Infections in Oncology

Toxoplasmic Lymphadenopathy Clinically Presenting as Lymphoma

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Introduction

The clinical spectrum of *Toxoplasma gondii* infection ranges from no symptoms to a syndrome of fever and lymphadenopathy to diffuse multisystem organ involvement. Lymphadenopathy occurs in 10% to 20% of acute cases and may be accompanied by constitutional symptoms. The differential diagnosis is broad, considering the diverse presentation. Symptomatic toxoplasmosis occurs with increased frequency in patients with hematologic malignancies and solid tumors that display defects in cell-mediated immunity. We present a case of toxoplasmic lymphadenitis clinically presenting as non-Hodgkin’s lymphoma and briefly review the literature.

Case Report

A 50-year-old man had lived in Peru since 1991 and worked as a security officer in the Cuzco jungle at 2,500 meters above sea level. In April 1996, he developed chills, night sweats, and fevers up to 105°F. He had eaten a local animal indigenous to the jungle a week prior to his illness. He had no prior medical illnesses, no risk factors for human immunodeficiency virus (HIV), and no known exposure to tuberculosis. He had been vaccinated for hepatitis A and hepatitis B. The region where he worked was infested with rats, and he has several cats at home. He is a Vietnam veteran diagnosed with posttraumatic stress disorder. Evaluation for malaria, typhoid fever, and brucellosis was negative. He was treated with oral ciprofloxacin for one week. Because of continued fever with new onset of dyspnea, he was admitted to a hospital in Lima, Peru, in May 1996. Fever, cyanosis, bilateral basilar rales, tachycardia, and hepatosplenomegaly were noted. Chest radiography revealed cardiomegaly and interstitial infiltrates with bilateral small pleural effusions. An abdominal ultrasound demonstrated hepatosplenomegaly with no focal lesions. Echocardiogram revealed no valvular abnormalities or vegetations. Thoracentesis was performed and the pleural fluid was consistent with a transudate, cultures were negative, and cytology was negative for malignancy. He was tentatively diagnosed with pneumonia and completed a nine-day course of intravenous antibiotics. Six weeks later, on June 18, 1996, he presented with adenopathy in the left postauricular and left inguinal region as well as in the cervical, supravacular, and epiploic areas. Blood and urine cultures were negative. A bone marrow biopsy revealed normal bone marrow cellularity with no evidence of malignancy. Further laboratory workup in Peru included a Creatine protein at 18 mg/dL (normal), an alkaline phosphatase of 386 U/L (elevated), and an alanine aminotransferase level of 110 U/L (elevated). Serology for *Brucella* sp, hantavirus, *Yersinia* sp, HIV-I and -II, leptospirosis, and cytomegalovirus were all negative. A urinalysis was also negative. Computed tomography scans of the chest, abdomen, and pelvis revealed no enlargement of the liver or spleen and showed no para-aortic adenopathy. On July 23, 1996, a left inguinal lymph node biopsy was interpreted as nonspecific inflammation. On August 5, 1996, a second opinion was sought and the lymph node biopsy was interpreted as non-Hodgkin’s lymphoma. Combination chemotherapy and radiation therapy were recommended but not administered. A third opinion at a cancer institute in Peru interpreted the biopsy as reactive lymphadenitis. Multiple serology testing confirmed the diagnosis of acute toxoplasmosis (Table). Sulfadioxide/pyrimethamine (Fansidar), sulphanethoxazole/trimethoprim (Bactrim), and clindamycin were given for four days followed by Fansidar for five weeks.

The patient presented to our center in September 1996 for evaluation and a fourth opinion. He had no symptoms other than fatigue and history of weight loss (20 pounds) over the last year. Physical examination was unremarkable with no fever, lymphadenopathy, or hepatosplenomegaly. No chills, night sweats, and fevers up to 105°F. He had eaten a local animal indigenous to the jungle a week prior to his illness. Ophthalmologic examination revealed no retinal lesions or visual impairment. Slides from the lymph node biopsy were reviewed at our institution and were consistent with florid follicular and interfollicular hyperplasia, with normal immunoblasts in the interfollicular regions. The germinal centers were enlarged and prominent. There was no evidence of malignancy, and no cysts with bradyzoites or detached tachyzoites were seen in the parenchyma of the biopsy. Further serology included negative cytomegalovirus titers and titers for HIV-I antibody, recombinant pseudo-retrovirus, human herpes simplex virus 6 IgM, and cat scratch fever (*Bartonella henselae*). Epstein–Barr virus (EBV) early antigen was <1:10 (normal), EBV nuclear antigen was 1:40 (normal <1:2), EBV viral capsid IgG was 1:640 (normal <1:40), and EBV viral capsid IgM was <1:10 (normal <1:10), consistent with past infection.

In March 1996, a diagnosis of acute toxoplasmosis with resolution of symptoms was made on the basis of history, clinical presentation, toxoplasma serology, and the absence of malignancy in histologic specimen. Although the May 2, 1996, titers show an elevated IgG and normal IgM for *T. gondii*, the remaining titers are consistent with acute infection.

Discussion

*T. gondii* is one of the most widely distributed intracellular parasites that infect humans and animals. It is an intracellular protozoan, a member of the phylum Apicomplexa that includes *Eimeria* sp, *Plasmodium* sp, *Cryptosporidium* sp, and *Sarcocystis* sp. The three life forms of *T. gondii* are oocysts, tachyzoites, and bradyzoites (tissue cysts). The oocysts contain sporozoites and are the product of the sexual cycle in the intestinal epithelium of its definitive hosts (cats and other felines), which form oocysts that are shed in their feces. The tachyzoite is the asexual invasive form, which replicates essentially within all nucleated cells. They reside within a vacuole that becomes incapable of fusing with any membrane-bound organelle within the host endocytic system and is effectively hidden from the host where it

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**Table: Toxoplasma gondii Titer**

<table>
<thead>
<tr>
<th>Dates</th>
<th>IgG</th>
<th>IgM</th>
</tr>
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<tbody>
<tr>
<td>May 2, 1996</td>
<td>1:4 (normal)</td>
<td>1:155 (positive - 1:64)</td>
</tr>
<tr>
<td>July 18, 1996</td>
<td>1:16 (positive - 1:128)</td>
<td>1:16 (positive - 1:128)</td>
</tr>
<tr>
<td>July 31, 1996</td>
<td>1:64 (positive - 1:512)</td>
<td>1:12 (positive - 1:128)</td>
</tr>
<tr>
<td>August 10, 1996</td>
<td>1:256 (positive - 1:1024)</td>
<td>1:12 (positive - 1:128)</td>
</tr>
<tr>
<td>September 4, 1996</td>
<td>1:512 (positive - 1:2048)</td>
<td>1:12 (positive - 1:128)</td>
</tr>
</tbody>
</table>

*The microfilariae were polymorphic and had no retinal lesions or visual impairment. Slides from the lymph node biopsy were consistent with florid follicular and interfollicular hyperplasia, with normal immunoblasts in the interfollicular regions. The germinal centers were enlarged and prominent. There was no evidence of malignancy, and no cysts with bradyzoites or detached tachyzoites were seen in the parenchyma of the biopsy. Further serology included negative cytomegalovirus titers and titers for HIV-I antibody, recombinant pseudo-retrovirus, human herpes simplex virus 6 IgM, and cat scratch fever (*Bartonella henselae*). Epstein–Barr virus (EBV) early antigen was <1:10 (normal), EBV nuclear antigen was 1:40 (normal <1:2), EBV viral capsid IgG was 1:640 (normal <1:40), and EBV viral capsid IgM was <1:10 (normal <1:10), consistent with past infection.*
Although cats serve as the definitive host, birds and domesticated animals may serve as reservoirs to transmit the infection. Humans acquire *T. gondii* infection mainly by ingesting food and water contaminated with oocysts passed in feces of infected cats or by ingesting tissue cysts in undercooked infected meat, as our patient did. After ingestion and dissemination of infection, the early phase is characterized by a rapid tachyzoite multiplying stage in different tissues causing mononuclear inflammatory reactions that lead to small necrotic foci. Parasite multiplication during this stage occurs in the liver, lung, lymphoid tissue, and brain. In the immunocompetent person, the tachyzoites are cleared from the host tissues, and necrotic foci are generated. The parasites then appear as the bradyzoites contained within cysts that predominantly form in the central nervous system, but they also may be present in the eye, heart, and skeletal muscle. Inflammation or necrosis in these organs is often insignificant, and the person can remain asymptomatic. The latent infection can become active when the immune system is severely compromised, especially with cell-mediated immunodeficiency (eg, AIDS, solid tumors, hematologic malignancies, and lymphoproliferative disorders). This expansion can also occur when treatment includes antineoplastic agents.

### Clinical Presentation

The clinical presentation of toxoplasmosis ranges from the absence of symptoms to a syndrome of fever and lymphadenopathy to diffuse organ system involvement. In the immunocompetent host, infection is frequently asymptomatic. Lymphadenopathy occurs in 10% to 20% of cases and may be accompanied by fevers, chills, night sweats, myalgia, sore throat, and enlarged liver and spleen. The clinical picture may be similar to that of a glandular, fever-like illness. Chronic or recurrent toxoplasmosis in the immunocompetent host is rare. In most cases, toxoplasmosis presents as asymptomatic cervical lymphadenopathy, but all lymph node groups may be enlarged. The nodes are usually discrete and nontender, are rarely more than 3 cm in diameter, may vary in firmness, and are not suppurative. However, they can be tender or matted. The lymph nodes most commonly involved are the cervical, suboccipital, supraclavicular, axillary, and inguinal nodes. Some of the symptoms are malaise, night sweats, myalgia, sore throat, maculopapular rash, hepatosplenomegaly, and an atypical lymphocytosis (<10%). In addition, retroperitoneal or mesenteric lymphadenopathy may produce abdominal pain.

The potential for confusion with lymphoma is clear. Lymphadenopathy may wax and wane and, in some unusual cases, may persist for one year or longer. Acute toxoplasmosis is usually characterized by isolated asymptomatic lymphadenopathy without a rash. In patients with AIDS, clinical presentation may include central nervous system involvement, acute hepatitis, or adult respiratory distress syndrome. Cerebral or disseminated toxoplasmosis may follow bone marrow transplantation, with the highest incidence occurring at two to three months following transplantation.
Diagnosis

The clinical manifestations of toxoplasmosis may be nonspecific; therefore, toxoplasmosis must be carefully considered in the differential diagnosis with a large variety of clinical presentations. The acute infection is diagnosed by the identification of *T. gondii* in blood or body fluids such as cerebrospinal fluid, by demonstration of characteristic lymph node histology, or by demonstration of toxoplasma tissue cysts in the placenta, fetus, or neonate. The diagnosis of toxoplasma lymphadenitis is established by histologic examination and confirmed by serologic studies. The toxoplasma serologic profile may include IgG (dye test) and IgM antibody test. IgA, IgE, IgM immunosorbent agglutination assay, and differential agglutination (AC/HS) test. In a recent study, *T. gondii* could be ruled out if the dye test and an IgM were negative for antibody within three months of clinical onset of adenopathy. Although a high titer of toxoplasma-specific IgM suggests acute infection, it may persist for 18 months or more. The other serologic studies aid in the diagnosis, especially when patients present with negative, low-positive, or equivocal titers on IgM, which is common when serum samples are obtained more than three months after the lymphadenopathy occurs. Very sensitive and specific "in-house" assays by the polymerase chain reaction (PCR) are being reported increasingly as powerful diagnostic adjuncts. In one study, PCR of peripheral venous blood was useful in the diagnosis of cerebral toxoplasmosis in AIDS patients. Other than a brain biopsy, PCR of peripheral blood or cerebral spinal fluid could be the most sensitive diagnostic tool for diagnosing cerebral infection. The PCR has also been very effectively applied to prenatal diagnosis of congenital toxoplasmosis on amniotic fluid, as well as cell lysates.

A lymph node biopsy is usually performed to distinguish malignancy from toxoplasmosis when lymphadenopathy occurs. The histopathologic changes in toxoplasma lymphadenitis are distinctive and often diagnostic. There is a striking degree of reactive follicular hyperplasia with numerous mitoses and karyorrhectic debris in the germinal centers. Clusters of histiocytes were observed in the interfollicular cortical and paracortical zones, and the histiocytes characteristically encroached on and blurred the margins of the reactive follicles.

Hodgkin's disease and toxoplasmosis can be difficult to differentiate since epithelioid histiocytes and prominent reactive follicles can occur in both disorders. The local reactive mechanism of lymph nodes to generalized infection has been described as Kikuchi's histiocytic necrotizing lymphadenitis (KHNL), a recognized cause of lymph node enlargement. Toxoplasma infection can mimic KHNL. Other causes of lymphadenitis include tuberculosis, *Yersinia* sp, EBV, human herpes simplex virus type 6, parvovirus B19, HIV, and systemic lupus erythematosus.

Treatment

The most effective therapeutic regimen includes pyrimethamine and either sulfadiazine or trisulfapyrimidines plus folinic acid. The duration of therapy is two to four weeks for acute disease and can range to months when visceral organ involvement is encountered or when severe symptoms persist. Alternative treatments include trisulfapyrimidines and sulfamethazine or sulfamethazine and sulfadiazine. All are active against tachyzoites and are synergistic in combination.

The tissue cyst form of toxoplasma is resistant to antimicrobial agents, except azithromycin and atovaquone. Clindamycin's mechanism of action on *T. gondii* is unknown. In combination with pyrimethamine, it has comparable efficacy and toxicity when compared with pyrimethamine and sulfadiazine.

Conclusions

Our patient probably acquired toxoplasmosis from consumption of wild animal meat followed by a systemic illness and then diffuse lymphadenopathy. The clinical presentation of toxoplasmosis can easily be confused with lymphoma both by clinicians and pathologists, as this case illustrates. However, after a careful history, appropriate serology, and a careful review of lymph node biopsy material, the distinction can be made between the two and unnecessary toxic therapy can be avoided.

References