Case Report

Refractory to Rituximab- Based B-Cell Depletion Therapy on Chronic Skin Manifestations of Systemic Lupus Erythematosus: Case Report

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Abstract

In this case report, we present a patient with systemic lupus erythematosus who has both refractory discoid lupus erythematosus lesions and refractory cytopenia under antimalarial, glucocorticoid and untarget immunosuppressant drugs. Rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of B-lymphocytes has been used as an additional therapy in systemic lupus erythematosus. Cytopenia has resolved and clinical response continues over two years but discoid lesions did not respond rituximab therapy within the same time.

ABBREVIATIONS

DLE: Discoid Lupus Erythematosus; SLE: Systemic Lupus Erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a set of clinical symptoms with recurrent flares causing tissue damage and dysfunction and laboratory signs associated with the presence of autoantibodies. In clinical practice, diagnosis of SLE is based on clinical and laboratory criteria described by American College of Rheumatology (ACR) and 2011 SLICC (Systemic Lupus International Collaberation Criteria) [1,2]. SLE is a clinically heterogeneous disease including cutaneous, haematologic, articular, renal and neuropsychiatric manifestations and serous membrane involvement. B cells play a central role in SLE pathogenesis with clinical features resulting from autoantibody formation, immune complex deposition, antigen presentation and cytokine activation [3,4].

Cutaneous lupus presents acute, subacute and/or chronic manifestations. Discoid lupus erythematosus (DLE) is a chronic form of cutaneous lupus erythematosus. It develops in up to 25 percent of patients with SLE [5], which is characterized by coin-shaped plaques, most often present on the face, neck, and scalp. Skin atrophy, scarring, and scarring alopecia may result. Sometimes biopsy may be needed, histopathology of discoid skin lesion reveals hyperkeratosis, follicular plugging, basal layer vacular changes, and a plasmacytoid dendritic cell and T cell infiltrate [5,6].

Initial treatment for DLE consists of photo protection in conjunction with topical or systemic corticosteroids, topical calcineurin inhibitors, and antimalarial therapy. In the treatment of some SLE patients, other immunosuppressive/immunomodulating agents with varying degrees of evidence may be added [5]. Disease activity in SLE may be inadequately controlled by traditional therapy. Biologics, i.e., B cell depletion therapy based on Rituximab (anti-CD20 monoclonal antibody) have been used as an off-label therapeutic option in SLE patients with intolerance or resistance to conventional therapy [7-9].

We report the efficacy of B- cell depletion therapy on refractory skin lesions and persistent haematological features in a SLE patient who has been followed as clinical and immunological for a long term with conventional therapy.

CASE PRESENTATION

We present a 43-year-old women with a 20-year history of SLE fulfilling ACR and SLICC classification criteria [1,2], who had skin (discoid lupus), renal (proteinuria microscopic hematuria) and central nervous system involvement (seizures),
haematologic abnormalities (leucopenia, lymphocytopenia and thrombocytopenia), positivity of antinuclear antibody (1/320 dilution, speckled staining pattern), and hypocomplementemia.

For 20 years she had cutaneous disease affecting her cheek and scalp. 18 year ago first skin biopsy revealed DLE. She intermittently used topical steroids and hydroxychloroquine 400 mg/day, and dapsone was tried for DLE. Immunosuppressants including firstly azathioprine and then mycophenolate mofetil therapy were unresponsive. Cyclophosphamide infusions started and continued 12 times at an interval of 4 weeks for active systemic disease. Seizures and renal disease were controlled, but chronic skin lesions and haematologic anormalities did not quitey resolve under these therapy.

On her follow-up, leukopenia, lymphocytopenia, thrombocytopenia and DLE findings continued to be present. For further examination she hospitalized. On her dermatologic examination cheeks, frontal, occipital haired area and behind the both ears erythematous, scaly plaques were observed. In some of the plaques, scar areas were also seen. On her appeal; she was taking methylprednisolone 12 mg/day, hydroxychloroquine 400 mg/day, carbamazepine 800 mg/day (for seizures a 10-year).

Skin lesions affecting her scalp and malar dermis (Figure 1) were confirmed as DLE by second skin biopsy (Figure 2-5). Bone marrow aspiration and biopsy were done because of history of long term use immunosuppressant agents and determination of pancytopenia and did not find specific or infiltrative pathology revealed.

In laboratory evaluation before Rituximab treatment; WBC: 2,6x 10^9/L, lymphocyte count: 0,8x 10^9/L, neutrophil count 1,4x 10^9/L, RBC: 3,76x 10^12/L, PLT: 143 x 10^9/L, Hb: 9.3 g/dl, MCV: 74.4, peripheral blood smear: atypical cell or blast not seen coherent with complete blood count. Creatinin, blood urine nitrogen, liver enzymes, urinalysis and CRP were usual values, eritrocyte sedimentation rate: 44 mm/h, positive ANA: 1/320 dilution (speckled, staining pattern) by immunoflouresence technique, positive nuclear autoantibodies with immunoblotting method: anti Sm +++ positive, anti- SS-A(Ro) 60 kD and anti-SS-A(Ro) 52 kD, negatif nucleuar antibodies: anti- SS-B(La), U1-nRNP, anti-ds: DNA and anti-nucleosome antibody. Direct and indirect Coombs were negative. Serum immunoglobulin levels: IgG 19,0 g/L(7,51 - 15,6), IgA 3,93 g/L (0,82 - 4,53), IgM 1,52 g/L (0,46 - 3,04). Complement levels: C3 0,87 g/L (0,79 - 1,52), C4 0,06 g/L (0,16 - 0,38)

After all these evaluation, Rituximab therapy was started. The treatment protocol of RTX has been described in previous reports.
Lupus erythematosus is a multifactorial disease with a role of genetic, environmental, and immunologic factors. There is tremendous variability and diversity in the type of involvement, including refractory cytopения and central nervous system involvement. Case series also suggest that rituximab ameliorates the disease and improves the quality of life for patients with systemic lupus erythematosus (SLE). Rituximab has also been applied in single cases or case series. Some case reports showed that acute or subacute cutaneous lupus erythematosus was successfully treated with rituximab.

In a prospective study, 82 patients with SLE, 26 with skin disease at baseline including 3 with discoid or chilblains cutaneous lupus erythematosus, were also treated with 1g rituximab two times two weeks apart with 100 mg methylprednisolone. None of chronic cutaneous lupus erythematosus individuals showed a response to therapy in 6 months of follow-up. Authors concluded that their findings indicate that activity of this lesions is not B cell dependent. Most treatments used for cutaneous lupus erythematosus are more efficient in treating of acute lesions than long-standing chronic cutaneous lupus erythematosus lesions.

In our case, we chose rituximab therapy for systemic involvement including refractory cytopenia and chronic skin disease to standard therapy. There was a beneficial response for cytopenias but not for long standing DLE in follow up for over two years.

**REFERENCES**


**DISCUSSION**

A broad range of skin involvement is seen in SLE. There is tremendous variability and diversity in the type of involvement, ranging from malar rash to DLE. Pathogenesis of cutaneous lupus erythematosus is a multifactorial, with a role of genetic, environmental and immunologic factors. Because of this heterogeneous responses to different therapies are greatly variable. Rituximab is a chimeric monoclonal antibody to B-cell specific antigen CD20 that causes B cell depletion via antibody-dependent cell-mediated cytotoxicity, complement activation and apoptosis induction. It is approved for non-Hodgkin lenfoma, rheumatoid arthritis. Two randomized controlled clinical trials (EXPLORER and LUNAR) failed to prove the positive effects of rituximab in SLE. The off-label of rituximab is mainly used to treat SLE patients with either life-threatening conditions, refractory or intolerant to traditional therapy. In case series reports, observational studies and systematic analysis, rituximab has demonstrated positive effect in lupus patients with visseral involvement. Case series also suggest that rituximab ameliorates thrombocytopenia and probably central nervous system vasculitis associated with SLE. We also observed beneficial effect of rituximab on cytopenia and probably preventing effect on seizures.

In different subtypes of cutaneous lupus erythematosus, rituximab has also been applied in single cases or case series. Some case reports showed that acute or subacute cutaneous lupus erythematosus was successfully treated with rituximab. In a prospective study, 82 patients with SLE, 26 with skin disease at baseline including 8 with discoid or chilblains cutaneous lupus erythematosus, were also treated with 1g rituximab two times two weeks apart with 100 mg methylprednisolone. None of chronic cutaneous lupus erythematosus individuals showed a response to therapy in 6 months of follow-up. Authors concluded that their findings indicate that activity of this lesions is not B cell dependent. Most treatments used for cutaneous lupus erythematosus are more efficient in treating of acute lesions than long-standing chronic cutaneous lupus erythematosus lesions.

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