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Case Report

Efficacy of Infliximab for the Treatment of Oral Manifestation of Crohn's Disease

Aibar Aginbay[a] Saule Khamzina[b] Marzhan Zhanasbayeva[a]
Kulpash Kaliaskarova[a] Kanat Batyrbekov[c] Gulnara Kulkayeva[a]

[a]Department of Gastroenterology, National Research Oncology Center, Nur-Sultan, Kazakhstan; [b]Department of Surgery, National Research Oncology Center, Nur-Sultan, Kazakhstan; [c]Department of Endoscopy, National Research Oncology Center, Nur-Sultan, Kazakhstan

Keywords
Crohn's disease · Extraintestinal manifestation · Inflammatory bowel disease · Infliximab

Abstract
Oral manifestations of IBD can be specific or nonspecific, due to intestinal malabsorption or induced by pharmacological treatments. Oral manifestations may precede the diagnosis of IBD or interfere with timely diagnosis and treatment. The paradigm of treatment for oral lesions in patients with IBD is based on treating and controlling the intestinal manifestations of the underlying disease as well as local methods of treatment can be used. Here, we report a case of a patient with the oral manifestation of IBD, who responded to treatment with infliximab. The patient was admitted with complaints of long-term nonhealing ulcers of the lips and oral cavity, odynophagia, and there were no intestinal manifestations at that time. The appearance of the disease in 2008 with lesions of the oral cavity, however, Crohn's disease was diagnosed in 2016. The patient began therapy with azathioprine and prednisolone, and later developed hormone dependence and osteoporosis. In 2020, against the background of immunosuppressive therapy, the patient has an exacerbation, especially increased symptoms from the lesion of the oral cavity. In 2020 was started therapy with vedolizumab, with slight improvement. Due to the ineffectiveness of the latter's therapy, therapy with monoclonal antibodies (infliximab) was started in February 2021. Currently, patient is in clinical, laboratory, and endoscopic remission.

Correspondence to:
Saule Khamzina, khamzina.saule88@gmail.com

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Introduction

CD is a systemic chronic disease characterized by transmural granulomatous inflammation. There are various clinical courses known as extraintestinal manifestations of inflammatory bowel disease (IBD), with an incidence of 6–47% [1]. The first description of ulcers in two CD patients was given by Dyes in 1969 [1]. In the same year, Dudeney described cases with oral lesions in two CD patients [2]. Since then, the issue of extraintestinal manifestations has been studied more actively; despite this, the involvement of the oral cavity is still a difficult task to diagnose.

The incidence of oral lesions in IBD varies widely, from 0.7 to 37% [3], occurs more often in CD than in ulcerative colitis (UC), and in more than half of cases (60%) precedes intestinal symptoms [4, 5]. The correlation between the activity of the process in the oral cavity and intestinal manifestations is weak, especially in childhood, and 30% of patients have active clinical manifestations, despite the achievement of remission of the process in the intestine [6, 7]. Oral manifestations of IBD can be specific or nonspecific, due to either intestinal malabsorption or drug-induced. A few of these manifestations, such as aphthae, buccal mucosal swelling, mucosal tags, deep liner ulcerations, and cobblestoned oral mucosa, are more demonstrative of CD, while pyostomatitis vegetans is correlated to UC. Especially, orofacial granulomatosis, a rare condition characterized by swelling of the lip and the oral cavity, must be investigated in young children, because it can conceal underlying Crohn's disease or be a presenting feature of other systemic diseases [8]. The paradigm of treatment for oral lesions in patients with IBD was achieved by treating and controlling the intestinal manifestations of the underlying disease. Here, we report a case of a patient with the oral manifestation of IBD, who responded to treatment with infliximab, the chimeric monoclonal antibody to tumor necrosis factor (TNF).

Case Presentation

In August 2020, a 55-year-old man with complaints of long-term nonhealing ulcers of the lips and mouth, odynophagia, was hospitalized in our clinic. The anamnesis of his disease begins in 2008, at the age of 43, when superficial ulcers on the tongue, aphthous stomatitis, began to appear, which easily responded to local antiseptic therapy. Since 2012, the number and size of ulcers have increased. Subsequently, the patient notes the appearance of intestinal symptoms: a tendency to constipation, with maximum stool retention up to 7 days. Since 2015, the patient developed abdominal pain. Gastroscopy showed a picture of gastritis and bulbitis. In May 2015, the colonoscopy revealed ulcer at the mouth of the bauhinia flap, without any stenotic lesions. Pathology reports from that lesion showed ulcerative defect. In June 2015, with insufficient preoperative examination, in another hospital, the patient underwent surgery – open extended right colectomy with the formation of ileotransversoanastomosis. Intraoperatively, in the area of the ileocecal angle of the colon, a tumor-like inflammatory infiltrate was revealed; along the right colonic artery, the lymph nodes were enlarged to 2.0 cm, what caused the extended right colectomy. Pathology reports from resected colon showed chronic ulcer of the colon, chronic colitis, and no signs of cancer. There was no postoperative management after discharge. Only in 2016, based on data such as the presence of ulcerative lesions of the tongue, gums, duodenum (single erosion up to 0.4 cm), large intestine, histologically revealed data on multiple granulations, high numbers of acute phase indicators: ESR-53 mm/h, CRP-56.0 μ/mL, a high level of fecal calprotectin (more than 1,000) was diagnosed Crohn's disease. In September 2016 started therapy with azathioprine 125 mg/day, and systemic steroids – prednisolone 0.5–25 mg/day. The patient

received these drugs for 2 weeks and then stopped taking the medication. In June 2017, prednisolone 40 mg/day and azathioprine 100 mg/day were restarted. The patient became steroid dependent, with recurrence of mouth ulcers after the reduction of dose steroids below 30 mg/day; consequently, he continued to take prednisolone at this dosage until mid-2018, when he developed a complication – drug osteoporosis. In August 2020, exacerbation of the disease was noted (Fig. 1, 2), taking into account the development of steroid dependence, resistance to therapy with immunomodulators, the start of therapy with monoclonal antibodies was recommended. Therapy with vedolizumab was started according to the standard regimen. At the initiation stage, the patient had the healing of ulcers in the pharynx, esophagus, and most ulcers in the oral cavity, except for the tongue (Fig. 3), but later, at the stage of maintenance therapy, the appearance of intestinal symptoms – abdominal pain, fever, and recurrence of oral ulcers. Due to the nonresponsiveness to the therapy, which was confirmed by ulcers in the tongue, colonoscopy showed ulcers in the anastomotic area (Fig. 4), a change in therapy was carried out, and in February 2021 therapy with monoclonal antibodies (infliximab) was started according to the standard scheme in combination with azathioprine. Clinical improvement was detected after the first dose: healing of most ulcers, restoration of the act of painless food intake and swallowing (Fig. 5), the stool acquired a formalized character, a decrease in CRP (Fig. 6). After 14s week of treatment, during maintenance therapy, escalated infliximab dose to every 4 weeks and azathioprine changed to 6-mercaptopurine 1 mg/kg, and intestinal and oral manifestations do not bother. Before starting infliximab therapy, histology was not taken from the oral cavity, we obtained histology against the background of clinical remission, and histological findings from the tongue showed the presence of inflammation, scattered infiltration by leukocytes, lymphocytes, and granulocytes, the edema of adjacent stroma (Fig. 7).

Discussion

The most common oral manifestation of IBD is aphthous stomatitis (aphthae with an atypical presentation or clinical course), which occurs from about 0.7–20% (this last one regarding only UC) in adults and from 3.2% to 41.7% in children [8–12]. They cannot be distinguished from usual aphthae unless a biopsy is performed, which must be based on clinical manifestation. The frequency of aphthous stomatitis was same as in the healthy population, with a tendency of recurring in time [13], and described as the presence of small, painful but benign oral ulcers, circumscribed by an erythematous halo, usually occurring on the buccal and labial mucosa or the vestibular sulci. In IBD, aphthous ulcerations also may be caused by a deficiency of iron, zinc, or vitamin B12 due to intestinal malabsorption and rectal bleeding linked to the main disease, or a side effect of their pharmacological treatment [10].

Oral manifestation of IBD can be specific or nonspecific and can precede (12.7–21%) [9, 14], or be the presenting sign of gut involvement. Our case was also no exception, and in the clinical picture, intestinal manifestations faded into the background, which led to some delay in the diagnosis. Among the specific lesions correlated to CD, there are mucosal tags, cobblestoning of the mucosa, and buccal swelling linked to granulomatous cheilitis. Cobblestoning of the mucosa is defined by a combination of deep, transversely, and longitudinally oriented ulcerations separating intact portions of mucosa giving the resemblance of cobblestones [15], and it can be seen in a range from 6% to 20%, respectively, in children and adults [12, 16].

Therapeutic management of oral lesions is multidisciplinary. It requires a reevaluation with a gastroenterologist as soon as the lesions appear. Overall, in most patients, clinical remission of IBD is associated with the healing of oral manifestations. The pharmacological

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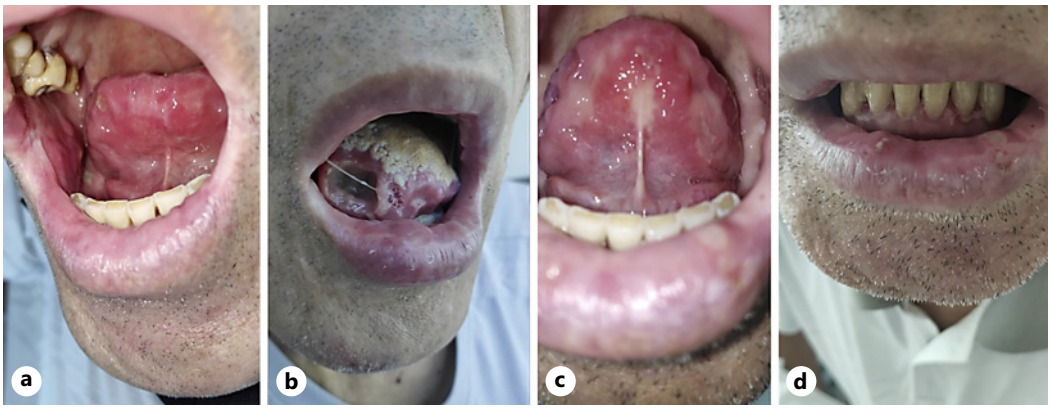

Fig. 1. a Moderate swelling of the lips, erosion and ulcers of the lips, stomatitis. **b**, **c** Deep ulcerative defects on the lateral surface of the tongue on the left and superficial ulcers on the right, erosion of tooth enamels. **d** Linear ulcer in the buccal sulcus on the right.

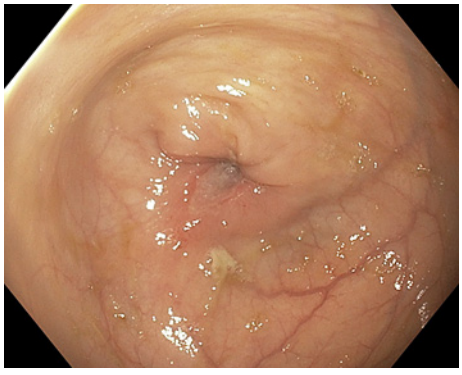

Fig. 2. Video esophagogastroscopy: ulcerative defects on the eve of the pharyngeal house and in the esophagus.

variety includes topical or systemic corticosteroids, immunosuppressive agents, and biologic (mainly anti-TNF-α) drugs. Topical treatment includes intralesional injections, mouthwashes, and ointments. This approach generally starts with corticosteroid ointments and/or mouthwashes and nonsteroidal anti-inflammatory pastes. In the case of nonresponse, intralesional injection of corticosteroids is prescribed. If the patient's symptoms do not improve, a systemic approach with corticosteroids is required [17]. In severe cases, for example of visualizing oral CD or diluting it to treat aphthous stomatitis, treatment with biologic drugs has obtained satisfactory results.

However, in the case of our patient, first-line treatment was based on the use of systemic steroids and maintenance therapy with thiopurine, which was complicated and formed development of steroid dependence and complications in the form of osteoporosis. The step-up approach was adopted, taking into account the history of suspected pulmonary tuberculosis in 2015, therapy with vedolizumab was started, which was not effective enough, and the next step was to start therapy with infliximab. Infliximab is a chimeric monoclonal IgG1 antibody that binds to both soluble and membrane TNFa and inhibits the binding of TNFa to its receptors [18]. The effectiveness of infliximab in extraintestinal manifestations of IBD, in particular in oral CD, has been shown more than once in other works [17, 19].

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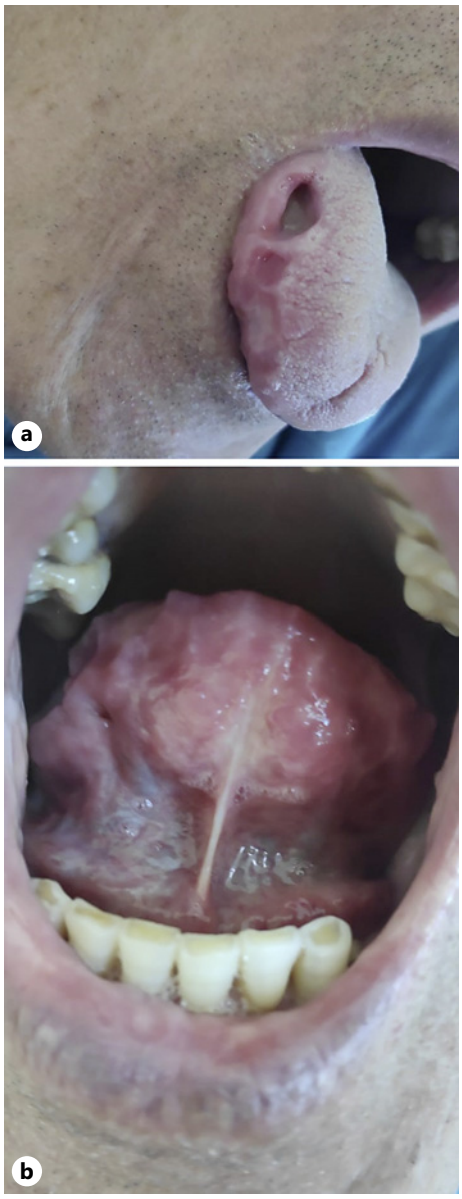

Fig. 3. a, **b** Preservation of ulcers in the tongue, healing of ulcers and erosion of the lips, superficial ulcers of the tongue during therapy with vedolizumab.

Conclusion

The list of oral lesions that may affect IBD patients is extensive. Lesions affecting orofacial regions may have devastating consequences, not only because of disabling symptoms and impairment in eating but also because of the cosmetic consequences in young patients. While most lesions are easily handled and respond to the treatment of intestinal IBD, others may face severe challenges and require escalation of medical therapy or even surgery. A multidisciplinary approach is essential for the correct diagnosis and management, and the patients with suspected IBD and the oral cavity should be thoroughly examined by an experienced specialist.

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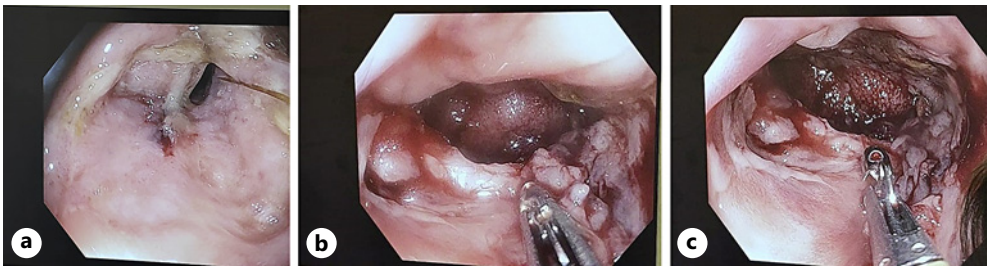

Fig. 4. a–c Ulcer of an ileotransversoanastomosis.

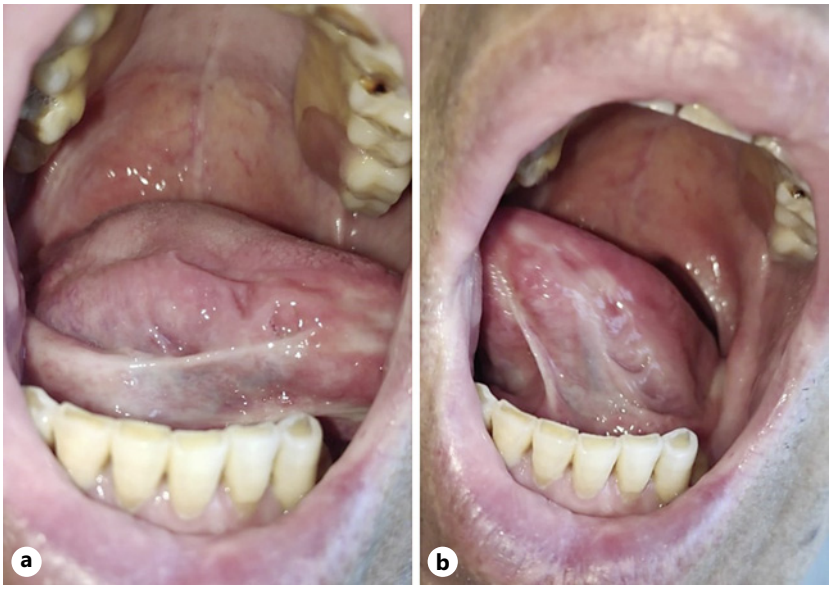

Fig. 5. a, **b** After initiation of two doses of infliximab.

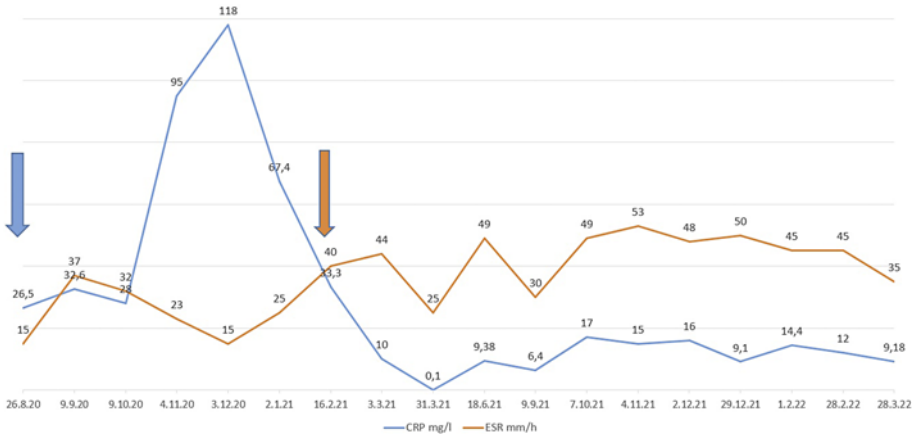

Fig. 6. Graph of changes in CRP and ESR indicating the time of initiation of therapy with vedolizumab (blue arrow) and infliximab (red arrow).

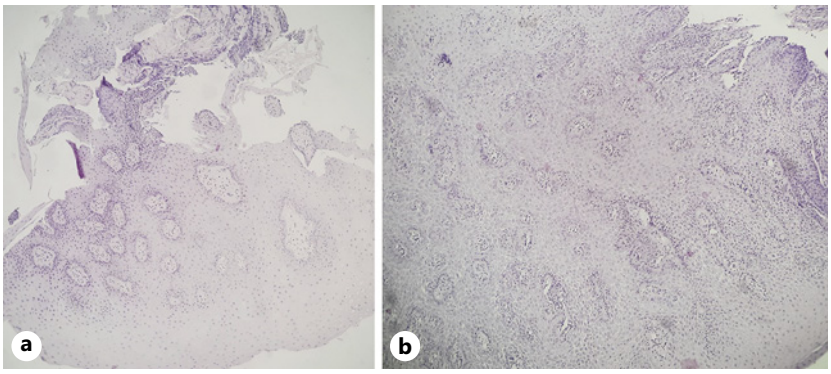

Fig. 7. a, **b** Histological findings from the tongue inflammation, scattered infiltration by lymphocytes, leukocytes and granulocytes, the edema of adjacent stroma (hematoxylin-eosin).

Acknowledgments

We would like to thank the patients who allowed us to share their details of the treatment.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This case report was conducted in compliance with the principles of the Declaration of Helsinki. The Ethical Committee of the National Research Oncology Center (permit No. 6) approved this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors were involved in the preparation of this manuscript. Aibar Aginbay, Kanat Batyrbekov, and Marzhan Zhanasbayeva treated the patient. Aibar Aginbay and Saule Khamzina collected the data and wrote the manuscript. Kulpash Kaliaskarova and Gulnara Kulkaeva summarized the data and revised the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author on request.

References

1 Lankarani KB, Sivandzadeh GR, Hassanpour S. Oral manifestation in inflammatory bowel disease: a review. World J Gastroenterol. 2013;19(46):8571–9.
2 Dudeney TP, Todd IP. Crohn's disease of the mouth. Proc R Soc Med. 1969;62(12):1237.
3 Lauritano D, Boccalari E, Di Stasio D, Della Vella F, Carinci F, Lucchese A, et al. Prevalence of oral lesions and correlation with intestinal symptoms of inflammatory bowel disease: a systematic review. Diagnostics. 2019;9(3):77.
4 Vind I, Riis L, Jess T, Knudsen E, Pedersen N, Elkjær M, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in copenhagen city and county, 2003-2005: a population-based study from the danish crohn colitis database. Am J Gastroenterol. 2006;101(6):1274–82.
5 Vavricka SR, Brun L, Ballabeni P, Pittet V, Vavricka BMP, Zeitz J. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106(1):110–9.
6 Rehberger A, Püspök A, Stallmeister T, Jurecka W, Wolf K. Crohn's disease masquerading as aphthous ulcers. Eur J Dermatol. 1998;8(4):274–6.
7 Laranjeira N, Fonseca J, Meira T, Freitas J, Valido S, Leitão J. Oral mucosa lesions and oral symptoms in inflammatory bowel disease patients. Arq Gastroenterol. 2015;52(2):105–10.
8 Grössner-Schreiber B, Fetter T, Hedderich J, Kocher T, Schreiber S, Jepsen S. Prevalence of dental caries and periodontal disease in patients with inflammatory bowel disease: a case-control study. J Clin Periodontol. 2006;33(7):478–84.
9 Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(1):63–8.
10 Scully C, Hodgson T. Recurrent oral ulceration: aphthous-like ulcers in periodic syndromes. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106(6):845–52.
11 Elahi M, Telkabadi M, Samadi V, Vakili H. Association of oral manifestations with ulcerative colitis. Gastroenterol Hepatol Bed Bench. 2012;5(3):155–60.
12 Harty S, Fleming P, Rowland M, Crushell E, McDermott M, Drumm B, et al. A prospective study of the oral manifestations of Crohn's disease. Clin Gastroenterol Hepatol. 2005;3(9):886–91.
13 Oviedo C, Yañez M, Pennacchiotti V. Frequency of oral manifestation in patients with inflammatory bowel disease in chile. Int J Odontostomat. 2017;11(3):267–71.
14 Greuter T, Bertoldo F, Rechner R, Straumann A, Biedermann L, Zeitz J, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease: prevalence, presentation and anti-TNF treatment. J Pediatr Gastroenterol Nutr. 2017;65(2):200–6.
15 Rubesin SE, Scotiniotis I, Birnbaum BA, Ginsberg GG. Radiologic and endoscopic diagnosis of crohn's disease. Surg Clin North Am. 2001;81(1):39–70.
16 Zervou F, Gikas A, Merikas E, Peros G, Sklavaina M, Loukopoulos J, et al. Oral manifestations of patients with inflammatory bowel disease. Ann Gastroenterol. 2004;17:395–401.
17 Katsanos KH, Torres J, Roda G, Brygo A, Delaporte E, Colombel JF. Review article: non-malignant oral manifestations in inflammatory bowel diseases. Aliment Pharmacol Ther. 2015;42(1):40–60.
18 Khanna D, McMahon M, Furst DE. Safety of tumor necrosis factor-a antagonists. Drug Saf. 2004;27(5):307–24.
19 Mahadevan U, Sandborn WJ. Infliximab for the treatment of orofacial crohn's disease. Inflamm Bowel Dis. 2001;7(1):38–42.