Case #135

NAME Educational Activities Committee

Case provided by:

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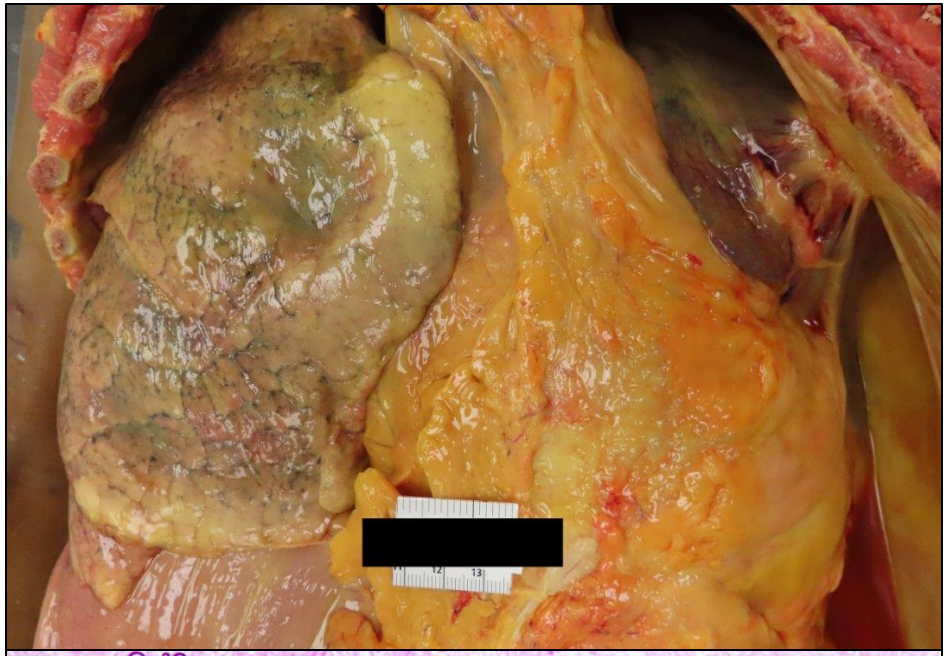
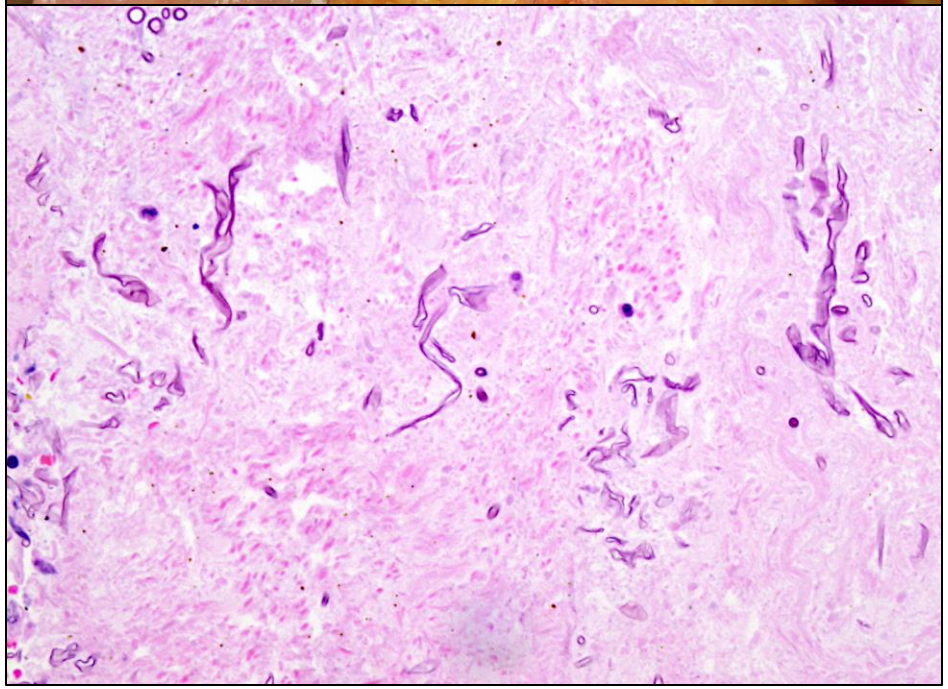
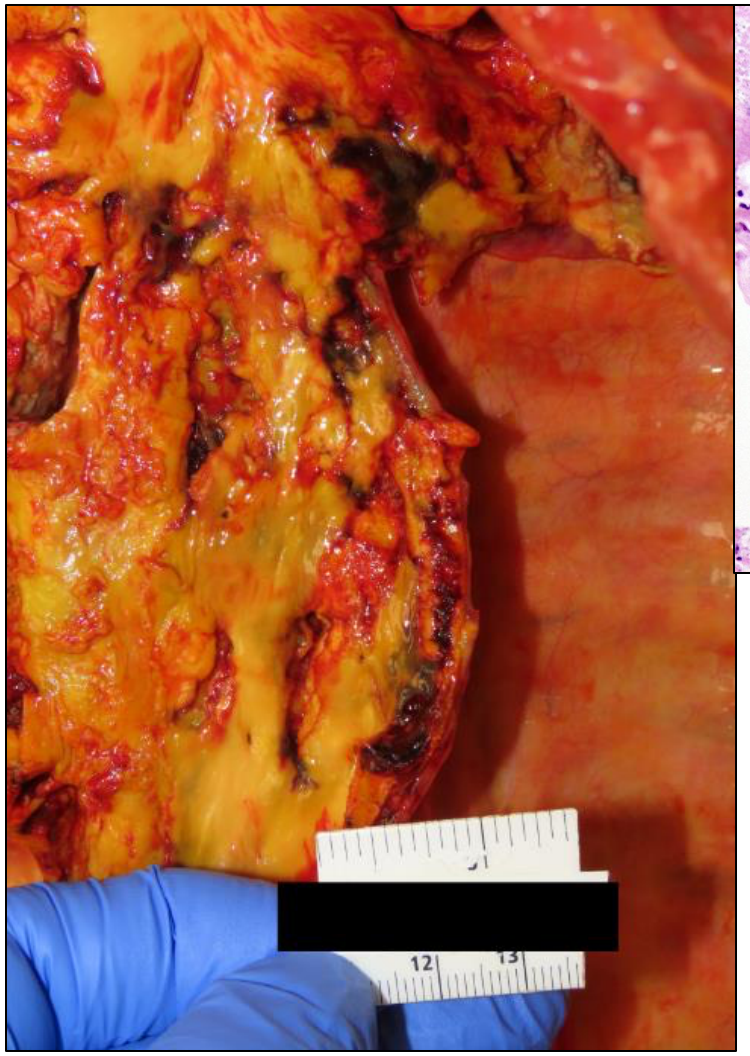
The case involved a 55-year-old man with a past medical history limited to alcohol-induced pancreatitis who was admitted to the hospital for acute liver failure secondary to combined toxic effects of acetaminophen and ethanol. During his admission, he developed a severe infection that ultimately proved fatal. The gross and histologic findings at autopsy are showed in the photos. Similar findings were additionally observed in the bronchi and lungs, right kidney and spleen.

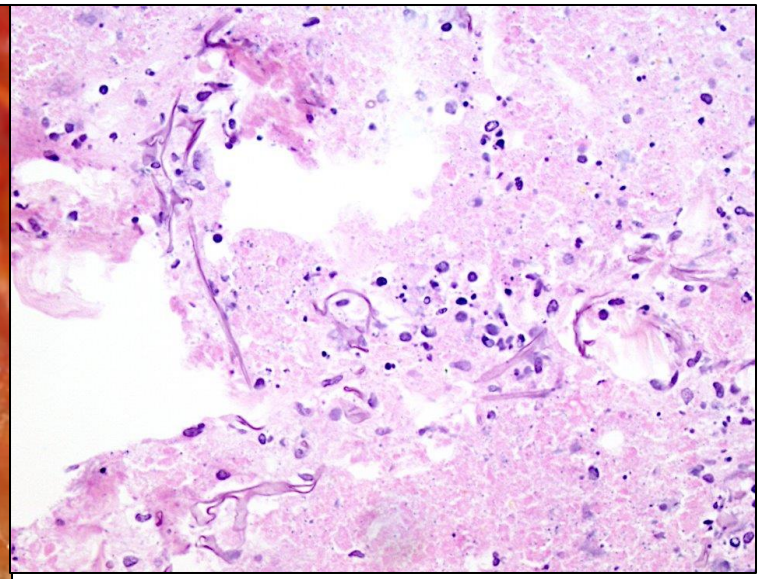
We asked you which of the listed options was the most common risk factor for development of this infection?

A. Alcohol-associated liver disease
B. Environmental exposure
C. Solid organ malignancy
D. Diabetes









Similar findings were additionally observed in the mainstem bronchi and lungs (L>R), right kidney and spleen.

Answer...

D. DIABETES (CORRECT ANSWER – 55.69 % of responses)

Explanation continued:

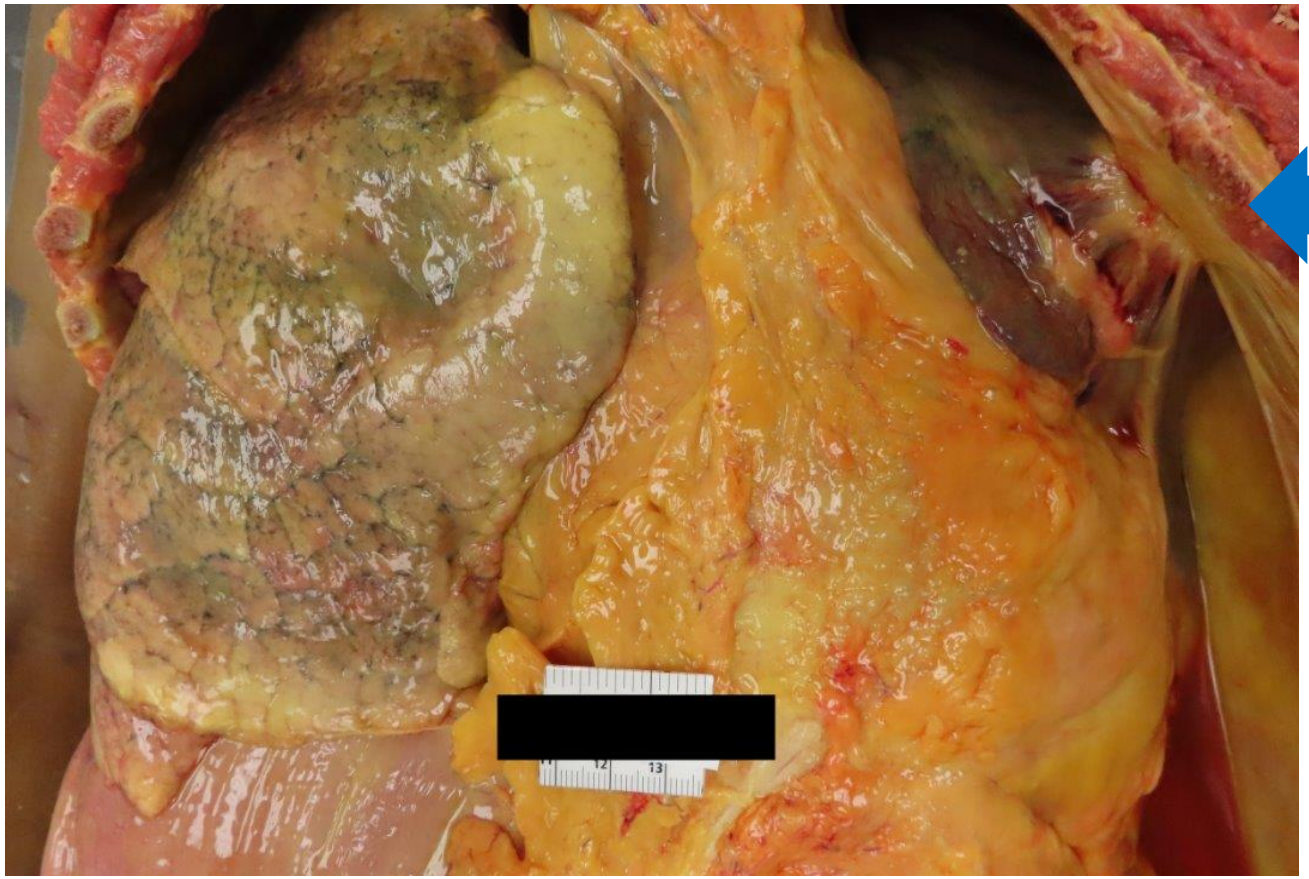
The findings shown demonstrate a disseminated fungal infection consistent with Mucormycosis. Speciation of fungus is limited on examination by H&E, but fungal elements were abundant and demonstrated a broad, pauciseptate, ribbon-like morphology consistent with Mucormycosis, ultimately supported by correlation with antemortem clinical laboratory growth of *Rhizopus* on sputum fungal culture. Additionally, this decedent developed a secondary gram-negative bacteremia with *Mycetohabitans endofungorum*, an endofungal symbiont of *Rhizopus,* that supported the diagnosis of disseminated mucormycosis.

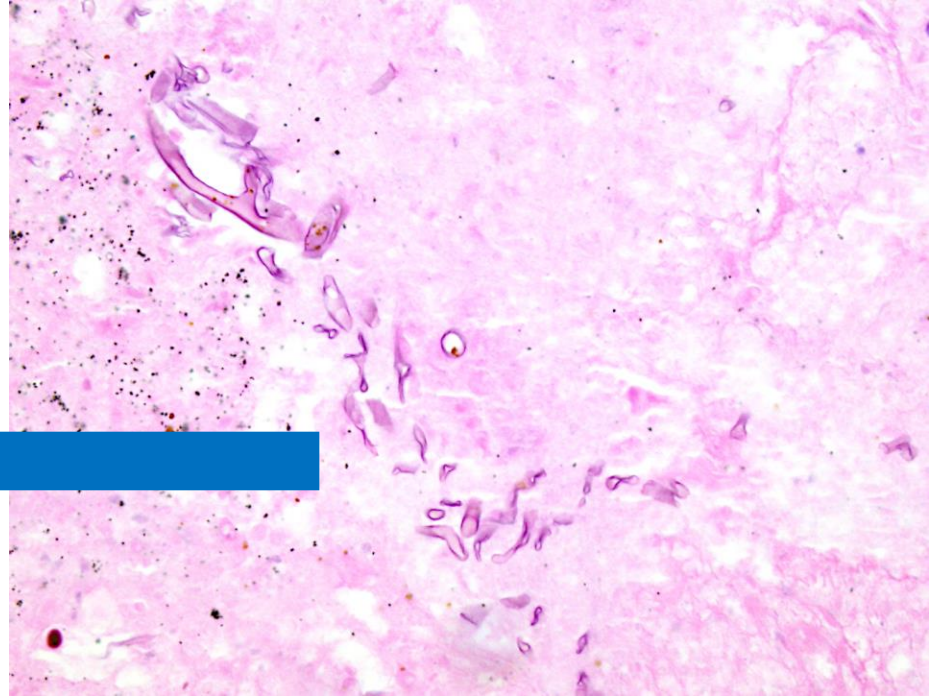
The findings presented represented the observed extensive thoracic disease, including involvement of the lungs, mainstem bronchi, and pleura (L>R), the aorta, and formation of a bronchoesophageal fistula (requiring antemortem stent placement). Additionally, splenic and renal infarcts were observed, and histology proved them to be the result of mycotic emboli.

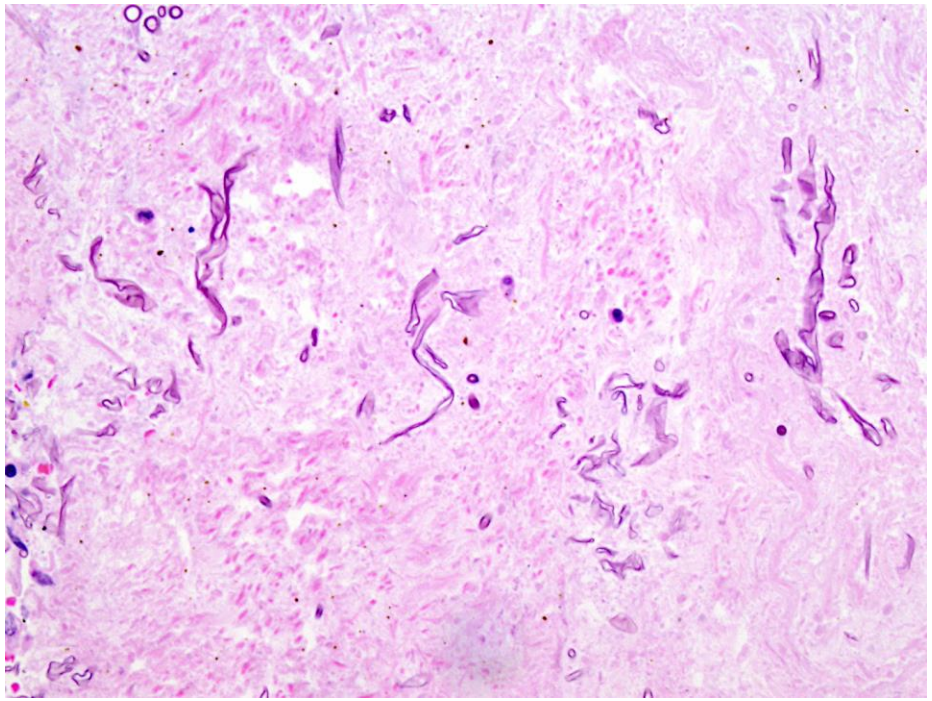
Disseminated mucormycosis is almost exclusively found in individuals with some underlying disease that predisposes them to the infection, the most common underlying disease being diabetes, particularly with ketoacidosis. This is because *Rhizopus* organisms possess an enzyme ketone reductase that allows them to thrive in high glucose, acidic conditions. The serum from individuals in active diabetic ketoacidosis stimulates growth of *Rhizopus*, while that from normal, healthy individuals inhibits growth.

Other risk factors are largely immunosuppressive in mechanism, with the next most common risk factor being hematologic malignancies, then solid organ or hematopoietic cell transplantation. Another known risk factor is treatment with deferoxamine. Deferoxamine is a chelating agent used in the treatment of iron overload, often in the setting of multiple blood transfusions. The deferoxamine-iron chelate, feroxamine, is a siderophore for the species *Rhizopus*, increasing iron uptake by the fungus and therefore stimulating fungal growth, culminating in tissue invasion.

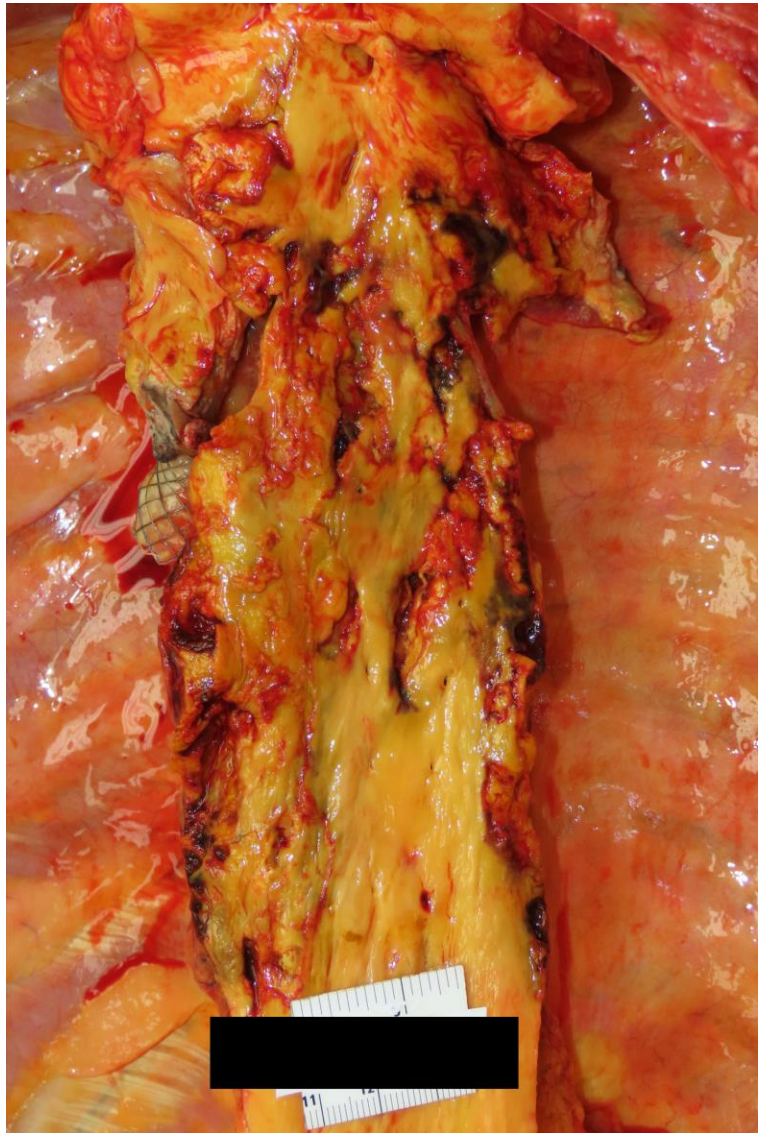
Other risk factors include treatment with glucocorticoids, iron overload, recent COVID-19 infection, acquired immunodeficiency syndrome (AIDS), injection drug use (IVDU), trauma/burns, and malnutrition.

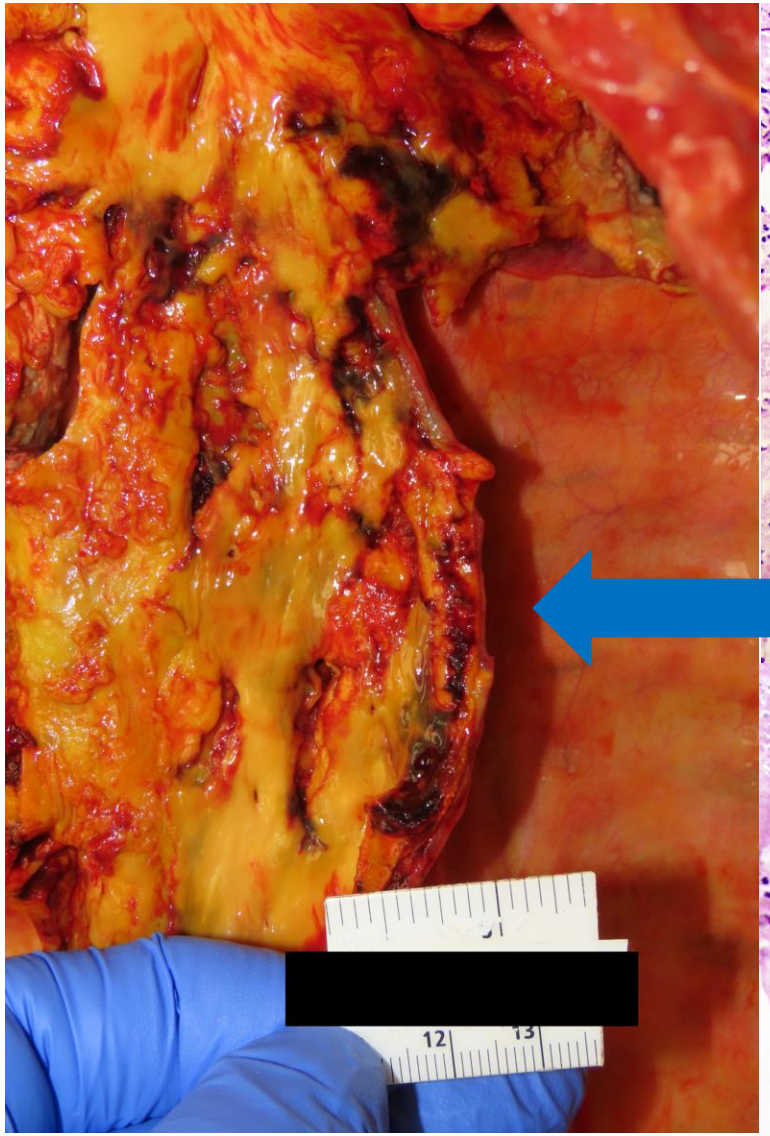


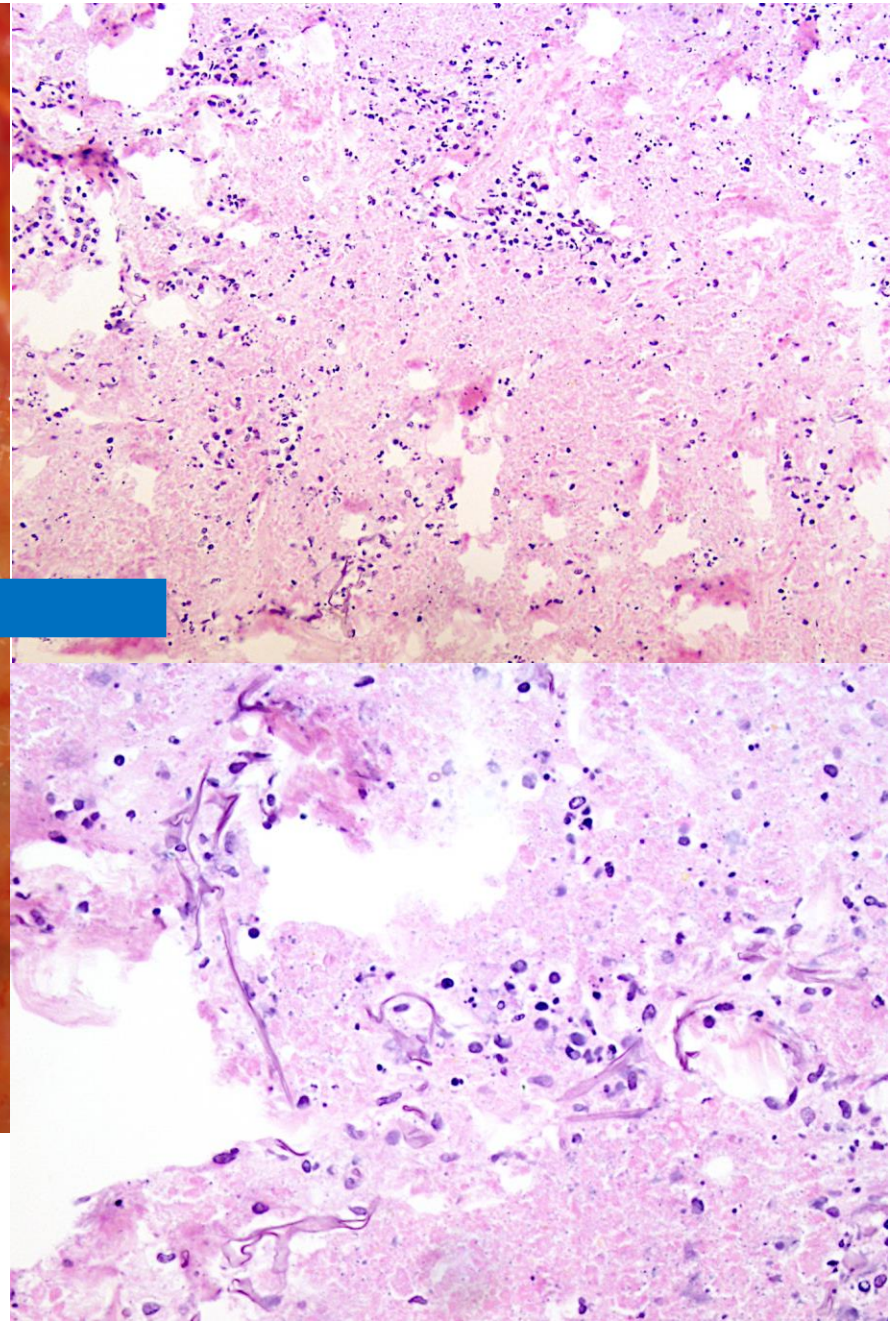




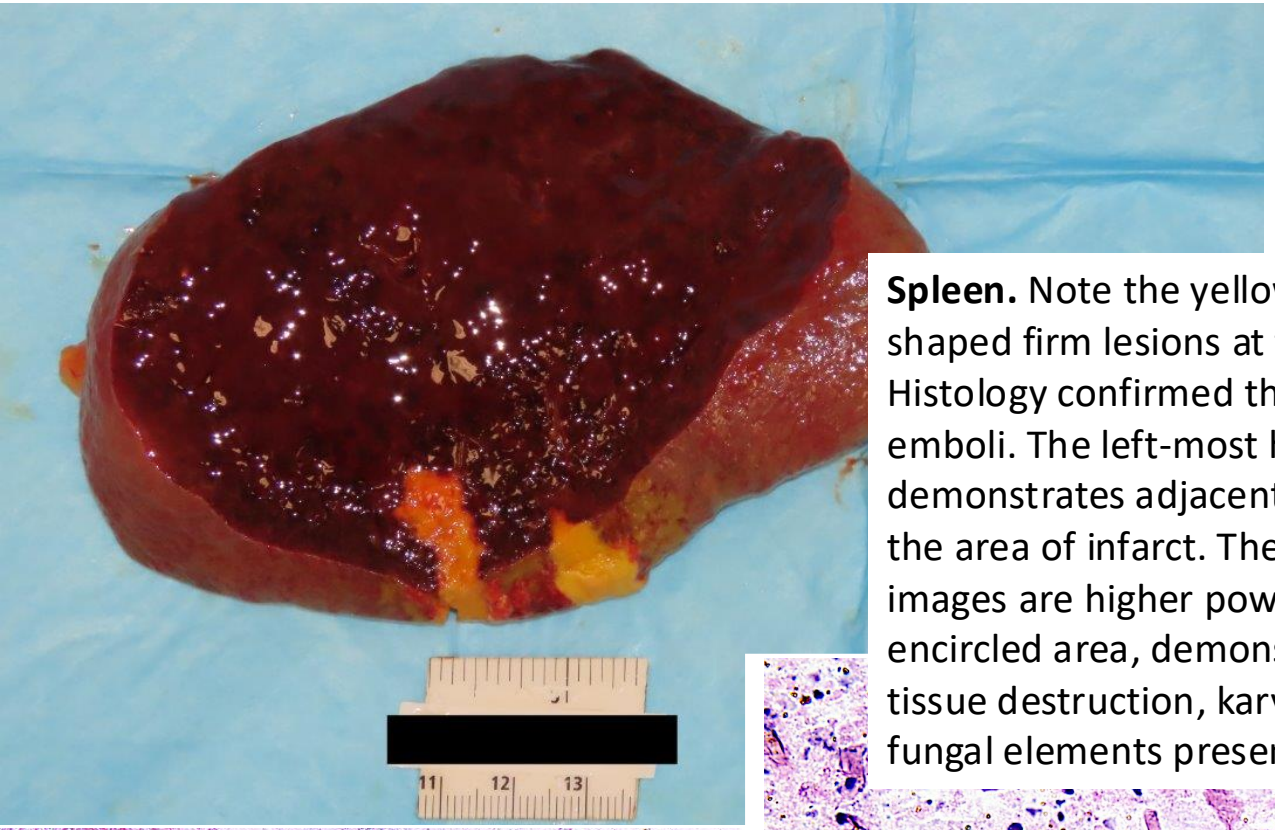
Thoracic cavity in situ. Note the collapsed left lung with adherence to the chest wall (arrow). The samples for the histology on this slide represent this adherence to the chest wall and the left mainstem bronchus.

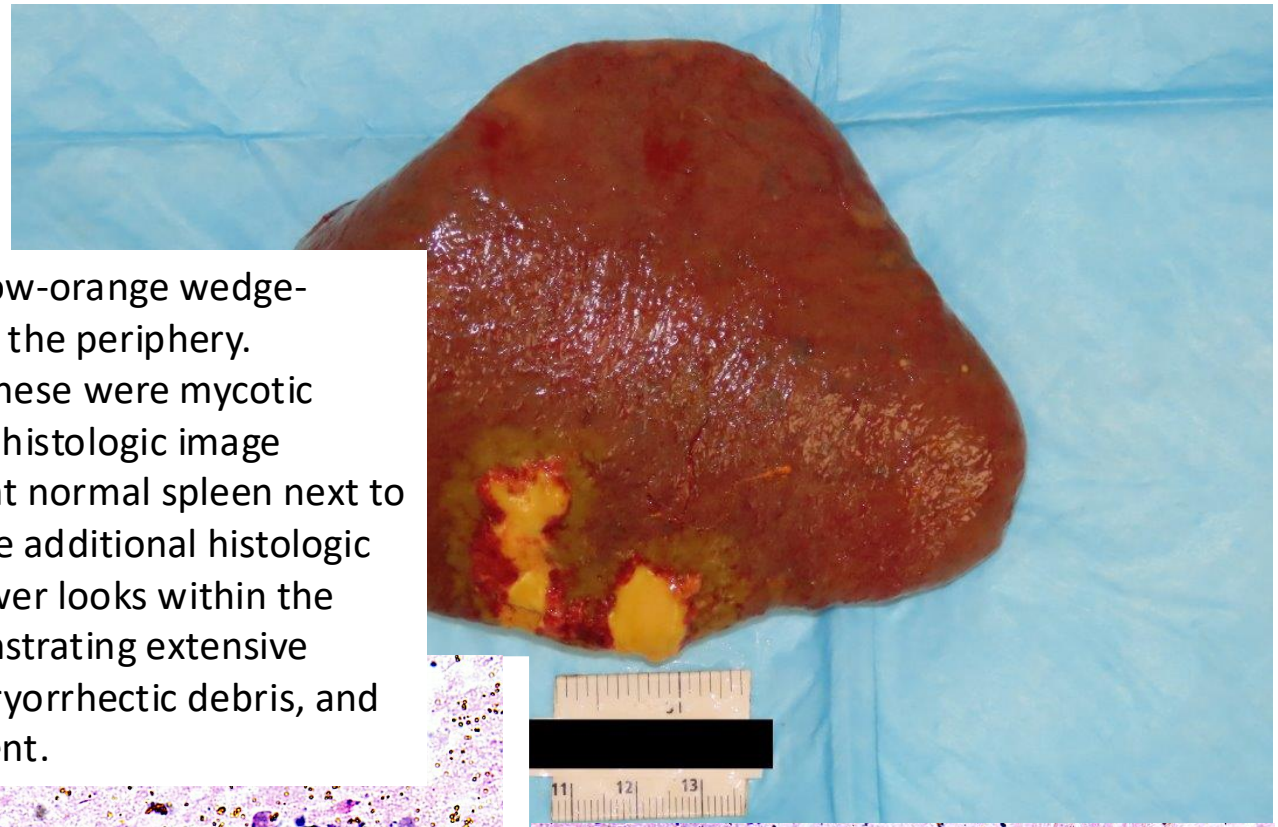




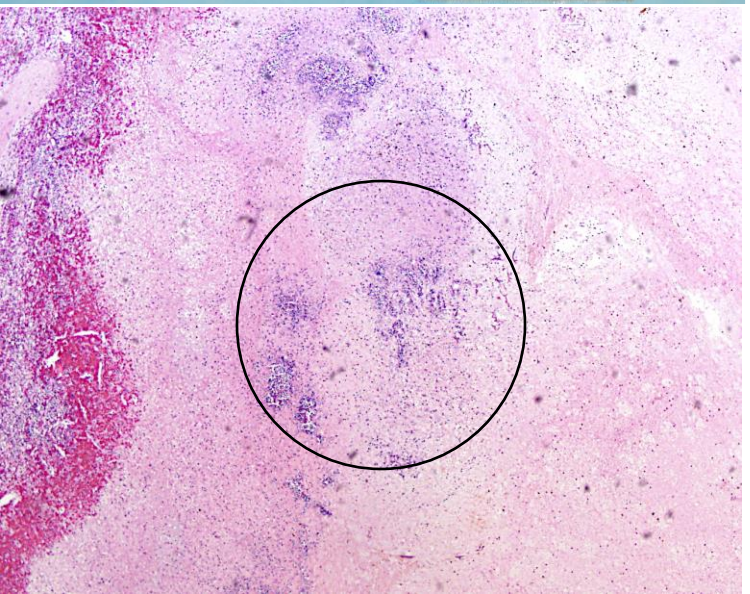


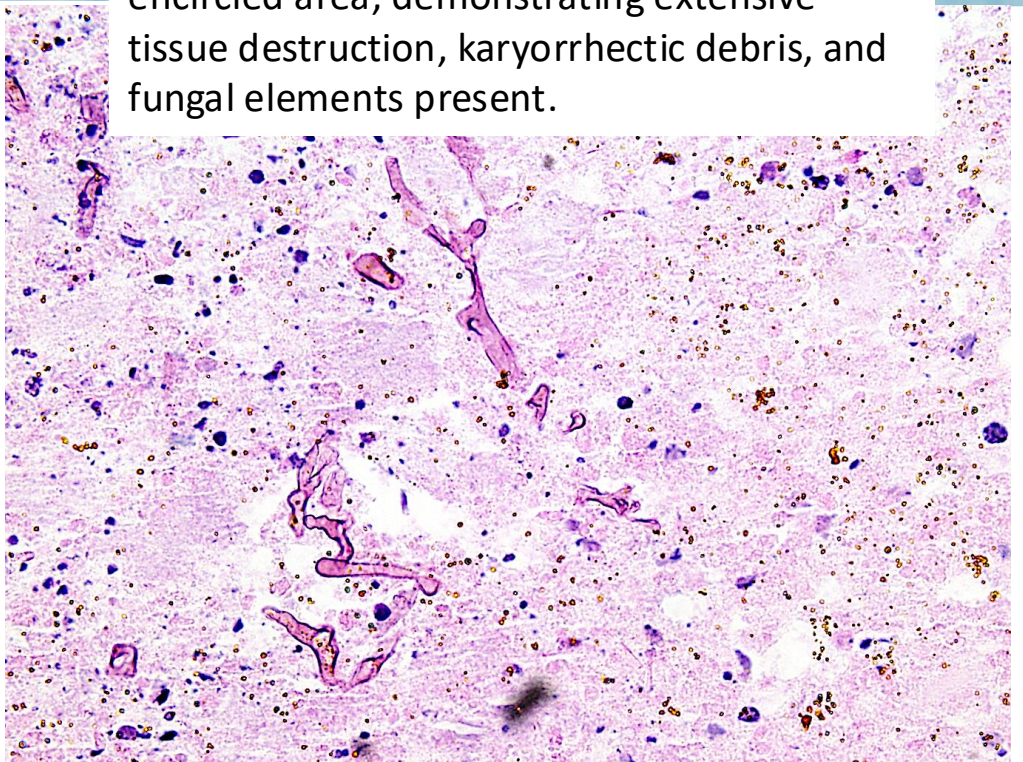
Aorta, opened, in situ. Note the roughened, shaggy, fibrinoid appearance and apparent aneurysm (arrow; this was supported by antemortem imaging studies). An esophageal stent is visible in the left-most image, which had been placed due to development of a broncho esophageal fistula.

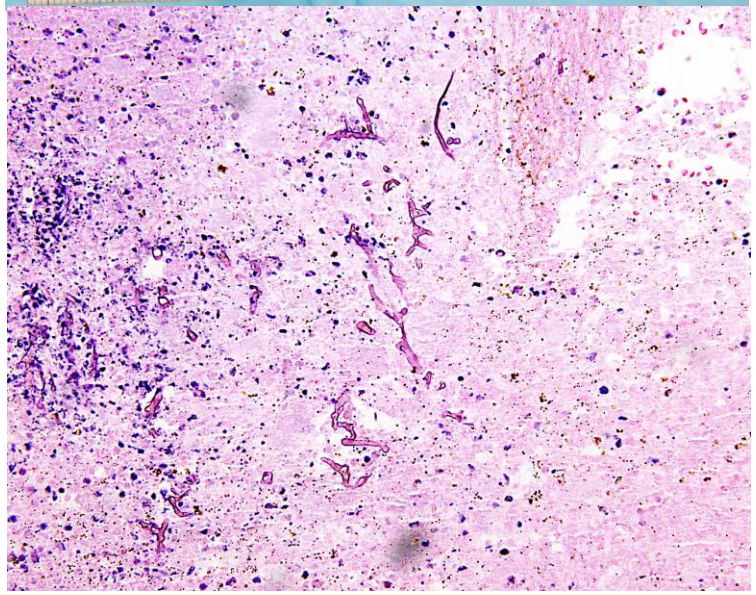


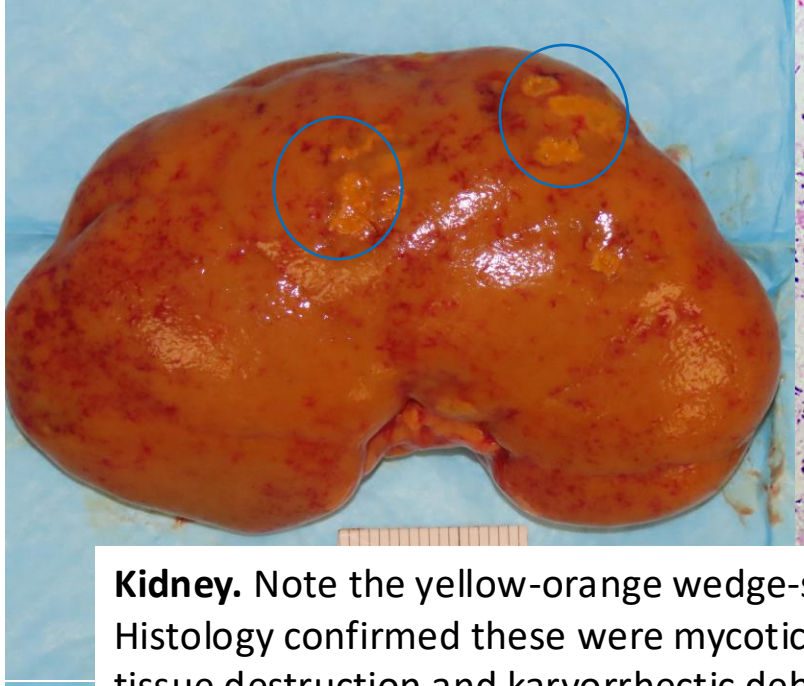


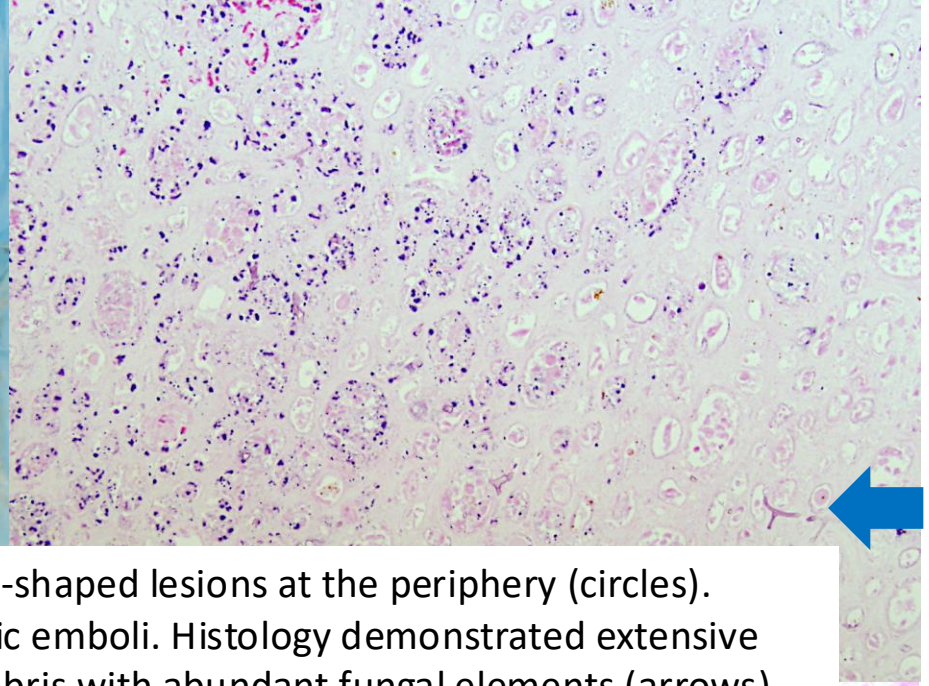
Spleen. Note the yellow-orange wedge-shaped firm lesions at the periphery. Histology confirmed these were mycotic emboli. The left-most histologic image demonstrates adjacent normal spleen next to the area of infarct. The additional histologic images are higher power looks within the encircled area, demonstrating extensive tissue destruction, karyorrhectic debris, and fungal elements present.



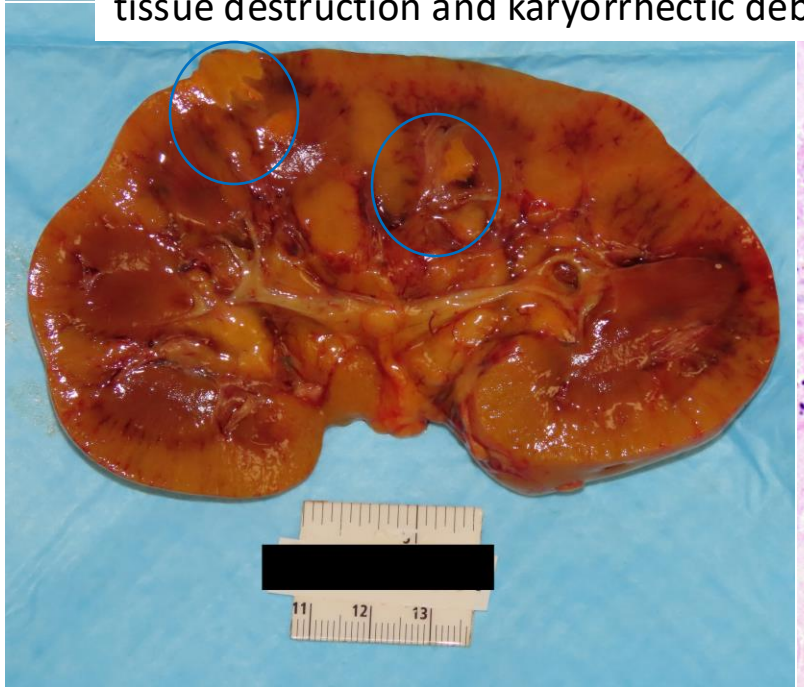


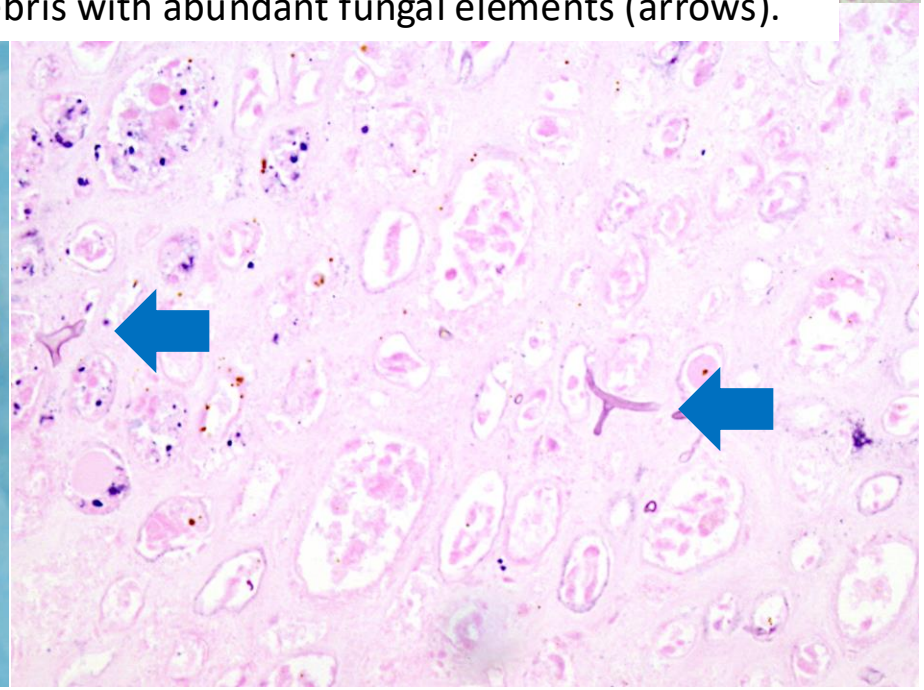


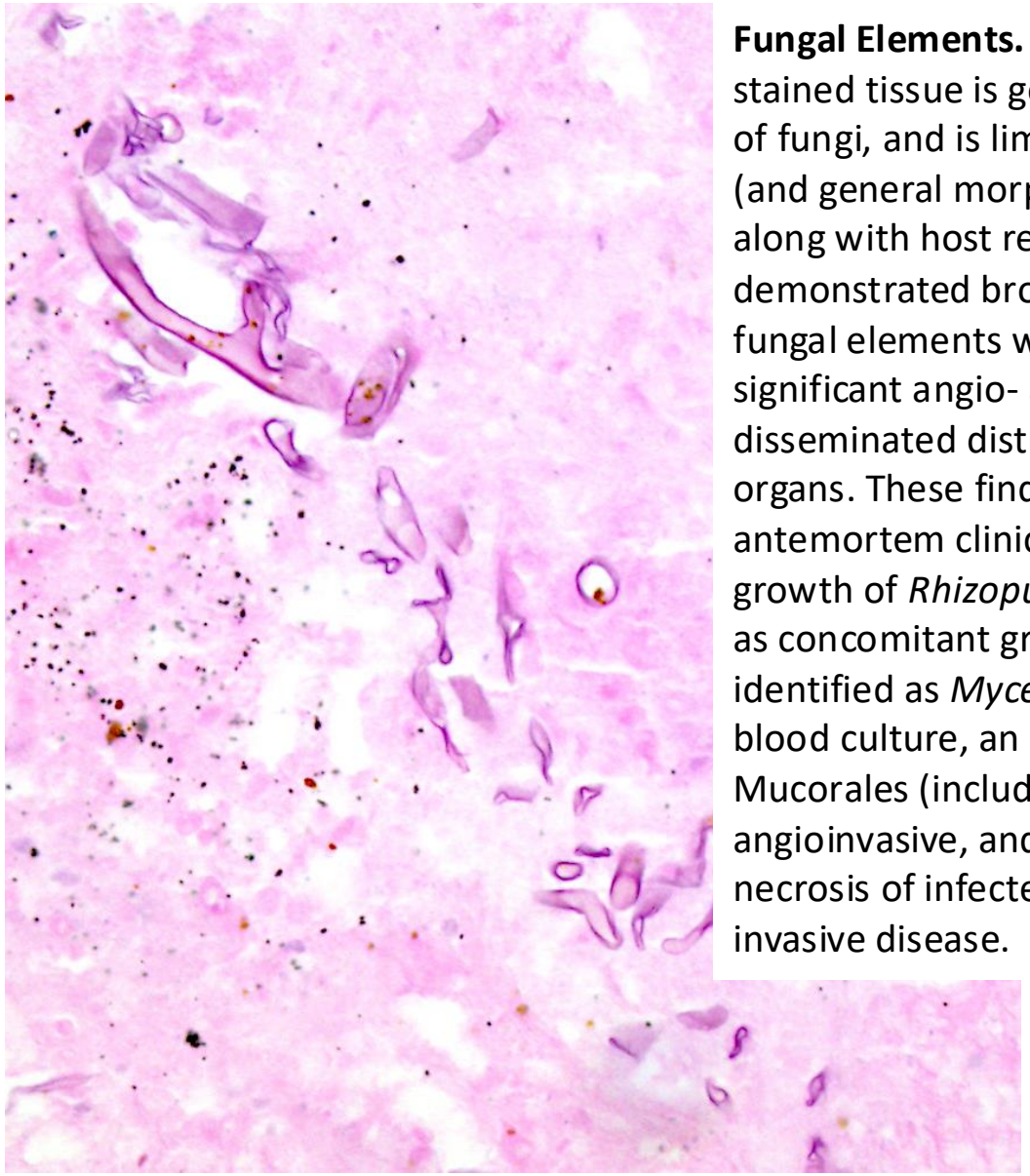




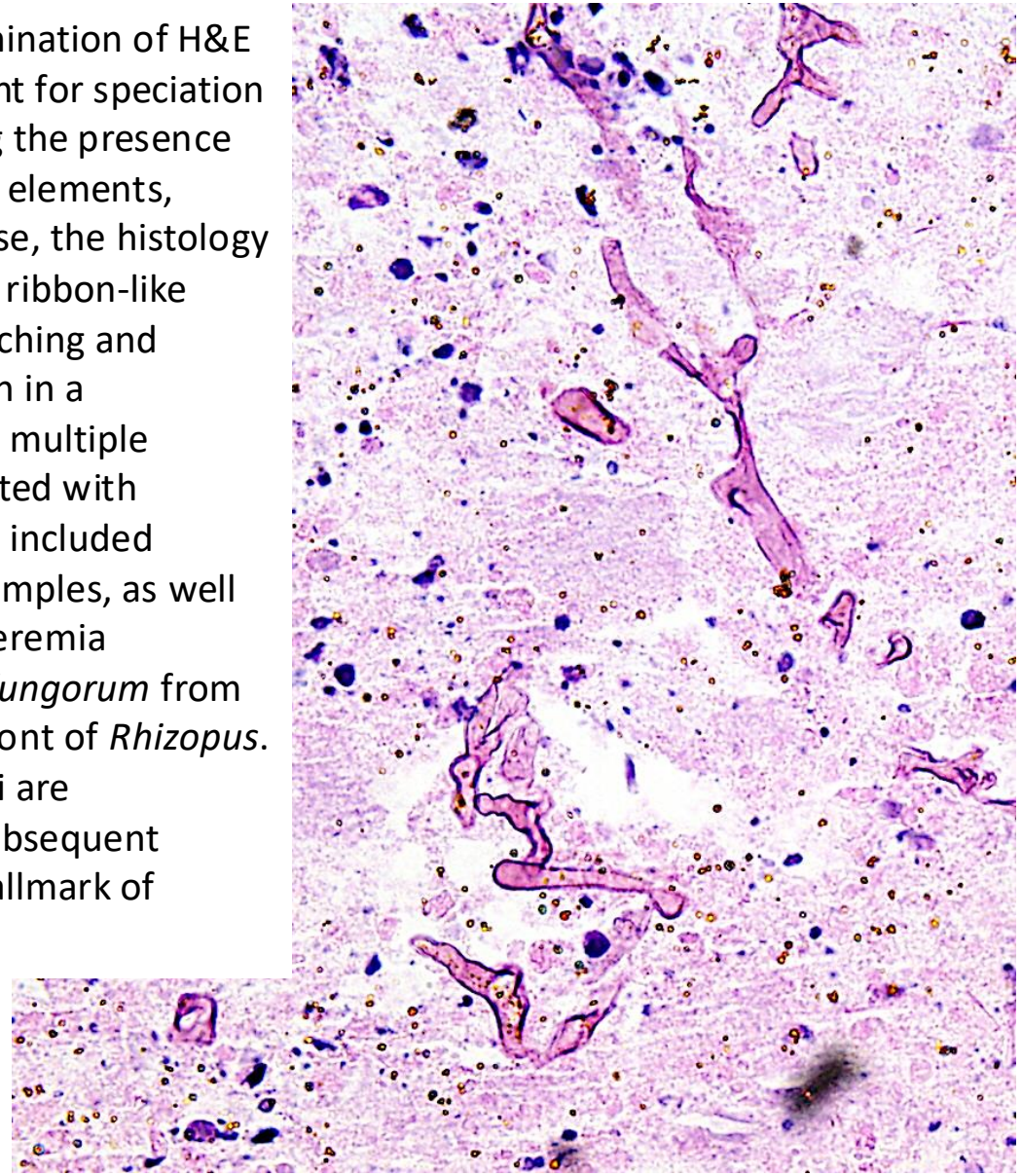
Kidney. Note the yellow-orange wedge-shaped lesions at the periphery (circles). Histology confirmed these were mycotic emboli. Histology demonstrated extensive tissue destruction and karyorrhectic debris with abundant fungal elements (arrows).







Fungal Elements. Microscopic examination of H&E stained tissue is generally insufficient for speciation of fungi, and is limited to describing the presence (and general morphology) of fungal elements, along with host response. In this case, the histology demonstrated broad, pauciseptate, ribbon-like fungal elements with irregular branching and significant angio- and tissue invasion in a disseminated distribution, involving multiple organs. These findings were correlated with antemortem clinical findings, which included growth of *Rhizopus* from sputum samples, as well as concomitant gram negative bacteremia identified as *Mycetohabitans endofungorum* from blood culture, an endofungal symbiont of *Rhizopus*. Mucorales (includes *Rhizopus*) fungi are angioinvasive, and infarction and subsequent necrosis of infected tissues is the hallmark of invasive disease.



Other responses…

A. Alcohol associated liver disease (16.47% of responses)
While this may contribute to poor outcomes as a significant contributory comorbidity, alcohol use with alcohol-associated liver disease is not itself alone characterized as a common risk factor for the development of disseminated mucormycosis. The association with diabetes is more supported and more common, making it the better answer choice.

B. Environmental exposure (20.66% of responses)
Fungi within the order Mucorales are ubiquitous in nature and can be found in the soil and on decaying vegetation, with rapid growth and the ability to release large quantities of spores than can become airborne. All humans have ample exposure to these fungi in day-to-day activities, and they are relatively frequent contaminants in the clinical microbiology laboratory. Almost all infections occur in the setting of some manner of immunocompromise.

C. Solid organ malignancy (7.19% of responses)
Diabetes is the most common risk factor associated with the development of disseminated *Rhizopus* and is therefore the best answer. The next best answer would be a hematologic malignancy, which are much more frequently associated with mucormycosis than solid tumors. Even still, the development of mucormycosis appears to occur in less than 1 percent of patients with hematologic malignancies.

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