Case 147

NAME Educational Activities Committee

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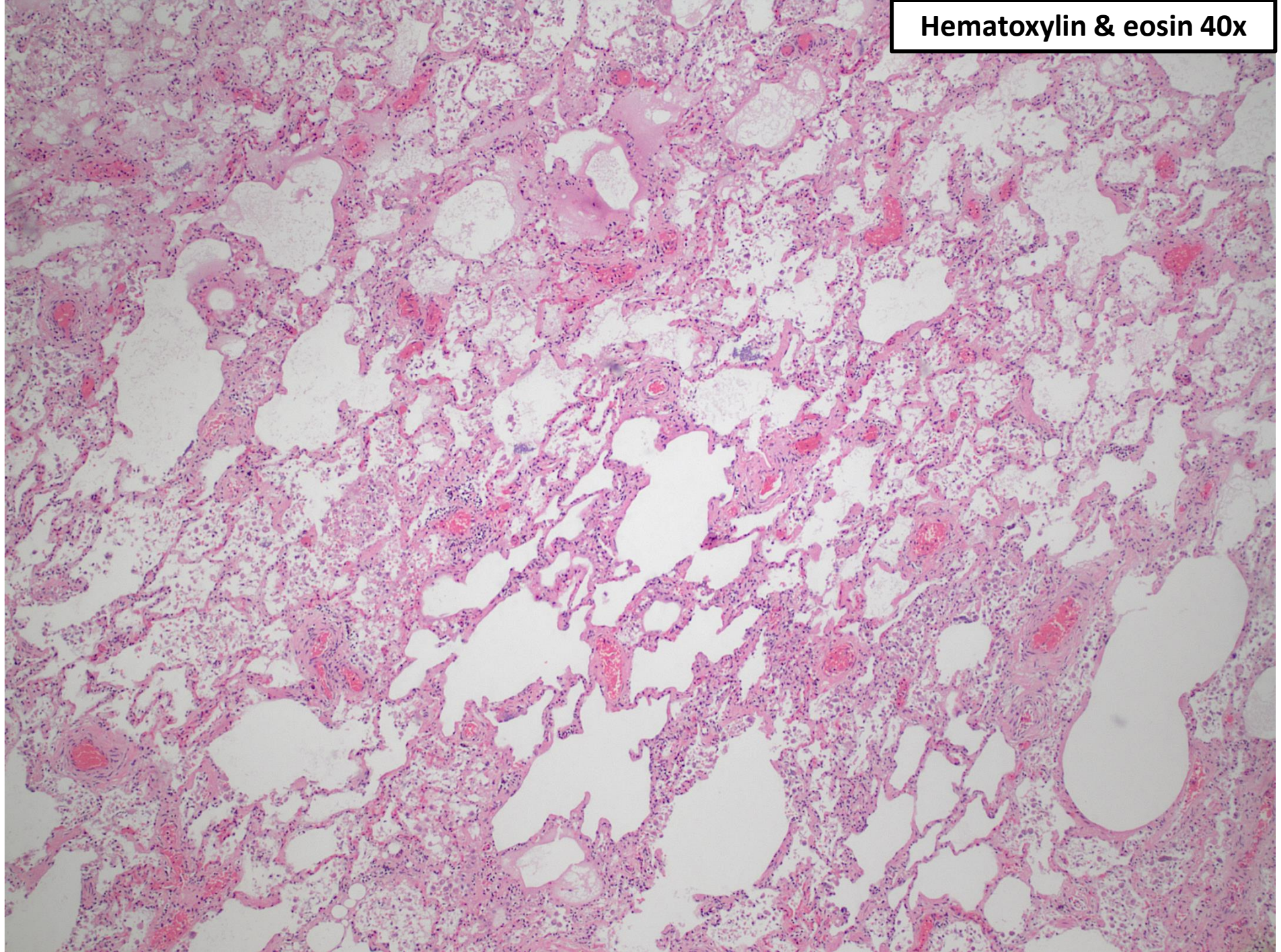
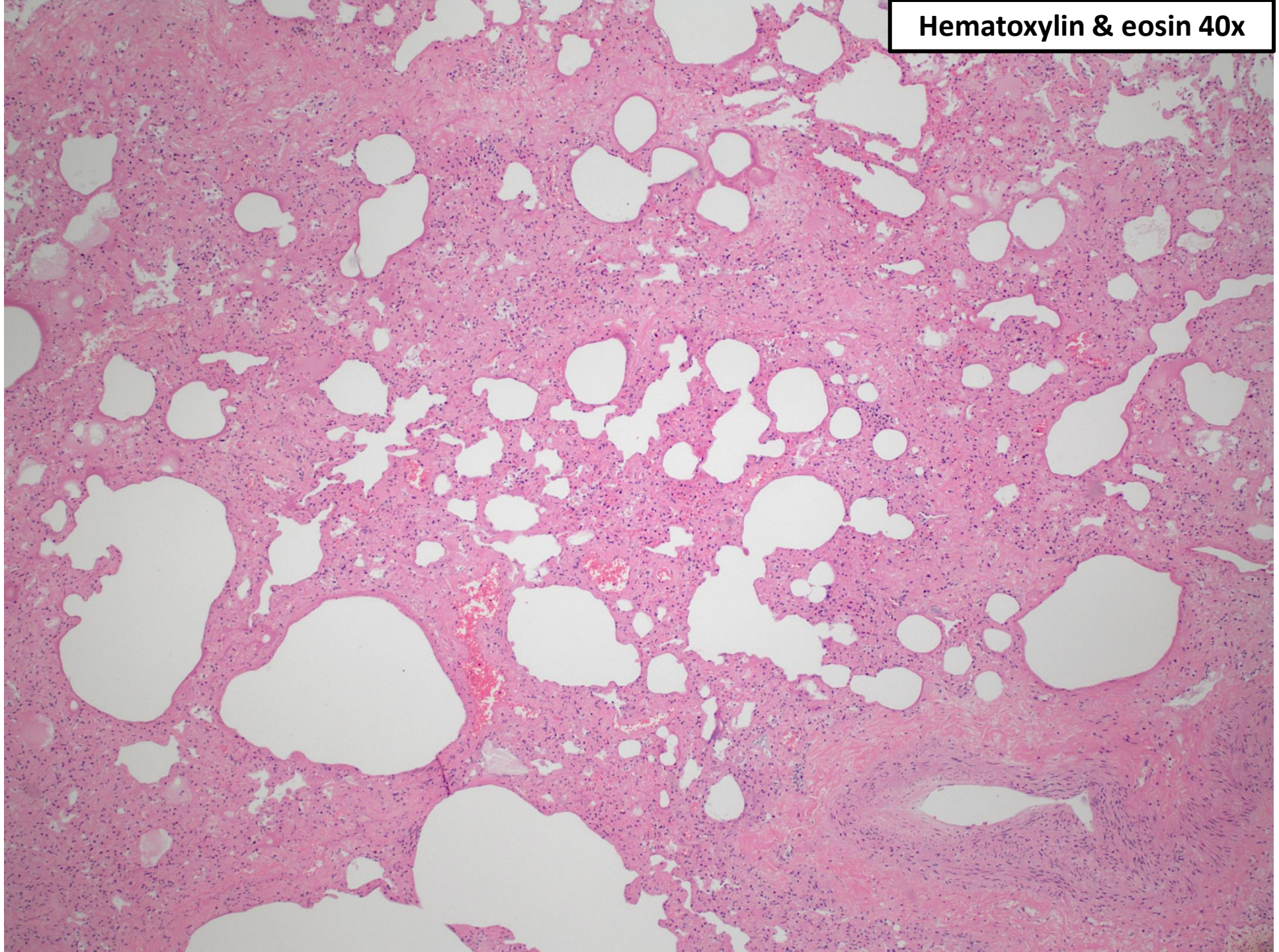
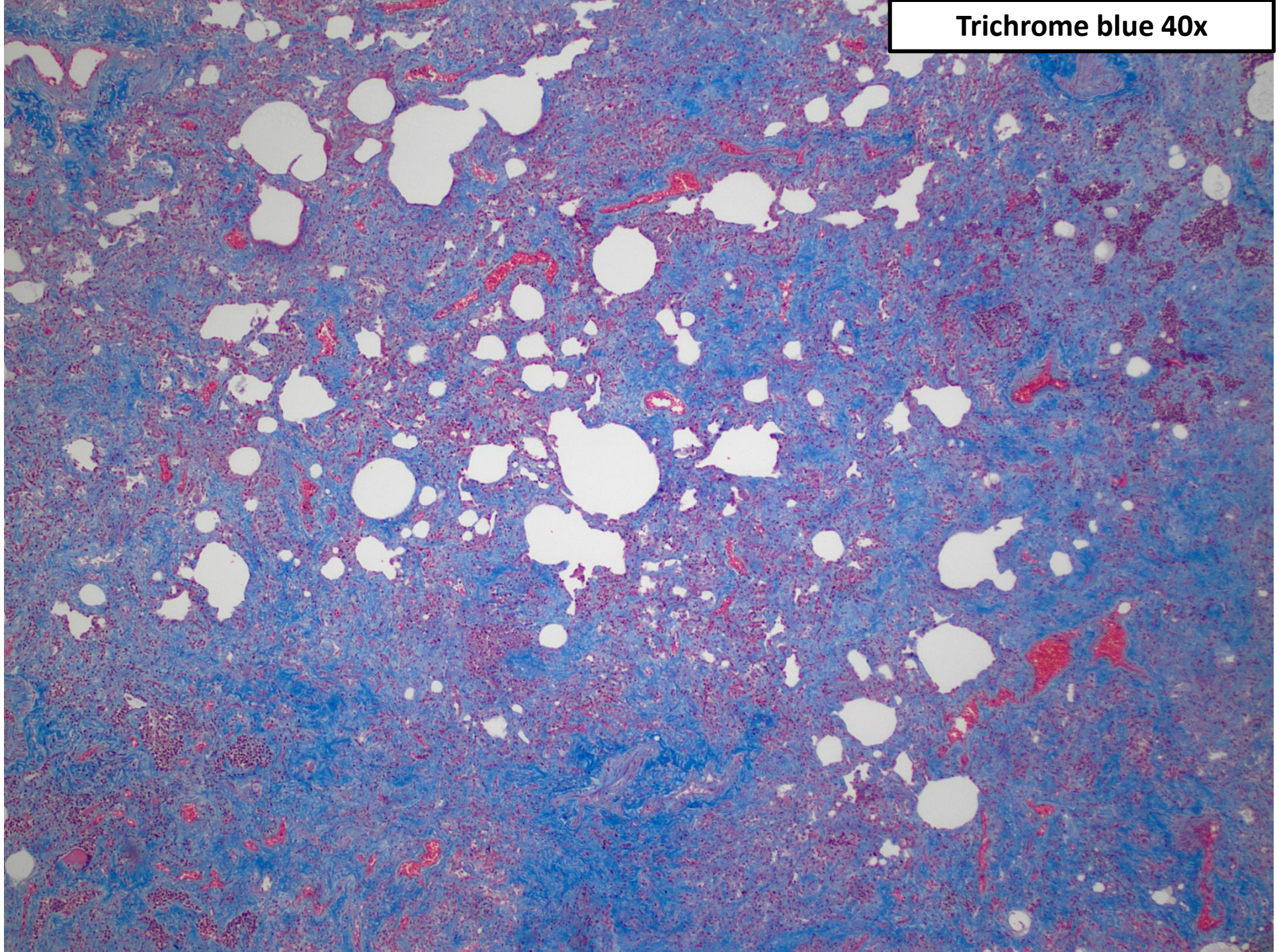

Hematoxylin & eosin 40x


Hematoxylin & eosin 40x


Trichrome blue 40x

A 23-year-old Black woman was pronounced dead several hours after abruptly stopping a hemodialysis session due to hypotension and lightheadedness.

Her medical history included chronic kidney disease, avascular necrosis of the bilateral hips, and recurrent severe musculoskeletal pain, treated with long-term oral oxycodone as needed. CT Pulmonary Angiogram (CTPA) performed the day of death showed, among other findings, dilation of the main pulmonary artery, low lung volumes, and prominent mediastinal lymph nodes.

External examination, including skin exam, was unremarkable. At autopsy, the heart weighed 378 g, the spleen weighed 1,074 g, the kidneys weighed 60 g (right) and 96 g (left). Extensive pleural adhesions were present.

Which of the following pathophysiological mechanisms most likely explains the pulmonary findings depicted in the images?

A. Chronic tissue injury secondary to prolonged opioid treatment
B. Microvascular obstruction by erythrocytes and leukocytes
C. Persistent autoimmune-driven fibroblast activation with excess collagen deposition
D. Increased hemolysis with microvascular endothelial dysfunction

Answer...

B. Microvascular obstruction by erythrocytes and leukocytes (Correct answer, 21.09% of responses)

Recurrent episodes of severe pain requiring opioid treatment in a young Black woman with end-stage renal disease, avascular necrosis of the hips, and splenomegaly suggest sickle cell disease (SCD). In this case, the diagnosis was established prior to death.

The underlying cause of SCD is the inheritance of two copies of a single-point mutation in the β-globin gene, which results in the production of a hemoglobin (Hb) S. HbS polymerizes upon deoxygenation, causing erythrocytes to become rigid and distorted in shape, leading to hemolysis and vaso-occlusive episodes. Repeated vaso-occlusion and hypoxia leads to upregulation of endothelial VCAM-1, which increases leukocyte adhesion and furthers microvascular obstruction. In the lungs, this occlusion of capillaries and postcapillary venules leads to infarction and is one of the primary mechanisms responsible for acute chest syndrome (ACS). ACS is one of the classic pulmonary complications of SCD and is associated with high mortality. Repeated episodes of vaso-occlusion and lung infarction from ACS may result in dysregulated repair by fibroblasts and eventual pulmonary fibrosis.

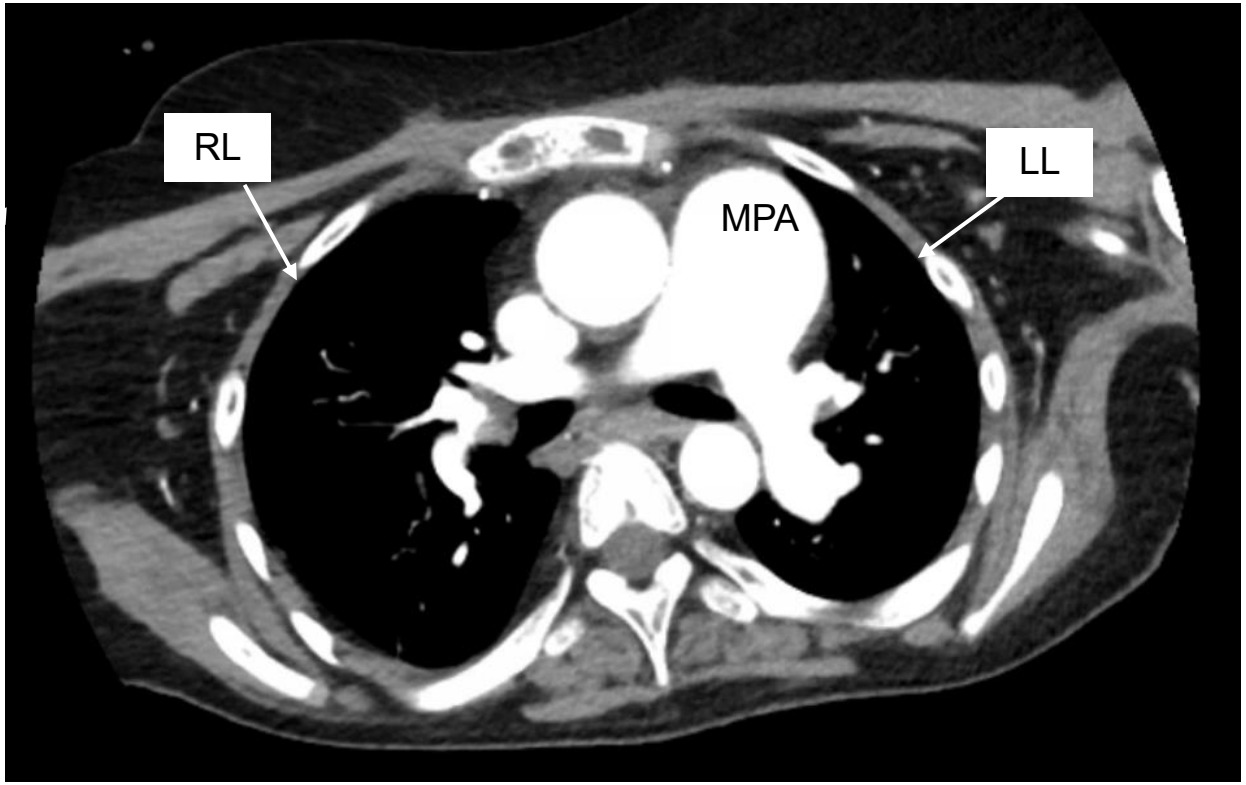
In the presented case, histological findings showed pulmonary fibrosis (trichrome stain with collagen in blue) from multiple episodes of microvascular obstruction (answer B).

Explanation continues on the next slide

In this case, medical records documented multiple hospital admissions for ACS. The fibrosis would also explain the low lung volumes detected on CTPA (see image), consistent with restrictive lung disease.

Autopsy also showed pleural adhesions, splenomegaly, and atrophic kidneys, all common findings in SCD. Pleural adhesions are caused by fibrotic remodeling from repeated lung infarction. Splenomegaly is due to splenic sequestration of red blood cells, which commonly transitions to splenic atrophy and autosplenectomy. However, in some cases, splenomegaly can persist into adulthood, providing an indication for splenectomy. Atrophic kidneys are due to repeated microinfarcts in the kidneys, leading to end-stage renal disease and dialysis. In this case, the incomplete dialysis session potentially acted as a trigger for ACS.

CTPA with contrast



MPA: main pulmonary artery. RL: right lung. LL: left lung

Of note, the presence of sickled erythrocytes in formalin-fixed tissue does not necessarily indicate sickle cell crisis, since formalin can cause sickling in histological sections in people with SCD and sickle cell trait.

Other responses…

A. Chronic tissue injury secondary to prolonged opioid treatment (Incorrect, 4.47% of responses)

While opioids are known to cause lung toxicity, the effects are usually due to respiratory depression, such as atelectasis, pulmonary edema, and aspiration.

Rarely, prolonged opioid abuse can contribute to pulmonary fibrosis through granulomatous reaction to IV drug filler substances, such as talc. However, this is seen when oral medications are ground up and injected intravenously, leading to talc accumulation in the pulmonary vasculature. This would not be expected in a person taking oral opioids.

Many drugs are associated with the development of interstitial lung disease include antimicrobial agents, anti-inflammatory agents, biological agents, and chemotherapeutic agents, including hydroxyurea for sickle cell disease treatment. Damage to the lungs caused by pneumotoxic substances results in alveolitis and fluid accumulation. When the lung parenchyma is injured, the body must promptly activate repair mechanisms to reestablish tissue integrity and restore the barrier function.

An acute insult can advance to persistent inflammation and ultimately produce fibrotic alterations that impair normal gas exchange. In addition, certain chemotherapeutic agents may exert direct toxic effects, which typically develop gradually and precede the clinical appearance of treatment-related pulmonary fibrosis.

C. Persistent autoimmune-driven fibroblast activation with excess collagen deposition (incorrect, 59.74% of responses)

This describes the pathophysiological mechanism of pulmonary fibrosis associated with systemic sclerosis (SS), an autoimmune connective tissue disorder characterized by vasculopathy and progressive organ fibrosis, leading to severe organ dysfunction.

In addition to involvement of the skin and joints, SS can also affect several internal organs including the lungs, kidneys, and gastrointestinal system. Pulmonary hypertension and interstitial lung disease (ILD) are the most frequently reported pulmonary complications.

Fibrosis results from the chronic activation of fibroblasts by inflammatory and profibrogenic cytokines such as IL-4, IL-6, IL-13 and transforming growth factor (TGF)-β. These mediators promote extracellular matrix production by increasing collagen synthesis while simultaneously inhibiting collagenase activity.

In the present case, the subject did not show any hardening of the skin at the extremities and in the face, or digital ulcerations - clinical features typically associated with advanced systemic sclerosis. Also, no other organs showed fibrosis besides the lungs, making the diagnosis less likely.

D. Increased hemolysis with microvascular endothelial dysfunction (incorrect, 14.70% of responses)

SCD causes vascular complications through multiple mechanisms. In addition to vaso-occlusive episodes, sickling of HbS also leads to intravascular hemolysis which drives other vasculopathic complications of SCD, including cutaneous leg ulceration, priapism, pulmonary hypertension, sudden death, and stroke.

Hemolysis and the subsequent increased free hemoglobin levels lead to underlying endothelial dysfunction through inactivation of nitric oxide (NO) and increased production of reactive oxygen species by free-plasma Hb, as well as reduced NO bioavailability due to arginine (Arg) catabolism by plasma arginase released from hemolyzed erythrocytes. While this contributes to vasculopathic complications of SCD, it does not lead to pulmonary fibrosis.

In the presented case, the subject developed pulmonary fibrosis from multiple lung infarctions in the setting of ACS, which is better explained by microvascular obstruction by rigid, deformed erythrocytes.

REFERENCES

1. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med. 2008 Nov 20;359(21):2254-65. doi: 10.1056/NEJMra0804411.

2. Schwaiblmair M, Behr W, Haeckel T, Märkl B, Foerg W, Berghaus T. Drug induced interstitial lung disease. Open Respir Med J. 2012;6:63-74. doi: 10.2174/1874306401206010063. Epub 2012 Jul 27.

3. Miller AC, Gladwin MT. Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med. 2012 Jun 1;185(11):1154-65. doi: 10.1164/rccm.201111-2082CI. Epub 2012 Mar 23.

4. Radke JB, Owen KP, Sutter ME, Ford JB, Albertson TE. The effects of opioids on the lung. Clin Rev Allergy Immunol. 2014 Feb;46(1):54-64. doi: 10.1007/s12016-013-8373-z.

5. Rosendahl AH, Schönborn K, Krieg T. Pathophysiology of systemic sclerosis (scleroderma). Kaohsiung J Med Sci. 2022 Mar;38(3):187-195. doi: 10.1002/kjm2.12505. Epub 2022 Mar 2.