Lymphomatoid Granulomatosis in a Patient with Rheumatoid Arthritis Receiving Methotrexate: Successful Treatment with the Anti-CD20 Antibody Mabthera

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The risk for malignant lymphoproliferative diseases (LPD), particularly aggressive lymphoma, is increased in patients with rheumatoid arthritis (RA). Chronic B cell activation due to chronic inflammation, long-term use of immunosuppressive drugs such as methotrexate (MTX) as well as Epstein-Barr virus (EBV) infection have been proposed as the etiologic cause [1, 2].

Lymphomatoid granulomatosis (LYG) is a rare, angio-centric and angiodestructive, EBV-driven LPD involving extranodal sites. Patients with underlying immunodeficiency are at increased risk. Predisposing conditions include allogeneic organ transplantation, Wiskott-Aldrich syndrome, human immunodeficiency virus infection, and X-linked lymphoproliferative syndrome. The clinical course is extremely variable, ranging from an indolent form to a disease that is similar to aggressive lymphoma. Due to the rarity of the disease, there is no standard treatment. Interferon (IFN) α -2b is usually recommended for treatment of LYG I–II°, whereas LYG III° is treated with combination chemotherapy used in aggressive B cell lymphoma, e.g. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) [3, 4]. Mabthera, a humanised monoclonal antibody, targets the B cell CD20 antigen and causes rapid and specific B cell depletion. It has been used for the treatment of CD20-positive non-Hodgkin's lymphomas usually in combination with cytotoxic drugs and has recently been approved for treatment of RA as well [5, 6].

Here, we report on a patient with RA who developed LYG under MTX therapy who was successfully treated with mabthera.

Case Report

A 74-year-old woman with a 28-year history of RA had been treated with a variety of antirheumatic drugs (piroxicam, prednisolone, leflunomide, meloxicam and MTX). She was receiving MTX 20 mg/week and mel-

Fig. 1. Left: Tumour-like lesion of the nasal skin (arrow); right: computed tomography scan of the head shows a thickness of the nasal septum (arrow).

oxicam 15 mg/day for 21 months, showing little inflammatory activity of the RA when she complained about impaired nasal breathing and a tumour-like lesion of the nasal wing. Computed tomography showed a mass in the nasal septum (fig. 1). Histologic examination revealed LYG II°. EBV-nuclear-IgG and EBV-capsid-IgG were positive whereas EBV-capsid-IgM was negative, consistent with prior but not acute EBV infection. MTX was discontinued immediately. Since IFN- α has been implicated in the activation of arthritis [7], we felt reluctant to its use. However, CHOP seemed too aggressive in this elderly patient with low-grade LYG. Because of its effectiveness in the treatment of B cell lymphoma as well as RA, we decided to give 4 doses of mabthera 375 mg/m² weekly. Complete remission (CR) of LYG was confirmed 4 weeks after the last dose. 19 months later, the patient was in ongoing CR of LYG and shows no clinical signs of active RA under sulfasalazine 2000 mg/day.

Discussion

The successful use of mabthera in LYG was first published in 2003 by Sebire et al. [8]. Further reports followed showing ongoing CR for up to 36 months [9, 10]. However, all patients reported in these publications had no underlying chronic autoimmune disease such as RA. Therefore, this is the first report of the use of an anti-CD20 antibody in a patient with RA who had developed LYG and achieved CR after only 4 doses.

It is still unclear if the higher risk for LPD in patients with RA is associated with the use of immunosuppressive therapy and whether drugs like MTX, cyclosporine A or azathioprine should be discontinued if LPD occurs. Since it has been noted that the risk of LPD in patients with RA correlates with disease activity, chronic inflammation itself leading to polyclonal and possibly subsequent monoclonal B cell activation may play a major role in lymphomagenesis [1, 6, 11]. Thus, control of inflammation and antiproliferative treatment seem warranted in this condition.

Since EBV-infected B cells in patients with LYG highly express CD20 [3], they are rapidly eliminated by antibody-dependent and complement-mediated cytotoxicity if exposed

to mabthera [5, 6, 8, 12]. In all reports published to date, mabthera was effective and well tolerated in EBV-driven LPD. Overall response rates ranged from 20 to 100%. Yet, early relapses were seen in about 25% [8, 12, 13], indicating that the anti-CD20 antibody alone may not be sufficient to cure this disease [12, 13]. In our patient, mabthera proved to be a very effective therapeutic alternative, successfully treating both LYG and RA at the same time.

Conflict of Interest

No conflict of interests to disclose.

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