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BRIEF REPORT

Expanding Spectrum of *Toxoplasma gondii*: Thymoma and Toxoplasmic Encephalitis

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In this brief report, we describe a 76-year-old patient with thymoma who underwent craniotomy for a left parietal lobe mass with pathologic findings consistent with *Toxoplasma gondii* encephalitis in the absence of any features of thymoma with immunodeficiency/Good's syndrome. His clinical course suggested likely *Toxoplasma* reactivation.

Keywords. parasitic infection; thymoma; *Toxoplasma gondii*.

CASE DESCRIPTION

A 76-year-old African American male patient diagnosed with World Health Organization (WHO) type B2 and B3, Masaoka-Koga Staging System stage III thymoma that invaded the pericardium and lung parenchyma in October 2016 who underwent single-modality therapy with surgical debulking in December 2016 was transferred to our facility with complaints of progressive headaches for 1 month's duration. Magnetic resonance imaging (MRI) of the brain revealed a 2.2-cm mass of the left parietal lobe (Figure 1). A computed tomography (CT) scan of the chest was remarkable for the primary mediastinal lesion and pleural and mediastinal metastases, which were reduced in size compared with prior studies. The patient underwent left parietal craniotomy for presumed tumor resection. Postsurgically, the patient began having seizures, and a CT scan of the brain revealed stable postsurgical changes of the left parietal lobe, no evidence of intra- or extra-axial hemorrhage, no mass effect or shift, no acute infarct or bleed. Pathological examination of resected brain tissue revealed necrotic brain parenchyma with predominately acute inflammation. The parenchyma was hypercellular due to inflammation, consisting of neutrophils, lymphocytes, and scattered macrophages, and gliosis, consisting of astrocytes and microglia exhibiting mild reactive-type atypia. Structures morphologically suspicious for microorganisms were present. This raised concern for the possibility of neoplasm. Flow cytometry reported no evidence of B-cell or T-cell lymphoma. Based on these findings, the sample was sent to a tertiary expert in neuropathology for further review.

Preliminarily, *Toxoplasma gondii* was suspected, leading to an infectious diseases consultation. While awaiting results from additional testing, trimethoprim/sulfamethoxazole (TMP/SMX) 5 mg/kg (TMP component) was given orally twice daily, as pyrimethamine, sulfadiazine, and leucovorin were unavailable. The patient could not respond to questions secondary to decreased mentation and mechanical ventilation, which led to discussions with the patient's family revealing a history significant for tobacco abuse with cessation approximately 30 years ago, but no history of immunosuppressive medications, including corticosteroids, exposure to animals, or travel. Laboratory testing revealed no leukopenia, neutropenia, or lymphopenia.

Review of the left parietal brain tissue by neuropathology revealed brain fragments with necrotizing inflammation and reactive astrocytes. Scattered structures morphologically consistent with *T. gondii* pseudocysts (Figure 2), filled with bradyzoites, and rare aggregates of tachyzoites were identified. Immunohistochemical staining was positive for toxoplasmosis and negative for JC virus (simian virus 40), cytomegalovirus (CMV), and fungal organisms (Grocott's Methanamine Silver; special stain). The original findings of atypia were believed to represent reactive cytomorphologic changes rather than neoplastic, consistent with that observed during active *T. gondii* infection.

Serologic testing for human immunodeficiency virus (HIV) was nonreactive, toxoplasma immunoglobulin G (IgG) was >400 IU/mL, and toxoplasma IgM was <8 IU/mL. Absolute lymphocyte and CD4+ T-cell counts (range) were 1819 (1000–3000) cells/mm^3 and 452 (400–1650) cells/mm^3, respectively. Upon receipt of the final pathology report, in combination with the aforementioned serologic tests, the patient was transitioned to pyrimethamine, sulfadiazine, and leucovorin, briefly. However, due to concerns of malabsorption and resultant subtherapeutic drug concentrations, intravenous TMP/SMX was started. Unfortunately, the patient did not have any meaningful neurologic recovery. Palliative care was consulted, and the patient was transferred to hospice services with comfort measures.

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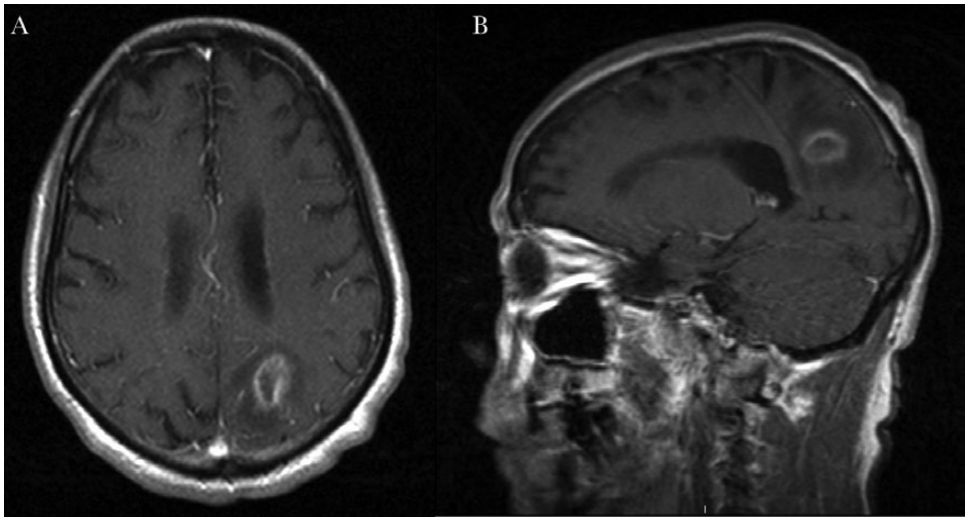

Figure 1. Magnetic resonance imaging of the brain (axial plane [A] and sagittal plane [B]) showing a ring-enhancing 2.2-cm mass in the left parietal occipital lobe with surrounding edema.

DISCUSSION

Thymoma, a rare neoplastic disease in the anterior mediastinum with an incidence of 0.13/100 000 person-years, presents as an asymptomatic mediastinal mass on chest radiograph, localized symptoms, or concomitantly with myasthenia gravis (MG), in equal proportions [1]. Thymectomy is recommended for all thymomas with the addition of chemotherapy and/or radiation, dependent upon disease severity and surrounding tissue invasion [2]. Prognosis is contingent upon staging with 10-year survival rates for Masaoka stages I–IV of 88%, 70%, 57%, and 38%, respectively. The risk of recurrent disease is correlated with higher-stage thymomas, whereas secondary malignancies, including non-Hodgkin lymphoma, occur in <25% following thymectomy [1]. Immunodeficiency observed concomitantly with thymomas or post-thymectomy may be the result of Good's syndrome, characterized by thymoma with immunodeficiency [3], combined B- and T-cell immunodeficiency causing hypogammaglobulinemia [4], autoimmune diseases such as MG or systemic lupus erythematosus (SLE), among many others [5], or T-cell immune dysfunction [1]. Often, treatment with intravenous immunoglobulin (IVIG) is required in the setting of humoral immunodeficiency [6, 7]. Additionally, immunosuppressive therapies, including corticosteroids, cyclophosphamide, and plasmapheresis, have been used to reverse granulocytopenia, with variable success.

T. gondii infects approximately one-third of the world's population, while causing disease in congenitally infected neonates or immunocompromised patients, and rarely in immunocompetent individuals [8]. In immunocompromised patients, toxoplasmosis occurs following reactivation of latent infection, most often affecting the central nervous system (CNS). The risk of reactivation is increased in settings of T-cell-mediated immune dysfunction, which may be the result of T-cell exhaustion, deterioration, or deletion.

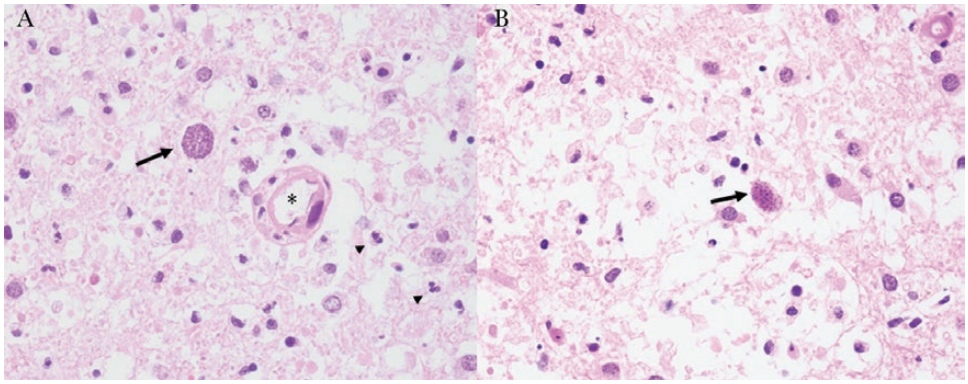

Figure 2. Toxoplasma pseudocysts containing bradyzoites (arrows) scattered within the brain parenchyma. A, Intraparenchymal blood vessel (asterisk). Neutrophils (arrowheads). A and B, Formalin-fixed paraffin-embedded 4-µm sections. Hemotoxylin and eosin. Magnification: 600x (A and B).

A case of toxoplasmic encephalitis (TE) was recently reported in a patient with metastatic thymoma, MG, and Good's syndrome, evidenced by absence of B cells and CD4+ T-cell lymphopenia [9]. Because an immunologic workup did not occur following diagnosis of thymoma or thymectomy in our patient, we were unable to conclude whether our patient had firm evidence of immune dysfunction. However, we observed that our patient did not experience lymphopenia or a significant reduction in absolute CD4+ T-cell lymphocytes. Although the precise mechanism remains unknown, we hypothesize that our patient's immune dysfunction was most likely due to defective expression of the autoimmune regulator (AIRE) in thymoma resulting in deficient selection and functional T-cell deficits, despite a normal absolute CD4+ T-cell count [5, 10, 11]. This process allowed reactivation of *Toxoplasma gondii* leading to encephalitis.

To the best of our knowledge, our case is the first to report TE in a patient with thymoma, following surgical debulking. Most likely, our patient did experience thymoma-associated immunodeficiency; however, immunodeficiency was not evaluated. We did not suspect TE as our patient had no known environmental risk factors or laboratory abnormalities supporting immune dysfunction. As a result, we support the recommendation made by Tarr and Lucey [4] that all patients with thymoma receive a baseline immunologic workup to include B-cell and T-cell subsets using flow cytometry and immunoglobulins, which should be repeated occasionally. However, due to the rarity of toxoplasmosis reactivation, serologic screening for toxoplasmosis in patients with thymoma/Good's syndrome cannot be recommended at this time, but routine testing may prevent associated morbidity and mortality. Furthermore, the role of prophylaxis in those who are seropositive is unknown as patients with thymoma/Good's syndrome experience opportunistic infections despite normal CD4+ T-cell counts [6, 7]. Finally, brain tissue with findings of severe necrotizing inflammation on pathologic examination should undergo additional workup for evaluation of a potential infectious etiology in patients with thymoma and radiographic findings of 1 or more brain lesions.

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