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Orthodeoxia as a presentation of intravascular large B cell lymphoma

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Abstract

Intravascular large B cell lymphoma (IVLBCL) is a rare and aggressive subtype of diffuse large B cell lymphoma, of which clinical presentations are highly variable among geographical areas. A case series of IVLBCL patients from Asian countries reported the disease to be more aggressive and associated with hemophagocytic syndrome than in cases from Western countries. Although published articles recently revealed hypoxemia as a presentation in IVLBCL patients, orthodeoxia has never been documented. A 71-year-old man presented with prolonged fever, cough, exertional dyspnoea, and orthodeoxia, later developing hypoxemic respiratory failure and refractory septic shock. Eventually, IVLBCL was diagnosed by random skin biopsy and bone marrow biopsy because of a high index of suspicion. We demonstrated the first case of orthodeoxia as an initial presentation of IVLBCL, clinically compatible with Asian-variant IVLBCL, which is commonly fatal and diagnostically challenging.

Introduction

Intravascular large B cell lymphoma (IVLBCL) is a rare haematological malignancy characterized by the proliferation of lymphoma cells within vessels. Although the most common presenting symptoms are fever and skin lesions, pulmonary symptoms have also been reported. However, primary pulmonary involvement of IVLBCL is uncommon, and we reported the first case of IVLBCL, proven by histopathology, presenting with orthodeoxia followed by septic shock and hypoxemic respiratory failure with a favourable outcome after definite chemotherapy.

Case Report

A 71-year-old man presented to our hospital with a 3-month history of prolonged fever, cough, and exertional dyspnoea. His past medical history included alcoholic hepatitis without cirrhosis.

He first visited an outpatient clinic with fever and cough 5 months before diagnosis. At that time, he had hypoxemia (oxygen saturation [SpO_2] on room air 88%), and a chest radiograph showed reticulation in both lungs with partial improvement after antibiotic treatment. Two months later, he was admitted as a result of developing fever with chills, cough, and dyspnoea, and his physical examination was unremarkable except for a moderate degree of hypoxemia with orthodeoxia. His oxygen saturation was 93% and 85% upon supine and upright position, respectively. An echocardiogram with bubble study revealed a extra-cardiac shunt with an ejection fraction of 57%. Neither pulmonary hypertension nor significant valvular abnormalities were detected. Computed tomography pulmonary angiography revealed sub-pleural reticulation at bilateral lower lobes without arteriovenous malformation or pulmonary embolism (Fig. 1). Laboratory studies showed anaemia and thrombocytopenia; therefore, a bone marrow biopsy was performed, which was non-diagnostic. He was discharged with remission of fever but slight improvement of oxygen saturation (SpO_2 on room air and upright position 93%).

One month later, he was readmitted with another episode of fever with chills, cough, and exertional dyspnoea.

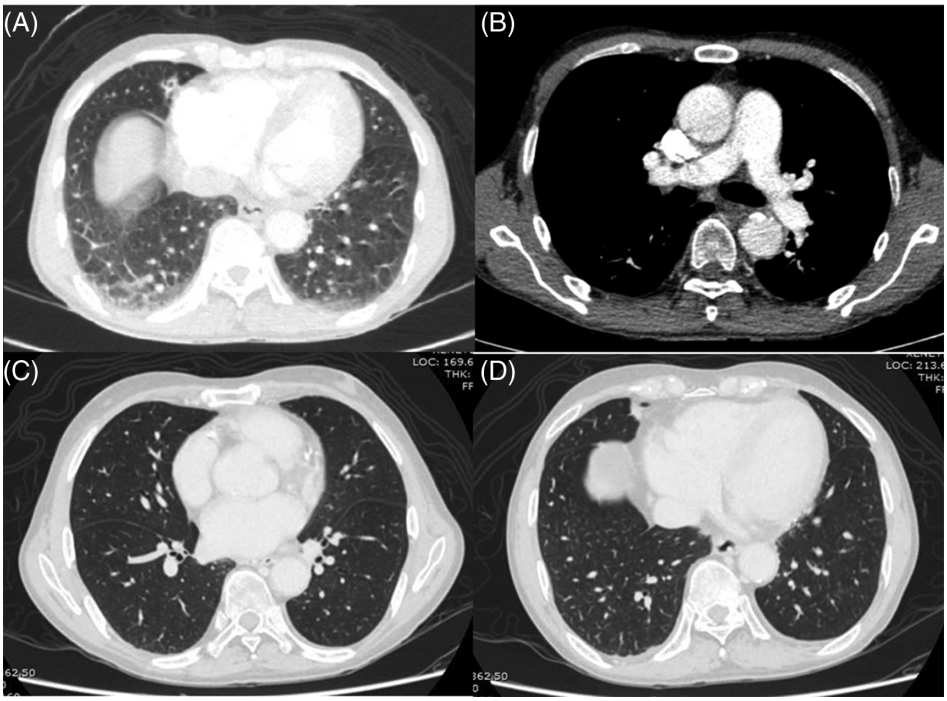

Figure 1. Computed tomography angiography of chest revealed sub-pleural reticulation at bilateral lower lobes (A) without pulmonary embolism (B). After definitive treatment, computed tomography of chest revealed complete resolution of sub-pleural reticulation (C, D).

Upon physical examination, the patient was febrile without evidence of lymphadenopathy, hepatosplenomegaly, skin lesion, or neurological deficit. Laboratory studies demonstrated the following: haemoglobin 11 g/dL, white blood cell count 6540/μL, Platelet 110,000/μL, lactate dehydrogenase (LDH) 3013 U/L, procalcitonin level 0.725 ng/mL, and lactate level 4.4 mmol/L. Chest radiograph revealed diffuse bilateral reticulation. Arterial blood gas analysis on room air showed pH 7.56, $PaCO_2$ 22 mmHg, PaO_2 45 mmHg, and SaO_2 88%. From his clinical data, typical and atypical pneumonia could not be ruled out at first presentation; thus, empirical antibiotics of potential pathogens were given. Investigations of infections, such as cytomegalovirus (CMV), Epstein–Barr virus (EBV), HIV, and mycobacterial infection, were all negative. The contrast computed tomography scan of the abdomen showed no significant lymphadenopathy. Subsequently, he developed hypoxemic respiratory failure and septic shock with impaired cardiac function [ejection fraction 35%], consistent with sepsis-induced cardiomyopathy. Despite providing broad-spectrum antibiotics, invasive mechanical ventilation, and fluid resuscitation with vasopressor therapy, he still had a persistent spike of fever with haemodynamic instability and a high blood lactate level. As no specific cause of septic shock was detected, intravascular lymphoma was considered. Consequently, random skin biopsy and bone marrow biopsy were performed, which were consistent with IVLBCL (Fig. 2). Moreover, immunohistochemical studies of skin tissue and bone marrow were compatible with IVLBCL [CD20+, CD79a+, PAX5+, CD10−, Bcl-6+, MIM1+, CD5+, cyclin D1−, SOX11−, c-Myc+, Bcl-2+, Ki67 + [100%], CD3−, in situ hybridization

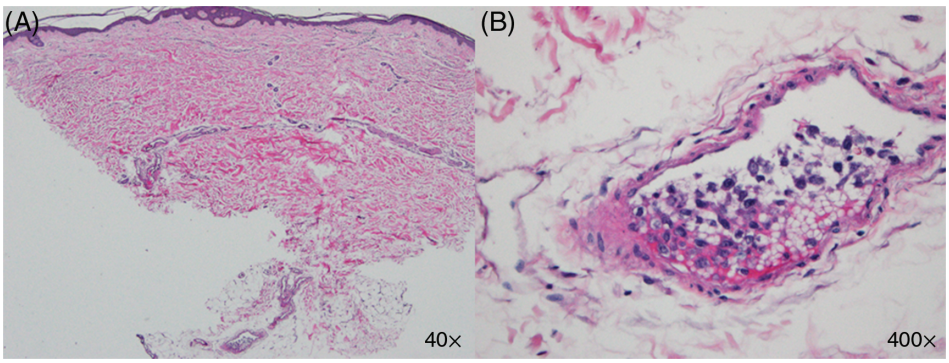

Figure 2. Histopathological findings from random skin biopsy: (A) atrophic epidermis with sparse perivascular lymphocytes in the dermis (haematoxylin–eosin, original magnification 40×). (B) Large atypical lymphocytes in the intravascular lumens in the deep dermis (400×).

Kappa/Lambda−). He was finally diagnosed as IVLBCL stage IV due to widespread disease within blood vessels. As a result, steroid treatment was initiated and followed by an R-miniCHOP regimen (rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisone). Surprisingly, his symptoms, haemodynamics, oxygenation, and blood lactate level dramatically improved within 2 days after this treatment, and cardiac ejection fraction also increased to 75%. Later, contrast computed tomography scans of the chest and abdomen were also performed after systemic chemotherapy, which revealed no significant lymphadenopathy. (Fig. 1).

Discussion

IVLBCL was first described by Pfleger and Tappeiner in 1959, which was known as the "oncologist's great imitator" [1,2]. Clinical presentations are elusive and highly variable, depending on involved organs. Hypoxemia is always observed in the case of pulmonary IVLBCL, but orthodeoxia has never been reported. In our case, orthodeoxia was detected, and extra-cardiac shunt was demonstrated by echocardiography. Interestingly, hypoxemia intermittently appeared, associated with particularly febrile events. This phenomenon could be derived from one of the following mechanisms: 1) lymphoma-related intra-pulmonary shunt or 2) ventilation-perfusion mismatch. In addition, the clinical features from the Asian series were mainly distinct from Western series. Dysregulation of inflammatory cytokines and hemophagocytic syndromes, rarely neurological or dermatological abnormalities, were preferentially documented in IVLBCL patients from Japanese series, the so-called Asian variant [3,4]. Similarly, our patient also had a history of cytopenia and subsequently developed refractory septic shock with a falsely elevated procalcitonin level from lymphoma-induced cytokine storm. Although his laboratory values did not fulfil the diagnostic criteria of hemophagocytic syndrome, the near-fatal inflammatory responses from lymphoma were compatible with the Asian variant IVLBCL.

In summary, as symptoms and radiographic findings are non-specific, diagnosis of this disease requires high clinical suspicion. To our knowledge, this is the first report of a case with biopsy-proven IVLBCL presenting with orthodeoxia, which might result from episodic intra-pulmonary shunt, developed from lymphoma cells, occluding pulmonary vessels. Clinicians should consider IVLBCL in patients with prolonged fever and unexplained high lactate and LDH level without clinical clues of infection. Interestingly, orthodeoxia might be an additional clinical feature for further investigation to the diagnosis. Moreover, a random skin biopsy is promisingly diagnostic, particularly in patients without localizing lesions [5]. IVLBCL is challenging to diagnose antemortemly, and early diagnosis including aggressive managements might contribute to a favourable outcome.

Disclosure Statement

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

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