Autopsy of an Elderly Woman with Recent History of Seizures

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Case History

A woman in her late 70s presented to the emergency department with seizures and loss of consciousness. She was managed at the ICU but later deteriorated and passed away suddenly. An autopsy was performed to determine the cause of death.

Microscopic Pathology

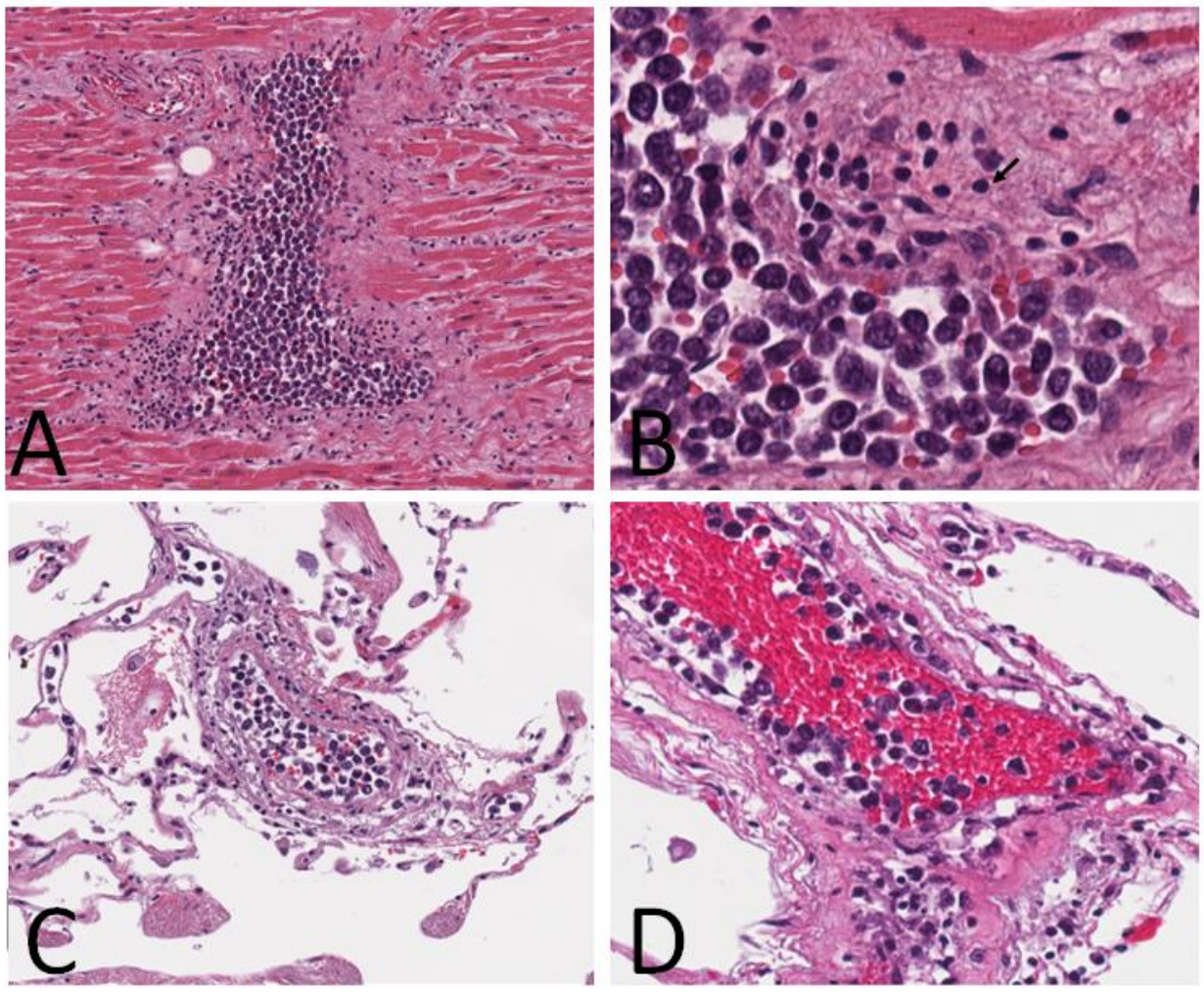

Figure 1 Intravascular large B-cell lymphoma (IVLBCL), diagnosed at autopsy, in an elderly woman who presented with seizure and loss of consciousness. Postmortem examination revealed intravascular lymphoma involving multiple sites. Low-power examination of the cardiac muscle **(A & B)** and pulmonary tissue **(C & D)** reveal intact architecture with vascular spaces engorged with atypical large lymphoid cells. **B & E**, high-power examination of vascular spaces of these specimens reveals filling or even distension with large cells having vesicular nuclei, prominent nucleoli, and scant cytoplasm. The nuclei size of the intravascular large, atypical lymphocytes is at least larger than 2 lymphocytes (arrow).

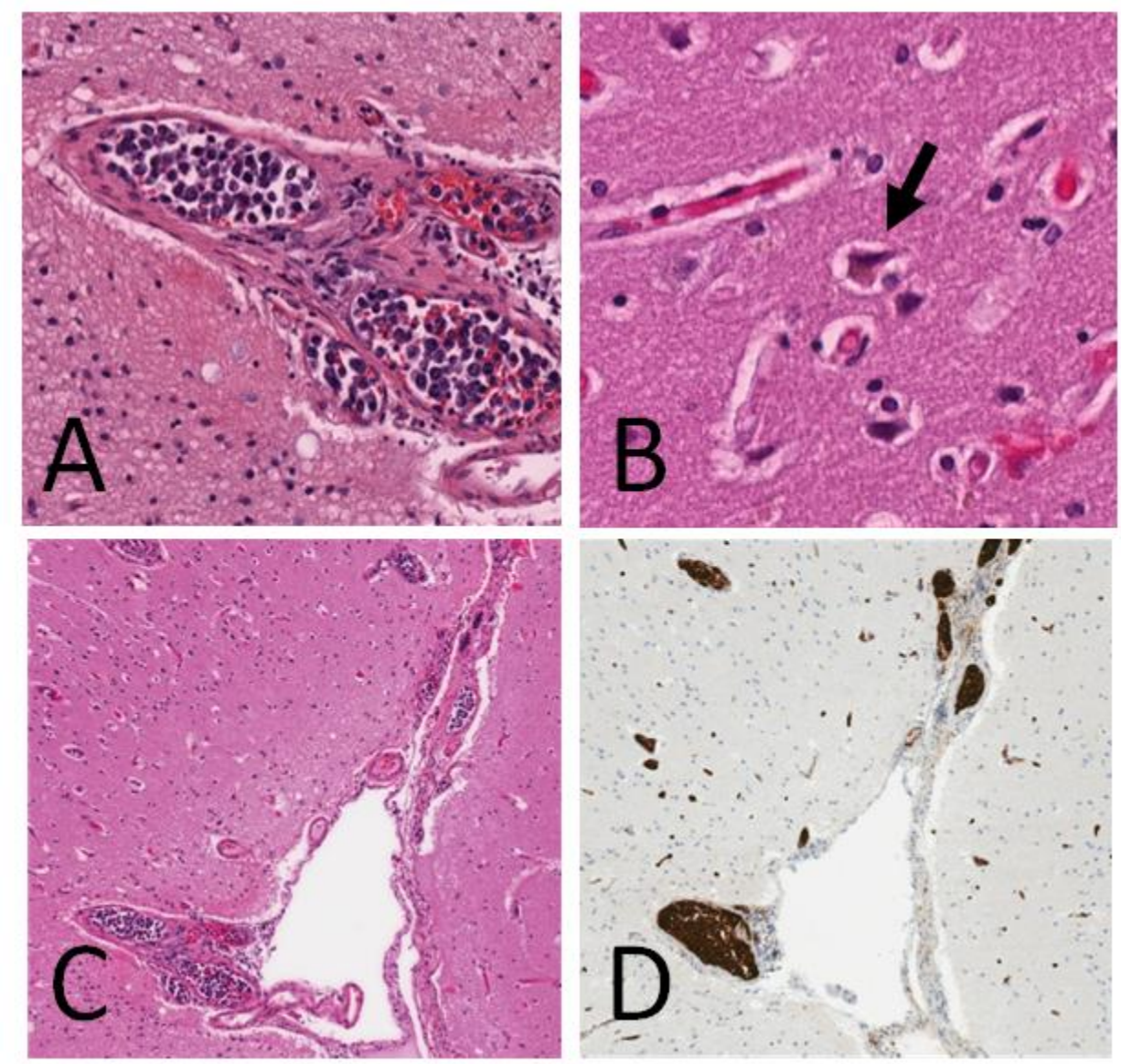

Figure 2 **A**, High-power magnification of the frontal lobe's cerebral cortex shows congestion of vascular spaces with atypical large lymphoid cells. **B**, Scattered "red neurons"

(black arrow) are indicative of acute-phase (12-24 hours) ischemia in the cerebral cortex. Their hypereosinophilic appearance is due to pyknosis and loss of basophilic Nissl bodies. Areas particularly vulnerable to cerebral ischemia include the arterial border zones, pyramidal cells in the hippocampal CA1 and CA4 area (in and adjacent to the dentate gyrus), and cerebellar Purkinje cells. **C & D,** Cerebral vascular structures were engorged with these atypical lymphoid cells with strong CD20 positivity.

Diagnosis

Atypical lymphoid cells point towards a hematological origin, with CD20 positivity indicating a B-cell origin. However, the intravascular presentation is unusual. The diagnosis in this case is an intravascular large B-cell lymphoma (IVLBCL), a subtype of diffuse-large B cell lymphoma. Differential diagnoses would include lymphomatoid granulomatosis, primary CNS lymphoma, reactive lymphoid hyperplasia, CNS vasculitis, acute leukemias, and other lymphomas which may present with an intravascular component such as peripheral T-cell lymphomas, NK/T-cell lymphomas, and KSHV/HHV8+ DLBCL. (1,2)

The WHO Classification of Tumors defines IVLBCL as an aggressive extranodal B-cell lymphoma characterized by the proliferation of large neoplastic B cells virtually exclusively within the lumina of blood vessels. The cells are CD20 and CD79a-positive, often with co-expression of CD5 and PD-L1/CD274. Most cases express *MUM1* and have a non-germinal center immunophenotype, although about 10% are CD10 positive, i.e. germinal center immunophenotype. (2,3)

Clinical Presentation

IVLBCL often has a diverse presentation, with disseminated involvement; its most common diagnostic sites are the CNS, skin, and bone marrow, with the CNS the most common site (41%) for primary disease. (4) The “classic” Western variant often presents with fever of unknown origin, multiorgan failure, neurologic and skin involvement (2,5,6). The Asian “haemophagocytic” variant is associated with fever, hemophagocytic syndrome, thrombocytopenia, hepatosplenomegaly, and bone marrow invasion (5,6). A cutaneous variant with a more favorable outcome has also been described, with a wide range of skin manifestations at presentation (1,2). Unfortunately, most cases with CNS involvement are diagnosed postmortem. (4) Common features of IVLBCL are fever of unknown origin, skin involvement (5), and neurological deficits or symptoms such as headache, vision disturbances, sensory deficits, dementia, encephalopathies, paralysis, paraplegia, and seizures, including myoclonic jerks and status epilepticus. (1,4) These neurological deficits may progress rapidly, without logical correlation to other symptomatology; an MRI may allow differentiation between IVLBCL and more common causes of such symptoms such as stroke and seizure. Similarly, multiorgan failure can occur with rash, dyspnea, B-symptoms, pulmonary embolism, renal and/or adrenal insufficiency (5); these and the neurological deficits are often linked to vascular occlusion. (4,6) Laboratory findings may include elevated LDH and β-2 microglobulin, hypoalbuminemia, anemia, elevated ESR, thrombocytopenia and leukopenia. (1,5) As with other cancers, a biopsy is required to make a diagnosis, although this is complicated by the fact that IVLBCL can be masked in the setting of an associated inflammatory infiltrate. It is important

to note that involvement of a predominant organ system may simulate clinical scenarios specific to that site of involvement, and a high degree of suspicion should be maintained when gross and histologic findings are not congruent with clinical findings. (3) It is not uncommon, however, for patients to be asymptomatic in settings where the diagnosis is incidental. (3)

Epidemiology

IVLBCL is rare: a population-based US study using data from 2000-2013 reported an annual age-adjusted incidence rate of DLBCL in general of 70 per 100,000, while IVLBCL had an overall age-adjusted incidence rate of only 0.095 per 100,000. Males and females are affected in roughly equal proportion, with the incidence increasing with age. It is most common in Caucasians. 52% are diagnosed at an advanced stage. (7)

Pathogenesis

The pathogenesis of IVLBCL is similar to other B-cell lymphomas, as the ultimate transformation of germinal or post-germinal B-cells to malignancy. This occurs via various mechanisms: genetic alterations such as *BCL6* dysregulation, *BCL2* overexpression, and *MYC* overexpression (8); immune evasion, and abnormal trafficking of lymphocytes via expression of *CXCR3* and *CXCR4*, and decreased expression of *CXR5-7*, all of which result in lymphocyte migration across vascular structures and attraction to small vessels (1). IVLBCL lacks CD29 (1,4,9), a B1 integrin subunit critical for extravasation of lymphocytes, which is responsible for the intravascular nature of IVLBCL as opposed to DLBCL; it further lack metalloproteinase-2 and -9, which are necessary for parenchymal invasion. (10) Genetic sequencing of case series have implicated the NF-κb pathway and other oncogenes implicated in IVLBCL to include *MYD88* L265P, *CD79B* Y196 and others, *PD-L1*/*PD-L2*, *SETD1B*, and *HLA-B*. (3) Despite these known pathogenic factors, there is far less known about IVLBCL than DLBCL.

Treatment

The most common treatment regimen for IVLBCL, as for many DLBCLs, is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone). (6,11) Rituximab treatment has shown to improved clinical outcomes for patients with IVDBCL, with a 3 year survival rate of 89% (12,13). Recently, the PRIMEUR-IVL trial for R-CHOP with high-dose methotrexate and intrathecal chemotherapy has shown safety and efficacy in treating IVLBCL involvement in the CNS (14).

Prognosis

IVLBCL is an aggressive lymphoma with poor prognosis, likely due to late stage of presentation. The cutaneous subtype has better prognosis, while the hemophagocytic subtype tends to have an aggressive clinical outcome (15). One meta-analysis from 2008-2018 estimated the 1- and 3-year survival rates are 42.3 and 11.5% when LDH was over 700U/L; CNS involvement, and hemophagocytic syndrome were identified as poor prognostic factors. (16) Additionally, time to diagnosis may be another factor in patient outcomes. (5)

Current Research

As IVLBCL is a rare disease, research is sparse. However, research areas include classification beyond immunohistochemistry, new prognostic factors, and innovative treatments. One study found an association PD-L1 expression and a significantly lower survival, suggesting a new prognostically useful disease category consisting of PD-L1 positive IVLBCL and extranodal DLBCL. (17) Another used microarray-based analysis to analyze a case of IVLBCL and found it to resemble non-GCB DLBCLs, suggesting molecular diagnosis microarray analysis may be warranted for cases of IVLBCL where cell of origin can have therapeutic relevance. (18) Prognostically, one study found that high-risk “rare” lymphomas did not differ in prognosis from lower-risk lymphomas if 24- and 60- month event-free survival was achieved; (19). Another investigated the association between post-treatment exosomal mRNA expression and circulating tumor DNA (ctDNA) with treatment outcome. (20) Finally, new treatments include auto-SCT in conjunction with chemotherapy, (21) and one case report showed complete remission at 22 months of relapsed/refractory IVLBCL treated with auto-SCT and CAR-T-cell therapy. (11)

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