Cerebral toxoplasmosis after rituximab therapy for splenic marginal zone lymphoma: a case report and review of the literature

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Introduction: *Toxoplasma gondii* is a parasite estimated to infect one-third of the global population, surviving in tissues in a latent form. Although cerebral toxoplasmosis is predominantly recognized as an opportunistic infection in hosts immunocompromised secondary to human immunodeficiency virus or bone marrow transplant, there is increasing recognition that this infection can occur in patients receiving immunomodulating agents such as mAb therapy targeted against T-cells, B-cells and TNF. The indications for these therapies are expanding, resulting in a larger at-risk population for this rare but serious and potentially avoidable complication.

Case Presentation: This is one of the few case reports of cerebral toxoplasmosis following rituximab-based chemotherapy in a patient with a haematological malignancy. We describe a patient presenting with focal neurological deficits and radiographic evidence of multi-focal cerebral ring-enhancing lesions following completion of rituximab therapy for splenic marginal zone lymphoma. Brain biopsy confirmed a diagnosis of cerebral toxoplasmosis. Antibiotic treatment with trimethoprim/sulfamethoxazole resulted in near-complete radiological and clinical resolution of the neurological deficits, and a return to baseline functional status.

Conclusion: Reactivation of toxoplasmosis resulting in intracerebral disease is a potential severe and preventable complication of rituximab therapy. Further studies are required to assess the need both for screening and prescribing primary chemoprophylaxis for toxoplasmosis when initiating rituximab therapy.

Keywords: cerebral toxoplasmosis; lymphoma; rituximab; toxoplasmosis.

Introduction

One-third of the global population has been estimated to be infected with *Toxoplasma gondii* (Halonen & Weiss, 2013). The seroprevalence of infection varies by country, with 10–20 % of the population of the USA exhibiting a positive test at some point during their lifetime (Jones et al., 2014). Cats, the definitive hosts for the organism, can pass millions of environmentally resistant oocysts in faeces that contaminate food, water and soil (Hill & Dubey, 2002). When humans are infected, symptomatic disease occurs in two distinct populations. Congenitally infected children manifest a spectrum of disease ranging from mild visual impairment to debilitating hydrocephalus and retinochoroiditis (Hill & Dubey, 2002). Disease in adulthood occurs mainly in immunocompromised hosts, such as antiretroviral treatment naïve individuals with advanced AIDS (Pereira-Chioccola et al., 2009), and solid organ and stem cell transplant recipients, in whom cerebral toxoplasmosis is the principal clinical manifestation (Halonen & Weiss, 2013).

Rituximab is a chimeric monoclonal IgG1 antibody targeting the transmembrane receptor CD20 found mainly on B-lymphocytes. Administered as an intravenous infusion, rituximab leads to directed cellular toxicity, complement-mediated cytotoxicity and induced apoptosis of CD20-positive cells. Secondary effects including modulation of T-cell-mediated immunity, delayed hypogammaglobulinaemia and neutropenia are also common (Kelesidis et al., 2011). Rituximab is an integral component of many chemotherapeutic regimens for oncologic and rheumatologic disorders, such as non-Hodgkin lymphoma, microscopic polyangiitis,
granulomatosis with polyangitis and severe rheumatoid arthritis refractory to alternative therapies (Kelesidis et al., 2011; Singh et al., 2011).

The drug has been associated with an increased risk for a variety of infections, likely secondary to these effects on the innate and adaptive immune system. Bacterial upper and lower respiratory tract infections and viral reactivation syndromes involving hepatitis B virus (HBV), herpes zoster virus, herpes simplex virus, cytomegalovirus and JC/BK viruses are the most frequent (Kelesidis et al., 2011). Fungal and parasitic infections are less commonly reported (Kelesidis et al., 2011; Singh et al., 2011). The risk period for infection is prolonged as the systemic immunosuppressive effects have been documented to persist for up to 6 months following completion of rituximab therapy (Singh et al., 2011).

**Case report**

A 77-year-old woman was admitted to hospital with a 2 week history of progressive left-sided weakness, gait disturbance, dysarthria, disorientation and vision loss. She had been diagnosed with stage IVB splenic marginal zone lymphoma ~8 months previously, and had completed six cycles of rituximab, cyclophosphamide vincristine and prednisone chemotherapy. The last cycle of chemotherapy was completed 3 months prior to the onset of her neurological symptoms.

Her past medical history included bilateral cataracts, hypertension and a cerebrovascular accident with no residual neurological deficits. She previously owned household cats. Human immunodeficiency virus serology was negative. There was serological evidence of past toxoplasmosis (IgG-positive).

On examination, she was not oriented to time or place. She was afebrile, haemodynamically stable and not in respiratory distress. There was no peripheral lymphadenopathy. Splenomegaly was present. Neurological abnormalities included bilateral lateral gaze palsy, a right-sided facial droop with sparing of the forehead, and increased tone and hyperreflexia of the right arm associated with 4/5 muscle weakness.

There was no leukocytosis and the renal function was normal. Serum quantitative immunoglobulin levels were not determined. A non-contrast computed tomography scan of the head demonstrated multiple areas of vasogenic oedema in both cerebral hemispheres and in the posterior limbs of the internal capsules. A 13 mm × 5 mm hyperdense lesion was present in the left frontal periventricular white matter. Gadolinium-enhanced magnetic resonance imaging of the brain showed innumerable lesions in both cerebral hemispheres with moderate surrounding vasogenic oedema (Fig. 1). The abnormalities exhibited a central core of hyperintensity surrounded by a peripheral rim of isointensity. Some of the lesions demonstrated central necrosis. There was no midline shift or hydrocephalus.

Radiographic findings were initially thought to be most in keeping with malignancy, therefore a biopsy of a right frontal lesion was performed via a right frontal craniotomy in order to establish a definitive histopathological diagnosis and guide therapy. Molecular testing for toxoplasmosis reactivation in serum and cerebrospinal fluid was not performed prior to biopsy due to the need for immediate tissue diagnosis. A dense lymphocytic-predominant inflammatory infiltrate with scattered toxoplasmic cysts and free organisms was seen on immunohistochemical staining (Fig. 2). Staining for CD20 cell surface marker revealed only scattered mature positive lymphocytes with no evidence of B-cell neoplasm. No SV-40 antigen was detected by immunostaining. Microbiological cultures of the brain biopsy were not performed.

**Outcome and follow-up**

As the diagnosis of reactivation of latent toxoplasmosis infection was confirmed by histopathology, directed anti-toxoplasmic antibiotic therapy with twice daily oral trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of 5 mg trimethoprim kg⁻¹ day⁻¹ and 25 mg sulfamethoxazole kg⁻¹ day⁻¹ was started. Oral dexamethasone 4 mg four times per day was concomitantly administered because of the significant cerebral oedema. Repeat magnetic resonance imaging of the brain 1 month after treatment demonstrated partial interval improvement with decreased size of the lesions. After 6 weeks of TMP/SMX...
therapy, all of the neurological deficits, other than a residual mild lateral gaze palsy, had resolved.

Discussion

Our patient is one of the few reported cases of cerebral toxoplasmosis occurring in the setting of rituximab-based chemotherapy for lymphoma. In one previous report, concurrent progressive multifocal leukencephalopathy and cerebral toxoplasmosis developed in a patient with chronic lymphocytic leukaemia following therapy with rituximab, cyclophosphamide and fludarabine (Desmond et al., 2010). A second report described a patient who developed toxoplastic encephalitis during treatment for diffuse large B-cell lymphoma with multiple rituximab-containing chemotherapy regimens (Savsek & Opaske, 2014). Outside of these, the recognition of the association between cerebral toxoplasmosis and biological agents has been limited to three case reports of patients afflicted with underlying rheumatologic disorders, only one of whom received rituximab (Safa & Darrieux, 2013). The remaining two patients were treated with an anti-TNF inhibitor, either infliximab (Young & McGwire, 2005) or adalimumab (Nardone et al., 2014).

Multiple inflammatory mediators such as IFN-γ, inducible nitric oxide synthase and various interleukins have been identified as essential for adequate host immune response to acute infection with T. gondii (Sturge & Yarovinsky, 2014). T-cells, via a direct cytotoxic effect mediated by NK-cells (Sturge & Yarovinsky, 2014), have been identified as the primary effector cells involved, as demonstrated by increased susceptibility to infection and mortality in mouse models depleted in CD4 and CD8 T-cells (Gazzinelli et al., 1992). Although less important in acute infection, evidence derived from the murine toxoplasmosis infection model has indicated that the humoral response is essential for controlling the reactivation of infection (Kang et al., 2000). B-cell-deficient mice who survive initial infection accumulate a significant burden of tachyzoites in pulmonary and central nervous system tissue, resulting in increased mortality compared with their control B-cell-replete brethren (Kang et al., 2000). Passive transfer of IgG-specific anti-toxoplasmic antisera protects B-cell deficient mice from lethal challenge with the organism (Johnson et al., 1983; Kang et al., 2000). Thus, in view of the profound B-cell depletion mediated by rituximab, patients with latent toxoplasmosis receiving this mAb therapy would be expected to be at particular risk for reactivation of this infection. This is likely further increased with inhibition of both humoral and cellular immunity via concomitant exposure to corticosteroids, cyclophosphamide (a nucleic acid alkylating agent) and vincristine (an inhibitor of mitotic spindle formation), although the specific risk of cerebral toxoplasmosis associated with each of these agents has not been well characterized.

The pronounced immunological deficit imposed by rituximab has several clinical implications. First, this case argues for the use of primary chemoprophylaxis with TMP/SMX in seropositive patients receiving rituximab in order to diminish the risk of cerebral toxoplasmosis – a consequence of the reactivation of latent infection. After stopping rituximab, maintaining the duration of primary chemoprophylaxis for 6 months until functional restoration of the immune system has occurred (Singh et al., 2011) is prudent. Second, secondary chemoprophylaxis with TMP/SMX should be considered in a patient with a prior history of treated toxoplasmosis infection who is to receive rituximab chemotherapy. Such a therapeutic approach has been clearly demonstrated to reduce the risk of this infection in human immunodeficiency virus patients (Gallant et al., 1994). Current guidelines also recommend this approach in seropositive haematopoietic stem cell transplant recipients, although it is noted that there are rare occurrences of disseminated toxoplasmosis occurring in seronegative patients (Gea-Banacloche et al, 2009; Sullivan et al., 2001). In a similar fashion, the initiation of antiviral chemoprophylaxis has been shown to prevent reactivation of HBV in rituximab-treated patients with chronic HBV infection (Perrillo et al., 2015).

Given the expanding clinical indications for targeted biological therapies and their prolonged immunosuppressive effects, the prevalence of reactivation of toxoplasmosis manifested as intracerebral disease is expected to increase. A high index of suspicion for cerebral toxoplasmosis in patients on rituximab or other biological therapies who present with neurological symptoms and supporting neuroimaging is emphasized. Further studies are required to support our recommendations for instituting both routine serological testing for toxoplasmosis and primary chemoprophylaxis in seropositive patients prior to the start of rituximab treatment.
References


