Case # 152

NAME Educational Activities Committee

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**denotes equal contribution*

The decedent was an 80 year-old male with past medical history of borderline HTN, prior TIA, osteoarthritis, and a 15-20 pk-yr smoking history. He initially presented to the hospital with progressive shortness of breath, fatigue, poor appetite, and weight loss over the course of months. During his hospital stay, he developed fevers, thrombocytopenia, and acute kidney injury. An *extensive* rheumatologic, infectious, and hematologic workup (including bone marrow biopsy) was unrevealing, except for some elevated nonspecific inflammatory markers. His fevers continued despite broad-spectrum antibiotic coverage. His clinical status continued to decline with interval development of transaminitis, hyperuricemia, markedly elevated LDH, and ongoing coagulopathy. Eventually, the patient developed multiorgan failure and was transitioned to comfort care. Autopsy was requested after the patient expired.

Notable labs/pathology prior to his death are as follows:

- C-Reactive Protein: 12.64 mg/dL (reference range, ≤ 0.80 mg/dL)
- Lactate Dehydrogenase: 2,380 IU/L (reference range, 125-240 IU/L)
- Interleukin-2 Receptor: 30,600 pg/mL (reference range, 532-1891 pg/mL)
- Protime: 26.9 sec (reference range, 9.4-13.0 sec)
- Partial Thromboplastin Time: 51 sec (reference range, 25-37 sec)
- Fibrinogen: 423 mg/dL (reference range, 200-393 mg/dL)
- International Normalized Ratio: 2.40 INR (reference range, 0.87-1.19 INR)
- D-dimer: 1,921 ng/mL DDU (reference range, ≤ 243 ng/mL DDU)

Autopsy revealed mild cardiomegaly, severe atherosclerosis, bilateral pleural effusions, pulmonary edema, and splenomegaly (Figure 1). Focal hepatic and splenic infarcts were noted. A congealed yellow-white mucoid material consistent with fibrin deposition was noted within the left mainstem bronchus and right cardiac ventricle. No lymphadenopathy was identified grossly. Representative sections of each organ were collected; cells with atypical morphology were noted within the small vasculature of most organs, including in immune-privileged areas(testes, brain, etc.). Photomicrographs of selected organs are shown.

Based on the expected immunophenotype of the disease entity, which of the following IHC markers will be most likely be NEGATIVE in the cells with atypical morphology?

A. CD20
B. BCL2
C. MUM1
D. CD30

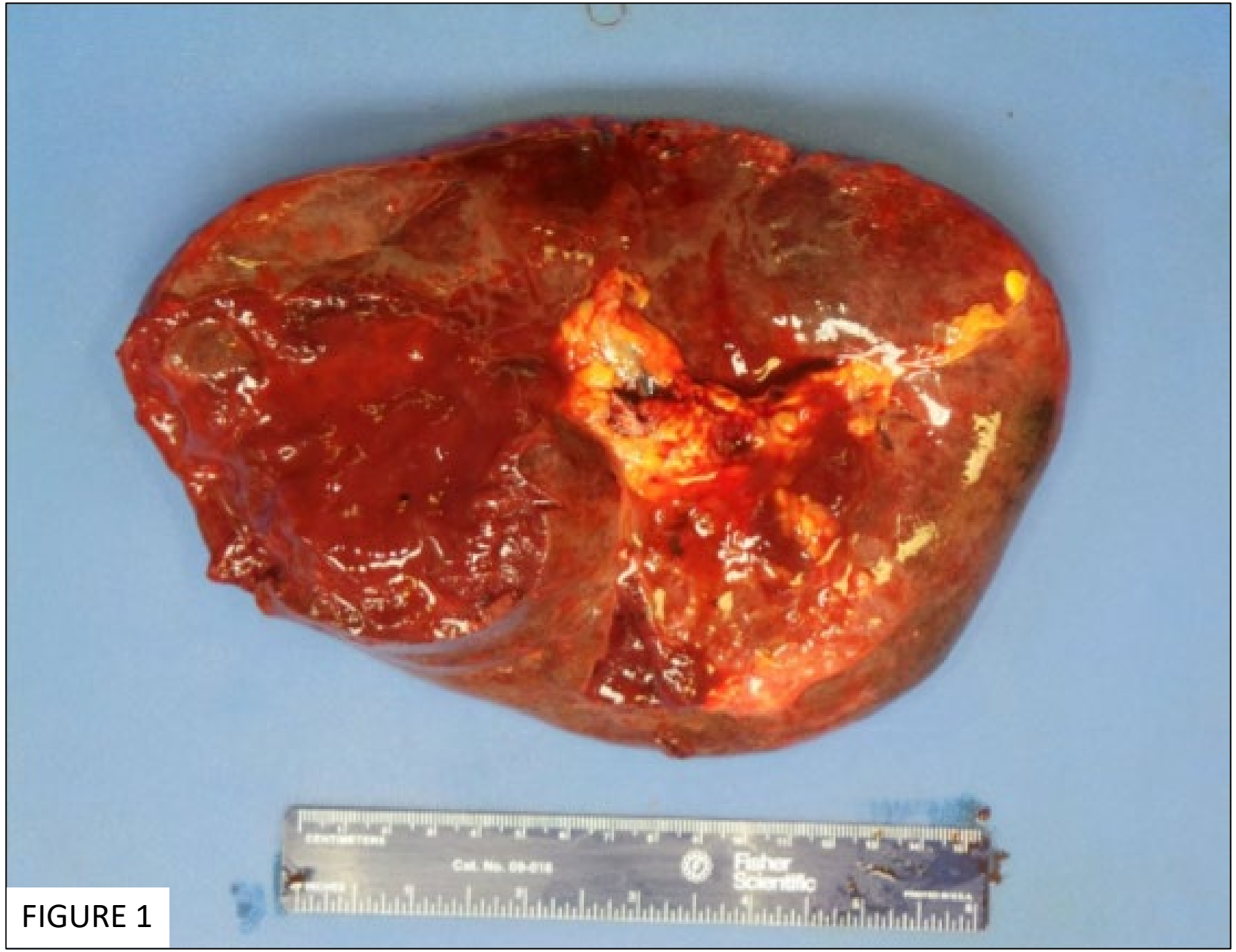
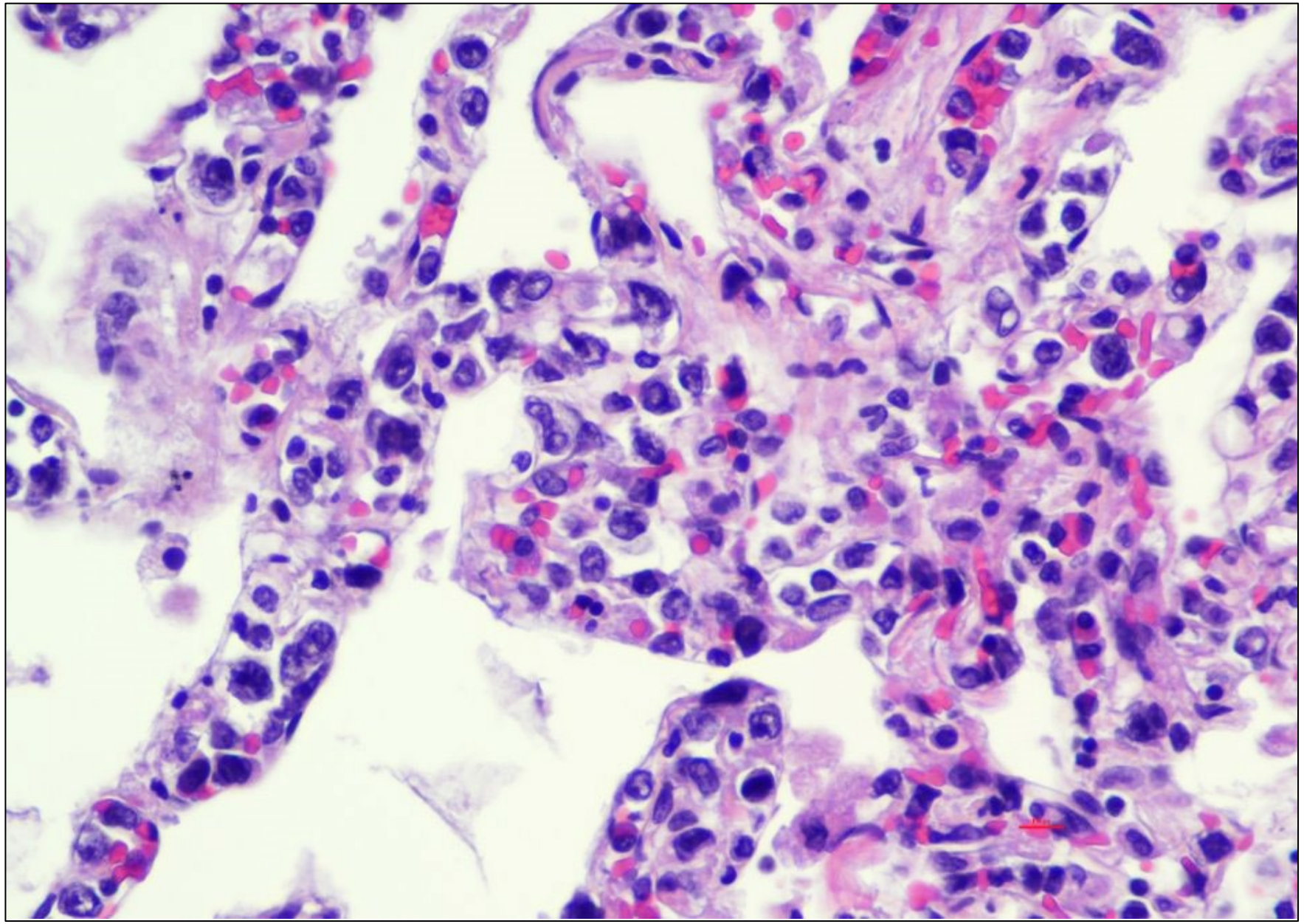
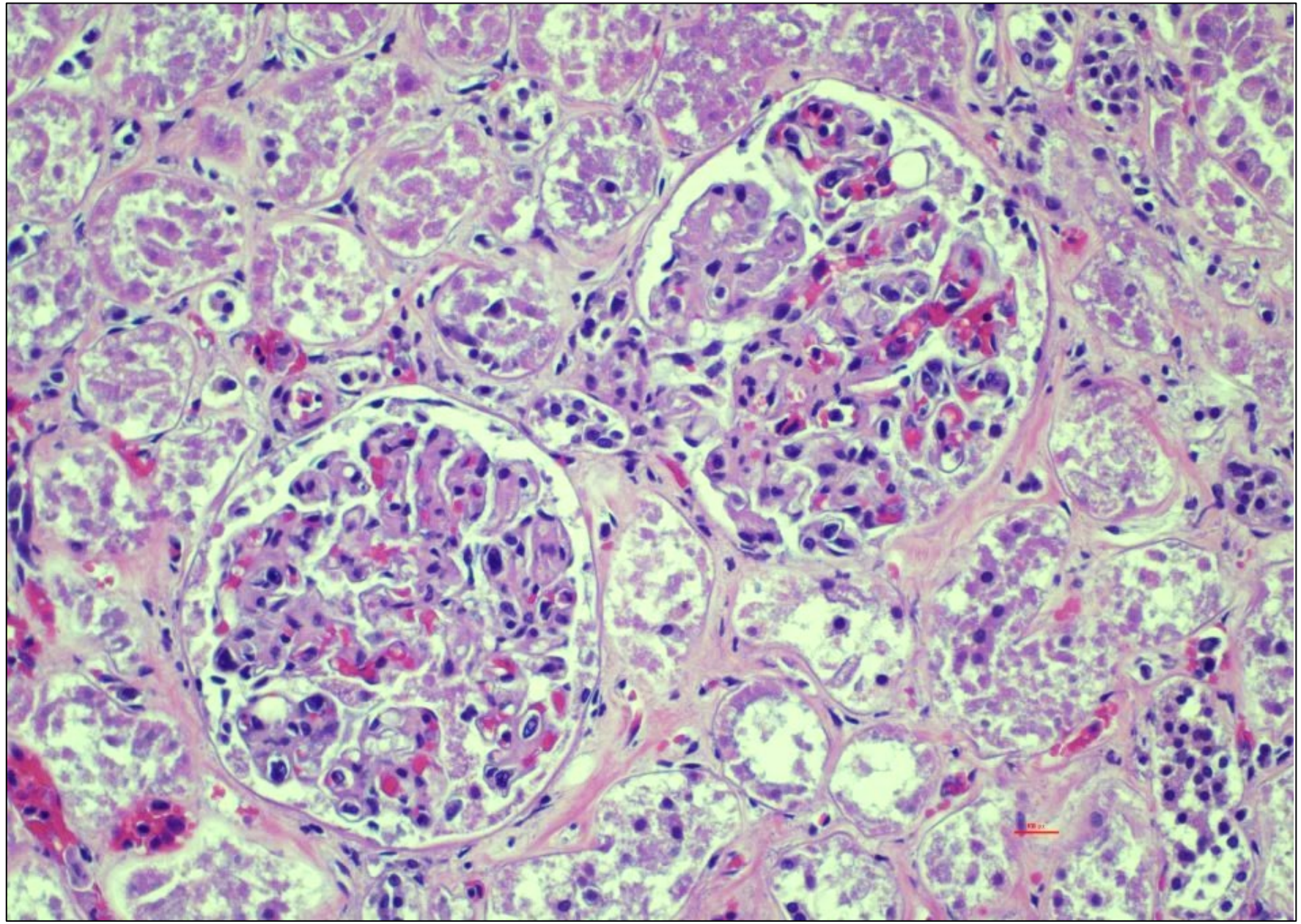


FIGURE 1

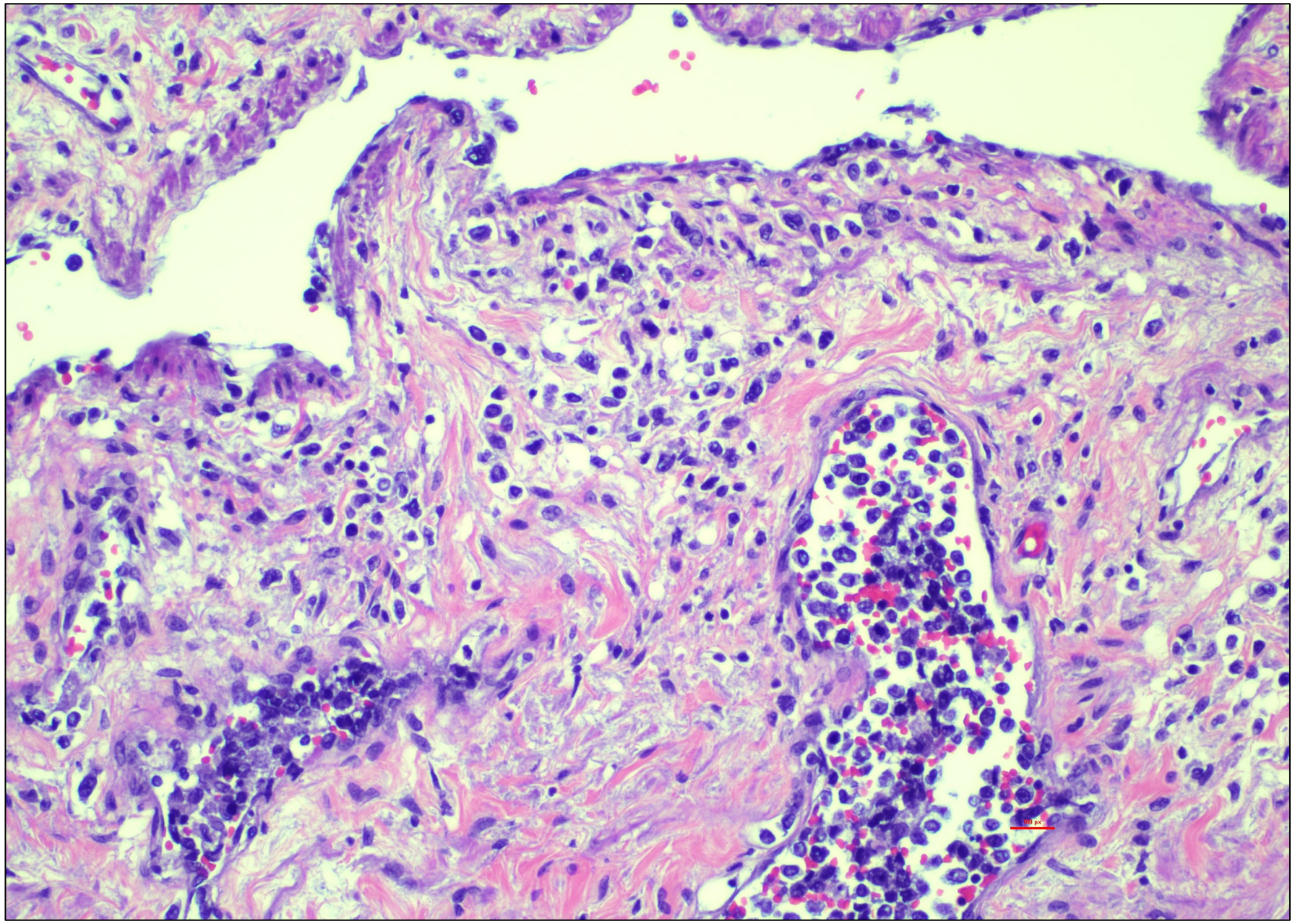
Gross photo of the spleen weighing 970 g (normal range, 75-120 g)



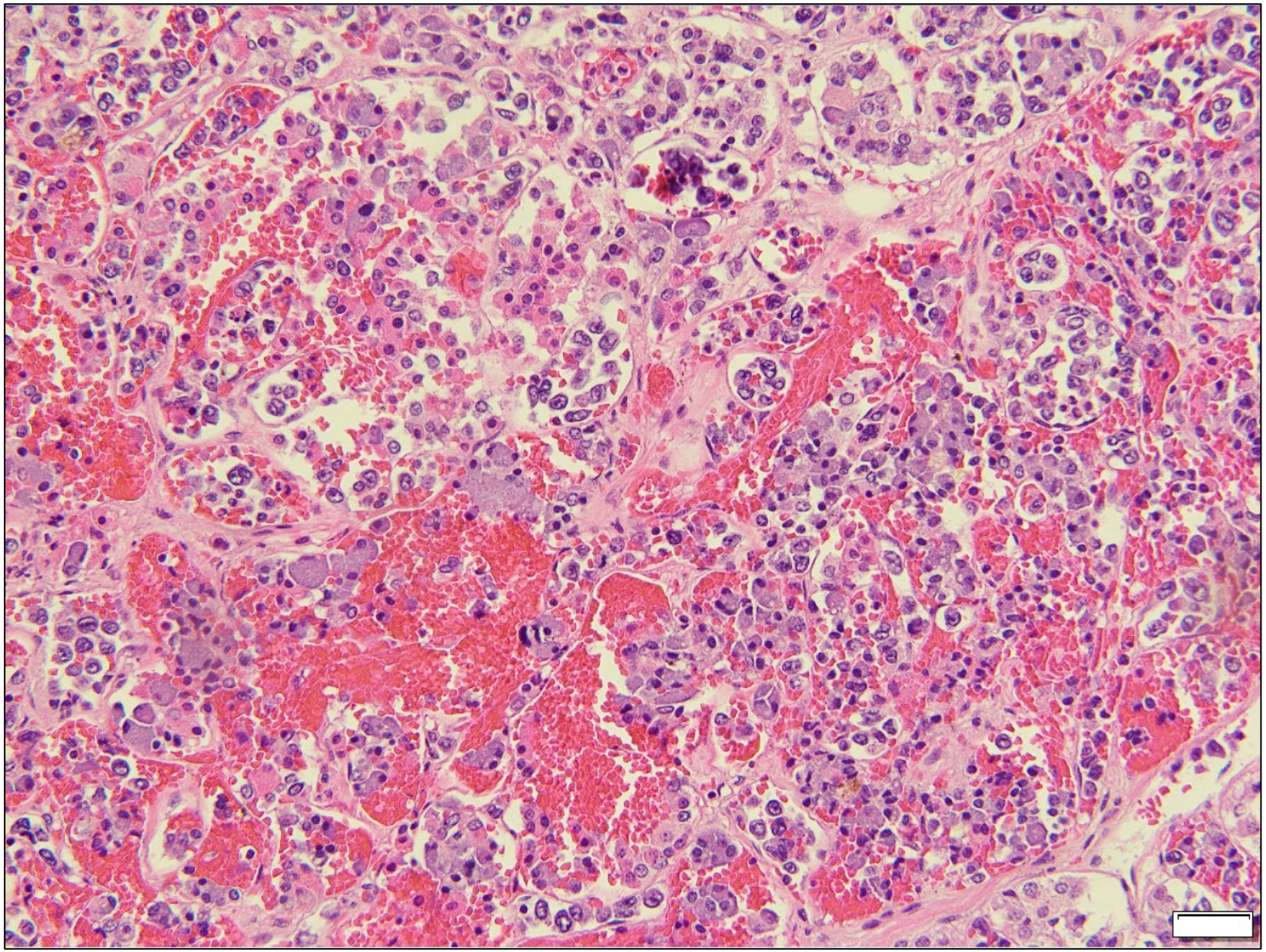
High-power view of lung parenchyma, H&E 400x



Glomeruli, H&E 200x



Peri-testicular tissue, H&E 200x



Pituitary gland, H&E 200x

Answer...

D. CD30 (Correct answer – 46.58% of responses)

At autopsy, this patient was diagnosed with intravascular large B-cell lymphoma (IVLBCL) with associated coagulopathy consistent with disseminated intravascular coagulation (DIC) secondary to diffuse vascular involvement by lymphoma cells across multiple organs. Extensive vascular occlusion likely contributed to the multiple infarcts identified in the liver and spleen. The patient's markedly abnormal coagulation studies are consistent with these findings. Histologically, lymphoma cells were noted within the small vessels and capillaries of the lungs, liver, spleen, kidneys, brain, thyroid, stomach, intestines, bladder, prostate, periadrenal tissue, and peritesticular tissue. Interestingly, the heart was spared in this case.

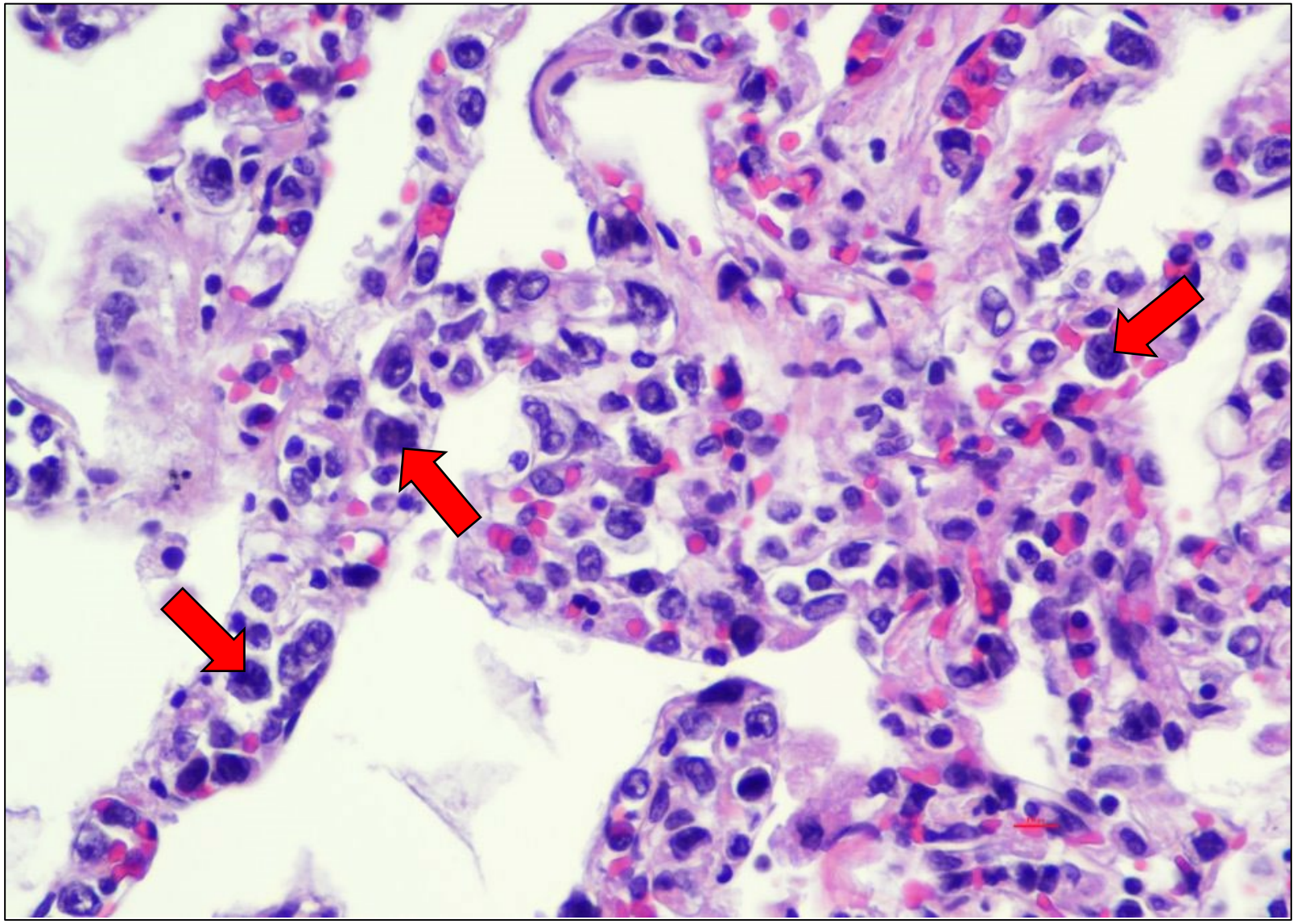
Immunohistochemical (IHC) workup:

The lymphoma cells are typically positive for pan B-cell markers (CD20, CD79a, PAX5) as well as BCL2. Although BCL2 is most often known for its usual positivity in follicular lymphoma but is also positive in other T/B-cell lymphomas, including IVLBCL. 95% of cases show nongerminal center phenotype with MUM1 positivity. CD34 is also helpful to highlight endothelial cells. Germinal center markers, such as CD10 and BCL6 are mostly negative. CD30, which is characteristically expressed in Hodgkins's lymphoma and anaplastic large cell lymphoma, is typically negative in IVLBCL.

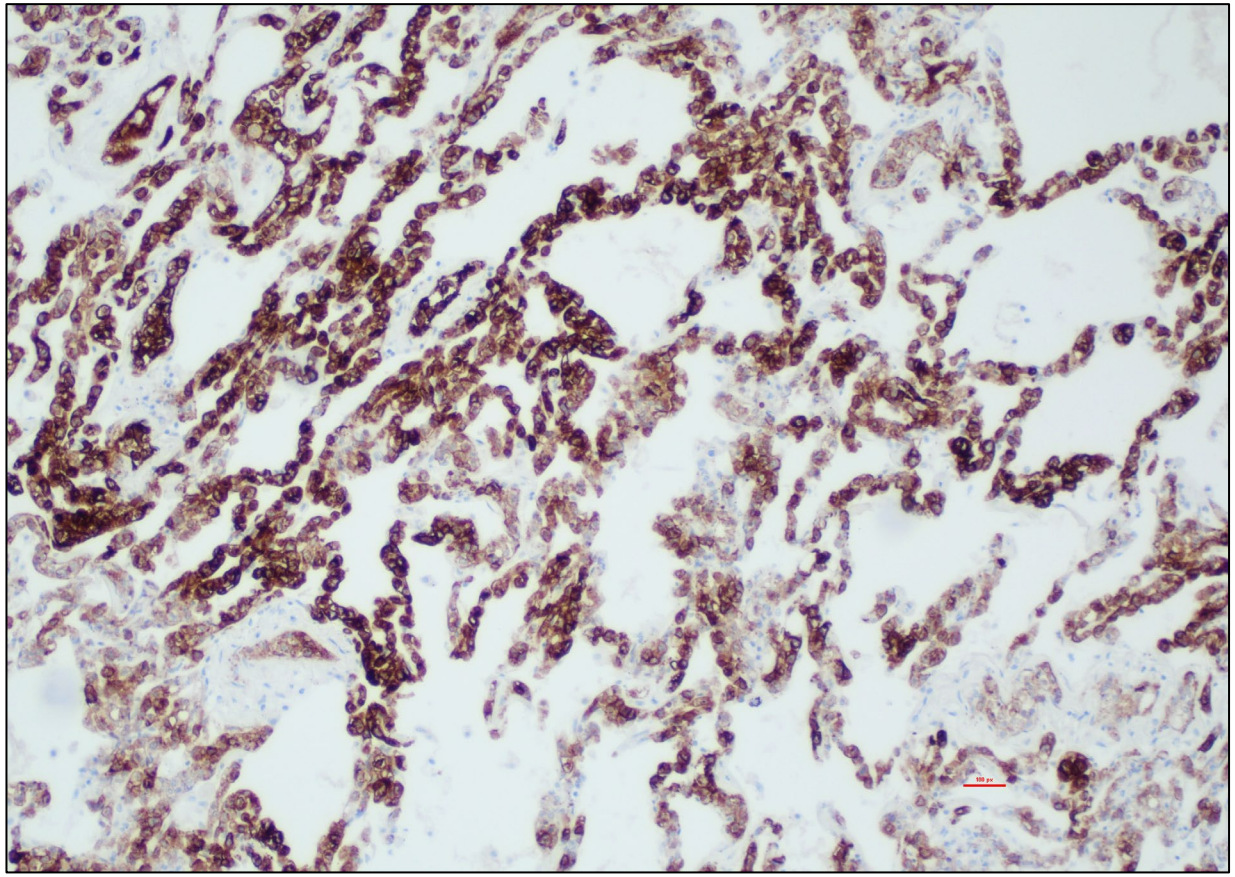
More on the disease:

IVLBCL is a rare and aggressive subtype of diffuse large B-cell lymphoma with an annual incidence of fewer than 0.5 cases per 1,000,000 individuals. The median age at diagnosis is approximately 70 years, and there is no gender predilection. The disease is characterized by proliferation of neoplastic B cells confined to small blood vessels and capillaries, generally without involvement of the peripheral blood. Consequently, peripheral blood flow cytometry may be unrevealing despite widespread disease. IVLBCL is diagnostically challenging through a combination of nonspecific symptom presentation and unrevealing diagnostic workup. Definitive diagnosis is made with a biopsy of any affected organ, with the caveat that IVLBCL must be considered in order for a biopsy to be performed. Unfortunately, this diagnosis is often made postmortem because patients frequently succumb to complications of the disease before the diagnosis is established.

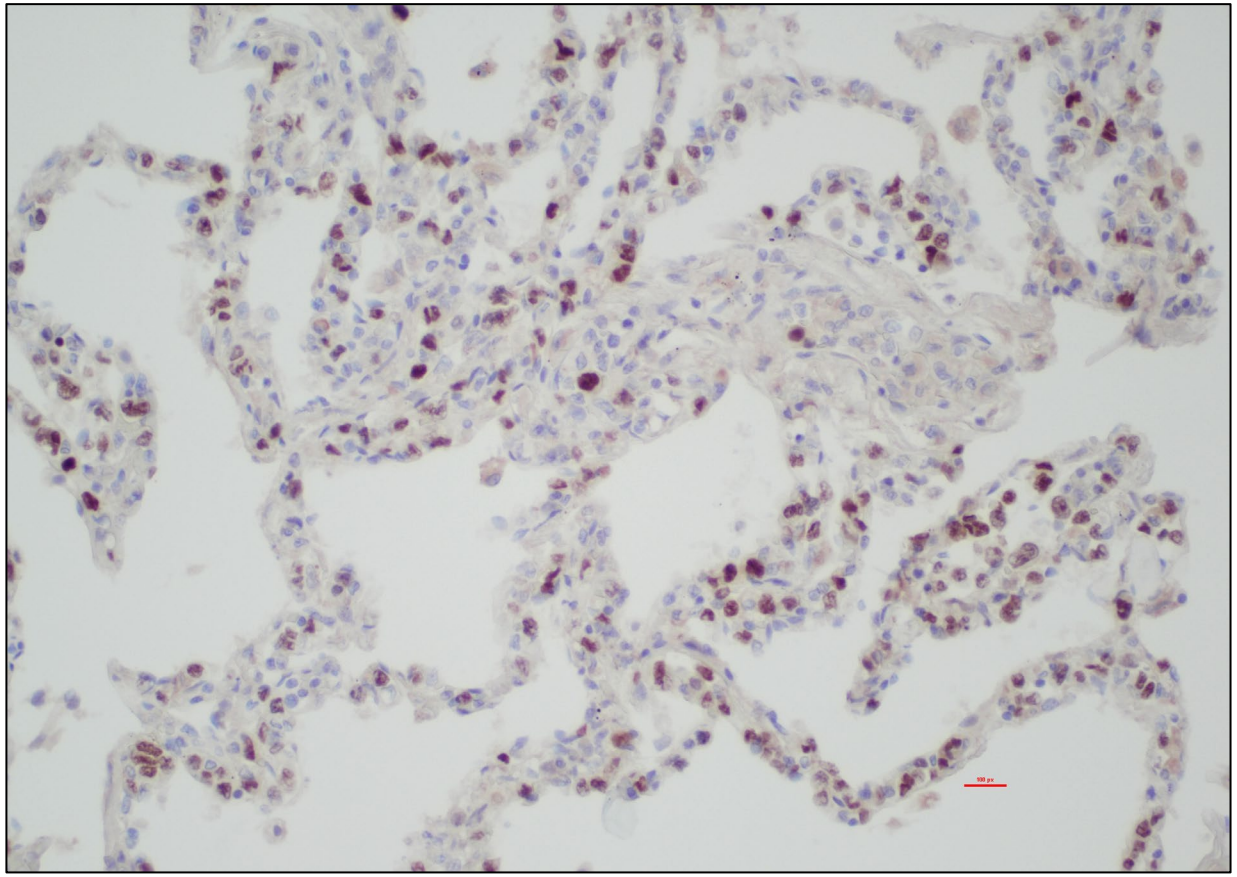
Retrospective studies on published case reports of IVLBCL have identified two major clinicopathologic variants of IVLBCL based on geographic origin. The Classical variant, seen in Western populations, is characterized by CNS and/or cutaneous involvement. Meanwhile, the Asian variant is associated with hemophagocytic syndrome, bone marrow involvement, and thrombocytopenia.



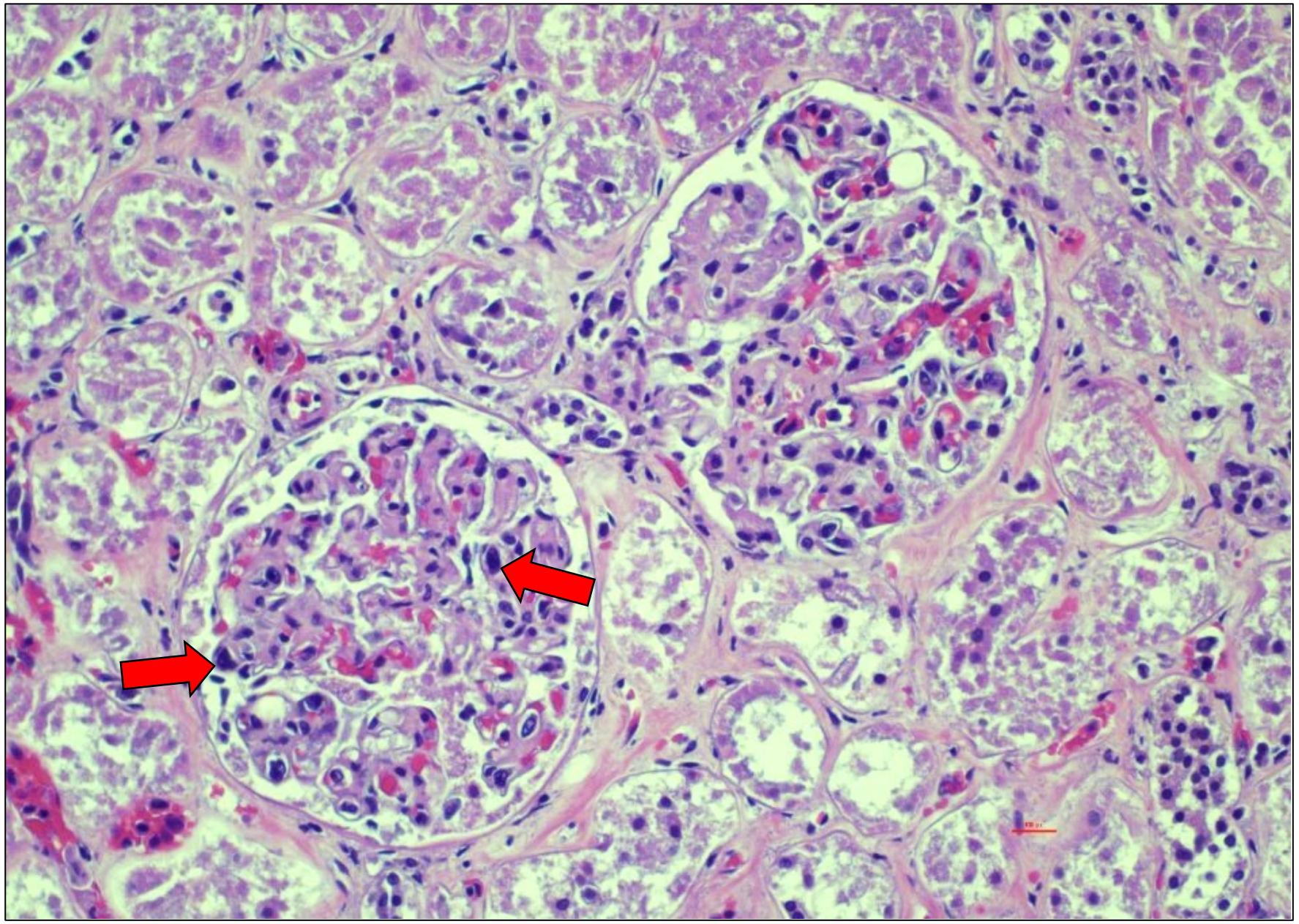
Morphologically atypical appearing lymphoma cells are diffusely present throughout the pulmonary capillaries.



CD20 IHC on lung parenchyma



PAX5 IHC on lung parenchyma



Morphologically atypical appearing lymphoma cells are present within the glomeruli.

- The typical staining pattern for intravascular large B-cell lymphoma includes:
  - Positive: CD20, PAX5, MUM1, BCL2
  - Negative: CD10, CD30

- Other choices:
  - CD20 (18.63% of responses)
  - BCL-2 (18.01% of responses)
  - MUM1 (16.77% of responses)

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