Case Report

Regression of Diffuse Large B-Cell Lymphoma after Discontinuation of Adalimumab for Rheumatoid Arthritis

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Abstract

Lymphoma is an increasingly well-recognized complication in patients receiving anti-tumour necrosis factor (TNF) therapies. We report a case of a man who presented with diffuse large B-cell lymphoma (DLBCL) while being treated with adalimumab for rheumatoid arthritis (RA) which showed complete, spontaneous regression following withdrawal of TNF inhibition. This case highlights the need for increased vigilance for lymphoma in patients receiving anti-TNF treatment; and in patients who develop lymphoma while receiving anti-TNF therapy, a trial of withdrawal of this medication, and monitoring for regression, should be considered where possible, before commencing chemo- or radiotherapy.

ABBREVIATIONS

TNF: Tumour Necrosis Factor; DLBCL: Diffuse Large B-cell Lymphoma; RA: Rheumatoid Arthritis; CT: Computed Tomography; NHL: Non-Hodgkin’s Lymphoma; EBV: Epstein-Barr Virus

INTRODUCTION

Adalimumab is a recombinant human monoclonal antibody to TNF-α. Lymphoma is an increasingly well-recognized complication in patients receiving anti-TNF therapies [1-4]. The cause of lymphomagenesis is multifactorial. There are only several cases in the literature demonstrating clear regression of lymphomas following withdrawal of anti-TNF therapy. We present a case of a man who had spontaneous regression of his extranodal DLBCL following discontinuation of adalimumab for his RA.

CASE PRESENTATION

An 81-year-old man with RA presented with a 3-week history of a rapidly enlarging nodule above his left upper lip. He had been receiving adalimumab for 5 years, methotrexate for 15 years, and prednisolone. He was systemically well with no B symptoms. His other comorbidities include ischaemic heart disease and renal impairment, of which he was on treatment for.

Clinical examination revealed a 2.5cm indurated, ulcerated, non-tender nodule above his left upper lip (Figure 1a). There was no associated lymphadenopathy.

On histological examination, there was diffuse infiltrate of pleomorphic lymphoid cells (Figure 2a). The infiltrating cells were positive by immunohistochemistry for CD20 (Figure 2b), bcl-6, bcl-2, Ki-67 and MUM-1; and negative for CD3, CD10 and EBV. In situ hybridization for Epstein-Barr-encoded RNA was also negative.

Staging evaluation by CT imaging of patient’s chest showed multiple bilateral pulmonary nodules throughout all lobes with no other abnormalities (Figure 3a). CT guided biopsy was attempted but unsuccessful due to his underlying comorbidities. Bone marrow examination was normal.

Based on the cutaneous and pulmonary findings, DLBCL was diagnosed. Treatment with adalimumab was immediately withdrawn, however due to the severity of our patient’s RA, methotrexate and prednisolone were continued. Management with radical radiotherapy was planned in view of his underlying comorbidities, however within 3-weeks of discontinuing adalimumab and before commencing radiotherapy, there had been resolution of the cutaneous lesion (Figure 1b). Subsequent CT chest especially at 3-months also showed marked decrease and resolution of the pulmonary nodules (Figure 3b), suggesting that these were likely to be lymphomatoid in aetiology, as

opposed to being rheumatoid nodules, which would be expected to remain static or flare upon discontinuation of adalimumab.

**DISCUSSION**

The cause of lymphomagenesis is multifactorial. It is established that RA alone increases the risk of lymphoma. DLBCL is the most common lymphoma subtype in RA patients, with a prevalence of 48%-67% among all NHL, as opposed to the slightly lower incidence of 30-40% of DLBCL of NHL in the general population of western countries [5]. Genetic factors, therapeutic agents, infection, and the sustained inflammatory activity of RA all contribute toward immune dysregulation which in turn increases the risk of lymphomagenesis [5]. In our patient, it is likely that aside from his underlying RA, his long-term exposure to methotrexate and anti-TNF therapy is also contributing factors. The results of a recent 3-year prospective French study had found that the risk of lymphoma is significantly higher in patients receiving anti-TNF therapy for all indications compared to the general French population ($p = 0.0001$). Furthermore, of the lymphoma cases that were confirmed, the vast majority had RA as their underlying disease [4]. There are only few other cases reported in the literature demonstrating clear regression of lymphoma following cessation of anti-TNF treatment, in the absence of specific cytotoxic therapy directed toward the lymphoma [2,3]. In these cases the indications for anti-TNF treatment were predominantly for Crohn’s disease or RA; the majority of lymphomas that occurred during anti-TNF treatment were NHL; and the TNF antagonists implicated were adalimumab, infliximab and etanercept. Our case demonstrates that in patients developing lymphoma while receiving anti-TNF treatment, a trial of withdrawal of this medication and monitoring for regression should be considered where possible before initiating any chemotherapy / radiotherapy treatment.

**REFERENCES**


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**Figure 1** (A) Lesion at presentation; (B) regressed lesion 3-weeks post-discontinuation of adalimumab.

**Figure 2** Incisional biopsies of left upper lip lesion showing (A) high grade proliferation of large atypical lymphocytes in the dermis (haematoxylin and eosin, original magnification x 400); (B) negative CD3 and positive CD20 immunohistochemistry (original magnification x 200).