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Skin and mucosal lesions in otolaryngological practice

Zmiany skórne i śluzówkowe w praktyce otolaryngologa

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ABSTRACT: Cutaneous and mucosal lesions are seen in many diseases, frequently being the main element of the clinical presentation. It is not uncommon that the patient with mucosal lesions of the upper respiratory tract consults the otolaryngologist first, therefore it is important that those specialists know the mucosal symptoms of dermatological diseases and consider them in the differential diagnosis. In this article diseases with the mucosal lesions of the upper respiratory tract are described, including pemphigus, pemphigoid, lichen planus, and Behçet's disease. Knowledge of the morphology of these mucosal manifestations is essential in the clinical practice of both dermatologists and otolaryngologists, and the diagnostic and therapeutic success may be achieved only with the cooperation of these specialists.

KEYWORDS: otolaryngology, dermatology, skin lesions, mucosal lesions, pemphigus, pemphigoid, Behçet's disease, lichen planus, Stevens - Johnson syndrome, Lyell's syndrome

STRESZCZENIE: Zmiany skórne i śluzówkowe towarzyszą wielu chorobom, często stanowiąc podstawowy element obrazu klinicznego. Niejednokrotnie pacjent ze zmianami w obrębie błon śluzowych górnych dróg oddechowych trafia w pierwszej kolejności do otolaryngologa. Dlatego tak ważna jest znajomość objawów chorób dermatologicznych wśród tych specjalistów i uwzględnianie ich w diagnostyce różnicowej. W niniejszej pracy opisano choroby przebiegające z zajęciem błony śluzowej górnych dróg oddechowych, takie jak: pęcherzyca, pemfigoid, liszaj płaski oraz choroba Behçeta. Znajomość morfologii zmian w tych jednostkach chorobowych jest istotna zarówno w praktyce dermatologicznej, jak i otolaryngologicznej, a sukces diagnostyczny i terapeutyczny może przynieść jedynie ścisła współpraca pomiędzy tymi specjalistami.

SŁOWA KLUCZOWE: otolaryngologia, dermatologia, zmiany skórne, zmiany śluzówkowe, pęcherzyca, pemfigoid, choroba Behçeta, liszaj płaski, zespół Stevensa - Johnsona, zespół Lyella

INTRODUCTION

Skin and mucosal lesions can accompany many diseases, and they often constitute the core of clinical manifestations. It is common for a patient with lesions of the oral, pharyngeal or laryngeal mucosa to be first referred to the otolaryngologist, and therefore it is important to consider various skin disorders in differential diagnosis. In this article, we described conditions involving the mucous membrane of the upper respiratory tract, such as pemphigus, pemphigoid, lichen planus, Behçet's disease, and granulomatosis with polyangiitis.

PEMPHIGUS

Pemphigus is an acquired chronic condition, in which blisters develop on a normal skin and mucosa. The peak incidence is observed between 30 and 60 years of age. [1] The disease affects both males and females equally. The pathogenesis includes autoantibodies directed against desmogleins – cadherins, which extend from the plaque to the extracellular matrix, where desmogleins from adjacent keratocytes join together. The autoantibodies attach to the outer dense plaque impairing the adherence to similar units on other

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cells, reducing the adherence and resulting in acantholysis on microscopic view [2,11].

The initial course is often insidious. Small fragile serous blisters develop on the skin of the torso. The blisters burst and form inflammatory erosions; crust can form centrally while the blisters spread peripherally. New blisters can develop peripherally to older lesions. In 80-90% of all patients, the lesions are located within the oral cavity, and in 60% of cases they are the first sign of pemphigus. [1] In that location, blisters are rarely seen because they promptly rupture resulting in painful erosions. The following are usually involved: the mucosa of the cheeks, soft palate, lips, and less often of other regions, e.g. gums as desquamative gingivitis – presenting as red lines along the teeth accompanied by xerostomia and flaking. The less common locations are nose, pharynx, conjunctiva, urethra, vagina, penis and rectum. With the progression of the disease, the successive regions of the body get involved, especially the intertrigo-susceptible sites, such as armpits, area beneath breasts, groin. Typically, Nikolsky's sign can be observed, i.e. exfoliation of the outermost layer of the epithelium when rubbing initially unaffected skin. The most important diagnostic study is direct immunopathological assessment of skin or mucosa. The immunological testing of serum is necessary. Direct immunofluorescence shows intercellular IgG and C3 deposits, and the indirect immunofluorescence reveals attaching autoantibodies from patient's serum to the intercellular keratocyte junctions. Pathology study is non-obligatory, however, it can be useful in some instances. Biopsy should be taken from the mucosa surrounding the lesion. The first-line treatment is systemic steroid therapy, and in more severe cases immunosuppressive treatment with azathioprine or other agents (cyclophosphamide, methotrexate, mofetil mycophenolate) can be considered. Additional treatment of mucosal pemphigus includes: fluocinolon gel, injection with triamcinolone acetonide, local use of antiseptics and analgesics. The course of pemphigus can be various, and better outcomes are observed in females. Response to treatment should be monitored with direct immunofluorescence, which allows to assess the level of antibodies. Depending on initial severity and treatment, even total remission is possible. [8,11]

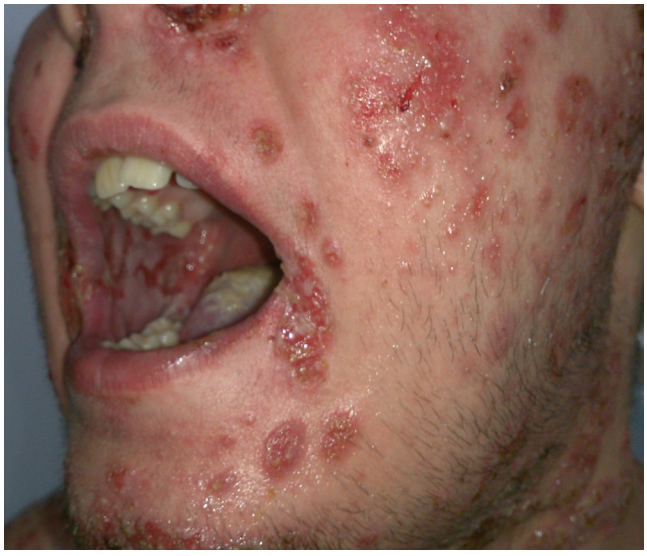

Fig. 1. Pemphigus lesions on oral mucosa and facial skin.

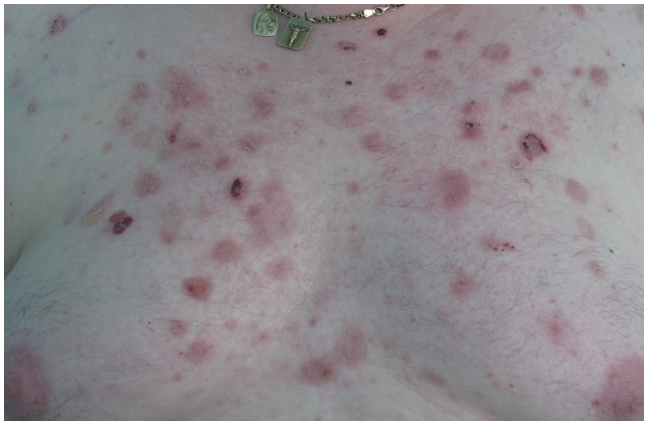

Fig. 2. Pemphigus skin lesions – typical fragile blisters and erosion can be seen.

PARANEOPLASTIC PEMPHIGUS

In the literature, there are reported cases of skin and mucosal lesions in patients with malignant neoplasms, usually blood cancers, which is referred to as paraneoplastic pemphigus (PP). This rare condition is characterized by a sudden onset and usually affects patients in their 50s. On examination, diffuse blisters filled with serosanguinous content are observed within the oral cavity, which may burst leaving erosions covered in crust, making eating difficult. The mucous membrane of other regions can be involved, including nose, pharynx, conjunctiva, anus, anogenital region and alimentary tract. The skin lesions are polymorphous – flat blisters, erosions, erythema and lichenification can be observed. The antibodies are usually directed against various autoantigenes of the epithelium and base membrane, which results in severe clinical course – potentially lethal in the case of pulmonary involvement. The mortality is high in such patients, also due to chemotherapy of concurrent cancer. The diagnosis of PP includes major and minor criteria. The major criteria consist of the following: polymorphous rash of skin and mucosa, coexisting cancer and presence of specific antibodies. Minor criteria include: histologically proven acantholysis, positive result of direct immunofluorescence of intercellular matrix of

the epithelium and base membrane, positive result of indirect immunofluorescence using the rat bladder. For the diagnosis, it is necessary to fulfill three major criteria or two major and two minor criteria. In cancer-induced PP, the prognosis is poor, and mean survival ranges from 2 to 24 months, however, the course of both conditions can be different and no correlation between severity and progression has been observed. [11]

PEMPHIGOID

Pemphigoid is the most common blistering autoimmune disease of the skin, affecting older patients aged over 60, and the incidence increases 30 times at the age of 80 compared to the age of 60. Two target antigens were identified on hemidesmosomes (BPAG1 and BPAG2 proteins). Splicing of the epithelium occurs in the outer layer of the base membrane, just beneath keratocytes of the basal layer, where the proteins are located. The typical clinical presentation includes two types of skin lesions: initially, erythema or erythema with edema (urticaria) predominate, accompanied by severe pruritus, followed by tense blisters filled with serous and/or bloody fluid, which are located on a normal or erythematous skin. Usually, the skin lesions are located on the flexor surface of upper extremities and trunk. In 20-30% of cases, the lesions involve the oral mucosa and include small blisters or painful erosions with well-defined borders. The lesions may be situated on erythema, although not necessarily, and resolve without scarring. They occur on the mucosa of the soft palate, cheeks, lips and tongue. Other regions are almost always spared, hence their involvement should raise suspicion of other diseases.

The most important for the diagnosis of pemphigoid is the confirmed presence of typical skin lesions and direct immunopathology study result with linear deposits of IgG and/or C3 complement component at the dermoepidermal junction.

Treatment of choice for pemphigoid is 0.05% clobetasol propionate in monotherapy. The crème should be evenly applied to the whole skin sparing the face, at the dose of 10-40 g/day depending on the severity of the disease. As an alternative, tetracyclines or methotrexate may be used. [11,12]

LICHEN PLANUS

Lichen planus is a relatively common non-infectious skin disease affecting 0.5-1% of patients. Its etiology is unknown, however, a clinical, histological and immunological similarity with graft versus host disease (GVHD) has been observed, and the epidemiological correlation between lichen planus and hepatitis was reported.

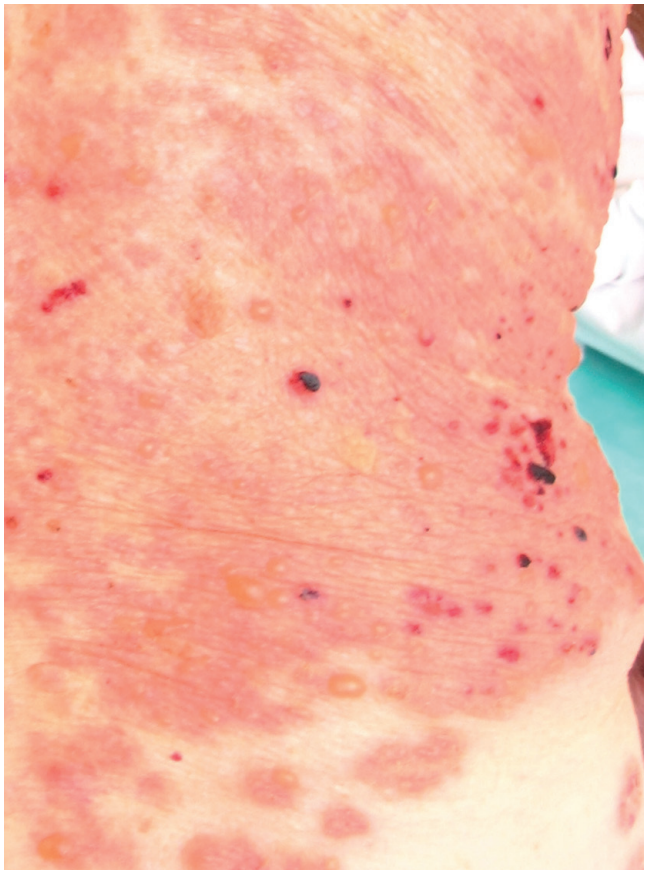

Fig. 3. Skin lesions in pemphigoid – thick blisters and erosions.

The typical skin lesion is a small smooth purple papule with a flat tip. The papules tend to fuse together forming a plaque, and they are limited by skin lines causing them to be polygonal in shape. The surface is often shiny, and on detailed inspection the classic Wickham striae can be seen forming a delicate network of white lines reflecting focal thickening of the stratum granulosum. The condition is usually self-limiting, and the lesions resolve in 70% of patients within a year, and in 90% within two years. It often leaves brownish post-inflammatory discoloration.

Oral lichen planus (OLP) is an important clinical presentation of LP and can precede or accompany skin lesions, or it can be the only manifestation of the disease. Oral lesions are estimated to be present in 50-77% of patients, and in 2-30% they are the only location of the disease. The morphology of lesions is different. There are no clear papules, and the Whickam striae are more pronounced, better visible, taking the form of a lacy network covering the mucous membrane. The lesions are usually located on the cheeks, most often at the second and third lower molars, and they can reach the lateral surface of the tongue and the vermillion, while gingival involvement is very rare. The most

common lesion is a painful erosion, which may progress to a flat ulceration. [3] In a large study on patients with oral lesions, 16% of patients reported previous or concurrent skin involvement, and in 19% the genitals were affected. It is estimated that 60-75% of patients with oral lichen planus are female, and 50% in the case of dermal lichen planus. Mean age at the diagnosis is 50-60 in the case of oral involvement and 40-45 in dermal type. [9,11]

Lichen planus is a disease that is hard to treat, and in severe cases it is only possible to alleviate symptoms until spontaneous healing. The best systemic treatment includes acitretin, however, steroids and cyclosporine A are also effective. In local treatment, the following are used: betamethasone, clobetasol, calcineurin inhibitors. [6]

BEHÇET'S DISEASE

It is a chronic multisystemic disease of unknown etiology characterized by acute episodes and alternating manifestation in various organs. Classic symptoms include the triad – ulcerartion of oral mucosa or genitals and uveitis. However, not all classic symptoms are present, especially in the initial phase. [7]

The etiology of Behçet's disease remains unknown. Environmental factors can contribute to its development. The disease is characterized by damage to the vessels, hyperreactive neutrophiles and autoimmune response. The pathogenesis seems to be associated with various cytokines released by Th1-cells, activating neutrophiles. Neutrophiles react with circulating immune complexes, which triggers autoimmune response leading to inflammation and damage to blood vessels. [5]

Ninety percent of patients present with recurrent painful aphtha-like ulcerations of oral mucosa affecting lips, gums, cheeks, tongue, which resolve without scarring. [7] In patients with multiple recurrent ulcers, the history should be taken regarding ulceration of genitals and ophthalmic symptoms. The typical location of ulcers within genitals are: scrotum, penis, labia. [4]

In the case of the involvement of the anterior segment of the eyeball, iritis, inflammation of the cilliary body, uveitis, cataract and glaucoma can be observed, while in the case of the posterior segment – vasculitis, vitritis, panuveitis, maculopathy, arterial and venous occlusion, papilledema, retinal detachment. Patients with eye symptoms often report blurred vision, excessive lacrimation, eye pain and photophobia. Anterior uveitis usually resolves spontaneously, however, recurrent episodes lead to permanent structural damage, including deformation of iris and secondary glaucoma. Recurrent occlusion of blood vessel leads to loss of vision. [5]

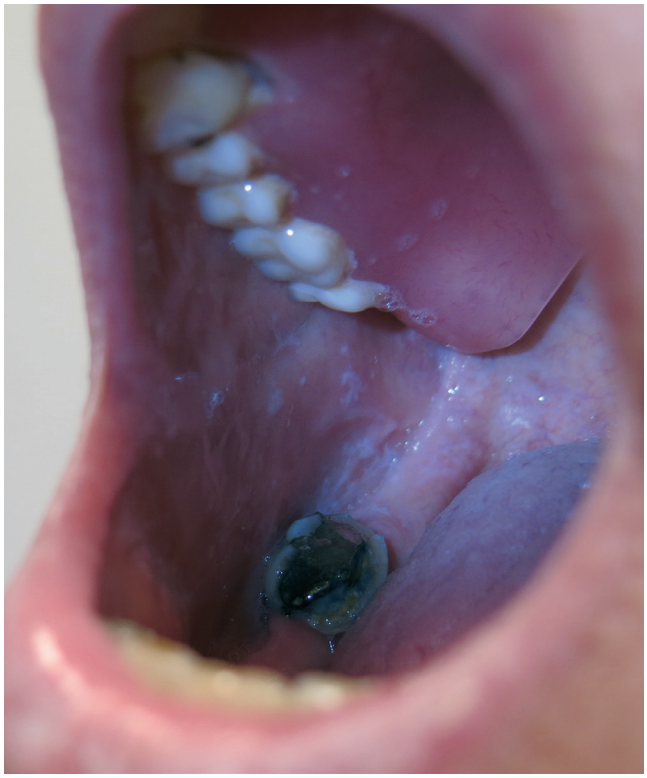

Fig. 4. Wickham striae on buccal mucosa in lichen planus.

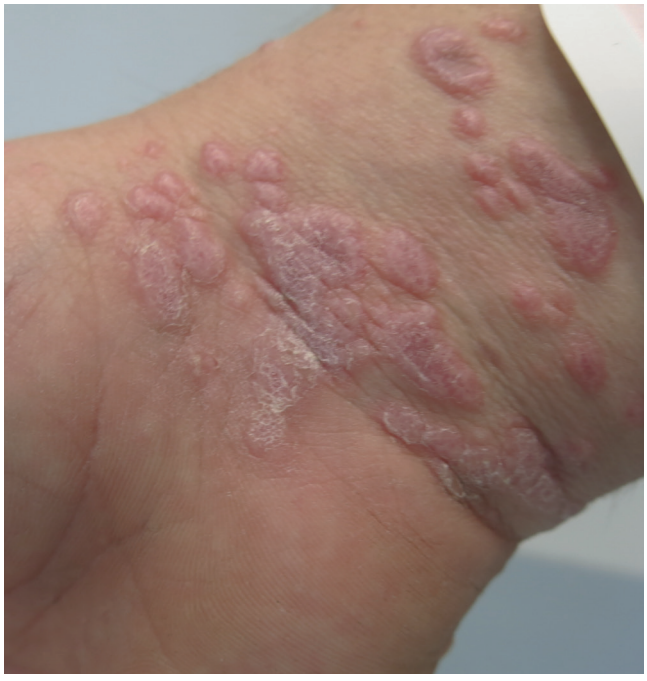

Fig. 5. Characteristic skin lesions of the wrist in lichen planus.

Patients can also develop erythema nodosum, superficial thrombophlebitis and pathergy, when a small injury, such as venipuncture or injection, leads to formation of pustule further evolving into erosion and ulcer. In rare cases, other systems are involved, including vascular (phlebitis and arteritis), central nervous (meningitis, encephalitis, psychiatric symptoms), gastrointestinal (enteritis), musculoskeletal (arthritis) and genitourinary (glomerulonephritis, testitis and epididymitis). [4]

There are no specific diagnostic tests for Behçet's disease, thus the diagnosis is based on clinical presentation with symptoms from multiple systems, according to the criteria of the International Research Group, and exclusion of other causes. The criteria include recurrent oral ulcers (at least 3 times within 12 months), and any two from the following: 1) recurrent genital ulcers 2) eye involvement, including anterior or posterior uveitis, cellular content within the vitreous humour on slit lamp examination, retinal vasculitis 3) skin lesions, such as erythema nodosum or pseudofolliculitis 4) positive skin prick test. [5]

Therapy is based on systemic administration of steroids, often combined with immunosuppressants, e.g. azathioprine. The most effective medication in eye involvement is cyclosporine, and therefore it is the drug of choice in the case of compromising loss of vision and other severe conditions. In the case of unsuccessful initial treatment or side effects, interferon α or TNFα inhibitors, such as etanercept or infliximab, can be used. [4,5]

STEVEN-JOHNSON SYNDROME (SJS) / TOXIC EPIDERMAL NECROLYSIS (LYELL'S SYNDROME - LS)

Those are acute life-threatening skin conditions, usually induced by drugs, leading to an extensive loss of epithelium. They are rare; less severe course is observed in younger patients, the disease is more severe in older patients, and the total mortality rate is about 18%. Risk factors include: HIV infection / symptomatic AIDS, brain tumors, head trauma, systemic lupus erythematosus. Most cases are induced by drugs, mean period between initiating therapy and developing skin lesions is about 10 days. The drugs that most commonly cause SJS/LS are: cotrimoxazole, sulfonamides, quinolones, cephalosporins, carbamazepine, phenytoin, phenobarbital, valproic acid, lamotrigine. Triggering factors also include herpes simplex virus, streptococcal infection, mycoplasma and other bacteria. [10]

Skin lesions found in SJS/LS include: target lesion (round in shape with hollow or vesicular center surrounded by edematous ring). Those lesions are typically located on the extremities, while on the trunk the lesions can have a less typical presentation of a dark-red macule with central vesicle. The lesions tend to join together as the disease progresses, evolving to large fragile blisters. It is followed by flaky skin desquamation, and the Nikolsky's sign is strongly positive. Depending on the area of the affected skin, the condition is referred to as Steven-Johnson syndrome (<10% body area), Lyell's syndrome (>30%) or SJS/LS overlap syndrome (10-30%).

In 90% of patients with severe drug-induced skin reaction, the mucous membranes and conjunctiva are also affected. Oral

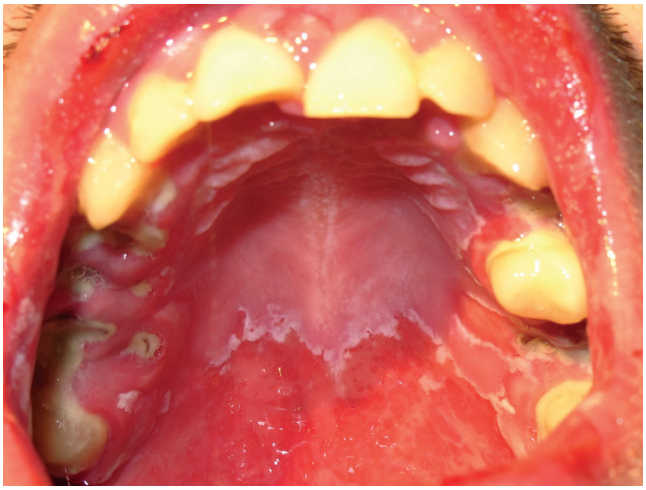

Fig. 6. Ulceration of palatine and gingival mucosa in Behçet's disease.

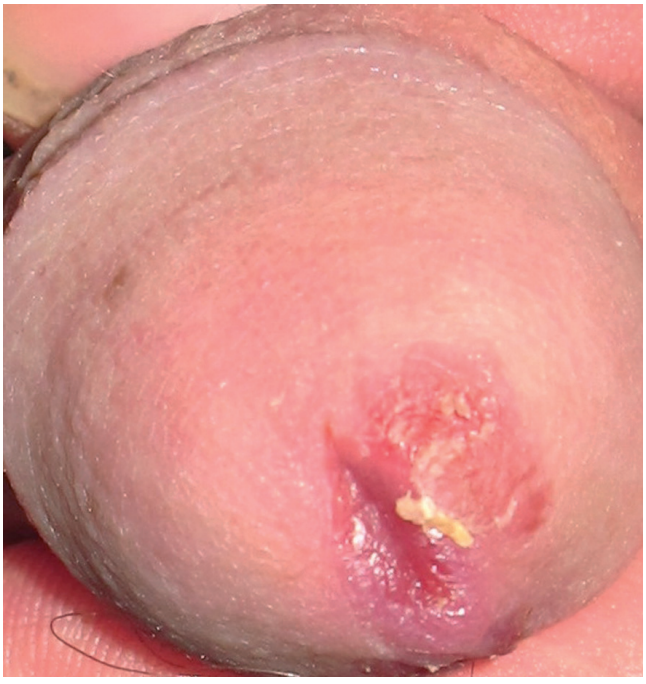

Fig. 7. Ulceration of the external urethral orfice in Behçet's disease.

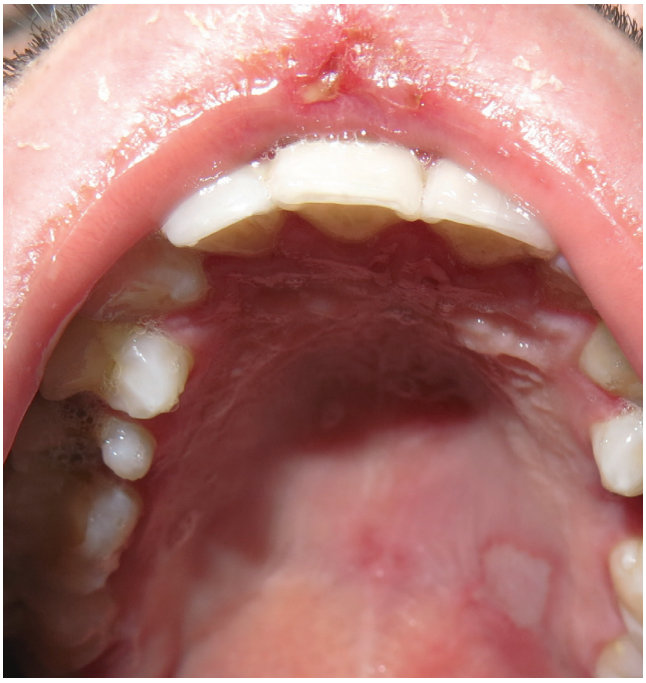

Fig. 8. Erosion of palatine mucosa and ulcer of upper lip in SJS.

lesions usually affect the lips, however, the tongue, palate and cheeks can be affected as well. Vesicles forming on the mucosa are fragile, therefore the most commonly encountered lesions are erosions and ulcers, which can reach the posterior part of the oral cavity, pharynx, larynx or even lungs and esophagus. Lesions can also affect genitals and anus.

If induced by the herpes simplex virus, usually treatment with acyclovir is sufficient, even for 5 years in the case of recurrent or chronic course. In SJS, local improvement can be observed after systemic steroid therapy. In LS, such treatment is not recommended, since it is ineffective and the most important part of managing LS is proper skin care, including all areas of burn care, such as infection prophylaxis, hydration and wound care. Supportive care includes local administration of steroids and antiseptics. Oral lesions can be treated with rinsing solutions with analgesics, which makes eating easier for the patient.

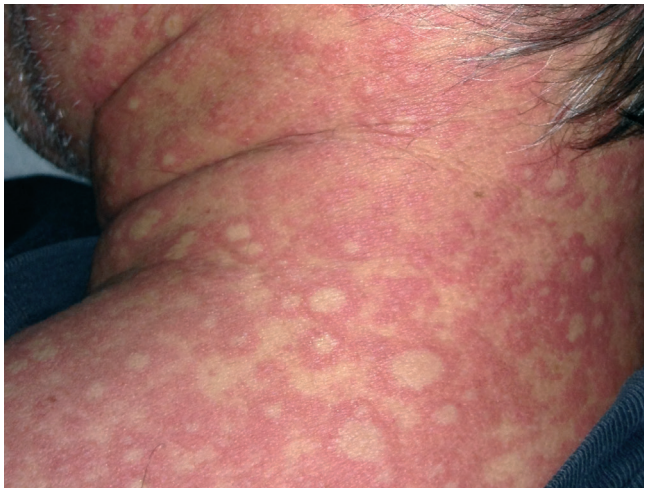

Fig. 9. Characteristic target lesion in SJS.

CONCLUSIONS:

Skin and mucosal lesions are common manifestation of skin diseases. The knowledge of such lesions is important in both dermatological and otolaryngological practice, and the diagnostic and therapeutic success can only be achieved by close cooperation between such specialists.

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