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CNS intravascular large cell lymphoma in a patient with autoimmune hemolytic anemia

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ABSTRACT

Intravascular large cell lymphoma (IVLCL) is a rare disease characterized by proliferation of malignant lymphocytes within the small blood vessel lumens. The association of IVLCL with autoimmune hemolytic anemia (AIHA) has been described in a single case report, but the true prevalence of this co-occurrence is not known because of declining autopsy rates. Here, we report a case of a 41-year-old woman who carried a diagnosis of AIHA for two years, with repeated hemolytic episodes that were initially well controlled with immunomodulatory treatment. At her last presentation, the patient developed rapidly progressive neurologic symptoms and leukoencephalopathy on magnetic resonance imaging; she died four weeks later with a clinical impression of thrombotic microangiopathy, a known complication of AIHA. At autopsy, the brain showed widespread platelet thrombi and intraparenchymal hemorrhages characteristic of this disorder. In addition, there was evidence of a clinically unsuspected IVLCL, most likely of B-cell lineage. This case illustrates a potential association between IVLCL and AIHA, highlights the need for broad differential diagnosis in cases with atypical disease presentation or progression, and underlines the importance of autopsy in establishing the full cause of morbidity and mortality.

KEY WORDS

Intravascular lymphoma, autoimmune hemolytic anemia, leukoencephalopathy

INTRODUCTION

Intravascular large cell lymphoma (IVLCL) is a rare and aggressive lymphoproliferative disorder that affects men and women equally¹. Most IVLCLs are B-cell in origin, although rare cases of T-cell and natural killer (NK)-cell intravascular lymphomas have also been reported^{2, 3}. Geographic differences in disease presentation have been noted: the central nervous system (CNS) and skin are more often involved in patients from Western countries, while preferential liver and bone marrow disease, along with fever and thrombocytopenia, are found in patients from Asian countries⁴. The most common CNS symptoms are subacute encephalopathy, dementia, seizures, and multifocal cerebrovascular episodes. Because the malignant lymphocytes grow within vasculature without creating nodal or extra-nodal masses, the diagnosis is often delayed and requires a high index of suspicion. The prognosis is poor, with an average survival of only 13 months⁵; frequently, the diagnosis is only made at autopsy. The co-occurrence of non-Hodgkin lymphomas (NHLs) and various autoimmune diseases has been described⁶, but IVLCL association with autoimmune hemolytic anemia (AIHA) has only been reported once⁷. Here, we present the second example of IVLCL-AIHA co-occurrence, this time with neurologic presentation.

CLINICAL SUMMARY

A 41-year-old woman with a two-year history of fatigue was found to have isolated anemia and a positive direct Coombs IgG test, suggesting hemolysis; a bone marrow biopsy and radiologic studies of the chest, abdomen and pelvis did not demonstrate any abnormalities. In the absence of increased specific antibody titers, she was diagnosed with AIHA and was treated intermittently with intravenous immunoglobulin, blood transfusions, and oral steroids; a pulse of four weekly doses of rituximab was also administered. After four months, steroids were tapered and the disease remained stable for one year. Following a new hemolytic episode, another pulse of rituximab was given and corticosteroid treatment restarted; a repeat bone marrow biopsy was unremarkable. The red blood cell count stabilized for a few months, but the patient experienced another episode of autoimmune hemolysis two months prior to her final presentation.

The last episode started similarly to previous episodes, with fatigue and lack of energy. The patient received three units of compatible blood without notable complications and returned to normal activity. Several days later, she developed new symptoms (insomnia accompanied by back and shoulder pain) and was brought to the local emergency department in a confused and agitated state. The initial workup was remarkable for a hemoglobin level of 7.7 g/dl. Cerebrospinal fluid (CSF) studies were unremarkable, but brain magnetic resonance imaging (MRI) demonstrated bilateral, multifocal cerebral white matter abnormalities consistent with leukoencephalopathy, scattered foci of reduced diffusion, and subtle microhemorrhages (Fig. 1, a-c). Treatment with cyclophosphamide and corticosteroids was initiated, but the patient's mental status deteriorated, requiring urgent intubation. The patient was transferred to our institution, where a neurological exam was notable for somnolence, movement in the right arm only, and no response to stimuli; the cranial nerve reflexes were preserved. In response to peripheral noxious stimulation, the patient showed extensor posturing and bilateral triple flexion of the legs. The reflexes were brisk throughout and clonus was noted in the ankles. On general exam, she had clear breath sounds to auscultation, no appreciable heart murmur, no organomegaly, no lymphadenopathy, no peripheral edema, and no abnormal skin findings. Laboratory tests showed a positive Coombs IgG; elevated erythrocyte sedimentation rate; elevated lactate dehydrogenase, C3, fibrinogen, and D-dimer levels; and low haptoglobin level. The anti-nuclear-antibody and serum electrophoresis assays were normal; the patient was HIV negative. The peripheral smear demonstrated reticulocytosis and 1-2 schistocytes per high power field. A repeat lumbar puncture was notable for an opening pressure of 17, increased red blood cells, protein concentration of 116 mg/dl, and glucose concentration of 118 mg/dl. CSF polymerase chain reactions for Herpes and Varicella viruses were negative; CSF cytology was unremarkable and no oligoclonal bands were identified. A repeat brain MRI showed marked progression of the white matter signal abnormalities along with accompanying increase in the number of foci of reduced diffusion and cerebral microbleeds (Fig. 1, d-f); signs of elevated intracranial pressure were also noted. Despite maximal medical management, brain swelling progressed and the patient was transitioned to comfort measures. Following death, she underwent a brain-only autopsy at the family's request.

PATHOLOGICAL FINDINGS

The brain weighed 1270 g and showed diffuse edema (widened gyri, narrowed sulci, and marked cortical effacement); numerous small petechial hemorrhages were notable on the leptomeningial surfaces. Coronal sections showed extensive petechial hemorrhages, many of which coalesced into larger areas of acute intraparenchymal hemorrhage (Fig. 2a). Microscopic examination showed frequent foci of fibrin-platelet thrombi and vascular fibrinoid necrosis surrounded by acute hemorrhage and eosinophilic neurons, consistent with microinfarcts in the context of thrombotic microangiopathy (Fig. 2b). In addition, a population of large, highly pleomorphic cells with high nuclear/cytoplasmic ratio, irregular nuclear contour, and coarse chromatin was present in the perforating arteries (Fig. 2c). Immunohistochemical stains showed that a substantial subset of these cells aberrantly co-expressed the B-cell marker CD20 (Fig. 2d) and the T-cell marker CD5 (Fig. 2e); the proliferation index was above 90% (Fig. 2f). Neoplastic cells were negative for other T-cell immunomarkers (CD3, CD4, CD7, CD8), other B-cell lymphoma immunomarkers (CD79a, PAX5, BOB1, Oct2, and Bcl2), plasma cell immunomarkers (MUM1 and CD138), anaplastic lymphoma immunomarker ALK1, lymphoblastic immunomarkers (TdT and CD117), mantle cell lymphoma immunomarker cyclin D1, NK-cell immunomarker CD56, and myeloblastic immunomarker CD34. In situ hybridization for kappa and lambda light chains was equivocal, while in situ hybridization for Epstein-Barr virus was negative. Together, these findings were diagnostic of intravascular large cell lymphoma; while the cell lineage was not entirely clear, the overall immunophenotype was most consistent with a B-cell origin (limited CD20 expression was attributed to the prior rituximab treatment).

DISCUSSION

This patient's clinical course was unusual for AIHA: the rapid progression of neurologic symptoms and lack of response to aggressive medical management were difficult to explain in the context of an autoimmune hemolytic crisis with a hemoglobin level that was only moderately decreased (7.7 g/dl). However, the brain autopsy showed features of two contributing diseases. Thrombotic microangiopathy, a known complication of AIHA, involved all areas of the CNS. In addition, the perforating arteries were distended by a population of malignant B-lymphocytes.

The co-occurrence of AIHA and IVLCL likely explains the treatment unresponsiveness of the patient's last AIHA recurrence and the disproportionate neurological outcome. Because IVLCL was diagnosed after death, it is not clear whether it preceded or followed the patient's AIHA, although the latter possibility fits better with the observed clinical course. (Two bone marrow biopsies performed in an outside hospital were interpreted as unremarkable during original clinical workup, but were not available for review.) Moreover, because the autopsy was limited to the brain, it is not known whether the patient's IVLCL affected only the CNS or was present systemically.

Most frequently, IVLCL involves small-sized vessels in the skin and CNS⁸; it is detectable in the peripheral venous or arterial blood in only 5-9% of cases⁹. The B-lymphocytes are thought to be of postgerminal center type and their predilection for intravascular growth is believed to result from defects in adhesions molecules CD29, CD54, and CD11a⁹. Although association of NHL with AIHA has been described in the literature^{6, 10, 11}, the specific association of IVLCL with AIHA is exceptional, with only one previously reported case⁷. While the mechanistic connection between the two diseases is not completely understood, it is probably similar to that of NHL and AIHA in general. In a pooled analysis of 12 case-control studies (12823 cases and 16444 controls)⁶, Ekstrom et al. studied the association of various autoimmune diseases with NHL. Of all the patients included in that study, 3242 had AIHA, and 21 of those (0.6%) had NHL; when compared with the incidence of NHL in the corresponding control group (0.2%), there was a 2.6-fold overall increase in the NHL risk. This risk was slightly more pronounced among men, and the association was most evident among patients with long standing AIHA (> 10 years). To explain the increased risk, the authors postulated that the immune dysregulation in autoimmune disease predisposes to NHL; it is proposed that a local antigenic drive significantly contributes to NHL development¹²⁻¹⁵ and that increased levels of interleukin 6 and macrophage colony-stimulating factor are central to the development of both NHL and intravascular lymphoma^{1, 5}. An alternate hypothesis is that NHL triggers AIHA because the rearrangement of immunoglobulin and T-cell receptor genes in NHL precursor cells creates the potential for generation of autoreactive lymphocytes¹⁶⁻¹⁹. Based on the current evidence, therefore, it is difficult to know which disease comes first. To investigate this further, Sallah et al.¹⁹ studied the clinical course of 16 patients carrying the diagnosis of NHL and AIHA. Not surprisingly, there was a significant survival difference between patients with both NHL and AIHA (22.5 months) and patients with only NHL (> 32 months). However, the occurrence of AIHA was not significantly different among the four clinical stages of NHL; in addition, there was no statistically significant difference in the interval to complete remission between the control

and study groups. While not definitive, these findings provide support for the hypothesis that in the majority of cases AIHA precedes NHL.

In conclusion, IVLCL is difficult to diagnose premortem due to nonspecific clinical presentation; the diagnostic challenge is even greater in an AIHA patient, because the two diseases have similar laboratory test profile and lack specific radiological findings. Frequent and difficult to control hemolytic crises can be considered a clue, albeit vague, and appropriateness of a skin biopsy should be evaluated in such a situation. Importantly, only autopsy can determine a definitive diagnosis and the extent of the disease. While sometimes challenging, obtaining an unrestricted autopsy permit is critical for establishing the true prevalence of IVLCL.

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FIGURE LEGENDS

Figure 1. MRI findings. Axial MRI obtained at the time of emergency room evaluation for agitation and confusion (top row), and 6 d later after the patient had lapsed into a comatose state (bottom row). T2*-weighted gradient echo (a and d), T2 FLAIR (b and e) and average diffusion images (c and f) showed initially subtle foci of microhemorrhage (a) and white matter signal abnormality (b) that rapidly progressed to multifocal, predominantly peripheral microhemorrhage (d) and confluent white matter abnormality (e) with increase in the brain swelling. Average diffusion images ($b=1000 \text{ s/mm}^2$) revealed multiple foci of punctate peripheral cytotoxic edema (c) that increased in number and become confluent over the 6 d time interval (f).

Figure 2. Autopsy findings. (a) Coronal section of the brain shows multiple areas of red-brown discoloration mostly involving deep grey nuclei and white matter, representing acute and subacute intraparenchymal hemorrhage. (b) H&E-stained section shows necrotic vessels with platelet-fibrin microthrombi (arrowheads) surrounded by a petechial microhemorrhage. (c) H&E-stained section shows a perforating artery with intraluminal highly atypical large lymphocytes. (d) A CD20 immunostain shows positivity in a subset of malignant lymphocytes. (e) Malignant lymphocytes aberrantly co-express CD5, which is also expressed by small mature T lymphocytes [same vessel as in (d)]. (f) A Ki-67 immunostain demonstrates a proliferation index that is close to 100%. Scale bar: (b) and (f), 40 μm ; (c)-(e), 16 μm .

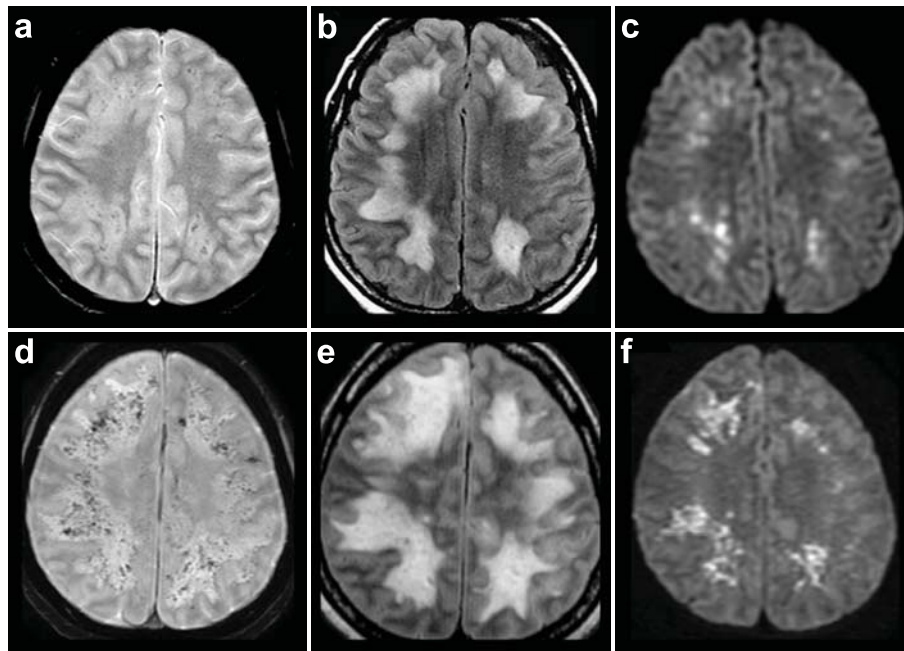


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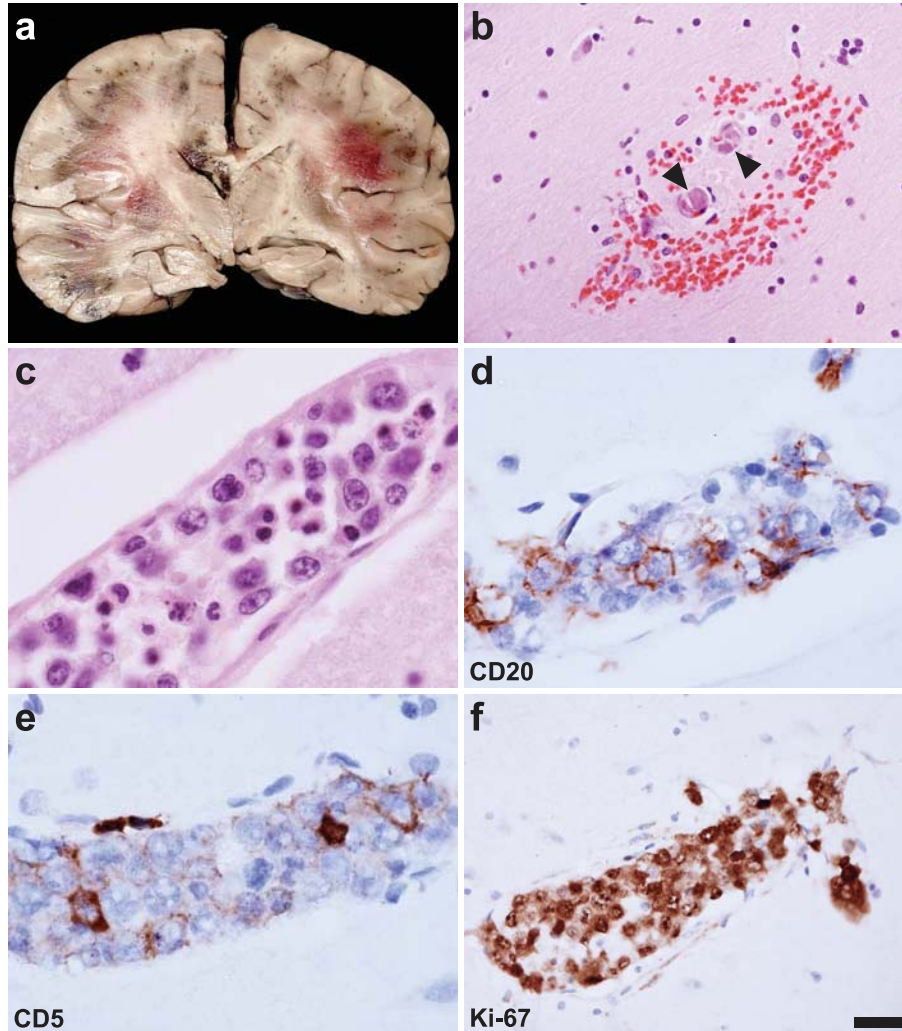


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