Reversible Hodgkin’s lymphoma associated with Epstein–Barr virus occurring during azathioprine therapy for SLE

Sir, We report the case of a 47-yr-old Caucasian female with a 20-yr history of SLE who had been treated with AZA, cyclosporin and prednisolone in 1998 for lupus pneumonitis. From 2005, AZA had been continued at a dose of 150 mg daily. In April 2007, she presented with weight loss and a mass on her tongue. MRI scan of the head and neck revealed a locally invasive mass associated with lymphadenopathy (Fig. 1). Histological examination showed a mixed lymphoid infiltrate consisting of T- and B-cell blasts, with strong positivity for the EBV marker EBER (EBV-encoded RNA). The infiltrate also appeared pleomorphic, and subsequent clonality studies confirmed classical Hodgkin’s lymphoma (HL) of the nodular sclerosing type. AZA was stopped and after 6 weeks the lesion had regressed significantly (assessed by a repeat MRI scan), and after a further 4 months had almost completely resolved without requiring chemotherapy.

EBV has been shown to transform B lymphocytes in vitro into immortal proliferating lymphoblastoid cell lines. In vivo, this is counteracted by EBV-specific cytotoxic T-lymphocytes (CTLs). In immunosuppressed hosts, loss of EBV-specific CTLs can enable unchecked viral proliferation predisposing to the development of lymphoma [1]. EBV-related lymphoproliferative disorders occur in immunosuppressed transplant recipients as well as patients with rheumatological disorders treated with MTX and other steroid-sparing agents. Withdrawal of these agents can lead to tumour regression [2]. The increased risk of lymphoproliferative cancer has been suggested in AZA-treated patients with RA, resulting in one extra case in 1000 patient-years of observation in one study [3]. Lymphomas associated with AZA tend to be EBV negative, and are more aggressive responding poorly to AZA withdrawal [4]. Previous reports of HL in AZA-treated SLE patients have all

---

**Disclosure statement:** The authors have declared no conflicts of interest.

**A. MILLAR, D. O’KANE, A. TAGGART**

*Department of Rheumatology, Musgrave Park Hospital, Belfast, UK*

*Accepted 3 March 2008*

Correspondence to: A. Millar, Department of Rheumatology, Musgrave Park Hospital, 20 Stockman’s Lane, Belfast, BT9 7JB, UK. E-mail: auleenmillar@hotmail.com

---

required combination chemotherapy and an association with EBV was not identified.

To summarize, our case illustrates that, albeit rarely, AZA can be associated with EBV-positive HL in SLE. Disappearance of the tumour after the withdrawal of AZA suggests that in this case the therapy was a major factor in the generation of this tumour. AZA remains an effective and important agent in the treatment of SLE. However, our case illustrates an extremely rare but potentially serious complication of this drug.

Rheumatology key message

- AZA can be associated with the development of an EBV-positive HL.

Disclosure statement: The authors have declared no conflicts of interest.

S. J. Evans1, D. K. Watson2, M. O’Sullivan1
1Department of Rheumatology and 2Department of Haematology, Wrexham Maelor Hospital, North East Wales NHS Trust, Wrexham, UK
Accepted 10 April 2008

Correspondence to: J. Evans, Rheumatology Department, Wrexham Maelor Hospital, Croesnewydd Road, Wrexham, LL13 7TD, UK. E-mail: jayneevans@tesco.net


Rheumatology 2008;47:1104–1105
doi:10.1093/rheumatology/ken175
Advance Access publication 20 May 2008

Rituximab is effective in the treatment of refractory Churg–Strauss syndrome and is associated with diminished T-cell interleukin-5 production

Sir, Churg–Strauss syndrome (CSS) is a necrotizing small-vessel vasculitis characterized by eosinophil recruitment and inflammation. IL-5 is a Th2 cytokine implicated in the pathogenesis of CSS by mediating eosinophil maturation, chemotaxis and adhesion to the vascular endothelium. Elevated levels of IL-5 are found in patients with active CSS, demonstrating that T-cell activation correlates with disease activity [1, 2]. Traditionally, treatment of CSS has consisted of immunosuppression with corticosteroids, and in more severe cases, the addition of agents such as AZA or cyclophosphamide [3–5].

Rituximab, the chimeric anti-CD20 monoclonal antibody, induces B-cell depletion and has been successfully used in numerous autoimmune diseases [6, 7]. There have been only a few reports of the use of rituximab as salvage therapy in the treatment of refractory CSS and its mechanism of action remains unclear [8, 9].

We describe two cases of CSS in whom rituximab was used as additional therapy. The first patient failed to enter sustained disease remission with conventional treatment while the second patient had a more protracted history of grumbling disease, and was not responding to conventional treatment. Rituximab resulted in a clinical, serological and biochemical improvement in both cases. In addition, we found that serum IL-5 was elevated in these patients during the active disease period despite conventional therapy, but reduced following rituximab treatment. This effect preceded the reduction in circulating eosinophils, suggesting that rituximab mediates its beneficial actions in CSS, at least in part, through the inhibition of T-cell IL-5 production.

A 40-yr-old asthmatic man was referred to our unit with a 6-week history of bilateral anterior uveitis and a week-long history of dyspnoea with recent onset haemoptysis, systemic malaise and small joint arthralgia. Blood tests demonstrated a normocytic anaemia, with haemoglobin 10.8 g/dl, eosinophilia (2.7 × 109/l), and an elevated CRP of 111 mg/l (0–10 mg/l). A chest radiograph demonstrated diffuse bilateral alveolar shadowing suggestive of pulmonary haemorrhage. Immunological testing revealed a C-ANCA, with a PR3-ANCA level of 593 IU/ml (0–251 IU/ml).

A diagnosis of CSS with pulmonary haemorrhage was made. Following treatment with intravenous methylprednisolone, pulsed intravenous cyclophosphamide and seven plasma exchanges, his systemic symptoms improved and chest radiograph cleared. However, 8 weeks after the initial diagnosis, and following four pulses of cyclophosphamide with high-dose steroids, disease recurred with arthralgia, nail-fold infarcts, skin nodules, red eyes and an active urinary sediment. PR3-ANCA remained elevated at 236 IU/ml. An increase in steroids resulted in no alleviation of symptoms. The patient was treated with rituximab, administered as 1 g doses, 2 weeks apart, while steroids and cyclophosphamide were continued. Subsequently, B cells were completely depleted and he rapidly entered disease remission. Serum IL-5, measured by ELISA (R and D systems, Abingdon, UK), was elevated at presentation (24.2 pg/ml), fell initially following treatment initiation, but rose again (to 59.7 pg/ml). Increasing steroids resulted in some decrease in IL-5 (39.7 pg/ml), but this stabilized and only following rituximab therapy, did the levels normalize (15.1 pg/ml 2 weeks later, and undetectable after 4 weeks). Circulating eosinophils subsequently fell (Fig. 1). Nine months post-rituximab he remains B-cell depleted, on low-dose steroids and AZA, with a negative PR3-ANCA and quiescent disease.

A 66-yr-old man, with a past history of asthma and nasal polyposis, and a 6-month history of a necrotic leg ulcer, presented with progressive, upper limb numbness and weakness, a right foot drop, worsening of his asthma and a purpuric lower limb rash. Investigations demonstrated an eosinophilia (15.1 × 109/l), positive P-ANCA, anti-MPO Ab 100 U/ml (normal range, 0–6),

---

**Fig. 1.** Graph demonstrating the anti-PR3-ANCA titre, eosinophil cell number and change in serum IL-5 levels compared to baseline, during the course of treatment, in Patient 1.