Case #142

NAME Educational Activities Committee

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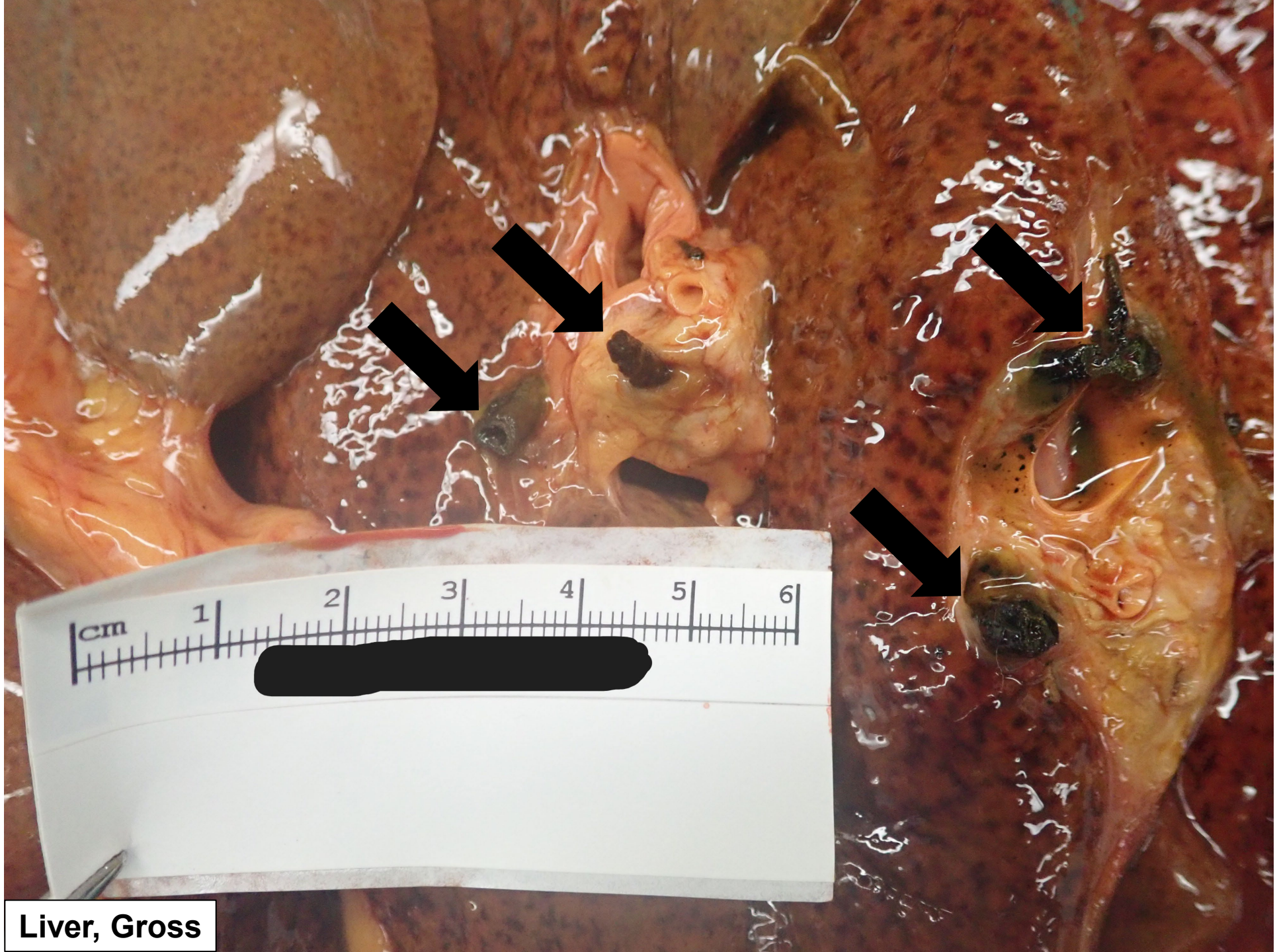
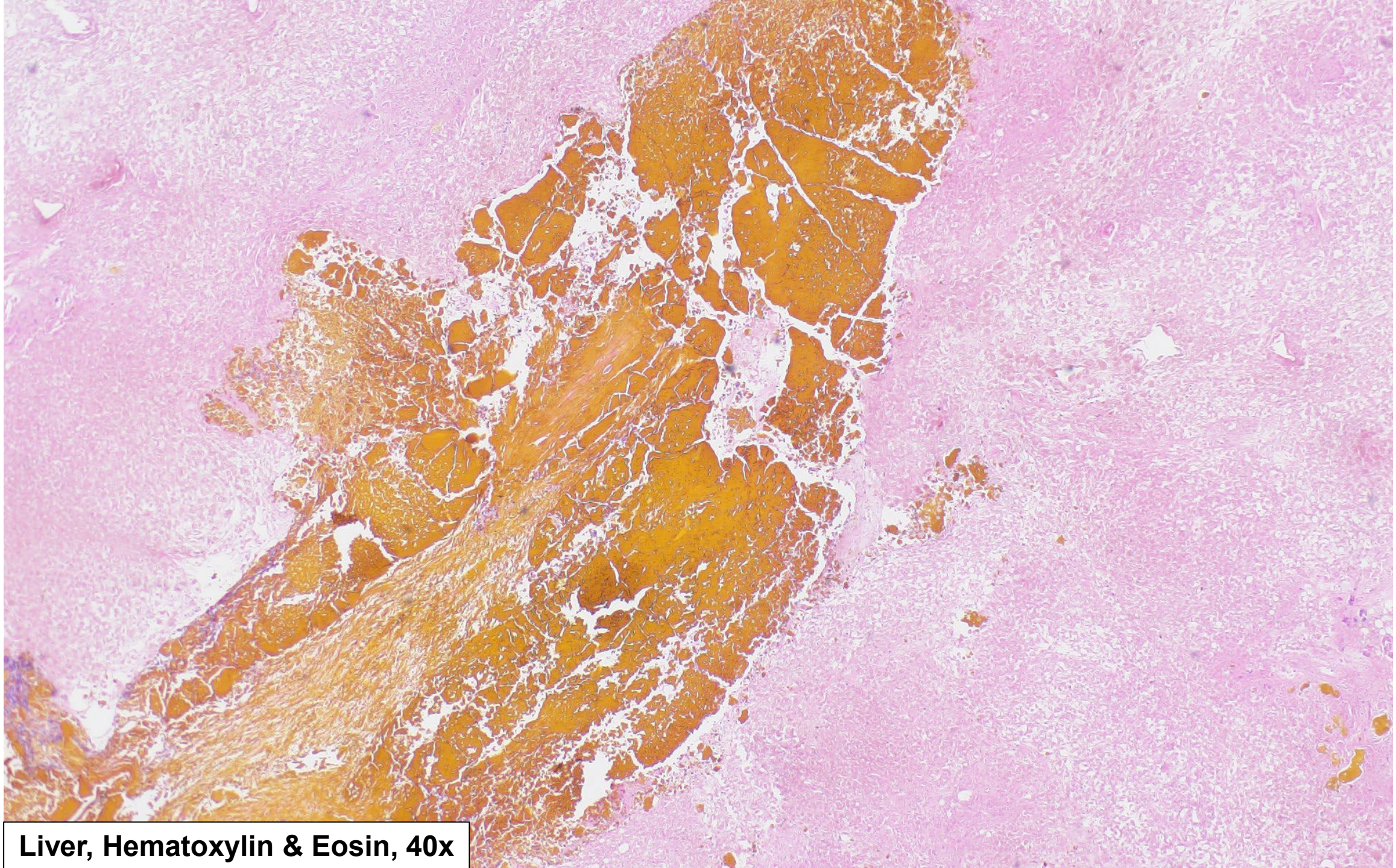
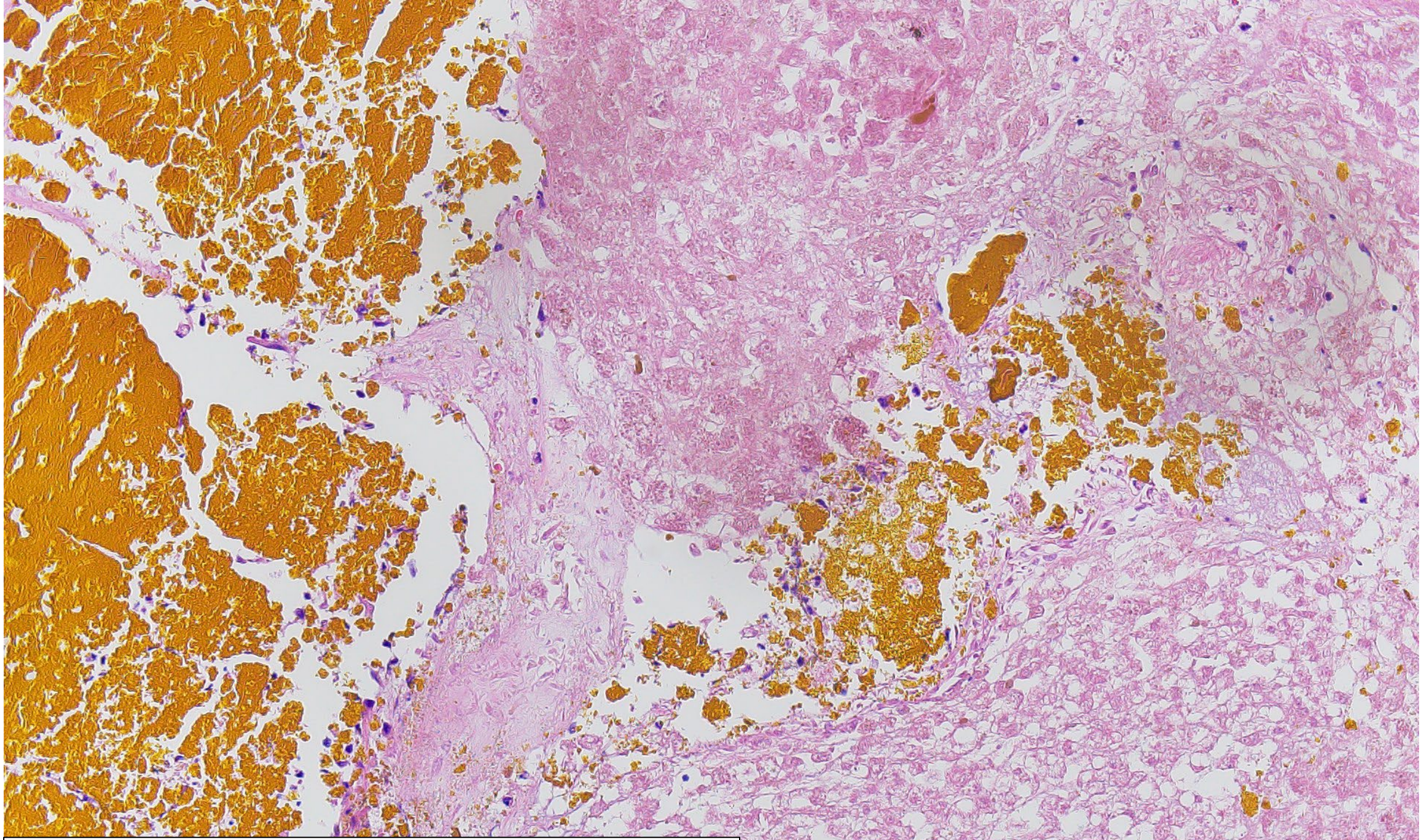


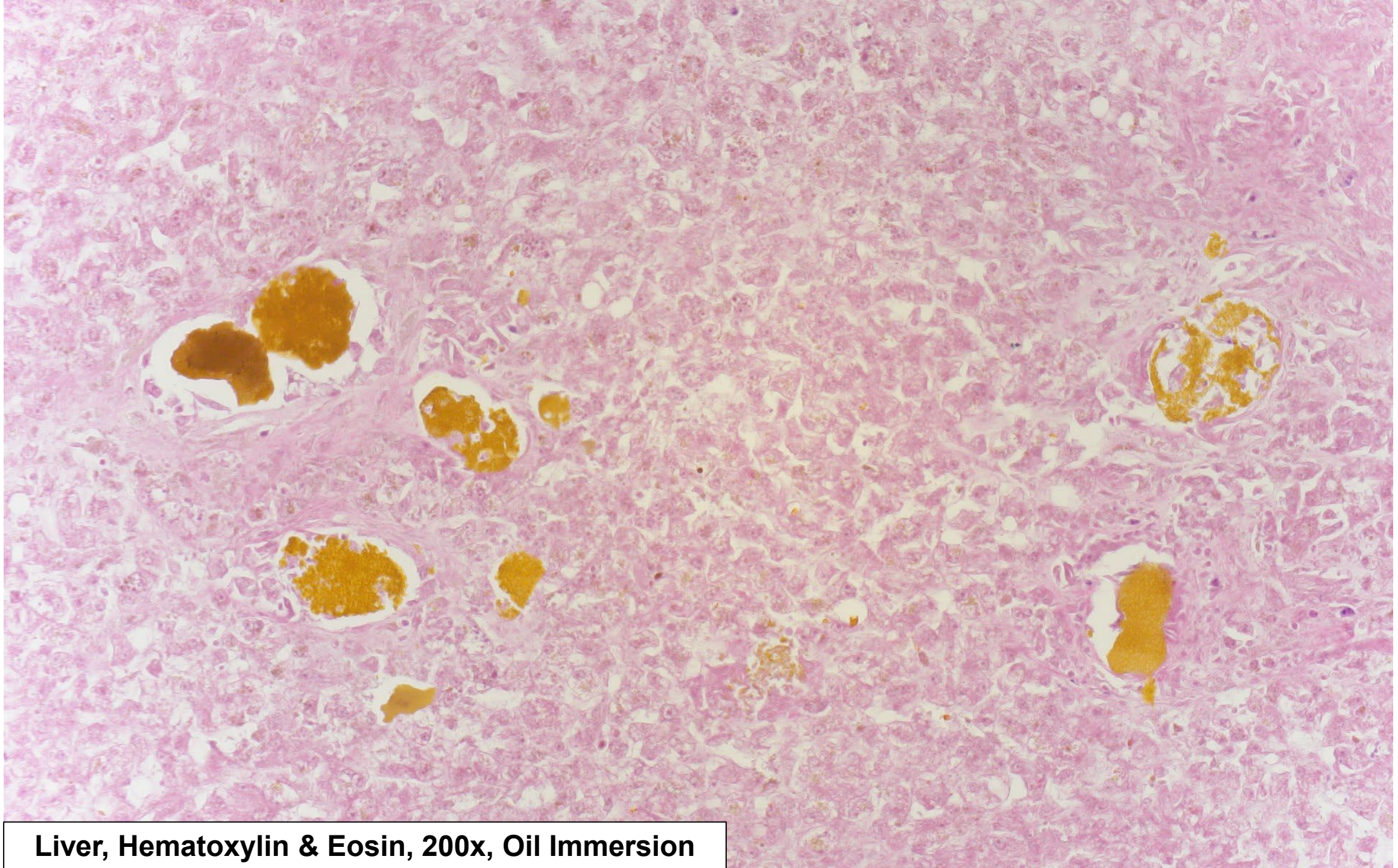
Liver, Gross



Liver, Hematoxylin & Eosin, 40x



Liver, Hematoxylin & Eosin, 200x, Oil Immersion



Liver, Hematoxylin & Eosin, 200x, Oil Immersion

The decedent was a 40-50 year-old male with multiple hospital admissions over several weeks for shortness of breath and atypical pneumonia, treated with antibiotic therapy. On his terminal admission, several months after the initial visit, his hospital course was complicated by hypoxic respiratory failure requiring intubation and admission to the intensive care unit for hypoxic respiratory failure. His stay was complicated by lower GI bleeds and ulcers (status post embolization), severe cardiac dysfunction, and tracheostomy. Ultimately, he was placed on veno-venous extracorporeal membrane oxygen (VV-ECMO) due to refractory respiratory failure and remained on VV-ECMO for about 3 months prior to death.

Notable labs prior to his death are as follows...

- Blood Cultures: Vancomycin-Resistant *Enterococcus* (VRE) positive
- C-Reactive Protein (CRP): 130.7 mg/dL (normal <8.0)
- Total Bilirubin: 21.8 mg/dL (normal 0.3-1.2)
- AST: 105 U/L (normal <35)
- ALT: 70 U/L (normal 9-47)
- Alkaline Phosphatase (ALP): 98 U/L (normal 33-120)
- Antinuclear Antibody (ANA): Negative

Autopsy was remarkable for scleral icterus, anasarca, and jaundice. Grossly the liver was golden-brown and weighed 2525 grams (normal 1000-1800) with numerous intraductal lesions present throughout the cut surface (cross section shown, black arrows). Histology of the liver was remarkable for acellular golden-yellow pigmented material throughout the large and small duct system with flattened biliary epithelium and marked background liver necrosis (images shown). No significant inflammation, fibrosis, passive congestion, hepatocyte ballooning/degeneration, or definitive eosinophilic cytoplasmic inclusions were identified.

What is the *most likely* etiology of these liver findings?

A. Alcohol
B. Autoimmune
C. Sepsis
D. Sudden acute ischemia

Answer...

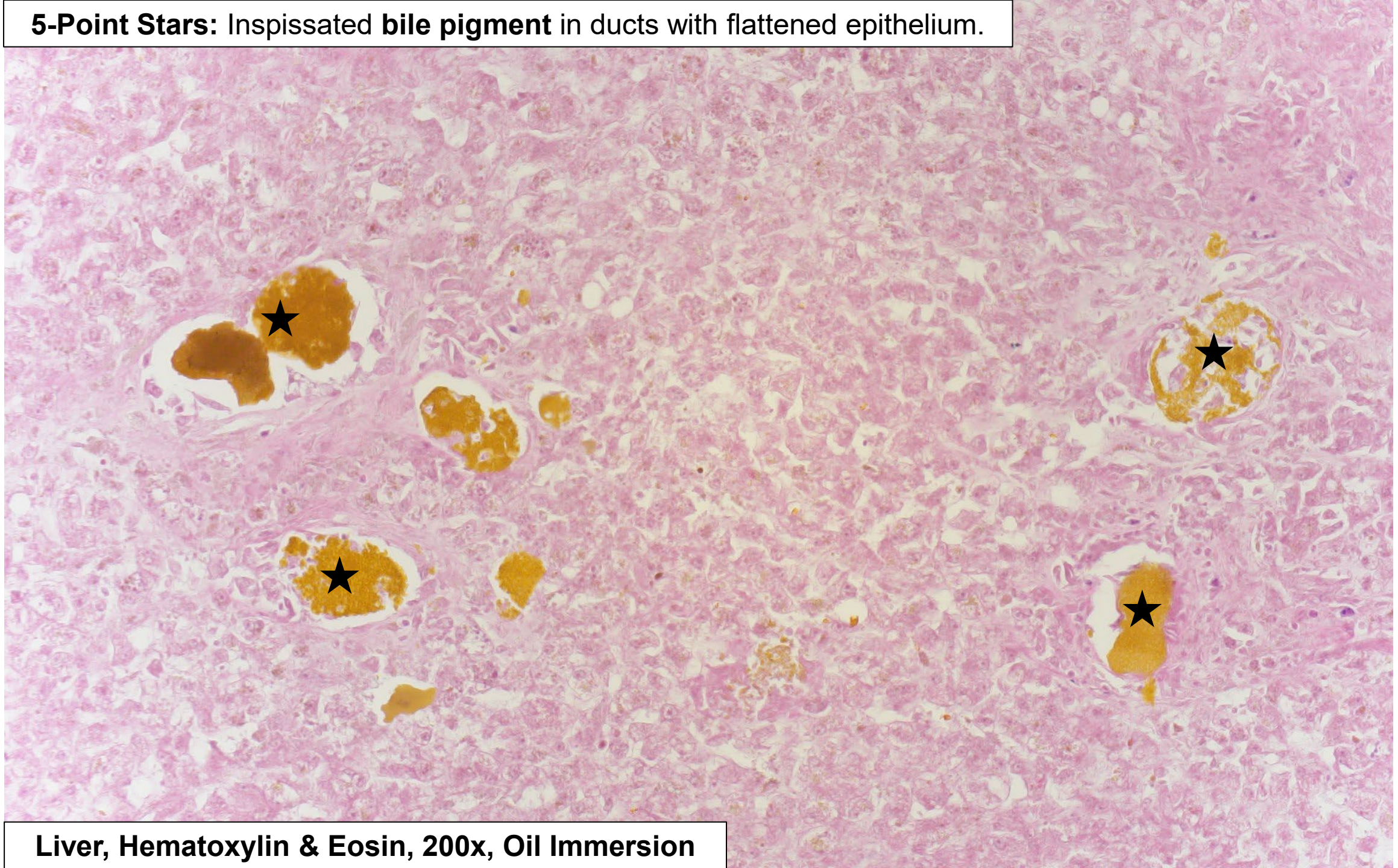
C. Sepsis (Correct answer – 62.27% of responses)

The condition highlighted in this case (critical illness state, positive blood cultures, transaminitis, marked inflammation, hepatomegaly with intraductular lesions, and prominent golden-yellow material within the duct system) is most consistently is **ductular (or biliary) cholestasis** (also sometimes referred to as ***cholangitis lenta***) which has been cited as a common histologic finding in livers of **septic patients** (Lefkowitch, 1982). It is often associated with **systemic/critically ill state**, which is clearly highlighted in this vignette (e.g., **ICU**). However, it should be noted that it is **not specific to sepsis** as cholestasis can be seen in other conditions with hepatic dysfunction.

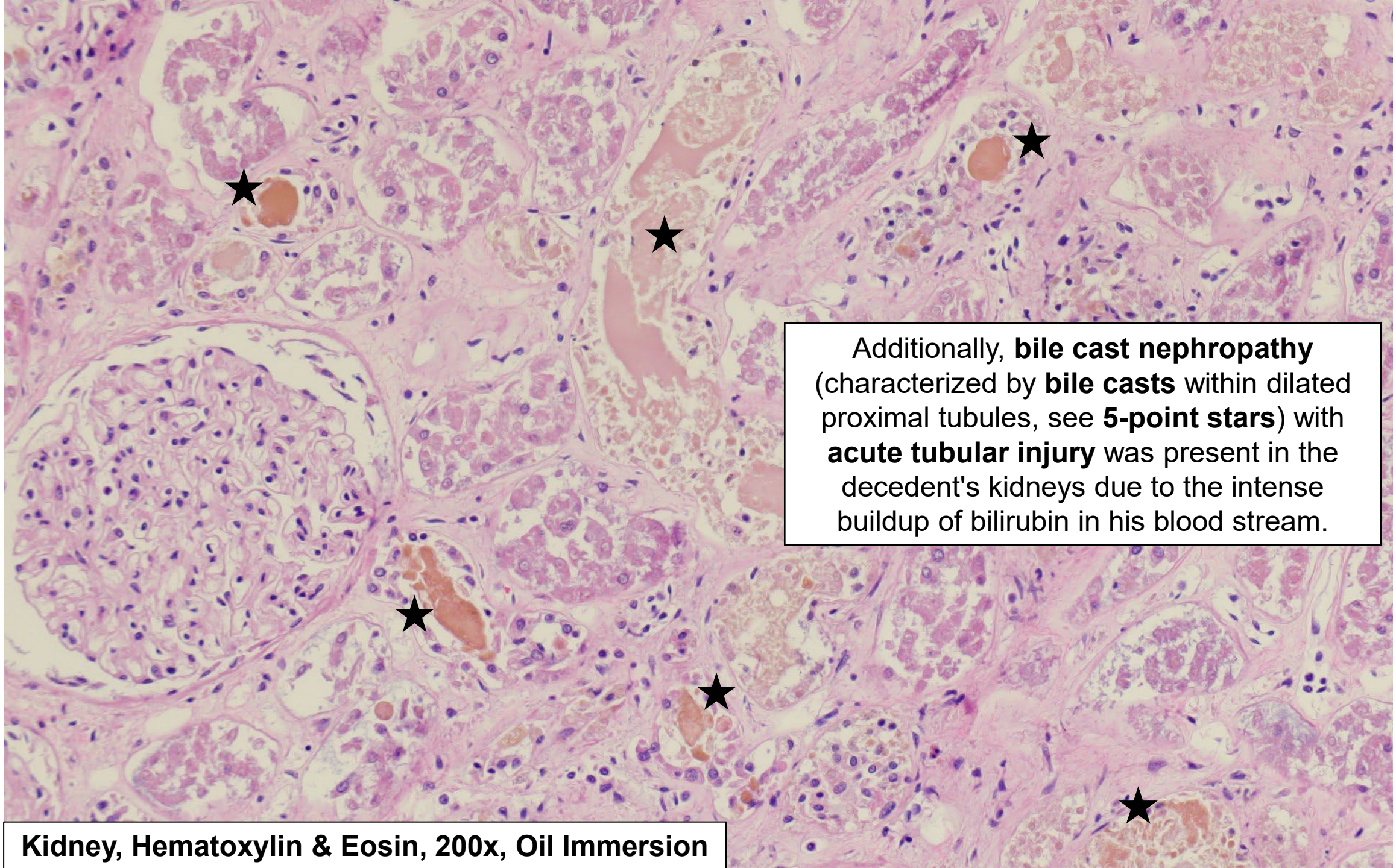
The pathophysiology is not entirely clear, but current literature suggests the presence of extensive **pro-inflammatory cytokine storm** (e.g., **IL-1, TNF-alpha**) seen in septic patients (e.g., **elevated CRP**) leads to **hepatocyte injury** and compromising bilirubin clearance, resulting in **cholestasis** and **jaundice** (characterized by markedly **elevated bilirubin**).

The case presentation here is exceptionally challenging, particularly as the decedent was admitted for over 3 months (while on VV-ECMO) prior to death with complex hospital course. The definitive etiology of the patient's pneumonia was undetermined, but sections of both lungs showed multiple abscesses as well as marked alveolar damage. The etiology of the patient's VRE positivity was also not entirely clear but may be related to GI disease (e.g., ulcers). ***Our primary take-away from the case is that ductular cholestasis, though not specific for sepsis, may be seen in sepsis and suggests a critically ill state. This differential is important to consider if this finding is identified during autopsy.***

5-Point Stars: Inspissated **bile pigment** in ducts with flattened epithelium.



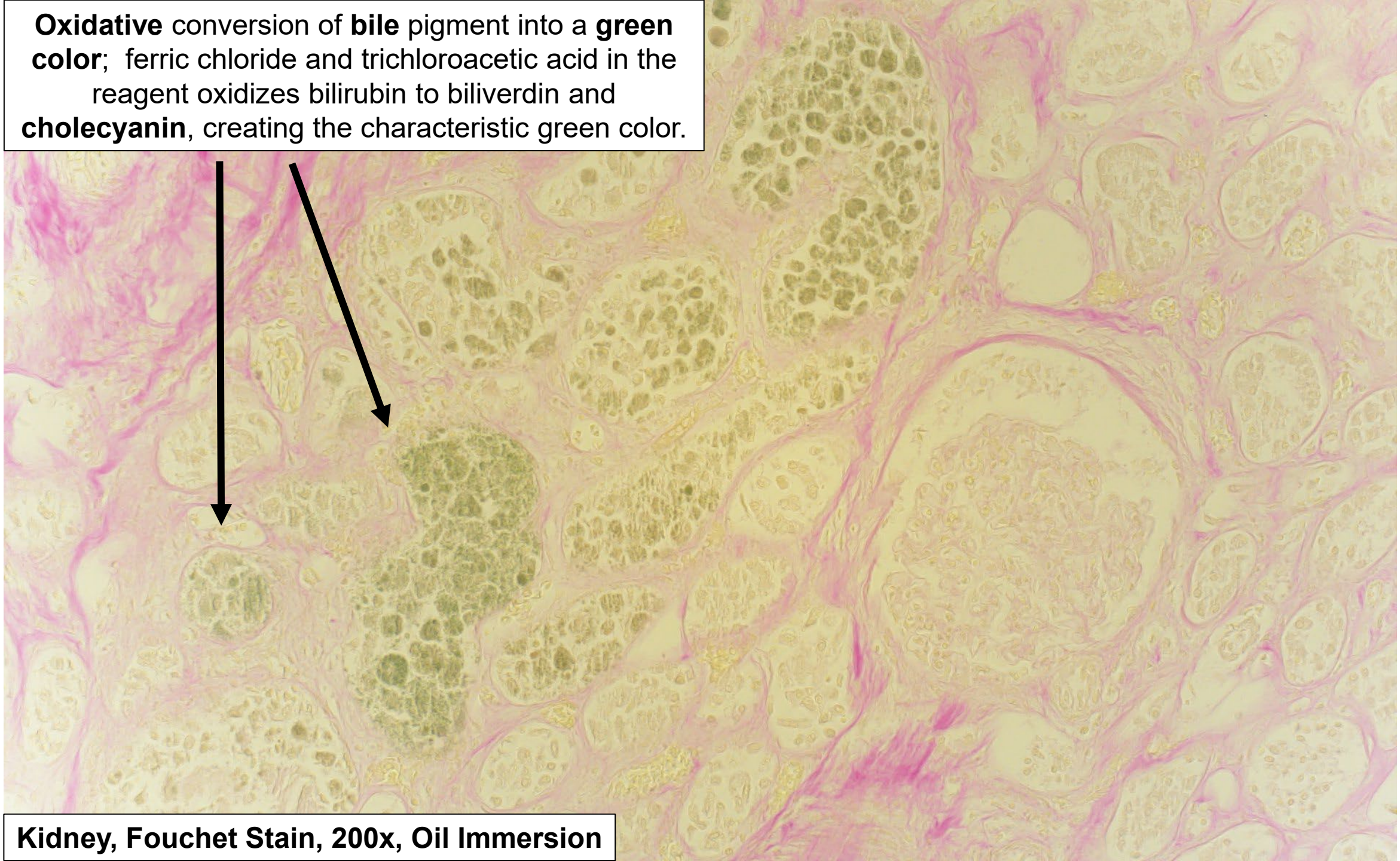
Liver, Hematoxylin & Eosin, 200x, Oil Immersion



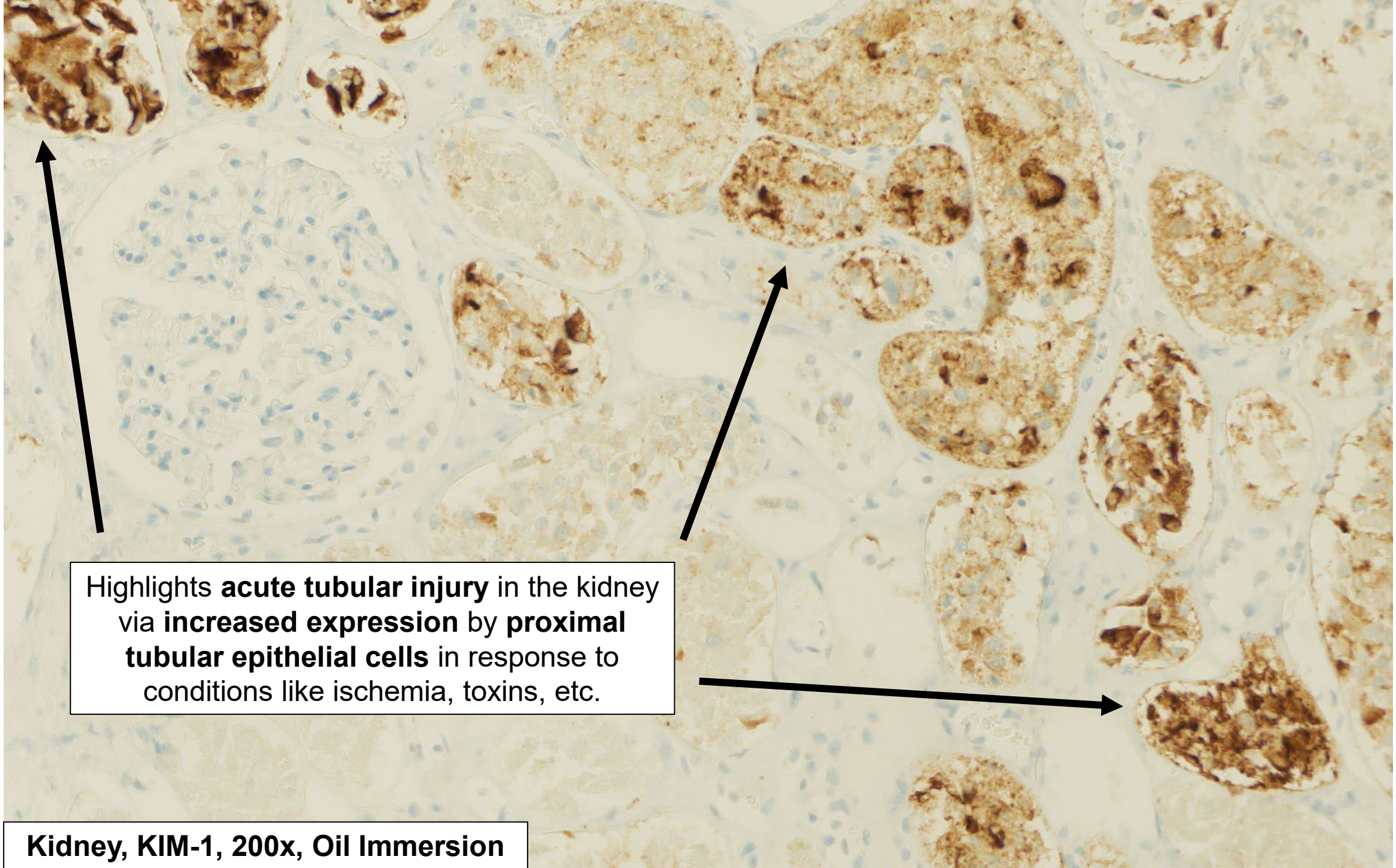
Additionally, **bile cast nephropathy** (characterized by **bile casts** within dilated proximal tubules, see **5-point stars**) with **acute tubular injury** was present in the decedent's kidneys due to the intense buildup of bilirubin in his blood stream.

Kidney, Hematoxylin & Eosin, 200x, Oil Immersion

Oxidative conversion of **bile** pigment into a **green color**; ferric chloride and trichloroacetic acid in the reagent oxidizes bilirubin to biliverdin and **cholecyanin**, creating the characteristic green color.



Kidney, Fouchet Stain, 200x, Oil Immersion



Kidney, KIM-1, 200x, Oil Immersion

Other responses…

A. Alcohol (4.71% of responses)
Though lobular cholestasis may be seen in alcohol-induced liver injury, typical histologic findings include steatosis with hepatocyte ballooning, neutrophilic lobular inflammation, fibrosis, and Mallory-Denk bodies (hepatocytes with eosinophilic cytoplasmic inclusions secondary to ubiquitinated cytokeratin accumulation), which were not described here. The transaminitis in this case is likely multifactorial (i.e., critical illness) rather than solely due to alcohol-induced liver injury (which is classically AST:ALT (greater than 2:1).

B. Autoimmune (15.82% of responses)
Autoimmune hepatitis is often characterized by interface hepatitis and portal/lobular lymphoplasmacytic infiltration, often with prominent plasma cells. Additionally, autoimmune cholangitis (e.g., primary sclerosis cholangitis and primary biliary cholangitis) also display marked portal lymphoplasmacytic inflammation and duct injury, sometimes with characteristic granulomas or "onion skinning", respectively. None of these features are present in this case, and ANA was negative.

D. Sudden acute ischemia (17.17% of responses)
While on the differential given the history of GI bleeds, "shock" liver (or ischemic hepatitis) is often characterized by a marked transaminitis (with AST and ALT characteristically greater than 1000 U/L) in the setting of *acute* hypotension/hypoperfusion (e.g., trauma, intense prolonged exercise). Though this differential is reasonable to consider given the patient's marked liver necrosis, the mild transaminitis and chronicity of the decedent's presentation/hospital stay argues against this.

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