Clinical and Histopathological Findings of Six Cases of Intravascular Large B-cell Lymphoma Diagnosed from 161 Random Skin Biopsy Cases

Tomomichi SHIMIZU, Fumikazu YAMAZAKI, Hinako CHIBA, Shinpei HAMASAKI, Sho ARAI, Tomomi INOMATA, Ayako HIROTA, Shiori MATSUMOTO, Reiko SAITO, Akio KONDOH and Tomotaka MABUCHI

Department of Dermatology, Tokai University School of Medicine

(Received June 20, 2025; Accepted November 18, 2025)

Objective: Intravascular large B-cell lymphoma is a rare type of extranodal lymphoma that has an aggressive and sometimes fatal course. Early diagnosis is necessary to improve the prognosis, but very few studies have reported random skin biopsies comparing positive and negative patients.
Methods: A total of 161 patients with malignant lymphoma in the differential diagnosis underwent random skin biopsies. Their clinical presentations included fever, night sweats, and unintentional weight loss. Their laboratory and radiological findings were evaluated.
Results: Six patients were diagnosed with intravascular large B-cell lymphoma, 12 patients were diagnosed with other malignant lymphomas, and the remainder were diagnosed with other diseases. Patients who were diagnosed with intravascular large B-cell lymphoma had a tendency to have B symptoms ($p = 0.046$), include senile/cherry angioma(s) at the sites of random skin biopsies ($p = 0.040$), and have thrombocytopenia ($p = 0.009$).
Conclusions: Patients with intravascular large B-cell lymphoma who have B symptoms and thrombocytopenia tend to be easily diagnosed. In cases with these manifestations, random skin biopsy is recommended, if the patients do not have hemophagocytic lymphohistiocytosis.

Key words: random skin biopsy, malignant lymphoma, intravascular large B-cell lymphoma, B symptoms, thrombocytopenia

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of non-Hodgkin lymphoma that is characterized by the selective growth of lymphoma cells within the lumina of vessels, in particular capillaries, excluding larger arteries and veins [1]. Early diagnosis is the most important issue for IVLBCL, but it is often difficult to diagnosis. The benefit of random skin biopsy (RSB) has been described in the literatures [2]. RSB is less invasive than bone marrow biopsy in the diagnosis of IVLBCL, and it can be performed for patients in poor general condition. In dermatologists' daily clinical practice, consultations for RSB from other departments are common, but few reviews of RSB have been published [3, 4]. The purpose of this study was to describe the characteristics of patients with IVLBCL whose diagnoses were made by RSB.

MATERIALS AND METHODS

Patient population

A retrospective review of cases seen by the dermatology department of Tokai university hospital, was performed. A total of 161 patients who underwent RSB from April 2016 to April 2023 were enrolled. Most patients were referred to our department from other departments due to the possibility of IVLBCL or other malignant lymphoma, whereas seven patients were referred for examination of cardiac amyloidosis and two for systemic amyloidosis. All patients underwent RSB at two or more locations including the epidermis, dermis, and subcutaneous fat tissue. This is a retrospective study. Consent from each participant was not applicable. This study was approved by the Institutional Ethics Board of Tokai University Hospital (approval number: 25R-102). The ethics committee approved a waiver of individual informed consent. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed using R (version 1.62, R Foundation for Statistical Computing, Vienna, Austria). A p-value of < 0.05 was considered significant.

RESULTS

A total of 161 patients underwent RSB, including 91 males and 70 females with a mean age of 60.16 [standard deviation (SD): 17.65] years, with an age range of 17 to 92 years (Tables 1, 2). The number of biopsy sites ranged from 2 to a maximum of 5, and the average number of biopsies per patient was 3.07 [SD: 0.42]. The biopsy sites included the abdomen in

Tomomichi SHIMIZU, Department of Dermatology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
Tel: +81-463-93-1121 Fax: +81-463-93-9387 E-mail: shimizu.t@tokai.ac.jp

Table 1 Clinical characteristics of 161 patients who underwent random skin biopsy

Clinical characteristic	Patients
Number of patients	161
Age, y; median (range)	60.16 (17-92)
Sex, male *n* (%)	91 (56.5)
Number of biopsy sites, median (range)	3.07 (2-5)
Biopsy lesion, including abdomen *n*	140
Including senile/cherry angioma(s) *n*	65
Malignant lymphoma, site of disease	
CNS *n*	8
Intravascular *n*	6
Lymph node *n*	3
Kidney *n*	1

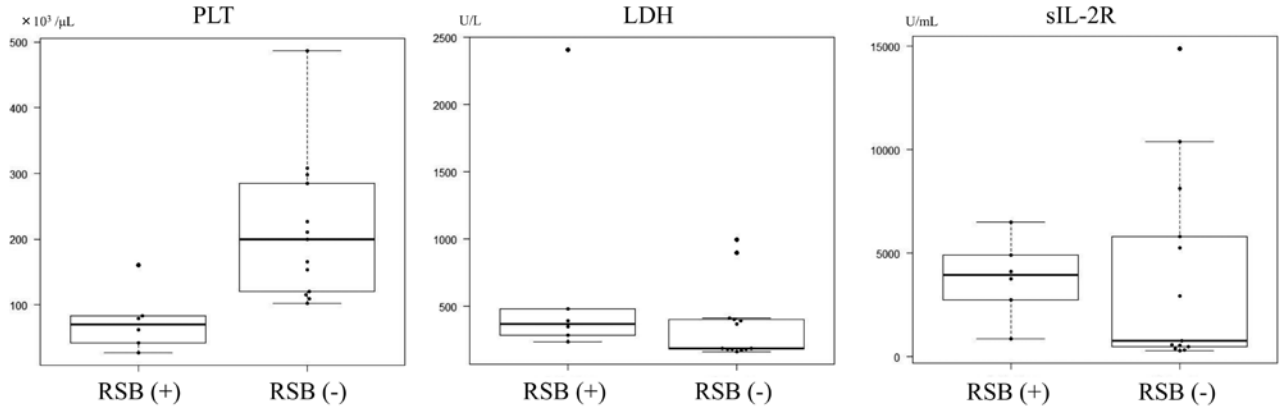
CNS = central nervous system.

Table 2 Clinical and laboratory findings of patients with malignant lymphoma

No.	Age (y)	Sex	B symptoms			Hepatosplenomegaly	PLT (/μL)	Final diagnosis	RSB (senile/cherry angioma(s))
			Fever	Night sweats	Unintentional weight loss				
1	84	M	+	-	-	+	27,000	IVLBCL	P +
2	51	M	-	-	-	-	83,000	IVLBCL	P +
3	73	M	+	+	+	+	161,000	IVLBCL	P -
4	55	F	-	-	-	-	79,000	IVLBCL	P +
5	77	M	-	-	+	+	62,000	IVLBCL	P +
6	71	F	+	-	-	-	42,000	IVLBCL	P +
7	68	F	-	-	-	-	166,000	DLBCL	N -
8	63	M	-	-	-	-	487,000	PTCL, NOS	N -
9	62	M	-	-	-	-	200,000	PCNSL	N -
10	76	M	+	-	+	+	154,000	DLBCL	N -
11	81	F	-	-	-	-	121,000	B cell lymphoma	N +
12	72	M	-	-	-	-	211,000	B cell lymphoma	N +
13	52	F	-	-	-	-	308,000	MALT lymphoma	N -
14	65	F	-	-	-	-	298,000	PCNSL	N -
15	48	F	-	-	-	-	227,000	DLBCL	N -
16	45	M	-	-	-	+	102,000	DLBCL	N -
17	75	M	+	-	-	+	115,000	ALCL	N +
18	83	M	-	-	-	-	285,000	B cell lymphoma	N -

PLT = platelet count, RSB = random skin biopsy, IVLBCL = intravascular large B-cell lymphoma, P = positive, N = negative, DLBCL = diffuse large B-cell lymphoma, PTCL, NOS = peripheral T-cell lymphoma, not otherwise specified, PCNSL = primary central nervous system lymphoma, MALT lymphoma = mucosa-associated lymphoid tissue lymphoma, ALCL = anaplastic large cell lymphoma.

140 patients, at least one senile/cherry angioma in 65 patients, and in 96 patients, no angiomas were included. The prevalence of senile/cherry angioma among IVLBCL cases was 7.69%. Overall, 6 (33.33%) of 18 cases with lymphoma showed positive results on RSB and were diagnosed with IVLBCL; 12 cases (66.66%) showed negative results on RSB, including 4 cases of diffuse large B-cell lymphoma, 2 cases of primary central nervous system lymphoma, 2 cases of B-cell lymphoma, 1 case of peripheral T-cell lymphoma not otherwise specified, and 1 case of malignant lymphoma (unclassifiable). There were no cases in which IVLBCL was not diagnosed in RSB but was diagnosed in other tissues. Malignant lymphomas were localized to the central nervous system in 8 cases (brain 5 cases, spinal cord 3 cases), intravascular in 6 cases, lymph nodes in 3 cases, and kidney in 1 case. The 6 RSB-positive patients included 4 males and 2 females, with a mean age of 68.50 [SD: 12.86] years, with an age range from 51 to 84 years. Of the 6 cases, 5 included at least one hemangioma at the RSB site, 3 patients had fever over 38.0 degrees Celsius, one had night sweats, 2 had weight loss, 5 had thrombocytopenia, 5 had low hemoglobin (Hb), 6 had high lactate dehydrogenase (LDH), 6 had low albumin (Alb), 3 had high aspartate aminotransferase (AST), 3 had high alanine aminotransferase (ALT), 4 had high gamma-glutamyl trans peptidase (γ-GTP), 6 had high C-reactive protein



Median and 25th and 75th percentile values are marked (boxes), as well as outliers (dots)-all measurements below the 10th and above the 90th percentiles (antennae).

Fig. 1 Box plot graphs of platelet counts, serum LDH levels, and sIL-2R levels of RSB-positive and RSB-negative patients.

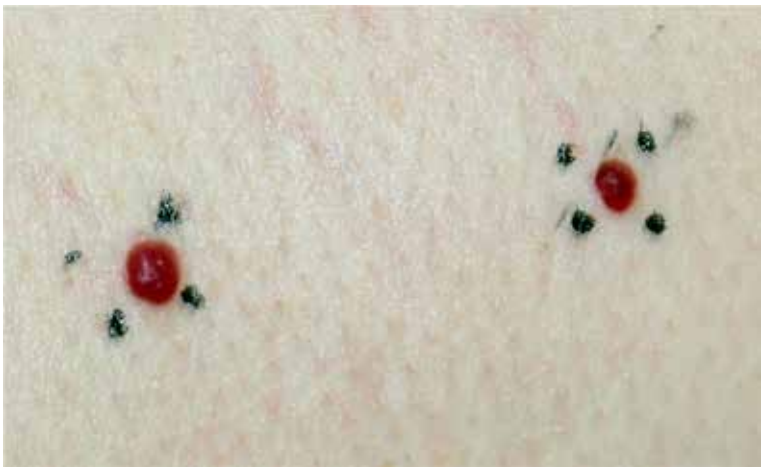


Fig. 2 Senile/cherry angioma showing dome-shaped, bright, ruby-colored papules.

(CRP), 5 had high ferritin, and 6 had high soluble interleukin-2 receptor (sIL-2R) levels. The 12 RSB-negative patients included 7 males and 5 females, with a mean age of 66.23 [SD: 12.06] years and an age range from 45 to 83 years. Of the 12 cases, 3 had at least one hemangioma at the RSB site, 2 patients had fever over 38.0 °C, one had night sweats, one had weight loss, 4 had thrombocytopenia, 5 had low Hb, 13 had high LDH, 10 had low Alb, 2 had high AST, 2 had high ALT, 5 had high γ-GTP, 9 had high CRP, 6 had high ferritin (5 cases not measured), and 7 had high sIL-2R levels. RSB-positive cases included more senile/cherry angioma(s) at the biopsy site than RSB-negative cases ($p = 0.04$). B symptoms were more common in RSB-positive cases than in RSB-negative cases ($p = 0.046$). There was no significant difference in hepatosplenomegaly between RSB-positive and RSB-negative cases ($p = 0.32$). Thrombocytopenia was predominantly observed in RSB-positive cases ($p = 0.009$) (Fig. 1). There were no significant differences in the other laboratory tests.

DISCUSSION

IVLBCL was originally reported as 'angioendotheliomatosis proliferans systemisata', whereas it was suggested to be a B-cell tumor in 1986 [5]. Today, IVLBCL is defined as a rare type of extranodal large B-cell lymphoma characterized by the selective growth of lymphoma cells within the lumina of vessels, in particular capillaries, excluding larger arteries and veins [6]. Since IVLBCL progresses rapidly and often has a fatal course, early diagnosis is of primary importance. RSB has been proposed for diagnosis, and its usefulness has been reported [7, 8]. In the present study, the medical records of 161 patients who underwent RSB were retrospectively reviewed. In the 18 patients who were finally diagnosed with malignant lymphoma, there were significant differences between the 6 RSB-positive IVLBCL cases and the 12 RSB-negative cases in senile/cherry angioma(s), B symptoms, and platelet counts.

The reason why RSBs from senile/cherry angiomas were more likely to be diagnosed as IVLBCL was thought to be because IVLBCL was characterized by a proliferation of large atypical lymphoid cells within the vascular lumina; the lymphoma cells might be trapped by the histological rich-in-vessel structure of the senile/cherry angioma vessels [9]. The senile/cherry angioma associated with IVLBCL showed no characteristic features (Fig. 2). In some of the present cases, IVLBCL cells were recognized in not only the capillary aggregation site of the hemangioma, but in deeper

dermal capillaries. Therefore, RSBs from senile/cherry angiomas do not always show IVLBCL cells within the senile/cherry angiomas, but in the present cases, there were significant differences in RSBs including angiomas. Therefore, RSBs should include angiomas if they are present. The usefulness of RSBs including senile/cherry angiomas has been previously reported [10].

It is known that the clinical presentation of IVLBCL is classified into the classic form and the Asian variant [6]. The classic form is mostly present in western countries, with central nervous system or cutaneous lesions [6]. In contrast, 'Asian variant of intravascular lymphomatosis' was proposed, in which hemophagocytosis and bone marrow lesions were common, and cutaneous lesions were rare [11]. The Asian variant is a subtype of IVLBCL, in which hemophagocytosis and multiorgan failure develop [6]. In the present RSB-positive and RSB-negative groups, there were significant differences in B symptoms and thrombocytopenia, even though none had hemophagocytosis. In other words, RSB-positive cases were significantly more likely to have B symptoms and thrombocytopenia. This could be explained by the fact that not only were B symptoms from malignant lymphoma seen, but fever and thrombocytopenia appeared as early symptoms of hemophagocytosis. It has been reported that 95% of hemophagocytosis patients present with fever, and especially more than 80% of patients with present with anemia and thrombocytopenia [12, 13]. In the present study, there were no significant differences in other laboratory and radiographic abnormalities, including splenomegaly and ferritin, AST, ALT, LDH, and D-dimer levels, between the RSB-positive and RSB-negative groups.

In conclusion, the present findings show that patients with B symptoms and/or thrombocytopenia are more likely to be RSB-positive in the malignant lymphoma group. These symptoms and laboratory abnormalities may increase the probability of IVLBCL, which is suggested as the rationale for aggressive RSB, even if patients are suspected to have malignant lymphoma, and they do not have a serious condition such as hemophagocytosis or disseminated intravascular coagulation.

CONFLICTS OF INTEREST STATEMENT

None declared.

REFERENCES

1) Ahmed F, Cree IA, Jong D, Fonseca AFA, Goldman-Lévy, Lokuhetty D. WHO Classification of Tumours, 5th Edition. Argonay: IRAC, 2024.
2) Pongpudpunth M, Rattanakaemakorn P, Fleischer Jr AB. Usefulness of Random Skin Biopsy as a Diagnostic Tool of Intravascular Lymphoma Presenting With Fever of Unknown Origin. Am J Dermatopathol 2015; 37: 686–690.
3) MacGillivary ML, Purdy KS. Recommendations for an Approach to Random Skin Biopsy in the Diagnosis of Intravascular B-Cell Lymphoma. J Cutan Med Surg 2023; 27: 44–50.
4) Kim SR, Ko CJ, Nelson CA, Ramachandran S, Gehlhausen JR. Random skin biopsies for diagnosis of intravascular large B-cell lymphoma: Retrospective analysis of 31 biopsies from a US dermatology inpatient consultative service with literature review. J Am Acad Dermatol 2023; 88: 714–716.
5) Sheibani K, Battifora H, Winberg CD, Burke JS, Ben-Ezra J, Ellinger GM, *et al*. Further evidence that "malignant angioendotheliomatosis" is an angiotropic large-cell lymphoma. N Engl J Med 1986; 314: 943–948.
6) Jong D, Nagane M, Batchelor T, Shimada K, Deckert M, Soffietti R, *et al*. Intravascular large B-cell lymphoma. In: Ahmed F, Cree IA, Jong D, Fonseca AFA, Goldman-Lévy, Lokuhetty D, eds. WHO Classification of Tumors, Haematolymphoid Tumours Part B, 5th ed. Argonay: IARC, 2024: 520–522.
7) Asada N, Odawara J, Kimura S, Aoki T, Yamakura M, Takeuchi M, *et al*. Use of random skin biopsy for diagnosis of intravascular large B-cell lymphoma. Mayo Clin Proc 2007; 82: 1525–1527.
8) Matsue K, Asada N, Odawara J, Aoki T, Kimura S, Iwama K, *et al*. Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. Ann Hematol 2011; 90: 417–421.
9) Satoh S, Yamazaki M, Yahikozawa H, Ichikawa N, Saito H, Hanyuu N, *et al*. Intravascular large B cell lymphoma diagnosed by senile angioma biopsy. Intern Med 2003; 42: 117–120.
10) Sakurai T, Wakida K, Takahaashi T, Ishida K, Iwata H, Nishida H. Usefulness of senile hemangioma biopsy for diagnosis of intravascular large B-cell lymphoma: A report of two cases and a literature review. J Neurol Sci 2017; 373: 52–54.
11) Murase T, Nakamura S, Tashiro K, Suchi T, Hiraga J, Hayasaki N, *et al*. Malignant histiocytosis-like B-cell lymphoma, a distinct pathologic variant of intravascular lymphomatosis: a report of five cases and review of the literature. Br J Haematol 1997; 99: 656–664.
12) Bergsten E, Horne A, Aricó M, Astigarraga I, Egeler RM, Filipovich AH, *et al*. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. Blood 2017; 130: 2728–2738.
13) Trottestam H, Horne A, Aricò M, Egeler RM, Filipovich AH, Gadner H, *et al*. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 2011; 118: 4577–4584.