# Intravascular large B-cell lymphoma diagnosed by skin biopsy from cherry angioma: A case report

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**Abstract.** Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of large B-cell lymphoma characterized by the exclusive growth of lymphoma cells within blood vessels. Due to the lack of lymphadenopathy and mass formation, the diagnosis of IVLBCL is frequently delayed. Random biopsies of normal-appearing skin are recommended to diagnose patients suspected of having IVLBCL. Although their usefulness is well recognized, the limitations and diagnostic utility of random skin biopsies for IVLBCL involving cherry angiomas have been reported in a limited number of cases. The current study presents the 21st reported case of IVLBCL with a cherry angioma, focusing on the strategies for diagnosing this malignant lymphoma. An 82-year-old Japanese man presented to Osaka Medical and Pharmaceutical University with a fever of unknown origin and general malaise. Laboratory tests revealed elevated levels of soluble interleukin-2 receptor and lactate dehydrogenase. No lymphadenopathies or masses were observed. Based on the results and presentation IVLBCL was clinically suspected, and a skin biopsy was performed at the site of the cherry angioma. The histopathological examination of the biopsy specimen demonstrated a collection of dilated capillary vessels in the upper dermis, filled with large lymphoid cells with irregularly shaped nuclei and nucleoli. Immunohistochemically, these lymphoid cells expressed cluster of differentiation (CD) 20, CD79a, multiple myeloma oncogene 1 and B-cell lymphoma 6. The patient was, therefore, diagnosed with IVLBCL within a cherry angioma. Although a limited number of cases of IVLBCL involving cherry angiomas have been reported, skin biopsies from cherry angiomas and random skin biopsies may be recommended for patients suspected of having IVLBCL, as they may be reliable detectors of lymphoma cells.

## Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of extranodal large B-cell lymphoma, characterized by the almost exclusive growth of large lymphoma cells within the lumina of blood vessels; particularly the capillaries, although not in large arteries or veins (1-3). One peculiar feature of IVLBCL is the lack of lymphadenopathy and/or mass formation. Non-specific symptoms such as fever, dyspnea and fatigue, have also been reported. Delayed diagnosis is common in patients with IVLBCL, and postmortem diagnosis is not unusual, even today. The early diagnosis of this subtype of malignant lymphoma is important to improve patient prognosis.

The current gold standard for the diagnosis of IVLBCL is the detection of lymphoma cells within the lumina of blood vessels (2,3). However, a precise diagnosis may not be straightforward as, typically, only a few lymphoma cells are detected in the specimens and the biopsy sites may be difficult to determine. Random skin biopsies performed on normal-appearing skin, including subcutaneous fatty tissues, have been found to be useful in the diagnosis of IVLBCL (4-7); however, the detection rates of IVLBCL in random skin biopsies have been reported to be no >22%, which are not necessarily

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*Abbreviations:* IVLBCL, intravascular large B-cell lymphoma; CD, cluster of differentiation; MUM1, multiple myeloma oncogene 1; Bcl-6, B-cell lymphoma 6; sIL-2R, soluble interleukin-2 receptor; LD, lactate dehydrogenase; CRP, C-reactive protein; CT, computed tomography

*Key words:* intravascular large B-cell lymphoma, cherry angioma, random skin biopsies and diagnosis

high (6,8). Therefore, more effective diagnostic methods are needed for patients with suspected IVLBCL. A few cases of IVLBCL involving cherry angiomas have been previously described (9-26), and the diagnostic utility of skin biopsy for cherry angiomas in patients suspected of having IVLBCL has also been reported (17).

Cherry angioma, also known as senile hemangioma or Campbell de Morgan spot, is a common vascular lesion that presents as multiple tiny red papules on the skin in middle-aged and older individuals (27). Patients suspected of having IVLBCL are usually middle-aged or older, and may have cherry angiomas, making it easier to perform skin biopsy for the diagnosis of IVLBCL. The present study describes the 21st reported case of IVLBCL involving a cherry angioma, with a focus on the diagnostic strategies for this rare subtype of malignant lymphoma.

## Case report

An 82-year-old Japanese man presented to a local clinic with mild lightheadedness and anorexia in June 2023. A few days later, the patient developed fever and penile enlargement. His medical history included epilepsy for 45 years, which was being treated with medication, and surgical resection for renal cell carcinoma with lung metastasis 3.5 years prior to his presentation, which was under observation without recurrence. The patient was suspected of having an infectious disease and was prescribed antibiotics; however, his symptoms did not improve. Approximately 1 week after his initial presentation, the patient was admitted to Daiichi Towakai Hospital (Takatsuki, Japan). As laboratory tests revealed elevated levels of soluble interleukin-2 receptor (sIL-2R), lactate dehydrogenase (LD) and C-reactive protein (CRP), malignant lymphoma was suspected (Table I). Contrast-enhanced computed tomography (CT) revealed no lymphadenopathy or mass lesions suggestive of malignancy throughout the body. In June 2023, ~3 weeks after the initial presentation, the patient was referred to Osaka Medical and Pharmaceutical University (Takatsuki, Japan) for further evaluation of fever of unknown origin. The aforementioned medical information and laboratory data of the previous hospital were obtained from the referral letter in the patient's medical record.

Upon admission to Osaka Medical and Pharmaceutical University, the condition of the patient was worse than reported, with disturbances in consciousness [Glasgow Coma Scale E3V4M5 (28)], general malaise and tachypnea with respiratory rate of 28 breaths/min, but no fever at 36.4˚C. Immediately after admission, the patient was oliguric with a urine output of ~10 ml/h; however, with intermittent administration of furosemide, the daily urine output was maintained at >1,000 ml thereafter. The patient also exhibited hypoxemia with an oxygen saturation of 92%, for which oxygen was administered up to 10 l with a reservoir mask, keeping the oxygen saturation >94%. A physical examination revealed no lymph node enlargement, although a small red papule, clinically diagnosed as a cherry angioma, was present on the trunk of the patient. Laboratory tests showed anemia and thrombocytopenia, with a white blood cell count within the normal range, accompanied by atypical lymphocytes (0.5%), whose clonality was undetectable (Table I). There were also elevations in sIL-2R, LD, CRP, urea nitrogen and serum creatinine (Table I). As for infectious diseases, T-SPOT.TB test was negative, Aspergillus antigen was 0.0 (reference range, <0.5), and CMV-C7HRP was negative, indicating that tuberculosis, Aspergillus and cytomegalovirus were not detected, respectively. Elevated levels of sIL-2R and LD suggested malignant lymphoma; however, repeat CT revealed no enlarged lymph nodes throughout the body (Fig. S1A). Based on these findings, the differential diagnoses included malignant diseases such as IVLBCL or penile malignancy, and infectious diseases such as tuberculosis. Of the aforementioned differential diagnoses, IVLBCL was the most suspected, because no causative infection or primary penile malignancy was detected in the laboratory data and imaging findings. Biopsies were performed, with specimens obtained from the cherry angioma and penile skin, and a bone marrow aspiration was also carried out. Considering the poor general condition of the patient, a random skin biopsy was not performed.

For the histological analysis, the biopsied specimens were fixed in 10% buffered formalin for 24 h at room temperature (RT) and embedded in paraffin. Sections of 4 $\mu$m-thickness from the paraffin block were stained with hematoxylin for 5 min and eosin for 1 min at RT. The stained sections were examined under a light microscope (BX53; Olympus Corporation). Histopathological examination of the skin biopsy from the cherry angioma with hematoxylin and eosin staining revealed a collection of dilated capillary vessels in the upper dermis, a typical feature of cherry angiomas (Fig. 1A and B). Large lymphoid cells with irregularly shaped nuclei and nucleoli filled the dilated vessels, and apoptotic bodies were scattered. No extravascular invasion of lymphoid cells was observed, nor were large lymphoid cells observed in the vessels of the dermis or the subcutis of the biopsy specimen. For further analysis, immunohistochemistry (IHC) was carried out. Briefly, 4 $\mu$m-thick sections obtained from the paraffin block were stained with primary antibodies shown in Table SI. For IHC, automated immunostaining devices, VENTANA BenchMark ULTRA (Roche) and Histostainer 48A (Nichirei), were used, and the procedures including antigen retrieval, blocking, washing and detection using secondary antibodies followed the manufacturer's instructions (Table SI). Briefly, before staining, to block endogenous peroxidases, the IHC device-dedicated reagent (ultra View DAB universal; Roche Tissue Diagnostics) was used in B-cell lymphoma 6 (Bcl-6), cluster of differentiation 10 (CD10), CD20, CD3, CD30, CD5, CD79a, and multiple myeloma oncogene 1 (MUM1) staining, and standard hydrogen peroxide (3%) was used in CD31 staining; their temperature/duration were 36˚C/4 min and RT/5 min, respectively. In the deparaffinization process, EZ prep (Roche Tissue Diagnostics) was used for Bcl-6, CD10, CD20, CD3, CD30, CD5, CD79a and MUM1 staining, and standard xylene and alcohol series for CD31 staining. The stained sections were observed under a light microscope (BX53, Olympus).

IHC revealed that the large lymphoid cells lodged in the cherry angioma expressed B cell-associated antigens, such as CD20, CD79a, MUM1 and Bcl-6 (Fig. 1C-F). However, the lymphoid cells did not express CD3, CD5, CD10 or CD30 (Figs. 1G and H, S1B and 1C). Additionally, the atypical cells were covered with CD31-positive endothelial cells, confirming

Table I. Laboratory data.

| Parameter | 11 days before admission[a] | Reference range[a] | On admission[b] | Day 13[b] | Day 17[b] | Reference range[b] |
|---|---|---|---|---|---|---|
| Hematocrit, % | 28.5 | 39.8-51.8 | 30.5 | 25.6 | 20.9 | 40.7-50.1 |
| Hemoglobin, g/dl | 9.4 | 13.5-17.6 | 10.1 | 7.8 | 7 | 13.7-16.8 |
| White-cell count, /μl | 4,100 | 3,900-9,800 | 8,350 | 150 | 110 | 3,300-8,600 |
| Myelocytes, % | 0.0 | 0 | 1.0 | 0.0 | 6.0 | 0 |
| Stab neutrophils, % | 84.4[c] | 44.0-72.0[c] | 6.5 | 0.0 | 36.0 | 0-5.0 |
| Segmented neutrophils, % | | | 83.5 | 16.0 | 14.0 | 35.0-68.0 |
| Monocytes, % | 8.8 | 0.0-12.0 | 3.0 | 2.0 | 18.0 | 3.7-8.8 |
| Eosinophils, % | 0.7 | 0.0-10.0 | 4.0 | 3.0 | 0.0 | 0-6.4 |
| Basophils, % | 0.2 | 0.0-3.0 | 0.0 | 5.0 | 2.0 | 0.2-1.4 |
| Lymphocytes, % | 5.9 | 18.0-59.0 | 1.5 | 74.0 | 24.0 | 22.2-50.9 |
| Atypical lymphocytes, % | 0.0 | 0 | 0.5 | 0.0 | 0.0 | 0 |
| Platelet count, /μl | 143,000 | 130,000-362,000 | 115,000 | 20,000 | 23,000 | 158,000-348,000 |
| LD, U/l | 739 | 121-245 | 963 | 216 | 147 | 124-222 |
| Urea nitrogen, mg/dl | 23 | 8-22 | 63 | 37 | 22 | 8-20 |
| Creatinine, mg/dl | 1.4 | 0.61-1.04 | 2.19 | 0.88 | 1.51 | 0.65-1.07 |
| CRP, mg/dl | 26.0 | 0-0.30 | 26.35 | 4.34 | 30.69 | 0-0.14 |
| sIL-2R, U/ml | 15,800 | 121-613 | 37,970 | ND | ND | 121-613 |

[a]Daiichi Towakai Hospital (Takatsuki, Japan). [b]Osaka Medical and Pharmaceutical University Hospital (Takatsuki, Japan). [c]The second (11 days before admission) and third (reference range) columns are data from the previous hospital, where neutrophils were not subdivided into Stab and Segmented, therefore, these values are combined in this row. CRP, C-reactive protein; ND, not determined; LD, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor.

intravascular localization (Fig. 1I). A bone marrow smear was air-dried, fixed with methanol for 20 sec, and stained with undiluted May-Grunwald for 2 min, with diluted May-Grunwald for 2 min, and then with Giemsa solution for 15 min at RT. The stained smear was observed under a light microscope (BX53; Olympus Corporation). The smear slide revealed hemophagocytosis and a few large vacuolated lymphocytes (1.9%) (Fig. S1D and E). While a histopathological examination of the penile skin revealed dilated dermal vessels and mild perivascular infiltration by small lymphocytes (Fig. S1F), no large lymphoid cells were observed in these vessels.

Based on the aforementioned results, the patient was histopathologically diagnosed with IVLBCL involving a cherry-shaped angioma. On the 3rd day of hospitalization, chemotherapy (a regimen of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) was initiated on the patient in the context of his rapid disease progression and worsening general condition, and his family's request for aggressive treatment. On the 13th day of hospitalization, after the first cycle of chemotherapy, LD and CRP levels of the patient decreased to 216 U/l and 4.34 mg/dl, respectively (Table I); however, the patient again developed a fever of 40.1˚C. Blood cultures were positive for *Corynebacterium striatum* and *Staphylococcus epidermidis* on the 15th day of hospitalization. On the 17th day of hospitalization, a catheter tip culture was positive for *S. epidermidis*, and the laboratory data showed prominent leukopenia and CRP elevation (Table I). In July 2023, the patient died of sepsis on the 19th day of hospitalization, but no autopsy was performed.

## Discussion

The present study, to the best of our knowledge, describes the 21st case of IVLBCL involving a cherry angioma (in English) since Rubin *et al* (9) first reported a case in 1997. Although the clinical presentation of IVLBCL is heterogeneous and lacks specific manifestations, two clinical forms have been recognized: the classic form (largely present in Western countries) and the hemophagocytic syndrome-associated form. The latter form is characterized by multiorgan failure, hepatosplenomegaly and pancytopenia, and is commonly observed in Asian countries (the so-called 'Asian variant') (1-3).

The patient described in the present study showed hemophagocytosis upon the analysis of the bone marrow; therefore, hemophagocytic syndrome-associated IVLBCL was suspected. The prognosis for this variant was poor, and the ultimate cause of death in the current case was considered to be sepsis due to opportunistic infection during chemotherapy. Table II summarizes the clinicopathological features of the previously reported cases, as well as the present case. The median age of the patients was 71 years (range, 51-86), and men and women were almost evenly affected (women: men, 9:10). The geographic regions in which cases were reported were Japan (11 cases), the United States (7 cases), Austria (1 case) and France (1 case). No specific trend was observed in the location of cherry angiomas with IVLBCL, although lymphoma cells were detected in two or more cherry angiomas in five patients. Of note, lymphoma cells were detected only in cherry angiomas and not in random

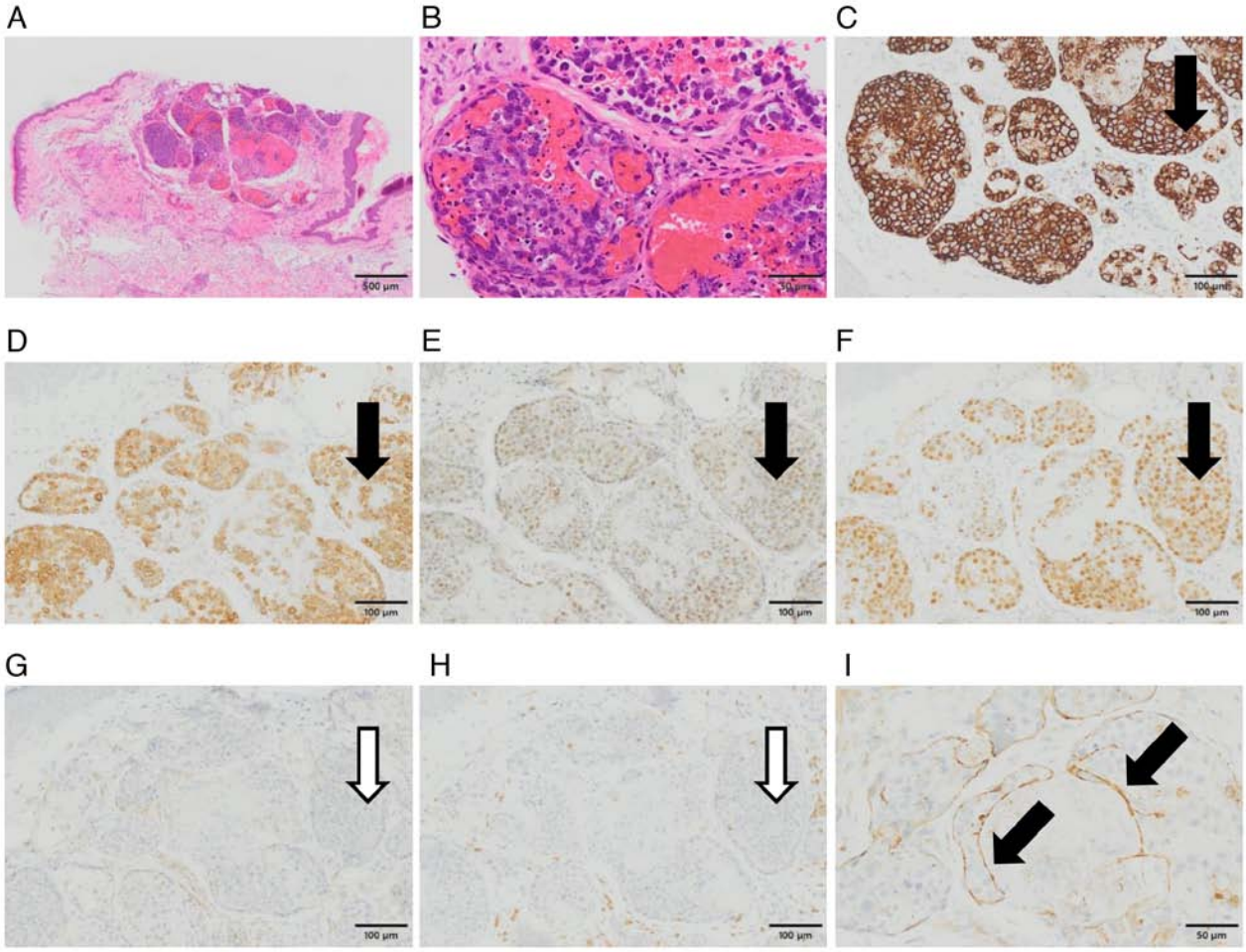


Figure 1. Histopathological and immunohistochemical features. (A) A collection of the dilated capillary vessels in the upper dermis, filled with lymphoid cells. No extravascular invasion of lymphoid cells was observed (hematoxylin and eosin staining; magnification, x4). (B) Large-sized lymphoid cells with irregular nuclei and nucleoli and apoptosis were scattered (hematoxylin and eosin staining; magnification, x40). Immunohistochemically, the lymphoid cells were positive for (C) CD20, (D) CD79a, (E) Bcl-6 and (F) MUM1 (magnification, x20). The black arrows indicated areas that were typically positive for lymphoma cells. The atypical cells were negative for (G) CD10 and (H) CD3 (magnification, x20). The white arrows indicated areas that were typically negative for them. (I) CD31 was expressed surrounding the lymphoma cell cluster (black arrows), indicating its intravascular localization (magnification, x40). Bcl-6, B-cell lymphoma 6; CD, cluster of differentiation; MUM1, multiple myeloma oncogene 1.

skin biopsies of three patients. It is worth mentioning that in the patient presented in the current study (Case 21), IVLBCL was diagnosed only by biopsy of a cherry angioma, while no random skin biopsies were performed. With regard to the positive rates per procedure for the diagnosis of IVLBCL according to the data in Table II, the positive rate was 67% (18/27) for biopsies of cherry angiomas and 25% (4/16) for random skin biopsies. In cases where both of them were performed (5 cases), the positive rate was 70% (7/10) for biopsy of cherry angioma and 25% (4/16) for random skin biopsy. Despite the small number of reports and possible publication bias, these findings reaffirm the utility of cherry angioma biopsy in the diagnosis of IVLBCL and may suggest that it is superior to random skin biopsy in its diagnostic sensitivity.

Although the usefulness of random skin biopsies in the diagnosis of IVLBCL has traditionally been well recognized (4-7), random skin biopsies are not necessarily the optimal strategy for the diagnosis of IVLBCL at present. For the concrete method of random skin biopsies, it is recommended that 3-4 specimens be obtained from the thigh, abdomen and/or posterior upper arm. However, these biopsies may increase the risk of unintended prolonged bleeding, especially in patients with pancytopenia, while the positive detection rates of random skin biopsies for IVLBCL are not necessarily high (6,8). Although only 20 patients with IVLBCL involving cherry angiomas have been reported in the relevant English literature (Table II), the strategy of performing skin biopsies targeting lesions, such as cherry angiomas, may lead to a more accurate and easier diagnosis of IVLBCL. Currently, a comprehensive clinical diagnostic approach to IVLBCL has been proposed, in which each cherry angioma should be considered as a biopsy site along with random skin biopsies (6). We expect that more clinical data will be collected in the future for the diagnosis of IVLBCL using biopsies targeting specific lesions, including cherry angiomas.

Although the mechanism of retention of lymphoma cells within cherry angiomas is unclear, cherry angiomas may represent areas of lower blood flow, leading to the entrapment and subsequent occlusion of lymphoma cells in the vessels of the cherry angiomas (11). There

Table II. Clinicopathological features, diagnostic procedures and outcome of intravascular large B-cell lymphoma involving in cherry angioma.

| Case no. | Age/Sex | Sampling of cherry angioma Positive/total no. | Location | Random skin biopsy Positive/total no. | Location/depth | (Refs.) |
|---|---|---|---|---|---|---|
| 1 | 66/M | 2/multiple | Chest, back | NA | | (9) |
| 2 | 52/M | 2/3 | Trunk | NA | | (10) |
| 3 | 82/M | 1/2 | Chest | NA | | (11) |
| 4 | 81/F | 3/6 | Upper arm, trunk | NA | | (12) |
| 5 | 67/M | 1/NA | Abdomen | NA | | (13) |
| 6 | 64/F | 1/1 | Scalp | NA | | (14) |
| 7 | 55/F | 1/1 | Shoulder | NA | | (14) |
| 8 | 66/F | at least 1/NA | Thorax | NA | | (15) |
| 9 | 78/F | 1/3 | Thorax | 0/3 | Upper arm, abdomen, upper thigh/NA | (16) |
| 10 | 79/F | 1/1 | Thigh | 0/3 | Upper arm, abdomen, thigh/NA | (17) |
| 11 | 86/M | 1/1 | Abdomen | 3/4 | Abdomen, thigh/subcutis | (18) |
| 12 | 74/F | at least 1/NA | Trunk | NA | | (19) |
| 13 | 76/M | 2/2 | Precordial region | 0/3 | Forearm, abdomen, thigh/subcutis | (20) |
| 14 | 51/M | 2/3 | Precordial region, upper arm | 1/3 | Forearm, abdomen, thigh/subcutis | (20) |
| 15 | 63/F | at least 1/NA | NA | NA | | (21) |
| 16 | 76/F | 1/1 | Neck | NA | | (22) |
| 17 | NA | at least 1/NA | NA | NA | | (23) |
| 18 | 77/M | at least 1/NA | Abdomen | NA | | (24) |
| 19 | 68/M | 1/2 | NA | NA | | (25) |
| 20 | NA | at least 1/NA | NA | NA | | (26) |
| 21 | 82/M | 1/1 | Trunk | Not performed | | |

F, Female; M, Male; NA, Not available.

may be a molecular mechanism linking the growth and localization patterns of IVLBCL to the characteristics of cherry angiomas, which further *in vivo* and *in vitro* studies may be able to elucidate. The mechanism of selective intravascular growth and localization of IVLBCL is also unclear; however, it has been suggested that CD44 expression in lymphoma cells and the lack of lymphoma cells expressing CD54 (intercellular adhesion molecule-1) may be related to the peculiar growth and localization patterns of IVLBCL (17).

In conclusion, the present study described the 21st reported case of IVLBCL involving a cherry angioma. Considering the poor general condition of the patient, random skin biopsies were not performed; however, IVLBCL was successfully diagnosed by a skin biopsy of the cherry angioma. Although random skin biopsies are recognized as a useful diagnostic tool for IVLBCL, the usefulness of skin biopsies from cherry angiomas in patients with suspected IVLBCL should be further explored, due to the overlap in average patient age and predilection for these diseases.

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**Availability of data and materials**

The data generated in the present study are included in the figures and/or tables of this article.

**Authors' contributions**

YF, MI and YH conceived and designed the study. YF, MI, EY, KS, SS, TH, TS, HK and SM collected and analyzed the data. YF and YH confirm the authenticity of all the raw data. YF, MI and YH drafted the manuscript and figures. All of the authors have read and approved the final version of the manuscript.

## Ethics approval and consent to participate

The present study was conducted according to the principles of the Declaration of Helsinki. All data were anonymized. Consent for participation in the present study was obtained from the family of the patient, as the patient was unable to express his intentions owing to a decreased level of consciousness.

## Patient consent for publication

Consent for the publication of the present case report was obtained from the family of the patient, as the patient was unable to express his intentions due to a decreased level of consciousness.

## Competing interests

The authors declare that they have no competing interests.

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