Spontaneous complete remission of angioimmunoblastic T-cell lymphoma

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Angioimmunoblastic T-cell lymphoma (AITL) is a rare hematologic neoplasm that typically presents with B symptoms, anemia, and lymphadenopathy. Its overall prognosis is poor, with a 5-year survival rate of 30%. We present a case of AITL that went into spontaneous remission, an uncommon occurrence.

Angioimmunoblastic T-cell lymphoma (AITL) is a rare hematologic neoplasm that classically presents with lymphadenopathy, hepatosplenomegaly, anemia, and B-type symptoms. Although the disease has a poor prognosis, we present a patient with a rare spontaneous remission.

CASE REPORT

A 63-year-old man with a congenitally bicuspid aortic valve and benign prostate hypertrophy presented to the emergency department complaining of cyclical fevers and 20-pound unintentional weight loss over the previous 3 weeks and was admitted to the hospital for workup of fever of unknown origin. These fevers reached 40°C and occurred regularly at 6- to 12-hour intervals, lasting 90 minutes each time before resolving completely. Review of systems was also positive for urinary retention, frequency, and perineal burning sensation.

The patient had spent large amounts of time in many countries in Africa, Eastern Asia, and South and Central America. While in Egypt 2 years earlier, he was bitten by a spider and developed significant left cervical lymphadenopathy. A cervical lymph node biopsy in Poland was reportedly benign. The procedure was complicated by left spinal accessory nerve damage, and 6 months prior to onset of his presenting symptoms he underwent surgical repair of the nerve at our institution. At that time another cervical lymph node was biopsied, which was benign, and his lactate dehydrogenase (LDH) level was 183 U/L (normal, 122–222 U/L).

Physical examination revealed bilateral tender cervical and submandibular lymphadenopathy, but no axillary or inguinal lymphadenopathy. A harsh precordial systolic murmur consistent with aortic stenosis was audible. No hepatosplenomegaly was found. Except for the presence of IgG antibodies to Epstein-Barr virus (EBV) viral capsid antigen and Epstein-Barr nuclear antigen, serologic testing for multiple infections was negative

Table 1. Infectious diseases tested and found to be negative

Bacterial	Viral	Fungal	Paracytic
<i>Bartonella henselae</i>	HIV	<i>Aspergillus</i> spp.	<i>Babesia microti</i>
<i>Bartonella quintana</i>	Hepatitis B	<i>Blastomyces</i> spp.	<i>Cryptosporidium</i> spp.
<i>Leptospira</i> spp.	Hepatitis C	<i>Coccidioides</i> spp.	<i>Giardia</i> spp.
<i>Ehrlichia chaffeensis</i>	Influenza A	<i>Cryptococcus</i> spp.	<i>Leishmaniasis donovani</i>
<i>Mycobacterium tuberculosis</i>	Influenza B	<i>Histoplasma</i> spp.	<i>Plasmodium</i> spp.
<i>Brucella</i> spp.	Cytomegalovirus	<i>Sporothrix</i> spp.	
<i>Borrelia burgdorferi</i>			
<i>Coxiella burnetii</i>			
<i>Rickettsia</i> spp.			
<i>Clostridium difficile</i>			
<i>Treponema pallidum</i>			
<i>Anaplasma phagocytophilum</i>			

(Table 1). Results of a peripheral smear, blood cultures, and urinalysis were all negative, and the chest x-ray showed no infiltrates. Computed tomography scan of the abdomen revealed periaortic and periportal lymphadenopathy and splenomegaly. Flow cytometry revealed no increase in aberrant CD3/CD16-positive T cells or increase in natural killer cells. T-cell receptor gene rearrangement showed clonal T cells. Due to the clinical presentation and elevated inflammatory markers (Table 2), he was diagnosed with acute prostatitis. Ciprofloxacin led to prompt resolution of fevers. He was discharged home on day 5 with antibiotics but returned within a week due to fever recurrence. At this time, magnetic resonance imaging of the prostate

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Table 2. Laboratory values from first hospitalization for fever (month 0) to month 10.5

Laboratory test	Reference range	Time (months)					
		+0	+0.25	+1	+4	+10	+10.5
Hemoglobin (g/dL)	13.5–17.3	13.5	10.9	6.7	13.5	11.1	6.2
Mean corpuscular volume (fL)	81.2–95.1	78.9	79.8	87.3	81.1	77.4	76.3
White blood cell count ($\times 10^9/L$)	3.5–10.5	7.4					
Neutrophils	42–75%	81%					
C-reactive protein (mg/L)	<8	110	38.3				
Total bilirubin (mg/dL)	0.1–1.0			1.4			
Lactate dehydrogenase (U/L)	122–222	476		301	293	380	235
Prostate-specific antigen (ng/mL)	<4.5	9.4					

ruled out prostatic abscess. Echocardiogram showed no sign of endocarditis, but revealed bicuspid aortic valve stenosis. He was continued on antibiotics for presumed persistent prostatitis.

Two weeks after this second discharge he was hospitalized again due to recurrent fevers and urinary symptoms. He now had progressive anemia and splenomegaly palpable to 2 cm below the costal margin. Biopsies of a hypervascular cervical lymph node revealed an atypical lymphoid infiltrate with clonal T-cell receptor gene rearrangements suspicious for T-cell lymphoma versus reactive paracortical T-cell hyperplasia. A positron

emission tomography–computed tomography (PET-CT) scan (*Figure 1a*) revealed significant fluorodeoxyglucose (FDG)-avid splenomegaly and lymphadenopathy both above and below the diaphragm, worrisome for lymphoma.

Bone marrow biopsy revealed an atypical T-cell infiltrate suggestive of peripheral T-cell lymphoma, with no cytogenetic abnormalities. Subsequently, excisional biopsy of two FDG-avid cervical lymph nodes confirmed a diagnosis of AITL with patchy EBV uptake (*Figure 2*). He was discharged on oral ciprofloxacin for outpatient follow-up.

Figure 1. PET-CT scan before and after remission. **(a)** Initial scan showing splenomegaly and diffuse lymphadenopathy. **(b)** Restaging scan demonstrating complete remission.

Figure 2. Excisional lymph node biopsy. **(a)** Hematoxylin and eosin staining of the excisional lymph node biopsy shows effacement of the lymph node by a paracortical infiltrate of small to intermediately sized lymphocytes with irregular nuclear contours (40× and 400×). Immunohistochemical staining (100×) demonstrates an infiltrate of **(b)** CD3-positive T cells which coexpress **(c)** CD4 and **(f)** CD279, and a small subset of which coexpress CD10 (not pictured). **(d)** Reactive CD8-positive T cells are interspersed. **(e)** CD20-positive B cells are displaced to the periphery of the node. Chromogenic in situ hybridization of Epstein Barr virus–encoded RNA shows patches of positive B cells.

His fevers improved and due to the clinical improvement, he sought out a second opinion on his diagnosis at a second large academic cancer center. This center confirmed that the clinical picture and histopathological specimen were most consistent with AITL and recommended a chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) and vorinostat. Prior to initiation of chemotherapy, he underwent successful aortic valve replacement

with a bioprosthesis and two-vessel coronary artery bypass grafting.

At his hematology follow-up 3 weeks after cardiac surgery, he was asymptomatic and denied recurrence of fevers, night sweats, and lymphadenopathy. Prechemotherapy PET-CT (*Figure 1b*) was performed, which showed no evidence of FDG-avid lymphadenopathy, suggesting complete spontaneous remission. He had received no therapy (including corticosteroids)

between the two PET-CT scans and thus he was not started on chemotherapy.

He returned for follow-up 6 months later and a repeat PET was performed, which showed no FDG-avid lymph nodes but did show increased marrow FDG avidity with elevated LDH. A bone marrow biopsy showed atypical lymphocytes and persistently decreased hematopoiesis but no signs of lymphoma. Two weeks later without any therapy, the LDH declined to 235 U/L and continued to decline. From this point forward he had no further lymphoma recurrence. For his hypoproliferative anemia, he was started on transfusions and prednisone therapy. He responded well and after 1 month was no longer transfusion dependent. Prednisone was subsequently tapered from 80 mg daily and discontinued 3 months later. At outpatient follow-up 12 months after being off corticosteroids, his lymphoma remained in remission.

DISCUSSION

AITL is a rare hematologic disease that classically presents with lymphadenopathy, hepatosplenomegaly, hypergammaglobulinemia, anemia, and B-type symptoms and is distinguished by distinctive lymph node architecture disruption. AITL subjects typically present with the previously mentioned symptoms and have a mostly nondiagnostic workup until a full lymph node excision is performed. The lymph node biopsies show effacement of the lymph node architecture. Bone marrow or other lymphoid organ biopsies can be abnormal but typically show a nonspecific polymorphic inflammatory infiltrate (1). Although the disease was thought to be possibly premalignant when first discovered, there are clonal T cells present (2), and research has been directed to identify the origin of these cells. The majority of cells are typically CD4 positive, but there does seem to be an overproduction of follicular helper T cells, showing CD10 positivity, PD-1 (CD279) positivity (3), and often Bcl-6 positivity (4), which are thought to be the likely precursor cells. Supporting this view is the finding of increased amounts of CXCL13, which is produced by follicular helper T cells for helping B cells migrate to germinal centers in and around the abnormal cells (5). Analysis also shows the presence of EBV-positive B cells, but the significance of EBV infection in the setting of AITL remains unclear. The presence of the EBV-positive B cells, which were present in our patient, may be a result of acquired immunodeficiency from the malignancy or a consequence of unregulated T and B cell interaction, with the proliferation of the abnormal B cells being merely a bystander phenomenon (2).

The disease has a relatively poor prognosis, with an overall survival at 5 years of 30% to 35% and a median survival of 36 months (2). Currently used regimens include CHOP (and rituximab plus CHOP as the role of B-cell proliferation is still uncertain in the disease process) (6) and cyclophosphamide, vincristine, and prednisone. Since it is a T-cell malignancy, the use of cyclosporine has been introduced as a potential therapy (7). In a retrospective study, 8 of 12 subjects responded to therapy, with 3 having a complete response. Another new therapy is alemtuzumab, a monoclonal antibody to CD52 expressed by most of the T cells in this disease (8). Interestingly in this disease, most subjects die from overwhelming infection rather than

direct lymphoma progression. This has led many to believe that this disease causes an acquired immunodeficiency that has yet to be elucidated (2). Our subject had most of the typical features at initial presentation, with anemia, lymphadenopathy, hepatosplenomegaly, B symptoms, and elevated LDH. Although some of the initial B symptoms could have been related to prostatitis, the subsequent anemia and fevers after antibiotics were more likely the direct result of the lymphoma and would have eventually led to his diagnosis.

The spontaneous remission of AITL without therapy is quite unusual and, although not unknown to the medical literature (9–11), is still a very rare occurrence. Little is known regarding predictors of spontaneous remission; however, one study showed factors that might predict this event (11). It showed that having an extra third chromosome was associated with a higher chance of spontaneous remission ($P = 0.02$) and an extra X chromosome showed an insignificant trend for less chance of remission ($P = 0.09$). Our patient did not have extra chromosomes. Careful surveillance following spontaneous remission is necessary, as many in the literature subsequently relapsed.

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