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Case Report

A case of central nervous system nocardiosis in a patient with lupus treated with belimumab

Richard HC Lai[1], Deborah Kim[1], Florina Constantinescu[1, 2]

Abstract

Belimumab was approved by the United States Food and Drug Administration in March 2011 as the first biological agent for treating active systemic lupus erythematosus (SLE). To the best of our knowledge, this is the first case report regarding a patient with SLE treated with belimumab who was diagnosed with central nervous system nocardiosis.

Keywords: Belimumab, systemic lupus erythematosus, norcardiosis, central nervous system, lupus

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory autoimmune disease. It is estimated that approximately 80% of patients with SLE have a persistently active disease with frequent flares (1). Belimumab is the first biological agent that has been approved by the United States Food and Drug Administration for treating active SLE. Belimumab is a monoclonal antibody that prevents the survival of B lymphocytes by blocking the binding of soluble human B lymphocyte stimulator protein (BLyS) to the receptors on B lymphocytes. This reduces the activity of B-cell-mediated immunity and the autoimmune response (1). Post-marketing reports of unanticipated side effects have been reported because there is a continuous increase in the use of belimumab in clinical practice.

Nocardiosis is an opportunistic infection that is often acquired by individuals who are immunocompromised. Manifestations of nocardiosis occur in cutaneous, pulmonary, central nervous system (CNS) and disseminated forms (2). We describe the first case of CNS nocardiosis in a patient with lupus treated with belimumab.

Case Presentation

Informed consent from the patient has been obtained in written and verbal forms. The patient is a 41-year-old white female with a history of SLE having Class IIIC lupus nephritis presented to the Lupus Clinic in December 2012 to consider belimumab treatment. SLE remained active while on immunosuppressive agents, with a persistent diffuse rash, arthralgia, and fatigue with abnormal serologies, including a low complement 3 (C3) level of 68 mg/dL (90–180 mg/dL) and a high titer anti-double-stranded deoxyribonucleic acid antibody (anti-dsDNA) level of 115 IU/mL (≤4 IU/mL). Her Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was 14 at initial evaluation on the basis of her low C3 level, elevated anti-dsDNA titer, rash, inflammatory arthritis, and proteinuria. At the time, she was on 3000 mg mycophenolate mofetil daily, 400 mg hydroxychloroquine daily, 10 mg prednisone daily, and isoniazid for treating latent tuberculosis.

In February 2013, 2 months after the initial visit, a standard regimen of belimumab at 10 mg/kg was infused every 2 weeks for the first 3 doses, followed by monthly infusions in addition to her other immunosuppressive therapy. Following her fourth infusion, she reported a marked improvement in her joint pain along with a reduction in her anti-dsDNA titer from 115 to 62 IU/mL, which further decreased to 43 IU/mL following her seventh infusion. Moreover, her C3 level was noted to increase to 79 mg/dL during the same period.

On her follow-up visit in August 2013, after a total of seven belimumab infusions, she presented with a complaint of a bitemporal headache that occurred at least 3-4 times/week, which was relieved by sleep but exacerbated by prolonged sitting. She denied any visual changes, fever, chills, respiratory symptoms, or other constitutional symptoms. Her neurological examination was unremarkable. As the patient was on immunosuppressants, brain magnetic resonance imaging (MRI) was performed on August 23, 2013, which revealed nonspecific supratentorial white matter signal abnormalities, possibly representing the sequela of migraine headaches and a 1.5×1.4×0.8-cm enhancing right parietal calvarial

1 Department of Rheumatology, Medstar Washington Hospital Center, Washington, USA

2 Department of Clinical Medicine, Georgetown University Medical Center, Washington, USA

Address for Correspondence: Richard Lai, Department of Rheumatology, Medstar Washington Hospital Center, Washington, USA

E-mail: richlai@rogers.com

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mass, possibly representing a hemangioma (Figure 1). This calvarial lesion was further evaluated using computer tomography (CT) of the head, which was the most consistent with hemangioma (Figure 2). She was subsequently referred to a neurologist for further evaluation, including a lumbar puncture (LP) on September 13, 2013. The initial results of the cerebrospinal fluid (CSF) analysis revealed the following: white blood cell, 1/mm^3 (0–5/mm^3); red blood cell, 1/mm^3 (0–3/mm^3); lymphocytes, 100%, protein, 21.8 mg/dL (15.0–40.0 mg/dL); glucose, 53 mg/dL (40–70 mg/dL); negative aerobic and anaerobic cultures; and negative cryptococcal antigen, venereal disease research laboratory test, and India ink stain for cryptococcus. Furthermore, fungal culture was negative after 4 weeks of incubation. Nevertheless, she continued to have recurrent episodes of the same type of headache. After 8 weeks following LP, the patient and neurologist were notified regarding a positive CSF acid-fast bacilli culture of *Nocardia* species.

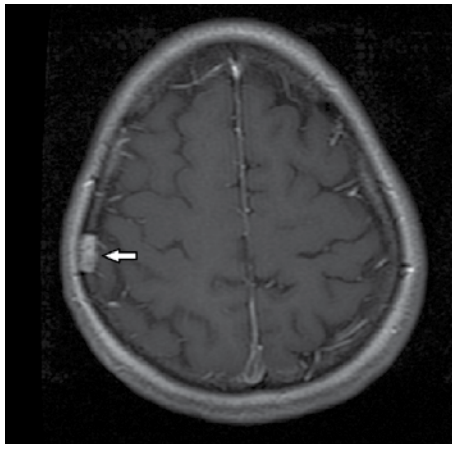

Figure 1. Chest X-ray: No acute pulmonary process

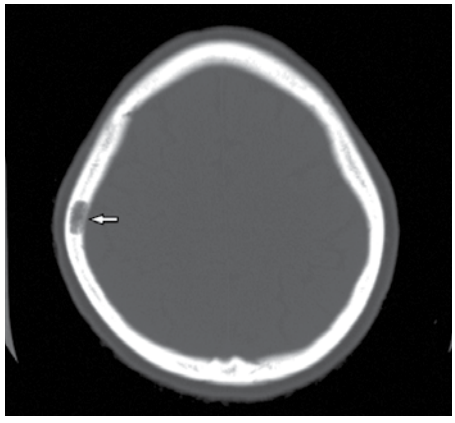

Figure 2. Magnetic resonance imaging (MRI) of brain with contrast, T1 axial image. An arrow indicates enhancing hypointense mass within the anterior right parietal calvarium, possibly representing hemangioma

Promptly, both belimumab and mycophenolate mofetil were discontinued, and the patient was hospitalized to receive intravenous meropenem and trimethoprim-sulfamethoxazole (TMP-SMX) as per the recommendations of an infectious disease specialist for the treatment of CNS nocardiosis. However, TMP-SMX had to be discontinued because of drug-induced dermatitis. Meropenem was continued for a total course of 3 months from November 2013 to January 2014 in addition to a 30-day course of minocycline. Repeat MRI following the completion of treatment in January 2014 revealed no radiographic change compared with the prior MRI. Moreover, a repeat LP culture revealed no organisms. She was subsequently restarted on 400 mg hydroxychloroquine daily and 2000 mg mycophenolate mofetil daily for her SLE after approximately 6 months post completion of antibiotic treatment. She reported a complete resolution of her headaches and is currently doing well with her active exercise routine.

Discussion

Belimumab is a recombinant human immunoglobulin G1-lambda monoclonal antibody against soluble BLyS, which is an essential growth factor for B-cell differentiation and activation. The binding of belimumab to BLyS ultimately leads to a reduction in autoantibody production (1).

Nocardia species is a gram-positive and slow-growing organism, most commonly introduced through the respiratory track (2). Nocardiosis is predominantly an opportunistic infection occurring in immunocompromised patients, such as patients on immunosuppressive therapy, those with transplants and human immunodeficiency virus positive, those with autoimmune diseases, and those with lymphoreticular neoplasms or solid tumors (2-4). A single nocardial colony that is isolated from CSF or other usually sterile regions, such as an abscess, pleural space, or joint fluid when an appropriate clinical setting is present, should never be overlooked because these organisms are rarely laboratory contaminants (2).

Approximately one-third of all *Nocardia* cases involve CNS (2). The signs and symptoms of CNS nocardiosis may be highly variable, ranging from headache, dizziness, hemiparesis, body tremors, Parkinsonian features, seizure, coma, ataxia, and meningoencephalitis to even psychotic personality and behavioral presentations. *Nocardia* species can subclinically invade the brain and persist for months to years until a clinical event occurs (2). Although abscess formation is the most common pathological finding, primary nocardial meningitis without pulmonary involvement or CNS abscess formation can also occur (2, 5, 6). Patients who are younger (mean age, 40 years) and who have lower initial CSF glucose levels (mean, 25 mg/dL) without neutrophilic pleocytosis or CNS abscess have better prognosis (6). The first-line antimicrobial agent for CNS nocardiosis is TMP-SMX and carbepenems.

Cases of nocardiosis have been reported in literature patients with SLE because of both their impaired autoimmunity and immunosuppressive drugs, including but not limited to high doses of intravenous methylprednisolone and prednisone, cyclophosphamide, azathioprine, and tacrolimus (3, 4, 7). Most incidents have pulmonary complications and rarely fatal CNS involvements (7). On the basis of the search of the entire Medline database, including the in-process file, cases of nocardiosis in the setting of mycophenolate mofetil, which our patient was on, have only been limited to patients with non-lupus renal and heart transplant (8, 9). No cases of nocardiosis have ever been reported in patients with lupus on mycophenolate mofetil, hydroxychloroquine, or isoniazid. Moreover, nocardiosis has never been reported in patients on belimumab in safety studies or in post-market analysis (10).

This is the first reported case regarding CNS nocardiosis in a patient treated with belimumab. As the patient was on mycophenolate and belimumab, one can argue whether this infection was because of belimumab or mycophenolate or a combination of both. We will argue that belimumab or the combination because of the timing of symptom onset and the diagnosis of nocardiosis in relationship to belimumab exposure. According to safety data from the extension study, the cumulative rate of severe infections in patients who received mycophenolate with belimumab over 4 years was 1.5-fold greater than that in patients who received immunosuppressants other than mycophenolate with belimumab (9.4 vs. 6.3/100 patient–years) (10).

Although headache is a common side effect of belimumab, CNS infections, such as nocardiosis, should be considered in the differential diagnosis of patients with SLE presenting with a new onset of unremitting headache even if other systemic signs remain unremarkable. When the clinical suspicion is high, head CT or brain MRI should be considered in addition to lumbar puncture for CSF analysis.

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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