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Psychiatric Comorbidity and Pharmacotherapy in Patients with Oral Lichen Planus

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1. Introduction

Lichen planus is a relatively common chronic mucocutaneous disease that exact etiology is not well understood so far. However immune system plays a primary role in development of this disease (Neville B 2009; Greenberg MS 2008). Prevalence of Lichen planus varies in different regions of the world (Greenberg MS 2008). It is reported about 1% for cutaneous lesions and 0.1-2.2% for oral lesions (Greenberg MS 2008). This disease was first described by Wilson in 1869(Neville B 2009).

Lichen planus is described as an adult disease. Most patients are in fifth decade of life with mean age of 55 years at the time of diagnosis (Silverman et al. 1991; Neville B 2009). Thirty five percent of patients are above 50 years old; however development of this disease also has been reported in children and adolescents (Silverman et al. 1991; Neville B 2009). Some familial cases have been reported in literature (Bermejo-Fenoll and Lopez-Jornet 2006). Although there is not any race predilection, the females are more affected than males (FreedbergIM 1999; Greenberg MS 2008).

In a study done on 420 Iranian patients, 64.9% were women with the mean age of 41.6 years (Pakfetrat 2009).

Prevalence of concurrent cutaneous and oral lesions is 20-50% in different studies and cutaneous lesions may be encountered in approximately 15% of patients with oral lichen planus (Greenberg MS 2008). Oral lesions are more frequent and 30-70% of the patients have oral lesions (Neville B 2009; FreedbergIM 1999; Greenberg MS 2008). In one study done in north -east of Iran, 83% of lichen planus patients had only oral lesions and the rest of the patients (17%) had lesions in other sites such as skin, hair and nail (Pakfetrat 2009).

2. Clinical findings

Lichen planus is a member of lichenoid reactions lesions. Lichenoid reactions are a family of lesions with various etiologies and similar clinical and histopathological appearance. Oral

lichenoid reactions include: lichen planus, lichenoid contact reactions, lichenoid drug eruption, lichenoid reactions of graft-versus-host disease (GVHD)(Greenberg MS 2008).

Cutaneous lesions of lichen planus appear as purple pruritic polygonal plaques or papules which are usually self limiting in contrast with oral lesions (Greenberg MS 2008). Initially, these lesions are erythematous macules which change into flat-topped purple papules in several weeks (Neville B 2009; FreedbergIM 1999; Burns T 2004). The skin lesions appear on the flexor surfaces of the forearm and wrist. Vagina, esophagus, anal canal and larynx may also be affected (FreedbergIM 1999; Burns T 2004). Nikolsky's sign could be positive in some patients. (Vincent et al. 1990)

Oral lesions are observed as either reticular, papular, plaque-like, atrophic (erythematous), erosive-ulcerative or bullous lesions (Greenberg MS 2008; Neville B 2009; FreedbergIM 1999). Some researchers divide the lesions into two group of erosive and non-erosive and other describe them as keratotic and non-keratotic. (Lacy, Reade, and Hay 1983; Bagan-Sebastian et al. 1992; Neville B 2009; Greenberg MS 2008). The most common oral site is buccal mucosa followed by lingual, gingival and labial mucosa. The majority of studies, revealed reticular type as the most common type of oral lesions which appears as bilateral lingual and buccal lesions. In reticular lichen planus, characteristic pattern of interlacing white lines (Wickham's striae) may be observed (Greenberg MS 2008; Neville B 2009). In one study done on 690 oral lichen planus patients, reticular form was the most common type of the disease and 95% of lesions appeared as bilateral (Ingafou et al. 2006). In another study done in Mashhad, Iran, the most common type was reticular form with 77% prevalence. Sixty six percent of lesions were associated with other types of disease. Atrophic was the second common lesions (38%). The most common sites of lesions were buccal, lingual, gingival and lower labial mucosa (Pakfetrat 2009).

Because of burning in erosive- atrophic type, most patients referring to clinics for treatment suffer from this form of disease. Atrophic (erythematous) lesions are defined as inflamed regions that are covered with a thin and red epithelium. Erosive lesions appear as red regions indicating loss of epithelium integrity. Erosive changes and pseudo-membrane formation associated with an ulcerative lesion (Greenberg MS 2008). The keratotic lesions appear as reticular, anular, papular and plaque-like which are mostly without any symptoms (Neville B 2009; Greenberg MS 2008). Because erosive-ulcerative and atrophic lesions are mostly associated with reticular pattern, finding of reticular lesions is important in clinical examination for confirming the diagnosis in suspicious lesions (Greenberg MS 2008).

3. Histopathological findings

In histopathological evaluation these changes are observed:

1. Hyperparakeratosis or hyperorthokeratosis on the surface of epithelium associated with increasing in thickness of spinous layer.
2. Ret ridges may be absent or hyperplastic and classically have a "saw- toothed" appearance.
3. Hydrophilic degeneration or destruction in basal cell layer.
4. Eosinophilic band under the basal cell layer may be present.
5. Band-like dense infiltrate of T lymphocytes at subepithelial layer which is characteristic of the disease.
6. Deposition of antibodies and complement may be observed that is not pathognomonic (Neville B 2009) (Greenberg MS 2008).

4. Risk of malignancy transformation

Oral lichen planus (OLP) is a premalignant condition. Risk of malignancy transformation is higher in erosive-atrophic type and in lateral border of tongue. Some studies revealed that plaque-like lesions have much more risk for malignant transformation. (Neville B 2009; Freedberg IM 1999; Greenberg MS 2008).

5. Association with other diseases

Idiopathic lichen planus is associated with other auto-immune diseases and immune disorders. In different studies, diseases such as ulcerative colitis, alopecia, areata, vitiligo, dermatomyositis, morphia, thymoma, myasthenia gravis, hypogammaglobulinemia and primary biliary cirrhosis are reported to occur in lichen planus patients (Burns T 2004; Greenberg MS 2008).

Some studies showed association of lichen planus with HIV and HCV (Gandolfo et al. 1994; Roy and Bagg 1999; Klanrit et al. 2003; Pilli et al. 2002; Emadi et al. 2010). Recent studies revealed that specific T lymphocytes related to chronic HCV infection have been defined in oral mucosa of chronic HCV and OLP patients (Pilli et al. 2002). Another study defined that patients with acute hepatitis or chronic liver disease or high level of liver enzymes or positive HBS antigen, may have OLP lesions twice than normal population (Gandolfo et al. 1994).

In some studies reported that patients affected by multiple endocrinopathy such as Turner's syndrome, psoriasis, lupus erythematosus, scleroderma, Crohn's disease, may have OLP lesions, because of more probably of association of multiple autoimmune diseases (Gardner 1967; Parodi et al. 1998; Kurgansky and Burnett 1994).

There are some challenges about relationship of OLP and diabetes. Some studies did not find any significant correlation between them; in contrast, other researchers reported glucose intolerance in OLP patients (Albrecht et al. 1992). It is not confirmed that OLP are more susceptible for diabetes. More OLP lesions in diabetic patients are as erosive-atrophic form and are much more located on lingual mucosa (van der Meij et al. 1999). Some researchers believed that higher prevalence of OLP lesions in diabetic patients is related to anti-diabetic drugs that cause lichenoid reactions (Albrecht et al. 1992).

6. Etiology and pathogenesis

OLP is an immunologic disorder by a T-cell mediated immune response. TCD8+ (cytotoxic) cells trigger apoptosis process in oral epithelial cells (Eisen 2003; Sugerman et al. 2002). Cell mediated immunity begins by endogen or exogen cells and consequently TNF- α and TNF- β are produced (Scully, Eisen, and Carrozzo 2000; Lodi et al. 2005). Some researchers have divided mechanisms of OLP pathogenesis into mechanisms of non-specific and specific for antigens (Sugerman et al. 2002). Specific mechanisms include:

1. Expression of antigen limited by MHC molecule class I and II by keratinocytes.
2. Activation of specific TCD8+ and TCD4+ helper cells for antigen (In OLP, most lymphocytes of epithelium are CD8+ and lymphocytes of lamina propria are CD4+).
3. Clonal specific lymphocytes for antigen.
4. Apoptosis of keratinocytes begins specific TCD8+ for antigen (Sugerman et al. 2002). Firstly, in development of OLP lesions, CD8+ cells in lesion can identify antigen in relation to MHC class I on keratinocytes surface. After defining antigen and activation

of TCD8+, apoptosis of keratinocytes begins. Activated TCD8+ cells and keratinocytes release cytokines that attract more lymphocytes and other cells (Yamamoto et al. 1994). Accumulation of cytokines plays an important role in development and progression of OLP (Santoro et al. 2003). Rhodus et al confirmed that the levels of TNF- α , IL-1, IL-6 and IL-8 decreased in whole saliva following the treatment of erosive OLP (Rhodus et al. 2006). Another study revealed that TNF- α plays an important role in pathogenesis of OLP. Treatment with fluocinolone acetonide decreases its expression (Thongprasom et al. 2006). Other factors that play a role in development and progression include: Matrix metalloproteinase (MMP) (causes lymphocyte migration), MMP/TIMP (inhibitors of MMP), RANTES (mast cell trafficking and degranulation) and release of TNF- α , impairment in suppression of Transforming Growth Factor B1 (GF- β 1), expression of epithelium adhesion molecules via TNF- α stimulated by mast cells, heat shock proteins, activation of TMMP and lymphocytes by mast cells chymase (Zhao et al. 2002; Sugerma et al. 2002). In recent years, it has been confirmed that antioxidant imbalance, in addition to cytokines and cell mediated immune response play a role in OLP pathogenesis. Free O₂ radicals produced by inducing lipo-peroxidase cause damage to cell membrane and consequently cell apoptosis and necrosis. In one study, a decrease in antioxidant defense and a significant increase in peroxidation products and increased oxidative damage to lipids and DNA and proteins mainly within the basal cell layer of the epidermis and at the dermoepidermal junction, have been demonstrated (Sander et al. 2005). One study in 2010 showed the serum level of nitritoxide and superoxide dismutase was greater than control group. In contrast, a decrease in erythrocyte catalase levels was observed (Aly and Shahin 2010). Mast cells and macrophage degranulation causes the release of cytokins; chymase and TNF- α (Tumor Necrotizing Factor- α), leading to expression of ELAM1(endothelial leukocyte adhesion molecule-1) , ICAM (intercellular adhesion molecule) and leukocytes adhesion molecules (Carrozzo and Thorpe 2009). Chymas released from mast cells acts as MMP. (Matrix metalloproteinase) and lead to basal layer degeneration. ICAM plays a role in the attraction and migration of lymphocytes to oral epithelium (Ismail, Kumar, and Zain 2007).

6.1 Psychiatric comorbidity and oral lichen planus

Although etiology OLP is unknown but, cell-mediated immune system plays an important role in OLP pathogenesis(Greenberg MS 2008) (Neville B 2009). Therefore, any factor that can influence the cell-mediated immune response can play a role in the development of the disease. Factors such as stress and psychological problems, especially depression and anxiety, have been mentioned as etiologic factors in lichen planus, but there is still controversy concerning the role of stress as a major or minor etiologic factor in the pathogenicity of lichen planus (Greenberg MS 2008).

Different studies have been done for the evaluation of the relationship OLP and psychiatric disorders. These studies used various psychiatric questionnaires, but any treatment intervention has not been used but in our study, after diagnosis of psychiatric disorders by psychiatric interview, we treated these disorders with psychiatric pharmacotherapy (Delavarian 2010). Among different studies, some found a positive correlation between OLP and psychiatric disorders; however other studies did not establish such a relationship.

One study with different psychiatric tests such as "General Health Questionnaire", "Hamilton Anxiety Scale", "Melancholia scale, depression", Hamilton Depression Scale" demonstrated that OLP patients had higher depression and anxiety scores (Colella et al.

1993). Another study showed 53% depression in OLP patients and 20% in control group by "Beck Depression Score". This study confirmed importance of depression assessment in skin diseases like lichen planus and psoriasis (Akay et al. 2002). Also, one study demonstrated that some skin diseases such as lichen planus develops in relation to stress, moreover emotional events and stressful life events exacerbate the lesions (Onder et al. 2000). A case-control study revealed that patients with cutaneous lichen planus had more been exposed to stressful life events and suggested the need for concurrently dermatological and psychological treatment intervention (Mansur, Kilic, and Atalay 2004). Also, another study showed OLP lesions became worse during times of mental stress, but most patients did not feel any need for psychiatric treatment (Hampf et al. 1987). Psychological Minnesota Multiphasic Personality Inventory (MMPI) was used in comparison of OLP patients and healthy persons. It showed prolonged emotional stress in OLP patients may lead to psychosomatization and can affect its expression. This study confirmed clinical trials is needed for determine effects of adjunctive psychological treatment of OLP patients (Ivanovski et al. 2005). Furthermore, significantly higher stress, anxiety, and depression levels were found in OLP patients than the general population that suggest probably role of stressors in OLP (Chaudhary 2004). Although there is a significant association between the stage of OLP, hypothalamic-pituitary-adrenal dysregulation, and altered responses of CD4+ cells, there is the need for studying the detail of these relationships in OLP (Prolo et al. 2002).

The rate of salivary cortisol can be an indicator of higher level of stress. Salivary cortisol and its correlation to OLP have been evaluated. A study on salivary cortisol showed the salivary cortisol and state and trait anxiety levels in OLP group were significantly higher than healthy group that concluded that oral lichen planus is closely related with stress. The findings suggested that besides routine treatment of OLP patients, psychological support is needed (Koray et al. 2003). Some studies on salivary cortisol showed that the salivary cortisol and also anxiety, depression, and stress levels in OLP patients were higher than healthy group. This result demonstrated a positive correlation between psychiatric disorders and salivary cortisol levels in OLP patients (Shah, Ashok, and Sujatha 2009) .

In contrast to these studies that show stress, anxiety, and depression had a positive effect on OLP, some studies didn't find any positive association between stress and OLP.

In one study, despite higher levels of anxiety in OLP patients, it was not confirmed that psychiatric changes are direct etiologic factor in OLP development or psychiatric disorders are OLP consequences (Rojo-Moreno et al. 1998).

Another study measured anxiety level on the Hospital Anxiety and Depression (HAD) Scale and demonstrated that there were no statistically significant association between erosive oral lichen planus and either anxiety or depression (McCartan 1995).

Salivary cortisol and dehydroepiandrosterone (DHEA) levels were measured in OLP patients. Furthermore, Beck Depression Inventory, Beck Anxiety Inventory and Lipp's Inventory of Stress Symptoms for Adults were used for evaluation symptoms of depression, anxiety and stress. Although the results suggested an association of OLP with anxiety, DHEA and cortisol levels did not differ between different groups, which does not support any neuroendocrine etiology for OLP (Girardi et al. 2011). In another study, saliva samples of ten OLP patients were collected and the amount of salivary cortisol was measured for assessment of temporary stress, OLP patients did not have higher level of stress (Rodstrom et al. 2001).

Briefly, studies revealed that there is a close correlation between immune system and central nervous system (CNS) that plays an important role in establishment of homeostatic condition in body and health maintenance or disease development. (Sadock BJ 2005). Immune system cells express some receptors for many molecules that are modulated by nervous system. These are receptors for neurotransmitters, neuropeptides and steroid hormones. Immune system response includes induction stage, activation stage and finally effectors stage. The consequences of system effect are dependent on which stage is influenced by the nervous system (Sadock BJ 2005). For example, norepinephrine in induction stage causes the acceleration of the immune system function. Inhibition or exacerbation of immune system function in activation stage is dependent on the concentration of epinephrine, but epinephrine leads to inhibition effect in effectors stage (Sadock BJ 2005). Therefore, both stage of effect and amount and type of substance play a role in the process (Sadock BJ 2005). In vitro and in vivo effects of these molecules are various. For example, β adrenergic system causes inhibition of lymphocyte activity in vitro. In contrast, increase in susceptibility of suppressor T lymphocytes with increase in number of receptors can lead to a higher immune response in vivo (Sadock BJ 2005).

Neuropeptides such as endorphins cause an increase in T lymphocytes and natural killer cells proliferation; and cause production of cytokines and cytotoxic T cells in vitro (Sadock BJ 2005). Inhibition effect of stress on natural killer cells acts as a mediator in vivo and in vitro (Sadock BJ 2005). Different studies demonstrated that stress influences development and exacerbation of disorders related to immune system such as infectious, cancerous and autoimmune diseases (Fink 2000). Stress can change immune response to antigens and alter ability of cells for expression of peptides to T lymphocytes (Fink 2000). Different agents influence final result of stress effects on immune system include: severity and type and duration of stress, coping with stress, type of affected immune system and host immune system (Sadock BJ 2005). For example; crowding stress causes increase in lymphocyte stimulation to antigens (Sadock BJ 2005). Institutionalizing of elderly (stress of care-giving) can cause depression and consequently a change in the immune system and increase in TCD8+ and reduction in natural killer cells activity. Professional stress is associated with altered immune cells function (increase in IL-2 expressing cells) and probably suppressing effect (reduction in natural killer cells). Post traumatic stress disorder (PTSD) is associated with an increase in IL-6. Influence of stress on humoral and cell-mediated immune system is different. Also, the amount of the effect of stress is dependent on the host psychological condition. In depression, immune system changes are various include: increase in white blood cells, increase in IL-6 and macrophages activity and neutrophilia, lymphopenia and impaired T cell function (Sadock BJ 2005). Coping with stress causes a change in immune response and reduction of its harmful effects. Prohibiting of the patient from doing what he likes (restraint), increases IL-6 (Sadock BJ 2005; Fink 2000). Considering the ability of stressful events to stimulate cytokines and the ability of cytokines in regulating CNS function, immune system may play a role in response to stress even without presence of pathogens (Sadock BJ 2005). Studies confirmed reduction in natural killer cells activity in stressful events e.g. test taking period. Also, stress can lead to reduction in interferon, antibody response, lymphocytes and lymphocytes response to mitogen.

Briefly, researchers showed a decrease in immune system activity in chronic stressful event (Sadock BJ 2005). Response to stress or psychological pressure can include changes in hormonal balance such as release of catecholamines, glucocorticoids and increase in

expression of heat shock proteins (Fink 2000). The studies confirmed role of released neuropeptides from non-myelinated axon terminals such as Substance P (SP), Vasoactive Intestinal Peptide (VIP), Calcitonin Gene-Related Peptide (CGRP) in stimulation of various immune cells, resulting cytokines release, chemotaxis, phagocytosis in cutaneous diseases. For example; Substance P causes stimulation of release of IL-1, Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) from keratinocytes, proliferation of IL-2 in lymphocytes, release of IL-6, IL-1, TNF from macrophages and migration of lymphocytes into skin (Fink 2000; Sadock BJ 2005). Also, CGRP causes proliferation of keratinocytes and increase in chemotactic T cell proliferation (Robert A 2001).

The role of proliferation and activation of lymphocytes and keratinocytes and release of cytokines in lichen planus has been confirmed. The evidences show stressful life events and psychological agents play a role in development and exacerbation of skin diseases (psoriasis) and patients with higher level of distress, experience exacerbated skin lesions (Robert A 2001).

It is confirmed that stress and hypothalamo-hypophyseal-adrenal axis and autonomous nervous system-as mediator of CNS effect on immune system- lead to reduction in humoral and cellular immune responses. Stimulation of release of various cytokines such as IL-1 β , IL-1 α , IL-2, IL-6 and TNF by corticotropin-releasing hormone (CRH); followed by stimulation of local inflammation, could be important in OLP development. On the other hand, different factors are effective in immune responses and effect of stress on immune system.

Conclusively, stress can play a role as a contributing factor in immune system function disturbance leading to production and release of cytokines and consequently destruction function of cytotoxic T cells (Sadock BJ 2005). Our experiences and different studies with various scales about association of psychiatric disorders and lichen planus showed that OLP patients respond to stress by development of oral lesions while other people may not react in the same way. Because of impaired immune system function, the possibility of development of other diseases such as neoplasm, infectious diseases and autoimmune disease should be considered in OLP patients.

7. Differential diagnosis

Oral lesions of lichen planus may be difficult to distinguish from other white and red and also chronic ulcerative lesions of oral mucosa. Lichenoid contact reactions, lichenoid drug eruption, lichenoid reactions of graft-versus-host disease (GVHD), lupus erythematosus, idiopathic leukoplakia, squamous cell carcinoma, benign mucous membrane pemphigoid and candidiasis should be mentioned in differential diagnosis of oral lichen planus. Obtaining complete history and proper examination of oral mucosa are useful. Although bilateral reticular or annular pattern on the buccal mucosa is pathognomonic, in erosive-atrophic form, biopsy is recommended for ruling out lupus erythematosus. Sometimes immunofluorescence tests are required for accurate diagnosis (Greenberg MS 2008; Neville B 2009).

8. Management

Because oral lichen planus is chronic disease, some patients seek treatment for many years. The mainstay treatment for OLP is topical corticosteroids (Lodi et al. 2005; Eisen 2003; Dalirsani 2010; Greenberg MS 2008). The topical Corticosteroids are used in different types,

forms and doses which are prescribed according to location, number, and extension of lesions. The topical corticosteroids which are used in the forms of paste, lotion, spray, mouthwash and intralesional injection, include dexamethasone, betamethasone valerate, clobetasol propionate, triamcinolone acetonide, fluocinonide acetonide, hydrocortisone, fluocinonide which have different potencies. Topical corticosteroids in orabase such as triamcinolone in orabase have better effect because of adhesion to oral mucosa (Dalirsani 2010; Lodi et al. 2005; Greenberg MS 2008).

The second alternate for OLP treatment are systemic corticosteroids which are prescribed in diffuse lesions or lesions that are resistant to topical treatment (Lodi et al. 2005). It is suggested that systemic corticosteroid prescribed as 1 mg/kg/day prednisolone for 7 days that is tapered with reduction in drug dose as 10 mg/day. In tapering duration, topical steroid may be needed (Greenberg MS 2008).

Topical corticosteroid may cause a wide spectrum side effects such as candidiasis, taste disorder, nausea, xerostomia, sore throat, oral inflammation and mucosal atrophy (in intralesional injection) (Thongprasom and Dhanuthai 2008). For the prevention of candidiasis after using topical corticosteroid, topical anti-fungal drugs are prescribed (Greenberg MS 2008). Systemic corticosteroid can cause fatigue, insomnia, fluid retention, mood alteration, hypertension, plasma glucose increase, osteoporosis, and adrenal suppression (Lin AN 2002).

Other alternates in OLP treatment include: topical immune suppressor or immune modulator agents e.g. cyclosporine (calcineurin inhibitor) or systemic immune suppression; azathioprine, dapsone, levamisole, hydroxychloroquine, anti-inflammatory drugs: doxycycline. Furthermore, other strategies suggested such as griseofulvin, glycyrrhizin, interferon, tacrolimus, retinoids, phototherapy with ultra violet (UV) and laser. (Jajarm, Falaki, and Mahdavi 2011; Greenberg MS 2008).

Concurrent use of several drugs causes different problems for patients. Some studies used combination of several drugs which is necessary especially in diffuse lesions with various forms (reticular, atrophic or ulcerative lesions).

In one study done in Tabriz, Iran demonstrated that mouthwash of combination of triamcinolone acetonide and vitamin A is significantly more effective than triamcinolone acetonide mouthwash alone in treatment of OLP lesions (Dalirsani 2010). In another study, combination of amitriptyline, ketokonazole, and clobetasol in mouthwash form was useful in OLP patients (Javadzadeh 2008).

For the first time, in one study, we evaluated the effects of concurrent routine treatment of OLP lesions with topical corticosteroid and psychiatric therapy of patients with psychiatric disorders (Delavarian 2010).

8.1 Suggestion of psychiatry therapy as a novel supplementary treatment for oral lichen planus

A randomized clinical trial study was designed to evaluate the effect of the drug therapy of psychiatric disorders on lichen planus. We filled out special examination forms for 55 OLP patients referring to the Oral Medicine Department in Mashad Faculty of Dentistry. Then, the patients were evaluated by a psychologist. Out of 55 patients, 53 patients were diagnosed with one of the psychological disorders according to the criteria set by DSM-IV-TR. The patients filled out informed written consent forms. The subjects having the inclusion criteria were chosen for the study (Delavarian 2010).

Inclusion criteria include:

1. patients with oral lichen planus (all forms) with or without skin involvement;
2. affliction with psychiatric disorders.

Exclusion criteria include:

1. patients exhibiting dysplasia in histopathological evaluation (1 patient);
2. patients with lichenoid reaction potential as evidenced by histopathological examination, drug intake or other predisposing conditions (5 patients);
3. patients diagnosed with acute psychosis with the potential of harming themselves or others (no patients);
4. patients who had received any medications for lichen planus during the past month (1 patient).

Forty-six patients; 31 subjects from the case group and 15 subjects from the control group were followed for 6 months. Patients' demographic information and location, form and size of the lesions and pain sensation of each patient were recorded in the questionnaires.

The severity of the signs in lichen planus depends on the form and size of the lesions. Oral lesions were described and classified in 3 forms:

1. keratotic (reticular form, plaque form or both).
2. atrophic (atrophic lesion with or without keratotic lesion).
3. erosive-bullous (erosive or bullous lesion with or without keratotic lesion).

The oral cavity was divided into ten areas to determine the percentage of lichen planus extension in the oral cavity. These areas were: oral vestibule, alveolar mucosa, lips, buccal mucosa, oral floor, fauces, gingiva, palate and the dorsal and ventral aspects of the tongue. Therefore, the percentages of the involvement for all areas of the oral mucosa were calculated and subsequently the percentage of the involvement of the oral cavity was calculated.

The severity of pain and pain sensation was evaluated according to following scales:

Scale 0: no pain: VAS=0

Scale 1: mild pain: $0 < VAS \leq 3.5$

Scale 2: moderate pain: $3.5 < VAS \leq 7$

Scale 3: severe pain: $7 < VAS \leq 10$ (Greenberg MS 2008).

Both groups received routine treatment for oral lichen planus consisted of topical corticosteroids, mostly triamcinolone paste along with nystatin (antifungal) mouthwash. Some patients suffered from diffuse lesions treated with dexamethasone mouthwash. Furthermore, the case group received drug therapy for psychiatric disorders. Then the patients were subjected to regular oral examinations every two weeks, carried out by an oral medicine specialist who was blinded to the treatment received by each patient, until the signs and symptoms were brought under control. The patients in the case group were evaluated for possible side effects of the medication(s) 2 weeks after the initiation of the study and afterwards were monthly examined by the psychologist, too. Treatment of patients continued until remission of signs and symptoms (Delavarian 2010).

The recovery rate (response to treatment) in each patient was evaluated according to Tables 1 and 2, based on the percentage of the area involved, form of the lesion and the severity of the pain. The psychiatric recovery of the patients has been classified in Table 3.

The comparison of the case and control groups regarding complete or partial response to treatment was carried out in the second and sixth months according to the codes depicted in

Tables 1 and 2. The results of the two groups as to the remission of the signs and symptoms of oral lichen planus were compared using the non-parametric Mann-Whitney test.

Response to treatment	Scale	Criteria
Excellent	0	recovery \geq 75%
Good	1	$50\% \leq$ recovery $<$ 75%
Fair	2	$25\% \leq$ recovery $<$ 50%
Poor	3	$0\% \leq$ recovery $<$ 25%
Exacerbation	4	increase in lesion size and extension

Table 1. Scaling of response to OLP treatment according to lesion size and extension

Response to treatment	Scale	Criteria for lesion form	Criteria for severity of pain
Excellent	0	conversion of scales 1,2 & 3 to 0 (without lesion)	conversion of scales 1,2 & 3 to 0 (without pain)
Good	1	conversion of scale 3 to 1	conversion of scale 3 to 1
Fair	2	conversion of scale 2 to 1 or conversion of scale 3 to 2	conversion of scale 2 to 1 or 3 to 2
Poor	3	no conversion in scale	no change in pain
Exacerbation	4	conversion of scale 1 to 2 or 3 or conversion of scale 2 to 3	conversion of scale 0 to 1 or 2 or 3 or conversion of scale 1 to 2 or 3

Table 2. Scaling of response to OLP treatment according to the form of the lesion and severity of pain.

Scale	Response to treatment
0	complete response
1	good response
2	little response
3	no response

Table 3. The classification of the psychological recovery of the patients

Also, the patients in the case group were subjected to Spearman's test to be evaluated in relation to the correlation between psychological recovery and oral lesion recovery, given the size and form of the lesions and the pain sensation.

The protocol of this study was approved by the Medical Ethics Panel of Mashhad University of Medical Sciences and all the patients were informed of all the procedures involved in the study and all had information about the anecdotal nature of the study (Delavarian 2010).

In this study; out of 55 patients, 53 patients were diagnosed with at least one of the psychological disorders according to the criteria set by DSM-IV-IR. Among them, 76.8% were above 40 years old with mean age of 47.2 ± 13 years and 39 patients (73.5%) were women.

Their psychiatric disorders consisted of anxiety, mood, somatoform, adaptation, drug withdrawal and personality disorders. Table 4 indicates prevalence of psychiatric disorders among studied patients. Nearly 93.5% of our patients, who had OLP, suffered from anxiety disorders, about 52.5% suffered from mood disorders, 10.2% had somatoform disorders. Some patients had several concomitant psychiatric disorders.

Type of Psychiatric Disorders	Psychiatric Disorders	Number	Percent
Anxiety Disorders	Generalized anxiety disorder	29	54.2
	Phobia	3	5.6
	Post traumatic stress disorder	2	3.7
	Obsessivecompulsive	6	11.3
	Nonotherwise specified anxiety	10	18.8
Depression disorders	Major depression disorder	21	35.5
	Dysthymia	9	16.9
Somatoform disorders	Somatization	1	1.8
	Hypochondriasis	1	1.8
	Conversion	3	5.6
	Pain disorder	0	0
Personality disorders	Obsessive-compulsive personality	1	1.8
Adjustment disorders	Adjustment disorders	1	1.8
Substance-related disorders	Substance- related disorders	1	1.8

Table 4. Prevalence of psychiatric disorders among studied OLP patients

The cases treated with psychiatric agents include anti-depressant, anti-anxious, anti-convulsive, non-selective beta blockers, anti-psychotic and muscle relaxer drugs (Table 5).

Comparison of response to treatment between the patients in two groups was evaluated according to:

Size of the lesions: Table 6 demonstrates that the patients in the case group had given a better response to lichen planus treatment. The size of the lesions had decreased to different degrees and this difference in response was significant in the sixth month ($P=0.026$).

Formof the lesions: According to Table 7, although there were differences in the response to treatment between the study group and the control group as to the conversion of severe symptomatic cases (erosive and atrophic) to milder cases (keratotic), these differences were not statistically significant in the sixth months ($P=0.31$) (Figures 1,2 and 3).

Drug Group	Name of Drugs	Percentage of patients taken drugs (the first visit)	Percentage of patients taken drugs (the visit)	Mean of the lastdose prescribed(mg)
Anti-depressant Agents	Tricyclic and tetracyclic antidepressant			
	Clomipiramin	0.8	1.1	25
	Nortriptyline	6.8	8.2	64.3
	Doxepin	5.1	4.7	27.5
	Amitryptilin	0.8	1.1	75
	Trimipramin	0.8	0	0
	Maprotilin	7.9	9.4	60.9
	Selective Serotonin Reuptake Inhibitor			
	Citalopram	6.77	5.81	35
	Fluvoxamine	25.6	29.4	28.8
Fluoxetine	0.8	1.1	100	
Anti-anxious Agents	Benzodiazepine			
	Alprazolam	22.88	16.27	0.52
	Diazepam	0.8	1.1	10
	Clonazepam	0.8	1.1	1
	Chlordiazepoxide	3.4	3.5	8.3
	Aza spiro decadion			
	Buspiron	2.5	3.5	16.7
Non-selective Beta Blockers	Metoral	1.7	0	0
	Propranolol	8.5	8.2	45.7
Anti-convulsive Agents	Carbamazepine	0.8	1.1	600
	Lamotrigin	1.7	2.3	37.5
Anti-psychotic Agents	Risperidone	1.7	2.3	1
Muscle relaxer Agents	Baclofen	0.8	1.1	75

Table 5. Prevalence of patients taken psychiatric drugs in the first and last visits

Response to treatment	Scale of response	Six			
		Case		Control	
		Number	Percent	Number	Percent
Excellent	0	6	19.4	0	0.0
Good	1	8	25.8	4	26.7
Fair	2	7	22.6	2	13.3
Poor	3	8	25.8	4	26.7
Exacerbation	4	2	6.5	5	33.3
Total		31	100	15	100
Mann-Withney test		Z=-2.22P=0.026			

Table 6. The comparison of the response to treatment between the case and control groups as to lesion size in the sixth months

Pain severity: According to Table 8, a higher proportion of patients in the case group had no pain or had mild pain in the sixth month compared to the patients in the control group. The difference was not statistically significant in the sixth months ($P= 0.476$).

Month		Six			
Response to treatment	Scale of response	Case		Control	
		Number	Percent	Number	Percent
Excellent	0	11	55.0	4	40.0
Good	1	1	5.0	0	0.0
Fair	2	3	15.0	2	20.0
Poor	3	3	15.0	4	40.0
Exacerbation	4	2	10.0	0	0.0
Total		20	100	10	100
Mann-Withney test		Z=-0.712 P=0.476			

Table 7. The comparison of response to treatment between the case and control groups as to the form of the lesions in the sixth months

Month		Six			
Response to treatment	Scale of response	Case		Control	
		Number	Percent	Number	Percent
Excellent	0	0	0.0	0	0.0
Good	1	4	12.9	2	13.3
Fair	2	14	45.2	3	20.0
Poor	3	11	35.5	10	66.7
Exacerbation	4	2	6.5	0	0.0
Total		31	100	15	100
Mann-Withney test		Z=-1.002 P=0.31			

Table 8. The comparison of response to treatment between the control and case groups as to the severity of pain in the sixth months

Correlation of response to treatment Spearman's correlation coefficient analysis demonstrated that, only, in the sixth month there was a significant and direct relationship between recovery from the psychiatric disorders and response to treatment of OLP lesions concerning the form of the lesions ($P=0.058$, $r=0.377$) (Delavarian 2010).

Briefly, our study determined the type of the psychiatric disorders through an interview with a psychologist. Contrary to present study; the vast majority of other studies have already been carried out on the role of psychiatric disorders in oral lichen planus, have used different questionnaires to compare anxiety and depression level of OLP patients with a control group. Some of these studies detected a higher level of stress and depression in patients suffering from OLP than healthy subjects but these studies were not interventional studies. Also, contrary to the vast majority of earlier studies which have only evaluated atrophic and erosive-bullous lesions, we incorporated keratotic lesions, too, into our study (Delavarian 2010). Keratotic lesions do not respond well to routine treatment and the evaluation of the effect of psychotherapy on these lesions is of utmost significance.



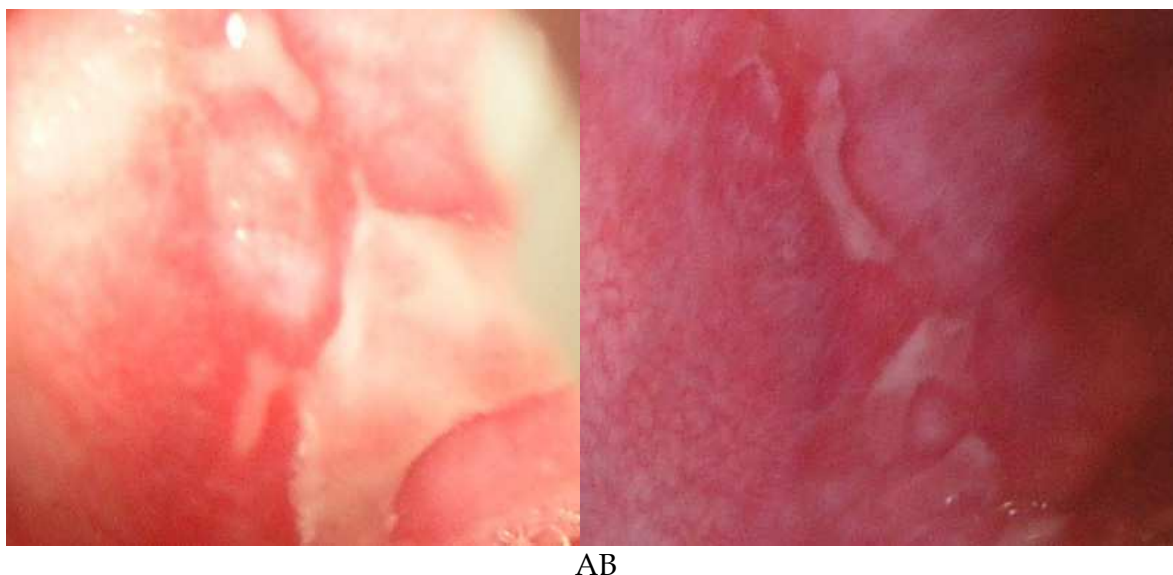
AB

Fig. 1. The patient in the case group had atrophy, erosion and moderate keratosis on the upper lip mucosa and atrophy and mild keratosis on the mucosa of the anterior upper gingival (A). Complete recovery was observed after psychiatric and routine OLP treatment (B).



AB

Fig. 2. The patient in the case group had large ulcer and keratosis on the ventral of the tongue and floor of the mouth (A). Complete recovery was observed after psychiatric and routine OLP treatment (B).



AB

Fig. 3. The patient belonged to the case group and had erosion and moderate keratosis on the right buccal mucosa (A). Relative recovery was observed after treatment (B).

The most important consideration in this study is determining all psychotic disorders. Most of our OLP patients suffered from anxiety disorders. Some patients had several concomitant psychiatric disorders. The most common disorder among our patients was generalized anxiety disorder (GAD) with a prevalence of about 54%; major depression disorder ranked second with a prevalence of 35.5% and only 5.08% of the patients did not have any psychiatric disorder (Delavarian 2010), which is consistent with the results of a study carried out by Collela, who had observed a higher level of anxiety and depression in OLP patients compared to a control group (Colella et al. 1993). Chaudhary concluded from a study in 2004 that OLP patients have a higher level of stress, anxiety and depression compared to healthy individuals (Chaudhary 2004). The level of depression observed in our patients was comparable to the level observed by Akay, who reported depression in 53% of the patients suffering from OLP (Akay et al. 2002).

However, here is controversy over the role of stress as a possible etiologic factor in OLP: some studies have demonstrated that stress may not result in OLP development but OLP may alter the individual's self-image and influence his/ her public relations and lead to secondary depression.

Some other studies have failed to establish a direct cause-and-affect relationship between psychiatric disorders and lichen planus (Rojo-Moreno et al. 1998). In addition, although there seemed to be a parallel relationship between the general response to psychotherapy and the general response to OLP treatment, we were not able to confirm this using Spearman's analysis of correlation coefficient (Delavarian 2010).

In study period, we observed some OLP patients were suffering from other diseases that have relationship with stress. Among them, one patient had Recurrent Aphthous Syndrome (RAS), another affected by Myofascial Pain Dysfunction Syndrome (MPDS) and four patients suffered from Burning Mouth Syndrome (BMS).

Before, another study revealed that the stress level is higher in patients with RAS and OLP, depression is particularly high in patients with BMS, and levels of anxiety are raised in the three diseases, in comparison with the group control (Soto Araya, Rojas Alcayaga, and Esguep 2004).

Our observation concerning the exacerbation of the signs and symptoms of the lesions concomitant with stressful experiences of the patients during study period, established the role of stressful life events in OLP process. Such stressors consisted of family members' disease, financial or legal problems, cancerophobia, and family disagreements (a second marriage of the husband, marriage of children despite parents' opposition, lack of understanding between spouses), loneliness, worries concerning childbirth, accidents, assault and battery and death of family members and relatives (Delavarian 2010). Exacerbation of OLP lesions associated with stressful experiences of the patients and the effect of psychotherapy in reduction of lesion size demonstrated that psychotherapy can be used, at least as an adjunct to routine OLP treatment, to minimize the use of corticosteroids and reduce their side effects.

9. Conclusion

Briefly, drug therapy of psychiatric disorders on OLP indicates that psychiatric treatment along with traditional OLP treatment can be effective in reducing the size of the lesions. With regards to the discussion above, it seems logical to claim that psychiatric evaluation and appropriate treatment of the patients along routine treatment of oral lichen planus lesions should be recommended.

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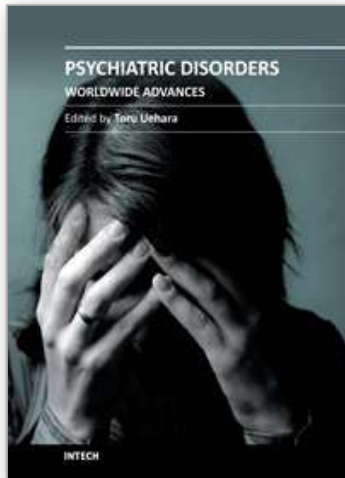
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A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the field. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in "world psychiatry".

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