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(CASE REPORT)

Intravascular large B-cell lymphoma: Case report of a rare lymphoma and a brief review of the literature

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Abstract

Intravascular large B-cell lymphoma (IVLBCL) is an uncommon, intensely aggressive extranodal lymphoma characterized by the proliferation of malignant lymphoid cells within the lumina of small and medium-sized blood vessels, most notably capillaries, while sparing large arteries and veins. The circulating lymphoma cells do not generally appear in peripheral blood, and unlike most other lymphomas, IVLBCL does not often appear as a distinct tumor mass. The most common sites of involvement are the skin, central nervous system, kidneys, lungs, and endocrine glands; lymph node disease is rare. A diagnosis is usually obtained through a biopsy of an affected body organ, most commonly a random skin biopsy and a bone marrow biopsy.

Due to its mixed and uncharacteristic manifestation, IVLBCL is often not diagnosed in time, which further leads to a poor prognosis. We report the case of a 68-year-old male patient with IVLBCL whose diagnosis was late and who consequently developed a fast progression and death despite conventional treatment. The case highlights the difficulty in determining diagnosis and the unfavorable outcomes associated with IVLBCL, particularly in cases involving multiple organs.

Keywords: Intravascular Large B-Cell Lymphoma; Diffuse Large B-Cell Lymphoma; Cutaneous; Immunohistochemistry; Ischemia

1. Introduction

IVLBCL is a rare and unfavorable extranodal diffuse large B-cell lymphoma (DLBCL). The selective growth of neoplastic B-cells in the lumina of small vessels, without the formation of a separate tumor mass or pronounced lymphadenopathy, is the characteristic pathological basis of IVLBCL. [1] This distinctive growth pattern causes vascular blackout, microinfarction, and the subsequent dysfunction of multiple organs. [2]

The disease is characterized by remarkable clinical heterogeneity, with nonspecific manifestations including fever, respiratory distress, neurological deficits, and cutaneous lesions. [2] This broad array of oncology presentations has given it the title of a great imitator. [3] The commonly affected sites include the central nervous system, bone marrow, and the skin, although any system of organs can be affected by the disease. [1]

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In the past, IVLBCL had a poor prognosis and a high mortality rate. Most cases were only diagnosed at autopsy because of their insidious clinical manifestation and the lack of nodal swelling. [3] The introduction of random skin biopsies has significantly improved the diagnostic method. These biopsies can detect malignant cells within dermal vessels even when the skin lesions are not visible. This has been significantly improved with the introduction of immunochemotherapy regimens containing rituximab, which have led to modern studies reporting progression-free and overall survival rates of over 70% and 90%, respectively. [1] Despite this progress, IVLBCL remains a severe malignancy, and its tendency to invade the nervous system underscores the urgent need for increased clinical attention and immediate medical intervention.

The current case of IVLBCL that we discuss is intended to add to the existing body of knowledge about the complex disease and raise the awareness of physicians to this rare tumor.

2. Case presentation

A 68-year-old male reported 2 months of progressive fatigue, night sweats, and involuntary weight loss, which he initially attributed to aging. He also complained of progressive exertional dyspnea and a high-grade fever of unknown cause, which had not responded to broad-spectrum antibiotics. The physical examination revealed mild cognitive impairment, a diffuse mottled rash (livedo reticularis) on the trunk and limbs, and splenomegaly. Laboratory results revealed pancytopenia, elevated lactate dehydrogenase (LDH), and elevated C-reactive protein (CRP), along with a normal peripheral blood smear.

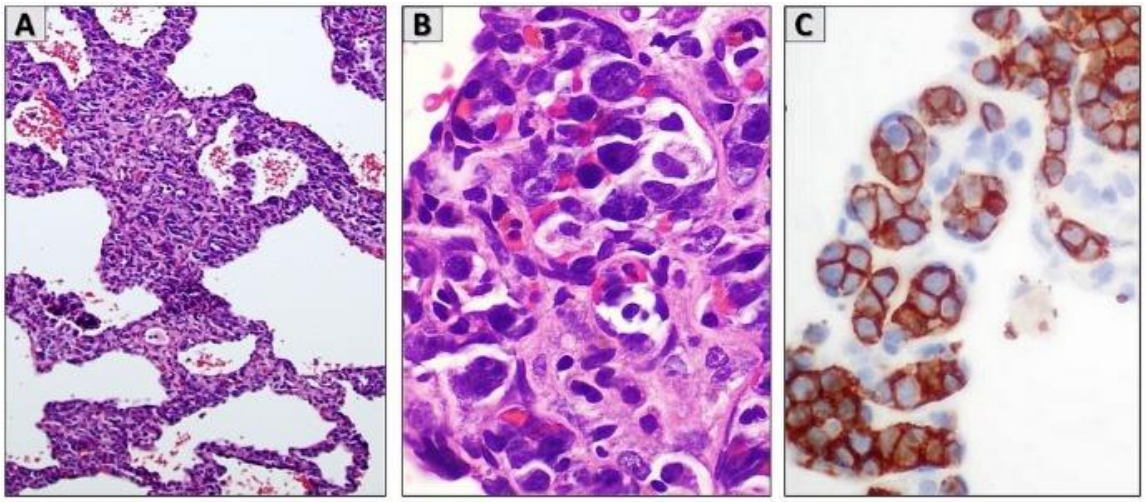
Considering these nonspecific findings, a comprehensive diagnostic workup was done. CT imaging of the chest, abdomen, and pelvis was unremarkable, as no lymphadenopathy or mass lesions were present. However, diffuse bronchial wall thickening and a small pleural effusion were noted. Cognitive changes were assessed using an MRI of the brain, which revealed several small, non-enhancing white matter hyperintensities indicative of microvascular infarcts. Persistent fever and systemic symptoms, accompanied by multiorgan involvement but without a palpable mass, raised concerns about uncommon vasculitides or an insidious malignancy.

A bone marrow biopsy, performed to determine the cause of the pancytopenia, revealed hypocellularity with aggregates of atypical, large lymphocytes between the sinusoids. Immunohistochemistry (IHC) showed the expression of the B-cell markers, CD20. Various skin biopsies were also obtained; histology showed centrifugal blocking of small blood vessels by large neoplastic lymphoid cells that resembled centroblasts. These cells had a high nuclear-cytoplasmic ratio, variably large nucleoli, and cytoplasmic morphologic features that ranged between those of centroblasts and immunoblasts/plasmablasts, as well as occasional anaplastic cells. Immunophenotyping identified a B-cell lineage, positive for CD20, CD79a, PAX5, BCL2, and MUM1, with an abnormal expression of CD5. Vascular spaces were marked by endothelial cells that were labeled with CD34. The tumor cells were negative for CD10, CD3, BCL6, Cyclin D1, and CD30. They were also EBV and HHV8-negative. (**Figure 1A, B, C**) These findings defined the diagnosis of intravascular large B-cell lymphoma. The absence of palpable mass and extensive organ involvement were some of the factors that led to a late diagnosis.

The patient was immediately initiated on the classic high-intensity regimen of chemoimmunotherapy using R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Rituximab is a monoclonal antibody (targeting CD20) that is pivotal in the treatment of IVLBCL. The patient had already shown improvement by the end of the first cycle, as he was no longer feverish and his fatigue and cognitive function had improved. However, within weeks of the second cycle, he began to grow progressively worse. He was found to have acute respiratory distress syndrome (ARDS), which required intubation and mechanical ventilation. Diffuse alveolar destruction and intravascular lymphoma cells in the pulmonary capillaries were identified by lung biopsy, which would reflect the results of previous bone marrow and skin biopsies.

Aggressive supportive care, which included plasmapheresis (due to the development of hyperviscosity syndrome) and high-dose steroids, did not help him but led to deterioration of his respiratory status and was followed by a multiorgan failure that also included progressive renal dysfunction and acute neurological decline with seizures and coma. His disease was not responsive to treatment, even though salvage therapy was tried. Three weeks after he was admitted to the intensive care unit, he died. Autopsy confirmed the widespread intravascular lymphoma that had widely infiltrated the lungs, kidney, brain, and liver. **Table 1** summarizes the timeline of the patient's clinical course.

The current case illustrates how IVLBCL can be intricate, challenging to diagnose, rapidly evolving, and have a poor prognosis, particularly when the disease coexists with multiple organs and goes undiagnosed early.



1A: Low power view showing infiltration of small pulmonary vessels by atypical lymphoid cells (H&E stain X20); **1B:** High power view showing morphologic cellular details of the lymphoma cells with a high nuclear-cytoplasmic ratio, variably large nucleoli, and cytoplasmic morphologic features that ranged between those of centroblasts and immunoblasts/plasmablasts, as well as occasional anaplastic cells (H&E stain X60); **1C:** Intravascular tumor B-cells positive for CD20

Figure 1 Microscopic features of lung biopsy with Intravascular large B-cell lymphoma

Table 1 Timeline of the patient's clinical course

Time (approx.)	Event/Findings	Notes
Month –2 to 0	Onset of progressive fatigue, night sweats, and unintentional weight loss	Initially attributed to aging
Presentation (Month 0)	High-grade fever (not responsive to antibiotics), exertional dyspnea, mild cognitive impairment, diffuse mottled rash (livedo reticularis), splenomegaly	Clinical exam + systemic symptoms
Initial labs	Pancytopenia, ↑LDH, ↑CRP, normal peripheral blood smear	Suggestive of systemic inflammatory/hematologic process
Initial imaging (CT chest/abdomen/pelvis)	No lymphadenopathy or masses; diffuse bronchial wall thickening; small pleural effusion	Consistent with IVLBCL (lack of nodal disease)
Brain MRI	Multiple small, non-enhancing white matter hyperintensities (microvascular infarcts)	Explained cognitive impairment
Bone marrow biopsy	Hypocellularity with atypical large lymphocytes in sinusoids; IHC CD20+, CD79a+, PAX5+, BCL2+, MUM1+, aberrant CD5+; CD10–, CD3–, BCL6–, Cyclin D1–, CD30–	Diagnostic hallmark of IVLBCL
Skin biopsies	Occlusion of dermal vessels by large atypical B-cells with a high N:C ratio, centroblast/immunoblast morphology	Confirmed intravascular lymphoma
Diagnosis	Intravascular large B-cell lymphoma (IVLBCL)	Multiorgan involvement, no palpable masses
Treatment – Cycle 1	R-CHOP chemoimmunotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)	Fever resolved; fatigue and cognition improved

Treatment – Cycle 2	R-CHOP continued	Patient worsened within weeks
ICU course	Developed ARDS → intubation/ventilation; lung biopsy confirmed diffuse alveolar destruction with intravascular lymphoma cells.	Aggressive supportive care was attempted.
Additional therapy	Plasmapheresis (for hyperviscosity syndrome), high-dose steroids; salvage therapy attempted.	No improvement
Outcome (Week 3 in ICU)	Multiorgan failure (respiratory, renal, neurologic with seizures/coma) → death	Autopsy confirmed widespread IVLBCL (lungs, kidney, brain, liver)

3. Discussion

3.1. History and etiology

The entity was originally described in the medical literature in 1959 by Pleger and Tappeiner. [4] Initially, because the malignant cells exhibited a unique angiotropic appearance, it was assumed that they were a proliferation of endothelial origin and were considered malignant angioendotheliomatosis. [4] [5] This knowledge continued into several decades. The lymphomatous nature of these cells was not definitively proven until the late 1980s, when immunohistochemistry was developed. Later research established their B-cell lineage and it was later renamed as angiotrophic large-cell lymphoma, and was later officially recognized by the World Health Organization as intravascular large B-cell lymphoma. [7] This acknowledgement established it as a unique hematolymphoid malignancy, differentiating it from the extremely rare T-cell and NK-cell intravascular variants. [7]

3.2. Epidemiology and risk factors

IVLBCL is a very rare malignancy, with an estimated prevalence rate of the disease of less than 1 in 1,000,000 per year. [1] One population-based study in the United States found the age-adjusted incidence rate (it was estimated at approximately 0.095 per 1,000,000 people). [1] In the classical form, the central tendency of disease occurrence is around 70 years of age, and neither sex is more prone to the disease. [8]

Interestingly, the clinical presentation has been cited to exhibit a range of geographical distinctions. The most prevalent type, known as the classical or Western type, is the most common in Europe and the Americas, and typically involves the occurrence of neurological and cutaneous symptoms. [9] In contrast, the more prevalent type is the so-called Asian one, which is associated with a hemophagocytic syndrome, fever, cytopenia, and hepatosplenomegaly. [9] Another cutaneous variant is usually experienced by younger individuals, almost exclusively by women, and has a significantly better prognosis. [10] There has been increased overlap in these presentations across different regions due to globalization and increased mobility. Even now, it is still not possible to find a risk factor, or a combination of etiologic agents, that is always observed in the pathogenesis of IVLBCL. [11]

3.3. WHO classification

In the current 5th edition of the 2022 World Health Organization (WHO) system of classification of hematolymphoid tumors, IVLBCL is a distinct form of DLBCL. [7] [8] This classification highlights the fact that the malignant cell is a mature B-lymphocyte and is aggressive in clinical manifestation, just as other forms of DLBCL. The fact that makes IVLBCL stand out in this classification is that the growth of the neoplastic B-cells occurs in a unique pattern when confined to the lumina of small and medium-sized blood vessels, but with no large extravascular tumor masses. [12]

The identification of IVLBCL as a distinct type of entity within the range of DLBCL is crucial for diagnosis and management. The WHO classification has confirmed the significance of IHC markers, including CD20 positivity, in establishing the B-cell lineage of intravascular lymphocytes. [7] Although the 4th edition of the WHO classification (revised in 2017) established its position, subsequent editions, i.e., the 5th edition, continue to improve the understanding and diagnostic criteria of large B-cell lymphomas, including IVLBCL, incorporating some molecular knowledge that further defines the subtypes and aids in their prognosis. [7] Such accurate categorization helps distinguish between IVLBCL and other lymphomas, as well as those that are reactive, leading clinicians to the right intervention at the right time.

3.4. Pathogenesis and pathophysiology

The distinctive and characteristic feature of the Intravascular IVLBCL is a selective proliferation of the malignant B-cells only in the lumina of the small- and medium-size blood vessels. [11] The pathophysiological mechanisms underlying this unusual angiotropic bidirectional behavior remain incompletely understood; however, the existing literature suggests a complex interaction of dysregulated adhesion molecules and chemokine receptors with the vascular microenvironment. [9] [12]

Another hypothesis that has been widely accepted regarding the intravascular confinement of IVLBCL cells is that it involves the abnormal expression of cell adhesion molecules. Extravasation of normal lymphocytes through a highly controlled mechanism of migration out of blood vessels into tissues occurs, involving other adhesion molecules, including integrins (e.g., β1 integrin, CD29) and selectins, which interact with endothelial cells. In IVLBCL, it has consistently been demonstrated that the major adhesion molecules, especially CD29 (β1 integrin subunit) and CD54 (ICAM-1), are not expressed or are minimally expressed on the surface of the lymphoma cells. [10] [14] It is believed that this lack of adhesion molecules is the reason the malignant B-cells are unable to adhere to the vascular endothelium and then move into the extravascular tissue. As a result, such cells cannot leave the vascular lumen and instead continue to circulate and grow within the blood vessels, rather than forming solid tumors in the organs. [13]

Moreover, the pathogenesis of the disorder, with the deregulation of chemokine receptors, is also of considerable importance. The chemokines and their receptors play a vital role in determining lymphocyte trafficking and homing to specific tissues. It has been hypothesized that IVLBCL cells exhibit distorted homeostatic chemokine receptor expression, which also contributes to their failure to survive the extravasation process and localize in lymphoid organs or other tissues. [13] Preferential intravascular proliferation of these cells may also be due to the specific microenvironment that the vessels provide, which may provide growth factors or survival cues. [10]

The pathophysiologic effects of this intravascular proliferation are varied and account for the protean clinical presentation of IVLBCL. [12] The buildup of large lymphoma cells in the capillaries and small vessels causes mechanical blockages and loss of blood flow, resulting in ischemic damage to various organs. This may take the form of neurological impairment (because of cerebral ischemia), skin disorders (because of the blockage of dermal vessels), impaired renal functioning, and multiorgan dysfunction. [10] The common occurrence of hemophagocytic syndrome in the Asian form is believed to be the result of a systemic inflammatory reaction caused by the lymphoma cells, leading to unchecked macrophage activation and subsequently causing cytopenias and organ destruction. [11] Because of the lack of palpable tumor or prominent lymphadenopathy, in addition to nonspecific manifestations of microvascular obstruction, IVLBCL is a problem in diagnosis, which results in late diagnosis and a poor prognosis. [12]

3.5. Comparative analysis of our case with the existing literature

3.5.1. Clinical presentation

IVLBCL is known to be extremely challenging to diagnose, as its clinical manifestations are nonspecific and diverse, and the disease can resemble other systemic conditions. Fever of unknown origin, night sweats, and weight loss are also common constitutional symptoms as per our patient's initial complaint [2]. It is characterized by neurological involvement, which may be cognitive impairment, manifestation of confusion, or focal disability, which is common in many patients (63-90%). [13] [14] This is further supported by the fact that microvascular infarcts can be observed in our patient on MRI, which is the manifestation of the pathophysiology of intravascular cellular occlusion. [15] IVLBCL well-documented cutaneous manifestations (i.e., livedo reticularis, erythematous plaques, nodules) were also a major finding in our case. [11] The mottled, diffuse rash in our patient is a typical dermatological indicator associated with microvascular damage. Although not a universal characteristic of systemic lymphoma, **s**plenomegaly may also be **noted in** IVLBCL**, as was the case in our patient** [2]

The lack of major lymphadenopathy or large tumor masses, which is observed in our patient, is a characteristic of IVLBCL and adds to delays in diagnosis. [5] The insidious progression and gradual course of the symptoms that were initially attributed to old age also add weight to the diagnostic dilemma caused by this rare lymphoma. [8] Thus, our case is a typical example of the clinical manifestation of IVLBCL, which has nonspecific symptoms and involves the work of many organs without specific tumor masses.

3.5.2. Imaging studies

In our case, the initial imaging studies were not homogeneous, which is also typical of IVLBCL. The CT scanning of the chest, abdomen, and pelvis was mostly unremarkable, especially without any lymphadenopathy or any mass lesions. Such a lack of macroscopic tumor burden is a characteristic feature of IVLBCL, as the malignant cells often grow in the

vascular lumen rather than forming solid masses. [15] Nevertheless, small indicators, such as diffuse thickening of bronchial walls and a small pleural effusion, were observed, which suggest involvement of the lungs at the microvascular level.

The brain MRI results were more revealing, indicating several small, white matter hyperintensities that are signs of microvascular infarcts. This result is highly congruent with the established pathophysiology of IVLBCL, in which intravascular lymphoma cells cause microvascular occlusion and ischemic injury, particularly in the central nervous system (CNS). [4]

Traditional imaging modalities, such as CT and MRI, which are likely to yield nonspecific or even normal findings in IVLBCL, particularly at an early stage, may also contribute to delays in diagnosis. [15] Nevertheless, in cases where an organ system is involved, imaging can provide indications. For example, when CNS is involved, MRI can demonstrate diffuse white matter changes, infarcts, or leptomeningeal enhancement, as seen in our patient. [4] Conversely, FDG PET/CT has become a more sensitive method for identifying disease activity in IVLBCL, frequently showing hypermetabolic lesions in the affected organs, even in the absence of macroscopic masses, and may be essential for guiding biopsies. [17] [18] The diagnosis of IVLBCL in our case, with its subtle CT and more reliable MRI images of microvascular infarcts, highlights the necessity of raising the suspicion of IVLBCL in those patients with unexplained dysfunction of multiple organs and nonspecific imaging, especially when neurological symptoms are involved.

Investigations: The diagnostic experience of our patient, the first nonspecific diagnosis, and the subsequent need for biopsy reflect the problems that may often be encountered in the diagnosis of IVLBCL. The laboratory findings in our case revealed pancytopenia, elevated lactate dehydrogenase (LDH), and increased C-reactive protein (CRP), along with a normal peripheral blood smear. These results are significantly in line with the systemic inflammatory reaction and involvement of bone marrow that is commonly observed in IVLBCL. [2] High LDH is a universal indicator of tumor load and tissue turnover in aggressive lymphomas, and cytopenias are very frequent because of bone marrow infiltration or because of hemophagocytic syndrome, especially in the Asian form. [19] It is also typical that peripheral blood does not show circulating lymphoma cells, making the initial diagnosis even more challenging.

The histological analysis of the affected tissues is almost always the only method for the definitive diagnosis of IVLBCL, which frequently requires multiple biopsies due to the patchy and intravascular character of the disease. [20] The bone marrow biopsy, which was performed in our case to establish the cause of pancytopenia, was important. It showed hypocellularity with masses of atypical and large lymphocytes between the sinusoids. This observation, along with the IHC results demonstrating the presence of B-cell markers (CD20), was a strong indication. Moreover, different skin biopsies were procured, and these were very diagnostic

The literature has firmly established the usefulness of random skin biopsies (RSB) in the diagnosis of IVLBCL, particularly in instances where nonspecific symptoms or fever of unknown origin are presented, and has reported sensitivities of up to 65.2%. [3] [21] The diagnostic value of skin biopsies is underscored by the fact that it was successful in our case, showing the typical intravascular proliferation. Bone marrow biopsies are usually positive, especially in patients with cytopenia. The association between clinical suspicion, nonspecific laboratory test abnormalities, and directed biopsies with detailed IHC studies, as shown in our patient, is key to attaining a timely diagnosis of IVLBCL.

3.5.3. Management and outcome

Our patient was promptly started on the standard high-intensity treatment of chemoimmunotherapy based on R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Rituximab is a CD20 monoclonal antibody, which plays a central role in the treatment of IVLBCL. [4] The patient experienced a positive response to the first course, and the fever, fatigue, and cognitive dysfunction subsided. Nevertheless, following this success of the initial response, the disease gained momentum in a few weeks after the second cycle. It resulted in acute respiratory distress syndrome (ARDS), multiorgan failure, and the eventual death despite the aggressive supportive care and attempted salvage therapy.

Unfortunately, this clinical course indicates the aggressive character of IVLBCL and difficulties in its treatment, especially in the context of the advanced or recurrent cases. The R-CHOP regimen is commonly regarded as the most widely used first-line therapy for IVLBCL, as it has proven effective in other aggressive B-cell lymphomas. [22] [23] Incorporation of rituximab with standard R-CHOP chemotherapy treatment has increased the outcome in patients with IVLBCL, with studies showing that complete remission is achieved by those who go through the course of treatment. [8] [24] Nevertheless, despite all these developments, the survival of IVLBCL is still cautious, particularly when invasion involves multiple organs or the central nervous system (CNS). [24]

Our patient deteriorated quickly and was unresponsive to treatment. The fact that he initially improved, brings up several important points about the treatment of IVLBCL. To start with, in the case of aggressive recurrent IVLBCL, especially for central nervous system prophylaxis, a combination of R-CHOP and high-dose methotrexate (HDMTX) is a better treatment option than R-CHOP alone. [4] [25] The resulting development of ARDS and pervasive organ infiltration, which was confirmed by autopsy, highlights the virulent and spread-out nature of the illness in our patient. Relapses or refractory therapy of IVLBCL cancer can be difficult to achieve salvage, and although new agents and methods are undergoing research, many patients still do not do well. [26] Our case highlights the importance of early diagnosis, initial intensive treatment, and attention to CNS prophylaxis, as well as close observation of the disease progression, particularly when patients present with dysfunction of multiple organs.

3.6. What have we learned from this case?

This is a significant case of IVLBCL, with several crucial learning outcomes for the medical community. Firstly, it highlights the real diagnostic difficulty of IVLBCL. This chameleon lymphoma can easily be confused with nonspecific constitutional symptoms, neurological impairment, and cutaneous appearance, and may even be associated with aging. The lack of any clear tumor masses or lymphadenopathy on standard imaging makes the issue of early detection even more complicated, resulting in considerable delays in diagnoses.

Second, the case highlights the importance of specific biopsies, particularly random skin biopsies and bone marrow biopsies, combined with investigative analysis using IHC tools, in making a conclusive diagnosis. Malignant B-cells' intravascular proliferation, even in tissues that appear not to be involved, is the diagnostic hallmark. Third, although there was an initial response to conventional R-CHOP chemoimmunotherapy, the rapid and aggressive deterioration of multiple organ failure and death underscored the virulent nature of IVLBCL, particularly when diagnosed late or with widespread systemic spread. It supports the clinical suspicion index and timely, adequate investigation, suggesting that possibly more aggressive or CNS-oriented treatment, such as the combination with high-dose methotrexate, may be used to enhance patient outcomes in this uncommon and devastating lymphoma.

Abbreviations

- Intravascular large B-cell lymphoma (IVLBCL);
- Diffuse large B-cell lymphoma (DLBCL);
- Immunohistochemistry (IHC)

4. Conclusion

This case report of IVLBCL serves as an essential reminder of this uncommon and malignant hematological malignancy, which is rarely encountered. This case is reported to demonstrate why IVLBCL is a rather complex diagnosis, with its protean clinical forms, frequent imitation of other systemic disorders, and lack of typical tumor masses. With the description of the insidious onset of the patient, the diagnostic process with specific biopsies and IHC, and the ultimately aggressive clinical outcome, even with treatment, we expect to contribute to the clinical awareness of practitioners. The current report highlights the importance of a high level of suspicion of IVLBCL among patients with unexplained dysfunction in several body organs, neurological, or cutaneous lesions, especially in older patients. The most important part in improving outcomes for this challenging disease is early awareness and the immediate provision of suitable chemoimmunotherapy, which may include CNS prophylaxis.

Compliance with ethical standards

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Disclosure of conflict of interest

All authors make the following declarations:

- Payment/services information: All authors have declared that they received no financial support from any organization for the submitted work.
- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of ethical approval

Ethical review and approval were not required for this study involving human participants. The paper has been sufficiently anonymized to maintain the patient's confidentiality.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

Statement of informed consent

The patient expired, and all attempts to reach the family members were unsuccessful. Therefore, the paper has been sufficiently anonymized to maintain patient confidentiality.

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