American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 482-486
DOI: 10.12659/AJCR.903816

Received: 2017.02.15
Accepted: 2017.03.02
Published: 2017.05.02

Intravascular Large B Cell Lymphoma Presenting as Fever of Unknown Origin and Diagnosed by Random Skin Biopsies: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Female, 66
Final Diagnosis: Intravascular B-cell lymphoma
Symptoms: Fever of unknown origin
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: Intravascular lymphoma (IVL) is a rare lymphoproliferative disorder characterized by the proliferation of large B lymphoma cells within the lumen of small-caliber blood vessels. Clinical features are nonspecific, presenting as a systemic disease with fever and may be life-threatening. Antemortem diagnosis is difficult but may be made with biopsies of affected tissues or with random skin biopsies.

Case Report: We report the case of a 66-year-old white woman presenting with fever of unknown origin (FUO) who developed neurologic, pulmonary, and hematologic manifestations. The diagnosis of intravascular large B cell lymphoma (IVLBCL) was made by random skin biopsies. She received treatment with steroids, rituximab, cyclophosphamide, vincristine, and doxorubicin (R-CHOP). Her disease evolution was unfavorable and she died after her first cycle of chemotherapy.

Conclusions: Our case illustrates that IVL can present as FUO and should be considered in the differential diagnosis of this syndrome, especially in patients with neurologic compromise and persistently elevated serum lactate dehydrogenase. In this case, the diagnosis was made with cutaneous biopsies of visibly unaffected skin. As in our patient, the course of IVL is usually fatal within a few months.

MeSH Keywords: Fever of Unknown Origin • Lymphoma, B-Cell • Lymphoproliferative Disorders

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/903816

Background

Intravascular lymphoma (IVL) is an uncommon subtype of lymphoproliferative disorder characterized by the proliferation of neoplastic cells within the lumen of small-caliber blood vessels [1,2]. This type of lymphoma was first reported in 1959 by Pfleger and Tappeiner in Germany as "angio-endotheliomatosis proliferans systemisata" and was considered to be endothelial in origin [1].

This disorder exhibits a life-threatening clinical course of a systemic disease, with predominant neurologic, hematologic, skin, bone marrow, and pulmonary involvement. The course and evolution are unfavorable due to aggressive behavior and late diagnosis. In recent years, the number of patients with IVL diagnosed antemortem has increased, mainly due to better knowledge of this disease [1–3].

The IVL diagnosis may be made by biopsies of compromised tissues or by random skin biopsy of visibly unaffected skin [4].

We describe the case of a 66-year-old white woman with IVL presenting as fever of unknown origin (FUO) of 1-year evolution and a progressive behavior with predominantly neurologic and pulmonary compromise.

Case Report

A 66-year-old woman was admitted for fever and left hemiparesis. One year before, she had FUO and pericardial effusion with a pericardial biopsy showing unspecified chronic pericarditis. The patient continued with recurrent fever in the last 12 months. One day before admission, she developed left hemiparesis and was admitted to our institution.

Physical examination on admission revealed fever (38–38.5°C), skin pallor, and mild left hemiparesis. No lymphadenopathy, hepatosplenomegaly, cardiac murmurs, pulmonary abnormal sounds, or cutaneous lesions were present.

Laboratory evaluations were: hemoglobin (Hb) 9.6 gr/dL with a mean corpuscular volume of 88 fl and reticulocytes of 1%. White blood cells were 4.7×10^9/L (neutrophils 80%, lymphocytes 12%, and monocytes 8%) and platelet count 240×10^9/L. Serum C-reactive protein (CRP) was 8 mg/dl and the erythroid sedimentation rate was 129 mm/h. Serum AST and ALT was slightly elevated and serum lactic dehydrogenase (LDH) was severely elevated (1692 UI/L). Serum ferritin was 1650 mg/dl. The total serum protein was decreased, as were albumin and gammaglobulin, without paraprotein. Urinalysis was normal. Blood and urine cultures were negative. An HIV antibody test was negative, as were HBsAg, HCV, Epstein-Barr virus IgM, Huddleson test, VDRL, toxoplasmosis antibodies, cytomegalovirus (CMV) antibodies, and CMV-polymerase chain reaction. The antinuclear antibody test was negative, as were anti-DNA antibody, antineutrophil cytoplasmic antibodies, rheumatoid factor, antiphospholipid antibodies, cryoglobulins, and serum complement.

A trans-esophageal echocardiogram, a computer tomography (CT) of the thorax, abdomen, and pelvis were normal, and a positron emission tomography (PET-CT) scan did not show abnormal images.

An MRI showed multiple and bilateral ischemic brain images (Figure 1A, 1B).

Cerebral spine fluid (CSF) cytology and flow cytometry examinations were normal.

Bone marrow (BM) examination with immunohistochemistry and flow cytometry showed normal cellularity without neoplastic cells.

Suspecting systemic vasculitis with central nervous system (CNS) compromise, 1000 mg/d IV of methylprednisolone for 3 doses was indicated. However, the patient continued with fever and worsening hemiparesis and she developed dyspnea with hypoxemia; a thoracic CT scan was performed showing bilateral consolidative images (Figure 2A, 2B).

Suspecting infectious pneumonia, antibiotic treatment was started without improvement and progressive hypoxemia developed. Cultures of blood, urine, and bronchoalveolar lavage fluid were negative.

Due to progressive neurologic manifestations, pulmonary involvement, unremitting fever without evidence of infectious or immunologic disease, and persistently elevated serum LDH, an intravascular lymphoma (IVL) was suspected. To confirm this diagnosis, cutaneous random biopsies were made. These biopsies revealed atypical lymphocytes within the small vessels of the dermis and hypodermis. The immunophenotype was consistent with B cell phenotype, showing CD20, PAX5, and BCL2 expression and high proliferation index with Ki67 (80%) (Figures 3, 4).

With the confirmed diagnosis of IVLBC, chemotherapy with R-CHOP was started. However, rituximab had to be withdrawn during the first infusion because the patient developed arterial hypotension and her hypoxemia worsened.

The patient's evolution was unfavorable, with respiratory insufficiency and new neurological events, and she died a few days after the first cycle of chemotherapy.

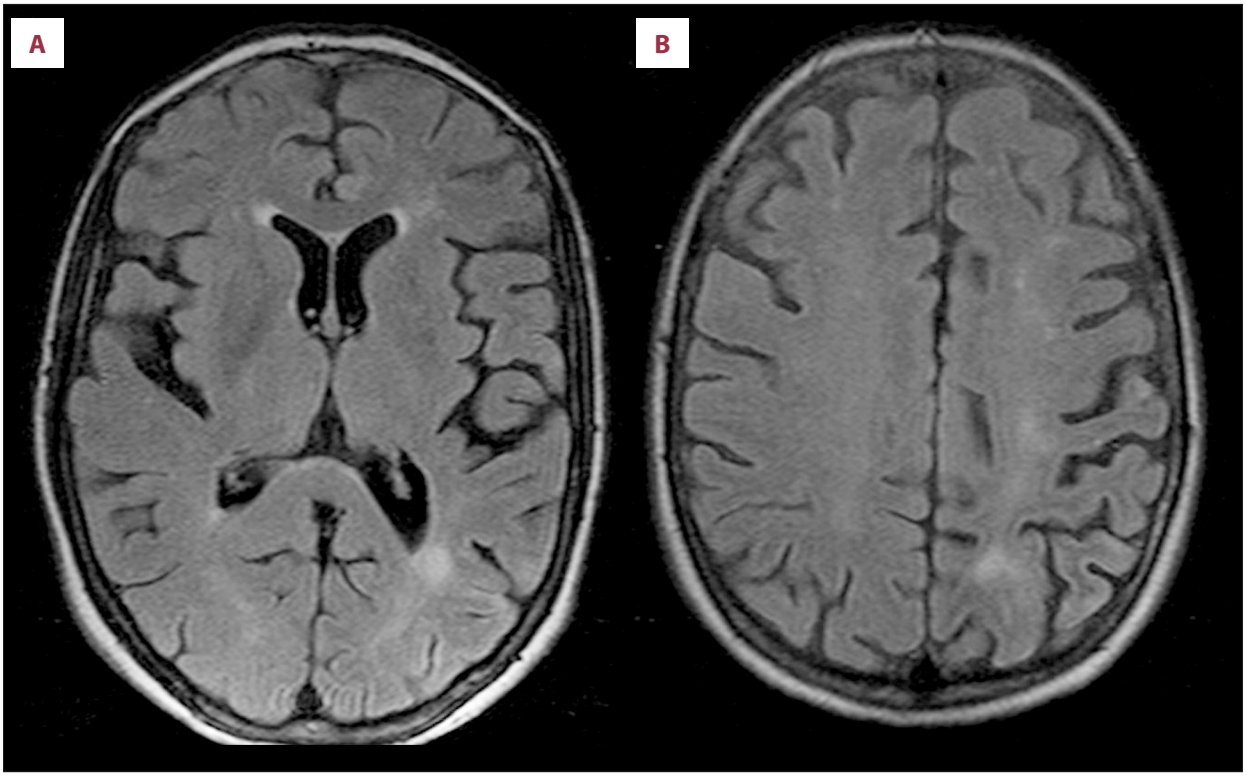

Figure 1. (**A, B**) Brain MRI. FLAIR (fluid attenuated inversion-recovery). Multiple hyperintense brain lesions.

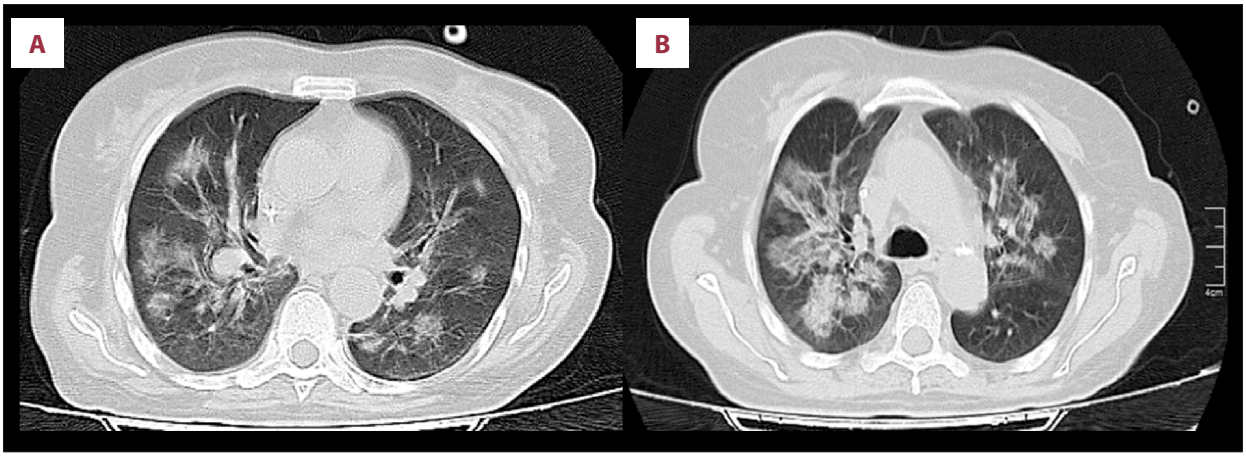

Figure 2. (**A, B**) Thoracic CT. Bilateral consolidative images.

Discussion

IVL is a clinically aggressive form of extranodal non-Hodgkin's lymphoma, characterized by the proliferation of neoplastic cells within the lumen of small blood vessels [1–3].

The confinement of lymphoma cells to the intravascular space may be explained by the absence of CD29 (b1 integrin) and CD54 (ICAM-1) surface ligands [5].

The most prevalent phenotype is B cell lymphoma. In a review of 740 patients with IVL, 651 (88%) had a diagnosis of B cell lymphoma. T cell lymphoma and NK cell lymphoma were infrequent [1,6].

IVL typically occurs in elderly patients and is equally common in men and women. In a review of 106 cases the median age was 67 years (range 34–84), and 72% were older than 60 years [7].

The clinical presentation is highly variable and antemortem diagnosis is difficult. A study of 10 cases of IVL reported that

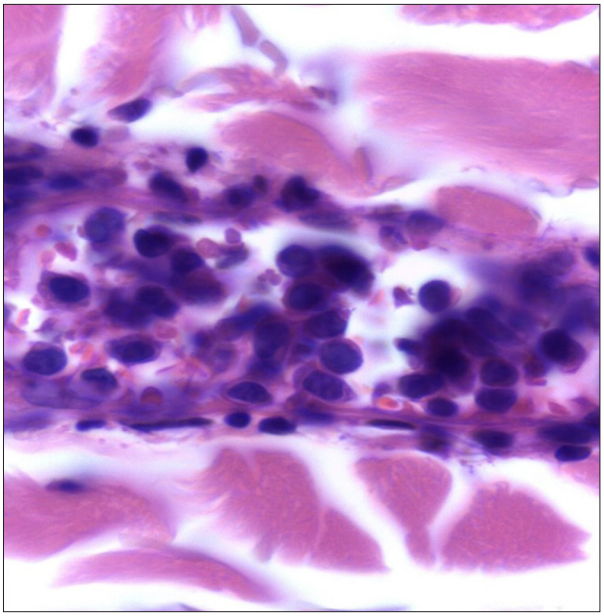

Figure 3. Atypical large lymphoid cells within the lumina of small blood vessels (H&E, 1000× immersion oil).

FUO and a neurologic disorder were the most common signs, present in 60% of cases [8]. The duration of FUO ranged from 2 to 6 months. In our patient, FUO had been present for 1 year until the diagnosis of IVL was made.

Laboratory tests are nonspecific and usually show anemia, and elevated serum LDH and CRP levels. All these alterations were present in our patient.

The central nervous system (CNS) is affected in almost two-thirds of cases in Western patients with IVL [3,4,6]. Asian and non-Asian patients may have different presentations of IVL. In IVL patients of Asian origin (the Asian-variant IVL), hemophagocytic syndrome is the most relevant clinical manifestation [9,10].

This disorder generally has a rapidly fatal outcome within a few months and the diagnosis is made postmortem in up to 50% of cases [1]. Because IVL is frequently not considered in the differential diagnosis, as well as the usual absence of BM and lymph nodes involvement, it is difficult to biopsy the affected tissue [1,6,11].

Patients with CNS IVL usually manifest stroke-like symptoms, as in our case [12,13]. The most commonly reported MRI findings in the CNS are multifocal lesions that are hyperintense on T2-weighted images, mimicking small infarctions. They usually do not cause gadolinium enhancement [14,15]. The role of PET-CT in IVL is limited. As shown by our patient's CNS involvement, advanced age, and very high serum LDH are factors of worse prognosis and are correlated with shortened survival.

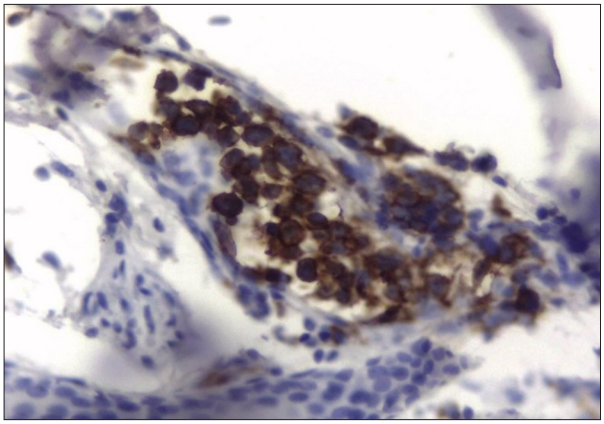

Figure 4. CD20-positive neoplastic lymphoid cells (IHQ, 400×).

Lung compromise may be demonstrated in up to 60% of IVL cases at autopsy. Primary lung IVL is extremely rare and only a few cases have been reported. Respiratory involvement is manifested clinically with dyspnea, fever, and hypoxemia, as in our case. Thoracic CT may show interstitial opacities, nodules, and alveolar infiltrates. Diagnosis may be made with transbronchial biopsies or lung surgical biopsy [16]. In our case, although postmortem examination was not performed, the lung manifestations were considered as probably due to IVLBCL.

Western and Japanese patients featured skin lesions in 34% and 28% of cases, respectively. This cutaneous compromise may be in the form of erythema, purpura, nodules, and plaques, with or without swelling. These skin manifestations often are misdiagnosed, but they are useful in diagnosis because of easy accessibility in obtaining multiple specimens [17].

Lack of cutaneous lesions does not correlate with the absence of skin compromise. The involvement of clinically unaffected skin has been reported in autopsy findings, and this involvement serves as the basis for a random skin biopsy. Random skin biopsies often demonstrate lymphoma cells in normal-appearing skin, as shown in our case [4,18,19].

Treatment for IVL is identical to that for systemic large B cell lymphoma. A combination of cyclophosphamide, doxorubicin, vincristine, and prednisone with the recombinant anti-CD20 antibody rituximab (R-CHOP) is the most common treatment and can improve complete remission and patient survival [7,20].

Conclusion

We report a case of IVLBCL in a 66-year-old women presenting with chronic FUO with stroke- like neurologic manifestations and progressive lung compromise.

IVL is a rare subtype of lymphoproliferative disorder that should be considered in differential diagnosis of FUO in patients with systemic compromise and persistently elevated serum LDH.

In this case, a random skin biopsy confirmed the diagnosis of IVLBCL.

Random skin biopsy is an easily accessible and minimally invasive method to confirm the diagnosis of IVL.

The overall prognosis of IVL is poor, but chemotherapy with rituximab-based regimens can improve evolution and survival.

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Acknowledgements

The authors would like to thank Andrea di Fonzo for her assistance in translating this paper.

Conflict of Interest

None declared.