Intravascular Large B-Cell Lymphoma

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● **A rare type of diffuse large B-cell lymphoma, intravascular large B-cell lymphoma primarily affects the middle-aged to elderly population, with a slight predominance in men. By the time of presentation, most patients have advanced, disseminated disease, and often the diagnosis is made at autopsy. Patients may present with any of a myriad of symptoms, with any tissue potentially being infiltrated. Central nervous system and cutaneous involvement is common, as is the presence of B symptoms including fever, weight loss, and night sweats. Morphologically, growth of neoplastic cells is restricted to the lumen of small vessels. The cells are large, with 1 or more prominent nucleoli, scant cytoplasm, and frequent mitotic figures, and are commonly positive for cluster of differentiation markers 79a, 20, and 19, as well as MUM1/IRF4 and Bcl-2. Intravascular large B-cell lymphoma is aggressive, and without treatment is rapidly fatal.**

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Intravascular lymphoma was first described in 1959 by Pfleger and Tappeiner[1] in Germany. Believing that the intravascular growth of malignant cells represented a neoplasm of the vascular endothelium, they described the disease as ''angioendotheliomatosis proliferans systemisata.'' In 1986 Sheibani et al[2] proved, via immunohistochemical investigation, that the cells of intravascular lymphoma were of lymphoid origin and described the disease as angiotropic (intravascular) large-cell lymphoma. In 2008, the World Health Organization[3] defined intravascular large B-cell lymphoma (IVLBCL) as a type of extranodal large B-cell lymphoma where growth is restricted to the lumina of vessels, particularly capillaries.

Intravascular large B-cell lymphoma is rare, occurring at an estimated frequency of less than 1 person per million.[4] Two forms have been described: classical, also known as Western form, with a cutaneous variant; and an Asian form occurring more frequently in the Far East.[5] Intravascular lymphoma is most frequently a disease of B lymphocytes, although rare cases of thymus-cell (T-cell) and natural killer–cell disease have been reported;[6] the World Health Organization considers these cases to be a separate entity.[3] Intravascular large B-cell lymphoma is

aggressive, and has historically been a rapidly fatal malignancy when diagnosis and treatment is delayed. Intravascular large B-cell lymphoma occurs slightly more frequently in men (male to female ratio of 1.1:1) and most often in the setting of advanced age (median age 67 years; range, 41–85 years).[7] There are some case reports of IVLBCL being preceded by different neoplasms of lymphoid tissues, including cases of follicular small cleaved cell lymphoma[8] and nodal diffuse large B-cell lymphoma,[9] suggesting that IVLBCL could occasionally represent an evolution of other lymphomas. A challenging diagnosis to make during the antemortem period, a definitive diagnosis of IVLBCL is often unobtainable until the postmortem period and diagnosed at autopsy. This owes in large part to the fact that IVLBCL may affect any organ and, as a result, may present with any of a myriad of nonspecific symptoms. There is significant variation in presentation and prognosis among the forms of IVLBCL.

CLINICAL FEATURES

In one large series the most common presenting symptoms were fever (45%), followed by cutaneous symptoms (39%), central nervous system (CNS) presentations (34%), pain secondary to cutaneous or abdominal involvement (21%), fatigue (16%), weight loss without fever (11%), gastrointestinal symptoms (5%), urinary symptoms (5%), cardiac dysfunction (5%), edema (5%), and dyspnea (3%).[10] Involvement of kidneys, lungs, and endocrine glands was common, whereas lymph nodes were typically spared. Patients most often present with disseminated and advanced disease, with one study reporting that 91% of IVLBCL patients presented with clinical stage III or IV disease.[7] Symptoms attributable to CNS involvement and ischemia are common and varied, with sensory and motor deficits, meningoradiculitis, paresthesias, hypostenia, aphasia, dysarthria, hemiparesis, seizures, myoclonus, transient visual loss, vertigo, sensory neuropathy, and altered conscious state all being reported.[7] Cutaneous lesions reflecting cutaneous vasculature involvement vary in appearance, and may occur as painful indurated erythematous eruptions, poorly circumscribed violaceous plaques (Figure 1), large solitary plaques, erythematous and desquamative plaques, peau d'orange change, cellulitis, painful blue-red palpable nodular discolorations, ulcerated nodules, palpable purpura, or small red palpable spots.[4,10,11]

The commonest laboratory findings were reported to be elevated serum lactate dehydrogenase (86%), elevated β_2 microglobulin (82%), anemia (63%), elevated erythrocyte sedimentation rate (43%), thrombocytopenia (29%), leukopenia (24%), hypoalbuminemia (18%), and presence
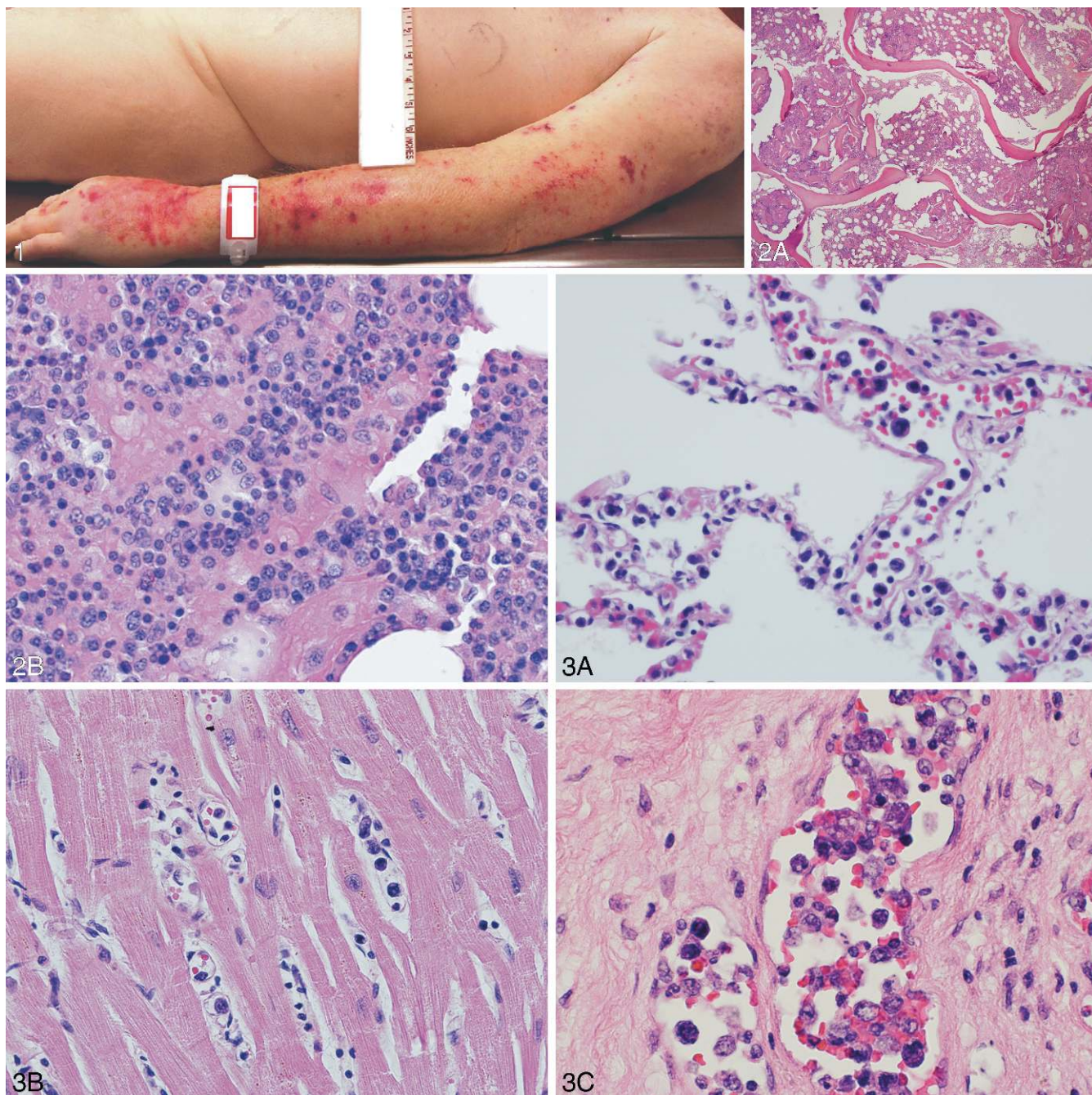
Figure 1. *Purpuric lesions on arms of deceased 70-year-old patient with intravascular large B-cell lymphoma.*

Figure 2. *Low-power view of bone marrow of a 70-year-old male at autopsy, demonstrating hypercellularity (A). Same specimen at higher magnification, demonstrating lymphoid infiltrate in bone marrow (B) (hematoxylin-eosin, original magnifications ×40 [A] and ×600 [B]).*

Figure 3. *Infiltration of capillaries in the lung (A), heart (B), and serosa of the large bowel (C) by large atypical lymphocytes with scant cytoplasm, irregular nuclei, and dispersed chromatin (hematoxylin-eosin, original magnifications ×400 [A and B] and ×600 [C]).*

of an immunoglobulin A, G, or M monoclonal serum component (14%).[12] One analysis of select laboratory data found C-reactive protein levels to be elevated (>3 mg/L) in 9 of 16 cases (56%); elevation of soluble interleukin-2 receptor (>5000 IU/mL) was found in 9 of 16 cases (56%).[11] Two recent series, each including 5 patients with IVLBCL, explored the potential utility of prostatic acid phosphatase (PAP) as a diagnostic marker of IVLBCL.[13,14] One study proved that PAP was present in the cytoplasm of IVLBCL cells, as was PAP messenger ribonucleic acid,

whereas PAP was absent in 17 cases of non-IVLBCL lymphomas.[14] Prostatic acid phosphatase was found to predict disease presence and response to treatment in both males and females; further studies investigating the usefulness of PAP in the setting of IVLBCL are desirable.

The Asian form of IVLBCL has been historically described as occurring predominantly in Japan, characterized by multi-organ failure, hepatosplenomegaly, pancytopenia, and hemophagocytic syndrome.[3] Some have suggested that concomitant presence or absence of
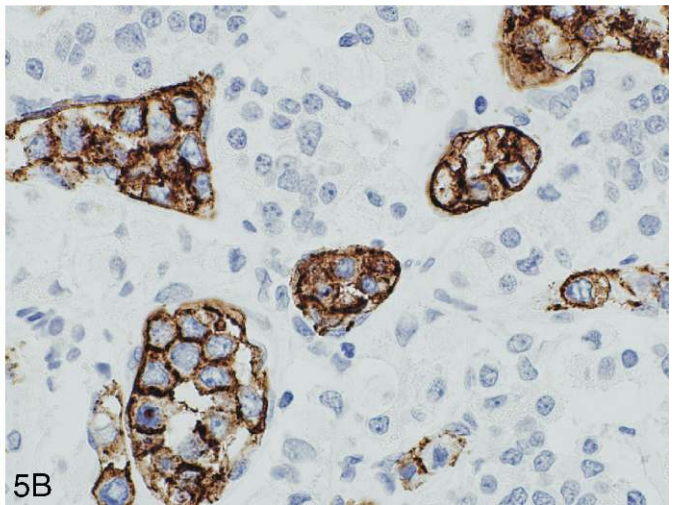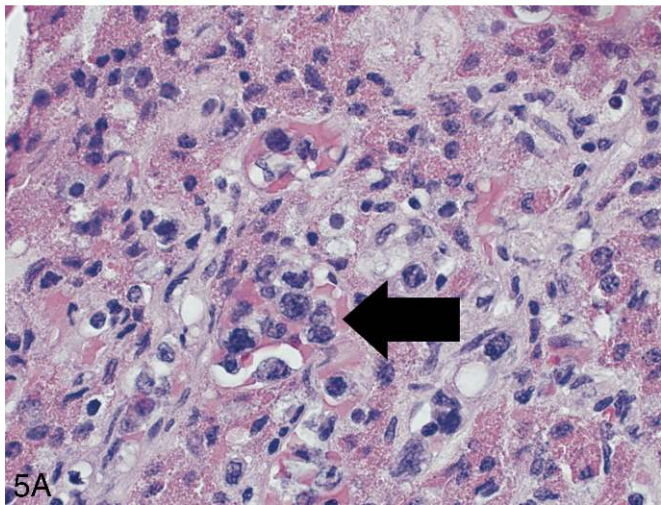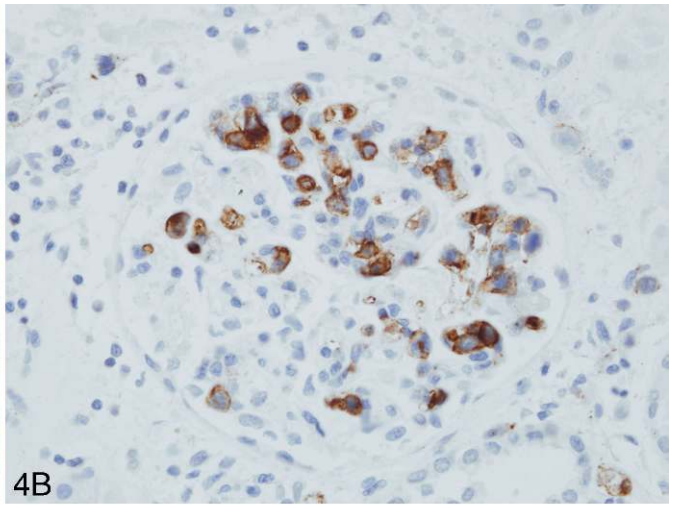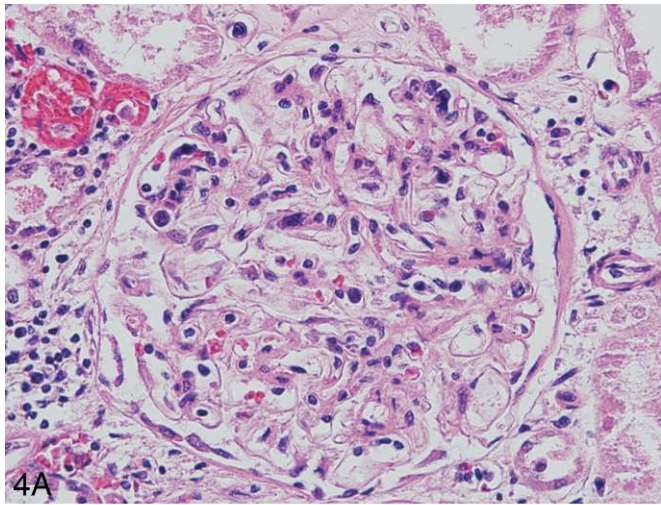
Figure 4. *Glomerulus demonstrating infiltration of the capillaries by neoplastic lymphocytes (hematoxylin-eosin, original magnification×400 [A]; CD20, original magnification ×400 [B]).*

Figure 5. *Infiltration of the pituitary gland, demonstrating occlusion of the gland's small vessels, and arrow demonstrating a nest of neoplastic cells (hematoxylin-eosin, original magnification ×600 [A]; CD20 immunohistochemistry, original magnification ×600 [B]).*

hemophagocytosis (HPC) with IVLBCL is of more utility in designating a given case as being consistent with an Asian form of IVLBCL, as opposed to basing the designation on geographic distribution alone.[5] Cases of IVLBCL with concomitant HPC occurring in Japan were not significantly different from those occurring in other countries, with the exception of a relationship in the frequency of the presence of cutaneous lesions (3% in Japan versus 33% in countries other than Japan).[5] Intravascular large B-cell lymphoma with HPC is more likely than IVLBCL without HPC, regardless of geographic location, to have the following characteristics: stage IV disease (100% versus 76%), fever (92% versus 42%), jaundice (17% versus 0%), hepatic involvement (58% versus 26%), splenic involvement (58% versus 26%), marrow involvement (75% versus 30%), thrombocytopenia (83% versus 32%), elevated alanine aminotransferase levels (42% versus 6%), and high bilirubin levels (42% versus 2%).[5]

A cutaneous variant of classical IVLBCL has also been described in which the skin is found to be the only involved organ.[10] Most characteristics of the cutaneous variant are consistent with those of the classical form of IVLBCL, with the notable exceptions that patients with cutaneous variant IVLBCL are more likely to have normal platelet and leukocyte counts, less commonly exhibit B-type symptoms, are almost exclusively female, and are younger than those affected with classical IVLBCL (mean ages of 59 years versus 72 years).[10]

PATHOLOGIC FEATURES

Tissue biopsy is mandatory for definitive diagnosis of IVLBCL, and any affected organ has the potential to demonstrate microscopic evidence of the disease process. The tissues most commonly reported to be involved include bone marrow (Figures 2A and B) and peripheral blood (67%), liver (17%), spleen (16%), skin (7%), lung (6%; Figure 3A), and lymph node (4%); however, any affected organ has the potential to demonstrate microscopic evidence of the disease process, including heart (Figure 3B), bowel (Figure 3C), kidney (Figures 4A and B), and CNS (Figures 5A and B).[7] As a result of ischemic changes, necrosis of affected tissue may be demonstrated. In addition to capillaries, the sinusoids of the liver and bone marrow and the red pulp of the spleen are commonly infiltrated with IVLBCL lymphocytes.[15,16] In cases in which

diagnosis and evidence of infiltrated tissues is elusive, sets of random skin biopsies from seemingly unaffected skin were found to be sensitive (sensitivity of 83% versus 92% for trephine bone marrow biopsy) in achieving a definitive diagnosis.[17]

The World Health Organization reports neoplastic cells will be found within the lumina of small and intermediate-sized vessels, with prominent nucleoli, scant cytoplasm, and frequent mitotic figures.[3] Some variability of IVLBCL cell characteristics has been observed, particularly including cases with coarse nuclear chromatin and irregular nuclei, cells of sizes smaller than expected, limited extravasation of neoplastic cells, involvement of larger veins and arteries than expected, and involvement of the walls of major vessels.[12,16]

RADIOGRAPHIC FINDINGS

In the setting of IVLBCL, radiographic findings consistent with ischemic changes of the CNS have been reported. These changes are similar to changes consistent with CNS vasculitis, are at least partially reversible, and correlate to some degree with disease course and response to chemotherapy.[18]

CYTOGENETICS AND MOLECULAR GENETICS

Intravascular large B-cell lymphoma has no specific chromosomal alterations, but many abnormalities reported in other B-cell lymphomas may be seen in IVLBCL. The most frequent of such patterns include −6 or 6q− and +18 or dup(18q), with a minimally deleted region located at 6q21–q23 and a commonly amplified region located at 18q13–q23.[19] There are few genetic differences between the classical and Asian forms of IVLBCL.[19] Clonal rearrangement of the variable region of the immunoglobulin heavy chain gene has been documented.[20] Prevalence of somatic mutations varies widely between cases of IVLBCL, with one study demonstrating complementarity determining region 2 and framework region 3 to have 74.7% to 99.4% homology to their closest germline genes.[20] Although isolated cases of viral infections of IVLBCL cells have been reported (ie, Epstein-Barr virus [EBV] and human herpesvirus 8),[21,22] to our knowledge, a causal relationship between infectious agents and IVLBCL has not yet been demonstrated. Active infections by EBV, cytomegalovirus, herpes simplex virus types 1 and 2, vesicular stomatitis virus, human herpesvirus 6, and human T-cell lymphotropic virus type 1 have been effectively ruled out as a mandatory prerequisite for disease development.[23]

IMMUNOHISTOCHEMICAL FEATURES

Intravascular large B-cell lymphoma cells have been demonstrated to lack cell surface proteins critical to lymphocyte transvascular migration, including CD29 (β1 integrin) and CD54 (ICAM-1 or CD11a ligand).[24,25] Aberrant expression of CD11a, allowing IVLBCL cells to be attracted to endothelial cells expressing CD54, while simultaneously being unable to migrate, could explain IVLBCL cells' capacity for sequestration to the lumen of small vessels with simultaneous leukopenia.[24] A second proposed mechanism for the aggregation of IVLBCL cells to the lumina of small vessels is the aberrant expression of G protein–coupled receptor 9 (CXCR3) among atypical lymphocytes, and aberrant expression of its ligand, chemokine ligand 9 (CXCL9), by the endothelial cells of small vessels, which may mediate atypical lymphocyte migration to these areas.[26]

Alternate theories of the mechanism of sequestration of IVLBCL to the intravascular space include deficient expression of receptors for peanut agglutinin and CD49d, both of which promote homing of tumor cells to endothelial cells via interaction with CD54 and CD106 (CD49d ligand).[24,27]

Intravascular large B-cell lymphoma cells irregularly express several immature and mature B-cell antigens, and may be of a germinal center (20%) or nongerminal center (80%) B-cell immunophenotype.[11] Common antigens demonstrated to be frequently expressed by IVLBCL cells include the following: CD79a (100%), CD20 (96%), MUM1/IRF4 (95%), Bcl-2 (91%), CD19 (85%), immunoglobulin κ light chain (71%), CD5 (38%), Bcl-6 (26%), immunoglobulin λ light chain (18%), CD10 (12%), and CD23 (4%).[7,24,28,29] Small series and case reports have demonstrated that CD22, CD43, CD45(PD7/26/16), and human leukocyte antigen subtype DR surface antigens are frequently expressed as well.[15,29] Several cases of IVLBCL with downregulated or absent CD20, especially in patients with a history of rituximab use, have been reported.[11,30]

DIFFERENTIAL DIAGNOSIS

The range of differential diagnoses for IVLBCL is wide, and in reaching a correct diagnosis careful clinical correlation and adequate tissue sampling is mandatory. The differential diagnoses include lymphomatoid granulomatosis, primary CNS lymphoma, CD5+ diffuse large B-cell lymphoma, reactive lymphoid hyperplasia, CNS vasculitis, HPC-associated disorders other than IVLBCL, the acute leukemias, and lymphomas with an intravascular component.

Patients with lymphomatoid granulomatosis, a lymphoma of large B cells, may present with fever, weight loss, neurologic deficits, and respiratory manifestations. Microscopy demonstrates an angiodestructive and angiocentric lesion with invasion of the vascular wall, where B cells are admixed with T cells, immunoblasts, and histiocytes. B cells are EBV positive and often only subtly atypical.

Primary diffuse large B-cell lymphoma of the CNS will present with behavioral and personality changes and focal neurologic deficits. It is a variant of extranodal non-Hodgkin lymphoma, with the majority of cases being positive for B-cell markers and histology similar to the other diffuse large B-cell lymphomas. Magnetic resonance imaging will demonstrate contrast-enhanced lesions similar to those of toxoplasmosis. Lesions may grow into and around blood vessels and demonstrate central necrosis, growth patterns will be diffuse, and tumor cells are likely to be intermingled with reactive lymphocytes and activated glial cells. Tumor tissue spreads outside the brain only rarely.

CD5+ diffuse large B-cell lymphoma encompasses a broad category of lymphomas, and has been reported to demonstrate an intravascular or sinusoidal growth pattern in 19% of cases that do not meet criteria for IVLBCL.[31] The bone marrow, liver, and spleen are the most common sites of involvement. Most cases express Bcl-2 and MUM1. The growth pattern tends to be diffuse, cells are medium to large with scant to moderate cytoplasm, and binucleated tumor cells are frequently observed.[31]

Reactive lymphoid hyperplasia can mimic IVLBCL, particularly when hyperplasia involves lymphatic sinusoids and channels. Regardless of the underlying etiology of the reactive process, there is typically preservation of lymphoid architecture, even when large degrees of distortion are demonstrable. Such distortions are particularly common in Kimura disease, Epstein-Barr lymphadenitis, human immunodeficiency virus–associated salivary gland disease, and chronic sialadenitis.[32] Polymerase chain reaction testing for clonal B- and T-cell receptor genes is useful to distinguish between benign and malignant lymphoproliferation, as is careful assessment of cellular features such as degree of atypia and inclusions indicating viral infection.[32]

Diagnosis and distinction of acute leukemias from IVLBCL is critical, with peripheral blood smear and analysis of degree of peripheral blood involvement being an important tool. Further distinction can be made by carrying out cytogenetic analysis, because the majority of lymphoblastic tumors have nonrandom karyotypic abnormalities. Immunophenotype of acute lymphocytic leukemia can also be diagnostic; terminal deoxynucleotidyl transferase is commonly expressed, and further subtyping is possible by immunophenotypic analysis for lineage-specific markers (eg, CD19 and CD3). Acute myelogenous leukemia is easier to distinguish from IVLBCL, because the immunophenotype is less similar (ie, myeloid-associated antigens such as CD13 and CD33 are noted, instead of the B-cell antigens of IVLBCL). Acute myelogenous leukemia is otherwise diverse in terms of cytogenetics and predominant line of differentiation.

Hemophagocytosis-associated IVLBCL (ie, the Asian form) is frequently associated with nonspecific findings such as fever, cytopenia, and hepatosplenomegaly. Several infectious, autoimmune, and lymphoproliferative disorders are also associated with HPC and these same findings, including EBV-associated lymphoproliferative disorders and B-cell lymphomas.[33] Several of the associated tumors include the following categorized by the World Health Organization: nasal type NK/T-cell lymphoma, aggressive natural killer–cell leukemia, subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous γδ T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, lymphoproliferative diseases associated with primary immune disorders, and Langerhans cell sarcoma. Making a distinction between potentially similar clinical presentations and the atypical histology of the described neoplastic cells will require tissue sampling and immunophenotypic analysis. Where the aforementioned disorders often will be positive for EBV infection, IVLBCL less often is.[23] A B-cell immunophenotype is expected for IVLBCL, and although the aforementioned tumors may occasionally involve the lumina of small vessels, in cases of IVLBCL extravasation is only minimal;[3] tissue sampling adequate to make these distinctions is critical to making a correct diagnosis.

Central nervous system vasculitis and IVLBCL may both be considered in cases of nonspecific, clinical manifestations of CNS involvement. Radiographic findings for each are nonspecific and reflect ischemia, and no laboratory test is diagnostic for either process. Presence of disease processes outside of the CNS also does not rule out CNS vasculitis, because CNS vasculitis may be secondary to more systemic disease processes, such as viral infections, which further confuse the clinical picture. Microscopy will differentiate between CNS vasculitis and IVLBCL; vessel walls will be involved in CNS vasculitis, whereas typically IVLBCL involves only small vessel lumina. At the cellular level the lesions of IVLBCL will be more atypical and homogenous, and it is necessary to make the aforementioned distinction between reactive lymphoid tissue and neoplastic cells.

Lymphomas besides IVLBCL may demonstrate an intrasinusoidal or intravascular component. Intravascular location of atypical lymphocytes is paired with small cell size or immunophenotypes distinct from IVLBCL in marginal zone lymphoma and hepatosplenic T-cell lymphomas.[16] The intravascular involvement of splenic marginal zone lymphoma and mantle-cell lymphoma is secondary to a more dominant extravascular component, mandating adequate tissue sampling for their exclusion.[16] Intravascular distribution of neoplastic lymphocytes alone is not diagnostic of IVLBCL. In order to verify or confirm diagnosis, the performance of a random biopsy of seemingly uninvolved organs may demonstrate IVLBCL,[12] reinforced by confirmation of IVLBCL immunophenotype.

TREATMENT AND PROGNOSIS

The treatment of choice for all patients with IVLBCL is combination chemotherapy. Cyclophosphamide, Adriamycin, Oncovin, and prednisone (CHOP) and CHOP-like chemotherapy have achieved positive objective responses; however, anthracycline-based chemotherapy has been associated with superior remission and overall survival rates.[5,7,34] Still, the prognosis of patients treated with any chemotherapy regimen alone remains disappointing however, with one large series of 62 patients receiving anthracycline-based chemotherapy reporting a mean survival of only 13 months.[7] Inclusion of autologous stem cell transplant into treatment regimens has been reported to significantly improve outcomes (reports exist of patients surviving to and being followed through 39 and 99.5 months),[7] but the number of patients who are candidates for autologous stem cell transplant is limited by the tendency for advanced age and poor performance status among the affected population.[10] In recent years the administration of rituximab has produced a profound positive response in cases of IVLBCL as both initial and salvage therapy, and is now frequently incorporated into combination chemotherapy. One analysis found complete remission to have occurred in 11 of 12 patients with no relapses at a median follow-up of 15 months.[5] It should be noted, though, that administration of rituximab for treatment of IVLBCL has also been noted to infrequently precede potentially devastating complications, including intracerebral hemorrhage and respiratory failure.[35,36]

The cutaneous variant of classical IVLBCL is associated with a better prognosis than the noncutaneous classical or Asian forms; one study demonstrated a 56% 3-year survival for cutaneous variant and 22% 3-year survival for other cases of IVLBCL.[10] Radiotherapy to treat a lone cutaneous lesion has been reported to result in cure, although it is recommended that all patients with IVLBCL be considered to have disseminated disease and be treated empirically.[10] The presence of HPC in conjunction with IVLBCL (ie, the Asian variant of IVLBCL) has been noted to be a negative prognostic indicator, as it is in cases of other hematologic malignancies.[5] Impaired performance status and advanced age correspond with negative prognosis, in large part because these factors make

administration of chemotherapy more difficult.[7,11] Other features indicative of poor prognosis include advanced clinical stage, elevated serum lactate dehydrogenase, involvement of more than one extranodal site, presence of B symptoms, and thrombocytopenia less than $100 \times 10^3/\mu L$.[7]

CONCLUSION

Intravascular large B-cell lymphoma is a rare type of extranodal large B-cell lymphoma. It tends to occur in elderly patients, occurs with only slight predilection for male sex, and is without known risk factors. Accurate diagnosis is elusive, requires strong clinical suspicion, and tissue sampling and microscopy of at least 1 of what is typically several disseminated lesions. Microscopy will demonstrate large B cells sequestered within the intravascular spaces; these cells inconsistently express several of the typical B-cell antigens, with CD79a, CD20, MUM1/IRF4, and CD19 being the most commonly expressed. With the exception of a cutaneous variant, IVLBCL is aggressive and carries a grim prognosis, although the prognosis has improved with recent introduction of rituximab to combination chemotherapy regimens. These anthracycline-based or CHOP-like regimens plus rituximab have resulted in improvement of clinical course, and prolonged remission and survival.

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