GRINSPAN’S SYNDROME

Tatiana Ţăranu1*, Irina Eşanu2, Mirela Grigorovici3, Mihaela Paula Toader1

1“Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, Faculty of Dentistry, Discipline of Dermatology
1“Grigore T. Popa” University of Medicine and Pharmacy - Iași, Romania, V-th Medical Clinic

*Corresponding author: Tatiana Ţăranu, Assoc. Professor, DMD, PhD
“Grigore T. Popa” University of Medicine and Pharmacy
- Iași, Romania

ABSTRACT

Aim of the study Oral lichen planus is a chronic inflammatory condition, etiologically obscure, affecting 0.1-4% of the general population. The erosive form of oral lichen planus is most severe, often unresponsive to systemic and topical therapies. A rare association between this form, diabetes mellitus and hypertension was first reported by Grinspan in 1966. The increased prevalence of diabetes mellitus and carbohydrate intolerance observed in patients with oral lichen planus suggests a possible pathogenic role of the metabolic disorder. Also, a pathogenic link may exist between dyslipidemia and oral lichen planus. Case report A 56 years old woman, presented with eroded and ulcerated extremely painful lesions all over the oral mucosa, but predominantly localized on the tongue, palate, buccal mucosa and attached gingiva, associated with white patches and evolving for 3 years. She was also suffering of type 2 diabetes mellitus, hypertension, gastric ulcer and chronic virus C hepatitis. Histopathological findings sustained the clinical diagnosis of erosive oral lichen planus. Laboratory data revealed high plasma levels of glucose, moderate liver cytolyses, increased levels of tryglicerides, an abnormal level of HDL-cholesterol with an aterogenic Castelli index of 3.09 and positive serological test for virus C hepatitis. The treatment we chose was topical tacrolimus 0.1% ointment twice a day and hyaluronic acid gel with satisfactory results after 4 weeks. Discussions Oral lichen planus represents a cell-mediated immune response with infiltrating T4 and T8 lymphocytes. The exact nature of the correlation between erosive oral lichen planus, diabetes mellitus, hypertension and dyslipidemia is not yet clarified but it is very well known that systemic inflammation is a contributor to ateromatosis. Also the nature of the correlation between oral lichen planus and chronic liver disorders is not yet fully understood. Conclusions All patients with oral lichen planus and particularly those with the erosive form should be examined in order to identify a metabolic syndrome and to initiate an early treatment to avoid future cardiovascular problems. The prognostic of our case correlates with the response of oral lesions to treatment (these lesions should be periodically clinically and histopathologicaly monitored for the malignant transformation risk), with the evolution of chronic virus C hepatitis, of diabetes mellitus and cardiovascular diseases.

Key words: Grinspan’s syndrome

INTRODUCTION

Oral lichen planus is a chronic inflammatory condition of unknown etiology, with a prevalence of 0.1-4%. Oral lesions of lichen occur in 70-77% of patients with cutaneous manifestations, but oral mucosa may also represent the only site of the disease. (1).

The disease mainly occurs in patients of medium age and in females.

In regard to the physiopathology, it is considered to be the result of an immune
response to antigens in the oral epithelium that are still unidentified.

Oral lichen planus may be associated with several other diseases. A rare association between the most severe form of oral lichen planus – the erosive form – diabetes mellitus and arterial hypertension is Grinspan’s syndrome. Other reported associations are with chronic liver disease and, more recently documented, with dyslipidemia. The nature of these associations is still not fully understood.

CASE REPORT

A 56 year old female patient presents with extremely painful, erosive, ulcerative and leucoplaziform lesions all over the oral mucosa with a progressive and persistent evolution of approximately 3 years.

Clinical history reveals that oral lesions were preceded by a cutaneous papulous pruritic eruption on the anterior aspects of the forearms and the abdominal flanks that remitted in several months, leaving residual pigmented macules. The treatment she underwent for the last 3 years with topical corticosteroids and antymycotic resulted in a partial and transitory effect for the oral lesions.

The patient had been diagnosed with gastric ulcer in 1992, arterial hypertension in 1996, type 2 diabetes mellitus in 2006 and chronic virus C hepatitis in 2008, being treated with Enalapril 10 mg/day, Metoprolol 50 mg/day, Gliclazid 80 mg/day and bouvable Arginine 2 ampoules/day.

Clinical exam revealed an astenic, depressive patient, with an important hepatomegaly (3 cm under the rim of the rib cage). Intraoral examination revealed multiple erosive and ulcerative lesions with fibrin deposits intermixed with leucoplaziform patches located on the lateral aspects of the tongue, ventral surface of the tongue (fig. 1), anterior half of the dorsum of the tongue, jugal mucosa, hard palate (fig. 2) and attached gingiva, accompanied by marked pain that was accentuated by speaking, mastication, deglutition that severely impaired the patient’s quality of life.

Histopathological examination of a biopsy from the lesional lingual mucosa revealed an atrophic squamous epithelium with a profound ulceration partially replaced by granulation tissue with numerous neoformation capillaries and microabcesses and a dense lymphocytic inflammatory infiltrate with a lichenoid aspect lateral to the ulceration, that remodeled the basement membrane (fig. 3, 4, 5, 6).
Laboratory investigations revealed the following pathological data: positive serology for HCV antibodies, leucopenia (3100/mmc), thrombocytopenia (75 000/mmc), moderately elevated levels of liver enzymes (ASAT=49U/l, ALAT=60 U/l), hyperglicemia (119 mg/dl), high tryglicerides (202 mg/dl), lower values for HDL-cholesterol (54 mg/dl). Aterogenic index of Castelli (total cholesterol – 167 mg/dl/HDL-cholesterol – 54 mg/dl) was 3.09, under the pathologic limit of 4.5.

Considering the general biological status of the patient, topical treatment with Tacrolimus ointment 0.1% 1-2 applications per day and Hyaluronic acid gel (Gengigel) was initiated. The evolution of the oral lesions after one month with this treatment was favourable with partial epithelisation and alleviation of functional symptoms. The patient needs further periodical clinical monitoring because of the risk of conversion to an invasive squamous cell carcinoma.

DISCUSSIONS
The association of erosive oral lichen planus with diabetes mellitus and arterial hypertension was first reported by Grinspan in 1966. (2).

The exact nature of the correlation between the elements of this symptomatic triad is unclear. The hypothesis of an iatrogenic origin of the oral lesions has also been stated, considering the inherent multiple drug association due to the two chronic
comorbidities with a lethal risk. (3).

Nowadays it is considered that the high prevalence of diabetes mellitus and hydrocarbonate intolerance in patients with oral lichen planus is suggestive of a possible pathogenic role of these conditions. (1,4). Also, a pathogenic link may exist between dyslipidemia (with a cardiovascular risk index of Castelli >5.1 in males and >4.5 in females) and oral lichen planus, triglycerides levels being significantly high (>150 mg/dl) in the erosive form of oral lichen planus. (1).

The etiology of oral lichen planus is not yet completely understood, but immunopathological data sustain the hypothesis of a T cell mediated dysfunction that leads to basal vacuolar change and death of the basal keratinocytes. Cytokines released from the apoptotic keratinocytes play an important proinflammatory role by selectively recruiting T cells and making up the characteristic subepithelial infiltrate. T cells are in turn the source of high levels of chemokines and cytokines such as IL2, IL6, IL10, TNFα, TGFβ in the subepithelial infiltrate, that promote inflammation. (5). The systemic chronic inflammatory process is a well known factor that contributes to the pathogenesis of the metabolic syndrome, as well as to ateromatosis. (6,7).

Patients with oral lichen planus should therefore be periodically investigated in order to identify and properly treat cardiovascular risk factors. (6).

Association with chronic liver disease (primitive biliary cirrhosis, C viral hepatitis, B viral hepatitis, autoimmune hepatitis) is reported with variable prevalence, with no established pathogenic correlation. Chronic C virus hepatitis is mainly associated with the erosive form of oral lichen planus and it is reported in areas with a high incidence of this infectious disease. This raises the problem of the need of interferone therapy which may potentially induce oral lichenoid reactions.

The treatment of choice for the oral lesions in Grinspan’s syndrome, especially when dyslipidemia and chronic C viral hepatitis are associated, is topical. Calcineurin inhibitors (nonantibiotic macrolides: tacrolimus, pimecrolimus), that inhibit the activation of the nuclear factor for activated T cells (NFAT), provide best beneficial effects while having the least adverse side effects when administered for long periods of time (at least 6 months) in order to obtain a significant therapeutic response. (8,9).

CONCLUSIONS

Oral erosive lichen planus is a chronic inflammatory condition with an immune substrate that may be part of morbid associations with a high cardiovascular risk. Grinspan’s syndrome is a rare association of a triad of symptoms: erosive oral lichen planus, diabetes mellitus and arterial hypertension.

Our case of Grinspan’s syndrome associates dyslipidemia with high levels of tryglicerides, lower HDL-cholesterol values and chronic C viral hepatitis. Aterogenic index of Castelli (3.09) must be interpreted in the context of the degree of liver insufficiency of the patient, to which the normal value of cholesterol may be due (167 mg/dl).

The prognostic of this case correlates with the evolution of the oral lesions that must be clinically and histopathologically monitored because of the risk of malignant transformation (evaluated at 5% in non-smoking patients with atrophic, erosive and ulcerative lesions of oral lichen planus), with the evolution of the chronic liver disease, diabetes mellitus and arterial hypertension. (10).
REFERENCES