Laryngeal Dysplasia and Chronic Laryngitis Associated with Infliximab Therapy for Ulcerative Colitis
Rebecca L. Chota, Paul C. Bryson MD
Head and Neck Institute, Cleveland Clinic Foundation; Cleveland, OH

Abstract

Educational Objective: At the conclusion of this presentation, the participants should be able to understand the potential for chronic laryngeal inflammation and malignant degeneration in patients undergoing therapy with tumor necrosis factor alpha (TNF-α) inhibitors.

Objective: The risk of malignancy in patients undergoing treatment with TNF-α inhibitors has not been completely elucidated. Current disease states encountered by the otolaryngologist treated with these agents include rheumatoid arthritis, Crohn's disease, sarcoidosis, ankylosing spondylitis, psoriasis, and granulomatosis with polyangiitis (formerly Wegener's granulomatosis). To date, there have been disparate reports regarding the risk of malignancy in these patients treated with these agents. There has been one reported case of early glottic carcinoma in a patient with sarcoidosis treated with infliximab. Herein is presented the first reported case of laryngeal dysplasia and chronic laryngitis in a patient receiving infliximab for ulcerative colitis. Upon discontinuation of infliximab, his voice improved and his endoscopic examination returned to normal.

Case Report

We present the case of a 44-year-old man with hoarseness and a past medical history of ulcerative colitis (UC) with chronic laryngitis and laryngeal dysplasia. Hoarseness coincided with the initiation of infliximab two years prior to chronic UC. Previously, his voice symptoms had failed a trial of nuxium, but improved temporarily with antibiotic treatment. He was on a regimen of 10 mg/kg infliximab infusion approximately every six to seven weeks. He had received a total of 20 doses at the time of presentation. He never smoked, but had a history of chewing tobacco and social alcohol use.

Four months prior to this visit, he underwent direct laryngoscopy with biopsy at an outside hospital with pathology reports indicating mild to severe dysplasia on both true vocal folds, both false vocal folds and the subglottic region. Review of the pathology slides at our institution confirmed moderate to severe dysplasia on the right true vocal fold.

Videostroboscopy showed thickened mucous, dehydrated, erythematous and edematous mucosa with scattered areas of keratin and erythroplakia.[see Fig. 1]. He was treated with maximal reflux therapy (omeprazole and ranitidine) as well as diflucan. After 1 month, the patient experienced subjective vocal improvement, however, his exam was stable showing focal areas of keratosis, edema and erythroplakia. He was prescribed another course of diflucan without improvement and was subsequently lost to follow-up.

Sixteen months after his initial visit to the Voice Center, he returned. The patient felt that his voice had returned to normal (pre-infliximab) within 1 month of discontinuing infliximab. Videostroboscopy showed significant improvement in the appearance of the mucosa with resolution of the erythema, erythroplakia, mucosal dehydratation and crusting in the subglottic mucosa (see Fig. 2).

Discussion

Infliximab is a monoclonal antibody used for a variety of rheumatologic disorders. Its primary mechanism is inhibition of TNF-α, which is known to play a key role in inflammation and a potential risk for tumor growth and carcinogenesis.1 Several side effects are well known, including infusion reaction and infection. Additionally, in combination with glucocorticoids and immunomodulators, TNF-α inhibitors may be associated with an increased risk of some cancers.2,3 To date, laryngeal side effects, pre-malignant and malignant transformation are poorly described.

The dysplasia present in our patient was an unexpected finding and may be related to previous studies linking TNF-α blockers and cancer. The temporal relationship between his symptom resolution and infliximab discontinuation suggests an association. His perceptual improvement, improving VHI scores and resolution of examination findings on videostroboscopy further substantiated this (Fig. 1-2).

Pre-malignant and malignant transformation in the larynx appears to be rare. There is one reported case of a patient who was diagnosed with T1a glottic carcinoma after receiving infliximab therapy for sarcoidosis. This patient also presented with hoarseness and had been previously diagnosed with chronic laryngitis.4 Additionally, a large, multicenter study of Crohn’s disease patients reported an infliximab-treated patient who developed laryngeal carcinoma however this study did not find a statistically significant association between general cancer incidence and infliximab treatment.4 Nonetheless, other literature suggesting an association between infliximab and non-squamous cell carcinomas, namely lymphoma, exists.5,6 This association has only been demonstrated with the concurrent use of other immunomodulators or immunosuppressants and no causal relationship has been demonstrated.6,7 Some studies have also suggested an increased risk of cancer in IBD patients regardless of treatment.8

Though the relationship between infliximab treatment and carcinogenesis is complex and not fully understood, we currently suggest that providers of infliximab therapy remain mindful of laryngeal symptoms. The case presented here suggests that hoarseness may represent a “red flag” for dysplasia. Providers should facilitate thorough evaluation including high resolution laryngoscopy of hoarseness lasting more than a couple weeks in this patient population and may want to consider discontinuation of infliximab if dysplasia is discovered.

We also recognize there is a need for more robust studies on this matter. The use of infliximab for treating UC is a relatively recent development and was first studied in the mid to late 1990s.9 Consequently, long-term studies of the effects of the agent and its association with cancer are lacking. The mechanism of this has not yet been fully elucidated, but further studies may help clarify the pathophysiology seen in this case.

References