Case Report

Refractory Oral Ulcer Responsive to Infliximab: A Case Report

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Keywords

Infliximab · Refractory oral ulcer · Intestinal Behçet disease · Ileocecal ulcer

Abstract

Purpose: Some oral ulcers are refractory to treatment. Recently, anti-tumor necrosis factor- α (anti-TNF- α) agents have been shown to induce relatively long remissions of refractory oral ulcers. **Methods:** A 69-year man presented with a sore throat caused by a pharyngeal ulcer in the soft palate and subsequently repeatedly developed oropharyngolaryngeal ulcers and an ulcer in the ileocecal region. Intestinal Behçet disease was suspected, but he did not meet the diagnostic criteria for this condition. Seven months after the initial presentation, he developed a lingual ulcer that did not resolve despite treatment with prednisolone. Given the suspicion of intestinal Behçet disease, 300 mg of infliximab was administered intravenously. **Results:** After the third dose of infliximab with prednisolone, the ulcer began to improve. He received infliximab every 8 weeks thereafter and developed no new oropharyngolaryngeal ulcers during the 17 months after the first infusion of infliximab. **Conclusions:** When a patient has refractory oral ulcers, attention must be paid to digestive symptoms and whether the patient has a systemic disease such as Behçet disease investigated. Furthermore, administration of infliximab to patients with refractory ulcers can be considered even when they do not fulfill the clinical criteria for a systemic disease.

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Introduction

Recurrent oral ulcers (ROU) are a common condition and frequently encountered by otorhinolaryngologists. Some ROUs are refractory to treatment and associated with systemic diseases, such as Crohn's disease, ulcerative colitis, and Behçet disease. Recently, anti-tumor necrosis factor- α (anti-TNF- α) agents have been shown to induce relatively long remissions of ROUs that are associated with these conditions and resistant to conventional therapies such as steroids and immune-suppressive medications [1–6]. Anti-TNF- α agents are also reportedly effective against ROUs that are not associated with systemic diseases [6–8]; however, no studies or recommendations are available for administration, dosage, or duration of treatment with anti-TNF- α agents for patients without systemic disease.

We herein report a patient with refractory ROUs and intestinal ulceration successfully treated with repeated infusions of infliximab at 8-week intervals. This patient's refractory ulcer resolved with infliximab treatment and did not recur for 17 months, without administration of steroids.

Case Report

A 69-year-old man presented with a sore throat associated with an ulcer in the left soft palate for 1 month (Fig. 1a). The ulcer had initially resolved with prednisolone (30 mg/day) for 6 weeks. Four months later, another ulcer had developed in the right tonsillar bed (Fig. 1b). This resolved with 1 month of treatment with vitamin B₂; however, he then developed another ulcer in the epiglottis (Fig. 1c). This ulcer resolved with 3 months of treatment with a vitamin compound. Apart from his oropharyngolaryngeal ulcers, he was asymptomatic and had no genital ulcers or folliculitis. A skin pathergy test was negative. Six months after resolution of the laryngeal ulcer, he underwent routine lower gastrointestinal endoscopy and an isolated ileocecal ulcer was detected. Histopathologic examination of a biopsy specimen showed nonspecific inflammation. A fourth ulcer developed simultaneously in the right soft palate (Fig. 2a), pathologic examination showed nonspecific inflammation (Fig. 2b). He was treated with prednisolone (30 mg/day) for 3 weeks. After 1 month, he reported diarrhea and upper digestive tract and large intestinal endoscopy revealed a deep, punched-out ulcer in the ileocecal region (Fig. 3a), histopathologic examination showed active colitis (Fig. 3b). There were no other localized lesions in his gastrointestinal tract. He was treated with mesalazine (2,400 mg/day) and the diarrhea and ulcer in the soft palate resolved after 1 month. Seven months later, he presented again with an ulcer on the tip of his tongue (Fig. 4a). After 1 month of follow-up, he was treated with prednisolone (30 mg/day) for 2 weeks. During the next 2 months, he lost 5 kg in weight because of decreased food intake due to enlargement of his painful tongue ulcer (Fig. 4b). Meanwhile, the ileocecal ulcer resolved, leaving endoscopically detected scarring. There were no abnormalities on ophthalmologic examination and HLA B-51 was negative. He was given 300 mg (5 mg/kg) of infliximab intravenously at 8-weekly intervals. Two months after the first infliximab infusion, he was treated with prednisolone (30 mg/day) in addition to infliximab, and the lingual ulcer decreased gradually in size. After the fourth dose of infliximab, the lingual ulcer finally resolved completely (Fig. 4c). During the 8-weekly cycles of 300 mg of infliximab, the dosage of prednisolone was decreased gradually until and stopped 5 months from the first dose of infliximab. Thereafter, he was treated with colchicine (1.0 mg/day) and mesalazine (2,400 mg/day) and developed no new ulcers in the oral cavity, pharynx, or larynx during 17 months of follow-up from the first infusion of infliximab.

Discussion

Here, we reported a patient with refractory oropharyngolaryngeal ulcers that occurred repeatedly in different locations over time. The fifth of these ulcers was unresponsive to prednisolone; however, the anti-TNF- α agent infliximab was effective. The patient had oropharyngolaryngeal ulcers, but no skin or ocular diseases, and no genital ulcers, which excludes a diagnosis of Behçet disease [9]. Additionally, the patient had no arthritis, epididymitis,

Color version available online

Fig. 1. Oropharyngolaryngeal ulcers. **a** The first pharyngeal ulcer in the left soft palate. **b** The second ulcer in the bed of the right palatine fossa. **c** The third ulcer on the epiglottis.

Color version available online

Fig. 2. **a** The fourth ulcer in the right soft palate. **b** Photomicrograph of the periulcerative region of the right palatine tonsillar mucosa showing granulation tissue with infiltration of macrophages, eosinophils, and neutrophils. Hematoxylin and eosin stain; bar = 20 μ m.

Color version available online

Fig. 3. **a** Endoscopic features of a deep punched-out ulcer in the ileocecal region. **b** Photomicrograph of the cryptal epithelium of the cecum mucosa showing decreased numbers of goblet cells and a prominent cryptal abscess. The lamina propria mucosa is widened and infiltrated by plasma cells, neutrophils, and eosinophils. Hematoxylin and eosin stain; bar = 50 μ m.

Fig. 4. **a** The fifth ulcer on the tip of tongue. **b** The ulcer of the tongue got worse before administration of infliximab. **c** The ulcer healed with scarring after the third dose of infliximab combined with prednisolone.

vascular disease, or neurologic disorders. Also, there was no evidence for inflammatory bowel disease such as Crohn's disease or ulcerative colitis. Although he has not fulfilled the criteria for diagnosis of intestinal Behçet disease thus far, he may in the future.

Recently, the use of anti-TNF- α agents for the treatment of mucosal lesions in the oral cavity and pharynx associated with systemic disease has been reported [1–6]. Notably, some patients who had been refractory to a combination of immunosuppressive drugs have had early responses to anti-TNF- α agents, within days to a few months [1–3], and some have had relatively long sustained remissions, varying from 6 to 12 months [5, 6].

Our patient's fifth ulcer occurred in the tongue and was treated with infliximab. His previous oropharyngolaryngeal ulcers took 1–6 months to resolve with prednisolone or vitamin compound treatment. The fifth oral ulcer got worse with the initial treatment of mesalazine and prednisolone. We therefore decided to administer infliximab despite the patient having no evidence of systemic disease. After the third dose of infliximab with prednisolone, the oral ulcer gradually resolved. In the 17 months since the fifth lingual ulcer resolved, there have been no further oropharyngolaryngeal ulcers with 8-weekly administration of infliximab. Meanwhile, the ulcer in the ileocecal region resolved before infliximab was administered. Consequently, we could not ascertain whether the gastrointestinal tract ulcer was responsive to infliximab.

In this patient, the ROU was the only manifestation initially. Subsequently, an isolated ulcer in the ileocecal region was diagnosed, this resolved with scarring after treatment. When assessing patients with refractory oral ulcers, attention must be paid to digestive symptoms such as diarrhea, abdominal pain, and melena, and it should be determined whether the patient has a systemic disease, such as Behçet disease or inflammatory bowel disease. If a patient has a refractory oral ulcer that does not respond adequately to prednisolone or an immunosuppressive agent, administration of infliximab may be considered even when the patient does not fulfill the criteria for diagnosis of a systemic disease. But it should be considered that in some cases, infliximab may be ineffective [6], and the use of infliximab in the absence of any systemic disease is off-label/out-with the licensed indications.

When treating ROUs with infliximab, one unresolved issue is the optimal treatment schedule. Decisions must be made regarding single-dose versus repeated administrations and duration of administration when the patient remains free of ulcers. Ryu et al. [6] reported a patient who was successfully treated with a single dose of infliximab. In our patient, it is not clear whether the lack of recurrence of oropharyngolaryngeal ulcers indicates remission or ongoing prevention by regular repeated administration of infliximab.

In treatment with infliximab, trough serum infliximab concentrations and antibodies to infliximab (ATI) influence prognosis. Higher infliximab trough concentrations are reportedly

associated with better outcomes in pediatric patients with inflammatory bowel disease [10]. Vande et al. [11] reported that low infliximab trough concentrations and ATI are associated with poor outcomes in patients with Crohn's disease. Although in this case, serum infliximab concentrations and ATI were not measured, monitoring for development of ATI when administering this agent will be necessary in the future.

Large randomized study samples are necessary to evaluate the safe and effective dosage of anti-TNF- α agents, the optimal duration of treatment, the place of combinations with other immunosuppressive agents in patients with refractory oropharyngolaryngeal ulcers, the role of measurement of serum TNF- α before administration of infliximab, the effects of trough serum infliximab concentrations and development of ATI. Accumulation of such data is needed to establish the clinical criteria, pathogenesis, and treatment guideline of patients who have ROUs.

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Statement of Ethics

A written informed consent was obtained from the patient, and the study received approval of the Institutional Review Board of Nishinohon Hospital (Permit No. H29–6).

Disclosure Statement

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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