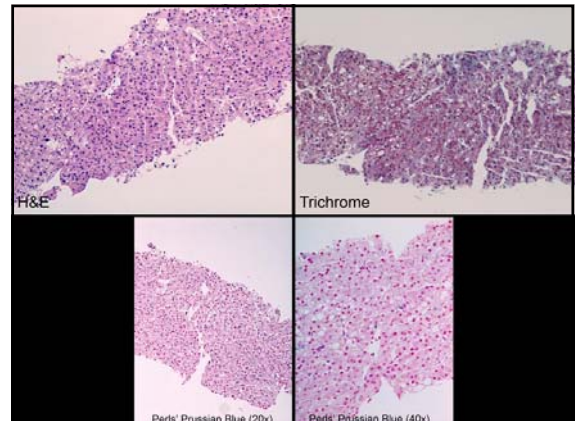
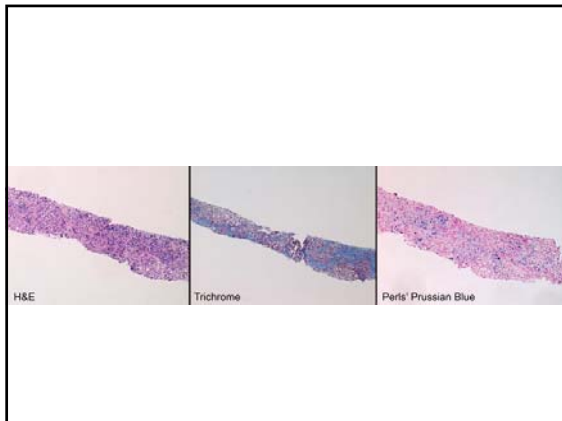


## The Significance of Iron-Free Foci on Liver Biopsy

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## Iron Overload Evaluation

- Clinical
- Biochemical
  - Transferrin saturation
  - Ferritin
- Liver biopsy
  - Performed if liver chemistry tests are abnormal or
  - A lesion is detected on imaging studies



## Diagnosis

- Cirrhosis
- Steatohepatitis
- 3-4+ iron deposition
- Iron-free focus

## Evaluation of iron in the liver

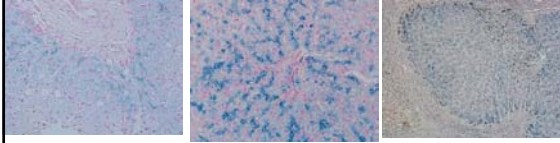
1. Determine the location: parenchymal, mesenchymal or mixed type
2. Quantify liver iron:
  - Histological
  - Biochemical
3. Look for associated iron-related lesions
  - Sideronecrosis
  - Fibrosis
  - Iron-free foci
4. Assess any other liver damage

## Histological Assessment Qualitative

### Distribution within the lobule – patterns

#### Parenchymal or hepatocellular pattern

- Iron predominantly within hepatocytes
- Gradient from periportal to centrilobular



Turlin 1998

## Histological Assessment Qualitative

- Mesenchymal pattern:
  - Parenteral iron overload
  - Iron within sinusoidal cells: Kupffer cells and connective tissue of portal tracts and fibrous septa
- Mixed pattern
  - Several causes: e.g. alcohol, hemochromatosis

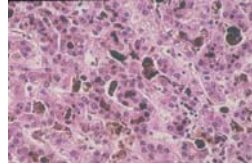


Table 1. Patterns and Pattern Scores for Histological Evaluation of Hepatic Iron Deposition

#### HH Pattern and Score

1. Any quantitative grade of iron granule deposition in scattered hepatocytes in acinar zone 1.
2. Hepatocytes in >50% of acinar zones 1 are reactive; Kupffer cells and/or portal macrophages = reactive.
3. Hepatocellular iron, zone 1 or panacinar, with zonal gradient in acini or within regenerative nodules. Kupffer cell aggregates, portal/portal macrophage iron common; may include reactivity in biliary epithelium or vascular endothelium.
4. Prussian Blue reactivity seen on glass slides by the naked eye. Microscopically, coalesced hepatocellular and Kupffer cell iron granules with little or no gradient are present. This grade includes iron-free foci. Biliary epithelium and vascular endothelium are commonly involved.

#### Non-HH Pattern and Score

1. Scattered sinusoidal lining cells or portal macrophages are reactive. May see occasional zone 1 hepatocytes with faint granular reactivity.
2. Panacinar Kupffer cell/sinusoidal lining cell reactivity, = portal macrophages are seen. May see occasional zone 1 hepatocyte reactivity.
3. Panacinar Kupffer cell reactivity and portal macrophage reactivity are present; diffuse zone 1 or periportal hepatocellular reactivity is noted.
4. As in 3, with iron deposition in fibrous tissue of portal tracts or septa.

Brunt 2000

## Iron Overload Syndromes

- Hereditary hemochromatosis (HH)
- Nonhemochromatosis iron overload syndromes
  - Juvenile hemochromatosis - rare
  - Secondary iron overload
    - Excessive iron supply
    - Transfusion
    - Inflammatory syndrome
    - Chronic liver diseases: alcohol, HCV, HBV
    - Cirrhosis
    - Hematological disorders

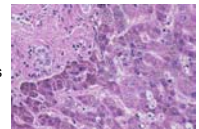
## Hereditary hemochromatosis (HH)

- Autosomal recessive disorder
- Intestinal hyperabsorption of iron
- Progressive iron deposition within parenchymal organs: liver, pancreas, heart
- 85% of patients are homozygous for C282Y mutation

## Pattern of iron deposition in HH

Parenchymal (HH) type with decreasing gradient from zone 1 to zone 3

- Iron predominantly within hepatocytes
- Mesenchymal deposits may be present but less abundant

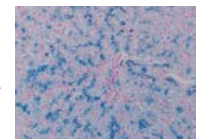


HH pattern:

- 58% PPV for C282Y homozygosity
- Non-HH pattern = 100% negative predictive value for C282Y homozygosity

Pattern scores + quantitation scores

- 3+ or 4+, the PPV = 73.2% for C282Y homozygosity

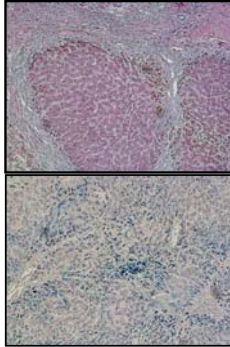


Turlin 1998, Brunt 2000

## Liver pathology in HH

- Sideronecrosis
- Mild inflammation
- Progressive fibrosis

\*Iron-free foci



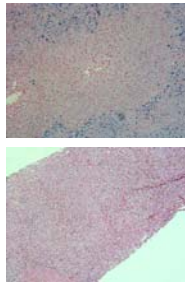
## Iron-Free Foci (IFF)

- Resistance to iron accumulation
- Sublobular nodules of hepatocytes free of iron *or*
- Hepatocytes exhibiting much less iron than the surrounding parenchyma (Deugnier 1993)
- Phenotypic marker of neoplasia and preneoplasia (Terada & Nakanuma 1989)
  - Iron stain valuable for identification of neoplastic or borderline lesions



## Iron-free foci

- Nodules comprising more than 20 hepatocytes free of iron or significantly less iron than the surrounding parenchyma



## Significance of IFF

- Proliferative lesions
- Preneoplastic foci
- The finding of IFF in the initial liver biopsy specimen from a patient with HH should lead to regular HCC screening

## Iron-free foci

- Hirota et al (1982) first suggested iron-free foci to be precursors to primary liver carcinoma
- Resistance to iron accumulation
- HCC usually free of stainable iron

Hirota 1982

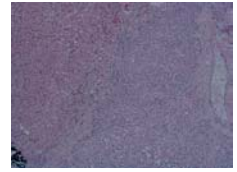
## Iron-free foci (IFF)

- Found in 14/185 patients (7.6%) with hereditary hemochromatosis
  - 6/12 (50%) developed HCC vs 2/24 (8%) in control group without IFF
  - Mean number of IFF = 3.2 +/- 2.1
  - 10/14 with dysplastic features
  - PCNA+ in 75% → proliferative lesion or preneoplastic foci

Deugnier 1993

## Primary Liver Cancer in HH

- Accounts for 6.7 up to 45% of deaths
- Relative risk for development >200
- Deugnier et al (Gastroenterology 1993)
  - 54 patients with liver cancer
    - 53 HCC, 1 CholangioCa
  - Male > female
  - > 55 y.o
  - Majority symptomatic
  - 8 macronodular, 8 micronodular cirrhosis
  - 3 were fibrotic and non-cirrhotic
  - 10/12 (83%) presented with IFF



HCC in a patient with HH



Dysplastic nodule with iron overload adjacent to an HCC