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Case Report Open Access

A Patient Having Recurrent Aphtous Stomatitis After Three Years of Smoking Cessation; A Case Report and Review of Literature

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Abstract

Cigarette smoking is the foremost health risk issue affecting individuals of all age groups globally. It is the most important causes of the preventable deaths and diseases. Aware of these facts many smokers wish to quit. However smoking cessation is though for smokers who experiences many unpleasant and troublesome physiological or psychological problems. After cessation oral ulcers and other oral aphtous lesions which are considered as mild and expected to disappear in time, can be seen. These problems are attributed with either nicotine withdrawal or nicotine replacement therapy. Recurrent oral aphtous stomatitis however can be very severe and diminish quality of life even some years after cessation. There are growing epidemiologic evidences for the effects of tobacco use and tobacco cessation therapy on a variety of oral diseases and conditions. In this case report we would like to introduce an ex-smoker patient who had severe recurrent aphtous stomatitis attacks for three years after he had quitted and the current data about the management of oral ulcers and aphtous stomatitis.

Keywords: Tobacco; Smoking; Cessation; Recurrent aphtous stomatitis; Resistant oral ulcers

Introduction

The use of tobacco products has significant effect on oral health such as tooth stains, abrasions and loss, smoker's melanosis, acute necrotizing ulcerative gingivitis and other periodontal conditions, burns and keratotic patches, black hairy tongue, nicotinic stomatitis, palatal erosions, leukoplakia, epithelial dysplasia and squamous-cell carcinoma. [1] Smoking cessation is a difficult process that causes some unwanted effects such as oral ulcers and aphtous lesions [2]. These problems are considered as frequent, normally mild and early to mid-term nicotine withdrawal symptoms. However some of them are quite severe and requires more investigation and intervention. The purpose of this paper is to present an ex-smoker whose main problem was not quitting smoking but suffering from recurrent aphtous stomatitis (RAS) even after three years and review the evidences about the topic. He had numerous attacks and among all treatment modalities he trusted oral vitamin B12 most.

Case (Part 1)

E.S. was a 46 year old male patient, security officer in the university, applied to smoking cessation clinic in Department of Family Practice, Medical Faculty of Ondokuz Mayis University. He had started smoking at 15 and buying package at 16. He had "9" points from Fagerstrom Nicotine Dependence Test and his tobacco consumption were calculated as 36 package/year. He had three attempts to quit smoking previously on his own without professional assistance. First was 22 years ago and relapsed in 10 days, second 20 years ago and relapsed after a week and last was 2 years ago and he relapsed again after a month. Quitting smoking was not a problem for him. But each time oral ulcers in various places were appearing and preventing him eating or drinking. He was seeking medical help visiting dermatologists and family physician, using various mouthwashes and local corticosteroids but nothing seemed working. At the end he was feeling compelled to start smoking again and soon after starting the ulcers was disappearing for good or recurring only mild form for a brief period. However, he was very motivated to quit smoking but afraid to have oral ulcers. Therefore first we explained that potential harms of smoking outweighs any unwanted effects of quitting including oral ulcers, secondly we offered him to device more effective strategies to combat the problem and lastly we reassured him to be on his side in every stages of the problems.

Oral Aphtous Lesions

This term comes from Greek word "aphtha", meaning ulceration [3]. It is a common condition which is characterized by multiple recurrent small, round ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors [4]. They appear on lips, gingiva, buccal mucosa, tongue and more rarely on palate, tonsil and pharynx. In our case the first attack after cessation was on right tonsil and when he complained about sore throat he was prescribed antibiotics by his family doctor. His tonsil was red but not swollen. Three types of aphthae are described; Minor aphthae, smaller than 1 cm in diameter and 1-5 in numbers are seen in 80-85% of the cases. They heal in 4-14 days without leaving any scars. Major aphthae, larger than1 cm in diameter and 1-10 in number are seen in 15% of the case. They are more painful, healing takes longer (2-6 weeks) and leave scar. Herpetiform aphthae (5%) are painful groups of many 2-3 mm aphthae that heal in 10-14 days without leaving scar [5]. They first

occur in earlier ages than other aphthae and if recurrent, an underlying systematic disease should be suspected [6].

Some patients feel tingling and burning 1-2 days before aphthae formation. The most common patient complaints are pain and difficulty of eating and swallowing. Speaking difficulty can be seen in some patients [7]. Behçet's syndrome should be suspected if genital ulcers are seen alongside with Aphthae. [8]. In recurrent aphthae, the patient should be examined for inflammatory intestinal diseases, Reiter syndrome, systemic lupus erythematosus, celiac disease, neutropenia, iron and folic acid deficiency [3-6]. Diseases and conditions associated with recurrent aphthae are seen in Table 1 [1-6,9].

The diagnosis of recurrent aphthous stomatitis (RAS) is made in the presence of typical ovoid or round ulcer on examination and history of oral ulcers since childhood. The prevalence of RAS in society is around 5-66% with a lifetime prevalence of 36.5 % [10]. Although RAS is considered more common in women, some studies claim the prevalence is equal in both sexes [11]. RAS is more common in people with high socioeconomic status, under the age of 40 and white race. The prognosis is worse in those with RAS beginning under the age of five [12].

Gastrointestinal diseases	**Rheumatoid Diseases**
Microbial Diseases	**Bullous and lichenoid dermatoids**
Reactive	**Other Diseases**
Malignant Diseases	

Table 1. The diseases and conditions responsible for RAS

Case (Part 2)

After a motivational interview with the patient we advise the patients to exercise some life style modifications described elsewhere [13]. In the initial physical examination the vital signs and all systems checks were normal (systolic and diastolic blood pressure 120 / 80 mm Hg). His body mass index was 25 kg / m2 with a waist circumference of 98 cm. He had no history of head trauma, epilepsy or seizures, eating disorders or any symptoms of cardiovascular disease. Hemoglobin level, differential white cell account, red cell indices and blood chemistry were all normal (Including lipid panel, ALT, AST, fasting blood glucose, urea, creatinine etc.). He used Bupropion 150 mg daily initially for three days and then the dose was increased to 300 mg a day. He tolerated the drug well with no important side effect. He quitted smoking at the 14th day totally and 2 mg nicotine gum 6 times a day started at the same day. When he came a week later for the first after cessation visit he had three ulcers about 1x1 cm in diameter, one on the soft palate, one on the right tonsil and one on the border of the tongue. He had several minor ulcers (<1 cm in diameter) at the tip of the tongue. Antiseptic mouth rinse (Chlorhexidine) and local corticosteroid is recommended first but he objected claiming he knew them and they were of no use. Topical anesthetics (Lidocaine) and B12 vitamin mouth rinse then recommended. Later he reported that among all the treatment he tried B12 mouth wash was the most effective. He continued to use Bupropion regularly but he stopped chewing nicotine gum at second week without any relapses or slips.

Etiology

The etiology of RAS is not entirely clear. Despite many studies trying to identify a causal microorganism, RAS does not appear to be infectious. A genetic predisposition is present, as 40 % of the patients have family history with a strong associations with genotypes IL-1beta; IL-6 [15]. Hematinic deficiency is found in up to 20% of patients. Ulcers similar to RAS may be seen in human immunodeficiency virus disease and some other immune defects, and drugs, especially non-steroidal anti-inflammatory drugs, captopril, gold salt, phenobarbital, sodium hypochlorite and nicorandil (a potassium channel activator used for angina treatment) [3]. Local anesthetic injection, dental treatments and traumas like brushing teeth may trigger RAS [3]. It is considered that the hormonal changes during pregnancy, premenstrual and menopausal period increase RAS prevalence [3]. The role of diet in the RAS etiology has been examined frequently. Gönül, et al, stated that parsley, orange, white cheese, tea, lemon, yoghurt and lettuce could have a role in RAS pathogenesis [16]. While walnut, chocolate and brown bread could provide protection, over consuming tea and herbs could cause aphtha. [9]. psychological factors are implicated in aphtha formation [17]. Iron, vitamin B12 and folic acid deficiencies are reported in RAS patients two times more than controls [18]. In patients with neutropenia RAS is seen more frequently [19]. Toothpastes containing sodium lauryl sulphate are blamed in RAS etiology [20].

Aphtous ulcers and RAS appear to occur less frequently in smokers than non-smokers [21, 22]. Smoking cessation results in worsening of aphtous ulcers, and resumption of smoking improves the condition [23]. Cessation of smoking may precipitate or exacerbate RAS in some cases. The hypothesis is that smokers develop mucosal hyperkeratinization, which protects mucosal surface better from the ulceration [21]. Another explanation is that nicotine triggers adrenal steroid production and influences macrophages directly causing decrease in the cytokine production hence decreases the RAS prevalence [24].

McRobbie et all. [25] Have shown that of the 1234 smokers, 40% of the patients developed mouth ulcers, 8% being severe, in the first two weeks. The ulcers resolved within 4 weeks in 60% of the patients. Mouth ulcers were correlated with other tobacco withdrawal symptoms and higher levels of addiction. Mouth ulcers were more prevalent in more dependent smokers, and the occurrence of ulcers correlated with other tobacco withdrawal symptoms. In another study with a relative small group of smokers (n= 90) who quitted revealed that point prevalence of RAS among the subjects on the first day of the quitting period and at the end of the first, third and sixth week after smoking cessation was 3.3%, 18.9%, 21.1%, 17.1% respectively [26].

Peculiarly nicotine used for tobacco cessation is shown to cause mouth ulcers in a recent systematic review and meta-analyses involving 177, 390 patients revealed mouth ulcer is one of the most frequent adverse effect of NRT (OR 1,49 %95 CI, 1,05-2,20) [27]. The

problem is made worse with oral nicotine compared to patch, nasal spray or bupropion in the first week of abstinence [25]. The relation between the duration, dosage and types of nicotine products to the mouth ulcers requires more research.

Case (Part 3)

At the end of the first smoke free month, the patient had severe and multiple mouth ulcers along with insomnia and loss of concentration that noted as midterm withdrawal symptoms of nicotine. But He was not concerned at all as he was sure with the B12 oral wash the ulcers were to heal quickly. Patient was advised to use topical analgesic and corticosteroid but he refused. Bupropion regiment of 300 mg a day is continued. At three months' consultation after the cessation he was doing so well that bupropion was stopped and he was put on the long term relapse prevention program of our clinic. As far as oral ulcers concerned he denied having any significant attack. He was confident to be able to deal with it by starting his B12 mouthwashes daily as soon as he feels burning and tingling sensation that he was sure fallowed by ulcers. He believed he was stopping attacks in this way effectively. He applied to our clinic sixth months from cessation with the most severe ulcer lesions. The lower palate and tongue were covered with multiple ulcers ranging diameters <1 and >1 cm. In his history he told that ulcers began to emerge two weeks ago with mild pain. As he was away with his family for a holiday he couldn't get any B12 vitamin flacons for rinsing his mouth. Moreover there was a big family argument between his mother and his wife. He tried to use topical anesthetics (Lidocaine), antiseptic mouth rinse (Chlorhexidine) and topical corticosteroid (Hydrocortisone sodium) he had, however the ulcers worsened. In his physical examination he had normal findings (including no lymphadenopathy). A full blood chemistry (hemoglobin level, differential white cell account, and red cell indices), iron, ferritin, folate and serum vitamin B12 levels reveled no abnormal findings. Erythrocyte sedimentation rate, pathergy reaction, anti-endomisium antibodies and anti-gliadin antibodies were normal. Lesion biopsy revealed chronic inflammation with nonspecific ulceration.

Management of Mouth Ulcers and RAS

Complete blood count, folate, vitamin B12 level, serum ferritin, iron, serum iron binding capacity, thiamine, riboflavin, pyridoxine, zinc, magnesium levels and erythrocyte sedimentation rates are recommended for RAS [13, 20]. In a study only the ferritin deficiency is found statistically significant for RAS and patients were not anemic [18, 28]. Behçet's disease should be suspected and pathergy test ordered if genital ulcers, eye or other systemic findings are present along with oral ulcers [12, 29, and 30]. Gluten sensitive enteropathy / Celiac disease should be suspected and tissue transglutaminase and anti-endomysial antibody levels ordered if severe malnutrition, anemia, chronic diarrhea, abdominal pain and recurrent oral aphthae are seen. [3]. inflammatory intestinal diseases are suspected if abdominal pain, hematochezia, fever and RAS are present. [13]. If the same oral ulcers not heal over three weeks neoplasia, immune deficiency, HSV, CMV , syphilis, HIV, tuberculosis, deep fungal infections, mucocutaneous rheumatologic diseases and serious systemic diseases like vasculitis should be excluded. [5].

Treatment

There is no reliable and effective treatment for RAS. In general, juices, citrus, tomato, spices like red pepper, curry, strong acidic and salty materials like alcoholic drinks and soda should be avoided. Dental care products containing sodium lauryl sulphate (SLS) should not be used. The recovery period and pain in oral aphthous ulcers can be decreased substantially by using toothpastes not containing SLS [31]. When there is no specific underlying reason, the aim of medical treatment is to reduce pain and inflammation. Different topical and systematic agents are used in RAS treatment and the treatment should always start with topical treatment. Nicotine replacement treatment reported to prevent RAS In ex-smokers. Nicotine has an anti-inflammatory effect on keratinocytes [32, 33]. Some reports total remission with nicotine gums [34]. Local anesthetics, antiseptics and anti-inflammatories can be used for topical treatment shown on Table 2. In RAS cases they mitigate the pain and speed up the ulcer healing [35]. If a combined treatment with local anesthetic and anti-inflammatory agents is not effective topical corticosteroids should be used. In Germany, a registered toothpaste containing prednisolone used commonly [36]. Topical corticosteroids generally reduce the pain and speed up healing but if used in late period they delay the scar formation and healing. [37]. oral candidiasis and systemic absorption are other side effects of steroids. Gargling with tetracycline reduces aphtha size, duration and pain. Tetracycline shouldn't be used under 8 years due to its negative influences on development of teeth [38]. Cephalexin and azithromycin are used in oral aphtha treatment with no effect on RAS incidence and recurrence [33, 35]. When azithromycin is used over five days side effects of taste disorders, skin reactions, oral candidiasis, angular cheilitis, burning and bitterness sense could occur. sucralfate solution used four times a day has recovery effects on lesions and forms a barrier on mucosa [13].

1.Antiseptic, anti-inflammatory and analgesic drugs (Chlorhexidine mouth rinse or gel 3x1, triclosan gel 3 x1; topical diclofenac %3 3 x1; Amlexanox %5 2-4 x1)
2. Antibiotics (tetracycline, Cephalexin, Azithromycin susp.)
3. Topical corticosteroids (triamcinolone acetonide %0.05-0.5 3-10 x1, fluocinolone acetonide %0.025- 0.05 5-10 x1; Clobetasol Propionate %0.025 3-5 x1).
4.Hyaluronic acid 0.2% gel 2 x1, two weeks
5.Topical anesthetics (topical lidocaine %2-5 , mepivacaine %1,5, tetracaine %0,5-1 spray or gel, mouth wash solution containing benzocaine and cetylpyridinium chloride)
6.Others: Sucralfate suspension, Laser, Cauterization, quercetin, myrtle, rosa damascene

Table 2. Local Pharmaceutical Treatment

In severe oral aphthae systemic treatments can be useful shown in Table 3. Colchicines may be used with pentoxifylline and prevent chemotaxis, mobilization and adhesion of inflammatory cells by depolimerizing microtubules proteins. Thalidomide and pentoxifylline have immunomodulator and anti-inflammatory qualities and inhibit anti-TNFα production. If colchicine and pentoxifylline fail, systemic corticosteroids should be considered with or without topical treatments [36]. Starting dose is 1, 0 mg/kg and increased slowly as

they cause serious side effects of hyperglycemia, lipodystrophy, moon face, hypothalamic-pituitary - adrenal axis suppression, depression and osteopenia/ osteoporosis [18] Dapsone inhibits the migration of polymorphonuclear leukocytes however its use is limited as it may cause hemolytic anemia and methemoglobinemia [39]. Volkov et al reported in a double blind randomized study that the use of oral B12 in RAS patients is cheap and effective treatment method with rare side effects and can be used without checking the serum levels [40]. In a systemic review Liu et al. [41] had concluded that although daily VitB12 supplement may have benefit on pain relief among RAS patients, the effectiveness of this therapy can't be decided due to the limited number of studies and small sample size. In our experience, use of vitamin B12 flacons for gargling and swallowing thereafter in oral aphtae yields good results. Daily vitamin C supplement for three months reported to be effective [42]. In placebo-controlled studies, azathioprine is shown to decrease prevalence and intensity of oral-genital ulcers [43]. Testosterone injection once a year In premenstrual period and estrogen dominant oral contraceptives use for 3-6 months are found effective [44]. There was no effect of treatments like cyclosporine and interferon- α were found ineffective for oral aphtha [36]. Very limited advantage of surgical and laser ablation was reported [18].

1.Antibiotics (penicillin G potasium, 50 mg tb 4 x1, 4 days)
2.Corticosteroids (Prednisolone or prednison equivalents 10-30 mg / day 1-2 months)
3. Colchicine 0,5-2 mg/ day, 7-14 days
4.Dapsone 25-100 mg / day, 3 days
5.Clofazimin 100 mg/ day, 6 months
6.Pentoxifylline 300-400 mg 1-3x1,1 month
7.Zinc sulphate, vitamin B12, iron, folic acid replacement
8.Immunomodulators: Thalidomide 50-100 mg / day, levamisole 150 mg 3 times a week, 6 months
9.Homeopathic materials (mercurius solubilis, Natrum muriaticum, phosphorus, sulphuric acid, nitric acid)

Table 3. Systemic Pharmaceutical Treatment

Case (Part IV)

After dermatology, rheumatology and gastroenterology consultation the patient received oral prednisolone (20 mg daily, scheduled for a month), topical analgesics (Lidocaine) and antiseptic mouth rinse (Chlorhexidine). However he confessed later he did not follow this regiment as it hurt his stomach. He went back to oral lavage of VitB12 and Oral Zinc supplement. After a week the ulcers disappeared fully. For the next two years he had three more mouth ulcer attacks which he cured with topical analgesics, oral VitB12 lavage and zinc supplements ranging from 4 – 10 days. In his last visit (20.8.2014) three years from the cessation he had multiple ulcers (ranging between <1 and >1 cm in diameter) in the soft plate and tongue. He said the treatment he trusted so long may not be working any more. This time he used 2 mg nicotine gum 6 times daily. His ulcers were disappeared in two days but he stated that he was craving for smoking. He was advised to quench this feeling with nicotine gums and resist urge to smoking.

As a conclusion although oral aphtous lesions are one of the most frequent problems seen in the ex-smoker patients after cessation there is lack of knowledge about the etiology and treatment about it. More data and study is needed in this topic.

References

1. Mirbod SM, Ahing SI (2000) Tobacco-associted lesions of the oral cavity: Part 1. Nonmalignant lesions. J Can Dent Assoc 66: 252-256
2. Warnakulasuriya S, Dietrich T, Bornstein MM, Casals Peidró E, Preshaw PM, et al. (2010) Oral health risks of tobacco use and effects of cessation. Int Dent J 60: 7-30.
3. Preeti L, Magesh K, Rajkumar K, Karthik R (2011) Recurrent aphthous stomatitis. J Oral Maxillofac Pathol 15: 252-256.
4. Yates PA, Michelson JB (2006) Behçet disease. Int Ophthalmol Clin 46: 209-233.
5. Scully C (2013) Oral and maxillofacial medicine: the basis of diagnosis and treatment (3rd edn.) Edinburgh: Churchill Livingstone 226-234.
6. Neville BW, Damm DD, Allen CM, Bouquot JE (2008) Oral & maxillofacial pathology (3rd edn.) Philadelphia: W.B. Saunders 331-336.
7. Boyvat A, Ekmekçi P, Gürgey E (2003) Bipolar aphthosis. A forme fruste of Behçet's disease. Long term follow-up of 26 cases. Adv Exp Med Biol 528: 321-322.
8. Rogers RS 3rd1 (1997) Recurrent aphthous stomatitis in the diagnosis of Behçet's disease. Yonsei Med J 38: 370-379.
9. Brocklehurst P, Tickle M, Glenny AM, Lewis MA, Pemberton MN, et al. (2012) Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). Cochrane Database Syst Rev 9: CD005411.
10. Kleinman DV, Swango PA, Pindborg JJ (1994) Epidemiology of oral mucosal lesions in United States schoolchildren: 1986-87. Community Dent Oral Epidemiol 22: 243-253.
11. Messadi DV, Younai F (2010) Aphthous ulcers. Dermatol Ther 23: 281-290.
12. Yalcin BM, Unal M, Pirdal H, Karahan TF (2014) Effects of an anger management and stress control program on smoking cessation: a randomized controlled trial. J Am Board Fam Med 27: 645-660.
13. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, et al. (2012) Recurrent aphthous stomatitis: a review. J Oral Pathol Med 41: 577-583.
14. Gönül M, Gül U, Cakmak SK, Kiliç A (2007) The role of the diet in patients with recurrent aphthous stomatitis. Eur J Dermatol 17: 97-98.
15. Odom RB, James WD, Berger TG, Recurrent aphthous stomatitis (2000) Andrews disease of the skin. (9th edn.) Philedephia: WB Saunders Company 1006-1008.
16. Porter SR, Scully C, Pedersen A (1998) Recurrent aphthous stomatitis. Crit Rev Oral Biol Med 9: 306-321.
17. Chen Y, Fang L, Yang X (2013) Cyclic neutropenia presenting as recurrent oral ulcers and periodontitis. J Clin Pediatr Dent 37: 307-308.
18. Scully C (2006) Clinical practice. Aphthous ulceration. N Engl J Med 355: 165-172.
19. Grady D, Ernster VL, Stillman L, Greenspan J (1992) Smokeless tobacco use prevents aphthous stomatitis. Oral Surg Oral Med Oral Pathol 74: 463-465.

20. Tüzün B, Wolf R, Tüzün Y, Serdaroğlu S (2000) Recurrent aphthous stomatitis and smoking. Int J Dermatol 39: 358-360.
21. Baron JA (1996) Beneficial effects of nicotine and cigarette smoking: the real, the possible and the spurious. Br Med Bull 52: 58-73.
22. Sawair FA (2010) Does smoking really protect from recurrent aphthous stomatitis? Ther Clin Risk Manag 6: 573-577.
23. McRobbie H, Hajek P, Gillison F (2004) The relationship between smoking cessation and mouth ulcers. Nicotine Tob Res 6: 655-659.
24. Marakolu K, Sezer RE, Toker HC, Marakolu I (2007) The recurrent aphthous stomatitis frequency in the smoking cessation people. Clin Oral Investig 11: 149-153.
25. Mills EJ, Wu Ping, Lockart I, Wilson K, Ebbert JO (2010) Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of 120studies involving 177, 390 individuals. Tobacco Induced Diseases 8: 8.
26. Porter SR, Scully C, Flint S (1988) Hematologic status in recurrent aphthous stomatitis compared with other oral disease. Oral Surg Oral Med Oral Pathol 66: 41-44.
27. Mendes D, Correia M, Barbedo M, Vaio T, Mota M, et al. (2009) Behçet's disease--a contemporary review. J Autoimmun 32: 178-188.
28. Oh SH, Han EC, Lee JH, Bang D (2009) Comparison of the clinical features of recurrent aphthous stomatitis and Behçet's disease. Clin Exp Dermatol 34: e208-212.
29. Shim YJ, Choi JH, Ahn HJ, Kwon JS (2012) Effect of sodium lauryl sulfate on recurrent aphthous stomatitis: a randomized controlled clinical trial. Oral Dis 18: 655-660.
30. Altenburg A, Abdel-Naser MB, Seeber H, Abdallah M, Zouboulis CC (2007) Practical aspects of management of recurrent aphthous stomatitis. J Eur Acad Dermatol Venereol 21: 1019-1026.
31. Bonitsis NG, Altenburg A, Krause L, Stache T, Zouboulis CC (2009) Current concepts in the treatment of Adamantadies-Behets disease. Drugs Future 34: 749-763.
32. Bittoun R (1991) Recurrent aphthous ulcers and nicotine. Med J Aust 154: 471-472.
33. Greer RO Jr, Lindenmuth JE, Juarez T, Khandwala A (1993) A double-blind study of topically applied 5% amlexanox in the treatment of aphthous ulcers. J Oral Maxillofac Surg 51: 243-248.
34. Altenburg A, Zouboulis CC (2008) Current concepts in the treatment of recurrent aphthous stomatitis. Skin Therapy Lett 13: 1-4.
35. Alpsoy E (2005) Behçet's disease: treatment of mucocutaneous lesions. Clin Exp Rheumatol 23: 532-539.
36. Mumcu G, Ergun T, Elbir Y, Eksioglu-Demiralp E, Yavuz S, et al. (2005) Clinical and immunological effects of azithromycin in Behçet's disease. J Oral Pathol Med 34: 13-16.
37. Cawson RA, Odell EW, Porter S (2008) Cawson's essentials of oral pathology and oral medicine (8th ed.). Edinburgh: Churchill Livingstone 220-224.
38. Volkov I, Rudoy I, Freud T, Sardal G, Naimer S, et al. (2009) Effectiveness of vitamin B12 in treating recurrent aphthous stomatitis: a randomized, double-blind, placebo-controlled trial. J Am Board Fam Med 22: 9-16.
39. Liu HL, Chiu SC, Chen KH (2013) Effectiveness of Vitamin B12 on recurrent aphthous stomatitis in long term care: a systematic review. The JBI Database systematic reviews and implementations reports 11.
40. Yasui K, Kurata T, Yashiro M, Tsuge M, Ohtsuki S, et al. (2010) The effect of ascorbate on minor recurrent aphthous stomatitis. Acta Paediatr 99: 442-445.
41. Yazici H, Pazarli H, Barnes CG, Tüzün Y, Ozyazgan Y, et al. (1990) A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 322: 281-285.
42. Zouboulis CC (2003) Adamantiades-Behets disease. In: Katsambas AD, Lotti TM, eds.: European Handbook of Dermatological Treatments (2nd edn.) Berlin: Springer 16-26.