

Intravascular B-cell lymphoma: case report of a rare cause of pulmonary arterial hypertension

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Background

Intravascular large B-cell lymphoma (IVLBCL) is a rare disease characterized by proliferation of malignant lymphoid cells within the small vessels of various organs resulting in diffuse thrombosis. It most commonly affects the central nervous system and the skin, but if it involves the pulmonary arteries it can cause acute severe pulmonary hypertension (PH) and right heart failure. Early diagnosis is essential as the clinical course is extremely aggressive. In this report, we present a case of rapidly progressive PH and subsequent right ventricular (RV) failure secondary to IVLBCL. We review the important differential diagnoses and diagnostic evaluation needed to make a correct and early diagnosis.

Case summary

A 53-year-old, previously healthy man developed 2 months of progressive shortness of breath. After being treated for presumptive pneumonia, he was admitted with hypoxic respiratory failure, altered mental status, and severe PH. He developed RV failure and subsequent liver failure. He was ruled out for pulmonary embolism. Despite aggressive management with inhaled nitric oxide and epoprostenol, inotropes, and continuous renal replacement therapy, the patient passed away. Post-mortem examination revealed the presence of IVLBCL with extensive involvement notable of the brain, heart, lungs, and pulmonary arteries.

Discussion

The acute development of severe PH and RV failure in the absence of pulmonary emboli is uncommon and represents a challenging diagnostic and management clinical scenario. When accompanied by altered mental status, constitutional symptoms and an elevated lactate dehydrogenase, clinicians should have a high index of suspicion for intravascular lymphoma, as early diagnosis is critical to maintain a reasonable chance of survival.

Keywords

Pulmonary hypertension • Intravascular lymphoma • Cor pulmonale • Case report

Learning points

- Only a few clinical entities cause acute pulmonary hypertension (PH) with cor pulmonale without significant parenchymal lung disease, and those include pulmonary embolism, tumour thrombotic microangiopathy, pulmonary lymphangitic carcinomatosis, and intravascular lymphoma.
- The presence of altered mental status, constitutional symptoms, and elevated lactate dehydrogenase in the presence of acute PH and cor pulmonale should lead to a high index of suspicion for intravascular lymphoma.

Introduction

The development of right heart failure is an ominous sign in patients with pulmonary hypertension (PH) and portends a poor prognosis.¹ The acute onset of both PH and right heart failure in the absence of pulmonary emboli has a limited differential and typically an even more aggressive clinical course.² Rapid recognition and diagnosis is necessary to allow the opportunity for treatment and survival. Here, we report a rare case of acute PH and right heart failure secondary to intravascular lymphoma. We focus on the narrow differential

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diagnosis and pertinent evaluation required to give clinicians the tools to make the correct diagnosis.

Timeline

Day	Events
0	Patient develops progressive dyspnoea with cough; treated for pneumonia as an outpatient.
1–60	Progression of symptoms with new fevers, anorexia, and night sweats.
61	Admitted to district hospital.
62	Echo shows mild right ventricular (RV) enlargement and estimate pulmonary artery (PA) pressure of 65 mmHg; patient requires BiPAP due to progressive hypoxia. Computed tomography pulmonary angiogram negative for pulmonary embolism.
65–70	Patient develops acute liver injury, encephalopathy, and oliguric renal insufficiency.
71	Transferred to our institution for consideration of liver transplantation. Repeat echo shows progressive RV dysfunction with systemic PA pressures. Started on pulmonary vasodilators.
72	Patient developed worsening shock requiring multiple vasopressors and is started on continuous renal replacement therapy. He suffers from cardiac arrest and expires.
101	Post-mortem examination reveals diagnosis of intravascular large B-cell lymphoma with extensive involvement of the brain, heart, lungs, and pulmonary arteries.

Case Presentation

A 53-year-old previously healthy man presented to a local hospital with 2 months of progressive dyspnoea, cough, and fevers. He had been previously treated for presumed bronchitis. Symptoms progressed with development of anorexia, nausea, night sweats, and pervasive fatigue. Past medical history was unremarkable except for history of prior smoking (accrued over 30 pack years) and occasional alcohol use. He was on no regular medications. He had immigrated from Iran to Los Angeles years prior. Per available documentation, physical examination at that time revealed a patient in moderate respiratory distress on Bilevel Positive Airway Pressure (BiPAP) but with clear lungs, normal heart sounds, no jugular venous distention or pedal oedema, and no murmurs. Electrocardiogram (ECG) revealed sinus tachycardia with normal axis and non-specific ST-T changes (Figure 1A). Chest X-ray showed mildly pulmonary oedema, and he was treated with ceftriaxone 1 g IV and azithromycin 500 mg IV daily for 5 days. Laboratory evaluation revealed a normal white blood cell count (6300 cells/L), haemoglobin 13.3 g/dL, and platelet

count of 226 000 per microliter. Serum creatinine was normal (1.2 mg/dL) and arterial blood gas (ABG) revealed a pH of 7.44, pCO₂ 30, and PaO₂ 145.

Transthoracic echocardiogram revealed normal left ventricular systolic function, mild right ventricular (RV) enlargement and severely elevated pulmonary artery (PA) systolic pressure (65 mmHg) with mild-to-moderate tricuspid regurgitation. With failure to improve and progressive hypoxia and development of encephalopathy, antibiotic therapy was broadened to include trimethoprim-sulfamethoxazole 800 mg/160 mg twice daily and fluconazole 400 mg IV daily. He underwent contrast computed tomography (CT) and CT pulmonary angiogram (CTA) (Figure 1C and D), which revealed multifocal patchy and nodular areas of alveolar consolidation in both upper and lower lung fields suspicious for pneumonia, with sub-centimetre mediastinal lymph nodes and bilateral pleural effusions. There was no peribronchial thickening or interstitial fibrosis noted. There was no evidence of pulmonary embolism and the PA was normal in size measuring 25 mm.

The patient developed progressive liver injury, with aspartate aminotransferase (AST) 450 U/L (nl <46 U/L) and alanine aminotransferase (ALT) 302 U/L (nl <66 U/L) and elevated total and direct bilirubin which peaked at 20 (nl <1.3) and 19 (nl <0.3) mg/dL, respectively. He had progressive encephalopathy and despite normal coagulation parameters, was treated for presumed acute liver failure with N-acetylcysteine 1200 mg twice daily, lactulose 30 g three times daily, rifaximin 550 mg twice daily, and methylprednisolone 40 mg IV every 6 h. There were no identifiable reversible causes of liver injury. He developed oliguric renal insufficiency with creatinine increasing to 1.9 mg/dL (nl 0.8–1.3), microcytic anaemia with haemoglobin 9.7 g/dL (nl 13–17), and thrombocytopenia with 101 000 platelets per microliter (nl 150–450 000). Serum lactate dehydrogenase (LDH) was elevated at 756 U/L (nl <260 U/L). Given his rapidly deteriorating clinical status, he was transferred to our institution for consideration of liver transplantation.

On arrival to our intensive care unit, he was noted to be afebrile with a heart rate of 124 b.p.m., blood pressure 124/79, and O₂ saturation of 85% on 5 L nasal cannula. On exam, he was ill-appearing with temporal wasting and notably jaundiced with scleral icterus. He was confused. He had coarse rales anteriorly, was tachypnoeic using his accessory chest wall muscles. Cardiac exam revealed elevated jugular venous pressure of 10 cm of water, a regular tachycardia with a prominent P2 component of the second heart sound and soft holosystolic murmur at the right sternal border. He had hepatomegaly without ascites or splenic enlargement. He had no rashes and no oedema.

His ECG showed rightward axis with incomplete right bundle branch block (Figure 1B). A transthoracic echocardiogram revealed a dilated (5.3 cm annulus, nl <4.2 cm) and severely hypokinetic right ventricle that, despite normal tricuspid annular motion (TAPSE 1.7 cm, nl >1.6 cm), had severely reduced systolic function with an akinetic apex and free wall. The left ventricle was underfilled, with ejection fraction of 75% and mild diastolic dysfunction. There was flattening of the septum in both systole and diastole, consistent with pressure overload, and estimated RV systolic pressure of 60 mmHg with a systolic blood pressure at the time of 104 mmHg (Figure 2). There was

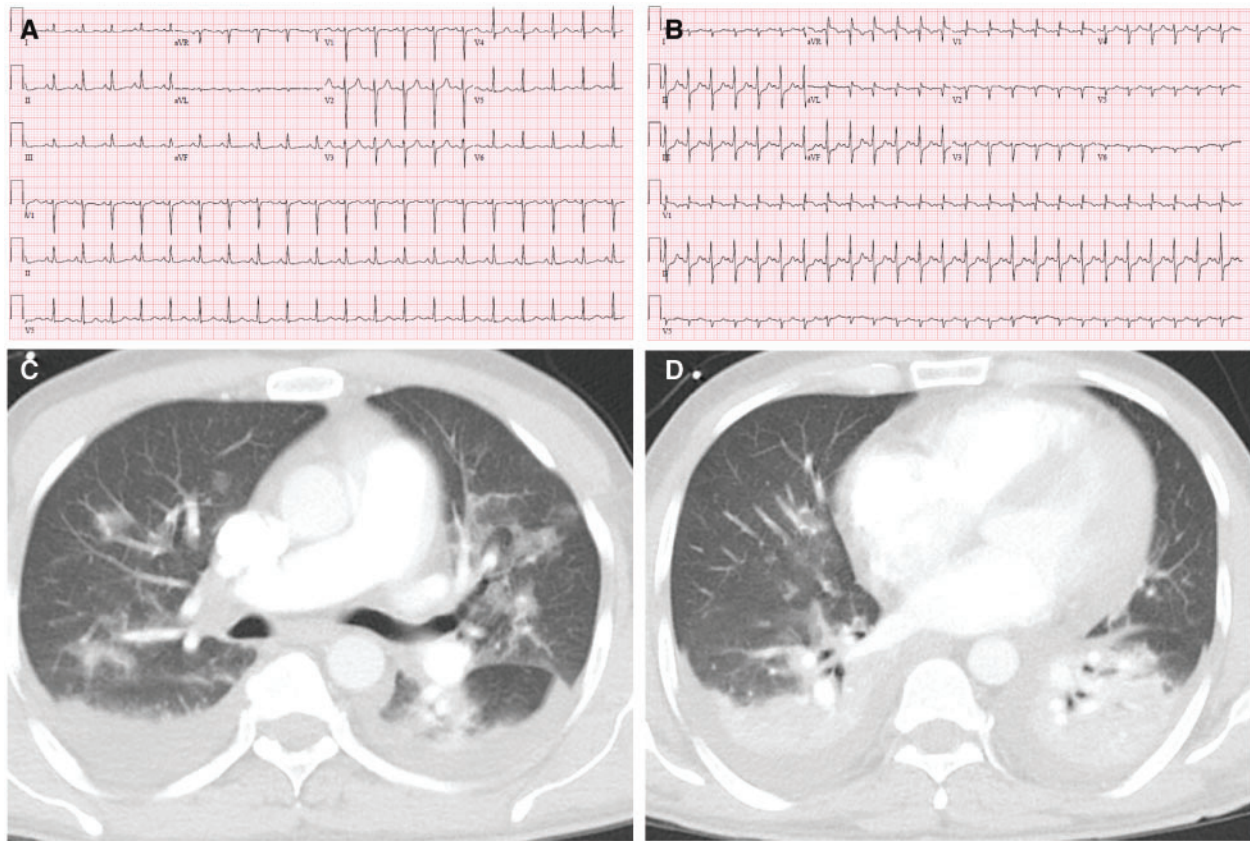


Figure 1 (A) Electrocardiograms on initial presentation and (B) on arrival to our intensive care unit. The admission electrocardiogram revealed sinus tachycardia and non-specific ST-T changes. On arrival to our hospital, he had developed an incomplete right bundle branch block and right axis deviation, consistent with a pattern of right ventricular strain. CTA of chest was performed (C and D) which ruled out pulmonary embolism. There was evidence of bilateral infiltrates and pleural effusions.

moderate, central tricuspid regurgitation, and mild mitral regurgitation, as well as a small pericardial effusion adjacent to the RV apex. Within few hours of arrival to the intensive care unit, he developed refractory shock. Cardiology was consulted for guidance in the management of RV failure in the setting of severe PH. He was started on dobutamine 3 µg/kg/min and epinephrine 10 µg/min, inhaled nitric oxide at 20 ppm, and inhaled epoprostenol 0.03 µg/kg/min. Continuous renal replacement therapy (CRRT) was initiated for severe metabolic acidosis with ABG showing pH 6.99, PaCO₂ 42 and PaO₂ of 63, and anuric renal failure with creatinine peaking at 2.6 mg/dL. He was urgently intubated, however, despite aggressive efforts his condition worsened and he passed away from refractory cardiogenic shock due to RV failure.

A post-mortem examination was notable for the demonstration of intravascular large B-cell lymphoma (IVLBCL) with extensive involvement of the brain, heart, lungs and pulmonary arteries, as well as the spleen, both kidneys, thyroid, gastrointestinal tract, prostate, and both testes. Specifically, noted was the invasion of lymphoma cells into the small coronary vessels as well as the myocardial interstitium, as well as into the large and small pulmonary arteries and veins (Figure 3).

Discussion

In this report, we describe a rare cause of rapidly progressive RV failure due to PH related to lymphomatous infiltration of the small pulmonary vasculature from IVLBCL.

Intravascular large B-cell lymphoma is a rare subtype of extranodal large cell lymphoma, characterized by proliferation of malignant lymphoid cells within the small vessels of various organs (with relative sparing of surrounding tissue). This multifocal vascular occlusion results in diffuse thrombosis.³ The clinical manifestations of IVLBCL are highly variable and depend on the preferentially involved organs.³ Non-specific symptoms (fever, weight loss, and malaise) and haematologic abnormalities such as haemolytic anaemia and the haemophagocytic syndrome are common, with a high incidence of neurologic and cutaneous involvement.³⁻⁹ The most common laboratory findings are elevated serum LDH (86%), elevated beta-2 microglobulin (82%), anaemia (63%), elevated erythrocyte sedimentation rate (43%), thrombocytopenia (29%), leukopenia (24%), and hypoalbuminaemia (18%).⁹ Overall, antemortem diagnosis is rare, and even when diagnosed early, IVLBCL shows a poor response to therapy and has an extremely aggressive clinical course.^{8,10}

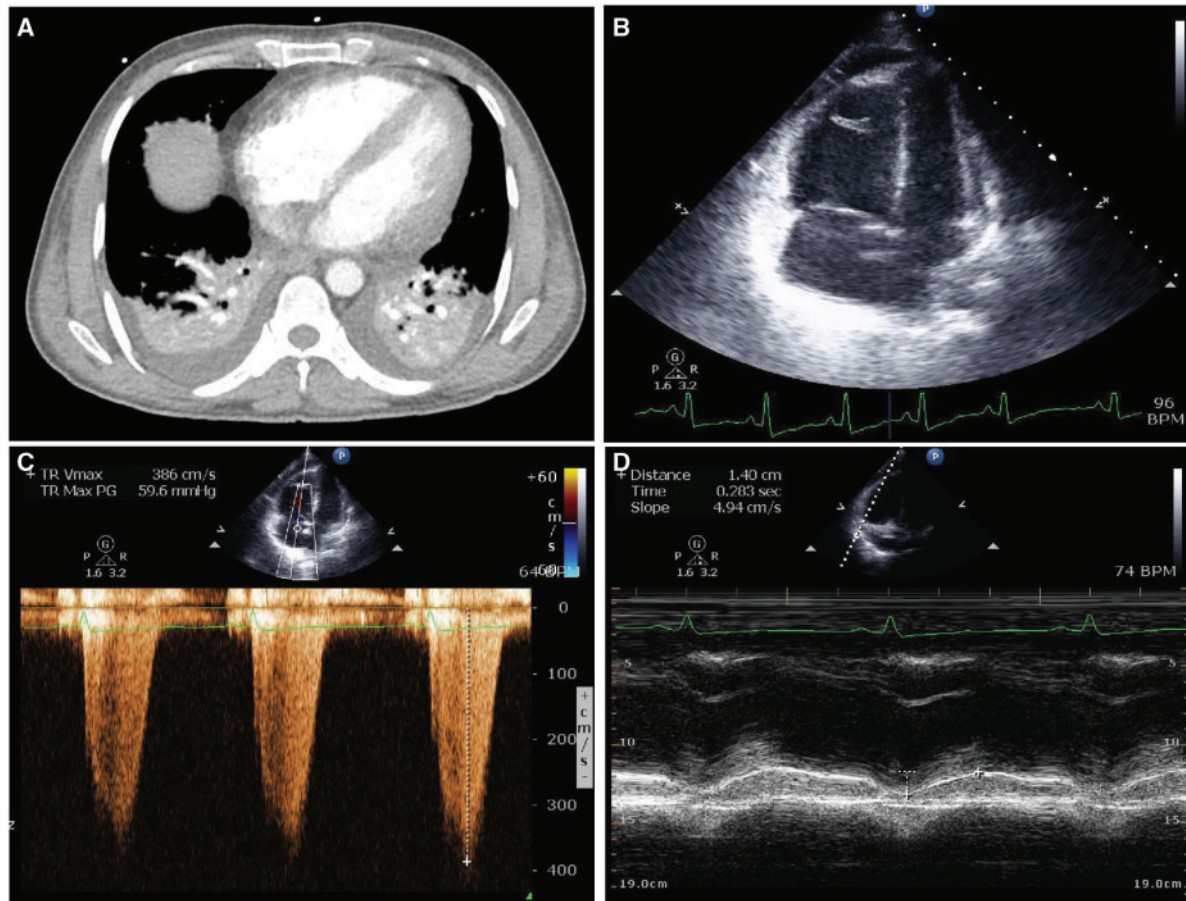


Figure 2 Evidence of pulmonary hypertension. (A) Contrast-enhanced computed tomography of the chest shows evidence of right ventricular hypertrophy and enlargement. (B) Transthoracic echo in the apical view shows severe right ventricular enlargement with an annular dimension of 5.2 cm ($nl < 4$) with bowing of the interatrial septum into the left ventricle. A small-to-moderate pericardial effusion adjacent to the right ventricular apex is present. There is evidence of severe pulmonary hypertension with an estimated right ventricular systolic pressure of 60 mmHg (C), as well as right ventricular dysfunction with tricuspid annular plane systolic excursion of 1.4 cm ($nl \geq 1.6$) (D).

Lung involvement can be seen in at least 60% of cases of IVLBCL, typically with interstitial infiltrates.¹¹ Cases of PH associated with IVLBCL, however, are very rare.^{5,8,10,12} Other primary pulmonary disorders that can present with rapidly progressive PH and constitutional symptoms without significant parenchymal disease include pulmonary tumour thrombotic microangiopathy and pulmonary lymphangitic carcinomatosis.^{2,13} Although antemortem diagnosis is difficult,³ fluorodeoxyglucose-positron emission tomograph (FDG-PET) imaging can be helpful in early diagnosis of IVLBCL.^{7,14} Ultimately, tissue diagnosis is needed and bronchoalveolar lavage and open lung biopsy have been useful.^{15,16}

Although PH secondary to IVLBCL would be classified as World Health Organization (WHO Group 5) PH, it has similar pathophysiology to chronic thromboembolic (WHO Group 4) PH.¹ As elevation in pulmonary vascular resistance and ensuing RV failure develop relatively acutely in affected patients, the use of standard PH therapies including pulmonary vasodilators and calcium channel blockers is limited due to haemodynamic instability and a relative absence of pulmonary vascular remodeling. Supportive

measures which include the use of diuretics in patients with signs volume overload, long-term oxygen therapy in those with $PaO_2 < 60$ mmHg and the correction of anaemia should be pursued in all patients.¹ In the critically-ill patient with PH and RV failure, reduction of RV afterload is usually achieved with parenteral prostacyclin analogues, and improvement of cardiac output with inotropes (with dobutamine being preferred).¹ Ultimately, expeditious diagnosis, initiation of chemotherapy and adequate response to chemotherapy are vital to survival.

Conclusions

In summary, there are only a few clinical entities that can cause acute PH and RV failure with minimal parenchymal lung disease. When faced with this clinical scenario, especially in the setting of altered mental status, constitutional symptoms, and elevated LDH, clinicians should have a high index of suspicion for intravascular lymphoma and hopefully lead to early diagnosis and treatment.

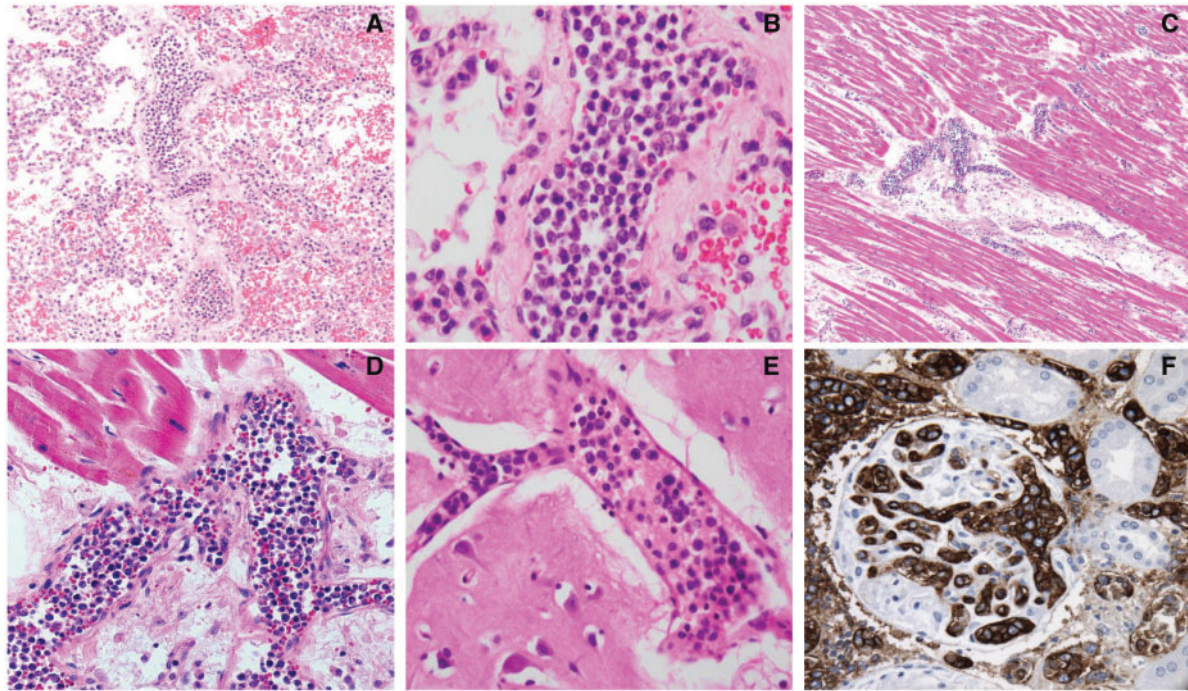


Figure 3 Histopathology. (A) Large atypical lymphocytes fill the pulmonary microvasculature, including veins, and alveolar capillaries (Haematoxylin and Eosin (H&E) stain, 10 \times). (B) The vascular lumina are packed with malignant lymphocytes with large atypical nuclei and frequent mitoses (H&E, 60 \times). (C) The cardiac microvasculature is filled with large atypical lymphocytes (H&E, 10 \times). (D) The small vessels in the heart are distended by collections of large centробlast-like lymphoma cells with irregular, pleomorphic nuclei, and frequent mitoses within the lumen (H&E, 60 \times). (E) Intravascular lymphoma fills the lumen of small vessels within the brain cortex (H&E, 60 \times). (F) Immunohistochemistry for CD20 demonstrates strong expression by large B-cell lymphoma cells in the glomerular capillaries of the kidney.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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