Spectrum of Fatty Liver Disease

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Steatosis – the accumulation of fat within the liver (principally hepatocytes) – is a very common histological abnormality in liver biopsy specimens. Two principal forms are identified – macrovesicular and microvesicular. In the former, hepatocytes contain a single large droplet which displaces the nucleus. In the latter, multiple small droplets are found within the cytoplasm; this form may be difficult to identify in routinely stained sections and may require the use of special stains such as oil red O or Sudan black. The macrovesicular form is the more common and is caused by increased mobilisation and supply of free fatty acids, increased synthesis of free fatty acids in the liver, increased estrification of free fatty acids to triglyceride and decreased mobilisation of triglycerides from the liver. The microvesicular form occurs in certain well defined settings, most of which are associated with impaired mitochondrial beta oxidation.

The causes of microvesicular steatosis include acute fatty liver of pregnancy, Reyes syndrome, drug induced injury (valproate, tetracycline), mitochondrial cytopathies and inherited urea cycle and fatty acid disorders.

Steatosis forms part of the spectrum of alcoholic fatty liver disease. This spectrum includes simple steatosis, steatohepatitis, micronodular cirrhosis, macronodular cirrhosis (following abstinence) and hepatocellular carcinoma.

The phase of steatohepatitis is important as it is associated with fibrosis and regarded as a precursor for cirrhosis. The histological components of steatohepatitis include the following:

- Steatosis (predominantly macrovesicular)
- Lobular inflammation (plus or minus lipogranulomas)
- Ballooning degeneration
- Mallory bodies
- Apoptotic hepatocytes
- Ductular metaplasia
- Fibrosis (pericellular and perivenular)
- Giant mitochondria
- (nuclear glycogenation)

It is important to recognise that the inflammatory component is not always of the classical textbook form which is polymorph rich but in many instances there is a mixture of cells including lymphocytes and macrophages.

Mallory bodies are an important feature of steatohepatitis but are not exclusive to this process being seen in cholestasis and Wilson's disease together with hepatocellular carcinomas. The inclusions contain cytokeratins, some of which are hyper-phosphorylated, and other proteins including tau protein. These abnormal proteins are ubiquitinated.

In 1981, an international working party outlined obligatory changes for the histological diagnosis of alcoholic hepatitis. They considered that one needed liver cell injury (in the form of ballooning), an inflammatory cell infiltrate, pericellular fibrosis and with the changes being of a perivenular distribution. Almost a quarter of a century on, the consensus remains much the same although it is recognised that a diagnosis of steatohepatitis can be made in the absence of any ongoing steatosis and there is increasing emphasis on the importance of ballooning degeneration.

For the past 30 years or so it has been increasingly recognised that the whole spectrum seen in alcoholic liver disease can be also observed in non-alcoholic individuals in which there is Type II diabetes, obesity and other features associated with the metabolic syndrome. It is recognised that so-called non-alcoholic steatohepatitis can occur following the use of some therapeutic agents including estrogens and anti-

estrogens and drugs used in cardiovascular medicine such as Amiodarone. It has been observed following some surgical procedures including jejuno-ileal bypass and more recently has been documented in response to environmental toxins, in particular petrochemicals. The spectrum of non-alcoholic fatty liver disease associated with the metabolic syndrome is of growing prevalence. It is thought to occur in some 75% of patients with Type II diabetes. Furthermore some population based studies have indicated that some degree of non-alcoholic fatty liver disease may be present in as much as one third of US adult males.

There is frequently a debate as to whether alcoholic steatohepatitis can be distinguished histologically from non-alcoholic steatohepatitis. There are no absolute defining features of either condition and in my opinion it is impossible to accurately distinguish between the two without adequate clinical information. In broad terms however the necroinflammation tends to be more severe in alcoholic hepatitis and the changes are much more often perivenular in distribution. Furthermore, sclerosing hyaline necrosis and phlebosclerosis are generally seen in alcoholic as opposed to non-alcoholic steatohepatitis and overall Mallory bodies tend to be more common in alcoholic steatohepatitis. By contrast, the presence of glycogenated nuclei is much more frequently seen in non-alcoholic steatohepatitis in which there may also be phospholipidosis (particularly if it is of drug origin).

The pathogenesis of fatty liver disease has received much attention in recent years. It is now believed that the spectrum of both alcoholic liver disease and non-alcoholic fatty liver disease is a multi-hit phenomenon. In non-alcoholic fatty liver disease the consequences of insulin resistance and other factors such as mitochondrial enzyme defects lead to steatosis. In the setting of oxidative stress and perhaps exposure to lipopolysaccharides with stimulation of tumour necrosis factor there is progression to steatohepatitis. Further factors determine whether this then progresses to cirrhosis; this includes genetic polymorphisms and a number of environmental and dietary factors.

The severity of both alcoholic fatty liver disease and non-alcoholic fatty liver disease cannot be easily predicted by traditional “liver function tests”. A recent study has demonstrated that the entire spectrum of non-alcoholic fatty liver disease can be seen in patients with normal ALT levels. Non-invasive methods for assessment of the severity of fatty liver disease remain of relatively low sensitivity and specificity. Protein NMR is the most effective but is a costly procedure and to date it has not been possible to use any form of radiological examination to distinguish accurately between steatosis and steatohepatitis.

For these reasons liver biopsy remains an important “gold standard” and recently several histological scoring systems have been designed to provide better data on the grade and stage of disease within individual patients and in cohorts as part of drug trials. One of the most commonly used systems in recent years has been that described by Dr Brunt in St Louis, USA, in which there is a clear separation between grade (based on the degree of steatosis, ballooning and inflammation) and stage which uses essentially the METAVIR scoring system for degree of fibrosis. As with the systems designed for assessment of viral liver disease this (and the more recently described NIH scoring system) are not without inherent problems but nevertheless will play an increasing role in documentation of fatty liver disease in individual patients and in evolving clinical trials. In my own practice I now complete a fatty liver proforma for all cases which documents on a semi-quantitative scoring system a number of the key features of fatty liver disease and it is my contention that the appropriate approach to reporting biopsies in patients with fatty liver disease is currently the following:-

1. Confirm the presence of fatty liver disease.
2. Define severity using a global assessment.
3. Indicate the aetiology (if known).
4. Provide a histological activity index (most important for research/epidemiological studies).