American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2015; 16: 65-68
DOI: 10.12659/AJCR.892635

Received: 2014.10.01
Accepted: 2014.10.24
Published: 2015.02.07

Brain Abscess following Rituximab Infusion in a Patient with Pemphigus Vulgaris

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ADEF 1 Talal M. Al-Harbi
BFG 1 Shahad A. Muammer
AEF 2 Ronald J. Ellis

1 Department of Neurology, Neuroscience Centre, King Fahad Specialist Hospital, Dammam, Saudi Arabia
2 Department of Neuroscience, California University, San Diego, CA, U.S.A.

Corresponding Author: Talal M. Al-Harbi, e-mail: talal563@yahoo.com
Conflict of interest: None declared

Patient: Female, 52
Final Diagnosis: Brain abscess
Symptoms: Fever • headache • weakness, left sided
Medication: Prednisolone • Azathioprine • Rituximab
Clinical Procedure: Stereotactic brain biopsy and LP
Specialty: Neurology

Objective: Rare disease

Background: Immunocompromised patients are at increased risk for developing meningitis or, rarely, brain abscess with opportunistic organisms like *Listeria monocytogenes*.

Case Report: A 52 year-old Saudi Arabian woman who was diagnosed with pemphigus vulgaris and diabetes and had been on prednisolone and azathioprine for about 4 years. She presented with headache, low-grade fever, and left-sided weakness 2 weeks after receiving the second dose of rituximab infusion. Magnetic resonance imaging revealed an enhanced space-occupying lesion with multiple small cyst-like structures and vasogenic edema in the right temporoparietal area. Her blood culture was positive for *Listeria monocytogenes*, and a brain biopsy showed necrotic tissues with pus and inflammatory cells. She recovered after a 6-week course of antibiotics with ampicillin and gentamycin.

Conclusions: Brain abscess due to *Listeria monocytogenes* is a risk that should be considered when adding rituximab to the regimen of a patient who is already Immunocompromised.

MeSH Keywords: Abnormalities, Drug-Induced • Brain Abscess • Listeriosis • Rituximab

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/892635

Background

The gram-positive bacillus *Listeria monocytogenes* (LM) is an opportunistic pathogen that can invade the central nervous system (CNS) and cause severe infections. The most common CNS manifestations of listeriosis are meningitis, meningoencephalitis, and, rarely, brain abscess [1]. Neonates, pregnant women, elderly, and immunocompromised individuals are particularly vulnerable to developing CNS listeriosis [2].

Rituximab (RTX) is a monoclonal anti-CD20 antibody that induces B cell depletion (2) and has been widely used for the treatment of follicular non-Hodgkin's lymphoma and several autoimmune disorders, including resistant cases of pemphigus vulgaris (PV) [3].

To our knowledge there have been no reported cases of listerial brain abscesses in patients treated with RTX. Here, we describe a patient with PV who developed a right temporoparietal brain abscess shortly after RTX was added to an existing regimen of corticosteroid and azathioprine.

Case Report

A 52-year-old Saudi Arabian woman presented to our hospital with low-grade fever, severe headache, and progressive left-sided weakness with numbness; she had developed these symptoms 5 days earlier following a second RTX infusion that was initiated 2 weeks earlier to treat PV. She had underlying type II diabetes mellitus, hypertension, and hypothyroidism, which she acquired during a course of corticosteroid therapy. She was taking prednisolone (60 mg once daily), azathioprine (250 mg once daily), simvastatin, atenolol, and chloroquine. On examination, her temperature was 38°C, blood pressure was 146/82 mmHg, pulse rate was 105 bpm, and her respiratory rate was 22/minute. The patient was obese, with a body mass index of 37.7, and she had a cushingoid appearance. She was lethargic but able to follow commands. Neurological examination revealed a gaze preference to the right, spastic tone, and hyperreflexia on her left side, with motor strength of 3/5 on the left and 5/5 on the right using the Medical Research Council (MRC) scale. Her plantar reflexes exhibited an extensor response on the left. No neck stiffness was detected. A complete blood count showed a hemoglobin level of 11.8 g/dL with a white blood cell count (WBC) of 8.0×10^9/L (neutrophils 82%, lymphocytes 7%, and monocytes 11%). The test for HIV was negative and her toxoplasma IgM titre was 0.00 and nonreactive for IgG. Computed tomography (CT) of the brain after contrast material administration revealed a hypodense lesion with abnormal enhancement of the right temporoparietal lobe with surrounding vasogenic brain edema and no midline shift. She was admitted to the medical ward with a tentative diagnosis of brain abscess,

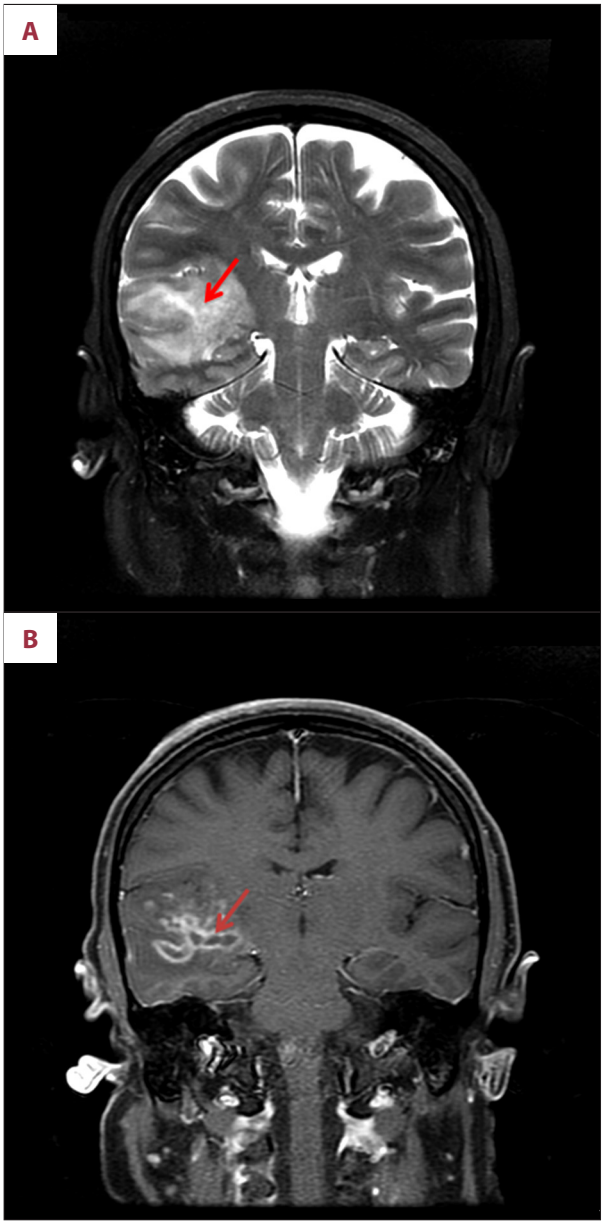

Figure 1. Brain MRI, next day of presentation to the emergency room. (**A**) Preoperative MRI scan, T2 coronal window, showing a large abscess in the right temporal lobe surrounded by extensive vasogenic edema. (**B**) MRI of the brain, T1 weighted images with gadolinium, coronal window showing multiple abscesses in the right temporal.

and empirical intravenous antibiotic treatment with vancomycin and meropenem was initiated. Brain magnetic resonance imaging (MRI) showed right temporoparietal enhancement with a central area of restricted diffusion representing multiple tiny abscesses with vasogenic edema (Figure 1). A lumbar puncture was performed on the same day, and her cerebrospinal fluid (CSF) contained 113 WBCs, predominantly lymphocytes, 393 red blood cells, and a high protein level 0.66 g/L. The CSF

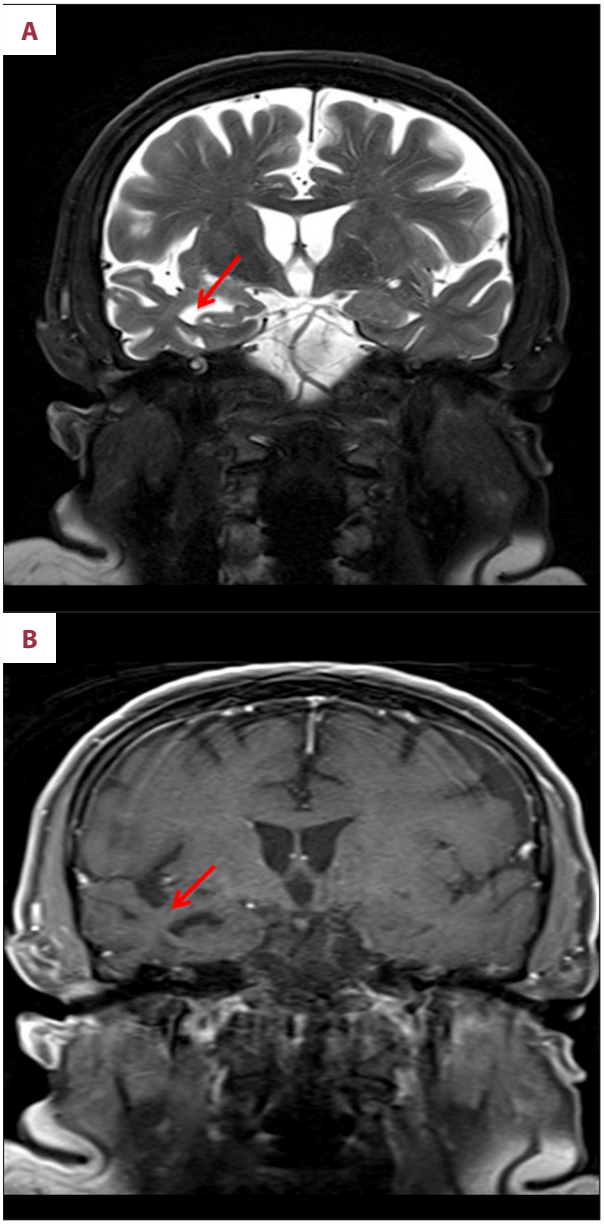

Figure 2. Brain MRI 4 months, post treatment. (**A**) MRI, T2 weighted image, coronal window, showing residual low signal intensity, gliosis and atrophy on the right temporal lobe. (**B**) MRI, T1 coronal window post contrast, showing right temporal low signal intensity, gliosis and atrophy with no contrast enhancement.

and serum levels of glucose were 3.0 and 8.0 mmol/L, respectively. Two tubes of blood for aerobic and nonaerobic culture were collected upon her presentation in the emergency room and before initiation of antimicrobial therapy. Subsequently, her prednisolone dose was tapered down gradually, and her azathioprine dose was reduced to 150 mg daily. Because of the failure to improve with empirical antibiotic therapy, on the second week of her admission she underwent a stereotactic brain biopsy. It revealed acute inflammatory cells, necrotic tissues debris, and macrophages, which indicated an infection although the tissue culture was negative. By that time, LM grew up on both tubes of the blood culture. According to the result of organism sensitivity, her antibiotics were adjusted to ampicillin (2 g every 4 hours for 6 weeks), administered in combination with adjuvant intravenous gentamicin (120 mg every 8 hours for 6 weeks). Her weakness abated within 2 weeks, and she was able to walk with unilateral support. A follow-up MRI of the brain after 4 months of treatment showed nearly complete resolution of the lesion, with residual hypodensity at the site of the abscess evacuation and no contrast enhancement of the right temporoparietal region (Figure 2).

Discussion

LM is a gram-positive, facultative, anaerobic, non-spore-forming rod. The organism is widely spread throughout the environment and can be found in soil and water, as well as in plants and animals commonly used for human consumption [4]. The principal route of transmission in humans is through the ingestion of contaminated food. Normally, the organism is rapidly cleared from the gastrointestinal tract. Alternatively, LM may cause illness after an incubation period of 11–71 days (median 31 days) [5].

LM is an uncommon cause of illness in the general population, but it can cause life-threatening infections in neonates, pregnant women, the elderly, and immunosuppressed patients. Protection against LM is predominantly cell-mediated [6]; therefore, conditions associated with impaired cellular immunity are risk factors for LM infection [7]. Rituximab depletes B cells, but *in vitro* studies have demonstrated that B cells are necessary for the induction of optimal CD4 memory [8]. Therefore, while rituximab directly impairs humoral immunity, it also has downstream effects on cellular immunity.

Meningitis is the most common CNS infection caused by LM [1], and brainstem encephalitis (rhombencephalitis) is also well recognized [9]. Brain abscess accounts for approximately 10% of CNS with LM infections [1]. LM brain abscesses are usually reported as an infectious complication in immunosuppressed patients and are commonly associated with positive blood culture in 85% of patients while concomitant meningitis in nearly 25% of patients [10]. The high rate of positive blood culture results suggest that the pathogenesis of *Listeria* brain abscess is secondary to hematogenous spread.

A recent review found that 56 cases of macroscopic brain abscesses due to *L. monocytogenes* have been reported between 1968 and 2011. Most patients (80%) had underlying conditions, such as a hematological malignancy (23%), autoimmune diseases treated with prednisolone (19%), having undergone solid organ

transplant (10%), diabetes mellitus (12%), human immunodeficiency virus (HIV) infection (7%), or others (9%). Positive blood cultures and CSF cultures were found in 79% and 23%, respectively. Ampicillin-based regimens were used in 37 patients (74%). Twenty-nine patients (51%) underwent surgery. A total of 19 patients died, giving a mortality rate of 33%. Patients who had underlying diseases and who did not undergo surgical interventions were more likely to die (63% and 74%, respectively) [2].

This patient presented with headache, fever, lethargy, and left-sided weakness; a combination of symptoms highly suggestive of CNS infection with space-occupying lesion-like pyogenic brain abscess. Infections with mycobacterium tuberculosis and toxoplasmosis were also considered due her immunosuppressed state. Primary CNS tumors and metastasis were also included in her differential diagnosis prior to the result of the blood culture.

In our patient, there was a strong temporal relationship between RTX treatment and the onset of neurologic symptoms, suggesting that RTX played a decisive role in the development of this opportunistic infection. RTX is a potent immunosuppressive medication that induces rapid and long-lasting depletion of circulating B cells. Indeed, although the patient had been using corticosteroids and azathioprine for several years, a cerebral abscess only developed after the initiation of RTX infusions.

While RTX is usually well tolerated, it poses the risk of opportunistic infections in at-risk patients, possibly because it induces hypogammaglobulinemia and causes delayed-onset neutropenia [11].

While *Listeria* abscess has not been reported previously following rituximab therapy, other similar, infrequent opportunistic neurological complications have been documented. Charles et al. [12] described a right frontal brain abscess due to *Legionella micdadei* in a 59-year-old man with Waldenström's macroglobulinemia who had completed a 6-month course of chemotherapy with RTX and a DNA synthesis inhibitor (fludarabine) 6 weeks prior to his initial presentation with recurrent falls, aphasia, confusion, and hallucinations [12].

Enteroviral meningoencephalitis following RTX therapy was also reported in a child with autoimmune thrombocytopenia and an adult patient with relapsed B cell lymphoma [13]. In another report, reactivation of cerebral toxoplasmosis after RTX therapy in a 71-year-old female with cutaneous vasculitis associated with type I cryoglobulinemia was described [14]. Furthermore, a recent study found 57 cases of progressive multifocal leukoencephalopathy associated with RTX use in HIV-negative patients; 90% of the patients had lymphoproliferative disorders, and 4 patients with rheumatoid arthritis were described in a separate cases series [15,16].

Conclusions

Adding RTX to an immunosuppressive medication regimen may increase the risk of a rare brain infection like LM, which can cause brain abscesses; therefore, close monitoring of patients who receive RTX is highly recommended.

References:

1. Lorber B: Listeriosis. Clin Infect Dis, 1997; 24(1): 1–9; quiz 10–11
2. Limmahakhun S, Chayakulkeeree M: *Listeria monocytogenes* brain abscess: two cases and review of the literature. Southeast Asian J Trop Med Public Health, 2013; 44(3): 468–78
3. Barrera MV, Mendiola MV, Bosch RJ, Herrera E: Prolonged treatment with rituximab in patients with refractory pemphigus vulgaris. J Dermatolog Treat, 2007; 18(5): 312–14
4. Siegman-Igra Y, Levin R, Weinberger M et al: *Listeria monocytogenes* infection in Israel and review of cases worldwide. Emerg Infect Dis, 2002; 8(3): 305–10
5. Laine RO, Zeile W, Kang F, Purich DL, Southwick FS: Vinculin proteolysis unmasks an ActA homolog for actin-based Shigella motility. J Cell Biol, 1997; 138(6): 1255–64
6. Mielke ME, Peters C, Hahn H: Cytokines in the induction and expression of T-cell-mediated granuloma formation and protection in the murine model of listeriosis. Immunol Rev, 1997; 158: 79–93
7. Stam J, Wolters EC, van Manen J, Verbeeten B: *Listeria monocytogenes* abscess in the basal ganglia. J Neurol Neurosurg Psychiatry, 1982; 45(8): 757–59
8. Mollo SB, Zajac AJ, Harrington LE: Temporal requirements for B cells in the establishment of CD4 T cell memory. J Immunol, 2013; 191(12): 6052–59
9. Armstrong RW, Fung PC: Brainstem encephalitis (rhombencephalitis) due to *Listeria monocytogenes*: case report and review. Clin Infect Dis, 1993; 16(5): 689–702
10. Eckburg PB, Montoya JG, Vosti KL: Brain abscess due to *Listeria monocytogenes*: five cases and a review of the literature. Medicine (Baltimore), 2001; 80(4): 223–35.
11. Feist E, Dorner T: [Rituximab]. Zeitschrift fur Rheumatologie, 2010; 69(7): 594–600 [in German]
12. Charles M, Johnson E, Macyk-Davey A et al: *Legionella micdadei* brain abscess. J Clin Microbiol, 2013; 51(2): 701–4
13. Quartier P, Tournilhac O, Archimbaud C et al: Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. Clin Infect Dis, 2003; 36(3): e47–49
14. Safa G, Darrieux L: Cerebral toxoplasmosis after rituximab therapy. JAMA Intern Med, 2013; 173(10): 924–26
15. Chakraborty S, Tarantolo SR, Treves J et al: Progressive Multifocal Leukoencephalopathy in a HIV-Negative Patient with Small Lymphocytic Leukemia following Treatment with Rituximab. Case Rep Oncol, 2011; 4(1): 136–42
16. Clifford DB, Ances B, Costello C et al: Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. Arch Neurol, 2011; 68(9): 1156–64