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Unmet needs of patients with intravascular large B-cell lymphoma: three case reports and a literature review

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Intravascular large B-cell lymphoma (IVLBCL), a rare subtype of non-Hodgkin lymphoma, is classified as an independent subtype of extranodal diffuse large B-cell lymphoma (DLBCL) in the 2008 World Health Organization (WHO) Classification (Turner et al., 2010). The 5th edition of the World Health Organization (WHO 2022) classification of hematolymphoid tumors retains this subtype (Alaggio et al., 2022). IVLBCL, which is characterized by neoplastic lymphocyte proliferation within the lumen of small blood vessels, tends to invade organs, such as the nervous system, skin, bone marrow (BM), and lung (D'Angelo et al., 2019; Satoh et al., 2019; Vásquez et al., 2019; Fukami et al., 2020).

Given the low incidence and diverse clinical presentations of IVLBCL, diagnosis and treatment of this disease are often overlooked, and IVLBCL patients have an inferior prognosis with a median overall survival (OS) time of less than one year (Chen et al., 2021). It is crucial for hematologists to understand the clinical presentations and pathological characteristics of IVLBCL. IVLBCL treatment strategy is mainly based on that used for DLBCL. The clinical outcomes of IVLBCL are highly diverse, although the addition of rituximab to chemotherapy has significantly improved the survival rate of these patients (Ferreri et al., 2008). Clinical issues related to central nervous system (CNS) prophylaxis and treatment remain unsolved, especially in patients with CNS involvement, whose prognosis is worse (Liu et al., 2020). For high-risk IVLBCL, the specific cytogenetic and molecular abnormalities, such as the high frequency of myeloid differentiation primary response 88 (*MYD88*) and cluster of differentiation 79B (*CD79B*) mutations and the disruption of programmed cell death ligand 1 (PD-L1), might be required to develop novel treatment strategies to improve the prognosis for this disease (Gupta et al., 2019; Shimada et al., 2021).

Further studies are warranted, given the variable clinical presentations and poor prognoses of IVLBCL patients. We hope that our findings will provide a reference for hematologists to improve the early diagnosis and appropriate management of IVLBCL.

Here, we retrospectively reviewed three Chinese patients newly diagnosed with IVLBCL between June 2021 and June 2023. The diagnosis of IVLBCL was confirmed according to the 2008 WHO classification by pathologists who had experience with hematopoietic malignancies (Turner et al., 2010). The data were collected via an electronic case report form.

The first patient was a 77-year-old man who was admitted to our hospital in June 2021, due to a 4-month history of dysuria. The patient underwent transurethral plasmakinetic resection of the prostate. Prostate pathology revealed the presence of atypical round cells in the small interstitial vessels, which was suspected to indicate DLBCL. After prostate surgery, the patient was noted to have cytopenia and an increased level of β_2-microglobulin (β_2-MG). Positron emission

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tomography/computed tomography (PET/CT) revealed no abnormal metabolic lesion in the operation area; however, glucose metabolism in the BM increased diffusely. A BM biopsy was performed, revealing abnormal large B cells infiltrating the myeloid tissue. The immunohistochemical results confirmed the diagnosis of IVLBCL (Fig. 1). The patient initially underwent systemic chemotherapy with R-CHOP-21 (rituximab, cyclophosphamide, doxorubicin, vinorelbine, and prednisone). Owing to the high risk of CNS involvement, Bruton tyrosine kinase inhibitor (BTKi) and high-dose methotrexate (MTX) were also integrated into the treatment strategy. After six cycles of immunochemotherapy, patient 1 experienced an improvement in cytopenia and a reduction in β_2-MG to normal level. BM re-examination revealed the disappearance of lymphoma cells, indicating complete remission (CR). Owing to poor performance status, autologous stem-cell transplantation (ASCT) was not suggested as a treatment. Instead, continuous administration of oral BTKi was recommended for post-remission consolidation, and the patient was still in CR 24 months after induction chemotherapy.

The second patient was a 66-year-old woman who presented to our hospital in December 2022 with a 5-month history of progressive neurological symptoms, including dizziness and recurrent falls. Blood tests revealed elevated lactate dehydrogenase (LDH) with a normal complete blood count, electrolytes, and β_2-MG. BM biopsy revealed normocellular marrow and PET revealed multiple lesions in the right cerebellar hemisphere, bilateral lateral ventricles, and semioval regions with increased glucose metabolism. Moreover, abnormal enlargement and increased glucose metabolism were detected in multiple lymph nodes located in right cervical region IV and the periportal zone. Magnetic resonance imaging (MRI) of the head was performed, revealing multifocal white matter lesions in the right cerebellar hemisphere, bilateral lateral ventricles, and semioval regions. CT-guided stereotactic biopsy of cerebral white matter lesions revealed the presence of large B-cell collections within the lumina of blood vessels, confirming the diagnosis of IVLBCL. The patient underwent six courses of R-CHOP-MTX-BTKi; however, the central lesion progressively enlarged. Follow-up was conducted for seven months until the patient succumbed to disease progression.

The third patient was a 59-year-old man with a previous history of essential hypertension and outmoded cerebral infarction, who presented to the local hospital with episodic syncope in September 2022. The patient denied fever, nausea, vomiting, or hyperspasmia. CT of the head revealed no cause. The patient

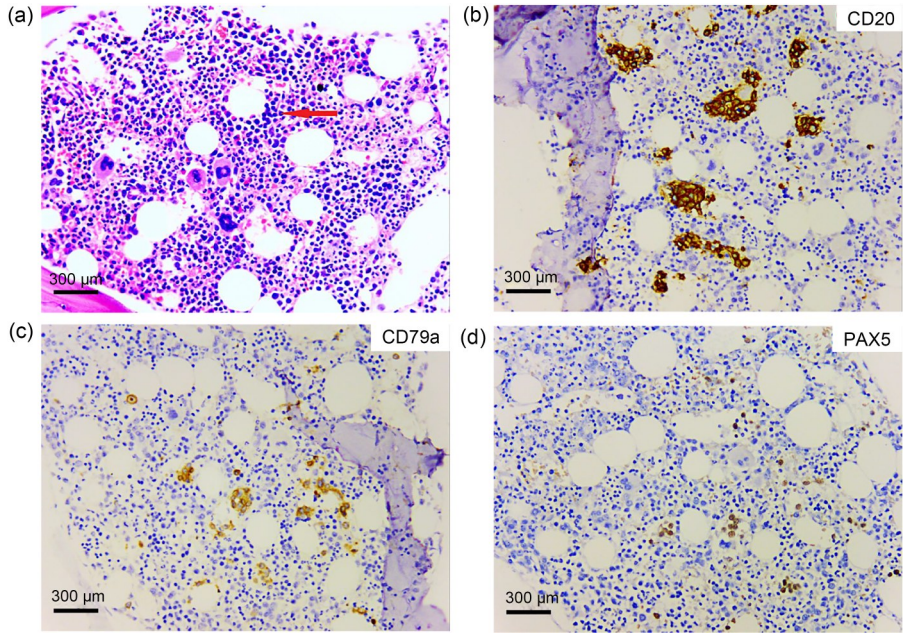

Fig. 1 Bone marrow histopathological images of case 1 by hematoxylin and eosin (H&E) staining. (a) In bone marrow biopsy, the atypical lymphocytes were focally arranged (red arrow). (b–d) The lymphoid cells were strongly positive for CD20 (b) and weakly positive for cluster of differentiation 79a (CD79a) (c) and paired box protein 5 (PAX5) (d).

was considered to have epilepsy after cerebral infarction and received antiepileptic treatment. Although there was no recurrence of epilepsy, the patient experienced progressive numbness of the lower limbs and was then transferred to our hospital for further evaluation. PET revealed slight low-density lesions in the left occipital lobe with abnormal glucose metabolism. MRI revealed lesions in the posterior horn of the left occipital lobe of the lateral ventricle. This presentation was investigated with lesion stereotactic biopsy, revealing findings suspicious of glioma. During this period, the patient gradually developed fever, splenomegaly, progressive confusion, and memory loss, leading to complete dependence on others for activities of daily living. Blood tests revealed pancytopenia and increased LDH, ferritin, and soluble CD25 levels. BM biopsy revealed hemophagocytosis without lymphoma infiltration. A repeat brain stereotactic biopsy was completed, and the diagnosis of IVLBCL (Figs. 2 and 3) was determined in April 2023. After a 7-month diagnostic period, R-CHOP-MTX-BTKi therapy was initiated. The patient did not achieve remission after three courses of systemic chemotherapy and demonstrated recurrent fever, cytopenia, and coma. MRI of the brain also revealed no improvement in the central lesion. Follow-up was conducted for 3.5 months until patient died from subdural hemorrhage after falling out of bed due to inadequate home care.

The major clinical manifestations of the three patients with IVLBCL are summarized in Table 1. The patients were between 59 and 77 years old at diagnosis, with a male-to-female ratio of 2∶1. The involved sites included the BM, CNS, lymph nodes, and prostate. Laboratory examination results indicated the presence of cytopenia, hypoalbuminemia, and elevated levels of serum LDH, ferritin, β_2-MG, and C-reactive protein (CRP) in two of the three patients. Notably, patient 3 presented with hemophagocytic syndrome according to the clinical manifestations and serological results. BM biopsies were performed, revealing lymphoma infiltration in one of the patients. In addition, patient 3 exhibited hemophagocytosis without any indication of lymphoma infiltration in the BM. All patients underwent lumbar puncture, and the results revealed an increase in protein content and nucleated cell levels in cerebrospinal fluid (CSF) in two of the three patients, which indicated CNS involvement. All three patients initially underwent systemic chemotherapy with R-CHOP-MTX-BTKi. Patient 1 improved and was still in CR 24 months after induction chemotherapy. In contrast, the other two patients (patients 2 and 3) experienced disease progression or complications within a limited follow-up period ranging from 3.5 to 7.0 months.

No significant skin lesions, including plaques, nodules, or telangiectasias, were observed in any of the

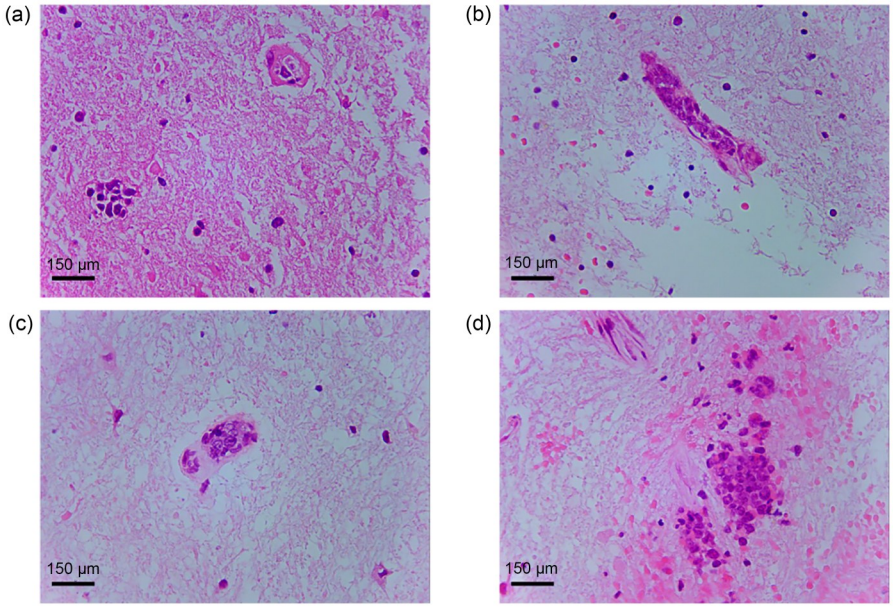

Fig. 2 Hematoxylin and eosin (H&E) staining of the occipital-lobe lesion in case 3. (a–c) The tumor cells were filled with small veins. (d) The lymphoid cells were large, with prominent nucleoli.

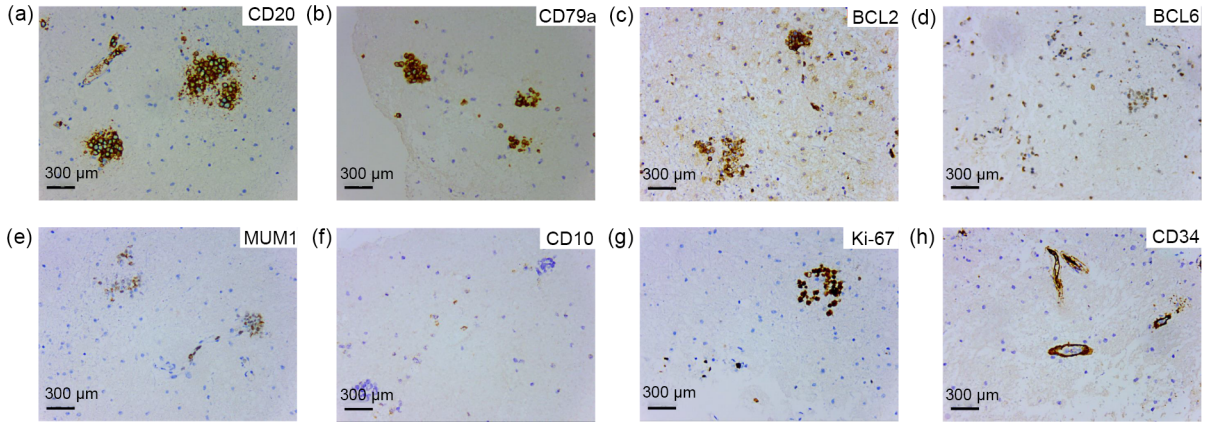

Fig. 3 Immunohistochemistry of the occipital-lobe lesion in case 3. (a–f) The lymphoid cells were strongly positive for cluster of differentiation 20 (CD20), CD79a, and B-cell lymphoma 2 (BCL2), weakly positive for BCL6 and multiple myeloma oncogene 1 (MUM1), and negative for CD10. (g) The Ki-67 proliferative index was high. (h) Neoplastic cells were confined in the blood vessels depicted by CD34 immunostaining.

Table 1 Summary of clinical manifestations of the three cases of IVLBCL

Characteristics	Case 1	Case 2	Case 3	Standard value
Sex/age (years)	M/77	F/66	M/59	
Biopsy site	Prostate, BM	CNS	CNS	
Involved site	Prostate, BM	CNS, lymph nodes	CNS	
Haemoglobin (g/L)	92	134	102	131–172
White cell count ($\times10^9$ L^{-1})	7.2	5.3	3.2	1.0–4.0
Platelets ($\times10^9$ L^{-1})	76	162	76	100–300
Lactate dehydrogenase (U/L)	223	277	669	120–250
β_2-Microglobulin (mg/L)	5.1	2.2	3.0	1.0–3.0
C-reactive protein (mg/L)	92.1	0.5	135.1	<10.0
Albumin (g/L)	25.9	43.8	28.6	35.0–52.0
Ferritin (ng/mL)	818.5	101.2	2244.0	23.9–336.2
PET imaging	BM	CNS, lymph nodes	CNS	
CSF nucleated cells (μL^{-1})	Normal	23	12	<8
CSF protein content (mg/dL)	Normal	69	390	8–43
BM biopsy	+	−	−	
Hemophagocytic lymphohistiocytosis	−	−	+	
sCD25 (IU/mL)			5981	<2400
Other			Splenomegaly	
Symptom-to-diagnosis interval (months)	4	5	7	
Treatment	R-CHOP-MTX-BTKi	R-CHOP-MTX-BTKi	R-CHOP-MTX-BTKi	
Response*	CR	PD	SD	
Follow-up (months)	24.0	7.0	3.5	
Outcome	Alive	Died	Died	

IVLBCL: intravascular large B-cell lymphoma; M: male; F: female; BM: bone marrow; CNS: central nervous system; PET: positron emission tomography; CSF: cerebrospinal fluid; sCD25: soluble cluster of differentiation 25 (CD25); R-CHOP-MTX-BTKi: rituximab 375 mg/m^2 intravenously on Day 0, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, and vincristine 1.4 mg/m^2 (maximum 2.0 mg) intravenously on Day 1, prednisolone 90 mg/d orally on Days 1–5, methotrexate 3.5 g/m^2 intravenously on Day 2, and Bruton tyrosine kinase inhibitor (orelabrutinib) 150 mg/d orally. * Efficacy criteria: Complete remission (CR): all clinical symptoms and abnormal laboratory indicators returned to normal, with no new manifestations; Progressive disease (PD): new abnormalities related to the disease appeared, or initial abnormalities related to the disease significantly worsened; Stable disease (SD): neither CR nor disease progression was achieved (Lymphoid Disease Group et al., 2023).

three patients. The patients were diagnosed via organ biopsy, which revealed involvement of the prostate gland (patient 1), BM (patient 1), and CNS (patients 2 and 3). Notably, two of the three patients requested a second biopsy to confirm the diagnosis. The clinicopathological and immunohistochemical characteristics of the three patients are summarized in Table 2. Pathology revealed large B lymphocyte proliferation within the lumen of small blood vessels, with tumor cells adhering to the vascular wall; however, the structure of the vascular wall remained intact. The tumor cells were positive for B-cell markers (CD20, CD79a, and paired box protein 5 (PAX5)), B-cell lymphoma 2 (BCL2) (one of three), and BCL6 (one of three). The Ki-67 proliferative index was generally high, ranging from 80% to 90% (Fig. 3). All patients in the study underwent cytogenetic analysis, and none had a specific chromosomal translocation. Only two patients had second-generation sequencing data available, with *MYD88 L265P* and *CD79b Y196* double mutations in patient 1 and notch homolog protein 1 (*NOTCH1*) (p.P2415del) and proviral integration site for Moloney murine leukemia virus 1 (*PIM1*) (p.P81S) mutations in patient 3. In addition, patient 3 was negative for PD-L1 expression (Fig. 4).

Table 2 Immunohistochemistry of the three cases with intravascular large B-cell lymphoma (IVLBCL)

Marker	Case 1	Case 2	Case 3
CD20	++	++	+++
PAX5	+	++	++
CD79a	+	+	+++
P53		Wild-type pattern	Wild-type pattern
MUM1			+
BCL2			++
BCL6			+
CD3	−	−	−
CD5		−	
CD10	−		−
Ki-67	90%	80%	90%

Immunohistochemistry samples were viewed at high magnification (×400), and ten fields of each sample were visualized for semiquantitative analysis. The total staining score was based on a system previously described by Fromowitz et al. (1987). Each field was scored as "0" (no staining), "1" (light yellow staining), "2" (light brown staining), or "3" (dark brown staining). The overall percentage of positive staining per field was scored as "0" (≤5% staining), "1" (6%–25% staining), "2" (26%–50% staining), "3" (51%–75% staining), or "4" (>75% staining). The final score was simply the sum of these two individual scores, and was "–" (0–1 points), "+" (2–3 points), "++" (4–5 points), or "+++" (6–7 points).

IVLBCL is a rare subgroup of large B-cell lymphoma with an annual incidence rate of no more than 0.5/100 000 (Ponzoni et al., 2018). According to retrospective research, IVLBCL can be classified into three clinical subtypes: classic, hemophagocytic, and cutaneous. Previously, it was thought that clinical subtypes were related to race. The hemophagocytic subtype, common in Asian individuals, is characterized by frequent BM involvement, fever, anemia, and hepatosplenomegaly, resulting in the worst prognosis. The classic subtype shows a propensity for nonspecific symptoms and CNS involvement, and the cutaneous subtype manifests with simple skin lesions and a better prognosis. The latter two subtypes are more common in Caucasian patients (Qiu et al., 2022). However, it is now recognized that the geographical affiliations among different clinical subtypes are not deterministic, and IVLBCL patients from different

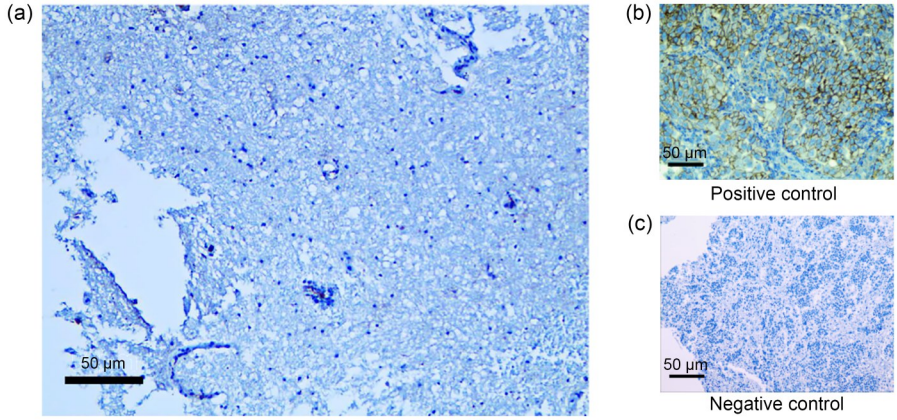

Fig. 4 Immunohistochemistry of programmed cell death ligand 1 (PD-L1) in case 3. (a) When assayed with 22C3 antibody, the expression of PD-L1 in tumor cells was found to be negative. (b) Positive control for PD-L1 staining. (c) Negative control for PD-L1 staining.

geographic origins share comparable clinical characteristics (Ponzoni et al., 2007).

The variable clinical presentation and low incidence rate of IVLBCL make this disease very difficult to diagnose. This situation implies that in addition to clinical manifestations, understanding of histopathological features is crucial for early clinical recognition of IVLBCL (Ponzoni et al., 2018). Histopathology is the key to definitive diagnosis and is necessary for confirming the diagnosis in cases of suspicious clinical manifestations. A review of the relevant pathological literature on IVLBCL revealed that large B-cell lymphoma cells are diffusely distributed or clustered within the lumens of small blood vessels, whereas the vascular structure remains intact. In some cases, fibrinous thrombi, bleeding, and necrosis can be observed in the vascular lumen. Immunohistochemistry has shown that IVLBCL cells express a diverse range of B-cell markers, such as CD20, PAX5, CD19, CD22, CD79a, organic cation transporter 2 (OTC2), and B-cell Oct-binding protein 1 (BOB1), which may partially overlap with those of DLBCL. The percentage range of patients with IVLBCL who express CD5 is 22%–38% (Murase et al., 2000; Yegappan et al., 2001; Brunet et al., 2017); in contrast, CD5 is detected in only 5% of DLBCL patients (Xu-Monette et al., 2015). Most IVLBCL patients (75%–80%) express multiple myeloma oncogene 1 (MUM1)/interferon regulatory factor 4 (IRF4), an immunophenotype of nongerminal center B-cell lymphoma (non-GCB) according to Han's classification, but CD10 is expressed in only 13%–22% of patients (Yegappan et al., 2001; Murase et al., 2007). The Ki-67 proliferation index is generally high, with approximately 81% of patients having Ki-67 of ⩾60%. In some cases, tumor cells express PD-L1 (Gupta et al., 2019), and research results suggest that PD-L1 may be related to immune evasion in IVLBCL (Sakakibara et al., 2018). Furthermore, CD34 and CD31, which are markers of endothelial cells, can be used to confirm that tumor cells are located within blood vessels (Davis et al., 2022). Numerous cases of IVLBCL have been reported to be masked by background inflammation and misdiagnosed as primary epithelial or interstitial tumors (Muftah et al., 2012; Zhang et al., 2015; Yuan et al., 2022). The key to identifying IVLBCLs with background inflammation lies in pattern recognition and comparison with lymphovascular space invasion under low-power microscopy. Malignant lymphocytes are confined to vessel lumens in IVLBCL, with a dense cell arrangement and occasionally a discohesive intravascular nature. Immunohistochemistry can be used for further analysis when a characteristic pattern is recognized. However, in some cases, IVLBCL may only be represented in local tissue sections, thus limiting the performance of immunohistochemistry (Davis et al., 2022). Given these diagnostic findings, further research is warranted to improve the early detection of this rare lymphoma.

Molecular biology and cytogenetics evaluations are also required for the diagnosis of IVLBCL. IVLBCL has no specific cytogenetic abnormalities due to the heterogeneity of the disease, complex karyotype patterns, and small sample size (Matsue et al., 2019). However, somatic hypermutation is commonly observed in clonally rearranged immunoglobulin heavy chains, with a preference for the variable region of heavy chain 3 (*VH3*) family (Kanda et al., 2001). Next-generation sequencing analysis has indicated that IVLBCLs exhibit genetic lesions characteristic of activated B-cell (ABC)-type DLBCL with nuclear factor-κB (NF-κB) pathway overactivation (Gonzalez-Farre et al., 2023). The rearrangement of BCL2 also confirms the origin of non-GCB. Some studies have revealed t(14;18) translocation, a tandem triplication of BCL2 at the 18q21 region, and recurrent alterations of chromosomes 1, 6, and 18 (Vieites et al., 2005; Klairmont et al., 2018). However, a widely recognized pattern of cytogenetic abnormalities in IVLBCL has not been well defined. Compared to nodal DLBCL, IVLBCL displays a significantly high frequency of mutations in *MYD88* (57%), *CD79B* (67%), SET domain-containing 1B (*SETD1B*) (57%), and human leukocyte antigen B (*HLA-B*) (57%) (Shimada et al., 2021). Whether complex karyotypes or molecular abnormalities have prognostic implications remains unclear, and further research is needed.

Due to the rarity of the disease and the absence of prospective trials with large sample sizes, the most appropriate treatment strategy for IVLBCL has not been defined. In addition to the primary cutaneous subtype, which has a 3-year OS rate ranging from 40% to 72% (Ferreri et al., 2004b; Ponzoni et al., 2007), IVLBCL is an aggressive disease (Rajyaguru et al., 2017). Without chemotherapy, the prognosis is extremely poor, with a 1-year OS rate of 2.7% (Chen et al., 2021), particularly for those with CNS involvement or hemophagocytic syndrome (Liu et al., 2020). Even with treatment, the 3-year OS rate of IVLBCL

patients is estimated to be between 11.5% and 35.0% (Ferreri et al., 2008; Liu et al., 2020). Therefore, the primary treatment for IVLBCL is combination chemotherapy, similar to the treatment approach for DLBCL (Luo et al., 2022). Anthracycline-based chemotherapy can improve the prognosis of IVLBCL patients, and the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen is crucial for appropriate management in most cases (Ferreri et al., 2004a). The addition of rituximab to chemotherapy can further improve the survival rate of patients with IVLBCL. The CR and 3-year OS rates of IVLBCL patients who receive immunochemotherapy in Western countries are reported to be 53%–90% and 42.7%–89.0%, respectively (Ferreri et al., 2008; Brunet et al., 2017). The reported 2-year progression-free survival (PFS) and OS rates in Asian patients are 56% and 66%, respectively (Shimada et al., 2008).

Rituximab has been demonstrated to prolong survival in IVLBCL patients. Nonetheless, long-term survival remains unsatisfactory, particularly after disease recurrence, and effectively preventing relapse is a significant clinical concern. The 3-year PFS and OS rates for IVLBCL patients receiving consolidative ASCT in frontline treatment are 83% and 89%, respectively, with a 3-year cumulative incidence of relapse of 14% (Meissner et al., 2017; Kato et al., 2019). Therefore, consolidative ASCT is recommended for patients younger than 65 years of age or in good physical condition (Lymphoid Disease Group et al., 2023). Nonetheless, this approach may only be a possibility for a small proportion of IVLBCL patients, as their median age is 70 years at diagnosis (Ponzoni et al., 2018), and most patients are unable to tolerate intensive chemotherapy because of their poor performance status.

Moreover, due to the high risk of CNS involvement and poor prognosis, CNS prophylaxis and treatment represent additional clinical concerns for patients with IVLBCL (Takahashi et al., 2022). Among patients with newly diagnosed IVLBCL without CNS involvement, the risk of CNS recurrence at three years was 25%; this risk reached as high as 18% even in the R-CHOP-treated group. During the course of the disease, patients with CNS involvement at diagnosis have a further 25% risk of recurrence within the first year (Shimada et al., 2010). Therefore, inclusion of drugs with superior CNS bioavailability in CHOP should be considered (Lymphoid Disease Group et al., 2023). A multicenter, single-arm, phase II clinical trial (PRIMEUR-IVL) evaluated the efficacy and safety of the R-CHOP regimen combined with high-dose MTX and intrathecal injection in IVLBCL patients as a first-line induction therapy. The reported 2-year PFS and OS rates were 76% and 92%, respectively, and the risk of CNS recurrence at three years was 3%. The results demonstrate that this regimen can be safely and effectively used for IVLBCL preventive CNS treatment (Shimada et al., 2020). However, current treatment strategies, including immunochemotherapy, high-dose methotrexate, and intrathecal injection, have improved the prognosis of patients with CNS involvement to a limited extent (Liu et al., 2020). Furthermore, despite intensifying treatment, some patients with unfavorable clinical features still have poor prognoses; hence, new treatment strategies deserve further investigation (Ponzoni et al., 2007).

Given the high frequency of *MYD88* and *CD79B* mutations in IVLBCL (Shimada et al., 2021), the addition of BTKi to immunochemotherapy may be a potential initial treatment option. A prospective, single-arm, phase II clinical trial evaluated the efficacy of zanubrutinib (a selective BTKi) in combination with R-CHOP (ZR-CHOP) for patients with previously untreated IVLBCL in China. A total of 23 patients were enrolled, and the overall response rate was 100%. The reported CR rates in the interim and end-of-treatment evaluations were 94.7% and 92.3%, respectively. Among the 14 patients with CNS involvement, all showed significant improvement in their symptoms on MRI. After a median follow-up of 439 d (range 266–693 d), no relapses were observed (Zhang et al., 2023). These results indicate that targeted therapeutic drugs can improve the outcomes of IVLBCL treatment. Thus, further research is needed on emerging genetic findings and crucial molecular markers. In daily clinical practice, due to technical limitations or a paucity of adequate tumor samples, it is usually difficult to assess genetic and molecular characteristics, which limits precise diagnosis and targeted therapy of IVLBCL.

In our study, the median age at diagnosis in patients with IVLBCL was 66 years, with an age range of 59 to 77 years. The symptom-to-diagnosis interval ranged from four to seven months, and two of three patients underwent a second biopsy to clarify the diagnosis. Notably, prolonged periods with unrecognized and untreated IVLBCL generally lead to a decline in

performance status and the ability to tolerate appropriate chemotherapy (Geer et al., 2019). Therefore, for patients with unexplained fever, cytopenia, or skin lesions, multiple multipoint biopsies on suspicious areas should be performed as early as possible. Moreover, additional research is necessary to explore pathological diagnostic criteria for the swift detection, diagnosis, and early treatment of this condition.

In our case series, all the patients underwent cytogenetic analysis, but none had complex karyotypes or chromosomal translocations. Fluorescence in situ hybridization analysis revealed that patient 1 had *MYD88* and *CD79B* mutations. As a result of these molecular alterations, this patient showed a favorable response to BTKi-based treatment and was still alive at the time of the last follow-up. Despite receiving the R-CHOP regimen combined with MTX and BTKi, the other two patients (patients 2 and 3) experienced ineffective treatment and early mortality.

The reasons may be summarized as follows. First, both patients had CNS involvement at diagnosis. One patient also had hemophagocytic syndrome, which is associated with an adverse treatment response and poor prognosis. Also, the second-generation sequencing analysis revealed mutations in *PIM1* (p.P81S) in patient 3. Expression of *PIM1* is often associated with a poor prognosis in DLBCL patients (Mahadevan et al., 2005). Point mutations in the kinase PIM1 impact upstream regulators and downstream targets of the NF-κB signaling pathway, decreasing the sensitivity of ABC-type DLBCL to BTKis. In patient 3, the response to BTKi could have been restricted by this resistance mechanism that blocks the therapeutic target. Notably, patient 3 also exhibited *NOTCH1* mutations (the N1-like subtype) and had a significantly poor response to R-CHOP. Given that this genetic subtype is predominantly associated with the ABC subgroup of DLBCL and highly expresses the T-cell gene signature, lenalidomide and immune checkpoint inhibitors could be explored as potential treatment options (Schmitz et al., 2018; Poletto et al., 2022). As a result of poor physical condition and rapid disease progression, none of the patients underwent ASCT, making it impossible to evaluate the efficacy of this treatment. In conclusion, given the currently recommended treatment strategies, the survival time of some IVLBCL patients remains poor, and the optimal method for the management of these patients is an open question because of the rarity of this disease. Further investigation is required to identify the molecular features and factors associated with disease prognosis, thereby improving therapeutic strategies.

Despite the limitations of our study, including its retrospective nature and small sample size, our findings accurately depict the current unmet need for early diagnosis and appropriate treatment of IVLBCL patients in clinical practice. Due to the rarity of IVLBCL, global multicenter studies are warranted. Moreover, precise prognostic stratification according to molecular genetic features and clinical subtypes can lead to appropriate therapeutic approaches to further improve the prognosis of patients with IVLBCL.

Data availability statement

The dataset used or analyzed during the current study is available from the corresponding authors on reasonable request.

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Author contributions

Xian LI, Xibin XIAO, and Wenbin QIAN contributed to the design and conception of the study; Xian LI and Weiqin WANG contributed to data collection; Xian LI and Ru LUO contributed to writing the initial drafting of the manuscript; Jiaming XU and Xueli JIN reviewed and edited the original draft. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Xian LI, Ru LUO, Jiaming XU, Xueli JIN, Weiqin WANG, Xibin XIAO, and Wenbin QIAN declare that they have no conflicts of interest.

The Medical Ethics Committee of The Second Affiliated Hospital, School of Medicine, Zhejiang University reviewed and approved the studies involving human participants (No. I2023042). The corresponding local ethics committee of each participating institution approved this study when applicable. All patients provided written informed consent before enrollment. All procedures in studies involving human participants were performed by the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

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