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# To Present a Case of the Disseminated Intravascular Large B-Cell Lymphoma Presenting as Fever of Unknown Origin

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## Abstract

**Background:** Intravascular large B-cell lymphoma (IVLBCL) is a rare type of non-Hodgkin's lymphoma (NHL) characterized by the selective growth of neoplastic cells within blood vessel lamina. The precise mechanisms responsible for this distinctive behavior are at the moment largely unknown. By the time of presentation, most patients have advanced, disseminated disease, and often the diagnosis is made at autopsy. Diagnosis requires skin, liver, lung, bone marrow, renal, meningeal, or brain vessel biopsy but is often made only when the illness has progressed or post mortem because early involvement of organs was not evident.

**Discussion:** We report a case of Intravascular lymphoma who presented as fever of unknown origin. In this case, initial laboratory test results were unremarkable. Computed Tomography of the chest and abdomen as well as bone marrow aspiration and biopsy were negative for malignancy. Patient developed neurologic symptoms and expired due to complications. Autopsy was done which revealed Disseminated Intravascular Diffuse Large B-cell Lymphoma.

**Conclusion:** Without treatment, intravascular lymphoma is rapidly fatal. Ante-mortem diagnosis is challenging and indefinable. A high index of suspicion followed by biopsy of the organs suspected to be involved, together with early institution of treatment are of utmost importance in approaching these kinds of patients.

**Keywords:** Disseminated;Intravascular; Lymphoma; B-Cell

## Introduction

Intravascular lymphoma (IVL) is an uncommon subtype of lymphoproliferative disorder characterized by the proliferation of neoplastic cells within the lumen of small-caliber blood ves-sels [1]. This type of lymphoma was first reported in 1959 by Pfleger and Tappeiner in Germany as "angio-endothelioma-tosis proliferans systemisata" and was considered to be en-dothelial in origin .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 bet-ter knowledge of this disease [2]. The IVL diagnosis may be made by biopsies of compromised tissues or by random skin biopsy of visibly unaffected skin [3].We describe the case of a 66-year-old white woman with IVL presenting as fever of unknown origin (FUO) of 1-year evolu-tion and a progressive behavior with predominantly neurolog-ic and pulmonary compromise.

A 66-year-old woman was admitted for fever and left hemipa-resis. One year before, she had FUO and pericardial effusion with a pericardial biopsy showing unspecified chronic pericar-ditis. The patient continued with recurrent fever in the last 12 months. One day before admission, she developed left hemi-paresis 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 4.7×109/L (neutrophils 80%, lympho-cytes 12%, and monocytes 8%) and platelet count 240×109/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, cytomegalo-virus (CMV) antibodies, and CMV-polymerase chain reaction [4]. 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 ab-normal images.An MRI showed multiple and bilateral ischemic brain imag-es (Figure 1A, 1B).Cerebral spine fluid (CSF) cytology and flow cytometry exam-inations were normal.Bone marrow (BM) examination with immunohistochemistry and flow cytometry showed normal cellularity

without neo-plastic 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. Suspecting infectious pneumonia, antibiotic treatment was started without improvement and progressive hypoxemia de-veloped. Cultures of blood, urine, and bronchoalveolar lavage fluid were negative.Due to progressive neurologic manifestations, pulmonary in-volvement, 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 ves-sels 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 arteri-al hypotension and her hypoxemia worsened.The patient's evolution was unfavorable, with respiratory in-sufficiency and new neurological events, and she died a few days after the first cycle of chemotherapy [5].

## 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.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 in-frequent. 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.The clinical presentation is highly variable and antemortem diagnosis is difficult. A study of 10 cases of IVL reported that FUO and a neurologic disorder were the most common signs, present in 60% of cases. 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 . Asian and non-Asian patients may have different presentations of IVL. In IVL patients of Asian origin (the Asian-variant IVL), hemo-phagocytic syndrome is the most relevant clinical manifesta-tion.This disorder generally has a rapidly fatal outcome within a few months and the diagnosis is made postmortem in up to 50% of cases. 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 af-fected tissue. Patients with CNS IVL usually manifest stroke-like symptoms, as in our case.

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 trans-bronchial biopsies or lung surgical biopsy. In our case, al-though 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 mis-diagnosed, but they are useful in diagnosis because of easy accessibility in obtaining multiple specimens.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 involve-ment 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.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 an-tibody rituximab (R-CHOP) is the most common treatment and can improve complete remission and patient survival.

## Conclusion

We report a case of IVLBCL in a 66-year-old women present-ing with chronic FUO with stroke- like neurologic manifesta-tions and progressive lung compromiseIVL 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 in-vasive 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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