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B-cell lymphoma of the larynx in a patient with rheumatoid arthritis

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Abstract
We report a case of B-cell lymphoma with the larynx as the primary site of presentation in a rheumatoid arthritis patient previously treated with methotrexate. Primary non-Hodgkin's lymphoma (NHL) of the larynx is rare. There may be an increased risk of lymphoma in patients with rheumatoid arthritis, with an even higher risk in those patients treated with methotrexate. The diagnostic and treatment options are discussed.

Key words: Lymphoma; Larynx; Arthritis, Rheumatoid; Methotrexate

Introduction

Primary non-Hodgkin's lymphoma (NHL) of the larynx is rare, accounting for less than 1 per cent of all laryngeal neoplasms.[1] There are fewer than 100 reported cases in the English medical literature. We present a case of NHL localized to the arytenoid cartilages in a patient with long-standing rheumatoid arthritis previously treated with methotrexate. There are several case reports in the literature showing an association between the development of lymphoma and rheumatoid arthritis patients treated with methotrexate.[2–5] To our knowledge primary NHL of the larynx presenting in a patient with rheumatoid arthritis has not been reported in the literature to date. We highlight the diagnostic challenge this presents.

Case report

A 69-year-old man presented with a sore throat and a three-month history of intermittent hoarseness. There were no other upper aerodigestive tract or systemic symptoms. There was a significant past medical history of long-standing rheumatoid arthritis and previous *Helicobacter pylori* gastritis. At the time of presentation the patient was not on any disease-modifying anti-rheumatoid drugs; previous treatment included methotrexate, sulphasalazine, azathioprine, gold and leflunomide. The rheumatoid arthritis had remained quiescent for several years. He was an ex-smoker of six months, having been a smoker for 40 years. Fibreoptic nasal endoscopy revealed inflammation of both cricoarytenoid joints with restricted movement of the right vocal fold. The true vocal folds were otherwise normal. There was no cervical lymphadenopathy and the remainder of the ear, nose and throat examination was normal.

Routine laboratory tests revealed raised inflammatory markers and a mild leukocytosis. A chest X-ray showed a moderate sized pleural effusion and signs of pulmonary fibrosis. A provisional diagnosis of rheumatoid disease affecting the cricoarytenoid joints was made. This was supported by computed tomography (CT) which showed oedema of both cricoarytenoid joints extending superiorly into both aryepiglottic folds and demonstrated a right laryngeal mass displacing the right vocal fold medially (Figures 1 and 2). The patient was treated with a short course of oral steroids which resulted in a symptomatic improvement but did not alter the appearance of the larynx.

The patient was reviewed by the rheumatologists who commenced disease-modifying anti-rheumatoid drugs including cyclosporin, hydroxychloroquine and prednisolone. Initially he responded to treatment with almost complete resolution of his symptoms and reduced swelling in the larynx. However, five months after initial presentation he developed increasing hoarseness and laryngeal discomfort. He presented as an emergency with stridor and underwent a tracheostomy and direct laryngoscopy which showed an inflammatory mass over both arytenoid cartilages and the interarytenoid area with normal, mobile vocal folds. Histological examination of biopsies taken from the larynx revealed a large population of atypical large lymphoid cells with positive immunohistochemical staining for CD20 and CD79a consistent with a diagnosis of diffuse large B-cell lymphoma (Figures 3 and 4).

Staging CT of the chest, abdomen and pelvis demonstrated a single enlarged para-aortic lymph node but no supradiaphragmatic lymphadenopathy. Bone marrow biopsies were suspicious of an underlying low-grade B-cell lymphoma. The final diagnosis was a stage IIIE diffuse large B-cell lymphoma with the larynx as the primary site of presentation.

The patient was referred to the haematologists for further management. Treatment was initiated using CHOP-R chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone with rituximab anti-CD20 monoclonal antibody immunotherapy). Nine months after initial presentation the patient was in remission on both clinical and radiological examination after four cycles of

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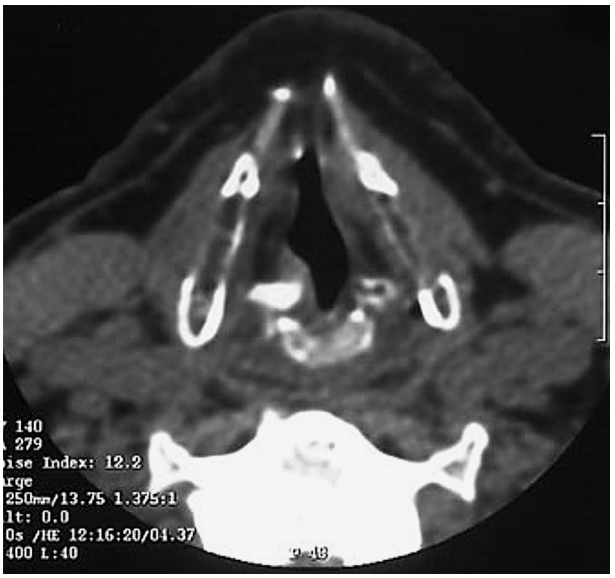

FIG. 1

Axial computed tomography scan showing oedema surrounding the cricoarytenoid joints with expansion of the arytenoid cartilage on the right side.

chemotherapy, with only the fourth cycle complicated by a neutropenic sepis and pneumonia which was treated successfully with antibiotics. A further two cycles were performed, making a total of six cycles of chemotherapy.

Discussion

NHL most commonly occurs in lymph nodes but approximately 25 per cent of cases originate from extranodal sites. NHL in the head and neck usually arises from Waldeyer's ring. In the larynx most NHL cases are centred in the supraglottic area, in particular the epiglottis and aryepiglottic folds, and spread to involve the glottis and less commonly the subglottis.[6]

Most reported primary lymphomas of the larynx have been NHL of a B-cell phenotype. There have also been reports of primary extranodal marginal zone B-cell lymphoma (of the mucosa associated lymphoid tissue (MALT) type) in the larynx and this has only been described in the supraglottic region. A study of 87 unselected cadavers found organized lymphoid tissue with the cytomorphological and immunophenotypic features of MALT in 100 per cent of false folds of children and in more than 90 per cent of adolescents, decreasing to 7.1 per cent of persons in their sixth decade, whereas MALT was completely absent in the subglottis in all age groups. This may explain why primary extranodal marginal zone B-cell lymphoma has only been described in the supraglottic region but is absent in the subglottis and why lymphomas of the larynx in general have a marked predilection for the supraglottis.[7]

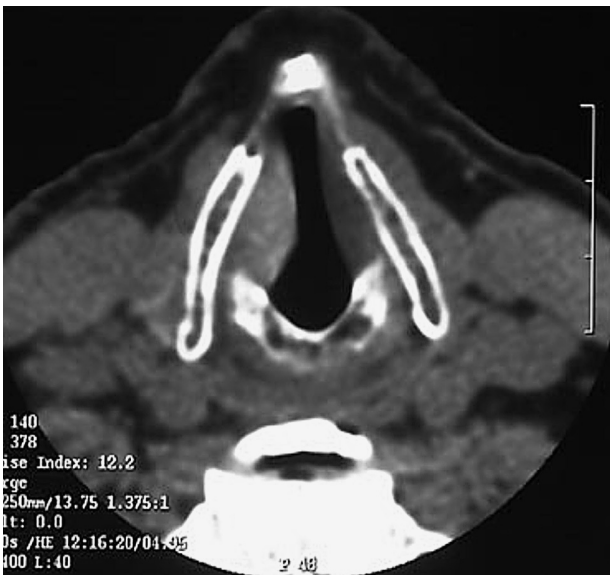

FIG. 2

Axial computed tomography scan showing right laryngeal mass displacing right vocal fold medially.

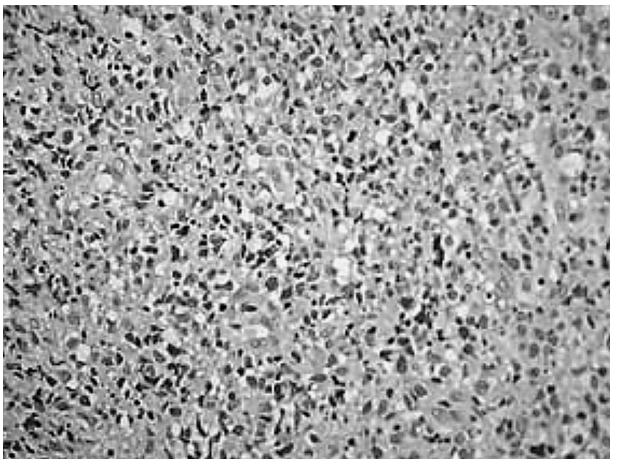

FIG. 3

Haematoxylin and eosin stain of laryngeal biopsy showing atypical large lymphoid cells (original magnification ×400).

Laryngeal NHL is usually submucosal or has a large submucosal component and has the macroscopic appearance of a smooth submucosal swelling or polypoidal mass without ulceration. This tumour tends to remain localized for long periods of time. Dissemination may eventually occur to other sites in the respiratory tract, stomach, lung, orbit or skin after a long disease-free interval.[8]

There have been several case reports of lymphoma developing in rheumatoid arthritis patients treated with methotrexate, although it has never been described in the larynx.[2–5] The question of whether methotrexate is

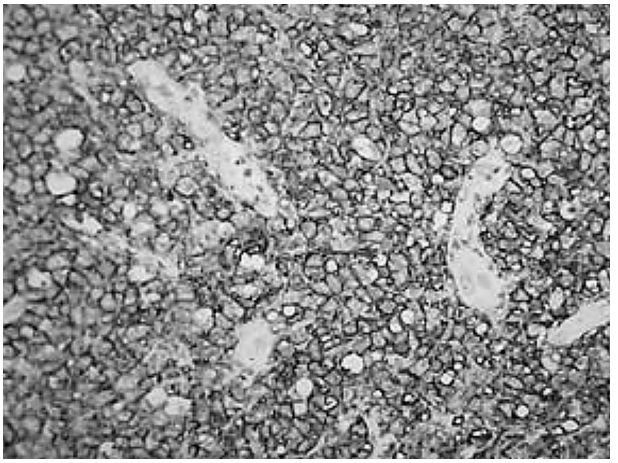

FIG. 4

Atypical lymphoid cells showing immunohistochemical positivity for CD20 (original magnification ×400).

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oncogenic in rheumatoid arthritis patients is controversial, mainly because of the already increased risk of lymphoproliferative disorders in these patients. The risk factors for rheumatoid arthritis patients to develop lymphoma while on methotrexate include severe disease, intense immunosuppression, genetic predisposition and an increased frequency of latent infection with pro-oncogenic viruses such as Epstein-Barr virus.[2]

The patient in this case presented with inflammation over the cricoarytenoid joints, making the differentiation between rheumatoid disease of the larynx and lymphoma difficult. The good clinical response to steroids further delayed the diagnosis. In this case the patient had stopped methotrexate prior to the diagnosis of lymphoma. NHL should be considered in the differential diagnosis of a laryngeal lesion presenting in the rheumatoid arthritis patient, particularly with a background of methotrexate treatment.

- **This paper presents a case of B-cell lymphoma within the larynx in a rheumatoid arthritis patient previously treated with methotrexate**
- **Primary non-Hodgkin's lymphoma of the larynx is rare**
- **There may be an increased risk of lymphoma in patients with rheumatoid arthritis, with an even higher risk in those patients treated with methotrexate**
- **The diagnostic and treatment options are discussed**

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