MICROSCOPIC ANALYSIS OF LIVER FIBROSIS: A LITERATURE REVIEW

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Introduction

Liver fibrosis is a histological consequence of chronic liver injury characterised by excessive deposition of extracellular matrix (ECM) proteins, particularly collagens, which progressively replace normal functional parenchyma and distort hepatic architecture (1). Microscopic evaluation of liver fibrosis remains the reference standard for diagnosis, staging, and assessment of treatment response (2). Fibrosis is an integral component of chronic liver disease; ensuing inflammation of the liver due to various aetiologies elicits deposition of fibrous tissue in the parenchyma, remodels the vasculature, and compromises liver function (1). On haematoxylin-eosin sections or with histochemical stains such as Masson's trichrome or Sirius Red, fibrosis is visualised as collagen deposition with varying degrees of architectural distortion (1).

Staining Methods for Microscopic Assessment

The accurate microscopic detection of liver fibrosis depends on appropriate tissue staining. Haematoxylin and eosin (H&E) staining provides an overview of hepatic architecture and allows identification of hepatocyte injury, inflammation, and steatosis, but early perisinusoidal fibrosis may be too thin to be reliably detected on H&E alone (3). Connective tissue stains are therefore essential for fibrosis assessment. Masson's trichrome stain highlights collagen fibres in blue, while Sirius Red staining visualises collagen in red (4). The perivenular and periportal intrasinusoidal collagen stains bright blue and red with Masson trichrome and Sirius Red, respectively (4). In addition, Masson's trichrome stain is helpful in identifying enlarged mitochondria, which stain bright red (4). Reticulin staining can demonstrate perivenular and periportal intrasinusoidal collagen deposition through reticulin condensation (4). Verhoeff-van Gieson elastic tissue stain is useful for highlighting sclerosis of terminal hepatic venules (4). The choice of stain depends on the specific question being addressed and the stage of fibrosis being evaluated (2,4).

Patterns of Fibrosis According to Aetiology

The microscopic pattern of liver fibrosis varies according to the underlying disease, and recognition of these patterns is important for accurate diagnosis and staging (1,5). Pinzani and Rombouts (2004) subdivided fibrosis patterns according to the underlying disease (5). The biliary pattern is associated with cholestatic conditions such

as primary biliary cholangitis and primary sclerosing cholangitis, and is characterised by fibrotic patterns originating from the biliary ducts in the portal tracts and extending towards neighbouring portal tracts (portal-portal fibrosis) (5). Chronic viral hepatitis leads to fibrotic septa originating from the portal tract and extending towards the central vein (portal-central fibrosis) (5). In alcohol-related liver disease or non-alcoholic steatohepatitis, perivenular and pericellular collagen fibres are interspersed in the liver parenchyma, resulting in a "chicken-wire" pattern of fibrosis (5). Chronic venous outflow problems, such as those seen in portal hypertension, cause deposition of collagen fibres around the central vein, leading to fibrotic bridges between neighbouring central veins (central-central fibrosis) (5).

In chronic hepatotropic virus infection, portal expansion is followed by periportal fibrosis, septal (bridging) fibrosis, and ultimately cirrhosis (1). In alcoholic liver disease or adult non-alcoholic fatty liver disease, fibrosis starts with a centrilobular perivenular distribution and sinusoidal fibrosis (1). The fibrosis pattern in paediatric fatty liver disease is similar to that observed in hepatotropic virus infection, featuring a periportal distribution (1).

Histological Scoring Systems

Several semiquantitative histological scoring systems have been developed to standardise the assessment of fibrosis stage. The Ishak system, described in 1998, employs a scale ranging from F0 to F6 and is most commonly used for fibrosis staging in patients with various types of hepatitis (6). The METAVIR scoring system uses a scale from F0 to F4 and is widely applied in chronic viral hepatitis and metabolic dysfunction-associated steatotic liver disease (6). Concordance between the Ishak and METAVIR systems is excellent for fibrotic change, with a weighted kappa of 0.998 in a study of 127 patients with chronic viral hepatitis (7). The METAVIR fibrosis stages are: F0 (no fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with few septa), F3 (septal fibrosis without cirrhosis), and F4 (cirrhosis) (6).

For metabolic dysfunction-associated steatotic liver disease (MASLD), fibrosis is histologically staged using the 5-tiered NASH CRN system, which scores fibrosis from F0 to F4 (8). More recently, the EPoS staging system has been proposed, comprising seven stages (0–6) to cover the full spectrum of MASLD fibrosis with greater granularity (8). Consensus position statements for the standardised application of histological grading and staging systems in MASH clinical trials have been developed to promote consensus among liver pathologists and ensure reproducibility (8).

Microscopic Features of Fibrosis Regression

A critical advance in hepatopathology has been the recognition that liver fibrosis and cirrhosis are potentially reversible (1,5). Distinctive histopathological changes are

observed during fibrosis regression (1,5). The fibrotic septa become thinner, periportal spicules and isolated thick collagen fibres can be seen in the parenchyma, and subsequently, isolated hepatocytes surrounded by a thin fibrotic layer in hepatic and portal veins can be observed (5). These features constitute the "hepatic repair complex" (1). During regression, the MMP-TIMP balance alters, with increased MMP activity and decreased TIMP levels leading to ECM degradation (5). Shortly after cessation of injury, approximately 50% of activated hepatic stellate cells undergo apoptosis, breaking the vicious circle of ECM production and HSC activation, while the remaining cells transition to an inactive state (5).

Conclusion

Microscopic analysis of liver fibrosis remains the cornerstone of diagnosis and staging in chronic liver disease. Histochemical stains such as Masson's trichrome and Sirius Red are essential for reliable detection of collagen deposition, particularly in early stages when perisinusoidal fibres may be too thin for H&E alone. Recognition of aetiology-specific fibrosis patterns guides accurate interpretation. Semiquantitative scoring systems, including METAVIR and Ishak, provide standardised frameworks for staging and have demonstrated excellent concordance for fibrotic change. The recognition of fibrosis regression and the hepatic repair complex has fundamentally altered the conceptual framework of chronic liver disease management. Future developments in digital pathology and artificial intelligence are expected to further enhance the reproducibility and precision of microscopic fibrosis assessment.

References

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