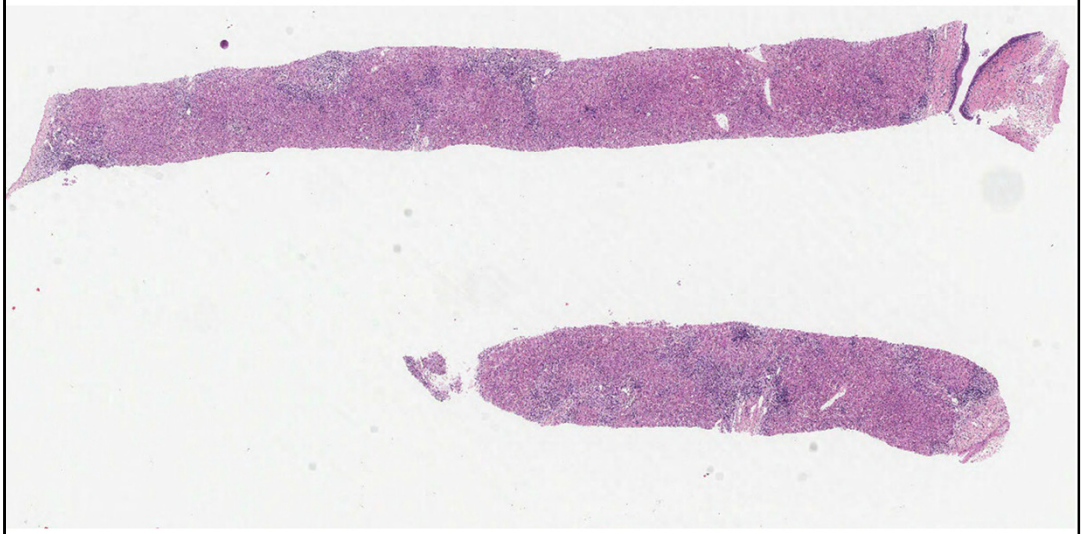
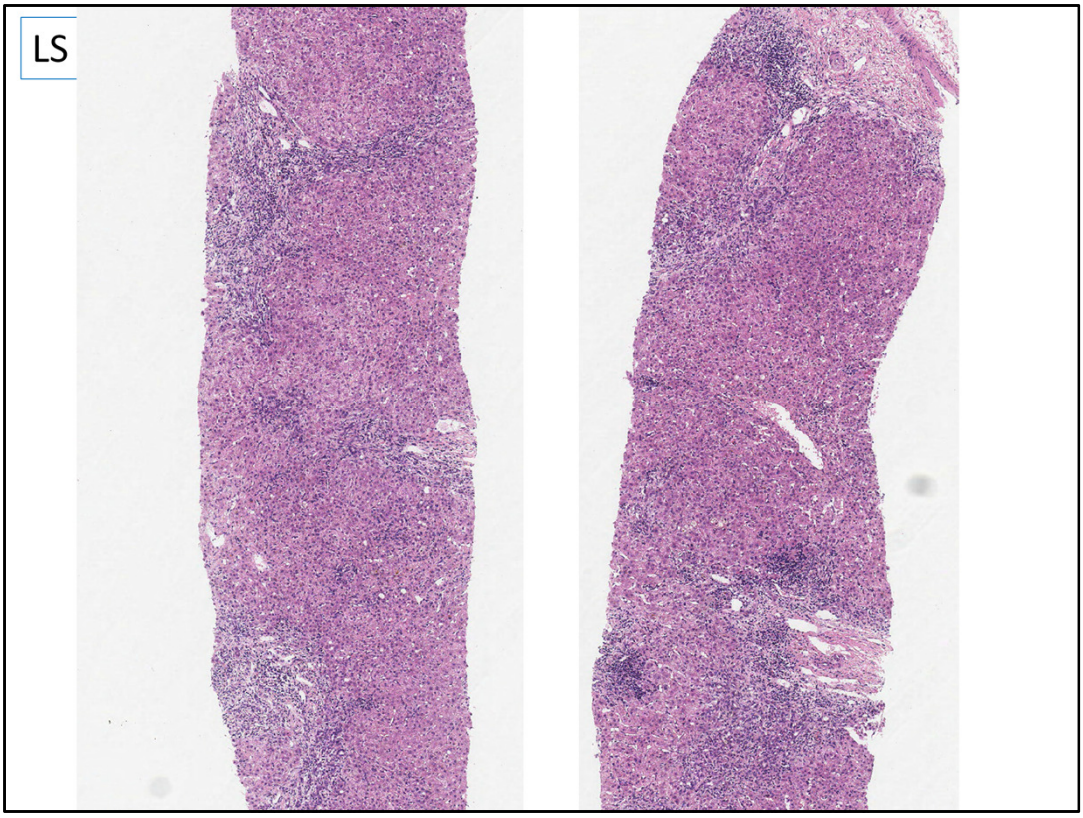
Case LS10 50F

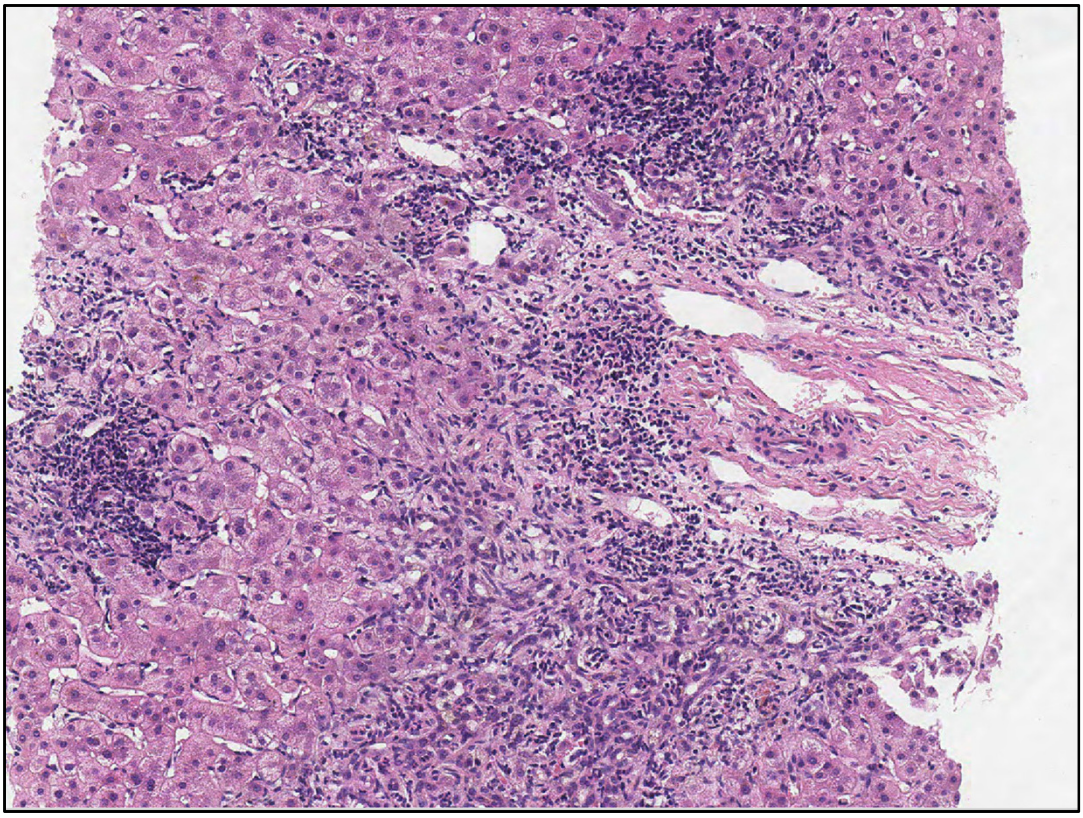
PBC, urso non-responder. Elevated ALT, ? AIH overlap. ALT 255, ALP 615, bilirubin 53, IgG 15.5

Also reticulin, Shikata, keratin 7

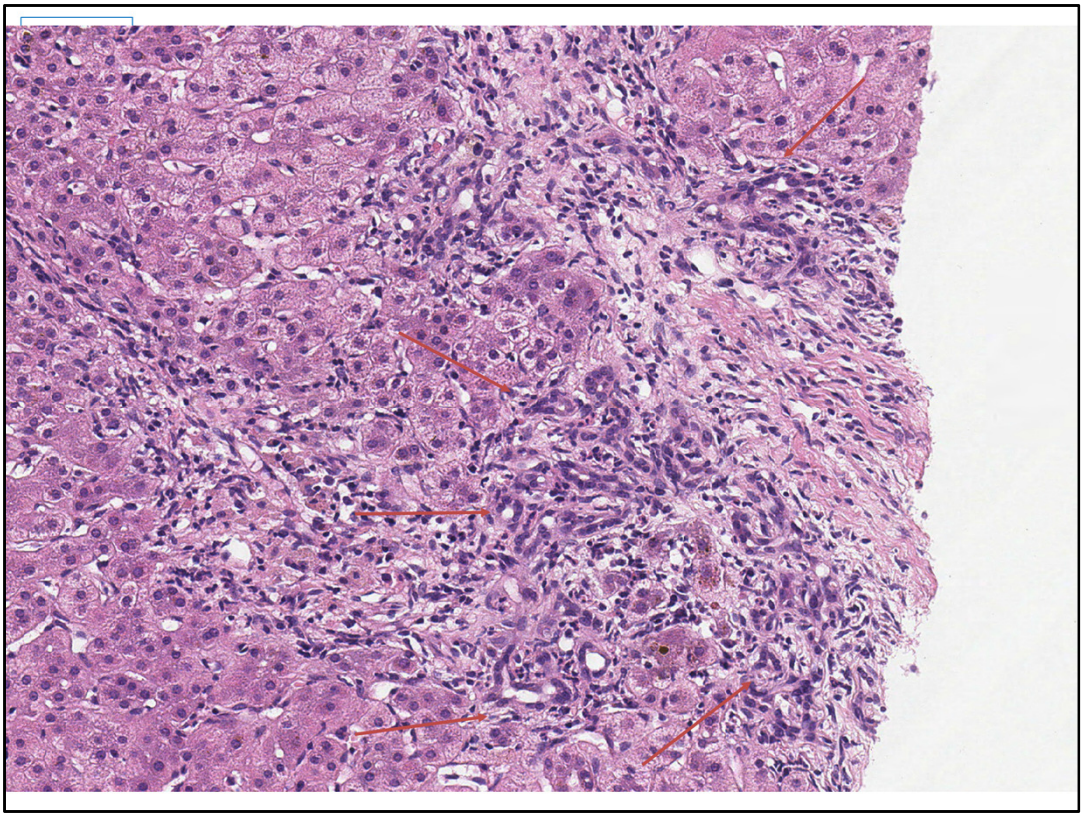




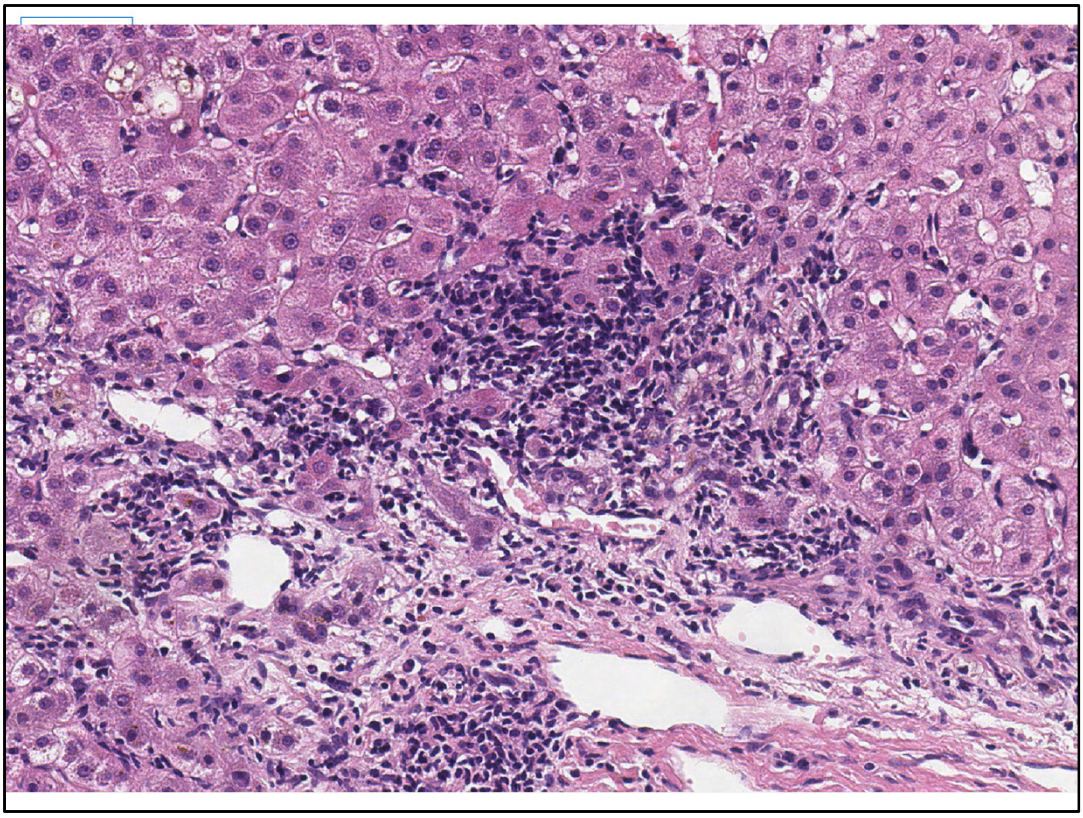
At this magnification, portal areas are expanded and inflamed; vascular relationships appear to be preserved, without bridging fibrosis.



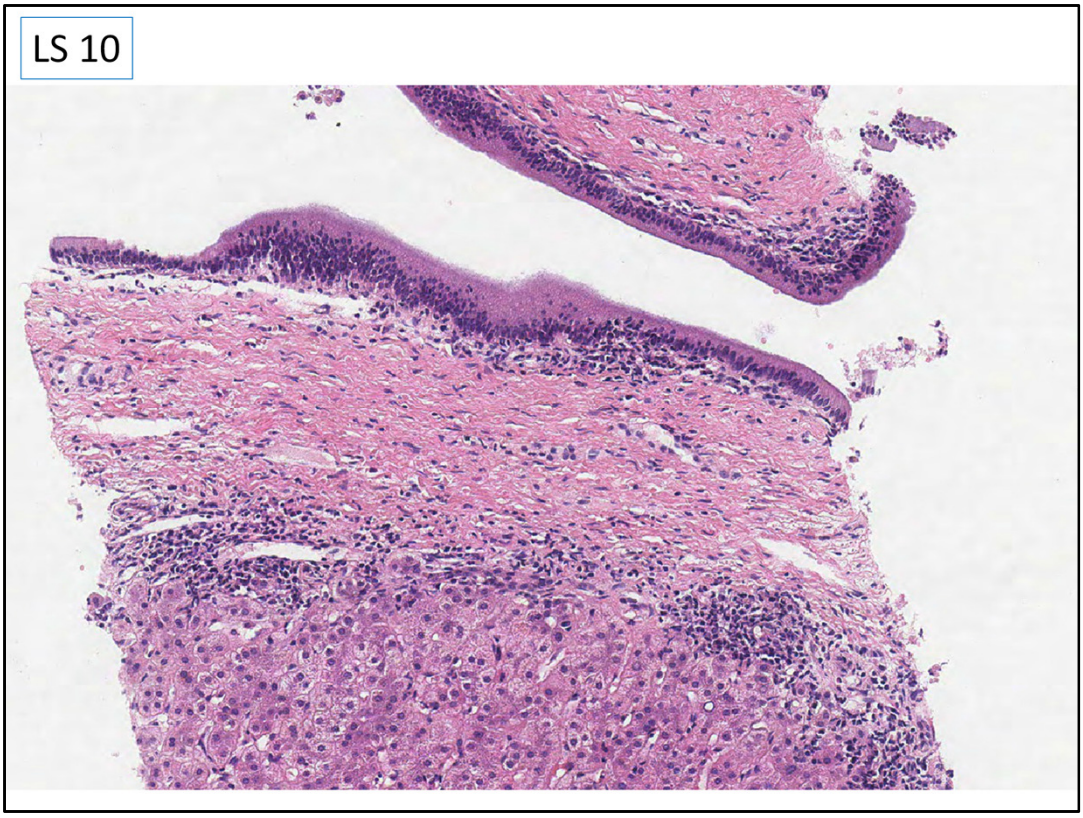
This portal tract has an unaccompanied hepatic artery, there is no central bile duct. There is some inflammatory infiltrate at the margin of the portal area, with interface hepatitis at the upper edge of the portal tract, and also more prominent ductular reaction at its lower edge.



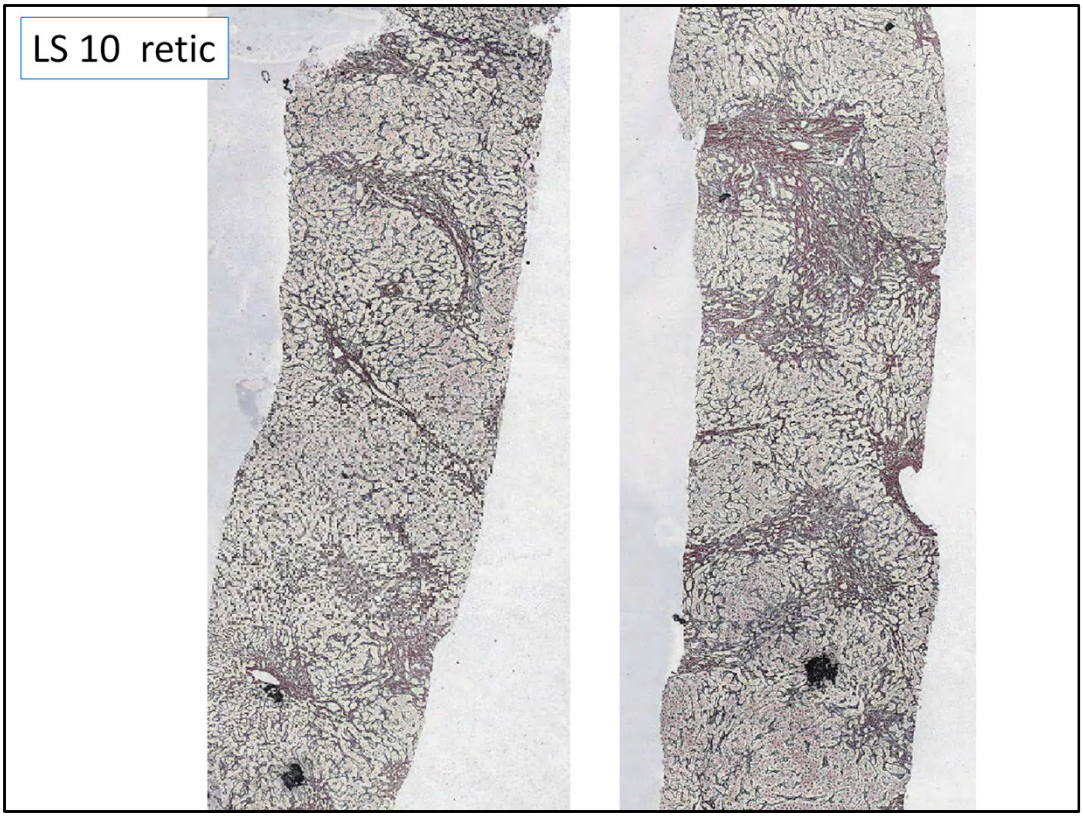
Another portal area, where the expansion is due to ductular reaction (arrows). There is no central duct – although since the portal tract is incomplete, ductopenia cannot be assessed in this tract.



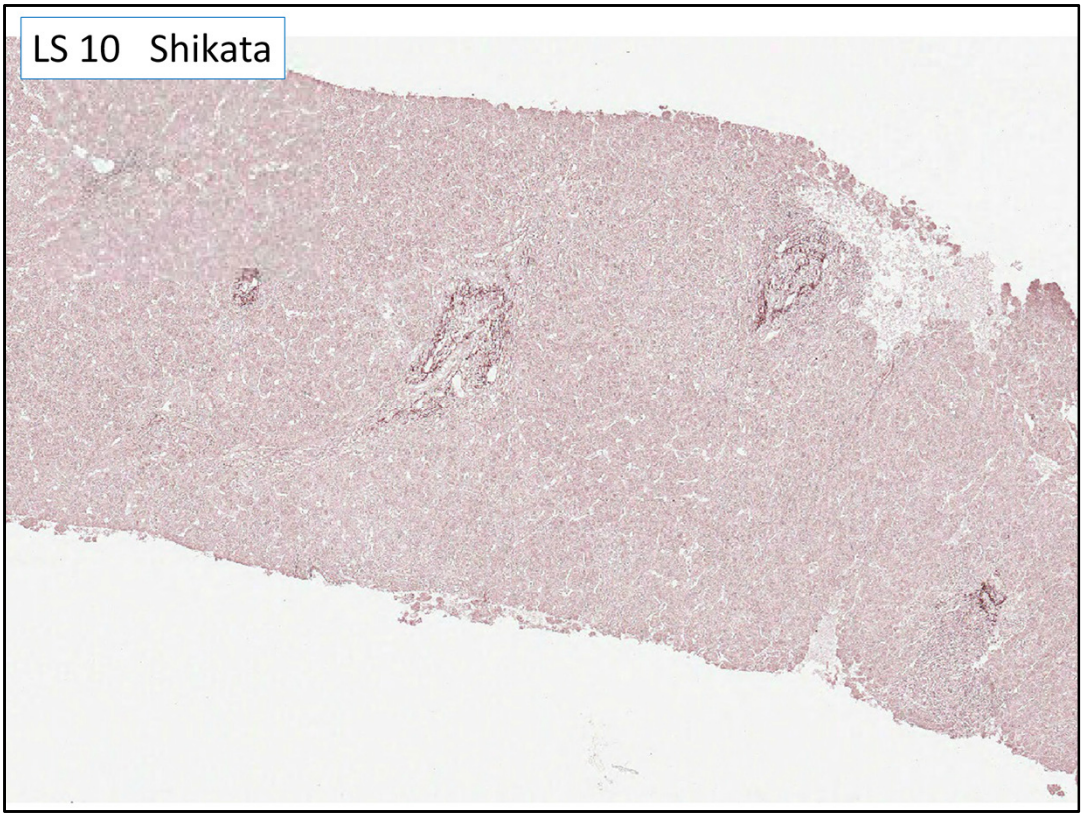
Where there is interface hepatitis enlarging the portal areas, this is mainly composed of lymphocytes in this case, although plasma cells can be more prominent than this in PBC.



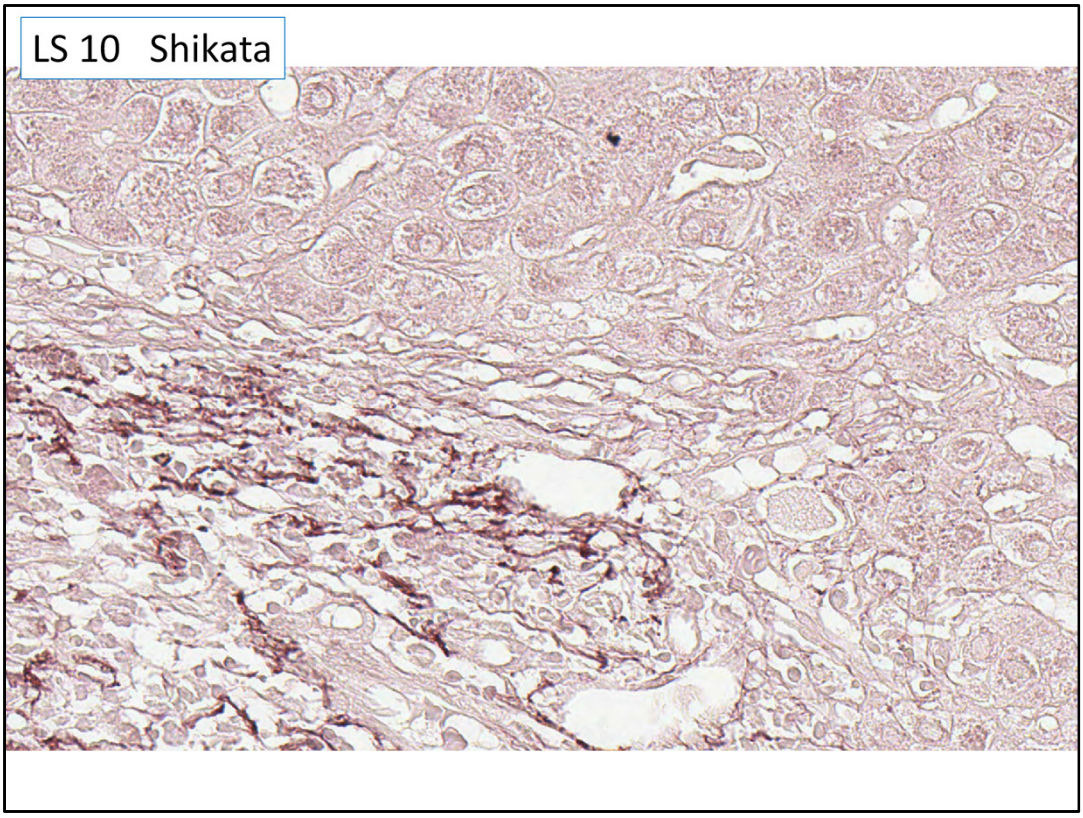
The large duct at the end of the biopsy core also has some mild chronic inflammation. The small ducts have almost completely disappeared. There are no granulomas in the biopsy.



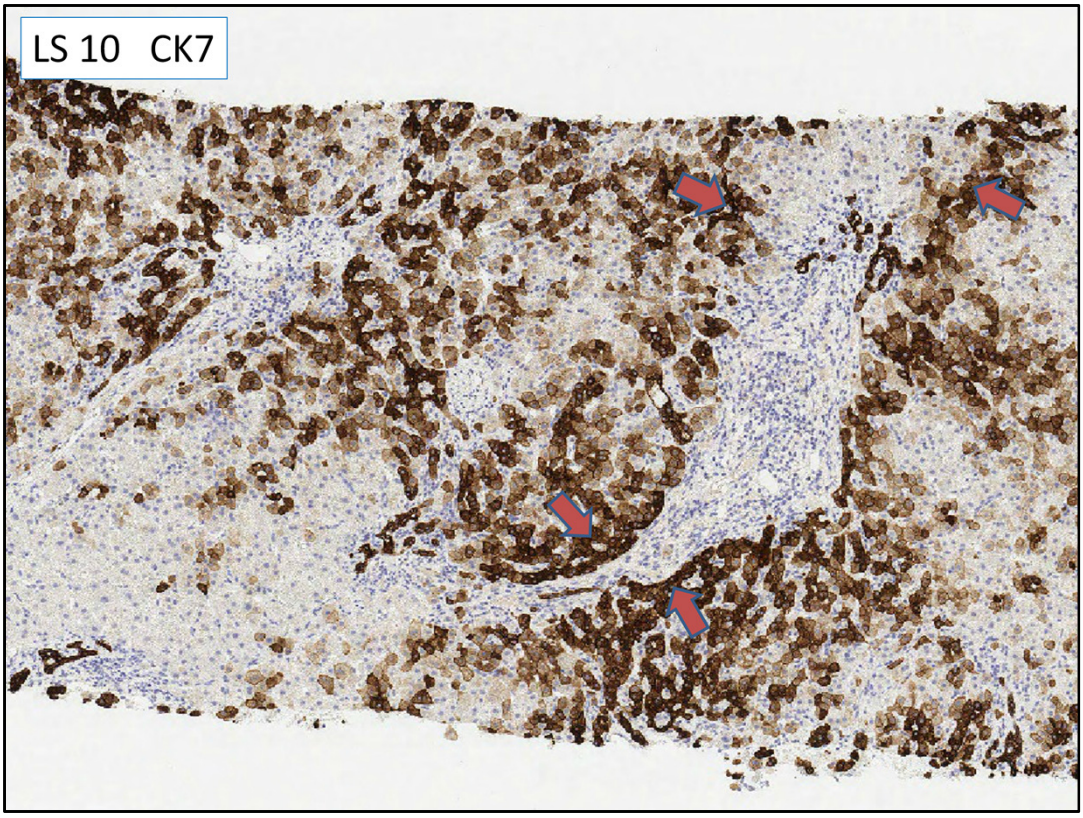
Reticulin – There is portal tract expansion and early portal to portal bridging fibrosis, but not cirrhosis.



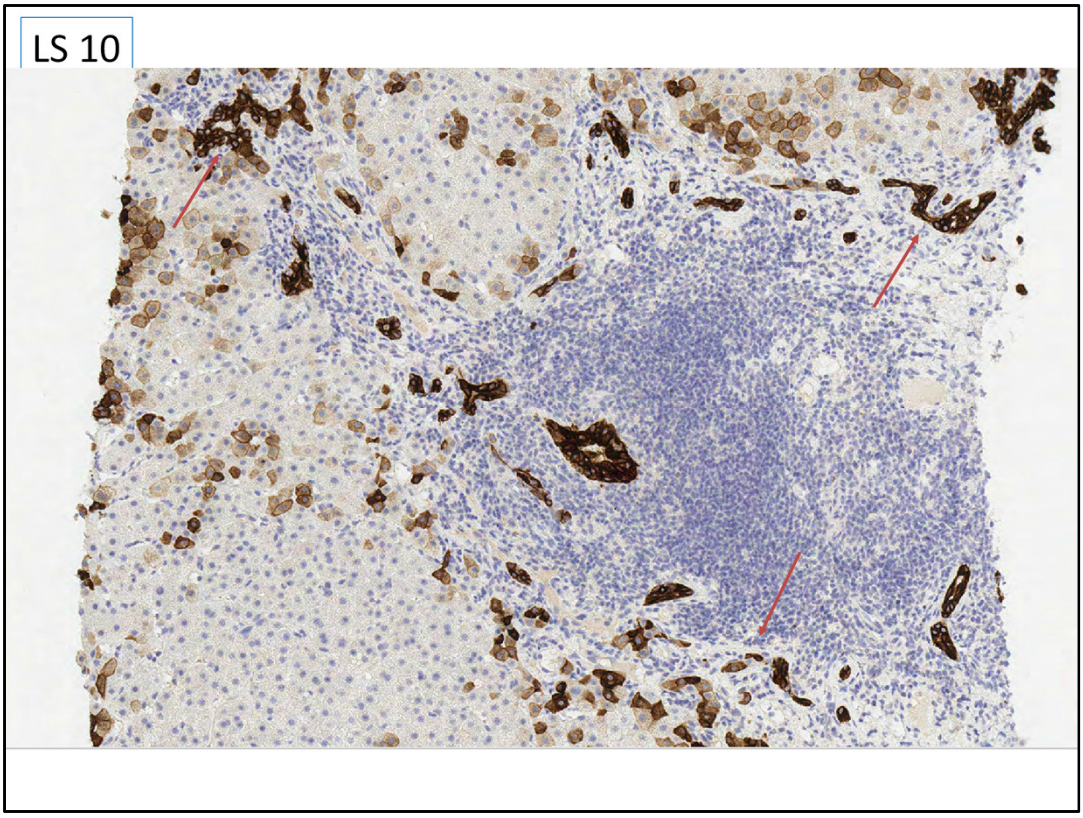
On Shikata, the original elastic defines the position of the portal tracts; the fibrous expansion of the portal tracts on reticulin is not positive on the Shikata stain, indicating that it is not of long standing (not present for years).



The Shikata stain deos not demonstrate copper associated protein in periportal hepatocytes. This is a surprise in a biopsy which otherwise shows clear evidence of ductopenia and chronic biliary disease. Either the Shikata stain has not worked well, or the chronic biliary disease is recent.



The keratin 7 stain is useful here. It confirms the absence of bile ducts within most portal areas. Meanwhile, the periportal hepatocytes are strongly positive Focally there is some ductular reaction, but in this field, most of the periportal cells are intermediate hepatobiliary cells (keratin 7 +ve but have morphology of hepatocytes rather than ductules, arrows).



This portal tract still has a duct – it is surrounded by a lymphocytic infiltrate, but does not have a granulomatous component. Granulomas are more commonly seen in earlier stage PBC, before advanced ductopenia. This tract has some ductular reaction around it (arrows) without the same degree of intermediate hepatobiliary cells as in the previous slide.

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A	PBC – pre-cirrhotic ductopenic
B	Overlap PBC and AIH
C	Large duct obstruction
D	Drug induced ductopenia
E	Primary sclerosing cholangitis

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Correct response: A
This biopsy shows chronic biliary disease with advanced ductopenia, without cirrhosis. The absence of elastic and copper associated protein suggests it is relatively short duration, and yet nearly all the ducts have disappeared. Recent studies have shown that some patients with PBC have more quickly progressive disease, with advanced ductopenia at an earlier stage, and tend to be non-responsive to urso deoxycholic acid (UCDA, urso). There may be some interface hepatitis, but not the full house of characteristics of autoimmune hepatitis in addition to the PBC. These patients may respond to second line treatment for PBC (obetocholic acid). For further information see the BSG/UK PBC treatment and management guidelines, Hirschfield GM et al, Gut 2018;1-27.

Comments on other options.
B: overlap PBC and AIH. The interface hepatitis is focal and not rich in plasma cells. There is not clinical support provided for AIH – the IgG is not quite raised (normal <16); autoantibody information is not provided, although there is some elevation of ALT. Moderate-severe interface hepatitis is a required feature for overlap with AIH, together with ALT >5 upper limit of normal and/or IgG >2 upper limit of normal.

C: large bile duct obstruction. There would typically be portal tract oedema and more uniform ductular reaction, but not loss of the central bile ducts. Bilirubinostasis is present in this biopsy, which is unusual in PBC except at the end stage of the disease – otherwise there are not features of large duct obstruction present.

D: Drug induced ductopenia. Cholestatic hepatitis in drug induced liver injury (DILI) is sometimes associated with ductopenia – if that happens the jaundice of DILI takes a long time to resolve. There is profound cholestasis with ductopenia, but not generally the portal fibrosis and severity of portal inflammation seen here. The history is of jaundice following a drug.

Primary sclerosing cholangitis – There are no fibro-obliterative scars in the ductopenic portal tracts, no periductal fibrosis, and minimal involvement of the larger duct. Therefore no histological features to suggest that this ductopenic biliary disease is due to PSC. However, clinical features are also needed for the diagnosis. The details here include PBC – presumably the patient has anti-mitochondrial antibodies, raised IgM and high alkaline phosphatase. If instead the history was of ulcerative colitis, pANCA antibodies, not mitochondrial antibodies or high IgM, then the recommendation would be for biliary imaging to investigate for PSC.