

Intravascular large B-cell lymphoma complicated by invasive pulmonary aspergillosis: a rare presentation

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Abstract

We describe a patient with persisting fevers, a progressive pulmonary infiltrate, and high levels of serum lactate dehydrogenase. No underlying cause for these changes was found prior to her death despite extensive investigations. Postmortem tissue revealed invasive pulmonary aspergillosis and subsequent brain examination revealed vascular changes in keeping with intravascular large B-cell lymphoma (IVLBCL). On review, subtle yet extensive lymphomatous infiltrates involved the vasculature of multiple other organs, including the lungs. Aspergillosis is a relatively rare presenting feature of lymphoproliferative disorders, and IVLBCL is a rare subtype of diffuse large B-cell non-Hodgkin's lymphoma with, to our knowledge, very few case reports to date. Lymphoma should be considered in patients presenting with pneumonitis with bilateral lung infiltrates on imaging, with a high serum level of lactate dehydrogenase.

Introduction

Intravascular large B-cell lymphoma (IVLBCL) is a rare subtype of diffuse large B-cell lymphoma with a distinct intravascular proliferation of clonal lymphocytes with little to no infiltration into the surrounding tissues resulting in the absence of marked lymphadenopathy. The clinical presentation is highly variable, ranging from no or limited organ involvement to multiple organ failure due to ischemic injury by the dense intravascular collections of lymphoma cells causing luminal obstruction and hence impeding vascular supply. These features often result in delayed diagnosis, further compounding the aggressive course and extremely poor prognosis of this disease. Furthermore, aspergillosis is a rare presenting feature in patients with IVLBCL, with only very few cases reported previously to our knowledge [1].

Case Report

A 70-year-old woman of Asian ethnicity was admitted to the respiratory unit of a tertiary referral hospital with a 4-month history of progressive dyspnea on exertion, dry cough, intermittent high fevers to 39°C, and weight loss. She had been treated with various wide-spectrum antibiotics without any improvement. She had an unremarkable medical history prior to this illness with no past history of lung disease and smoking. Her physical examination was normal.

Blood findings were all within the normal range, except for a very high lactate dehydrogenase (LDH) 1977 U/L ($n < 220$), a mildly elevated aspartate transaminase 117 U/L (normal range: 5–55) and an erythrocyte sedimentation rate of 46 mm/h ($n < 20$). Viral serology for human immunodeficiency virus, hepatitis B and C were negative. Flow

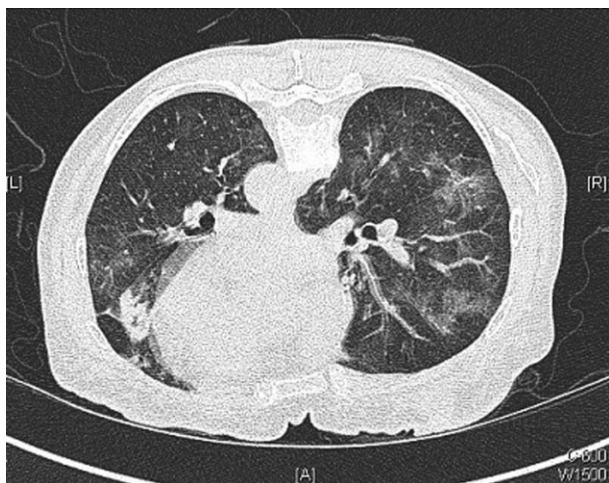


Figure 1. Computed tomography scan shows patchy ground-glass opacities throughout both lungs with lower-lobe predominance.

cytometry on blood did not show any abnormal lymphoid population.

Pulmonary function tests showed severe reduction of diffusing lung capacity for carbon monoxide and normal lung volume. High-resolution computed tomography of the lungs revealed ground-glass change in the right-middle and left-lower lobes with no lymphadenopathy (Fig. 1). Ziehl–Neelsen staining of sputum was negative for acid-fast bacilli. Bronchoscopy, bronchoalveolar lavage, and transbronchial lung biopsies from the right-middle and lower lobes were reported as being suggestive of nonspecific interstitial pneumonitis, for which she was treated as an outpatient with oral corticosteroids (25 mg daily) for 3 weeks with some clinical improvement in terms of symptoms and lung function. However, the fevers recurred and she was readmitted for further investigation to exclude infection.

Her clinical condition progressed over a period of approximately 10 weeks. She was transferred to the intensive care unit where she received broad-spectrum antibiotics and antifungal cover. Despite this, she developed progressive multiorgan failure and died.

At autopsy, there were multiple small solid-grey nodules within the lower lobes of both lungs, 3–6 mm in maximum dimension. Microscopically, these nodules were necrotic foci containing large amount of septate fungal hyphae branching at acute angles, consistent with necrotizing pneumonia caused by invasive aspergillosis. This was confirmed on cultures of the lung tissue and respiratory secretions.

In the preliminary autopsy report, no underlying cause for the pulmonary aspergillosis was identified. Several weeks later, brain examination revealed multiple macroscopic areas of purple discoloration 0.2–3.0 cm in dimen-

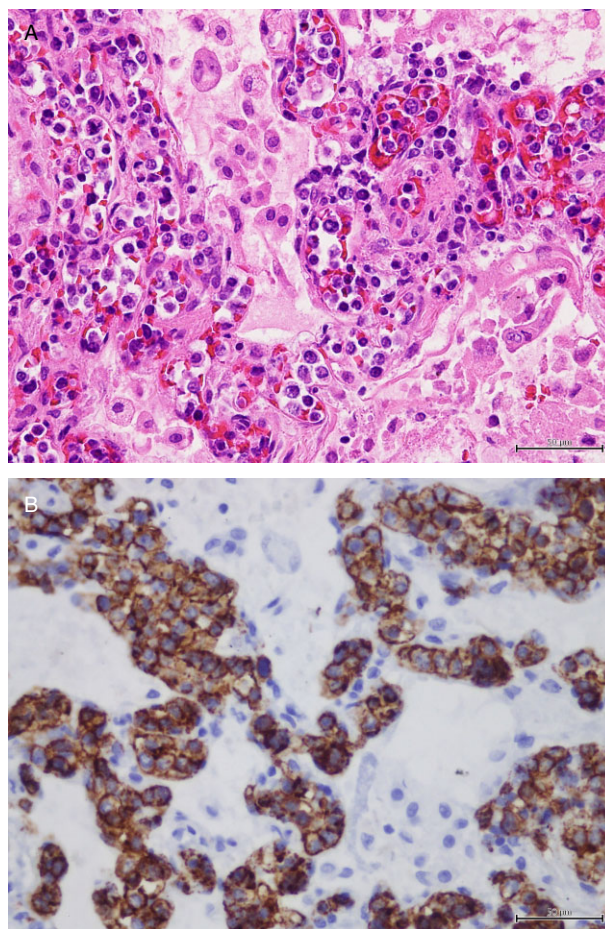


Figure 2. (A) Large atypical lymphoid cells within the interalveolar septal capillaries (H&E, original magnification $\times 400$). (B) Strongly positive CD20 immunostaining of the same cells (original magnification $\times 400$).

sion on the external cortical surfaces. Microscopically, these areas corresponded with blood vessels that were markedly distended by large, atypical lymphoid cells.

Subsequent review of the previously sampled sections from multiple other organs revealed small subtle yet widespread similar changes involving vessels within, among others, the liver, kidneys, pituitary glands, and lungs. In the latter, focal congestion of interalveolar septal capillaries by the described cells were noted, which stained strongly with immunohistochemistry for CD20 (Fig. 2). These cells were also positive for CD5, and the overall features were in keeping with IVLBCL.

Discussion

IVLBCL typically occurs in elderly patients and is slightly more common in men, with male to female ratio of 1.3 to 1. Tumor cells can involve the vessels of any organ and be

associated with constitution symptoms, including fever of unknown origin, weight loss, night sweats, and general fatigue as well as organ-specific symptoms. Identifying this disease in patients with such heterogeneous and nonspecific symptoms can be challenging. Although the diagnosis is made post-mortem in half of the cases, with better awareness antemortem diagnosis of this disease is believed to be increasing.

Invasive aspergillosis can be associated with hematological malignancies. Young *et al.* [2]. stated that lymphoma is second only to leukemia as the most common underlying malignancy associated with invasive aspergillosis. Lungs are the classic sites of this airborne infection, which occurs particularly in patients who remain neutropenic for a prolonged period of time. The incidence of invasive aspergillosis in immunosuppressed “high-risk” patients, as reported by Boon *et al.* [3]. is surprisingly high, although their review included postmortem cases. The true clinical frequency of this complication is probably very low, as published previously [1].

While there are no standard established guidelines for an accurate diagnosis of IVLBCL, clues such as fevers and markedly elevated LDH levels should raise the clinical suspicion of this and other lymphoproliferative diseases. Biopsy and histopathological examination of organs affected by IVLBCL can be conclusive, depending on the extent of involvement. As IVLBCL can occur in any organ, selection of the most appropriate tissue site for biopsy and obtaining an adequate material for assessment whenever feasible are keys to an antemortem diagnosis. In Asian patients, the most relevant diagnostic site seems generally to be the bone marrow. Tumor cell involvement with intrasinusoidal pattern in the bone marrow biopsy is the commonly seen finding, though it may be obscured by the accompanying histiocytic infiltration with hemophagocytosis. In this case, however, the bone marrow biopsy was unremarkable. The latter was not repeated, which at least one previous report has suggested as a means of achieving the accurate diagnosis of IVLBCL. Regarding pulmonary investigations, transbronchial lung biopsies may be useful for diagnosis, especially in patients with respiratory symptoms. Our patient’s initial lung biopsy report was negative, although on review of the histological slides small collections of atypical lymphocytes were apparent in several of the interalveolar capillaries. Therefore, repeating the lung and/or bone marrow biopsies could be considered in cases with negative first biopsy but with high index of clinical

suspicion. We also recommend adding a random skin biopsy to the list of possible diagnostic investigations whenever IVLBCL is considered as a differential diagnosis, when a specific organ involvement cannot be defined.

A timely and accurate diagnosis is extremely important for patients with this disease. Appropriate treatment with chemotherapy can significantly improve the clinical outcomes. In 1994, Di Giuseppe and colleagues [4] reported clinical outcomes for 10 patients at Johns Hopkins Hospital (MD). In their report, four of the 10 patients received chemotherapy for IVLBCL, and two of the four patients receiving chemotherapy survived for around 4 years after diagnosis. The median survival of the remaining six patients without chemotherapy was 3 months (range 1–19). Ferreri and coworkers [5] reported clinical outcomes for 22 patients who received chemotherapy in 2004. Their mean 3-year overall survival was 33 months.

Finally, evaluation of a patient with pyrexia of unknown origin may be intensive and laborious, and despite a clinical suspicion of lymphoma a definitive diagnosis may remain elusive. In such cases, a rarer subtype such as IVLBCL, which usually does not present with obvious lymphadenopathy and which is superimposed by an opportunistic infection, should be considered.

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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