Hidden in Plain Sight:
False Reassurances Obscuring a Case of Intravascular Lymphoma

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Introduction

An ill 67 year old man presents with weakness and profound failure to thrive immediately following an episode of syncope.

Background

- For the preceding **6 months**, he has been undergoing an exhaustive workup for chronically progressive B-symptoms and elevated inflammatory markers, including ferritin 1600 ng/mL, CRP 18 mg/L, ESR 94 mm/hr, and LDH 300U/L without hemolysis.
- Wife additionally describes **1 year** of "personality changes" including sudden anger, anxiety, and extremely vivid dreams – all new.
- Thought to have polymyalgia rheumatica, he received escalating doses of prednisone, up to 60mg daily for over a month, which briefly improved symptoms though were stopped given transient efficacy and development of significant anasarca, transudative pleural effusion, pericardial effusion, and progressive weakness.
- Over the **2 months** preceding admission, he experienced progressively worsening dyspnea, weakness, and dysphonia against a background of a more gradual decline in renal function and persistent sinus tachycardia without a satisfactory diagnosis.
- Outpatient workup includes:
  - negative ANA, ANCA, RF, PPD, viral hepatitis, HIV, lyme testing
  - SPEP, UPEP, IgG, IgA, and iron studies within normal limits
  - reassuring CT Chest, Abdomen, Pelvis (mild splenomegaly)
  - normal bone marrow biopsy
  - PFTs notable for obstructive disease with low DLCO
- Unremarkable past medical history, family history, medications
- Social history: Accomplished jazz saxophonist, working "up until a few weeks ago". No cigarettes or alcohol since age 27. No IVDU.

Presentation

- Reports syncope while walking slowly after 1 day of acute on chronic dyspnea in setting of a week of worsened fatigue, lack of appetite, dysphonia, and profound weakness.
- **Review of Systems:** Continued B-symptoms. No chest pain, palpitations, cough, urinary symptoms, diarrhea, vomiting, or evidence of bleeding.
- **Vitals/Exam:** afebrile, HR 111, BP 81/50, RR 26, O2 93% on room air. Thin white male, no acute distress, mildly confused though otherwise neurologically intact, dry mucous membranes, irregularly irregular tachycardia, decreased left base breath sounds with normal work of breathing, 3+ lower extremity edema to mid back.
- **Pertinent Labs:** Hb 7.1, MCV 74, WBC 6.8, platelets 168, Na 126, Cr 1.7, CK 2, Albumin 1, and lactate 5.5 which improves with crystalloids. CRP 18, ESR 140, LDH 287

Hospital Course and Transfer

- Initially admitted to the ICU, presumptively treated for septic shock, adrenal insufficiency, and anemia with antibiotics, 2g methylprednisolone IV daily and blood transfusions for several days without clinical or diagnostic progress.
- **Consideration for insidious malignancy such as intravascular lymphoma entertained, but ruled out** due to normal peripheral blood flow cytometry and cytogenetics (along with recent normal bone marrow biopsy).
- Transferred to tertiary care center for continued workup and care.
- Upon arrival, noted to be mildly tachycardic and tachypneic though saturating 100% on room air. Recommendations placed for further imaging, labs, and studies **including a skin and fat pad biopsy**.
- However, within 24 hours of arrival patient suddenly began gasping for air with rapidly deteriorating bradycardia. He was found to be in PEA arrest and unfortunately died.
- Autopsy confirmed **diffuse organ involvement of intravascular diffuse large B-cell lymphoma.**
- Immediate cause of respiratory arrest attributed **to "severe leukostasis" of "alveolar capillaries congested with neoplastic cells".**

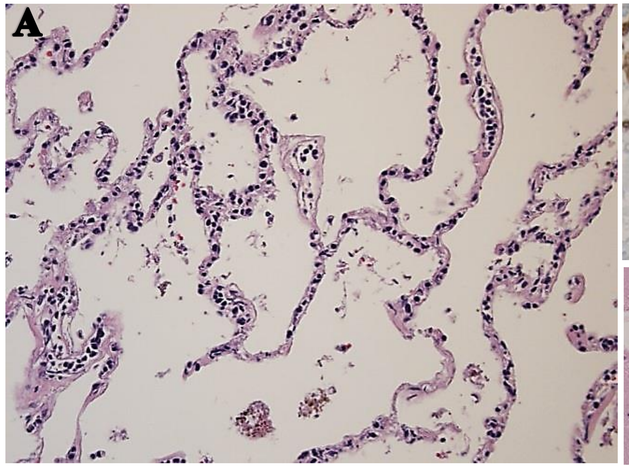
Extent of Organ Involvement

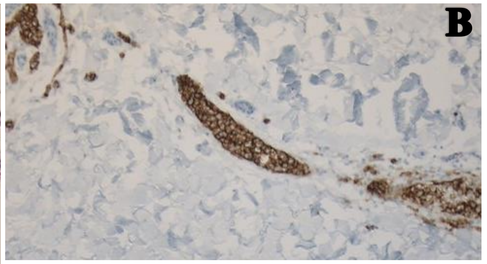
Specifically noted on pathologic examination to involve microcirculation of the following organs:

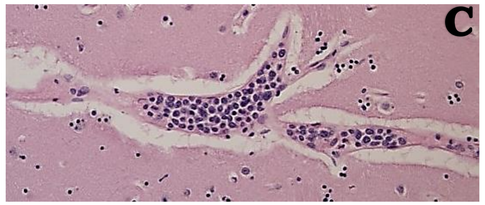
- Lung **(fig. A)**
- Aortic vasa vasorum
- Thyroid
- Kidney
- Prostate
- Stomach
- Spleen
- Skin **(fig. B)**
- Central Nervous System:
  - Basal ganglia **(fig. C)**
  - R frontal **(fig. D)** & occipital cerebral cortex
  - Pituitary gland (anterior and posterior)
  - Choroid plexus of medulla
  - Thalamus
- Coronary arteries
- Skeletal Muscle
- Adrenal glands
- Bladder
- Testicle
- Colon
- Liver

Note: **NOT** seen in bone marrow or lymph nodes

Pathologic Findings







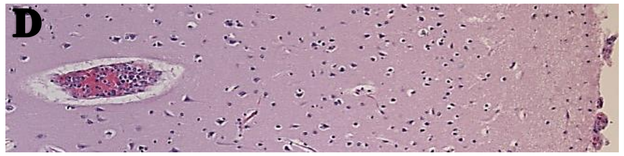


Figure A: Diffuse congestion of neoplastic B cells within pulmonary alveolar capillaries
Figure B: CD20+ staining of transected microcirculation from a superficial skin biopsy
Figure C: Densely packed neoplastic cells within vasculature of the basal ganglia
Figure D: Transected microcirculation of the frontal cortex exhibiting diffuse involvement of neoplastic cells

Discussion

- Intravascular lymphoma is an extremely rare subtype of extranodal diffuse large B-cell lymphoma characterized by **tumor proliferation within the lumina of small blood vessels**.[1]
- The entity was first described in 1959 as "angioendotheliomatosis proliferans systemisata" by Pfleger and Tappeiner, who theorized the malignancy derived from the endothelial cells themselves.[2]
- Given its rarity and nonspecificity of symptoms, diagnosis is difficult: over 60% of cases involving CNS are diagnosed postmortem.[3]
- **Only 5-9% of cases of intravascular lymphoma are detectable in peripheral blood.**[1] Small studies point to aberrant expression of markers which home to endothelial cell surface ligands, or aberrant lymphocyte homing and transvascular migration signaling.[4,5]
- Therefore, a **random skin biopsy is the diagnostic test of choice.**[6,7,8]
- In this case, presence of intravascular lymphoma was in fact suspected at the referring hospital, **though prematurely ruled out given normal bone marrow negative peripheral cytogenics and peripheral flow cytometry.** Nevertheless, disease involvement was clear on postmortem skin biopsy.
- This case illustrates key characteristics that can increase suspicion:[9]

	Anemia	↑LDH; B_2-microglobulin	↑ESR	Hepatic/renal/thyroid dysfunction
Incidence	65%	80-90%	43%	15-20%

- The literature further describes two distinct phenotypes: Western and Asian, which vary in organ involvement.[9] Interestingly, this case transcends the International Consensus Guidelines:

	CNS	Skin	Bone Marrow	Liver, spleen
Western	+	+		
Asian			+	+

- Early-diagnosed cases have been successfully treated with aggressive chemotherapy such as R-CHOP.[1]

Teaching Points

- Symptoms of intravascular lymphoma are nonspecific, though the **presence of an inexplicable inflammatory state, elevated LDH, anemia, and organ dysfunction** can raise suspicion.
- Definitive diagnosis is made via **random skin biopsy.**
- Distinction between Asian and Western phenotypes are not clear-cut.

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