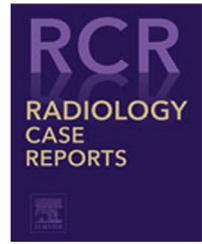


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Case Report

Intravascular large B-cell lymphoma presenting with diffusely increased pulmonary fluorodeoxyglucose uptake without corresponding CT abnormality

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ABSTRACT

A 60-year-old male presented with complaints of dyspnea, intermittent fever, and 40 pounds of weight loss over the previous 9 months and was admitted for acute hypoxemic respiratory failure. Labs demonstrated elevated inflammatory markers, mild anemia, and thrombocytopenia. Fluorodeoxyglucose-positron emission tomography scan demonstrated diffusely increased pulmonary fluorodeoxyglucose uptake without corresponding abnormality on CT images. Excisional lung biopsy demonstrated intravascular large B-cell lymphoma (IV-LBCL). Presentation, imaging findings, and diagnosis of IV-LBCL will be discussed, as well as differential considerations for pulmonary involvement by IV-LBCL.

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Case report

A 60-year-old male presented to the emergency department with chief complaint of dyspnea and was admitted for acute

hypoxemic respiratory failure. The patient reported intermittent, recurrent fever up to 102 °F and 40 pounds of weight loss over the previous 9 months.

Medical history was significant for recent admission to an outside hospital, 1 month prior to this admission, for

Abbreviations: IV-LBCL, intravascular large B-cell lymphoma; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; CTA, computed tomography angiogram; MIP, maximum intensity projection; ARDS, acute respiratory distress syndrome; H&E, hematoxylin-eosin.

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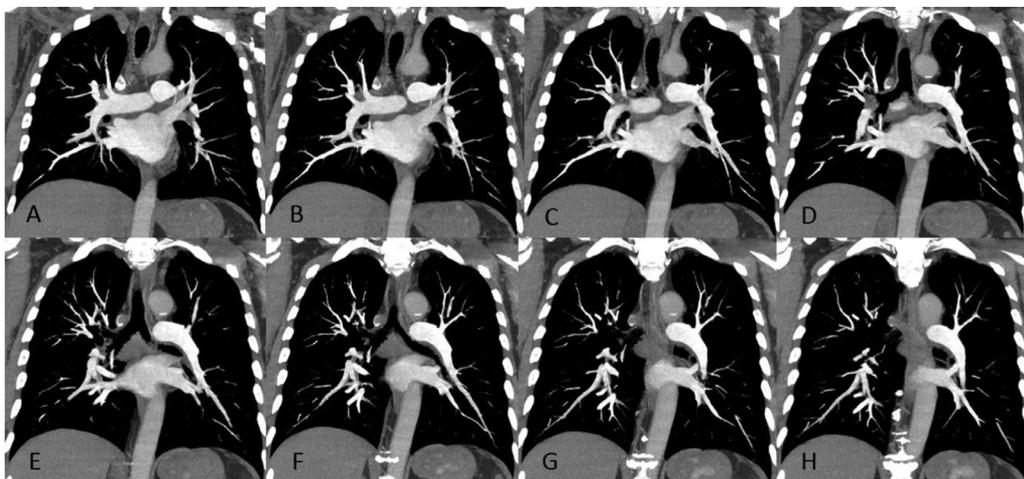


Fig. 1 – Sixty-year-old male with dyspnea and hypoxemia, diagnosed 4 days later with pulmonary involvement by intravascular large B-cell lymphoma. Coronal 10 mm maximum intensity projection computed tomography angiogram images from anterior to posterior (A-H) demonstrate normal caliber pulmonary arteries without evidence of intraluminal filling defect.

pancytopenia and splenomegaly. Splenic biopsy demonstrated marginal zone lymphoma and splenectomy was performed. Bone marrow biopsy performed at that time was negative. Family history revealed similar presentation years earlier by the patient's mother of unknown etiology, despite extensive medical workup in the months prior to her death.

Labs on admission demonstrated mild anemia and thrombocytopenia. Lactate dehydrogenase and inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate, were significantly elevated. White blood cell count and differential were normal and infectious workup was negative. Liver transaminases were mildly elevated. Initial imaging evaluation in the emergency department (ED) included computed tomography (CT) angiogram of the chest, which was negative for pulmonary embolism and demonstrated no significant abnormalities (Fig. 1). Further extensive imaging workup was obtained following admission which included echocardiogram, CT abdomen and pelvis with contrast, and CT maxillofacial. No significant abnormalities were identified.

Given the history of splenic marginal zone lymphoma, PET-CT was ordered to evaluate for recurrence. PET-CT was obtained on day 4 of admission and demonstrated changes of prior splenectomy without hypermetabolic lymphadenopathy. There was, however, the unusual finding of diffusely increased fluorodeoxyglucose (FDG) uptake throughout both lungs, greater than background hepatic uptake, without corresponding abnormality on CT images (Fig. 2 and Fig. 3). Pneumonitis was considered although there were no pulmonary opacities on CT to support this diagnosis. This prompted a literature search to explain the findings.

A case report of diffuse pulmonary uptake on FDG-positron emission tomography (PET) with normal CT diagnosed as biopsy-proven intravascular lymphoma was found upon literature review. This study was referenced and differential diagnoses of intravascular lymphoma versus pneumonitis were

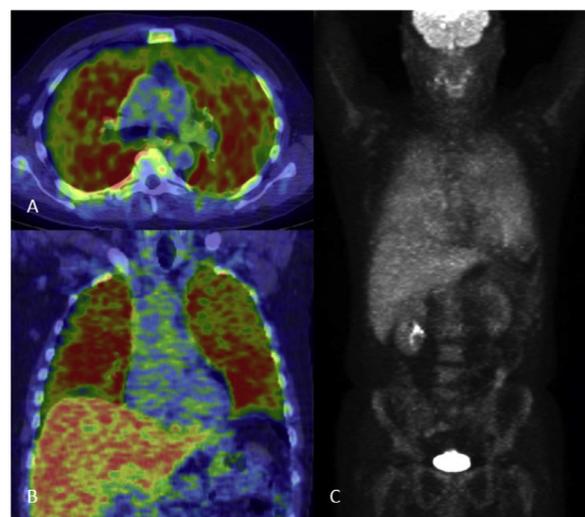


Fig. 2 – Sixty-year-old male with intravascular diffuse large B-cell lymphoma. Axial (A) and coronal (B) fused PET-CT images and 3D attenuation corrected maximum intensity projection (C) obtained 60 minutes after IV administration of 17.7 mCi F-18 FDG demonstrate diffuse hypermetabolic bilateral pulmonary FDG uptake, greater than physiologic hepatic uptake.

included in the PET-CT report. Bronchoalveolar lavage was performed and flow cytometry was negative. Due to high clinical suspicion for lymphoma, excisional lung biopsy was performed. Biopsy was interpreted as intravascular large B-cell lymphoma (IV-LBCL) with cell markers positive for CD5, CD20, and CD79a, and negative for CD3 and Pan-CK, supporting this diagnosis (Fig. 4).

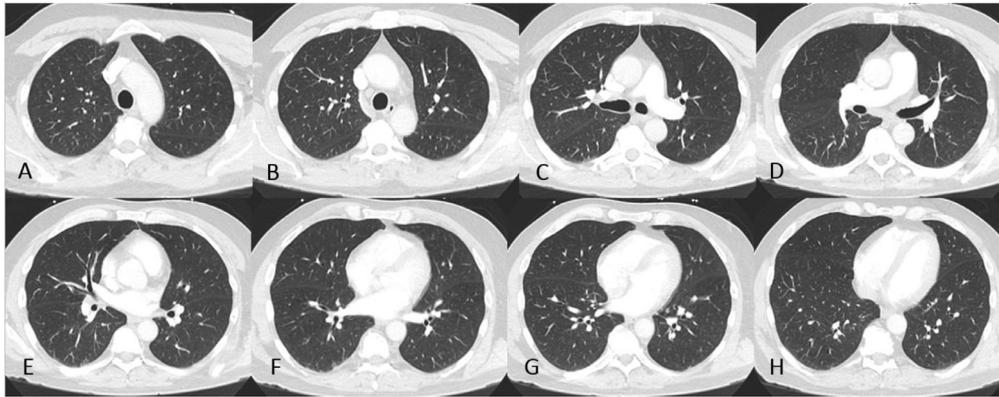


Fig. 3 – Sixty-year-old male with intravascular diffuse large B-cell lymphoma. Axial lung window CT images reconstructed with high spatial frequency algorithm, 1.25 mm slice thickness at 2 cm intervals from superior to inferior (A-H) demonstrate normal lung parenchyma without airspace or interstitial opacities corresponding to hypermetabolic uptake on PET images.

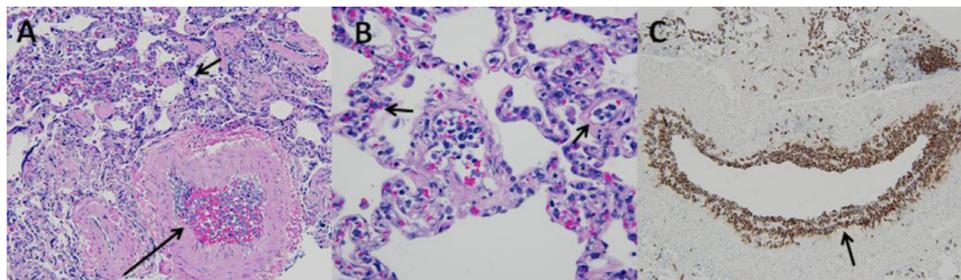


Fig. 4 – Sixty-year-old male with intravascular large B-cell lymphoma. Hematoxylin-eosin (H&E) stain of right middle lobe excisional lung biopsy at 20 \times magnification (A) and 40 \times magnification (B) demonstrate atypical lymphocytes within the lumen of a pulmonary artery (long arrow) and within surrounding capillary beds (short arrows). CD-20 immunohistochemical stain (C) demonstrates that the atypical lymphocytes stain positive for CD-20 (arrow).

Discussion

Etiology and demographics

IV-LBCL is a rare type of non-Hodgkin lymphoma, usually B-cell immunophenotype, characterized by preferential growth of malignant lymphocytes within the lumina of small vessels, aggressive behavior, and often fatal course [1]. IV-LBCL usually affects elderly patients with median age at diagnosis in the sixth-seventh decades.

Clinical and imaging findings

Patients with IV-LBCL may present with poor performance status, elevated lactic dehydrogenase serum levels, anemia, and B symptoms (Table 1) [1,2]. In contrast to other types of lymphoma, the bone marrow, lymph nodes, peripheral blood, and cerebrospinal fluid are often uninvolved in IV-LBCL. Clinical presentation is highly variable with the most pronounced differences related to the geographical origin of the patient, although it often includes organ dysfunction related to obstruction of blood vessels. Fever, skin lesions, and rapidly progressive neurologic symptoms are more common in Western countries, while bone marrow, spleen, and liver

Table 1 – Summary.

Epidemiology	<ul style="list-style-type: none"> • Median age at diagnosis is in the sixth to seventh decades, no sex predilection. • True incidence unknown, until recently it was usually only recognized at autopsy.
Clinical presentation	<ul style="list-style-type: none"> • Western countries: fever, skin lesions, and prominent, rapidly progressive neurologic signs (eg, dementia, progressive cerebral vascular accident, peripheral neuropathy). • Asia: bone marrow, spleen, and liver involvement more common. May present with hemophagocytic syndrome.
Labs	<ul style="list-style-type: none"> • Elevated lactate dehydrogenase and beta 2 microglobulin (80-90%), anaemia (65%), elevated sediment rate (43%), altered hepatic, renal, or thyroid function, serum monoclonal protein (14%). • Thrombocytopenia and hypoalbuminemia more common in Asia (76% and 84%) than Western countries (29% and 18%).
Treatment	<ul style="list-style-type: none"> • Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) more effective than CHOP alone.
Prognosis (R-CHOP)	<ul style="list-style-type: none"> • Complete response (82%), 2-year overall survival (66%), 2-year progression free survival (56%).

Table 2 – Differential diagnosis.

Differential diagnosis	CT chest/X-ray findings	PET findings
Intravascular large B-cell lymphoma	X-ray, CT, and CTA normal	Diffuse hypermetabolic FDG uptake
Inflammatory or infectious pneumonitis	Ground glass opacity/ consolidation (within 3-5 d)	Focal or diffuse hypermetabolic FDG uptake
Pulmonary contusion	Ground glass opacity/ consolidation (within 3-5 d)	Focal or diffuse hypermetabolic FDG uptake
Acute respiratory distress syndrome (ARDS)	Ground glass opacity/ consolidation (within 3-5 d)	Diffuse hypermetabolic FDG uptake

involvement are more common in Asia [1,3,4]. central nervous system (CNS) involvement may present similar to an ischemic stroke. Pulmonary artery involvement results in dyspnea and hypoxemia, presenting similar to a pulmonary embolism or pulmonary hypertension [5–7]. Filling defects are usually not identified on computed tomography angiogram [5,8,9]. This is presumably due to lymphomatous cells being primarily located in small peripheral pulmonary arteries and capillary beds. Five case reports of isolated pulmonary artery involvement presenting with diffuse or regional increased pulmonary FDG uptake and normal appearance on CT have been published [10–14]. In 1 study, gallium scintigraphy demonstrated similar increased pulmonary uptake although was less pronounced than FDG uptake [14].

Diagnosis

Biopsy is generally required to make the diagnosis since the malignant cells are located within the lumina of small vessels, with percutaneous, transbronchial, and excisional lung biopsies reported in confirmed cases. Multiple cases have reported, successfully confirming the diagnosis by random skin or subcutaneous biopsy, demonstrating proliferating lymphoma cells within the lumina of vessels [11,15,16]. B-cell origin is the most common immunophenotype. Immunohistochemistry in almost all cases of IV-LBCL stains positive for surface antigen CD-20, with CD-5 and CD-10 being the next most common [17]. CD-29 and CD-54, surface antigens involved in transvascular migration into organs or lymph nodes, are consistently absent in IV-LBCL, which explains the preferential intravascular growth [18].

Differential diagnosis

Diffusely increased pulmonary FDG uptake has also been reported in cases of inflammatory and infectious pneumonitis, pulmonary contusion, and acute respiratory distress syndrome in which CT findings were initially absent or disproportionately less than FDG-PET findings. In each of these cases, CT findings progressed over 3-5 days with development of ground glass opacities or consolidation corresponding to the areas of increased uptake (Table 2) [19–21].

Treatment and prognosis

Nonspecific, variable clinical presentation, and occult radiologic features, including absence of significant lymphadenopathy often results in diagnostic delay, which in combination with its aggressive behavior, result poor prognosis for

IV-LBCL [22]. In fact, diagnosis at autopsy is not uncommon [23,24]. Prognosis was extremely poor prior to the advent of rituximab [25], although, it is now considered that detection and treatment at an early stage can improve survival [25,26]. In 1 case report of isolated pulmonary involvement by IV-LBCL, diagnosed by PET-CT, complete remission was achieved for over 24 months, supporting the role of PET-CT in early diagnosis [14]. Current standard of treatment is rituximab plus anthracycline-based chemotherapy, which has been shown to be superior to chemotherapy alone. The largest retrospective study demonstrated complete response in 82%, 2-year overall survival in 66%, and 2-year progression-free survival in 56% of patients treated with anthracycline-based chemotherapy plus rituximab [25].

Conclusion

In high-risk patients with suggestive clinical presentation, IV-LBCL should be considered for the finding of diffusely increased pulmonary FDG uptake when there is no corresponding abnormality on CT. The diagnosis requires high degree of suspicion, as scintigraphy may be the only clue to the diagnosis of this aggressive disease, which may otherwise be clinically and radiologically undetectable in its early stages. There are a few differential considerations for the PET-CT findings, although, CT is less likely to remain normal for more than 3-5 days in these conditions. Without alternative explanation, biopsy should be considered and, based on promising results from prior studies, initial attempt at diagnosis via random skin or subcutaneous biopsy may be considered prior to lung biopsy.

Author contributions

Jayden Spencer, MD as primary author.
Reginald Dusing, MD as faculty mentor.
Wendell Yap, MD as faculty mentor.
Jacqueline Hill, MPH as radiology department research director.
Carissa Walter, MPH as radiology department research coordinator.

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