior chest radiography indicated a heterogeneous density increase in the right upper zone and a fracture in the left clavicle (Fig. 1).

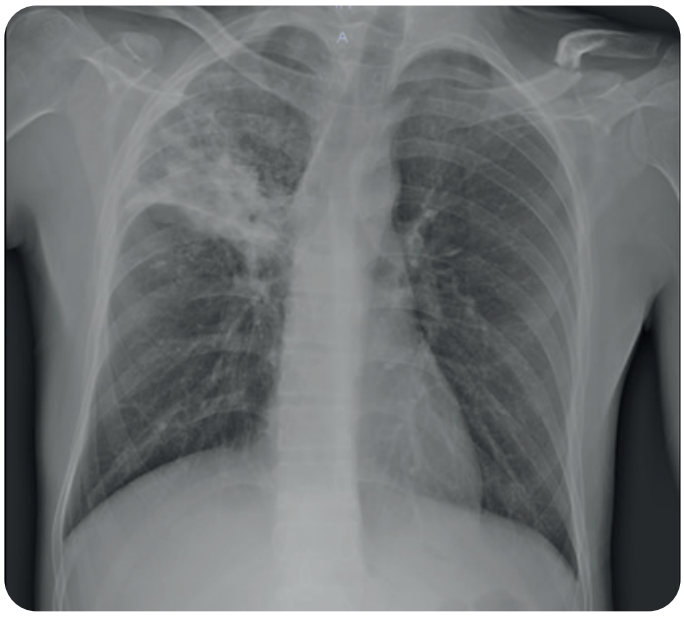

Fig. 1. A heterogeneous density increase in the right upper zone and a fracture in the left clavicle

Thorax CT revealed consolidation with air bronchograms in the right upper lobe, in addition to significant micronodular infiltration regions, and a cavitary lesion with a diameter of about 1.5 cm in the apical section of the right upper lobe (Fig. 2a-c).

Sputum microscopy and a culture antibiogram were done on the patient, who was being evaluated for pulmonary tuberculosis. Direct microscopy revealed no acid-fast bacilli (AFB) in any of the three sputum samples examined. The sputum *M. tuberculosis* polymerase chain reaction (PCR) result was negative [Xpert MTB (*mycobacterium tuberculosis*) /RIF (rifampicin) Ultra test (Real-time PCR)]. Non-specific antibiotic therapy was continued until the patient's sputum *M. tuberculosis* culture test results were available. During antibiotic therapy, the patient's fever was detected at 38.5 °C. *M. tuberculosis complex* was isolated from the patient's sputum in two different cultures. Isoniazid, rifampicin, ethambutol, and streptomycin susceptibility were revealed. Treatments with isoniazid 225 mg, rifampicin 450 mg, pyrazinamide 1000 mg, and ethambutol 1000 mg were initiated. A SARS-CoV-2 RT-PCR nasopharyngeal swab sample was collected from the patient, because fever had returned on the tenth day of antituberculosis medication. In compliance with Ministry of Health recommendations, favipravir therapy was begun for the patient who tested positive for COVID-19. The patient experienced no negative effects as a result of the anti-tuberculosis and favipiravir therapy. The patient's clinical condition improved throughout his 14-day isolation in the COVID program, and his COVID-19 RT-PCR test resulted in a negative result. As a result, the patient's COVID-19 therapy was completed, but his anti-tuberculosis medication is still ongoing.

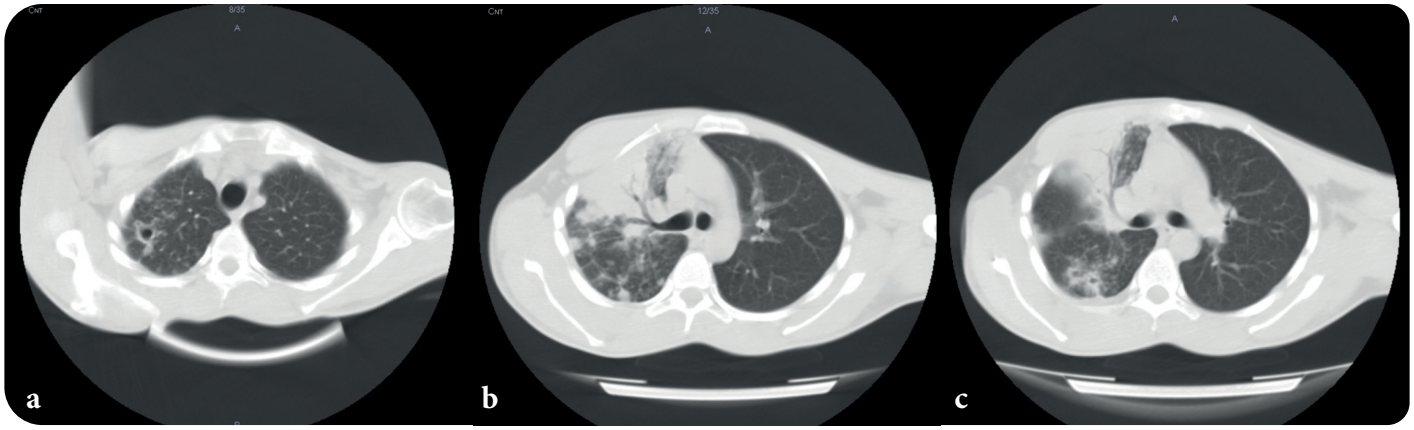

Fig. 2a-c. Consolidation with air bronchograms in the right upper lobe, in addition to significant micronodular infiltration regions, and a cavitary lesion with a diameter of about 1.5 cm in the apical section of the right upper lobe

Case-2

A 64-year-old male patient was referred to our hospital after his liver function test (LFT) revealed that his levels had risen while on anti-tuberculosis therapy. He didn't have any complaints. He was found to have a history of hypertension and to have undergone surgery for malignant melanoma on his left lower extremities about five months earlier. Due to mediastinal lymphadenopathy indicated by F-18 FDG (fluorodeoxyglucose) involvement in his positron emission tomography (PET)-CT scan taken during the surgical follow-up, the patient underwent an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Owing to TB lymphadenitis, the patient was given anti-tuberculosis medication that included isoniazid, rifampicin, pyrazinamide, and ethambutol. His EBUS-TBNA material revealed *M. tuberculosis complex* growth, but his treatment was stopped due to hepatotoxicity.

His chest examination were normal, as were the findings of his other systemic exams. His laboratory test results were as follows: white blood cell count 5.800/mm^3, neutrophil count 2.900/mm^3, hemoglobin concentration 13.2 mg/dL, C-reactive protein concentration 0.43 mg/dL, aspartate aminotransferase (AST) concentration 57 U/L, alanine aminotransferase (ALT) concentration 47 U/L, and total bilirubin concentration 1.58 mg/dL. His renal function tests were also normal. The aortic ball was visible on his postero-anterior chest radiography recorded after admission, but the parenchyma was normal (Fig. 3).

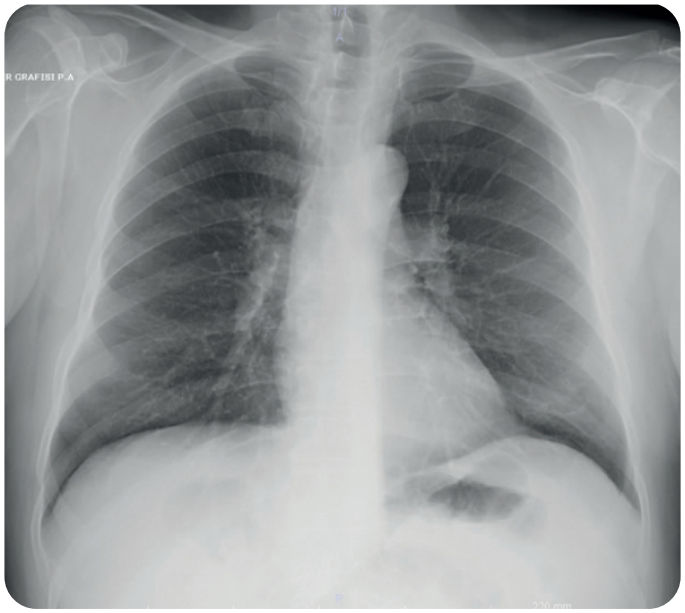

Fig. 3. The aortic ball was visible, the parenchyma was normal

The patient, who was being monitored for hepatotoxicity without treatment, tested positive for COVID-19 based on the results of the RT-PCR (reverse transcription polymerase chain reaction) test, which was done during the regular examination for admission to the TB service. Due to the patient's high LFT values, favipiravir could not be provided, thus preventive enoxaparin sodium therapy was initiated. After 14 days of isolation, the patient's COVID-19 PCR test resulted in a negative result. During the follow-up period, the patient's LFT values declined, so he was given an anti-tuberculosis medication that included ethambutol,

rifampicin, and moxifloxacin. Because he did not develop hepatotoxicity throughout the follow-up period, isoniazid was added to his medication. The patient was discharged, whereas his anti-tuberculosis treatment currently continues.

Discussion

COVID-19 illness, which was proclaimed a pandemic by the World Health Organization (WHO) on March 11th, 2020, displays symptoms comparable to influenza, severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and TB in general, despite distinctions in prognosis and sequelae.[4,5] The majority of COVID-19 individuals experience mild symptoms; nevertheless, it worsens rapidly in people with comorbidities and advanced age.[6,7]

There is very little clinical experience with TB and COVID-19 comorbidity. We described two examples of active TB in which the patients were infected with the COVID-19 virus during their therapy. According to a Chinese study, active or latent tuberculosis infection may enhance susceptibility to COVID-19 and the severity of the condition. According to this study, COVID-19 causes more severe symptoms in people who have both COVID-19 and TB.[8] In each of our patients, the COVID-19 infection was modest. Our first patient had no symptoms other than a high temperature, and our second case had COVID-19 symptom-free.

Tadolini et al. reported a research on 49 individuals with active TB and COVID-19 comorbidity and found that 34 patients had pulmonary tuberculosis and 1 patient had extrapulmonary tuberculosis.[9] The authors of this study provided the clinical features of patients in different age groups who have varied clinics, and despite the fact that the pandemic is still in its early stages, they concluded that additional instances of TB and COVID-19 comorbidity need to be examined.

In conclusion, we would like to report that our two cases, infected with COVID-19 while receiving active TB therapy, were effectively treated for COVID-19 and that their tuberculosis treatment is still ongoing.

Informed consent: The author certifies that they have obtained all appropriate consent forms from the patients.

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Drafting the manuscript or revising the content: YV, HOD, OK, TA, DO

Final approval of the version to be published: YV, HOD, OK, TA, DO

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Case report

mucosa

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Post-COVID-19 presentation of black hairy tongue

COVID-19 enfeksiyonu sonrasında gelişen siyah kıllı dil

Sebnem Yildirici[1], Secil Vural[1]

[1]Dept. of Dermatology and Venereology, Koç University School of Medicine, Istanbul, Turkey

Abstract

Since the COVID-19 pandemic started in 2019, the involvement of the oral mucosa is observed in many patients, the tongue being the most affected area. In the recent literature, there is a wide range of lesions reported such as enanthema, Kawasaki-like disease, oral ulcers, and atrophic glossitis. This paper addresses a black hairy tongue case in a 47-year-old woman presenting after two weeks of COVID-19 infection. The patient was responsive to topical retinoid therapy.

Key words: *Black hairy tongue, COVID-19, SARS-CoV-2, oral lesions, oral conditions*

Öz

2019 yılında COVID-19 pandemisi başladığından beri, en çok etkilenen bölge dil olmak üzere birçok hastada oral mukoza tutulumu gözlenmektedir. Yakın dönem literatürde, enantem, Kawasaki benzeri hastalık, oral ülserler ve atrofik glossit gibi çok çeşitli lezyonlar bildirilmiştir. Bu makale, iki haftalık COVID-19 enfeksiyonundan sonra başvuran 47 yaşındaki bir kadındaki siyah kıllı dil olgusunu ele almaktadır. Hasta topikal retinoid tedavisine yanıt vermiştir.

Anahtar kelimeler: *Siyah kıllı dil, COVID-19, SARS-CoV-2, oral lezyonlar, oral durumlar*

Introduction

After the onset of the COVID-19 pandemic, many patients with oral manifestations have been reported.[1,2] The most common findings are Kawasaki-like syndrome, oral ulcers including aphthous, hemorrhagic, and necrotic ulcers. Dysgeusia is another symptom frequently reported in patients with COVID-19 infection. Rare manifestations include reddish macules, pustular enanthema, loss of dermal papilla and white hairy tongue.[3,4] We have recently encountered a patient who developed a black hairy tongue (BHT) after a COVID-19 infection. The treatment was resistant to topical antiseptics, and systemic and topical antifungal therapy. Lesions resolved two weeks after treatment with tongue brushing daily with topical tretinoin cream.

Corresponding author: Sebnem Yildirici, Department of Dermatology, Koç University School of Medicine , Istanbul, Turkey
Phone: +905332494904, E-mail: syildirici14@ku.edu.tr
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Case report

A 47-year-old female was referred to the dermatology clinic with dysgeusia and discoloration of the tongue for three months (Fig. 1). Her complaints started after she had a COVID-19 infection two weeks ago. Her diagnosis was confirmed with an RT-PCR test. The medical history was insignificant, and the patient was a non-smoker. Physical examination revealed a thickened brown lesion on the dorsum of the tongue accompanied by a yellowish discoloration. Complete blood count was normal, anti-HIV ELISA and VDRL test were negative. She had previously used fluconazole 200 mg orally twice in a week combined nystatin oral suspension and chlorhexidin mouthwash for one month, however the lesion was not resolved after this treatment. Later, she was treated with oral tretinoin cream daily and was advised tongue brushing. Consequently, her lesion disappeared after two weeks.

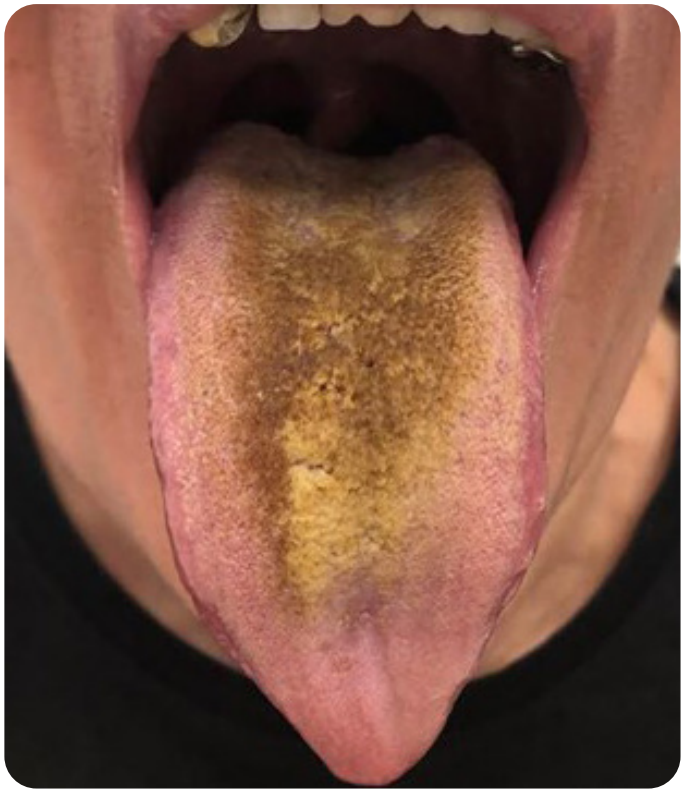

Fig. 1. Thickened brown-yellow discoloration on the dorsum of the tongue

Discussion

BHT is a disease characterized by the papillary appearance of the tongue with black to yellow discoloration, mostly associated with poor oral hygiene, smoking, hyposalivation, infection and medications such as antibiotics and antipsychotics.[5] Interrupted desquamation and consequent hyperkeratosis of papillae of the tongue give a "hairy" character, along with black-brown color caused by modified oral microbiota. It is generally asymptomatic; however, nausea, altered taste sensation and halitosis can accompany it in some cases. For the management, the first-line treatment is to eliminate provoking agents and focus on oral hygiene. Second-line treatment options include antifungals, retinoids, antibiotics, topical urea solution, trichloroacetic acid, salicylic acid, and thymol.[5]

Predisposing factors for the development of the wide range of oral lesions reported in COVID-19 infected patients include hyposalivation, compromised immune system, and medications used in the treatment of COVID-19.[6] Besides, there can be opportunistic infections such as *Candida albicans*, causing ulcers.[7] The proposed mechanism for oral involvement in COVID-19 infections is via angiotensin converting enzyme 2(ACE2) receptors. There are numerous ACE2 receptors in the epithelium of the oral cavity and the SARS-CoV-2 virus binds these receptors, therefore the oral cavity is a significant involvement site causing various lesions during infection.[8] Diminished or altered taste sensation also can be linked to this phenomenon.[8] Additionally, according to Diaz Rodriguez et al, physical stress and immunosuppression are associated with oral involvement severity in COVID-19 infections. Another study by Ganesan et al, found a significant correlation between oral involvement and disease severity.[8]

To our knowledge, there are no cases in the literature reporting the co-occurrence of BHT and COVID-19 infection. This can be due to underdiagnosis of BHT since it is mostly an asymptomatic condition, and it possibly spontaneously resolves after a period following COVID-19 infection. Additionally, oral exami-

nation and even physical examination are not required for every mild course patient considering the high-risk contagiousness of COVID-19 infection. This persistent BHT in a patient developed after COVID-19 infection resolved with a short course application of tretinoin cream and tongue brushing.

Informed consent: The author certifies that she has obtained all appropriate consent forms from the patient.

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Authorship contributions:

Conception and design, or analysis and interpretation of data: SY, SV

Drafting the manuscript or revising the content: SY, SV

Final approval of the version to be published: SY,SV

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Case report

mucosa

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Sialolithiasis perforating the floor of mouth: a case report

Ağız tabanını perfore eden tükürük bezi taşı: Olgu sunumu

Osman Erdoğan[1]

[1]Dept. of Otorhinolaryngology, Sanliurfa Training and Research Hospital, Sanliurfa, Turkey

Abstract

Sialolithiasis is the most common disease of the salivary gland. It is most commonly found in the submandibular gland, but less frequently in the parotid and sublingual glands. The submandibular gland is more prone to sialolithiasis than the parotid gland, because Wharton's canal is wider and longer, it angulates against gravity at the posterior border of the mylohyoid muscle and submandibular gland secretion is more alkaline, mucinous, richer in calcium and phosphate and slower flow rate. In this case report, a patient whose floor of the mouth mucosa was perforated by a sialolith was presented. Although sialoliths are infrequently seen, they cause severe recurrent infections and pain in patients and adversely affect the quality of life. Therefore, the clinician should consider submandibular sialolithiasis in case of foreign body sensation in the floor of the mouth or swelling under the chin associated with a meal.

Key words: *sialolithiasis, submandibular gland, sialolithotomys*

Öz

Sialolithiasis, tükürük bezinin en sık görülen hastalığıdır. En sık submandibular bezde bulunur, ancak daha az sıklıkla parotis ve sublingual bezlerde ortaya çıkar. Submandibular bez parotis bezine göre sialolitiazise daha yatkındır. Çünkü Wharton kanalı daha geniş ve daha uzundur, milohyoid kasın arka sınırında yerçekimine karşı açılanma yapar ve submandibular bez sekresyonu daha alkali, müsinöz, kalsiyum ve fosfattan daha zengin ve daha yavaş akış hızına sahiptir. Bu olgu sunumunda ağız tabanı mukozası bir sialolit tarafından perfore edilmiş bir hasta sunuldu. Sialolitler nadiren görülmekle birlikte tekrarlayan ciddi enfeksiyonlara ve hastalarda ağrıya neden olarak yaşam kalitesini olumsuz etkiler. Bu nedenle klinisyen ağız tabanında yabancı cisim hissi veya çene altında yemekle ilişkili şişlik olması durumunda submandibular tükürük bezi taşını aklına getirmelidir.

Anahtar kelimeler*: sialolithiasis, submandibular bez, sialolitler*

Introduction

Sialolithiasis, the most common salivary gland disease affects 1.2% of the population.[1] Sialolithiasis is mainly seen in the submandibular gland (94%) and less often in the parotid and sublingual glands.[2] The submandibular gland is

Corresponding author: Osman Erdogan, Dept of Otorhinolaryngology, Sanliurfa Training and Research Hospital, Yenice street, 63300, Sanliurfa, Turkey, Phone: +904143171717, Fax: +904143172621, E-mail: osman_erdogan@outlook.com
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more prone to sialolithiasis than the parotid gland, because Wharton's canal is wider and longer, it angulates against gravity at the posterior border of the mylohyoid muscle and submandibular gland secretion is more alkaline, mucinous, richer in calcium and phosphate and slower flow rate.[3,4] Submandibular gland sialoliths tend to be more in the duct (70%), whereas parotid gland sialoliths are usually located in the hilum or intraglandular ducts.[1,2] Depending on the localization and size of the sialolith, surgical methods such as salivary gland excision, intraoral sialolithotomy, or papillotomy have traditionally been used in the treatment. Sialendoscopy, a minimally invasive method, has recently been used for diagnostic and interventional purposes alone or assisted in extracorporeal or intracorporeal lithotriptic procedures.[5]

Case report

A 28-year-old male patient was admitted to the ENT outpatient clinic because of a foreign body he had noticed under his tongue for a week. He had complaints of swelling and pain in the right under-chin area after meals for six months. He received antibiotic treatment for salivary gland infection twice. Physical examination revealed a sialolith perforating the canal at the floor of the mouth where the anterior part of the right Wharton canal is. (Fig. 1) Posterior extension of the sialolith was noticed with intraoral bimanual palpation.

Under local anesthesia, an incision was made over the canal overlying the sialolith in the mucosa of the floor of the mouth and the elongated sialolith into the canal was removed. The extracted sialolith was 25x7 mm in size. (Fig. 2) In order to investigate the obstruction in the distal from the sialolith for the etiology of sialolithiasis, the right Wharton canal caruncula was found and the examination with a lacrimal probe revealed that the distal canal was obstructed. Intravenous catheter stent placement was performed into the perforated localization of the duct to ensure normal salivary flow and prevent the recurrence of sialolithiasis due to canal obstruction.

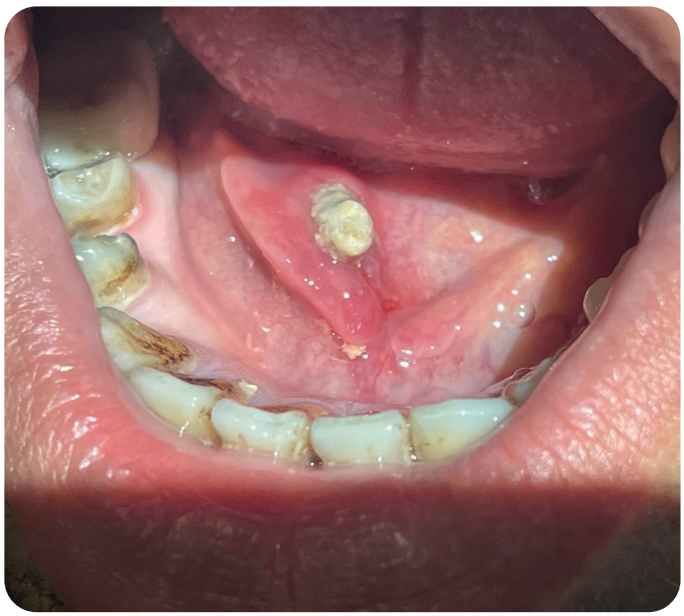

Fig. 1. Sialolith perforating the floor of the mouth on intraoral examination

Fig. 2. Macroscopic view of the extracted sialolith

Discussion

Sialolithiasis is slightly more common in males and usually occurs in the third to fifth decade of life.[6] Although its etiology is not known exactly, it is thought to occur due to the deposition of mineral salts around a nucleus consisting of mucin, bacteria or desquamated epithelium. While the pH value, which falls below 5.5 due to the toxins produced by the bacteria, is increased to 7.2 with tissue healing, crystallization occurs in the salivary ions, especially calcium and phosphate. High alkalinity, slower salivary flow, and increased calcium content facilitate the formation of sialolith.[3,7] The tendency for sialolithiasis to occur most commonly in the submandibular gland is generally due to slower salivary flow and more calcium phosphate-containing salivary secretion. The slowing of salivary flow in Wharton's canal is due to its long course, wide diameter, angulation against gravity posterior to the mylohyoid muscle, and the more mucinous secretion it carries.[4]

Although sialoliths in the canal may show symptoms such as dry mouth and foreign body sensation, they remain asymptomatic until they cause mechanical obstruction in the canal. Since the annual growth rate of the sialolith is about 1-1.5 mm, it can be asymptomatic for a long time.[4] The canal widens in response to the slow growth of the sialolith. As the canal widens, it allows the formation of a sialolith with any dimension greater than 15 mm in size.[3,7] Since the Wharton's canal diameter is 0.5-1.5 mm on average and its narrowest part is the ostium, sialolithiasis can not come out of the canal spontaneously.[8] In the present case, it has been observed that the 25x7 mm in size sialolith perforated the floor of the mouth overlying the anterior part of the Wharton's canal instead of spontaneously exiting the ostium. Recurrent sialadenitis and mechanical compression on the canal wall may cause this perforation.

The main aim of the treatment of sialolithiasis is to maintain the continuity of salivary flow. Treatment options vary depending on the size, number, localization of the sialolith and whether it is in the canal. Treatment options include conservative treatment, intraoral sialolith removal interventional sialendoscopy or sialoadenectomy.[6,7] With conservative treatment, small sialoliths can be spontaneously removed from the canal ostium by applying local heat, sialagogues and gland massage. Antibiotic therapy should be given when signs of infection are present and hydration should be provided in patients whose oral intake is limited due to pain.[8] Sialendoscopy, which provides a minimally invasive, safe and effective diagnosis and treatment option, can be used for sialoliths with a size of 4-5 mm. Larger sialoliths (4-8 mm in size) require sialendoscopy-assisted laser, extracorporeal or intracorporeal lithotripsy. Interventional sialendoscopy is more effective in improving symptoms and removing sialoliths in patients with submandibular gland sialolithiasis than those with parotid gland sialolithiasis.[5,8] Submandibular gland excision is indicated in sialoliths larger than 12 mm located in the gland or the hilum, or unsuccessful intraoral surgery.[7] Sialoliths located in distal Wharton's canal can be removed from the canal ostium by milking along the canal at the floor of the mouth. The ostium can be enlarged using lacrimal probes and dilators for sialoliths that cannot pass through the canal ostium. Sialolithotomy is performed by making an intraoral incision on the canal for proximal sialoliths. For this procedure, local anesthesia is preferred for sialoliths located anterior part of the canal, and general anesthesia for those located posterior part of the canal.[6] In the present case, the sialolith located in the anterior part of Wharton's canal spontaneously perforated the canal. To remove the sialolith, a posterior canal incision from the edge of the perforation was necessary because of the larger size of the sialolith than the perforation. The examination of Wharton's canal with a lacrimal probe revealed a canal obstruction, probably due to infection-related fibrosis. For this reason, the continuity of salivary flow was ensured by placing a stent in the area where the stone was removed.

Informed consent: The author certifies that he has obtained all appropriate consent forms from the patient.

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