Mod Rheumatol (2008) 18:306–308
DOI 10.1007/s10165-008-0057-9

CASE REPORT

Treatment of retinal vasculitis in Behçet's disease with rituximab

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Received: 12 October 2007 / Accepted: 24 January 2008 / Published online: 26 April 2008

Abstract Behçet's disease (BD) is more common in eastern than western countries. Physicians have frequently encountered problems in its treatment, especially eye involvement. Recurrent oral and genital aphthous ulcerations are the hallmarks of Behçet's disease but other organs can be involved and ocular disease is one of the most disabling manifestations. Up to now, there are some problems in treatment of the retinal vasculitis due to Behçet's disease. We reported one patient, with visual loss due to retinal vasculitis that was resistant to prednisolone and azathioprine. Our patient was treated successfully with rituximab and his remission was sustained for 24 months of follow-up. Rituximab is a chimeric monoclonal antibody that acts against the specific B cell antigen, CD20. The recent success of rituximab in autoimmune diseases, which is considered to be T cell-mediated, indicates that B cells must have a much broader role in the pathogenesis of autoimmune diseases than generally appreciated.

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Keywords Rituximab · Behçet's disease · Retinal vasculitis

Case report

In May 2005, a 29-year-old man with Behçet's disease (BD) was admitted to Sina Teaching Hospital, Tabriz Medical University, northwest of Iran, for the first time due to blurring of vision in the right eye. The patient had a history of chronic renal failure (unknown origin), oral and genital aphthae from the age of 20, episodes of arthritis in ankle joints and arthralgia in hands and knees from 22, left acute anterior uveitis from 25, there was no history of neuro-Behçet.

In 2002 a diagnosis of BD was made (based on international study group criteria) and treatment with oral corticosteroid (10 mg/day) was begun. Mucosal aphthae improved and articular symptoms decreased. Corticosteroid gradually tapered to 2.5 mg/day and the patient had a few episodes of oral aphthae, treated with topical steroids. Until December 2004 he had no relapse episode.

In February 2005 posterior uveitis of the right eye was diagnosed. Treatment with azathioprine 150 mg/day was added to 50 mg/day oral prednisolone and topical mydriatic. This treatment led to a non-complete improvement (visual acuity 7/10) and prednisolone tapered to 20 mg/day. However, in May 2005, the patient experienced an acute decrease in visual acuity (4/10) in the same eye. Ophthalmological consult was sought and active retinal vasculitis with posterior uveitis was diagnosed. Upon admission, the patient had oral aphthae and arthralgia in both hands and ankle joints. Physical examination was normal with no evidence of pathergy reaction at sites of needle pricks. Blood analysis showed the following: a normal white blood cell count and

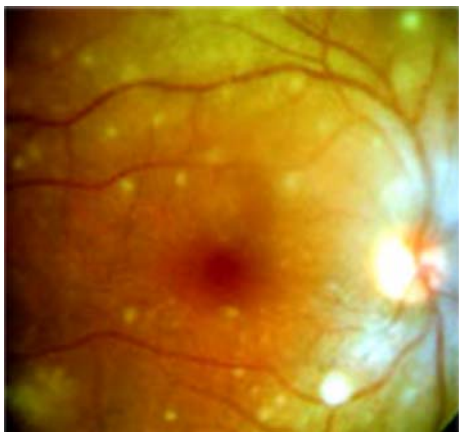

Fig. 1 Pre treatment

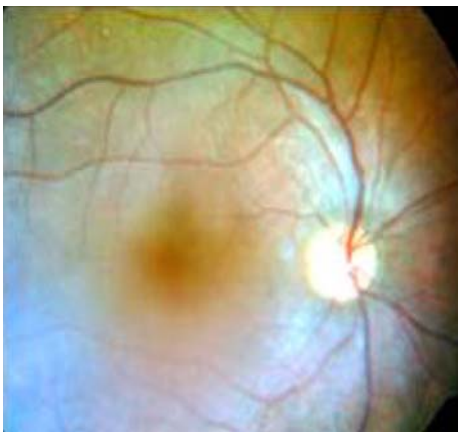

Fig. 2 Post treatment

differentiation, mild anemia (Hb = 12.5) with normocytic–normochromic pattern, erythrocyte sedimentation rate (ESR) 46-mm/1st h, C reactive protein (CRP) 13 mg/l, blood urea nitrogen (BUN) 34 mg/dl and serum creatinine 3.5 mg/dl. Urine analysis, stool exam, liver tests, serum complements were normal and serologic tests for HBV, HCV, and HIV were negative. Rheumatoid factor, antinuclear antibody, anti-dsDNA, antineutrophil cytoplasmic antibodies (C-ANCA, P-ANCA) and serum angiotensin converting enzyme (ACE) all were negative. HLA typing for HLAB27 and HLAB25 were positive. There was no sign or symptom of axial involvement due to suspected spondyloarthropathies. His pelvic, chest and hands radiographic views were normal. Treatment with corticosteroid ocular injection, methyl prednisolone infusion 1,000 mg/day for 3 days and etanercept (Enbrel) 25 mg/twice per week was started but etanercept discontinued after 2 weeks because of anti TNF adverse effects (fever, urticaria and macular rushes, angioedema with transient new lymphopenia and ANA positive test). Azathioprine (150 mg/day) and prednisolone (1 mg/kg) caused no significant amelioration in visual acuity (2/10) and fundoscopic examination after 2 months (Fig. 1). Optic disc edema and retinal vasculitis were still present. Since the retinal vasculitis was refractory, we decided to treat the patient with rituximab, so we obtained his written informed consent after complete description of this new treatment.

We infused rituximab 1,000 mg/dose, which the same dose was repeated 2 weeks later. Treatment with rituximab led to significant improvement in ophthalmic vasculitis and visual acuity (8/10) during 6 weeks (Fig. 2).

Two weeks after the second infusion, ESR and the CRP level decreased to 21-mm/1st h and 5 mg/l, respectively, and remained within the normal range for the rest of the follow-up time (18 months). Serum immunoglobuline (Ig) levels were within the normal range except for IgG and IgA. There was a transient decrease in serum IgA and a decrease in IgG level, maximum at 4th week.

All of the serum immunoglobulines returned to normal range after 3 months of second rituximab infusion. From Sep 2006 prednisolone reached 10 mg/day and then the remission of disease was sustained with prednisolone 5 mg/day. There was no serious adverse event or deterioration of renal function up to the follow-up period.

Discussion

Ocular involvement is the most common cause of morbidity in Behçet's disease and if the disease is not treated may lead to blindness in about 5 years.

Several studies report ophtalmic disease in 43 to 65% of patients with BD. Ocular disease usually develops at least 3 years after the oral aphthae [1].

Eye manifestations in BD include panuveitis, anterior and posterior uveitis, optic neuritis (unilateral or bilateral), retinal vasculitis, bilateral lamellar macular hole**,** vein and artery occlusions. Anterior uveitis has a relatively good prognosis that is opposite to retinal involvement [2].

The main mechanism of Behçet eye inflammation is believed to represent a CD4+ T cell and macrophages mediated pathology, in which cell adhesion molecules, cytokines, oxygen-free radicals and prostaglandines (as molecular mediators) play an important role [3]. Because of the lack of adequate data from well-controlled clinical trials to compare different treatment strategies, uncertainties about the obvious etiology and pathogenesis of disease so the treatment of ocular-Behçet remains unsatisfactory.

There are now some treatment options for retinal vasculitis such as high-dose corticosteroid, different type of cytotoxics, anti TNF and interferon-α but existence of refractory cases, need to seek for newer treatments [4].

Rituximab is a chimeric monoclonal antibody against CD20 that is expressed on immature, pre and memory B cells, but not on plasma cells so it has no major effect on

immunoglobuline production. CD20 function is not exactly known but it is suggested that it acts as a calcium channel subunit. Since rituximab contains murine CD20-binding Fab region the half-life of the antibody is prolonged and with the human Fc region, a more effective complement activation and attraction of cytotoxic cells can be achieved [5].

Rituximab rapidly redistributes into the cell lipid layer after binding to the CD20 that is involved in signal activation through tyrosine kinases. These cell membrane changes are long-standing, so it can be an explanation for late responses to rituximab. Some mechanisms have been suggested by which rituximab depletes B cells, including complement activation, cytotoxicity via antibody action, induction of apoptosis, and inhibitory effect on B cells proliferation. Interestingly, the human Fc receptor polymorphism is also associated with different responses to rituximab in both autoimmune and malignant diseases [6].

However, recently, conditions that are considered as being predominantly T cell-mediated autoimmune diseases have been treated successfully with rituximab. Rheumatoid arthritis (RA) [7], ocular involvement in Wegener's granulomatosis [8], refractory scleritis in primary Sjogren's syndrome [9] and recalcitrant Churg–Strauss syndrome [10] are examples of these conditions. Certainly, B cell has a major role in T cell activity in addition to its antibody secretion role.

Although the total B cell number in patients with BD is normal but increased numbers of spontaneous Ig secreting B cells and elevated immunoglobuline levels have been previously described. In addition to changes in numbers and activities of T cells, increased levels of activated and memory B cell subsets suggest a modified B cell function in Behçet's disease. CD13- and CD33-positive B cells are more numerous in BD compared to healthy controls and patients with RA and SLE. This may be related to a stimulus by an unknown external antigen or internal antigens such as heat-shock proteins (HSP) [11]. Furthermore, the efficacy of rituximab for the treatment of SLE in the absence of change of serum autoantibody levels shows that the secretion of autoantibody is not the sole function of B cells in the pathogenesis of autoimmune diseases [12].

It is very difficult to assess the efficacy of rituximab on Behçet's disease due to the variation in treatment regimens and heterogeneity of the few studied patients. This is among the first reports about the treatment of retinal vasculitis in Behçet's disease with rituximab. Treatment with this drug led, in our patient, to a complete remission of ocular inflammatory manifestations and there was no relapse after the steroid tapering period. Although such reports are promising, further studies are required to evaluate the efficacy of rituximab in ocular Behçet's disease, especially in retinal vasculitis.

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