

# Inflammatory diseases of the bile ducts (cholangiopathies)

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Injuries which primarily affect the biliary tree – cholangiopathies - can be distal obstructive (large duct obstruction), mainly the right of radiologists and surgeons. In contrast, ‘non-obstructive’ cholangiopathies, in which various segments of the extra and / or intrahepatic bile ducts undergo inflammatory destruction and scarring, are relevant to pathologists. The clinical onset may be insidious, the bile ducts are not significantly dilated on ultrasound scan and a liver biopsy is often part of clinical investigations.<sup>1</sup>

Histological cholestasis is absent in the early stages and peripheral cholestasis will not appear until late in the course of the disease when significant stricture affects large bile ducts distal to the confluence of right and left hepatic ducts or destruction of small interlobular bile ducts is near complete. This is at variance with clinical cholestasis defined as elevation of serum alkaline phosphatase (AP),  $\gamma$ -glutamyltranspeptidase ( $\gamma$ GT), and to a variable extent bilirubin which are present from the onset. In absence of cholestasis and the frequent failure of needle biopsy to sample characteristic bile duct lesions the recognition of liver changes due to partial interference with bile flow is important to at diagnosis and to understand disease progression. ‘Cholate-stasis’, ductular reaction, copper associated protein deposition and oedematous fibroplasia are characteristic of biliary interface activity which has to be distinguished from lymphocytic (hepatitic) interface activity, the hallmark of both autoimmune hepatitis (AIH) and chronic viral hepatitis. Peripheral cholestasis with Mallory body and ‘halo’ formation occur in late stages. In addition chronic cholangiopathies may lead to progressive loss of bile ducts or ductopenia as evidenced by arteries unaccompanied by ducts of matching size.

Primary biliary cirrhosis (PBC) has distinctive clinical features (F / M ratio 9 / 1, exceptional under 30 years of age, raised serum IgM and antimitochondrial antibodies) that are often diagnostic. A biopsy may still be performed to confirm the clinical diagnosis, to establish how far the lesion has progressed (staging), to assess abnormal liver enzymes prior to full clinical work up, or when there are confounding features of AIH.<sup>2</sup>

Key points to remember in interpreting needle biopsy are:

- Exclusion of PBC should be avoided on a needle biopsy specimen
- Staging may have a prognostic value, but is also subject to sampling variation
- Interface activity may mimic that seen in AIH, a finding not necessarily associated with PBC–AIH overlapping features clinically.<sup>3</sup>

Sarcoidosis and drug injury are main differential diagnoses.

‘Primary’ sclerosing cholangitis (PSC) is a more heterogeneous disorder in which non-specific inflammatory fibrosis in the wall of the biliary tree leads to unevenly distributed stenosis and beading of the large extrahepatic and intrahepatic bile ducts; small intrahepatic bile ducts are often affected, exclusively in some 5 per cent of cases (*small-duct primary sclerosing cholangitis*).<sup>4</sup> Imaging (MRCP or ERCP) is essential part of diagnosis, but histology provides useful information regarding stage, activity and degree of small duct involvement.

Over 75% of the patients with PSC suffer of chronic inflammatory bowel disease (IBD). Liver histology may show considerable similarities with that of PBC, but there are striking clinical differences in that the disease affects all age groups, has a male to female ratio approx. 2-3 to 1 and has no strong laboratory markers (AMA negative; pANCA and elevated AP/γGT lacking specificity and sensitive). Antinuclear and anti-smooth muscle antibodies may be found in a third of the patients, particularly in children and in young adults, a clinical overlap with AIH which may be reflected histologically.<sup>5,6</sup>

The various conditions listed in the Table as *acquired or secondary sclerosing cholangitis* may be radiologically and histologically indistinguishable from PSC, except that a cause is identified.

Points relevant to liver biopsy interpretation:

- Given the random distribution of the affected bile ducts, histological changes at the liver periphery are very variable; ducts involved are often beyond the reach of biopsy needles, and characteristic ‘onion-skin’ periductal fibrosis and bile-duct replaced by fibrous cords are seen in less than 40 per cent of needle specimens
- Histological changes are classified into four stages applying the scoring system used for PBC; the sampling error may be even greater due to the variability of the bile-duct segments affected and frequent areas of parenchymal extinction
- As with PBC interface changes may mimic an AIH, in which case autoantibodies and elevated IgG may be associated, but not necessarily. Conversely, prominent autoimmune features clinically may not be evident on biopsy, presumably due to severe lymphoplasmatic infiltration targeting bile ducts larger than the ones sampled.

**Table: Classification of sclerosing cholangitis**

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| <p><b>‘Primary’ sclerosing cholangitis ± IBD</b></p> <ul style="list-style-type: none"> <li>- Autoimmune features (Autoimmune sclerosing cholangitis)</li> <li>- Perinatal onset</li> <li>- ± chronic pancreatitis (IgG4 disease)<sup>7</sup></li> </ul> | <p><b>‘Acquired’ sclerosing cholangitis</b></p> <ul style="list-style-type: none"> <li>- Opportunistic (primary or secondary immunodeficiency)</li> <li>- Ischaemic (arterial cytotoxic infusion, liver allograft)<sup>8</sup></li> <li>- Toxic (treated hydatid cyst)</li> <li>- Mechanical (choledochal varices)</li> </ul> |
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A rare causes of chronic cholangiopathy in young adult is deficiency in multidrug resistance 3 (MDR3) - due to a mutation in the encoding gene *ABCB4*.<sup>9</sup> In addition an obscure condition referred to as adulthood ductopaenia has been identified in young adults in whom clinical, radiological and immunological features did not satisfy the criteria for any of the recognized causes of ductopaenia.<sup>10</sup>

In conclusion inflammatory disorders of the biliary tract present difficult diagnostic problems in needle biopsy interpretation. Awareness of these relatively uncommon conditions, their clinical presentation and histology drawbacks, such as lack of sampling of the bile duct lesion, overlapping features with chronic hepatitis, absence of cholestasis, and the recognition of subtle biliary features (orcein/copper) are clues to improve the diagnostic yield.

**References**

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