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Intravascular Large B-Cell Lymphoma, an Updated Review

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Abstract

Intravascular large B-cell lymphoma (IVBCL) is a rare but aggressive form of non-Hodgkin lymphoma. It is characterized by the malignant proliferation of lymphocytic tumor cells in the lumens of capillaries, small arterioles, and post-capillary venules. There exists two clinical variants: the Asian variant and the Western variant. The former is associated with neurologic and dermatologic signs and symptoms, whereas the latter often presents with splenomegaly, jaundice, and hemophagocytosis. Lymphadenopathy is uncommon, and patients typically have nonspecific symptoms. This vague symptomatology is the main culprit behind the delayed diagnosis and consequently poor prognosis of IVBCL patients. Radiologically, neurologic IVBCL presents as multifocal lesions on diffusion-weighted MRI with T2 abnormalities. FDG-PET is especially valuable when highly perfused organs such as the lungs and kidneys are involved. Typical laboratory findings are low serum albumin and elevated LDH, sIL2R, and ferritin. The first line systemic therapy for IVBCL is a combination of cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOP-R regimen).

Keywords: IVBCL; Intravascular Lymphoma; Neurologic Manifestations; Cancer

Introduction

Intravascular large B-cell lymphoma (IVBCL) is a rare but aggressive form of non-Hodgkin lymphoma characterized by the malignant proliferation of lymphocytes in the lumens of capillaries, small arterioles, and post-capillary venules [1]. Unlike most other hematopoietic malignancies, there are no obvious extravascular masses and nodal disease is rare. Thus, the tumor is exclusively found in blood vessels and spares the surrounding parenchyma [2].

It was first described in 1959[3], and its lymphoid nature was confirmed by Wick et. al in 1986 after the identification of common leukocyte antigen on the surface of the malignant cells. [4] Due to the extremely rare nature of the disorder (with an estimated incidence of less than one per million), reports of IVBCL cases in the literature are usually made in the form of case series [5].

One of the key characteristics of the pathophysiology of IVBCL is the main predilection of the malignant cells to the intravascular space, and the organ-specific distribution associated with each IVBCL variant. The two variants are the Asian variant and the Western variant. The exact reason behind the restriction of tumor cells to the lumen of blood vessels has not been clearly elucidated yet, but it is hypothesized that the lack of β1 integrins and homing receptors might play a role [6]. The available literature presents inconclusive data concerning the specific markers mediating the Asian variant's tropism. On the other hand, the predilection to the skin and nervous system in the Western type is related to the presence and type of B2-integrins, matrix metalloproteinases, and intercellular adhesion molecules on the surface of the cancer cells [7]. These surface antigens, such as CD29 and CD54, dictate the migration, adhesion, and invasive behavior of the malignant lymphocytes through interaction with tissue-specific endothelial cells and adherence to the vasculature of target organs. Consequently, the organ-specific symptoms ensue from the malignant cells' microvascular occlusion of this organ's vascular supply, resulting in organ damage [8].

According to the "WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues", IVBCL can be classified as an independent subtype of diffuse large B-cell lymphoma.

Moreover, IVBCL is a subtype of a larger category of cancers called intravascular lymphomatosis (IVL). It is the most common subtype of intravascular lymphoma as the malignant cells are most commonly of B-cell origin. However, rare cases of T cell or NK cell lymphoma have been reported in the literature [9]. Effectively, among the 740 IVL cases published between 1959 and 2011, 651 (88%) were diagnosed with B-cell lymphoma, 45 (6%) with T-cell lymphoma, and 12 (2%) with NK cell lymphoma [10].

Risk Factors and Clinical Variants

This malignancy is most common in the elderly (median age is 70). There are no proven risk factors besides age associated with the development of IVBCL and it is equally prevalent in men and women.[11] However, significant geographical variation in the clinical manifestations of IVBCL has been reported. A considerable difference in symptomatology exists when comparing Western and Asian populations. As a result, the two clinical variants respectively exist [9].

The Western variant most often presents with cutaneous manifestations, thus Ferreri et al. adequately refer to it as the "cutaneous variant"[12]. It is also commonly associated with neurological manifestations, which are present in 34% of cases at initial diagnosis [13]. It is more prevalent in females and has a better prognosis compared to the Asian variant.

In the Asian variant, in contrast, CNS symptoms and cutaneous involvement are rare. This variant is typically associated with hemophagocytic syndrome. Consequently, it often presents with fever, splenomegaly, jaundice, and hemophagocytosis, where macrophages in the bone marrow, lymph node, liver, or spleen phagocytose different hematopoietic cells. Accordingly, hemolymphatic organs, namely the liver, spleen, and bone marrow are significantly more commonly involved in the Asian variant. In a retrospective study by Ferreri et. al evaluating 173 patients with the Asian IVL, the presence of liver, spleen, and bone marrow involvement were each reported, respectively, in 66%, 77%, and 74% of Japanese patients with hemophagocytosis, whereas each was

only present in 26%, 26%, and 30% of patients with the Western variant [12].

Lastly, the Asian variant is specifically the most prevalent in Japan. It commonly exhibits a less favorable prognosis than the Western variant.

Signs and Symptoms

The remarkable ability of IVBCL to exhibit various clinical manifestations is secondary to its purely vascular nature. Effectively, the clinical signs and symptoms depend on the type of organs involved, and the extent of the invasion. The lymphoma cells plug the lumen of the vessels they invade and compromise blood flow, resulting in organ-specific manifestations [7].

In addition, unlike most other hematopoietic malignancies, lymphadenopathy is uncommon, and patients typically present with nonspecific symptoms. The most common generalized symptoms are B symptoms, which are namely fever, night sweats, malaise, and weight loss.

As noted earlier, the western variant of IVBCL most commonly affects the nervous system (42%) and skin (38%) [12]. The cutaneous manifestations are most commonly macules, nodules, and plaques (49%), edema (28%), and telangiectasia (20%). However, cutaneous IVBCL may present clinically with the absence of any cutaneous lesions but with the presence of tumor cells on pathology from blind deep surgical biopsy sampling blood vessels [14]. Lastly, it may also mimic vasculitides and manifest as purpura, vascular ectasias, petechiae, and Campbell de Morgan spots (cherry angiomas). Skin lesions are most commonly non-painful, but in a literature review of 224 cases of IVBCL by Roglin et. al, 24% of patients reported pain as an accompanying feature of the skin lesions [15].

On another hand, IVBCL can present with a large array of neurological symptoms ranging from an altered level of consciousness to cerebral hemorrhage and coagulopathy. These are most associated with the Western variant as stated earlier but have also been reported less frequently with the Asian variant (25%) [16]. Due to its low prevalence, IVBCL is rarely considered in the differential diagnosis of patients with neurological complaints [17]. The pathophysiology of the neurological manifestations of IVBCL is similar to that of most other IVBCL symptoms: ischemia, whereby vascular obstruction by large migrating lymphoma cells results in nerve ischemia, demyelination, and axonal neuropathy [18].

The central nervous system is much more commonly affected than the peripheral nervous system. Malignant infiltration may affect the brain, the spinal cord, the nerve roots, and less commonly the peripheral nerves.[19] Moreover, the central nervous system has the highest proportion of relapse (88%)[17], and the highest rate of postmortem diagnosis (60%) [10].

Previously, the most common central nervous system manifestations reported were dementia and altered mental status, hemiparesis, and myelopathy, followed by aphasia, transient neurological deficits, headaches, and seizures [20]. However, a more recent review of the literature was recently performed by Fonkem et. Al in 2016. This meta-analysis with 654 patients revealed that the most common central nervous system manifestations are cognitive impairment (61%), followed by motor impairment (22%), and seizures (13.4%) [21]. Moreover, IVBCL may also be associated with cerebrovascular events (including hemorrhage) and cauda equina syndrome [22]. The most common neurological complications of IVBCL are subsequent dementia and seizure disorder [21].

Other neurological manifestations of IVBCL include myelopathy, radiculopathy, and neuropathy. Nauman et. al reports a case of a patient with signs and symptoms suggestive of radiculopathy but had a normal spine MRI. It was later found that she had IVBCL which presented as lumbosacral radiculopathy [23].

Peripheral nervous system involvement manifests most commonly as sensory neuropathy, specifically numbness in the upper and lower extremities [17]. Peripheral neuropathy can also be in the form of impaired vibration sensation and thermal hypoalgesia

[24]. In some cases of patients with IVBCL, vascular occlusion by tumor cells can result in motor neuropathy which manifests as weakness and hyporeflexia [9].

Moreover, IVBCL can cause both axonal neuropathy and demyelinating neuropathy. Fukami et. al. reported a case involving a patient diagnosed with IVBCL with only neurological manifestations. He suffered from a demyelinating polyneuropathy secondary to the lymphoma, confirmed by nerve conduction studies and the appearance of an onion-bulb formation on sural nerve biopsy [24]. Conversely, Tahsili-Fahadan et al. documented a clinical case of a patient presenting with IVBCL-associated neurological manifestations, specifically paraparesis and urinary retention. Subsequent electrodiagnostic studies revealed these symptoms to be attributed to sensorimotor axonal polyneuropathy [25].

Lastly, IVBCL might be mistaken for myositis, because proximal muscle weakness is a rare but possible manifestation. Although myopathy is not a main symptom of IVBCL, muscle involvement can occur secondary to occlusion of muscular arteries by tumor cells, which impairs blood flow and nutrient delivery to the respective muscle. This results in pain, weakness and atrophy. Mirza et al. reported 2 cases of patients presenting with signs and symptoms suggestive of myositis, only to be diagnosed with IVBCL on muscle biopsy.[26] Similarly, Marini-Bettolo et. al. explained that the changes found on the biopsy of affected muscles are non-specific myopathic changes including fiber atrophy and hypertrophy. However, there was no inflammatory or necrotic component, unlike the myopathy associated with paraneoplastic syndrome [27].

Diagnosis

Laboratory Findings

In an analysis of 42 cases of IVBCL, Matsue et al. found that the most frequently reported laboratory abnormalities were unspecified anemia (69%), thrombocytopenia (81%), and unexplained hypoxemia (80%). All 42 patients in their analysis had low serum albumin and elevated LDH, sIL2R, and ferritin [28].

Cheng and Hoffman report a case of an elderly female with recently diagnosed autoimmune hemolytic anemia. Bone marrow biopsy later revealed the diagnosis of IVBCL with hemophagocytic lymphohistiocytosis. She had a low haptoglobin of less than 20mg/dL and an elevated ferritin of 9833 ng/mL. Her peripheral blood smear showed agglutination, normocytic anemia, significant anisocytosis, and polychromasia.[29] Patel et al. and Alexandrescu et al. each also report a case diagnosed initially with autoimmune hemolytic anemia on presentation which was subsequently found to have IVBCL [30,31].

In their case series of 38 patients with IVBCL, Ferreri et al. observed elevated LDH (in 86% of patients) and β2-microglobulin (82%) levels. In terms of cytopenias, anemia was the most common (63%). Leukopenia occurred in 24% of patients and thrombocytopenia occurred in 29%, and both were always concurrent with anemia. 43% of patients had an elevated ESR. Other abnormalities included monoclonal immunoglobulin in 14%, and abnormal liver, renal, and thyroid function tests in 16%. When patients with the cutaneous variant of IVBCL were analyzed alone, findings were similar to other patients, with elevated ESR, elevated LDH, and anemia. However these patients did not have leukopenia, thrombocytopenia, nor monoclonal components [11].

In the case reported by Fischer et al., the patient had elevated CSF protein, normal CSF glucose, and no malignant cells on CSF cytology [32]. In a retrospective study of 29 case reports, Brunet et al. had 22 IVBCL patients who underwent spinal tap analysis. An elevated CSF protein was observed in 11 cases and an elevated glucose was observed in 5 cases. 17 out of the 22 cases had neurological symptoms, and in these, an elevated CSF protein was observed in 9 cases and an elevated glucose was observed in 2 cases. Five of the 17 cases had suspicious cells in their CSF, but none were confirmed to be malignant [33].

Imaging Findings

As the pathophysiology of IVBCL does not include tumor formation, standard imaging modalities yield mostly nonspecific results.

In Matsue et al.'s study, all 42 IVBCL patients had undergone CT scans which yielded nonspecific results [28].

Brain MRI findings in the study by Matsue et al. were abnormal in 86.4% of cases, with hyperintense lesions in the pons on T2 weighted image being the most common (54%), followed by nonspecific white matter lesions (45.9%), infarct-like lesions (27%), and meningeal enhancement (10.8%) [28].

In patients with CNS involvement, characteristic findings of neurologic IVBCL on MRI are multifocal lesions on diffusion weighted imaging with T2 abnormalities indicating ischemia or infarction, with subsequent resolution of some of these lesions and the development of others, and enhancement which persists or enlarges near these lesions [34]. In their study, Baehring et al. found that all patients had at least two of the above described findings [34].

In their analysis of three cases of IVBCL, Tobin-Vealey et al. found that all three cases had negative CT scans but were subsequently found to have sites of active disease on biopsy or autopsy. This is in line with their review of the literature where they found 21 cases that were reported to have had nonspecific and non-diagnostic findings on either CT, magnetic resonance, ultrasound, bone scan, or gallium scintigraphy. However on follow-up with FDG-PET, the scan was positive in 19 cases and led to the diagnosis of IVBCL [35].

FDG-PET is especially valuable for diagnosis when highly perfused organs such as the lungs and kidneys are affected [36]. In the brain, IVBCL results in infarcts and small vessel occlusion. Thus, an FDG-PET scan would show decreased uptake in affected brain areas, unlike in other organs such as bone marrow [28,37].

Biopsy Findings

IVBCL presents a diagnostic challenge and is typically established on extra-nodal tissue. Histopathology of IVBCL shows small vascular lumina filled by large malignant lymphocytes [38]. In random skin biopsy, these malignant lymphocytes are usually found in the vessels of subcutaneous adipose tissue and they would not only be found in visible skin lesions but also in biopsies of healthy-appearing skin [39]. Some authors have recommended that the skin be biopsied in at least three different locations [40]. Affected blood vessels may not be abundant and may be found alongside unaffected ones. Therefore, a biopsy should be deep and large enough to capture the affected vessels [15].

On flow cytometry, the malignant lymphocytes in IVBCL are positive for CD19, CD20, CD22, and CD79 [38]. In addition, many cases have been shown to express CD5 [41]. In a study including 96 patients, Murase et al. analyzed the clinical characteristics of IVBCL and found that 53 patients were CD5-CD10-, 31 were CD5+CD10-, and 12 were either CD5+CD10+ or CD5-CD10+[41].

Differential Diagnosis

As evident from the various clinical presentations discussed previously, any organ may be affected by IVBCL depending on which blood vessels are affected. Thus the differential diagnosis is extensive, which leads to frequent delays in the diagnosis of IVBCL [43].

Even when it presents with skin lesions, the cutaneous findings of IVBCL are non-specific, and may be associated with pain, telangiectasia, and edema in proximity to the lesions [43]. As such, the differential for cutaneous IVBCL may include primary B-cell lymphoma of the skin, thrombophlebitis, Kaposi and pseudo-Kaposi sarcoma, lupus panniculitis, erythema nodosum, and many others [43].

In cases of CNS involvement, the clinical presentation of IVBCL may be nonspecific, difficult to diagnose, and may be mistaken for other disease processes. Based on a case report by Detsky et al., IVBCL may present with acute stroke-like symptoms, with MRI findings that shortly resolve spontaneously, making the diagnosis of a transient ischemic attack high on the differential. Moreover,

symptoms and imaging findings may recur after initial resolution, resulting in a clinical picture suggestive of a stuttering lacunar stroke (which usually presents with fluctuating neurological abnormalities and imaging markers of stroke). The diagnosis of an autoimmune inflammatory process such as vasculitis may also be considered, especially in light of positive serum antibodies and when other diagnoses have been ruled out [44].

Another case report by Fischer et al. presented a case with multifocal neurological signs including cognitive deficits, aphasia and paraparesis, and imaging findings suggestive of vasculitis. Steroid treatment for the diagnosis of vasculitis subsequently failed and the patient was diagnosed post-mortem with IVBCL [32].

As further shown in a report of two cases by Hundsberger et al., the non-specific symptoms of IVBCL make its diagnosis challenging. The main diagnoses on the differential are vasculitis, infections of the CNS, or encephalopathy. Patients are often treated with immunosuppressive treatment for a diagnosis of cerebral vasculitis which delays the diagnosis of IVBCL, especially as its symptoms may transiently and spontaneously resolve and then recur [45].

Therefore, in patients who present with multifocal non-localizing neurological deficits or stroke-like symptoms with no history of risk factors, the possibility of IVBCL should be considered to reach the diagnosis with minimal delay [44].

Prognosis

Intravascular large B-cell lymphoma typically has a poor prognosis. The progression of the disease depends on multiple variables including the histology of the cells, the degree of systemic dissemination, and the individual organs involved [46].

Moreover, one of the major contributors to the dismal prognosis of this malignancy is the delay in diagnosis due to the large myriad of clinical symptoms that accompany it. Hence, Ponzoni et al. aptly described this malignancy as "a chameleon with multiple faces", shedding light on its non-specific and variable clinical presentations that elude straightforward diagnosis. As a result, a delay in early and accurate diagnosis is often witnessed [47].

Additionally, the absence of lymphadenopathy and the possible lack of hepatomegaly which are usually common in hematopoietic malignancies, the aggressive clinical behavior, and the fatal consequences of the disease all contribute to the poor prognosis of these patients [48]. As a result, these patients are usually diagnosed late in the disease course, and many are not diagnosed until post-mortem.

Treatment

The treatment of intravascular large B cell lymphoma is a combination of both systemic therapy and CNS targeted therapy. Though the evidence is quite scarce in regards to the optimal systemic therapy for the treatment of IVBCL due to the rarity of the disease, case reports and retrospective studies provide the insight on which we currently base our treatment plan. In particular, studies have shown that the combination of cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab, also known as the CHOP-R regimen, has proven to be most effective in achieving complete response and prolonging long term survival.

Patients who received rituximab in addition to chemotherapy had a higher complete response rate (82%) than those who received chemotherapy alone (51%). At 18 month follow-up, patients who received rituximab also had a higher 2-year progression-free survival (56 vs 27 percent) and 2-year overall survival (66 versus 46 percent) [16].

Another report of 3 cases of IVBCL showed complete remission with a follow-up of 24-45 months was achieved in all three patients after having received anthracycline-based chemotherapy in combination with the anti-CD20 monoclonal antibody rituximab [49]. This suggests that the CHOP-R regimen is able to alter the clinical course of this fatal disease and achieve positive results.

However, systemic therapy has not been enough when CNS manifestation in the form of extravascular dissemination is present. These malignancies require an addition of CNS-targeted therapy such as intrathecal chemotherapy, methotrexate, or radiation targeted at specific lesions. However, these therapies remain case-specific and are tailored based on the extravascular implications of IVBCL [33, 50-51].

Conclusion

In conclusion, intravascular large B-cell lymphoma (IVBCL) is a rare but aggressive form of non-Hodgkin lymphoma characterized by the malignant proliferation of lymphocytes in the lumens of capillaries, small arterioles, and post-capillary venules. Two main clinical variants have been described, commonly referred to as the Western variant and the Asian variant. The western variant presents with cutaneous manifestations commonly associated with neurological manifestations. In contrast, CNS and cutaneous involvement is rare in the Asian variant, which is instead associated with hemophagocytic syndrome.

The vast range of clinical manifestations in addition to the rarity of this condition make it low on the list of differential diagnoses of patients presenting with neurological complaints. The most common generalized symptoms are B symptoms, namely fever, night sweats, malaise, and weight loss. Yet, neurological symptoms ranging from altered level of consciousness to cerebral hemorrhage and coagulopathy may also be found at initial presentation. Cognitive impairment followed by motor impairment and seizures were found to be the most common central nervous system manifestations of IVBCL.

In the workup of IVBCL, studies have shown that CT scans of the brain yield nonspecific results and are not a reliable imaging modality in the diagnostic process. Brain MRI however has proven to be a reliable tool with MRI findings of multifocal lesions on diffusion-weighted imaging with T2 abnormalities indicating ischemia or infarction, resolution of some of these lesions and the development of others, and enhancement which persists or enlarges near these lesions, all proving to be characteristic findings in patients with CNS involvement of IVBCL. FDG-PET was shown to be especially valuable when highly perfused organs such as the lungs and kidneys are affected, yet was not effective in cases with brain involvement. In addition to imaging studies, there is a beneficial role for laboratory workup in the diagnostic process of IVBCL, with low serum albumin and elevated LDH, sIL2R, and ferritin all proving to be important markers for the disease. IVBCL typically has a poor prognosis. One of the major contributors to this disease's poor prognosis remains the delay in diagnosis which can be attributed to the vast number of presentations.

The treatment of intravascular large B cell lymphoma is a combination of both systemic therapy and CNS-targeted therapy. Though the evidence remains quite scarce in regard to the optimal systemic therapy for the treatment of IVBCL due to the rarity of the disease, studies have shown that a combination of cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab, also known as the CHOP-R regimen, has proven to be most effective in achieving complete response and prolonging long term survival. However, systemic therapy has not been enough with CNS manifestations, with such cases requiring additional CNS-targeted therapy such as intrathecal chemotherapy, methotrexate, or radiation targeted at specific lesions.

What we know so far about IVBCL should lay the groundwork for further research to expand our knowledge and understanding of this rare but fascinating disease. Current treatment options have yielded positive results and provide an optimistic view concerning the advancement of treatment in IVBCL and possibly altering the clinical course of this fatal disease.

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References

1. Han Y, Li Q, Wang D, et al. (2022) Case report: Intravascular large B-cell lymphoma: A clinicopathologic study of four cases with review of additional 331 cases in the literature. Frontiers in Oncology, 12.

2. Koyano S, Hashiguchi S, Tanaka F. Brain Nerve (2014), 66: 927-46.

3. Pfleger L, Tappeiner J (1959) "Zur Kenntnis der systemisierten Endotheliomatose der cutanen Blutgefasse." Hautarzt. 10: 359-363.

4. Wick MR, Mills SE, Scheithauer BW, Cooper PH, Davitz MA, Parkinson K (1986) Reassessment of malignant "angioendotheliomatosis." The American Journal of Surgical Pathology, 10: 112-23.

5. Devitt KA, Gardner J-A (2018) Intravascular large B-cell lymphoma: The great imitator. Autopsy and Case Reports. 8.

6. Ponzoni M, Arrigoni G, Gould VE, et al. (2000) Lack of CD 29 (B1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Human Pathology. 31: 220-6.

7. Pless ML, Chen Y-B, Copen WA, Frosch MP (2010) Case 9-2010. New England Journal of Medicine. 362: 1129-38.

8. Stefanidakis M, Koivunen E (2006) Cell-surface association between matrix metalloproteinases and integrins: Role of the complexes in Leukocyte Migration and cancer progression. Blood. 108: 1441-50.

9. Dou L, Wu C, Zeng Z, Zhu J, Su L, Wang T (2021) Hemophagocytic syndrome and neurological involvement in a case of intravascular large B-cell lymphoma. Journal of International Medical Research. 49: 030006052110066.

10. Fonkem E, Lok E, Robison D, Gautam S, Wong ET (2014) The natural history of Intravascular lymphomatosis. Cancer Medicine. 3: 1010-24.

11. Ferreri AJ, Campo E, Seymour JF, et al. (2004) Intravascular lymphoma: Clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. British Journal of Haematology. 127:173-83.

12. Ferreri AJ, Dognini GP, Campo E, et al. (2007) Variations in clinical presentation, frequency of hemophagocytosis and clinical behavior of intravascular lymphoma diagnosed in different geographical regions. Haematologica. 92: 486-92.

13. Piccaluga PP, Paolini S, Campidelli C, Vianelli N, Bolondi L (2019) A western case of intravascular large B-cell lymphoma as an unusual cause of persistent fever. Case Reports in Hematology. 2019: 1-6.

14. Charifa A, Paulson N, Levy L, et al. (2020) Intravascular Large B-Cell Lymphoma: Clinical and Histopathologic Findings. Yale J Biol Med. 93: 35-40.

15. Röglin J, Böer A (2007) Skin manifestations of intravascular lymphoma mimic inflammatory diseases of the skin. British Journal of Dermatology. 157: 16-25.

16. Shimada K, Matsue K, Yamamoto K, et al. (2008) Retrospective analysis of intravascular large B-cell lymphoma treated with Rituximab-containing chemotherapy as reported by the IVL Study Group in Japan. Journal of Clinical Oncology. 26: 3189-95.

17. Cancer Therapy Advisor (2019) Intravascular large B-cell lymphoma.

Available at https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/hematology/intravascular-large-b-cell-lymphoma. Accessed November 21, 2023.

18. Sawada T, Omuro Y, Kobayashi T, et al. (2014) Long-term complete remission in a patient with intravascular large B-cell lymphoma with Central Nervous System Involvement. OncoTargets and Therapy. Published online 2014: 2133.

19. Glass J, Hochberg FH, Miller DC (1993) Intravascular lymphomatosis a systemic disease with neurologic manifestations. Cancer. 71: 3156-64.

20. Chapin JE, Davis LE, Kornfeld M, Mandler RN (2009) Neurologic manifestations of Intravascular lymphomatosis. Acta Neurologica Scandinavica. 91: 494-9.

21. Fonkem E, Dayawansa S, Stroberg E, et al. (2016) Neurological presentations of intravascular lymphoma (IVL): Meta-analysis of 654 patients. BMC Neurology. 16.

22. Moling O, Piccin A, Tauber M, et al. (2016) Intravascular large B-cell lymphoma associated with silicone breast implant, HLA--DRB1*11:01, and HLA-DQB1*03:01 manifesting as macrophage activation syndrome and with severe neurological symptoms: A case report. Journal of Medical Case Reports. 10.

23. Nauman F, Mohammed N, Hussain M, Shah A (2012) Intravascular Large B-cell Lymphoma Presenting as Lumbosacral Radiculopathy. Neurology. 96.

24. Fukami Y, Koike H, Iijima M, et al. (2020) Demyelinating neuropathy due to intravascular large B-cell lymphoma. Internal Medicine. 59: 435-8.

25. Tahsili-Fahadan P, Rashidi A, Cimino PJ, Bucelli RC, Keyrouz SG (2015) Neurologic manifestations of intravascular large B--cell lymphoma. Neurology: Clinical Practice. 6: 55-60.

26. Mirza MA (2021) P024 The Mighty Mimic: Intravascular large B-cell lymphoma masquerading as myositis: A case series. Rheumatology. 60.

27. Marini-Bettolo C, Lane R, Charles P, et al. (2009) Myopathy secondary to intravascular large B-cell lymphoma. Neuromuscular Disorders. 19: 856-9.

28. Matsue K, Abe Y, Narita K, et al. (2019) Diagnosis of intravascular large B cell lymphoma: Novel insights into clinicopathological features from 42 patients at a single institution over 20 years. British Journal of Haematology. 187: 328-36.

29. American Society of Hematology (2021) Intravascular DLBCL with associated hemophagocytosis.
Available at https://imagebank.hematology.org/reference-case/70/intravascular-dlbcl-with-associated-hemophagocytosis. Accessed November 21, 2023.

30. Patel SS, Aasen GA, Dolan MM, et al. (2014) Early diagnosis of intravascular large B-cell lymphoma: Clues from routine blood smear morphologic findings. Laboratory Medicine. 45: 248-52.

31. Alexandrescu S, Orengo JP, Toossi S, et al. (2014) Intravascular large cell lymphoma in a patient with autoimmune hemolytic anemia. Neuropathology. 35: 170-4.

32. Fischer M, Iglseder S, Grams A, et al. (2017) Intravascular large B-cell lymphoma mimicking central nervous system vasculitis.

Human Pathology: Case Reports. 8: 3-8.

33. Brunet V, Marouan S, Routy J-P, et al. (2017) Retrospective study of intravascular large B-cell lymphoma cases diagnosed in Quebec. Medicine. 96.

34. Baehring JM, Longtine J, Hochberg FH (2003) A new approach to the diagnosis and treatment of intravascular lymphoma. J Neurooncol. 61: 237-48.

35. Tobin-Vealey K, Jain S, Al Diffalha S, et al. (2016) Use of Fluorodeoxyglucose-Positron Emission Tomography in the Diagnosis of Intravascular Diffuse Large B-Cell Lymphoma. Fed Pract. 33: 32S-S.

36. Shiiba M, Izutsu K, Ishihara M (2014) Early detection of intravascular large B-cell lymphoma by (18)FDG-PET/CT with diffuse FDG uptake in the lung without respiratory symptoms or chest CT abnormalities. Asia Ocean J Nucl Med Biol. 2: 65-8.

37. Boslooper K, Dijkhuizen D, van der Velden AW, Dal M, Meilof JF, Hoogenberg K (2010) Intravascular lymphoma as an unusual cause of multifocal cerebral infarctions discovered on FDG-PET/CT. Neth J Med. 68: 261-4.

38. Zuckerman D, Seliem R, Hochberg E (2006) Intravascular lymphoma: The oncologist's "great imitator." The Oncologist. 11: 496-502.

39. Matsue K, Asada N, Odawara J, et al. (2010) Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. Annals of Hematology. 90: 417-21.

40. Kiyohara T, Kumakiri M, Kobayashi H, Shimizu T, Ohkawara A, Ohnuki M (2000) A case of intravascular large b-cell lymphoma mimicking erythema nodosum: The importance of multiple skin biopsies. Journal of Cutaneous Pathology. 27: 413-8.

41. Kanda M, Suzumiya J, Ohshima K, Tamura K, Kikuchi M (1999) Intravascular large cell lymphoma: Clinicopathological, immuno-histochemical and molecular genetic studies. Leukemia & Lymphoma. 34: 569-80.

42. Murase T, Yamaguchi M, Suzuki R, et al. (2006) Intravascular large B-cell lymphoma (IVLBCL): A clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. Blood. 109: 478-85.

43. Breakell T, Waibel H, Schliep S, et al. (2022) Intravascular large B-cell lymphoma: A review with a focus on the prognostic value of skin involvement. Current Oncology. 29: 2909-19.

44. Detsky ME, Chiu L, Shandling MR, Sproule ME, Ursell MR (2006) Heading down the wrong path. New England Journal of Medicine. 355: 67-74.

45. Hundsberger T, Cogliatti S, Kleger G-R, et al. (2011) Intravascular lymphoma mimicking cerebral stroke: Report of two cases. Case Reports in Neurology. 3: 278-83.

46. Mukherjee A (2018) Intravascular large B-cell lymphoma: An elusive diagnosis with challenging management. The Journal of Community and Supportive Oncology. 16.

47. Ponzoni M, Campo E, Nakamura S (2018) Intravascular large B-cell lymphoma: A chameleon with multiple faces and many masks. Blood. 132: 1561-7.

48. Obiorah IE, Ozdemirli M (2018) Intravascular large B-cell lymphoma mimicking temporal arteritis. Case Reports in Rheumatology. 2018: 1-4.

49. Bouzani M, Karmiris T, Rontogianni D, et al. (2006) Disseminated intravascular B-cell lymphoma: Clinicopathological features and outcome of three cases treated with anthracycline-based immunochemotherapy. The Oncologist. 11: 923-8.

50. Ferreri AJM, Dognini GP, Govi S, et al. (2008) Can rituximab change the usually dismal prognosis of patients with intravascular large B-cell lymphoma? Journal of Clinical Oncology. 26: 5134-6.

51. Ponzoni M, Ferreri AJM, Campo E, et al. (2007) Definition, diagnosis, and management of intravascular large B-cell lymphoma: Proposals and perspectives from an international consensus meeting. Journal of Clinical Oncology. 25: 3168-73.