Sarcoidosis-like granulomatosis of the hypopharynx as a complication of anti-TNF therapy

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ABSTRACT

Introduction: Sarcoidosis is a multisystem granulomatous disease of unknown etiology, occasionally presenting with signs and symptoms that occur within the head and neck. Recently, granulomatous reactions and cases of sarcoidosis have been reported in patients treated with anti-TNF agents.

Methods: This report describes a 56-year-old man who developed sarcoidosis in the hypopharynx during adalimumab therapy for psoriatic arthritis. A retrospective review of the literature was performed using the PubMed database.

Results: In our patient, a chronic granulomatous reaction consistent with sarcoidosis developed after 2 years of continuous treatment with adalimumab. The diagnosis of sarcoidosis was established by the typical well-formed non caseating granulomas on biopsy, after excluding all other granulomatous conditions. Following withdrawal of anti-TNF agents and a course of steroids, the clinical picture resolved.

Conclusions: The development of sarcoidosis during treatment with TNF-a antagonists represents a rare and paradoxical adverse event. To our knowledge this is the first case of sarcoidosis of the hypopharynx reported in the literature.

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1. Introduction

Sarcoidosis is a chronic inflammatory systemic disorder of unknown etiology with both pulmonary and extrapulmonary manifestations. Lung involvement is the predominant clinical feature; however, it can affect almost any organ [1].

It is typically characterized by non-caseating granulomas [2,3] that can virtually develop in any organ [4]. The disease was first described in 1875 by Hutchinson, but it was not until 1899 that Boeck reported the histological appearance of the lesions—hence it is also known as Boeck’s Sarcoid [2,5]. The diagnosis is based on clinical presentation, histopathological findings and exclusion of other granulomatous disorders [2,6].

A growing number of reports concerning the development of granulomatous diseases as a result of paradoxical adverse effects of therapy with tumor necrosis factor (TNF) blocking agents have been reported in the literature [3].

TNF inhibitors are efficacious for treating rheumatoid arthritis and various other chronic inflammatory diseases [7]. TNF plays a key role in the pathogenesis of sarcoid granulomas, along with other pro-inflammatory cytokines. It is a mediator of the molecular cascade that leads to chronic inflammation through the induction of chemokine production [3].

Treatment with monoclonal anti-TNF antibodies (infliximab, adalimumab) has been recently investigated for treating also refractory sarcoidosis and has been proven to be effective...
as they reduce inflammation by altering the human immune response [3]. Therefore, the development of sarcoidosis in patients treated with these agents represents an unexpected adverse event [4,6].

2. Case report

A 66 year old man presented to our department with a two-month history of hoarseness and dysphagia. He also complained of a small ulcer on the left side of his tongue. His past medical history consisted of coronary artery disease for which he had undergone coronary artery bypass surgery 20 years earlier. He was also suffering from psoriatic arthritis that had been diagnosed by skin biopsies and a bone scintigraphy. He was on therapy with antihypertensive, anticoagulant and antihyperlipidemic agents. Since his psoriatic arthritis had been poorly responsive to conventional treatment regimens, he had also started therapy with adalimumab 6 years ago that had improved his symptoms.

Clinical examination of the oral cavity revealed a small ulcer on the left side of his tongue that was relatively soft, well circumscribed and had no signs of inflammation (Fig. 1).

Flexible endoscopy revealed edema of the postcricoid area and the aryepiglottic folds and a lesion in the left pyriform sinus (Fig. 2). Reduced mobility of the left vocal cord and sielostasis were also noted.

There was no evidence of regional lymphadenopathy.

The patient was admitted for further investigation and treatment of a suspected tumor of the hypopharynx. Routine hematologic and biochemical studies were normal. A chest radiograph was also within normal limits.

A computed tomography of the head and neck revealed a large soft tissue lesion on the left side of the hypopharynx, the oropharynx and the supraglottic area, pushing forward the left arytenoid (Fig. 3). Marginally enlarged jugular lymph nodes were also present in the left side of the neck.

Computed Tomography of the thorax and abdomen was within normal limits apart from limited bronchiectasis in the upper lobe of the left lung.

The patient underwent a microlaryngoscopy and biopsy under general anesthesia that revealed a big edematous enlargement on the left hemilarynx. A hard mass with irregular surface was discovered on the postcricoid area, on the front wall of the entrance of the esophagus. Several biopsies were taken. At the same time, the ulcer of the left lateral side of the tongue was removed and sent for histopathologic examination.

Routinely Hematoxylin-and-eosin-stained sections of the biopsied material showed numerous epithelioid, non-necrotic granulomas with giant cells formation at the lamina propria in both sites (Fig. 4A). Granulomatous reaction was also found between striated muscle fibers (Fig. 4B). The covered epithelium showed focal hyperplasia and ulceration. The histochemical Ziehl–Nielsen stain for acid-fast bacilli was negative.

The findings were compatible with a chronic granulomatous inflammation such as sarcoidosis.

Consequently the patient’s treatment with adalimumab was discontinued and treatment was initiated with steroids, methotrexate and anti-tuberculous drugs. His symptoms soon resolved and he still remains in remission, two years after the initial diagnosis.

3. Discussion

Sarcoidosis is a multiorgan disorder with 90% of the patients having pulmonary involvement [2]. It affects primarily young and middle-aged adults (20–40 years). Incidence is higher in women (1.3%) than in men (1%), and higher in blacks (2.4%) than in Caucasians (0.8%). A possible etiopathogenetic mechanism is that various antigens, either infectious or environmental, can trigger an immune reaction in genetically susceptible hosts [8].

Symptoms and findings in sarcoidosis vary according to the organs affected. The most common sites affected in the head and neck region are cervical lymph nodes, facial skin, eye and lacrimal gland, cranial nerves, tonsils, sinonasal tract,
middle ear, larynx and salivary glands [2]. However, involvement of nearly every part of the mucosa of the respiratory tract from the nasal cavity to the peripheral bronchioles has been described [9]. Localized, symptomatic laryngeal involvement is relatively rare [10]. A 31-year review at Mayo clinic identified 220/2319 (9%) patients with head and neck manifestations suffering from sarcoidosis. Thirteen patients had laryngeal involvement, eleven of which had supraglottic involvement. Several other studies have confirmed the rare involvement of the larynx in sarcoidosis [10]. A laryngoscopy with biopsy under local or general anesthesia is required for confirmation of sarcoid histopathology [10]. Granulomatous laryngitis more commonly presents in conjunction with generalized sarcoidosis, with a reported incidence of 0.6% to 1.3% [9].

Laryngeal sarcoidosis classically involves the supraglottic region, and less commonly the subglottis, while true vocal fold involvement is considered rare [9,10]. To our knowledge this is the first case of sarcoidosis of the hypopharynx reported in the literature.

The most common complaints on clinical presentation include hoarseness, dyspnea, dysphagia and chronic cough.

Fig. 3 – CT scan: soft tissue lesion on the left side that extends from the oropharynx and the adjacent part of the soft palate to the hypopharynx and the supraglottic area, pushing forward the left arytenoid.
Systematic symptoms may include low-grade fevers, fatigue, and weight loss [9].

The diagnosis of sarcoidosis is established on clinical and radiological findings supported by histological evidence of non-caseating epithelioid cell granulomas. It remains a diagnosis of exclusion, since there is no specific diagnostic test available [4]. Other diseases with similar presentation have to be excluded, especially mycobacterial infections [3].

Early diagnosis and management of the disease are the best ways to prevent impending upper airway obstruction and potentially obviate the need for emergent surgical intervention.

Blockade of tumour necrosis factor (TNF) has been reported as one of the most promising therapies and is widely used in the management of various inflammatory diseases such as psoriatic arthritis [4,11]. Internationally, there are three agents available as specific TNF antagonists: a soluble receptor fusion protein (etanercept), a chimeric monoclonal antibody (infliximab) and a human monoclonal antibody (adalimumab) [11].

TNF-a also plays a key-role in the pathogenesis of sarcoidosis, both for initiation and at the chronic stage. Consequently, TNF blockers may have a therapeutic effect on the disease. The use of anti-TNF drugs has been recently investigated for treating refractory sarcoidosis and could be effective.

The classical non-caseating granulomatous infiltration seen with sarcoidosis is composed primarily of macrophages and CD4+ T lymphocytes. Activated CD4+ T cells generate interleukin-2 and interferon-γ, which combined with TNF-a, secreted by activated macrophages, promote the formation of granuloma [11].

In contrast, cases of sarcoidosis and granulomatosis after TNF blocker introduction have recently been described [6]. It has been noted that cytokine imbalance due to neutralization of peripheral TNF-a could lead to the development of other autoimmune diseases related to anti-TNF-a agents, such as sarcoidosis and ‘lupus-like’ syndrome, by permitting the activation of specific autoreactive T cells [11].

The first case of sarcoidosis associated with anti-TNF treatment was reported in 2002 [3]. Anti-TNF-a therapy could promote sarcoid like granulomatosis by altering the level of triggering infectious antigens and/or modification of the cytokine environment and cellular recruitment within the tissues [6].

The mechanism of action of all the different anti-TNF drugs is blocking the TNF-a proinflammatory cytokine. However the differences in their structure as well as in their pharmacokinetic and pharmacodynamic characteristics could explain the differences that can be observed in their clinical efficacy and the different frequency of side effects, including the induction of granulomatous lesions [12].

The occurrence of this granulomatous disease process appears to be more frequent with TNF soluble receptors (etanercept) compared to monoclonal anti-TNF antibodies (adalimumab and infliximab) [1].

Usually, the granulomatosis resolves with discontinuation of the anti-TNF factors. In cases of severe symptoms systemic corticosteroid therapy may be necessary, as in usual sarcoidosis [6]. Recurrence of symptoms may be observed when an anti-TNF drug (the same or a different one) is restarted [3,6] but not in a predictable way.

Intralesional steroid injections for focal disease can be beneficial in selected individuals. The carbon dioxide laser can be used to remove lesions causing airway obstruction; it is preferable to address sarcoid lesions while they are non-obstructive and possibly avoid the need for a tracheotomy [10].

Fig. 4 – Histological findings: (A) Epithelioid, non-necrotic granuloma with giant cells formation at the lamina propria. (B) Granulomatous reaction with giant cells between striated muscle fibers.

REFERENCES


