J Oral Pathol Med (2007) 36: 444–6

doi: 10.1111/j.1600-0714.2007.00430.x
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CASE REPORT

The management of fistulizing oral Crohn's disease with infliximab

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A 20-year-old female patient with oral Crohn's disease developed a fistula in her neck from a focus of intra-oral infection. Despite repeated courses of antimicrobial therapy over a period of several months, the fistula failed to resolve. However, following administration of infliximab, a monoclonal antitumour necrosis factor-α antibody, the fistula resolved spontaneously without the need for any further treatment.
J Oral Pathol Med (2007) **36:** 444–6

Keywords: Crohn's disease; fistula; infliximab; oral

Case report

The patient was a 20-year-old female who originally presented to the Department of Oral Medicine, Glasgow Dental Hospital and School in 2002 following a referral from her general dental practitioner. At that time she reported a 4- to 5-month history of lip swelling and swelling involving the buccal mucosa. She reported a long-standing history of gastrointestinal symptoms which was previously attributed to a diagnosis of irritable bowel syndrome following earlier negative investigations including a normal barium meal and follow through and sigmoidoscopy. Clinically she had marked swelling of the upper and lower lips together with some mucosal tags on the buccal mucosa and in the lower labial sulcus. The differential diagnosis included orofacial granulomatosis and oral Crohn's disease. A biopsy from the buccal mucosa demonstrated non-caseating granulomas and the pattern was suggestive of Crohn's disease. She subsequently developed significant gastrointestinal symptomatology and at that point she was referred for further gastrointestinal assessment. Colonoscopy and small bowel imaging studies demonstrated features consistent with Crohn's disease limited to the colon and rectum.

The management of the oral component of her underlying disease was undertaken in the Oral Medicine Department. A combination of prednisolone and azathioprine was used successfully as maintenance therapy.

In November 2003, the patient presented as an emergency to the Department of Oral Medicine with a soft, fluctuant swelling over the right cheek extending to the lower border of the mandible (Fig. 1). This had developed over the course of a week. Intra-orally, no swelling was noted although there was a painless fissured ulcer in the buccal sulcus adjacent to 46, 47 (Fig. 2). No pathology relating to the dentition could be identified and this was confirmed following radiographic examination.

She was referred to the Oral Surgery Department where incision and drainage was carried out under local anaesthesia using an intra-oral approach. This produced a reduction in the size of swelling but not complete resolution. Despite repeated local measures and sequential administration of erythromycin, metronidazole, phenoxymethylpenicillin and amoxicillin she had a purulent discharge from the lower right buccal sulcus that persisted for 5 months.

Eventually in May 2004, the sinus in the right lower buccal sulcus healed, leaving a residual blind ending pouch, but she subsequently developed a fluctuant extraoral swelling overlying the right mandible. A 1 ml aspirate of thick pus was taken and sent for microbiological analysis. Microbiological investigations confirmed a sterile collection. At that time her maintenance medication was prednisolone 15 mg daily together with azathioprine 200 mg daily. She had significant bowel symptoms characterized by formation of an ischio-rectal abscess, increasing abdominal pain and bloody diarrhoea. In an attempt to improve control of her overall condition, oral methotrexate was introduced instead of azathioprine. Unfortunately, this again did not have any significant beneficial impact on her symptoms.

In view of her ongoing symptoms a decision was made to administer a course of infliximab utilizing a standard

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Accepted for publication February 2, 2006

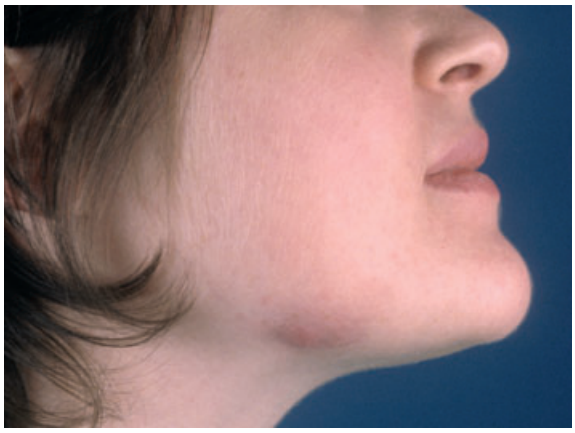

Figure 1 Skin fistula at presentation.

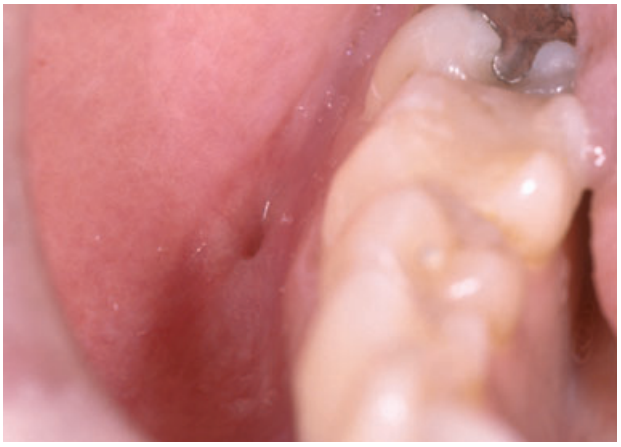

Figure 2 Intra-oral fistula at presentation.

dose regime of 5 mg/kg. She continued on methotrexate whilst getting infliximab as this reduces the incidence of anti-infliximab antibodies and has been shown to sustain remission in those who respond.

The patient commenced treatment with infliximab in August 2004. She was reviewed following the second infusion when it was noted that the discharging sinus in the right submandibular region and associated swelling had now resolved. Unfortunately, she developed a widespread skin rash following the second infusion and accordingly it was initially decided not to progress with any further infusions. However, in view of ongoing symptoms she subsequently had further infusions of infliximab with corticosteroid cover and antihistamines that she tolerated uneventfully. Her Crohn's disease is now well controlled.

Comments

Crohn's disease is a chronic granulomatous inflammatory disorder that can affect any part of the gastrointestinal tract, including the oral cavity. When oral involvement is present, the term oral Crohn's disease may be used. The oral features of the condition are lip swelling and fissures, mucosal tags, cobblestoned buccal mucosa, linear-fissured ulceration and gingivitis.

The pathogenesis of Crohn's disease seems to involve an unbalanced host response to environmental factors in a genetically susceptible individual. This leads to Th1 cell over activity with resultant general over production of proinflammatory cytokines such as tumour necrosis factor (TNF)α (1).

Infliximab is a chimaeric monoclonal IgGκ1 antibody that binds to both soluble and membrane-bound TNFα and inhibits binding of TNFα with its receptors. The mechanism of action of infliximab does not solely involve the neutralization of TNFα but downregulation of TNFα producing cells through an unknown mechanism (2).

Infliximab was first licensed in 1998 and since then over 500 000 patients have been treated worldwide. It is currently licensed by the FDA for use in rheumatoid arthritis and Crohn's disease. It is indicated in patients with moderate to severe Crohn's, which has been refractory to conventional therapy and in fistulizing Crohns disease. There are reports suggesting therapeutic benefit in treating severe refractory oral aphthous ulceration in Behçet's syndrome (3) and in the extra luminal manifestations of inflammatory bowel disease (4).

Overall the safety profile of infliximab has been shown to be good; most cases reported being limited to headaches, nausea, upper respiratory tract infections and infusion reactions. In patients who are unable to tolerate infliximab or have a poor response there is some evidence that a recently available non-chimaeric antibody (adaluminab) may offer an alternative beneficial option (5, 6).

However, serious complications as a result of use of infliximab do occur and include congestive heart failure, liver injury, reactivation of latent tuberculosis and hepatitis B. There is a known and documented higher risk of developing lymphomas compared with controls (2).

Formation of a fistula as a complication of oral Crohn's disease as in this case report is well documented and can be notoriously difficult to treat (7, 8). This is the first case reported in the literature describing the use of a biological agent in such a case. The dramatic resolution of the fistula suggests that use of infliximab should be considered in the management of refractory cases as described in this case report.

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Acknowledgement

The authors would like to thank the Department of Medical Illustration, Glasgow Dental Hospital and School for the help given and permission to use the clinical photographs.