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Case Report

Going Skin Deep: Finding Answers to a Complex Condition

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Abstract

A fever of unknown origin is often pursued diagnostically under the framework of infectious, rheumatologic, and neoplastic causes. When encephalopathy ensues, the differential diagnosis narrows, but can remain elusive, particularly when dealing with an unusual presentation of a rare disease. We present the case of a patient with fever of unknown origin and intermittent encephalopathy that spanned multiple hospital admissions and ultimately was diagnosed as intravascular large B cell lymphoma complicated by hemophagocytic lymphohistiocytosis. We review the varying presentations of this rare disease, when to consider this as a diagnosis, and how to most accurately make the diagnosis.

Keywords: Fever of unknown origin; Intravascular large B cell lymphoma; Hemophagocytic lymphohistioctyosis

Case Report

Case

A 70-year-old Caucasian woman was admitted for evaluation of subacute fever of unknown origin associated with waxing-and-waning encephalopathy. This was her fourth admission in the last four months. She initially presented with weight loss, and anemia; but over the ensuing months, she developed progressive nocturnal fevers, intermittent encephalopathy, visual hallucinations, and diplopia.

An extensive outside workup failed to identify a culprit infectious, neoplastic or rheumatologic etiology. Notable labs showed a platelet count of 75 K/cu mm (normal, 150-400), hemoglobin of 7.7 g/dL (normal, 12-16), normal leukocyte count, ferritin of 3516 ng/ml (normal, 11 - 152), and erythrocyte sedimentation rate and C-reactive protein level of 112mm/h (normal, 0 – 15) and 96.1 mg/L (normal, 0-10), respectively.

Diagnostic tests for infectious etiologies were all either normal or negative: plasma regain for syphilis; PCR testing of blood samples for human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus; respiratory viral panel, *Borrelia burgdorferi* IgG/IgM, *Bartonella henselae* IgG/IgM, cryptococcal antigen. Results of diagnostic testing for rheumatologic causes of fever, including antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti-double-stranded DNA, thyroid stimulating hormone, rheumatoid factor, were unremarkable. Lumbar puncture (LP) revealed colorless cerebrospinal fluid (CSF) with five nucleated cells (normal, 0 - 5 / MM3), elevated protein, 89 mg/dL (normal, 15-45), and negative gram stain and culture.

Antimicrobials were initiated for empiric treatment of aseptic meningitis; however, the patient's fevers continued despite treatment. Brain magnetic resonance imaging (MRI) revealed multifocal punctate diffusion restrictions in the pons, initially concerning for central pontine myelinolysis despite persistent eunatremia throughout her hospital stay (Figure 1). A cardioembolic source was considered, but transthoracic

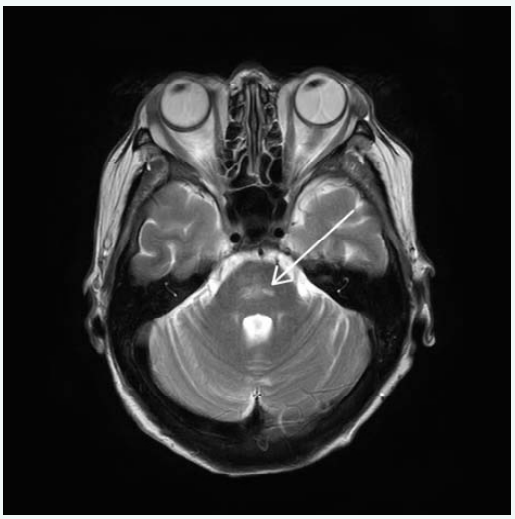

Figure 1 MRI Brain T2 - Hyperintensity lesions in the pons.

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echocardiogram did not reveal vegetation and the insults within the pons were not considered typical for a cardioembolic vascular distribution. Cross-sectional imaging of the chest, abdomen, and pelvis showed mild splenomegaly in the absence of significant lymphadenopathy. Given her progressive deterioration in mental status and ongoing, unexplained nocturnal fevers, the patient was transferred to a tertiary medical center for further evaluation. Upon arrival, the patient complained of visual hallucinations and double vision and was found to have a dysconjugate gaze with intermittent left eye esotropia. Repeat LP demonstrated elevated CSF protein and IgG levels (CSF IgG, 359 mg/dL; normal 0-6.0). An expanded CSF evaluation, including an autoimmune encephalitis panel and flow cytometry, was normal. A second brain MRI revealed interval increase in the number and size of lesions within the pons, with additional supratentorial lesions noted bilaterally (Figure 2).

Serum ferritin remained persistently elevated at 8324 ng/mL (normal, 100-200). Despite absence of lymphadenopathy on imaging, an underlying lymphoma was considered plausible given the patient's age, negative infectious disease workup, and an elevated serum beta-2 microglobulin and lactate dehydrogenase (LDH) at 5.4 (normal, 1.1-2.4) and 605 u/L (normal, <250), respectively. Multidisciplinary discussion prompted evaluation for intravascular large B cell lymphoma (IVLBCL) and concomitant hemophagocytic lymphohistiocytosis (HLH) given her elevated ferritin, cytopenias, and splenomegaly. Hemangioma skin biopsies revealed atypical CD20+ large lymphoid cells, clustered within capillaries and post-capillary venules, consistent with a diagnosis of IVLBCL**.** Bone marrow biopsy identified a low-level (1%) monoclonal B-cell population (CD 19+, CD20+) with clusters of atypical large B-cells and hemophagocytic histiocytes (Figure 3). Fasting triglycerides returned elevated at 282 mg/dL (normal, <150) and soluble IL-2 receptor was elevated at 11070 pg/mL (normal, < 1033) confirming the additional diagnosis of secondary HLH.

Discussion

IVLBCL is an exceedingly rare variant of lymphoma characterized by proliferation of neoplastic lymphocytes within the lumen of small to medium sized vessels, with little to no involvement of peripheral blood or lymph nodes [1]. Although a majority of patients present with nonspecific B-symptoms (fever, night sweats, weight loss), case reports of IVLBCL reveal highly variable clinical presentations [2]. In the Western variant of IVLBCL, central nervous system (CNS) (39-76%) and cutaneous (17-39%) involvement are common; whereas HLH, bone marrow involvement, and hepatosplenomegaly, are common in Asian variants, particularly Japan [3]. This case is unique in that neurologic involvement and secondary HLH were features of the patient's presentation.

CNS manifestations of IVLBCL, including neuropathies, paresthesias, aphasia, dysarthria, altered conscious state are present in approximately one-third of patients [4]. Brain MRI is an invaluable tool for the assessment of CNS intravascular involvement. Similar to our patient, one small IVLBCL case series demonstrated hyperintense lesions in the pons on T2WI in 45% of patients [5]. These lesions replicate findings in pontine osmotic demyelination syndrome and in the brain stem. It is speculated that vascular occlusion in small veins and arteries by tumor cells results in venous congestion that could manifest as hyperintensity in the central pons on T2WI [5]. The most common alternative diagnosis considered in cases of IVLBCL with these MRI findings is CNS vasculitis. Lumbar puncture findings in IVLBCL rarely show malignant cells, whereas, like the index patient, increased cerebrospinal-fluid protein levels are common.

HLH is a rare, life-threatening disorder associated with abnormal activation and proliferation of macrophages. The diagnosis is met if a culprit mutation in a known causative gene is identified or if at least 5 of 8 diagnostic criteria are met [6]. Persistent fevers, elevated ferritin, cytopenias, and splenomegaly sparked suspicion of HLH in this patient, but the diagnosis was confirmed with hypertriglyceridemia, elevated IL-2 receptor, and hemophagocytosis on bone marrow biopsy. Historically, HLH was associated with the Asian variant of IVLBCL, given the findings of one retrospective analysis, in which HLH was absent in all patients from Western countries [7]. The present case is one of the few examples of a patient from a Western country with IVLBCL complicated by both HLH and CNS involvement.

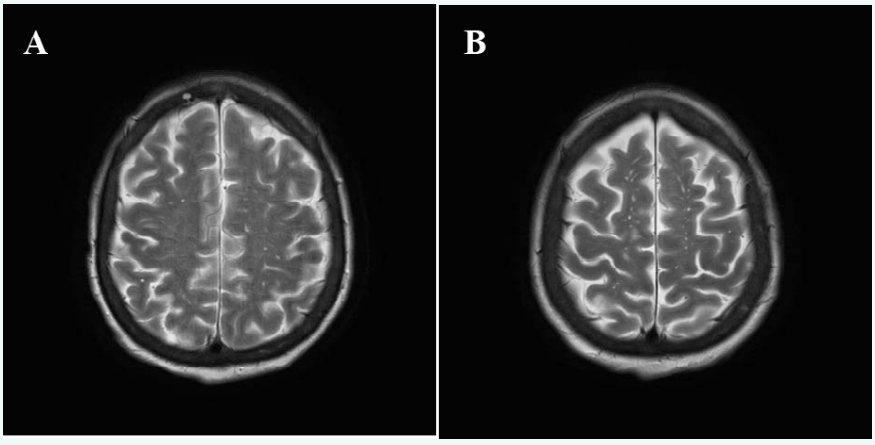

Figure 2 MRI Brain T2 – Multiple small supratentorial diffusion restrictions.

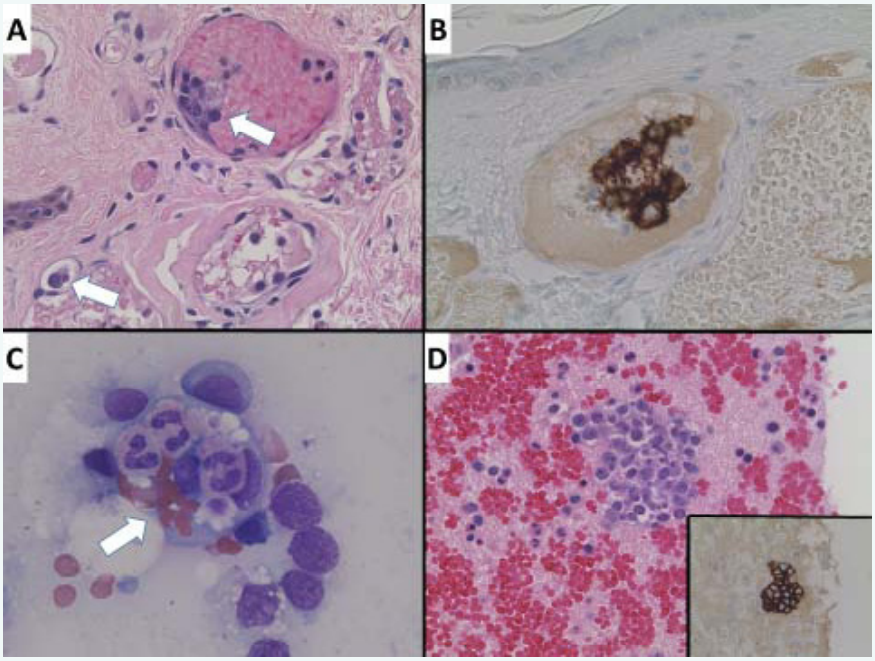

Figure 3 Pathologic findings: (a) H&E skin biopsy showing large, atypical lymphoid cells (arrows) within vascular spaces. (b) Intravascular lymphoid cells stain positive for CD20. (c) Bone marrow aspirate showing increased hemophagocytic histiocytes (arrow). (d) Bone marrow clot H&E section showing groups of atypical lymphoid cells, which are positive for CD20 (inset).

Laboratory findings are not specific to the diagnosis of IVLBCL, but often LDH and Beta-2 microglobulin are elevated (80-90% of patients) and anemia is present [8]. The histopathology of IVLBCL is characterized by the presence of large, neoplastic lymphocytes in small and medium sized blood vessels [3]. Although random skin biopsy (RSB) is an effective tool for establishing the diagnosis of IVLBCL, method and location appear to affect diagnostic yield. Atypical lymphoid cells are usually present in capillaries of subcutaneous adipose tissue; thus, some case reports speculate a higher diagnostic yield with biopsy of hemangiomas compared to random skin biopsy [9]. Although punch biopsy with 4 to 5 mm depth is traditionally used, a more recent report has suggested that approximately one-half of the patients diagnosed with IVLBCL only have lesions in deep adipose tissues found via incisional biopsy [10] (Figure 3).

Treatment of the index patient required consideration of a three-pronged approach in order to address her intravascular lymphoma (IVLBCL), HLH, and underlying CNS involvement. Chemotherapy regimens are derived from treatment of diffuse large B cell lymphoma using cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP) [11]. Due to the concomitant presence of HLH, our patient also received etoposide (R-EPOCH). The addition of etoposide is derived from the HLH-94 protocol, which guides treatment of HLH using a combination of etoposide, dexamethasone, and intrathecal (IT) chemotherapy for CNS involvement [12]. Following the first cycle of chemotherapy, the patient's mental status markedly improved from obtundation to alert, oriented, and participating in aspects of her care. She was ultimately discharged to a skilled nursing facility with the aim to complete six cycles of R-EPOCH and IT methotrexate.

This case highlights an unusual presentation of a rare disease. An extensive workup over four hospital admissions led to the diagnosis of IVLBCL with CNS involvement and HLH. Any further delay in diagnosis would have undoubtedly been fatal. Timely recognition of this disease's various phenotypes and consideration of skin biopsy are essential in order to provide the necessary therapy for this treatable condition.

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