

Suppression of Hepatic Hematopoiesis with Radioactive Gold (^{198}Au)

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A patient with idiopathic myelofibrosis of some 20 yr duration developed esophageal varices and ascites. No explanation for increased portal pressure other than hepatic hematopoiesis was found. Consequently, a trial of cobalt irradiation to the liver was undertaken with definite but transient decrease in ascites. Subsequently, two courses of radioactive colloidal gold were given, again with definite but transient beneficial effects on the degree of ascites. This latter benefit occurred without suppression of marrow function.

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Patients with idiopathic myelofibrosis have a chronic course extending over many years. The major cause of morbidity is reduced levels of hematopoietic cells, but a variety of complications attend the course of some patients. One serious complication is portal hypertension with esophageal varices and fluid accumulation (1). In one series, all patients were dead within 1 yr after appearance of ascites (1). Hepatic hematopoiesis has been considered to be a primary factor in producing portal hypertension (2). We encountered such a patient and report here attempts to treat the complication by cobalt-irradiation of the liver and by administration of radioactive colloidal gold.

CASE REPORT

A 67-yr-old man was noted to have splenomegaly in 1955. In 1965, a bone marrow biopsy revealed myelofibrosis. Radiographic examination at that time showed no esophageal varices. There was no history of alcohol abuse. He never required blood transfusion.

Between May 1974 and February 1975, he gained approximately 14 kg, but denied abdominal pain, nausea, jaundice, hematemesis, or melena. The spleen filled the entire left abdomen. The liver span was 16 cm. Neither the spleen nor liver had changed detectably from the previous examination, but he had developed obvious ascites and edema. Heart and kidney functions were normal. Varices were demonstrated on an esophagogram. The portal system was patent on angio-

graphy. A liver biopsy showed extramedullary hematopoiesis. On spironolactone (100 mg per day) and a 500 mg salt diet, he lost 10 kg. Diuretics were stopped to see if he would regain weight and he promptly did.

In April 1975, 300 rad cobalt-irradiation was given to the liver. Following this, his weight declined 2 kg and remained stable without diuretics. However, after 1 mo he again began to accumulate fluid and required diuretics. The low dose of irradiation had resulted in depression of his white blood cell and platelet count (Table 1). In July 1975, after demonstrating equal uptake in the liver and spleen by technetium-99m (^{99m}Tc) colloid scan, 5 mCi of gold-198 (^{198}Au) was given i.v. Diuretics were discontinued and no weight gain occurred for 10 wk. A second dose of ^{198}Au was administered in November by way of a catheter in the hepatic artery in the hope of achieving a higher uptake of radioactivity by the liver as compared to the i.v. route. Two millicuries were injected every other day for a total of 8 mCi. This resulted in a decrease in weight of 3 kg which lasted 1 mo. Neither dose resulted in depression of blood counts (Table 1). During therapy there was no obvious change in organomegaly but ascites decreased with each treatment. The alkaline phosphatase (liver origin) decreased by >50% as well. Subsequently, stable weight was maintained with low doses (25-50 mg/day) of spironolactone.

The patient elected to have a splenectomy with which decision we reluctantly concurred. In February 1977, repeat angiography of the portal venous system and splenic and superior mesenteric arteriogram showed all vessels to be fully patent. On March 16, 1977, a splenectomy was performed. Portal venous pressure was 77 cm of water with a central venous pressure of 20; these values declined to 20 and 11, respectively, immediately after removal of the spleen. He did well for the first 5 postoperative days. However, his bilirubin then began to rise and he began vomiting bright red blood. Endoscopy

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TABLE 1
Sequential Hematologic and Biochemical Values

| Item | Date | | | | |
|-----------------------------|---------|------------------------------|--------|--------------------------------|--------------------------------|
| | 5/74 | 4/75 | 6/75 | 8/75 | 12/75 |
| | | Before Cobalt-irradiation | After | After 1st ¹⁹⁸ Au | After 2nd ¹⁹⁸ Au |
| Hgb g% | 10.1 | 9.9 | 8.6 | 7.8 | 8.2 |
| Neutrophils/mm ³ | 1,700 | 1,700 | 850 | 1,200 | 2,900 |
| Platelets/mm ³ | 115,000 | 109,000 | 54,000 | 85,000 | 97,000 |
| LDH | 3 × N* | 3.3 × N | 3 × N | — | 3 × N |
| Alk. Phos. | N | 4 × N | 6 × N | — | 2.4 × N |
| SGOT | N | N | N | — | N |

* N = Normal.

revealed bleeding varices, and superior mesenteric arteriography revealed intrahepatic portal vein thrombosis. He developed pneumonia and died 9 days after the splenectomy.

Autopsy confirmed all premortem findings and there was a fairly fresh, organized thrombus originating in the splenic vein and extending into and completely occluding the portal vein. The liver contained extensive extramedullary hematopoiesis and multiple, fresh infarcts.

DISCUSSION

Portal hypertension with ascities and esophageal varices may occur in as many as 17% of patients with idiopathic myelofibrosis (IMF) (2). Often, this is due to causes unrelated to IMF, such as alcoholic cirrhosis or may be related to IMF with respect to thrombotic tendencies (Budd-Chiari syndrome or portal vein thrombosis) or various other complications (1-3). Increased portal flow secondary to splenomegaly has been imputed as a cause of portal hypertension but there must be an element of obstruction involved as well (2). Obstruction is presumed to be due to portal blockade by mass effects of the extramedullary hematopoiesis (EMH) in some patients.

Therapeutic intervention in these patients has been fraught with complications. Removal of the spleen has a high mortality rate (4) and the use of cytotoxic drugs to suppress the EMH aggravates the cytopenia that complicates the course of many of these patients (2).

Hepatic irradiation (internal and external) has been used with effect in the treatment of lymphomas (5). In our patient, a low dose of externally applied cobalt-irradiation to the liver (one-tenth of liver tolerance) had

a transient effect on the ascites but produced a suppression of blood counts. The 50 to 75 rad that the liver may have absorbed from each of the ¹⁹⁸Au injections appeared to have more marked and prolonged effect without exacerbating the cytopenia.

Experimentally, ¹⁹⁸Au has been shown to be phagocytosed by the Kupffer cells in the periphery of liver lobules where it releases beta-particles (6). This would be in close proximity to the nodules of EMH and might account for the improvement in the patient's clinical situation. It is conceivable that the radioactivity suppressed EMH in the spleen and thereby helped reduce portal flow although no change in organomegaly was appreciated. This relatively benign treatment may be of benefit in controlling a serious manifestation of myelofibrosis.

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