DEVELOPMENT OF HEMOSIDEROSIS AFTER SIDE-TO-SIDE PORTACAVAL SHUNTING

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Hemochromatosis following side-to-side portacaval anastomosis is rare, although well documented after end-to-side anastomosis or in unoperated patients with large portal-systemic collaterals. We report a patient with alcoholic cirrhosis and portal hypertension who had a side-to-side portacaval anastomosis in October, 1967, for repeated bleeding. Liver biopsy then revealed cirrhosis but no increased hepatic iron. At autopsy in June, 1970, extensive iron deposits were found throughout the liver and in many tissues, although not in marrow or spleen. Total hepatic iron was estimated to be 3.3 g. The etiology of hemosiderosis following portacaval shunting is unknown. It is probably due to increased iron absorption. This may be related to increased gastric acid secretion, or to a factor produced, or not inactivated, by the shunted liver.

In Conn's recent comprehensive review of the world literature, there are 26 reported cases of siderosis developing after end-to-side anastomosis, but only 2 cases after side-to-side shunting are noted. This report adds a 3rd case, with quantitation of hepatic iron.

Case Report

MHMCLB Case no. A141-70. A 44-year-old white housewife first presented in 1953 with minimal hematemesis following an alcoholic binge. She admitted heavy alcohol ingestion over many years.

In 1955 she had a gastrointestinal hemorrhage requiring 9 U of blood; ascites, spider angiomas, an enlarged liver, and minimal jaundice were first noted.

She did well until 1965 when she had a second episode of hematemesis and required 3 U of blood: esophageal varices were demonstrated radiographically.

After two additional episodes of gastrointestinal bleeding requiring blood transfusions, a portacaval anastomosis was undertaken. At surgery, in October, 1967, the portal pressure was found to be 48 cm of water which fell to 32 cm after shunting, with no measurable change in vena cava pressure. A side-to-side anastomosis was performed, portal vein to inferior vena cava, with a 1.5-cm elliptical opening between the two. This was less than the 2 cm desired by the surgeon, but was necessitated by difficulty in mobilizing the portal vein. The liver had a grossly hobnail appearance and a portion near the hilus was removed for easier approximation of the portal vein and vena cava. Histological examination revealed a 1-cm diameter biopsy showing micronodular cirrhosis with moderate fibrosis, no fatty change or Mallory bodies, but marked lymphocytic infiltration of the interlobular septa. No stainable iron was detected.

She did well, requiring neither hospitalization nor transfusions until June, 1970 when she rapidly developed hepatic decompensation with encephalopathy and coma and died 12 days after admission to the hospital. Her admission hemoglobin was 13.3 g per 100 ml, and, due to gastrointestinal blood loss, this fell, despite one transfusion, to 10.9 at the time of death. Platelets were always adequate, and the white blood count ranged from 9,000...
to 16,000. Other pertinent laboratory data are shown in table 1.

Pathology
At necropsy, the esophagus had dilated veins both with and without thrombi. The portacaval shunt was intact and patent. There was fluid present in pleural and peritoneal cavities, and peripheral edema.

The liver was small (650 g), diffusely dark brown, and revealed a micronodular cirrhosis (up to 0.6 cm). Microscopically, the fibrotic interlobular septa were much thicker than in the biopsy taken in 1967. There was again extensive lymphocytic infiltration of the septa, but in addition, there were many Mallory bodies and a few scattered foci of polymorphonuclear leukocytes. Scattered mild fatty change was present. The most notable difference from the biopsy taken in 1967 was the heavy iron deposition. (Therefore, the original biopsy paraffin block was resectioned and restained, and again found negative for iron.)

Iron deposits were present in all the parenchymal cells with larger particles present in cells at the periphery of the lobule. Iron was also present in connective tissue, kupffer cells, and bile duct epithelium. On the basis of the 0 to 3+ grading system suggested by MacDonald and Pechet, this was graded 2+. Then, having no other liver tissue available, that which had been fixed in buffered formalin and embedded in paraffin, was heated, deparaffinized, its volume measured, and the total iron therein determined (Bioscience Laboratories). From this and an estimate of the total volume from the known 650-g weight of the liver, total hepatic iron was calculated to be of the order of 3.3 g.

The pancreas showed a moderate chronic pancreatitis with fibrosis and scattered lymphocytes. There was marked prominence of the islet cell tissue which was not involved in the fibrosis. There was extensive iron deposition in the acinar cells and to a lesser extent in the islet cells. Moderate amounts of iron were noted in the mucosa of the stomach, the tubular cells of the kidney, scattered throughout the cardiac muscle, follicular lining cells of the thyroid, glomerulosal layer of the adrenal glands, the parenchymal cells of the parathyroid, and the choroid plexus. Lesser, but still abnormal accumulations of iron were noted in the mucous glands of the esophagus and Brunner's glands of the proximal duodenum, and in macrophages of the lamina propria of the small intestine. Iron was notably absent from the bone marrow and splenic parenchyma. The spleen weighed 150 g.

Discussion
There is abundant evidence showing an association between parenchymal iron overload and end-to-side portacaval shunts although in a recent review it was found that the hepatic iron content in postshunt hemosiderosis had been measured quantitatively in only 1 previous case, and found to be 2.5 g, which is similar to the 3.3 g found in our patient. Although several times normal, this is much less than has been reported in idio-

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<thead>
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<th>Table 1. Laboratory values</th>
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<tr>
<td>Total serum bilirubin (mg/100 ml)</td>
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<td>Serum glutamic oxaloacetic transaminase (U)</td>
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<tr>
<td>Alkaline phosphatase (international units)</td>
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<td>Prothrombin (%)</td>
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<td>Serum albumin (g/100 ml)</td>
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<td>Fasting blood sugar (mg/100 ml)</td>
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<td>Serum ammonia (µg/100 ml)</td>
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<td>Serum iron (µg/100 ml)</td>
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<tr>
<td>Total iron binding capacity (µg/100 ml)*</td>
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<tr>
<td>% Saturation*</td>
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<td>Transfusions (U)</td>
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* Representative preoperative values.
* Performed after autopsy on stored blood that had been collected shortly before death.
* Received blood transfusions in July, October, and at time of surgery in October, 1967.
pathic hemochromatosis.\(^3,4\) Postshunt iron overload has been shown both in man\(^1\), \(^5\)-\(^9\) and experimentally in rats\(^10,11\) and dogs.\(^12-15\) It has even been documented in cirrhotic patients with large collaterals but no surgical shunt.\(^7,16,17\) There is, however, no reason to believe that side-to-side shunting is protective against the development of hemochromatosis as has been inferred,\(^11,18\) since increased iron deposition has recently been reported 6 weeks after experimental side-to-side shunts in monkeys,\(^19\) and in two previous reports in man.\(^1,2\) Indeed, it has been suggested that the amount of shunting around the liver is directly related to the accumulation of iron therein, regardless of the form of the shunt, be it massive collateral circulation without any surgical shunting procedure, or an end-to-side anastomosis.\(^20\) Most authorities believe hemosiderosis is less common following side-to-side than end-to-side shunts,\(^11,18\) although this may not be true.\(^1\) If indeed it is rarer, this may be because there is less shunting around the liver in a side-to-side shunt; with an end-to-side shunt all portal blood is diverted from the liver. The surgical anastomosis in our case may indeed have abetted the iron deposition by increasing the shunting.

The finding of extensive iron deposition in this and similar patients may be due to: increased iron intake; redistribution of iron from the bone marrow and spleen to other organs; increased absorption.

Our patient did not receive iron injections, oral iron, or transfusions after the shunt. We cannot entirely reject the possibility that this patient had a marked increase in marrow and spleen iron before the shunt which for unknown reasons dramatically shifted its location. This seems unlikely, since decreased hematopoiesis follows both end-to-side and side-to-side experimental shunts in dogs,\(^12\) and it is also improbable that there was sufficient iron in the marrow or spleen before the shunt to provide for the extensive deposits we found at necropsy. Therefore, we feel that the observed tissue iron was due to increased iron absorption. The absence of marrow and splenic iron was probably secondary to recent chronic blood loss with utilization of this readily mobilized iron. Splenic iron is more readily mobilized than that in other organs,\(^21\) and this may be why splenic iron content is so variable in hemochromatosis.

Phenobarbital increases intestinal iron transport,\(^22\) and we speculate that a substance produced or not inactivated by the shunted liver could similarly enhance iron absorption. This may be the same substance that enhances gastric secretion following a portacaval shunt,\(^23\) or it may be that the increased acid itself is responsible,\(^24\) although other gastric factors may be involved.\(^25-28\)

REFERENCES