Case Report
Asymptomatic diffuse “encephalitic” cerebral toxoplasmosis in a patient with chronic lymphocytic leukemia: case report and review of the literature

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Abstract: Opportunistic infections account for the majority of central nervous system lesions in adult immunosuppressed patients. In this setting, toxoplasmosis typically manifests as multiple abscesses readily seen on routine neuroimaging studies. Asymptomatic, widely disseminated Toxoplasma cysts without parenchymal reaction are also recognized. In contrast, widespread parasites in the brain parenchyma with an inflammatory “encephalitic” reaction and little or no necrosis have been reported in only four patients with acquired immune deficiency syndrome (AIDS). We describe a 70 year old male with stage IV chronic lymphocytic leukemia complicated by aplastic anemia. Neurological examination and imaging revealed no significant abnormalities. At autopsy, the brain revealed multifocal cysts and free tachyzoites of Toxoplasma gondii with diffuse microglial nodules and no necrosis. To the best of our knowledge, this case represents the first report of the “encephalitic” form of toxoplasmosis in a non-AIDS patient.

Key words: Toxoplasmosis, chronic lymphocytic leukemia, central nervous system, Toxoplasma

Introduction

Central nervous system (CNS) toxoplasmosis is a major opportunistic infection in patients with human immunodeficiency virus (HIV) infection. In this setting, the disease manifests as multiple necrotizing lesions, commonly in the deep central nuclei, posterior fossa or lobar regions at the gray-white junction. Microglial nodule inflammation accompanied by extensive necrosis is commonly seen. There are only few cases in the literature of CNS documenting toxoplasmosis during the course of malignant blood diseases. In these examples, the histopathologic features were similar to those described in immunosuppressed patients. The diffuse, non-necrotic, “encephalitic” form of cerebral toxoplasmosis has been uniquely associated with HIV-related immunosuppression and, to our knowledge, has never been reported in patients with leukemia/lymphoma. The clinical and pathological findings of this rare form of CNS toxoplasmosis are presented.

Report of a case

Clinical course

This 70 year old male with stage IV chronic lymphocytic leukemia (CLL), first diagnosed in 2002, received his last cycle of chemotherapy [fludarabine, cyclophosphamide, and rituximab (FCR)] one year prior to presentation. His past medical history included diabetes, hypertension and hypercholesterolemia. The patient was HIV negative. A routine outpatient bone marrow biopsy revealed aplastic anemia with concurrent involvement by CLL or small lymphocytic lymphoma (SLL). The patient’s condition worsened in the following three weeks. He had another bone marrow biopsy done and was admitted for further evaluation. His hospital course was significant for febrile neutropenia, which prompted transfer to the ICU. The patient was pancytopenic, and started empirically on cefepime and vancomycin, fluconazole and acyclovir. His pancytopenia was unresponsive to
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Further treatment and recurrent neutropenic fevers were ascribed to the tumor burden. Neuroimaging studies of the head and a fluoroscopy-guided lumber puncture revealed no significant abnormalities. In addition, the patient developed supraventricular tachycardia, atrial fibrillation and began showing signs of total organ failure, including worsening renal function. Despite extensive medical intervention, the patient continued to deteriorate and died two weeks after admission.

Pathologic findings

Both premortem and postmortem bone marrow examination showed severe depletion of the normal bone marrow elements with loss of the granulocytic and megakaryocytic series and only rare erythroid elements present accompanied by hyalinization which is diagnostic for aplastic anemia and scattered nodular lymphoid aggregates consistent with residual CLL/SLL, confirmed by immunohistochemistry.

Gross inspection of the formalin-fixed brain disclosed mild opacification of the leptomeninges, but no edema, hemorrhage or exudate. Patchy non-occlusive atherosclerosis was seen in the larger branches of the Circle of Willis. There was no evidence of herniation or focal lesions of the cerebrum, brain stem or cerebellum.

Microscopic examination of brain revealed widespread microglial nodules, many containing bradyzoites and tachyzoites of Toxoplasma gondii (Figure 1A-C). Neither multinucleated giant cells nor necrosis of the type usually seen in cerebral toxoplasmosis was observed. Immunohistochemical preparations with antibodies to Toxoplasma were positive (Figure 1D). No other opportunistic infection, leukemic infiltrate, or lymphoproliferative disorder was identified in

Figure 1. Representative images of cerebrum section showing microglial nodules associated with Toxoplasma cysts (A, hematoxylin-eosin, x100 and B, hematoxylin-eosin, x400) and trophozoites (C, hematoxylin-eosin, x200). Immunohistochemistry with antibodies to Toxoplasma highlights the organisms (D, x200).
the brain. Toxoplasma organisms were also identified in a few pretracheal and hilar lymph nodes but not in other organs. Also no other infectious agents were identified in other organs examined. Based on these findings, this case was classified as the diffuse, “encephalitic” form of toxoplasmosis.

Discussion

Our case illustrates the first example of the non-necrotic form of cerebral toxoplasmosis in a patient with CLL. Of further note, despite significant postmortem cerebral involvement, the patient did not display clinical evidence of neurological disease during life. Non-necrotizing, diffuse, “encephalitic” toxoplasmosis appears to be seen at autopsy. This unusual form was previously thought to be unique to HIV-infected patients. Gray et al described four patients with acquired immunodeficiency syndrome (AIDS) who, with the exception of one patient with symptoms limited to fever and general malaise, developed fulminating global neurological deterioration [1]. In three cases, computed tomography (CT) examination of brain appeared normal; however, postmortem microscopic sections in all four showed microglial nodules in the brain parenchyma, most containing central Toxoplasma cysts or free tachyzoites.

In HIV-negative immunodeficient patients, toxoplasmosis may be newly acquired or may represent reactivation. Fifty percent of these patients exhibit CNS disease including encephalitis, meningoencephalitis, or mass lesions. Hemiparesis, seizures, and mental status changes are among the reported neurological manifestations.

CNS Toxoplasma infection has been reported following bone marrow transplantation. Most of reported patients had underlying lymphoma or leukemia. The infection is caused by reactivation of prior, latent infection upon intense immunosuppression [2]. Although the brain imaging studies were normal in some of the patients, the histopathologic findings were that of typical, necrotizing toxoplasmosis. In addition, toxoplasmic encephalitis has been described in a patient with T-cell leukemia, immunocytoma [3] and in a patient with follicular lymphoma [4]. However, in these patients classic ring enhancing lesions were found in the brain on computed tomography.

Other unusual manifestations of CNS toxoplasmosis include ventriculitis [5]. Eggers et al [6] reported an unusual pattern in an adult AIDS that resembled the congenital form of the disease. In their example, extensive exudative ependymitis and plexitis caused obstruction of the CSF pathways leading to the rapid development of hydrocephalus.

The most common cause of death in patients with CLL is progressive immunodeficiency complicated by infections [7]. The pathogenesis of these complications is twofold, with immune defects associated with the primary disease and compounded by chemotherapy [8]. Severe lymphopenia is one of the most profound hematologic effects of the chemotherapy, often predisposing to a variety of infectious complications such as herpes simplex virus, cytomegalovirus, and Pneumocystis jiroveci pneumonia. Opportunistic infections secondary to mycobacteria have been documented less frequently [9]. The respiratory tract remains the most common recurrent infections at mucosal sites. In contrast, fungal and viral infections occur much less frequently in chlorambucil-treated patients, generally in the setting of therapy-related neutropenia in patients with advanced disease [10].

The combination of fludarabine, cyclophosphamide, and rituximab (FCR) has been studied in both treatment-naive and previously treated patients with CLL [11, 12]. The majority of these patients receive antiviral and Pneumocystis prophylaxis. Although one-third of previously untreated patients had infectious complications, only 2.6% had major infections [11]. Five percent suffered reactivation of herpes simplex or herpes zoster, but only in patients who had not received prophylactic antiviral therapy. When FCR was used in 177 relapsed patients, major infections occurred in 16%, including one case of CMV pneumonitis [12]. Herpesvirus infections occurred in 1% of treatment courses. The incidence of major infections was found to be comparable in fludarabine-sensitive and fludarabine-refractory patients.

According to alternative pathogenetic theory, infections may be related to the quantitative and qualitative T-cell abnormalities induced by chemotherapeutic agents. A significant decline in the peripheral blood T-cell level occurs early in therapy, via the mechanism of inhibition of cytokine-induced activation of STAT-1 and
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STAT-1–dependent gene transcription. The impact is greater on CD4+ than on CD8+ or natural killer (NK) cells, and may persist for 1 to 2 years after discontinuation of therapy [13]. This relative decline in the CD4 count is similar to that encountered in the HIV-infected patients; however, qualitative differences or other unknown factors may account for the different patterns of toxoplasmosis infection.

Despite therapeutic advances, infectious complications continue to play a significant role in the clinical course of patients with CLL. The development of novel therapeutic agents for this disease will hopefully focus on minimizing infectious co-morbidities. This case is reported because of its rarity and fatal consequences due to under-recognition of this entity. Awareness of this unusual manifestation of toxoplasmosis should lead to earlier diagnosis and treatment.

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References