

IRON OVERLOAD AND THE LIVER

Professor Alastair D Burt

Institute of Cellular Medicine, Newcastle University and Department of Cellular Pathology, Newcastle upon Tyne Hospitals NHS Foundation Trust
e-mail: a.d.burt@ncl.ac.uk

Histopathologists encounter hepatic iron overload in a variety of settings. It can be seen in specimens from those with suspected genetic haemochromatosis; here biopsies are used to assess the degree of iron loading as well as establishing the stage of the disease and excluding co-morbid conditions. Biopsies are still sometimes used to monitor response to iron depletion in those in whom a diagnosis has already been made. It can also be seen in the context of investigation of secondary iron overload and as an incidental finding during the assessment of some other liver condition such as HCV or NAFLD.

Iron pigment in biopsies needs to be distinguished from other pigments including formalin deposits, lipofuscin, bilirubin, gold, titanium, schistosomal and malarial pigment, thorotrast, porphyrins and melanin. Perl's stain which is based on the Prussian Blue reaction remains the most widely used histochemical stain for the detection of ferrous ions in tissue; other methods will also pick up ferric ions and may be more sensitive but are more capricious. Quantitation of iron overload in liver tissue can be achieved reliably by atomic absorption; this is equally effective on fresh or formalin fixed paraffin embedded material and can be used to measure the hepatic iron index. Other approaches include a variety of semi-quantitative scoring systems and image analysis. The Scheuer method remains the most widely approach in routine practice but other more sophisticated systems such as those described by Deugnier et al are of value in research studies.

The commonest inherited disorder of iron overload is HFE-associated genetic haemochromatosis. The iron deposition in this condition is typically parenchymal with progressive loading of hepatocytes in acinar zone 1 initially with involvement of the rest of the acini over time (if untreated). This is associated with portal fibrosis which may progress to a micronodular cirrhosis. During the past decade a number of other inherited conditions have been identified which differ genetically and phenotypically from HFE-associated disease. These include juvenile haemochromatosis, TFR2 associated iron overload and ferroportin disease (some authorities have classified these as type 2 to 4 haemochromatosis). The juvenile form is characterised by a similar distribution of iron deposition to that of HFE; TFR2 associated disease shows a variable pattern while ferroportin disease is classically non-parenchymal. While these conditions are relatively uncommon they need to be considered in all patients where there is significant hepatic haemosiderosis where they are found to be wild type HFE. A distinct form of iron overload also occurs in the neonatal period; this disorder is generally fatal and appears to have an autoimmune basis.

African (American) iron overload was previously referred to as Bantu siderosis. It is still prevalent in Southern Africa. It is associated with high oral intake of local beers brewed in iron pots. It has long been considered therefore to be a form of secondary iron overload but recent studies suggest that ferroportin gene mutations may play a role in determining the disease phenotype. Secondary iron overload is seen in the context of iron overloading anaemias such as thalassaemia major, porphyria cutanea tarda, multiple transfusions, anaemia of inflammation and in a variety of chronic liver diseases including HCV infection and alcoholic liver disease. A mixed (parenchymal/non-parenchymal) pattern of iron deposition is commonly seen in conditions of ineffective erythropoiesis.

There is a well recognised association between haemochromatosis and hepatocellular carcinoma. Although the risk of developing malignancy is reduced in those that are treated it does not completely disappear. Liver tumours also develop in African iron overload and can be reproduced in animal models of iron loading. A precursor of hepatocellular carcinoma in this setting is the presence of iron free foci which represent areas of proliferative activity associated with dysplasia.

Finally, detection of iron in the liver occasionally represents a surrogate for extrahepatic disease. Thus, nuclear iron is a unique feature of neuroferritinopathy, a late onset basal ganglia disease.

SUGGESTED READING

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