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BRIEF REPORT

Toxoplasma Encephalitis in Atypical Hosts at an Academic Cancer Center

Sejal Morjaria,[1,a] David J. Epstein,[5,a] Fabian A. Romero,[1] Ying Taur,[1,6] Susan K. Seo,[1,6] Genovefa A. Papanicolaou,[1,6] Vaios Hatzoglou,[2,7] Marc Rosenblum,[3] Miguel-Angel Perales,[4,6] Michael Scordo,[4] and Anna Kaltsas[1,6]

[1]Infectious Disease Service, Department of Medicine, [2]Neuroradiology Service, Department of Radiology, [3]Department of Pathology, and [4]Bone Marrow Transplant Service, Memorial Sloan-Kettering Cancer Center, New York; [5]Division of Infectious Diseases and Immunology, Department of Medicine, New York University School of Medicine; Departments of [6]Medicine, and [7]Radiology, Weill Cornell Medical College, New York

Toxoplasma encephalitis is a well recognized complication of acquired immune deficiency syndrome, solid organ transplantation, and allogeneic hematopoietic stem cell transplantation (HSCT). However, patients with hematologic malignancies not treated with allogeneic HSCT may also develop this condition, which requires high clinical suspicion and consideration for prophylactic therapy.

Keywords. autotransplantation; immunosuppression; leukemia; lymphoma; toxoplasmosis.

CASE 1

A 59-year-old human immunodeficiency virus (HIV)-negative man with diffuse large B-cell lymphoma affecting the left cavernous sinus received multiple anti-neoplastic therapies from September 2013 through October 2014, including 1 cycle of rituximab, methotrexate, procarbazine, and vincristine; 4 cycles of methotrexate, rituximab, cyclophosphamide, doxorubicin, vincristine, and dexamethasone; 2 cycles of methotrexate, rituximab, and temozolomide; and 3 cycles of lenalidomide, rituximab, and intraventricular liposomal cytarabine. He also received over 15 treatments with intraventricular rituximab via an Ommaya intraventricular catheter and external beam radiation therapy to the affected site.

After achieving remission, he underwent an autologous hematopoietic stem cell transplantation (HSCT) in November 2014 with busulfan, thiotepa, and cyclophosphamide conditioning. His posttransplant course was complicated by cytomegalovirus (CMV) viremia and BK virus viremia and viruria; he also had a possible autologous graft-versus-host-like syndrome with rash and colitis treated with prolonged courses of corticosteroids.

For prevention of *Pneumocystis jiroveci* pneumonia (PJP), the patient received trimethoprim-sulfamethoxazole (TMP-SMX) pretransplant, which was changed to aerosolized pentamidine after transplant to avoid myelosuppression. Pretransplant serologic testing for toxoplasmosis was not performed.

Several months after transplant, the patient had persistent lymphopenia of 216/μL (normal 500–5300/μL) with normal ratio of $CD4^+$ to $CD8^+$ T lymphocytes and an absolute $CD4^+$ T lymphocyte cell count of 48/μL (normal 429–1131/μL). In April 2015, he presented with fever and mental status changes. Magnetic resonance imaging (MRI) of the brain showed multiple new lesions hyperintense on fluid-attenuated inversion recovery sequences, predominantly involving the basal ganglia bilaterally but also within the bilateral parietal-occipital lobes and cerebellar hemispheres. Several of the lesions enhanced with intravenous contrast and 2 basal ganglia lesions were partially hemorrhagic. Cerebrospinal fluid (CSF) sampled via lumbar puncture (LP) showed a normal cell count and differential and a normal glucose level, but the protein level was 46 mg/dL (normal 21–38 mg/dL). Cerebrospinal fluid *Toxoplasma* polymerase chain reaction (PCR) detected 1100 copies/mL. Polymerase chain reaction of blood plasma detected *Toxoplasma* at below the limit of detection of 376 copies/mL. Routine blood and CSF cultures for bacteria and fungi were negative. Cryptococcal antigen testing performed on CSF was negative, as were PCR tests for herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella-zoster virus, and *Human herpesvirus 8*. Cerebrospinal fluid cytology was unremarkable. (PCR detected CMV in the CSF at below the limit of detection.) *Toxoplasma* encephalitis (TE) was diagnosed and intravenous TMP-SMX was begun, although the patient's condition deteriorated and he died on hospital day number 37. Autopsy was not performed.

CASE 2

A 79-year-old HIV-negative woman with pulmonary B-cell lymphomatoid granulomatosis (LYG) associated with EBV infection was treated with 6 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone ending in October 2012 with radiographic improvement.

In October 2013, she presented with inattention, left-sided weakness, and hyperreflexia of the left leg. Magnetic resonance imaging of the brain revealed a ring-enhancing lesion in the right frontal lobe measuring 1.1 × 1.1 cm with mild surrounding

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[a]S. M. and D. J. E. contributed equally to this work.

Correspondence: S. Morjaria, 1275 York Avenue Box 9, New York, NY 10065 (morjaris@mskcc.org).

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edema. Her complete blood count and differential were normal; she had no $CD4^+$ T lymphopenia. On hospital day 3, CSF analysis via LP revealed a leukocyte count of 25/μL (normal 0–10/μL) (86% lymphocytes, 2% reactive lymphocytes, and 12% monocytes). Glucose and protein levels were normal. Cerebrospinal fluid studies were negative including the following: bacterial and fungal cultures; cryptococcal antigen; and PCR testing for CMV, HSV, EBV, JC virus, and *Toxoplasma*. Cerebrospinal fluid cytology showed no evidence of malignancy.

Initial brain histology from stereotactic needle biopsy sampling of the right frontal lobe lesion revealed only an atypical lymphoid infiltrate. A right frontal craniotomy with open brain biopsy was pursued. Histologic examination of the neurosurgical material demonstrated cerebral involvement by both LYG and active toxoplasmosis. The former process was characterized by a polymorphous mononuclear cell infiltrate that included a subpopulation of enlarged and atypical B lymphocytes exhibiting immunohistochemical expression of CD19, CD20, and CD30, but not CD3 or CD15. In situ hybridization studies demonstrated kappa light chain restriction and the presence of lymphocyte labeling for EBV-encoded RNA (EBER1). Involvement of blood vessel walls was conspicuous, as were large zones of necrosis. Bradyzoite-laden cysts and tachyzoites, confirmed by positive labeling on immunohistochemical study, were identified mainly in tissues adjoining areas of necrosis (Figure 1A and 1B).

Toxoplasma serologies had not been performed. After 10 weeks of treatment with clindamycin and pyrimethamine, neurologic signs improved but she remained ataxic; sequential imaging showed stable disease. She was started on secondary prophylaxis and remains on TMP-SMX with stable neurologic findings.

CASE 3

An 82-year-old HIV-negative woman was diagnosed with large granulocytic leukemia and initiated treatment with oral cyclophosphamide in December 2013 with subsequent clinical improvement.

In June 2014, while still receiving cyclophosphamide, she presented with acute onset of left-sided weakness. Complete blood count demonstrated lymphopenia of 200/μL. Magnetic resonance imaging of the brain showed multiple enhancing and partially hemorrhagic lesions involving both cerebral hemispheres. The dominant lesions were ring-enhancing and involved the left frontal lobe and right caudate nucleus, measuring 1.3 × 1.1 cm and 1.2 × 0.8 cm (Figure 1C). Cerebrospinal fluid was sampled via LP and revealed a white blood cell count of 8 cells/μL with normal levels of glucose and protein. Cerebrospinal fluid *Toxoplasma* PCR was negative.

On hospital day 10, an open biopsy was performed of the left frontal lobe lesion. Histopathology showed necrotizing lesions with a lymphocytic infiltrate containing structures consistent with *Toxoplasma* tachyzoites. Pyrimethamine and sulfadiazine were begun, with resultant neurologic improvement. It is worth noting that her hospital course was complicated by CMV reactivation with 313 000 copies/mL in peripheral blood for which she was successfully treated with valganciclovir. Her most recent brain MRI from February 2016 showed diminution of the lesions and vasogenic edema.

DISCUSSION

Reactivation TE has been commonly described in patients with acquired immune deficiency syndrome (AIDS) and is increasingly recognized as a complication of allogeneic HSCT and solid organ transplantation (SOT), conditions characterized by impaired cell-mediated immunity [1–3]. *Toxoplasma* infection in immunocompetent hosts is characterized by persistence of the organism in a dormant state in the form of intracellular bradyzoites. Type 1 cytokine production prevents clinically apparent reactivation of latent *Toxoplasma* infection by controlling replication of tachyzoites, the pathogenic form of the parasite responsible for TE, and possibly by inducing tachyzoite transformation into bradyzoite form [4].

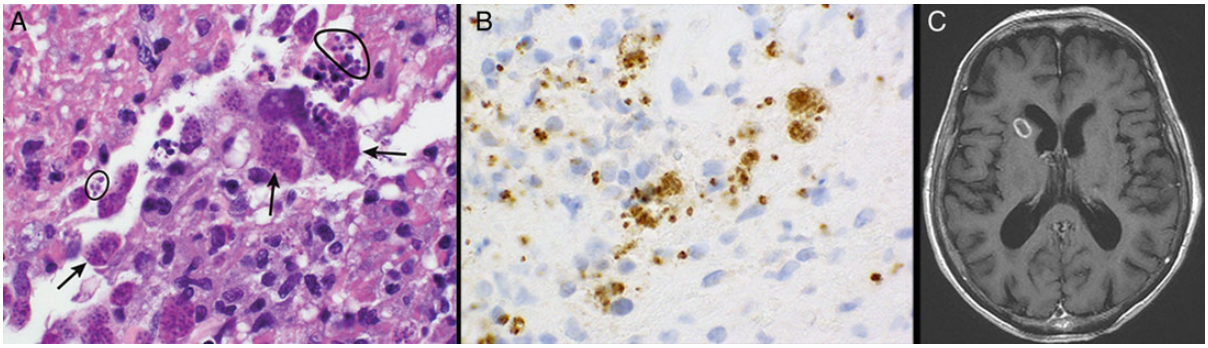

Figure 1. (A) *Toxoplasma* cyst forms (circled) and tachyzoites (arrows) are seen bordering a focus of necrosis (hematoxylin and eosin, ×100). (B) Labeling with anti-*Toxoplasma* antibody confirms the nature of the cyst forms and tachyzoites (anti-*Toxoplasma* immunohistochemistry with hematoxylin counterstain, ×100). (C) An axial T1-weighted image obtained after intravenous contrast injection demonstrates a ring-enhancing toxoplasmosis lesion in the right caudate nucleus measuring 1.2 × 0.8 cm.

Although unusual, TE has been reported elsewhere in patients with hematologic malignancies without typical risk factors for TE (such as allogeneic HSCT) [5]. The pathogenesis of TE in these patients is poorly understood but may involve an occult immune deficiency, which predisposes patients to both malignancy and TE, modulation of immunity by the malignancy itself, or iatrogenic immunosuppression. Subclinical immune deficits have been linked to an increased risk of both hematologic malignancies and infections, including through identified genetic polymorphisms, although this relationship has not been specifically demonstrated for *Toxoplasma* [6–8]. In addition, some lymphomas are known to produce wide-ranging effects on systemic immune responses, increasing the risk of infections, although, again, this link has not been established with *Toxoplasma* infections [9, 10].

The most clinically apparent link between lymphoma and TE relates to the administration of purine analogs, corticosteroids, and other therapies known to affect cell-mediated immunity [5, 11]. In addition to these drugs impairing cell-mediated immunity, patients in the first 2 cases described above received rituximab, which has been posited as a risk factor for TE, although evidence is anecdotal [12, 13].

In patients without AIDS, allogeneic HSCT, SOT, or other profound impairments of cellular immunity, we suggest that reactivation TE occurs due to a combination of risk factors that by themselves might not lead to disease. These risk factors may include sequential or overlapping highly immunosuppressive therapies such as seen in Case 1, lymphomas with particular affinity for immune dysregulation and infection, and underlying occult immune deficits.

Some of the highest risk patients (apart from allogeneic HSCT or similar patients) often receive medications that incidentally prevent *Toxoplasma* reactivation when given for PJP prophylaxis, mitigating the risk for reactivation. Autologous HSCT recipients, those with acute lymphocytic leukemia, and those treated with purine analogues or corticosteroids, among others, generally receive TMP-SMX or atovaquone for prevention of PJP and are somewhat protected against *Toxoplasma* reactivation [14]. The patient in Case 1 received inhaled pentamidine, an agent without activity against *Toxoplasma*, for prevention of PJP, and the patients in Cases 2 and 3 received no relevant antimicrobial prophylaxis.

CONCLUSIONS

We draw several conclusions from these cases. *Toxoplasma* encephalitis should be considered in the differential diagnosis of otherwise unexplained neurologic deficits in patients with hematologic malignancies even when these patients are traditionally thought of as being at low risk for TE. At this time, there is insufficient evidence to recommend routine *Toxoplasma* screening with serology or prophylactic therapy in patients with hematologic malignancies who are not receiving allogeneic HSCT. However, the anti-*Toxoplasma* activity of TMP-SMX and atovaquone (in contrast with dapsone and pentamidine) can be considered when choosing an agent for PJP prophylaxis in these patients. Furthermore, presence of severe and prolonged lymphopenia or diagnosis of CMV disease, BK virus viremia, or other infections that are rarely seen in patients with a hematologic malignancy who have not received an allogeneic transplant, should be viewed as a marker of impaired cellular immunity; in such patients, prophylaxis against infections such as *Toxoplasma* could be considered. Finally, more research is needed to determine additional risk factors for *Toxoplasma* reactivation, and the risks and benefits of prophylactic therapy in patients with malignancy without other high-risk features.

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