

Received: 2019.01.16
Accepted: 2019.03.29
Published: 2019.06.03

Timely Diagnosis and Successful Treatment of Intravascular Large B-Cell Lymphoma in an Elderly Patient with Poor Performance Status

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1,2 **Satoshi Kaito**
ABDEFG 1 **Hideharu Muto**
ADF 1 **Shuichi Miyawaki**
ADF 2 **Kazuteru Ohashi**
ADFG 1 **Junji Tomiyama**

1 Hematology Division, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan
2 Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

Corresponding Author: Hideharu Muto, e-mail: hydemu2010@gmail.com
Conflict of interest: None declared

Patient: Male, 82
Final Diagnosis: Intravascular large B cell lymphoma
Symptoms: Altered mental state
Medication: —
Clinical Procedure: Random skin biopsy
Specialty: Hematology





Objective: Management of emergency care
Background: Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma characterized by involvement of lymphoma cells in the lumina of small blood vessels in various organs. Although many studies have claimed that timely diagnosis and early initiation of chemotherapy are important, the literature on the successful treatment of IVLBCL in elderly patients over the age of 80 years is scarce.

Case Report: An 82-year-old man presented with abnormal elevation of lactate dehydrogenase at 1605 IU/L and altered mental status, which manifested as forgetfulness, abnormal behavior, and worsening performance status for 2 days. There was no evidence of lymphadenopathy or skin lesions, but a computed tomography scan of the chest showed bilateral diffuse ground-glass opacities. With a primary consideration of IVLBCL, random skin biopsy and transbronchial lung biopsy were performed. Immediately after the pathologic findings on hematoxylin-eosin staining alone revealed abnormal large cells in the small vessels, chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) at half the usual dose was started; later on, immunostaining revealed CD20 expression in the abnormal lymphoid cells. Immediately after CHOP administration, his mental and physical symptoms rapidly resolved. After 8 cycles of dose-reduced CHOP with rituximab, he remained free from disease progression 2 years after the diagnosis.

Conclusions: We presented a case of successful early chemotherapy for IVLBCL in an elderly patient with poor performance status. Early chemotherapy with CHOP, even before obtaining a definitive diagnosis based on immunostaining, may contribute to good outcomes.

MeSH Keywords: Antineoplastic Agents • Frail Elderly • Lymphoma, B-Cell

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/915189>

 1592   3  15



Background

Intravascular large B-cell lymphoma (IVLBCL) is a rare type of extranodal large B-cell lymphoma that is characterized by the involvement of lymphoma cells within the lumina of small blood vessels, without an obvious extravascular tumor mass [1]. The nonspecific clinical symptoms, such as malaise, neurologic disturbances, and deterioration in performance status (PS), as well as the absence of lymphadenopathy, make accurate and timely diagnosis difficult [2]. IVLBCL typically occurs in patients older than 60 years [2]. In several cases of elderly patients with IVLBCL, time had been usually insufficient for clinicians to make a definitive diagnosis, and the general status of patients declines due to disease progression. Delayed diagnosis and hesitation to start treatment can result in fatal organ failure due to the occlusion of blood vessels and cytokine storm.

The diagnosis of IVLBCL requires histologic confirmation by organ biopsies; however, no standard procedure has been established. In an Asian cohort, although the most relevant diagnostic site seemed to be the bone marrow, 1/3 of the cases had no bone marrow involvement or hemophagocytic syndrome [2]. In such patients, random skin biopsies are promising for prompt diagnosis [3,4]; in fact, its use has increased in a number of IVLBCL patients who were diagnosed antemortem. In patients with respiratory symptoms or radiologic findings, lung biopsy could be a useful diagnostic procedure [5–7].

Although many studies claimed that timely diagnosis and early initiation of chemotherapy are important, the literature on the successful treatment of IVLBCL in elderly patients over the age of 80 years is scarce. In this report, we present an 82-year-old patient with poor PS and who was successfully treated

for IVLBCL, which was diagnosed by random skin biopsy and transbronchial lung biopsy (TBLB).

Case Report

An 82-year-old Japanese man presented to our hospital because of altered mental status, which manifested as forgetfulness, abnormal behavior, and worsening PS for 2 days. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain indicated no abnormal results. However, blood test showed abnormal elevation of lactate dehydrogenase (LDH) at 1605 IU/L. At this time, the etiology of the symptoms and elevated LDH was unclear and we continued the follow-up observation with planned further examinations. There was transient improvement, but the symptoms recurred immediately. Eight days later, he visited our hospital again for emergency admission and detailed examination of increasing LDH level. He had been prescribed an antiandrogen agent for his prostate cancer, which was well-managed. His family and social history were unremarkable. Upon physical examination, there was no evidence of lymphadenopathy, skin lesions, or focal neurologic deficit. The lungs were clear on auscultation. The abdomen was non-tender, without a palpable mass or hepatosplenomegaly.

Laboratory data on admission were as follows: white blood cell count 5300/ μ L, hemoglobin 12.7 g/dL, platelets 200 000/ μ L, LDH 3040 IU/L, C-reactive protein 4.30 mg/dL, soluble interleukin-2 receptor 1263 U/mL, and normal Krebs von den Lungen-6 (KL-6) at 284 U/mL. An LDH isozyme test suggested a potential for hematologic malignancy. There was no abnormal finding on cerebrospinal fluid examination. A CT scan of the chest showed bilateral diffuse ground-glass opacities (GGOs) (Figure 1A).

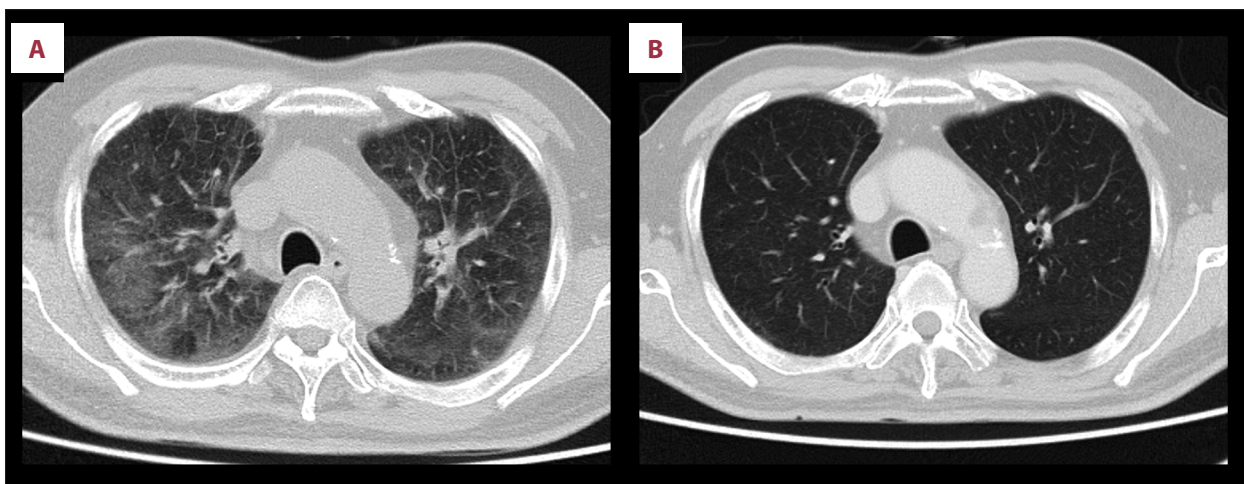


Figure 1. Computed tomography of the chest in the patient. (A) Upon diagnosis, there were bilateral diffuse GGOs. (B) These GGOs disappeared after 2 cycles of R-CHOP. GGOs – ground-glass opacities; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone.

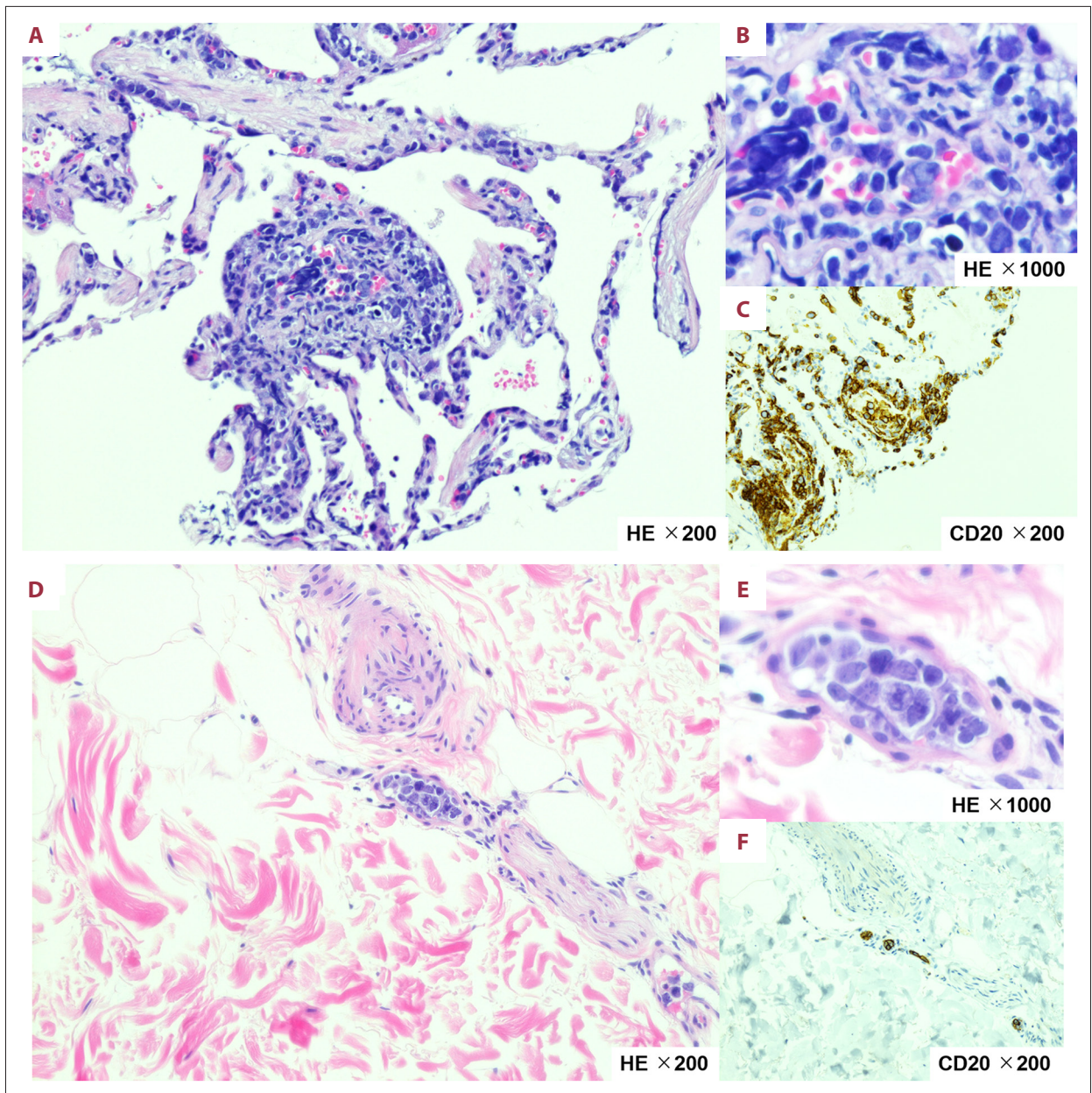


Figure 2. Pathological studies on transbronchial lung and skin biopsies. Tissue obtained by transbronchial lung biopsy reveals large intravascular lymphoid cells with atypical nuclei in the alveolar capillaries (A, HE $\times 200$ and B, HE $\times 1000$); these cells were positive for the B-cell marker CD20 on immunostaining (C). Skin biopsy of the subcutaneous adipose tissue of the abdomen (D, E) showing large intravascular lymphoid cells with atypical nuclei (HE), which were positive for the B-cell marker CD20 on immunostaining (F). HE – hematoxylin-eosin.

Random skin biopsy, bone marrow test, and TBLB were performed on hospitalization days 2 to 4. There was no abnormal finding on bone marrow testing. Soon after these tests and while waiting for the results, we started 1 mg/kg of prednisolone for rapidly progressive disease, which we strongly considered as IVLBCL at this point.

On hospitalization day 10, his LDH level increased to 4433 U/L despite the prednisolone treatment. At this time, the skin biopsy and TBLB specimens revealed abnormal large cells in the small vessels on hematoxylin-eosin (HE) staining (Figure 2). Although the results of immunostaining were not available yet at this time, we started to administer half the usual dose of CHOP (cyclophosphamide 375 mg/m², doxorubicin 25 mg/m², and vincristine 0.7 mg/m² on day 1, and prednisolone 100 mg

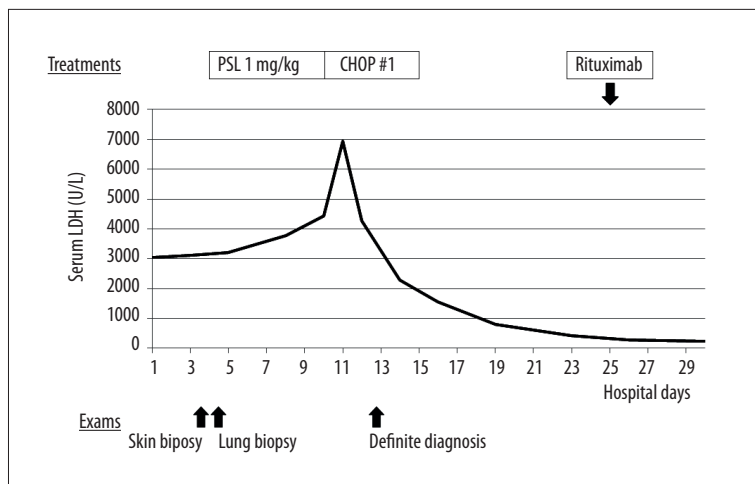


Figure 3. Clinical course of the patient, focusing on the initial therapy. CHOP – cyclophosphamide, doxorubicin, vincristine and prednisolone; HE – hematoxylin-eosin; LDH – lactate dehydrogenase; PSL – prednisolone.

on days 1 to 5). Immediately after CHOP administration, his mental and physical symptoms rapidly resolved.

On hospitalization day 13, the definitive diagnosis of IVLBCL was confirmed by positive CD20 immunostaining. The TBLB specimens and subcutaneous adipose tissue samples from the abdomen revealed large CD20-positive lymphoid cells with prominent nucleoli within the lumina of the alveolar capillaries (Figure 2). Thereafter, on hospitalization day 25, rituximab (375 mg/m²) was additionally administered to avoid tumor lysis syndrome.

The serum LDH level decreased to within the normal range after the 1st cycle of chemotherapy (Figure 3). No severe adverse effects were found, except for grade 4 leukopenia and neutropenia during the 1st cycle. After the 2nd cycle of chemotherapy, there was resolution of the GGOs on a repeat chest CT scan (Figure 1B). On hospitalization day 40, he was discharged ambulatory. He eventually underwent a total of 8 cycles of dose-reduced CHOP with rituximab (R-CHOP) every 3 weeks. We avoided intrathecal anticancer agents for prophylaxis because of his vulnerability and the possible adverse effect of dementia progression. Thus far, no disease progression has been recognized 2 years after diagnosis.

Discussion

The diagnosis of IVLBCL can be challenging because of its nonspecific presentation. In this case, aside from IVLBCL, interstitial pneumonia was considered as another differential diagnosis based on the bilateral diffuse GGOs. However, the normal value of KL-6 was not consistent with interstitial pneumonia [8]. Our primary diagnosis was IVLBCL because of the marked LDH elevation, the LDH isozyme test that showed a potential for hematologic malignancy without lymphadenopathy, and his symptoms.

Although a bone marrow biopsy is performed in almost all cases suspected to have IVLBCL, its sensitivity is relatively low. However, random skin biopsy was reported to be a useful minimally invasive procedure for the definitive diagnosis of IVLBCL [3,5,9,10]; in such cases, the specimens are usually taken from the middle adipose tissue of the extremities and the abdomen because these contain a higher percentage of atypical lymphoid cells compared with the other layers of the skin [9]. Although several reports have indicated that IVLBCL cells were detected more frequently in skin lesions such as erythema, purpura, pigmented macules, or senile hemangioma than in normal-appearing skin [10], it is still important to perform random skin biopsy in cases without any skin lesions, such as the present case.

Although relatively rare, IVLBCL presenting as a primary lesion in the lung, as seen on autopsy findings, has been reported [11]. Therefore, in patients who have respiratory symptoms or radiologic findings that are suspicious for IVLBCL, a lung biopsy should be considered. Among the several biopsy options of transbronchial, open lung, or video-assisted thoracoscopic surgery, we chose TBLB because of the general condition of the patient. TBLB is less invasive and is performed without general anesthesia; although its sensitivity might be lower than that of the other options [6,7], it remains an important diagnostic option.

Although the standard therapy for IVLBCL has not been established, addition of rituximab, which is a chimeric anti-CD20 monoclonal antibody, to CHOP has been widely accepted to improve the outcome of IVLBCL, with estimated progression-free and overall survival rates of 56% and 66%, respectively, 2 years after diagnosis [12]. These data indicated that a good prognosis could be expected if the diagnosis is confirmed antemortem and the patients receive appropriate chemotherapy. In the present case, CHOP at only half the usual dose was administered as soon as the pathologic findings of HE staining

alone revealed abnormal large cells in the small vessels and before immunostaining revealed CD20 expression in the abnormal lymphoid cells; we believed that this rapid decision could have led to a good outcome in this case.

We chose half-dosage CHOP because of our primary concerns for safety and sustainability in a very old patient. Although several studies included IVLBCL patients over 80 years old [2,3,10,12], few studies have focused on the treatment or survival outcome of this subgroup. An attenuated CHOP regimen, which has almost the same dose as that of our case, was reported to be generally tolerable among diffuse large B-cell lymphoma patients over 80 years old, with 2-year overall survival of 59% [13]. We speculated that the attenuated CHOP regimen would also be tolerable and contribute to good outcomes in IVLBCL patients over 80 years old.

Because IVLBCL is a very rare disease and the amount of tumor cells that can be obtained from specimens is usually insufficient, the underlying pathogenesis has been difficult to understand. A recent xenograft mouse models study revealed that the IVLBCL cells demonstrated suppression of the gene sets associated with cell migration and survival dependency on vascular endothelial cells [14]. A combination of these mechanisms might produce the specific characteristics of IVLBCL and make the diagnosis difficult. A recent report by Suehara et al. showed the usefulness of liquid biopsy to detect specific gene

mutations in IVLBCL cells by targeted sequencing [15]. This method could be a powerful tool for earlier diagnosis of IVLBCL.

Conclusions

In summary, we showed the successful treatment of an 82-year-old man with poor PS who was diagnosed with IVLBCL by random skin biopsy and TBLB. Prompt performance of these examinations entailed cooperation among the departments of dermatology, pathology, respiratory, and hematology. Even in elderly patients over the age of 80 years and with poor PS, timely diagnosis and early initiation of chemotherapy can lead to successful management of IVLBCL. Early initiation of chemotherapy with CHOP before obtaining a definitive diagnosis by immunostaining can contribute to good outcomes, as shown in this case.

Acknowledgement

The authors would like to thank the nursing staff at Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan, for their excellent patient care.

Conflict of interest

None.

References:

1. Ponzoni M, Ferreri AJ, Campo E et al: Definition, diagnosis, and management of intravascular large B-cell lymphoma: Proposals and perspectives from an international consensus meeting. *J Clin Oncol*, 2007; 25: 3168–73
2. Murase T, Yamaguchi M, Suzuki R et al: Intravascular large B-cell lymphoma (IVLBCL): A clinicopathologic study of 96 cases with special reference to the immunophenotypic heterogeneity of CD5. *Blood*, 2007; 109: 478–85
3. Matsue K, Asada N, Odawara J et al: Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. *Ann Hematol*, 2011; 90: 417–21
4. di Fonzo H, Contardo D, Carrozza D et al: Intravascular large B cell lymphoma presenting as fever of unknown origin and diagnosed by random skin biopsies: A case report and literature review. *Am J Case Rep*, 2017; 18: 482–86
5. Shimada K, Kinoshita T, Naoe T, Nakamura S: Presentation and management of intravascular large B-cell lymphoma. *Lancet Oncol*, 2009; 10: 895–902
6. Peng M, Shi J, Liu H, Li G: Intravascular large B cell lymphoma as a rare cause of reversed halo sign: A case report. *Medicine (Baltimore)*, 2016; 95: e3138
7. Takamura K, Nasuhara Y, Mishina T et al: Intravascular lymphomatosis diagnosed by transbronchial lung biopsy. *Eur Respir J*, 1997; 10: 955–57
8. Ohnishi H, Yokoyama A, Kondo K et al: Comparative study of KL-6, surfactant protein-A, surfactant protein-D, and monocyte chemoattractant protein-1 as serum markers for interstitial lung diseases. *Am J Respir Crit Care Med*, 2002; 165: 378–81
9. Maekawa T, Komine M, Murata S et al: Random skin biopsy of patients with intravascular large B-cell lymphoma associated with thrombocytopenia and coagulation abnormalities: Proposal of a modified biopsy method. *J Dermatol*, 2015; 42: 318–21
10. Arai T, Kato Y, Funaki M et al: Three cases of intravascular large B-cell lymphoma detected in a biopsy of skin lesions. *Dermatology*, 2016; 232: 185–88
11. Wick MR, Mills SE, Scheithauer BW et al: Reassessment of malignant “angioendotheliomatosis”. Evidence in favor of its reclassification as “intravascular lymphomatosis”. *Am J Surg Pathol*, 1986; 10: 112–23
12. Shimada K, Matsue K, Yamamoto K et al: Retrospective analysis of intravascular large B-cell lymphoma treated with rituximab-containing chemotherapy as reported by the IVL study group in Japan. *J Clin Oncol*, 2008; 26: 3189–95
13. Peyrade F, Jardin F, Thieblemont C et al: Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol*, 2011; 12: 460–68
14. Shimada K, Shimada S, Sugimoto K et al: Development and analysis of patient-derived xenograft mouse models in intravascular large B-cell lymphoma. *Leukemia*, 2016; 30: 1568–79
15. Suehara Y, Sakata-Yanagimoto M, Hattori K et al: Liquid biopsy for the identification of intravascular large B-cell lymphoma. *Haematologica*, 2018; 103: e241–44