Comparison of serum sIL-2R and LDH levels in patients with intravascular large B-cell lymphoma and patients with advanced stage diffuse large B-cell lymphoma

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Running title

sIL-2R and LDH levels in IVL and DLBCL

Abstract

Intravascular large B-cell lymphoma (IVL) is a rare type of lymphoma characterized by tumor growth selectively within the vessels. The 5th edition of the World Health Organization classification defines IVL as a large B-cell lymphoma, the same as diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS). Since the clinical manifestations of IVL are nonspecific, the diagnosis is time-consuming, and the course is often fatal.

Serum soluble interleukin-2 receptor (sIL-2R) and serum lactate dehydrogenase (LDH) levels are known to be elevated in a variety of lymphomas. However, the mechanism of sIL-2R elevation in B-cell lymphomas is not fully understood.

In this study, we analyzed the serum level of laboratory findings, including sIL-2R and LDH, as well as the presence of B symptoms in 39 patients with IVL, and compared them with 56 patients with stage IV DLBCL. Both sIL-2R and LDH levels were significantly higher in IVL than in DLBCL ($p = 0.035$ and $p = 0.002$, respectively). In IVL, there were no significant differences in both sIL-2R and LDH levels between patients with and without B symptoms ($p = 0.206$ and $p = 0.441$, respectively). However, in DLBCL, both sIL-2R and LDH levels were significantly higher in the presence of B symptoms ($p = 0.001$ and $p < 0.001$, respectively).

The high sIL-2R and LDH levels in IVL may be related to the peripheral blood microenvironment, but further studies are needed to verify this.

Keywords: Intravascular large B-cell lymphoma, Diffuse large B-cell lymphoma, sIL-2R, LDH, B symptoms

Introduction

Intravascular large B-cell lymphoma (IVL) is a rare extranodal large B-cell lymphoma characterized by tumor growth selectively within the lumen of small-caliber blood vessels[1]. IVL is defined as a large B-cell lymphoma, the same as diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS), by the 5th edition of World Health Organization classification[2]. IVL usually occurs in adults older than 65 years and presents with various clinical symptoms without significant lymphadenopathy and extranodal tumor formation[3]. The neoplastic cells can involve almost any blood vessel, commonly affecting the central nervous system, skin, bone marrow, and lungs. IVL presents with systemic symptoms, such as a fever, general fatigue, and a marked deterioration in performance status[4]. Since IVL does not form extravascular tumor masses, many cases have been diagnosed postmortem[5].

Serum soluble interleukin-2 (IL-2) receptor (sIL-2R) has been recognized as a tumor-related biomarker of lymphomas. IL-2R is expressed on the cell membrane of T lymphocytes and plays an important role in their activation and proliferation[6]. IL-2R is composed of three units, α (CD25), β (CD122), and γ chain (CD132), and the binding of IL-2 to IL-2R initiates proliferation and differentiation of T lymphocytes. IL-2R bound to IL-2 is cleaved by matrix metalloproteinases (MMP)-9 released from tumor-associated macrophages, and the α chain is released[7], resulting in serum sIL-2R. Serum sIL-2R levels have been found to be elevated in some hematolymphoid neoplasms, including non-Hodgkin lymphomas (NHL) [8]. Also, sIL-2R levels have been proposed as a diagnostic and prognostic factor for NHL[9, 10].

Given the highly aggressive nature of IVL[11], prompt and accurate diagnosis and initiation of treatment

are critical. However, the annual incidence of IVL is estimated to be less than 1 per million people[12], making it challenging to obtain cases to establish an evidence-based diagnostic algorithm. Given the possible predictive utility of sIL-2R in DLBCL[13], we hypothesized that sIL2R could be a useful diagnostic biomarker and comparable to Lactate dehydrogenase (LDH) in prognostication.

Here, we performed a retrospective investigative analysis of patients with IVL and DLBCL, NOS stage IV, the most common subtype of B cell lymphoma[14], with a focus on sIL-2R and LDH levels.

Materials and methods

Patients

We analyzed the clinical features of 39 patients with IVL and 56 patients with Ann Arbor classification stage IV DLBCL, NOS. All the cases were Japanese and retrospectively identified from surgical pathology consultation files from the Department of Pathology, Okayama University, between 2002 to 2020 (IVL) and 2017 to 2018 (DLBCL, NOS). Clinical data were extracted from clinical records, including age, sex, serum sIL-2R levels, serum LDH levels, biopsy site, and presence of B symptoms.

The study protocol was approved by the Institutional Review Board of Okayama University (reference numbers: 2102-002). Comprehensive informed consent was obtained from all patients through an opt-out methodology at Okayama University.

Statistical analysis

We employed the Mann-Whitney U test to evaluate differences in ordinal or continuous variables. Categorical variables were evaluated using the Chi-square test; *p*-values less than 0.05 were considered

statistically significant. All the data were inputted into the computer, and IBM SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Result

Clinical features

The clinical characteristics of the patients are summarized in **Table 1**. There were 40 cases of IVL diagnosed during this period, but we excluded one case (cutaneous variant) in which the lesion was limited to the skin for several years and the patient had a remarkably favorable clinical course. A significant male dominance was noted in the DLBCL, NOS group ($p = 0.034$). The median age of patients was 74 (range: 44−91) years for IVL and 74 (range: 42−91) years for DLBCL, NOS, without significant differences between the groups. Patients with IVL were most commonly diagnosed using bone marrow (64.1%) and skin (35.9%) biopsy, whereas those DLBCL, NOS were most commonly diagnosed using the lymph nodes (39.3%). Both sIL-2R (median = 6190, range: 1090 − 32900 vs median = 3974.5, range: 357 − 65369) and LDH (median = 812.5, range: 147 − 3262 vs median = 431, range: 144 − 4886) levels were significantly higher in those with IVL than in those with DLBCL, NOS ($p = 0.035$ and $p = 0.002$, respectively) (**Figure 1**). Hemoglobin, platelet counts and albumin level were significantly lower in the IVL group than in the DLBCL group (all $p<0.001$), and CRP was significantly higher in the IVL group than in the DLBCL group ($p<0.001$). White blood cell counts and creatinine levels did not show significant differences between the two groups. B symptoms were significantly more common in the IVL group ($p = 0.027$).

At least one B symptom was present in 64.1% (25/39) of IVL patients and 32.4% (27/71) of DLBCL, NOS patients. Of the 25 IVL patients with B symptoms, 22 only had a fever, 1 had a fever and night sweats,

1 had a fever and weight loss, and 1 had a fever, night sweats, and weight loss. The 10 IVL patients who did not present with B symptoms had a diagnostic biopsy because of elevated serum LDH levels (>1000 U/L) (2/10, 20%), elevated serum sIL-2R levels (2/10, 20%), pancytopenia (2/18, 20%), hepatosplenomegaly (2/11, 20%), altered mental status (1/10, 10%), or unilateral upper extremity numbness (1/10, 10%).

A representative histology image of the skin lesions of the IVL cases included in this study is shown in **Figure 2**.

Comparison of sIL-2R and LDH levels by presence or absence of B symptoms

A comparison of laboratory values in patients with and without B symptoms is shown in **Table 2**. In IVL, there were no significant differences in both sIL-2R and LDH between patients with and without B symptoms ($p = 0.206$ and $p = 0.441$). On the other hand, in DLBCL, NOS, both sIL-2R and LDH levels were significantly higher in the presence of B symptoms ($p = 0.001$ and $p < 0.001$, respectively).

In the presence of B symptoms, there were no significant differences in sIL-2R and LDH levels between IVL and DLBCL, NOS patients ($p = 0.270$ and $p = 0.774$, respectively). However, in the absence of B symptoms, IVL patients had significantly higher sIL-2R and LDH levels than DLBCL, NOS patients ($p = 0.005$ and $p = 0.002$, respectively).

Comparison of sIL-2R and LDH levels in DLBCL by presence or absence of bone marrow involvement

We also investigated whether there were differences in sIL-2R and LDH values between groups with and without bone marrow involvement in 56 stage IV DLBCL patients. All of the stage IV DLBCL patients included in the study had extranodal involvement, with 13 (23.2%) cases involving the bone marrow alone

(BM alone), 23 (41.1%) cases involving extranodal lesions other than bone marrow (Extranodal involvement without BM involvement), and 20 (35.7%) cases with both bone marrow and other extranodal involvement (Both BM and other extranodal involvement). A comparison of sIL-2R and LDH levels between the three groups is shown in **Figure 3**.

It was found that sIL-2R and LDH levels were significantly higher in the "BM alone" group than in either the “Extranodal involvement without BM” (p=0.0098 for sIL-2R and p=0.0118 for LDH) or "Both BM and other extranodal involvement" (p=0.0131 for sIL-2R and p=0.0177 for LDH) groups. On the other hand, there was no significant difference between the "Extranodal involvement without BM" and "Both BM and other extranodal involvement"(p=0.876 for sIL-2R and p=0.842 for LDH) groups.

Discussion

In this study, sIL-2R and LDH levels were significantly higher in IVL patients than in DLBCL, NOS patients. sIL-2R is generated by the proteolytic cleavage of membrane-bound IL-2Rα (CD25), and the levels of sIL-2R in sera have proven to be a useful marker of CD4+ T cells, due to CD25 being expressed primarily on CD4+ T cells[15]. Therefore, the serum level of sIL-2R is thought to reflect tumor volume in T-cell lymphoma, such as adult T cell lymphoma [10, 15]. However, an increase in sIL-2R in B-cell lymphomas is not fully understood, as B-lymphoma cells are typically CD25-negative. Recent studies have reported that lymphoma cells in DLBCL, NOS and follicular lymphoma (FL) partially express CD25, but in small numbers, and that there is no clear correlation between CD25 expression and sIL-2R levels in B-cell lymphomas[7]. On the other hand, MMP-9, which is thought to cleave IL-2Rα (CD25) and release sIL-2R, is mainly produced by tumor-associated macrophages, and a positive correlation between sIL-2R and the number of MMP-9-producing

macrophages in the tumor microenvironment has been reported in DLBCL, NOS and FL[7, 16]. Furthermore, several studies have shown that lymphoma cells in IVL lack MMP-9 expression[16, 17]. Taking these results together, serum sIL-2R levels in IVL seem to reflect a microenvironment in peripheral blood, such as abundant bystander T cells and MMP-producing macrophages, but further experiments and studies are needed to draw conclusions.

The LDH levels are significantly higher in patients with aggressive B-cell lymphoma and can be used as a screening tool to determine the response of a particular treatment or its recurrence[18]. Tumor lysis occurs in both IVL and DLBCL, NOS, but in the case of IVL, it occurs intravascularly and might be acutely reflected in laboratory values. It may also be possible that in tumor cells decay is more likely to occur when tumor cells are in the blood vessels than when they are present as a mass, and that tumor proliferation and destruction may be occurring at a faster rate in IVL, resulting in higher LDH levels.

Hemoglobin, platelet counts and albumin level were significantly lower in the IVL group than in the DLBCL group, and CRP was significantly higher in the IVL group than in the DLBCL group. This result is consistent with a previous report[19] and is probably the result of dysregulation of inflammatory cytokines in IVL. In addition, IVL is often complicated by hemophagocytic syndrome, which is known to cause cytokine storms, and the resulting persistent inflammatory condition may have affected these laboratory values.

IVL had significantly more B symptoms than stage IV DLBCL, NOS. The Ann Arbor classification defines B symptoms as (a) unexplained weight loss of more than 10% of the body weight in the six months previous to admission; (b) an unexplained fever with temperatures above 38°C; and (c) night sweats[20]. Tumor cell proliferation is thought to cause cell disruption, which activates the arachidonic acid cascade, resulting in

the appearance of B symptoms. In stage IV DLBCL, NOS, sIL-2R and LDH levels were higher in patients with B symptoms (Table 2). Interestingly, in patients with IVL, there were no significant differences in sIL-2R and LDH levels depending on the presence or absence of B symptoms. It is suggested that tumor volume and/or the rate of tumor cell turnover via proliferation and cell death may increase the associated elevated laboratory values and appearance of B symptoms in DLBCL, NOS. On the other hand, in IVL, the intravascular proliferative environment may have a much more significant influence, and the relationship between tumor volume and elevated laboratory values, as well as the appearance of B-symptoms, may differ.

Finally, in the DLBCL cases included in this study, significantly higher sIL-2R and LDH levels were found in cases with selective bone marrow involvement. Interestingly, on the other hand, there was no significant difference between multiorgan lesions with or without bone marrow involvement in stage IV DLBCLs. Although these results seem contradictory at first glance, they might suggest that the pathophysiology differs in some way between cases that happen to involve bone marrow as part of the process of multiorgan involvement and those that selectively involve bone marrow, with higher sIL-2R and LDH levels in the latter. Further studies are needed to clarify whether lymphomas that tend to have high sIL-2R/LDH levels are more likely to selectively infiltrate the bone marrow, or whether the effect of the tumor growth environment of the bone marrow is associated with elevated sIL-2R/LDH levels.

In conclusion, in patients with a fever of unknown origins and other systemic inflammations (including anemia, thrombocytopenia, hypoalbuminemia, and elevated CRP), elevated serum sIL-2R and LDH levels may be helpful in diagnosing IVL by triggering a bone marrow aspiration/biopsy or random skin biopsy. The

increased serum sIL-2R and LDH levels and the high frequency of B symptoms in IVL might be due to the tumor growth environment of IVL in the peripheral blood, including the amount of bystander T cells or MMP-producing macrophages. Moreover, in DLBCL, sIL-2R and LDH levels were found to be higher in patients with selective bone marrow involvement, which may also be related to the tumor growth environment in the bone marrow. Further research is needed to test these hypotheses.

Author Contributions

Conceptualization, Y.H., M.F.N. and Y.S.; methodology, Y.H. and Y.S.; formal analysis, Y.H. and M.M.; investigation, Y.H.; resources, Y.H.; data curation, T.U. and Y.M.; writing—original draft preparation, Y.H.; writing—review and editing, M.F.N and Y.S.; supervision, M.F.N and Y.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest The authors declare no conflict of interest.

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Tables

Table 1. Patients' characteristics.

		IVL (n=39)	DLBCL (n=56)	*p-Value*
Sex	male	18 (46.2%)	38 (67.9%)	**0.034***
	female	21 (53.8%)	18 (32.1%)	
Age [median (range)]		74 (44–91)	74 (42–91)	0.955
Laboratory data [median (range)]	sIL-2R (U/mL)	6190 (1090–32900)	3974.5 (357–65369)	**0.035***
	LDH (U/L)	812.5 (147–3262)	431 (144–4886)	**0.002***
	WBC (/μL)	5100 (1200–17150)†	6010 (366–50480)‡	0.115
	Hb (g/dL)	9.8 (6.4–12.2)†	11.8 (4.8–17.6)‡	**< 0.001****
	Plt ($\times 10^4/\mu$L)	8.3 (1.0–43.7)†	22.2 (2.5–40.5)‡	**<0.001****
	Alb (g/dL)	2.3 (1.9–4.1)†	3.5 (1.7–4.7)‡	**<0.001****
	Cre (mg/dL)	0.8 (0.5–1.7)†	0.9 (0.5–1.8)‡	0.515
	CRP (mg/dL)	9.4 (0.9–24.8)†	1.6 (0.03–17.3)‡	**< 0.001****
Presence of B symptoms	≥1	25 (64.1%)	23 (41.0%)	**0.027***
Biopsy site	bone marrow	25 (64.1%)	4 (7.1%)	
	skin	19 (48.7%)	3 (5.4%)	
	liver	2 (5.1%)	4 (7.1%)	
	lung	2 (5.1%)	0	
	spleen	2 (5.1%)	0	
	duodenum	1 (2.6%)	0	
	epipharynx	1 (2.6%)	0	
	gallbladder	1 (2.6%)	0	
	bladder	1 (2.6%)	1 (1.8%)	
	cerebrum	1 (2.6%)	1 (1.8%)	
	stomach	1 (2.6%)	4 (7.1%)	
	adipose tissue	1 (2.6%)	0	
	lymph node	0	22 (39.3%)	
	gastrointestine	0	3 (5.4%)	
	testis	0	2 (3.6%)	
	nasopharynx	0	1 (1.8%)	
	femur	0	2 (3.6%)	
	paranasal sinus	0	1 (1.8%)	
	kidney	0	1 (1.8%)	
	pharynx	0	1 (1.8%)	
	nasal mucosa	0	1 (1.8%)	
	abdominal mass	0	1 (1.8%)	
	tonsil	0	1 (1.8%)	
	maxillary sinus	0	1 (1.8%)	
	pelvic tumor	0	1 (1.8%)	

sIL-2R, soluble interleukin-2 receptor; LDH, lactate dehydrogenase. * $p < 0.05$. **$p<0.001$.

† WBC, Hb, Alb, Cre, and CRP were available for 33, 32, 31, 26, 20, and 30 patients with IVL, respectively.

‡ WBC, Hb, Alb, Cre, and CRP were available for 48, 47, 47, 45, 31, and 45 patients with DLBCL, respectively.

Table 2. Patients' characteristics according to the presence of B symptoms

		IVL			DLBCL		
Presence of B symptoms		Present (n=25)	Absent (n=14)	*p*-Value	Present (n=23)	Absent (n=33)	*p*-Value
Sex [n (%)]	male	12 (48.0)	6 (42.9)	0.757	15 (65.2)	23 (69.7)	0.724
	female	13 (52.0)	8 (57.1)		8 (34.8)	10 (30.3)	
Age [median (range)]		73 (44-91)	78 (63-89)	0.289	73 (42-91)	74 (54-87)	0.623
sIL-2R (U/mL) [median(range)]		6190 (1090-16516)	6500 (2480-32900)	0.206	6743 (870-65369)	2063 (357-22600)	**0.001***
LDH (U/L) [median(range)]		844 (147-3262)	736 (291-1851)	0.441	815 (180-4886)	283 (144-2415)	**<0.001****

sIL-2R, soluble interleukin-2 receptor; LDH, lactate dehydrogenase. * $p < 0.05$, ** $p < 0.001$.

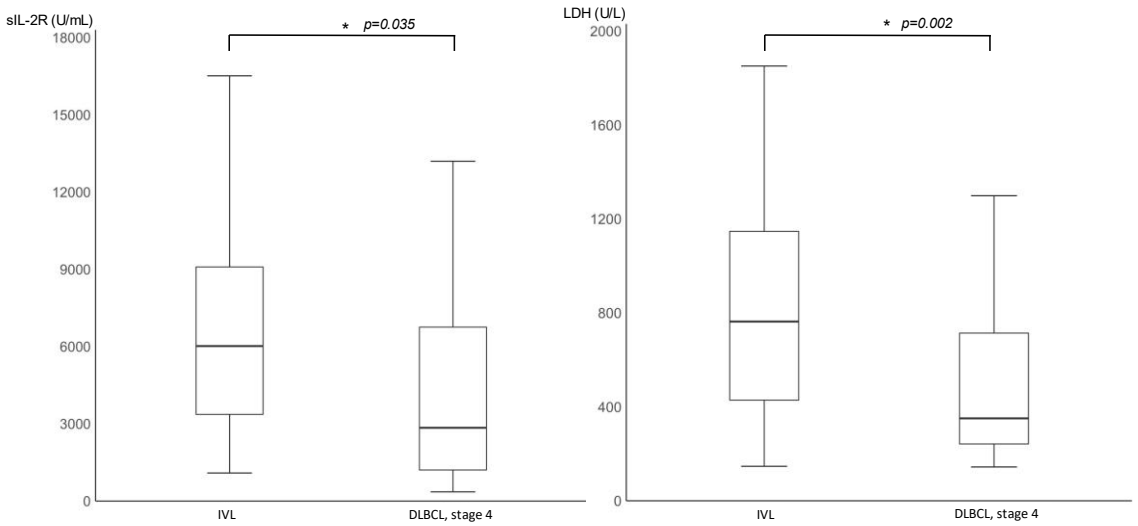

Figure 1. Comparison of serum levels of sIL-2R and LDH in patients with IVL and DLBCL, stage IV.

Both sIL-2R and LDH levels were significantly higher in patients with IVL than those with DLBCL, NOS ($p = 0.035$ and $p = 0.002$, respectively). Boxplots display the median and interquartile range (IQR; 25–75%), with whiskers representing the upper- and lower-quartile ±1.5× IQR. Differences between the two groups were evaluated by the Mann-Whitney U test (*$p<0.05$).

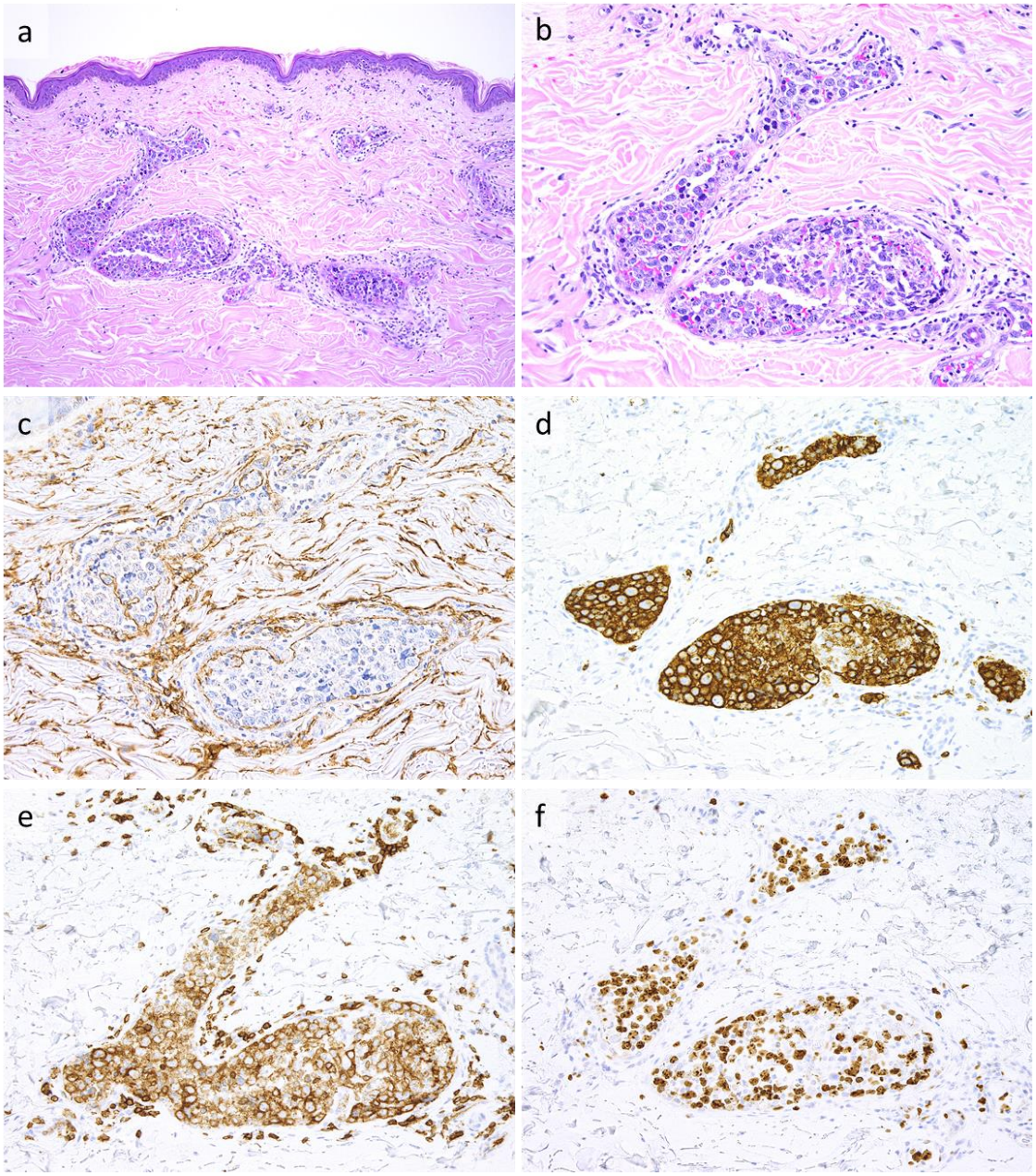

Figure 2. Representative histology of skin lesions in an IVL case.

(a) Large atypical tumor cells fill small vessels in the superficial dermis of the skin (H&E, 10x objective). (b) A higher magnification image of tumor cells is shown (H&E, 20x objective). (c) CD34 staining is positive for vascular endothelium, emphasizing the intravascular localization of the lesion (20x objective). (d) Tumor cells are diffusely positive for CD20 staining (20x objective). (e) In this case, tumor cells were also positive for CD5 (20x objective). (f) Ki-67 staining is positive for most of the tumor cells, indicating a tumor with high proliferative activity (20x objective).

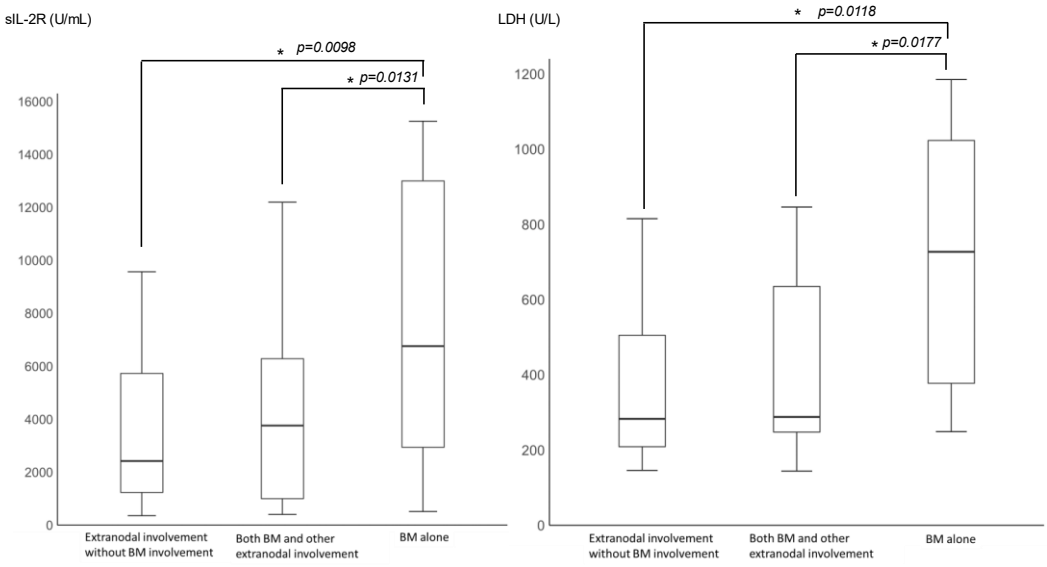

Figure 3. Comparison of sIL-2R and LDH in stage IV DLBCL according to presence and absence of bone marrow involvement.

sIL-2R and LDH levels were significantly higher in group "BM alone" group than in either the "Extranodal involvement without BM involvement" or "Both BM and other extranodal involvement" groups. There was no significant difference between the "Extranodal involvement without BM involvement" and "Both BM and other extranodal involvement" groups. Boxplots display the median and interquartile range (IQR; 25–75%), with whiskers representing the upper- and lower-quartile ±1.5× IQR. Differences between the two groups were evaluated by the Mann-Whitney U test (*p<0.05).