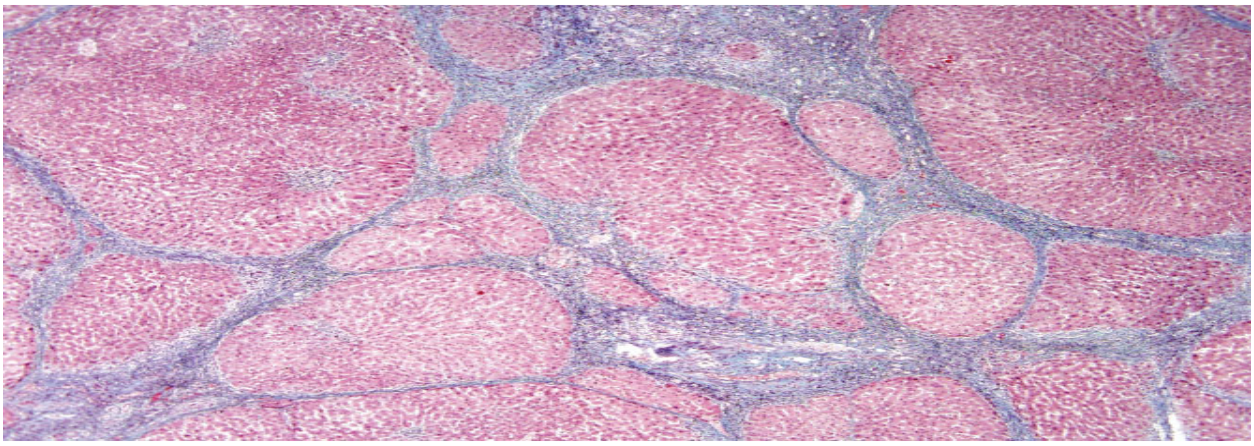

Cirrhosis (Chronic Liver Disease)

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Background

Cirrhosis is a nonspecific end-stage finding at autopsy, specifically a late stage of progressive hepatic fibrosis which distorts hepatic architecture, leading to the formation of regenerative nodules. The role of the autopsy pathologist is to provide pertinent positives and necessary negatives to help guide the clinical differential regarding its etiology.

In developed countries, common causes of cirrhosis include:
Chronic viral hepatitis (hepatitis B & C)
Alcohol-associated liver disease
Hemochromatosis
Non alcohol-associated fatty liver disease
Less common causes include:
Autoimmune hepatitis
Primary and secondary biliary cirrhosis
Primary sclerosing cholangitis
Medications (eg, methotrexate, isoniazid)
Wilson disease
Alpha-1 antitrypsin deficiency
Celiac disease
Idiopathic adulthood ductopenia
Granulomatous liver disease
Idiopathic portal fibrosis
Polycystic liver disease
Infection (eg, brucellosis, syphilis, echinococcosis)
Right-sided heart failure
Hereditary hemorrhagic telangiectasia
Veno-occlusive disease

(List adapted from UpToDate, login required)

Quick Tips at Time of Autopsy

Clinical History

Medical records may contain pre-mortem diagnostic information such as

- Hepatic ultrasound
- Liver biopsy
- Colonoscopy/endoscopy for work-up of gastrointestinal bleed
- Liver function tests including
    - ALT/AST and/or alkaline phosphatase
    - Gamma-glutamyl transpeptidase is commonly significantly elevated in cases of alcohol-induced cirrhosis
    - Bilirubin may be normal in the case of well-compensated cirrhosis
    - Albumin levels decrease in conjunction with decreased hepatic function
    - Similarly, the liver's production of coagulation factors diminishes as cirrhosis progresses, leading to an elevated prothrombin time
- Infectious workup such as for acute hepatitises

External examination

- Consequences of portal hypertension
    - Caput medusae (congested peri-umbilical veins)
    - Digital clubbing (the etiology is not fully understood but is proposed to be a consequences of venodilation in the fingers)
        - Clubbing is more common in biliary causes of cirrhosis (particularly primary biliary cirrhosis)
        - Hypertrophic osteoarthropathy consists of the presence of digital clubbing, increased periosteal activity of the tubular bones, arthralgias, and joint effusion and is characterized by abnormal proliferation of the skin, soft tissues, and osseous tissues in the distal parts of extremities
- Consequences of hormone dysregulation

    - Spider angiomata
    - Gynecomastia
    - Loss of chest or axillary hair and/or inversion of the normal male pubic hair pattern
    - Testicular atrophy
    - Palmar erythema (most frequently found on the thenar and hypothenar eminences, while sparing the central portions of the palm)
- Consequences of impaired hepatic function
    - Jaundice is detectable when bilirubin is >2-3 mg/dL
        - It is classically appreciated in the sclera but can also be present in mucous membranes and skin (especially palms and soles)
        - Yellowing of the skin in carotenemia (//excessive carrot consumption) can be distinguished from jaundice by the absence of yellow discoloration in the sclera in the former
    - Muehrcke nails: paired horizontal white bands on the nail caused by low albumin
    - Terry nails: the proximal 2/3rds of the nail is white and the proximal 1/3rd is red; also due to low albumin
    - Dupuytren's contracture (most commonly seen in alcoholic cirrhosis)
- Parotid gland enlargement can sometimes be appreciated in alcohol-induced cirrhosis. The enlargement is likely due to the alcohol, not the cirrhosis
    - Although histological examination would not be done routinely, if sampled it would demonstrate enlargement secondary to fatty infiltration, fibrosis, and edema rather than a hyperfunctioning gland

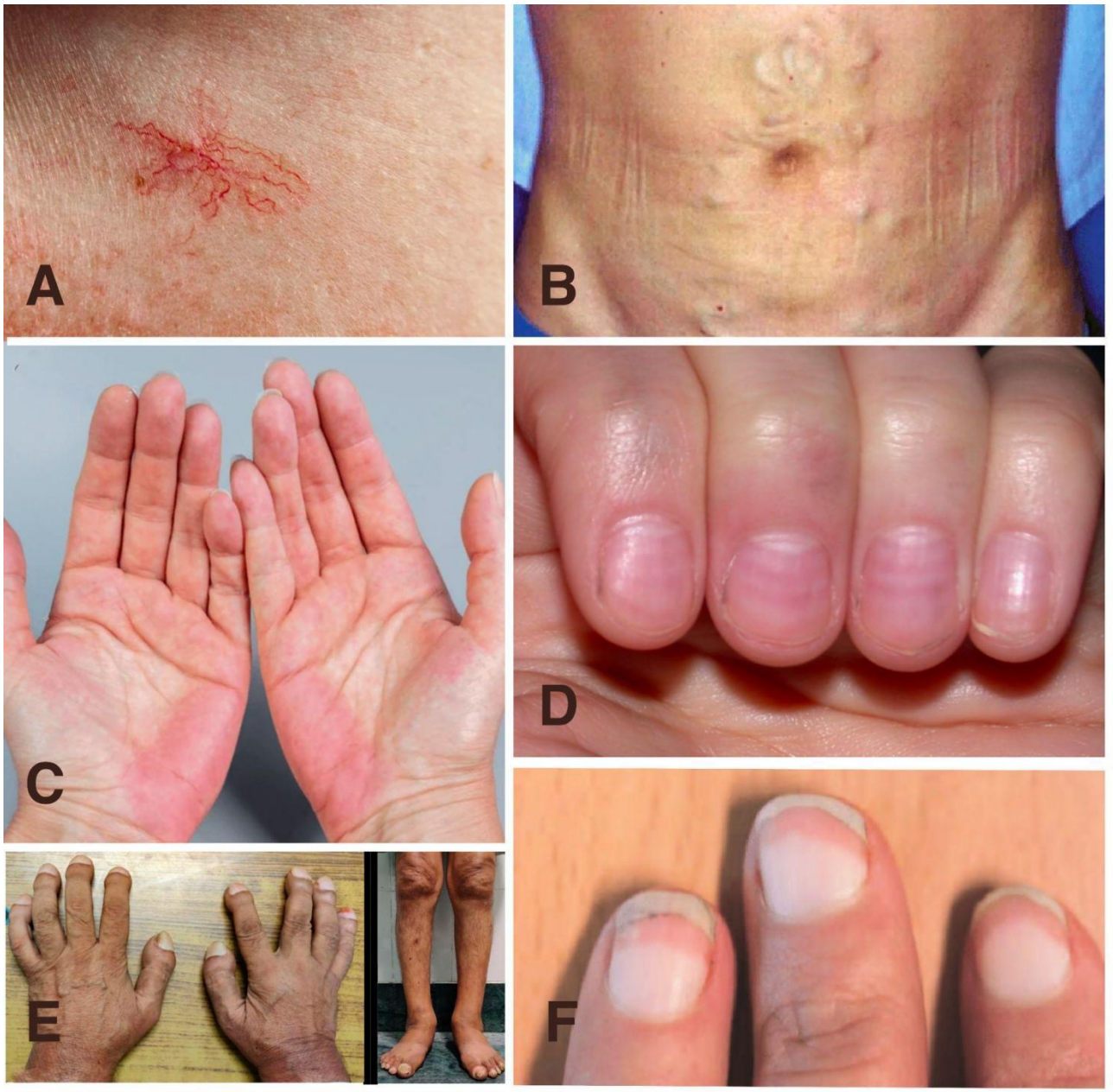

Image: Examples of grossly observed pathologies in cirrhosis: spider angiomata (A), caput medusae (B), palmar erythema (C), Muehrcke nails (D), hypertrophic osteoarthropathy including clubbing (E - left image) and enlarged distal joints such as knees (E - right image), and Terry nails (F). (Image credit: A - VeryWellHealth, B - HealthLine, C - Clinikally, D - Wikipedia, E - Avijeet Prasad, F - Juan-Manuel Fernandez-Somoza)

Gross examination

Findings

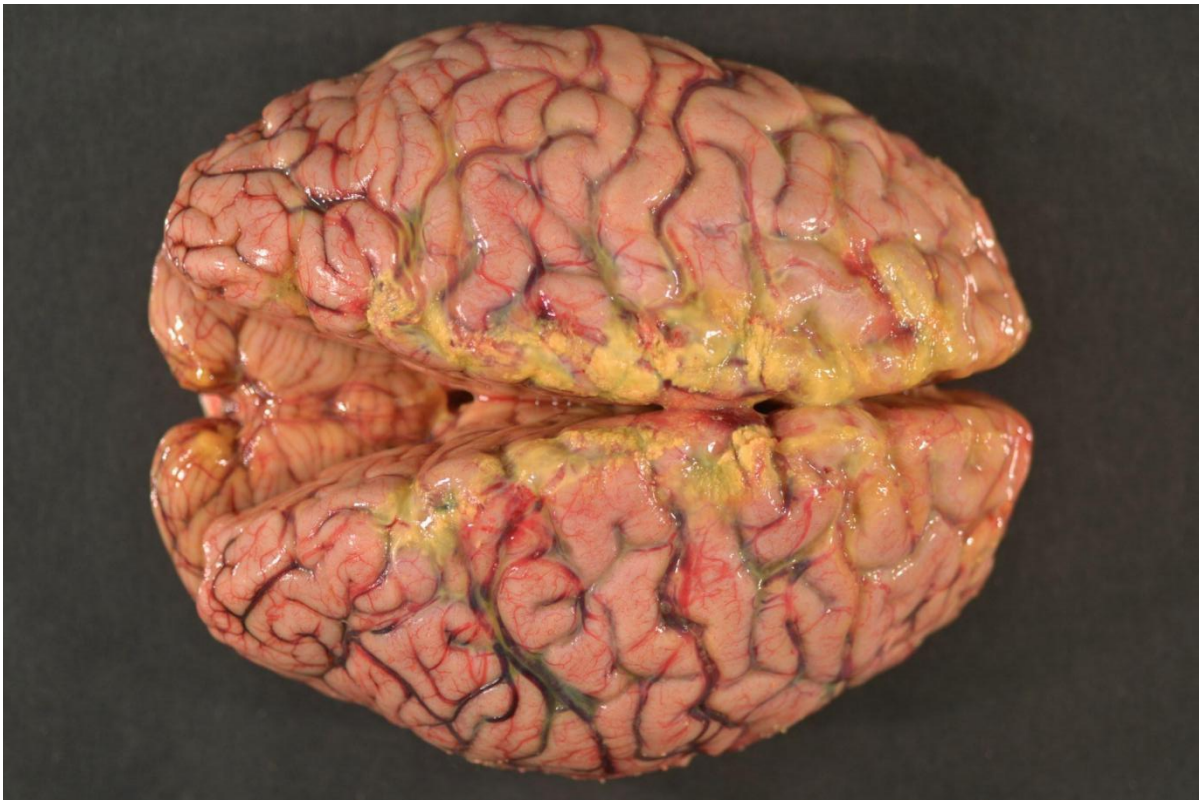

Image: In addition to external findings, jaundice can be appreciated in many tissues internally. In this case, the meninges are yellow due to hyperbilirubinemia in the setting of cirrhosis. (Image credit: Meagan Chambers/University of Washington)

- Consequences of portal hypertension
    - Peritoneal ascites (can also be appreciated on external exam as a fluid wave)
    - Esophageal varices (rupture of which can be an important cause of death discovered or confirmed at autopsy)
    - Congested splenomegaly
    - Portal vein thrombosis
- Consequences of impaired hepatic function
    - Hyperbilirubinemia may also cause the urine to appear dark or "cola" colored
    - Liver neoplasm; the most common is hepatocellular carcinoma

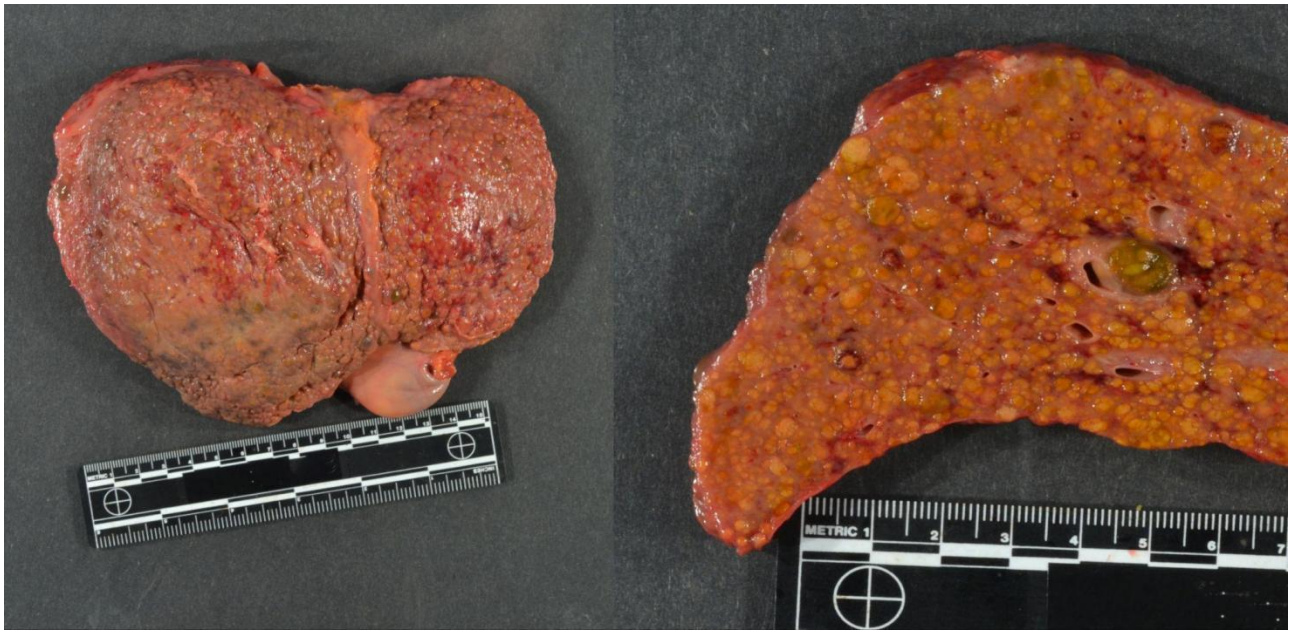

Image: a small, cirrhotic liver with characteristic nodularity before (left) and after (right) sectioning. (Image credit: Meagan Chambers/University of Washington)

Grossing and sections for histology

- The surface of the liver appears shrunken and nodular in advanced cirrhosis
- “Breadloaf” liver into approximately 1 cm thick slices
- Liver consistency can be evaluated by compressing a section between the thumb and index finger. While the liver is normally soft, increased fibrosis makes the cirrhotic liver firm
- For histology, include one section of parenchyma away from the capsule
- Other sections demonstrating abnormalities should be sampled (such as lesions concerning for a hepatocellular carcinoma)
    - Generally, sampling any nodules >1 cm is recommended

Ancillary testing

- If not well documented prior to death, antemortem testing for specific blood analytes can be performed to narrow the postmortem differential

Quick Tips at Time of Histology Evaluation

The main imperative for the autopsy pathologist is to find clues as to the possible/probable etiology of cirrhosis (especially if it is unknown at the time of death). As cirrhosis is an

end-stage process, it is often not possible to confirm the underlying etiology, but even in these cases, pertinent negatives can narrow the differential for the clinical team

Etiology	**Pattern of Fibrosis**
Viral infection	Periportal and septal (bridging) fibrosis
Alcohol-induced liver disease/Adult non-alcoholic fatty liver disease	Centrilobular perivenular distribution and sinusoidal fibrosis
Pediatric fatty liver disease	Periportal distribution-perisinusoidal or perivenular fibrosis is usually not apparent
Biliary tract disease	Irregular-shaped nodules (“jigsaw” micronodular pattern) and the presence of “halos” due to degeneration of periseptal hepatocytes
Venous outflow obstruction	Veno-centric (“reversed lobulation” cirrhosis) or veno-portal cirrhosis

Etiology	**Pattern of Inflammation**
Viral infection	Lymphocytes
Autoimmune	Plasma cells
Primary biliary cirrhosis	Granulomas

Etiology	**Hepatocellular changes**
Viral infection	Viral cytopathic effect (such as nucleomegaly with CMV or nuclear

	inclusion bodies with HSV)
Hemochromatosis	Parenchymal iron deposition
Fatty liver disease	Steatosis
Alcoholic liver disease	Mallory-Denk hyaline changes (common in alcoholic liver disease not not specific)
Venous outflow obstruction	Veno-centric (“reversed lobulation” cirrhosis) or veno-portal cirrhosis

Immunohistochemistry

- It is the author’s recommendation that the following stains be done routinely in all cases of cirrhosis

Stain	**Findings**
Trichrome	Highlights fibrosis and collagen deposition
Reticulin	Evaluates collagen deposition (specifically type III collagen)
PAS with and without diastase	Confirms the presence of glycogen deposition in suspected glycogen storage diseases. Alpha-1-antitrypsin globules are positive for PAS and PAS with diastase
Iron	Nonspecific but significantly increased in hemochromatosis

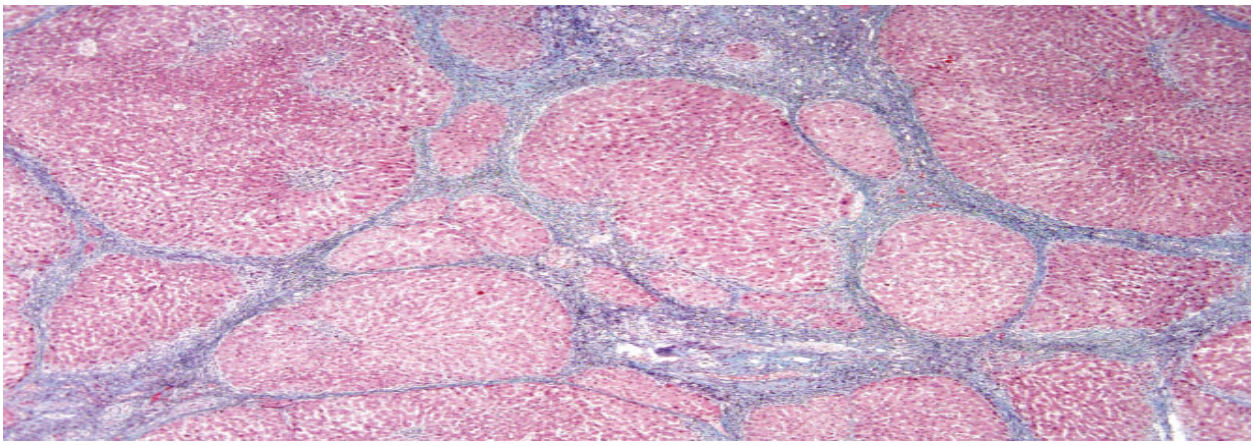

Image: Classic low power histology of cirrhosis demonstrating bridging fibrosis and reticulin meshwork between regenerative nodules. (Image credit:

- In cases with a concurrent neuro exam, Alzheimer's type II glia can be identified in the setting of hyperammonemia
    - These astrocytes have a larger, slightly irregular nucleus which is unusually pale and empty. PAS-positive perinuclear bodies may be present. The cell body is usually not well visualized on H&E or GFAP. These can be present diffusely but are most easily identified in the deep gray nuclei and cortex

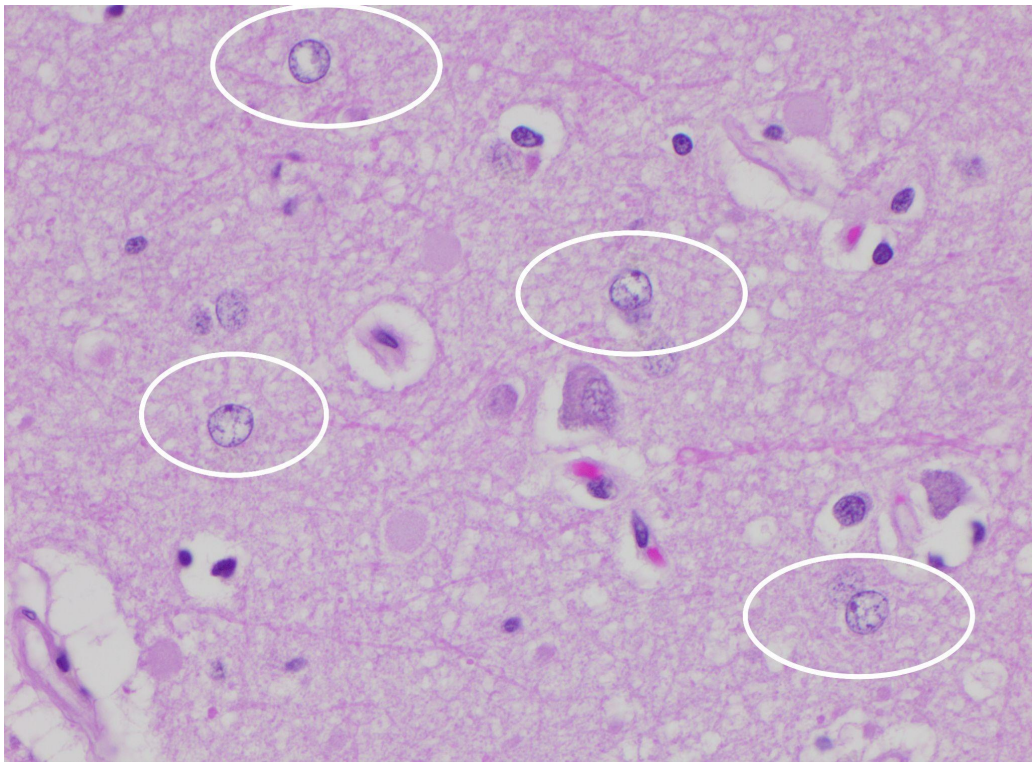

Image: Alzheimer's Type II astrocytes (circles) can be seen in hepatic encephalopathy/hyperammonemia. (Image credit: Meagan Chambers/University of Washington)

Quick Tips for Autopsy Report

- If the etiology of the cirrhosis is not clear after combined ante-mortem and post-mortem work up, then it is reported as cryptogenic cirrhosis
- Relevant pertinent positive *and* negative macroscopic and microscopic (e.g., inflammation, steatosis, Mallory hyaline, iron, and PAS) findings should be included in the respective sections
- In the case of hereditary conditions, discuss the implications and relevant follow up for family members

Recommended References

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