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CASE REPORT

Fatal Hepatic Necrosis Associated with Parenteral Gold Therapy

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Parenteral gold therapy is widely used in the long-term management of rheumatoid arthritis. Prolonged cholestasis is a well-recognized toxic manifestation of this form of therapy and is not life-threatening. Severe hepatocellular disease, including fatal hepatitis, was observed during the early clinical experience with chrysotherapy (1–4). However, with the possible exception of a single case (5), this form of liver injury has not been associated with gold since disposable needles and hepatitis B serologic testing have been in routine clinical use. It has therefore been suggested that these early reports represented concomitant viral hepatitis rather than an idiosyncratic reaction to gold (6).

Two patients who were receiving parenteral gold recently presented to our institutions with fulminant hepatic necrosis that could not be ascribed to hepatitis A or hepatitis B. The striking similarity of these cases suggested the strong possibility that parenteral gold contributed to the fatal liver injury.

CASE REPORT

Case 1. A 33-year-old black male with seronegative rheumatoid arthritis was admitted to a Detroit hospital on February 3, 1983, with a three-day history of right upper quadrant pain, fever, and jaundice. He noted these symptoms one day after his second injection of aurothioglucose (75 mg total gold dose). His only daily medication was indomethacin 50 mg qid, but compliance with and the duration of this therapy was not documented. He denied alcohol intake or exposure to hepatitis and had no history of blood transfusions. Serum ALT, AST, and bilirubin levels were normal one month earlier.

On examination he was jaundiced and in acute distress because of right upper quadrant abdominal pain. Blood pressure was 96/48 mm Hg, pulse 110/min, and respiratory rate 20/min. Temperature was 103.4° F. Examination of the skin revealed no rashes. Liver span could not be assessed because of exquisite right upper quadrant tenderness; splenomegaly was not evident. Neurologic examination was within normal limits.

Admission laboratory studies included a hemoglobin of 7.3 g/dl; WBC 11.7 cells/mm^3 with 49 polys, 21 bands, and no eosinophils; platelets 315,000 cells/mm^3; AST 3430 IU/liter; ALT 2380 IU/liter; LDH 2080 IU/liter; bilirubin 20.7 mg/dl; and alkaline phosphatase 342 IU/liter. The prothrombin time was prolonged by 4 sec, BUN was 21 mg/dl, and creatinine was 1.6 mg/dl. On the second hospital day the patient's hemoglobin fell to 6.1 g/dl and melena was noted. The bilirubin level climbed to 46 mg/dl on the fourth hospital day. Abdominal sonography revealed no obstruction of the biliary tree. On the fourth hospital day ascites was noted. On the sixth hospital day the patient became lethargic; arterial ammonia was 150 μM/liter. On the seventh day urine output ceased and the patient developed pulmonary edema. Hemodialysis was begun, and the patient was flown to the University of Pittsburgh for possible liver transplantation 10 days after initial presentation.

On admission to Presbyterian University Hospital, the patient required immediate intubation and positive end-expiratory pressure ventilation. Dialysis was continued, and periodic blood transfusions were given for persistent gastrointestinal bleeding. Laboratory studies revealed a white blood cell count of 18,900 cells/mm^3 with a left shift (2% eosinophils), platelets 20,000 cells/mm^3, alkaline phosphatase 24 IU/liter, ALT 10 IU/liter, total bilirubin 32.1 mg/dl, arterial ammonia 63 μM/liters, and prothrombin time was 5 sec prolonged. Alpha$_1$-antitrypsin and ceruloplasmin levels were normal. Hepatitis A IgM antibody was negative, and HB_sAg, anti-HB_c, and anti-HB_s were absent.

The patient underwent orthotopic liver transplantation on February 14, 1983, two weeks after the onset of his illness. The resected liver weighed 2000 g. Microscopic

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examination revealed hepatocellular drop-out in the centrilobular region and portal–central bridging necrosis (Figure 1). On February 17, the patient was reexplored due to persistent intraabdominal bleeding. He did not regain consciousness and died soon after the second procedure.

Case 2. A 23-year-old black male presented to the Medical College of Virginia on September 10, 1982, with a one-week history of progressive malaise, anorexia, and jaundice. He admitted to drinking one six pack of beer on weekends, but denied hepatitis contact or intravenous drug abuse and had never received a blood transfusion. The patient's only daily medication was ibuprofen 400 mg qid which he had been taking intermittently for several months. He had been started on weekly aurothiomalate injections two months before for seronegative rheumatoid arthritis and had received a total of 385 mg gold.

During the examination, the patient was pleasant and cooperative and did not appear ill. His blood pressure was 130/80 mm Hg, pulse 56/min, and respiratory rate 20/min. He was afebrile. There were no stigmata of chronic liver disease and no rashes, petechiae, echymoses, or edema. He had mild right upper quadrant tenderness with a liver span of 13 cm without a palpable edge. No spleen was felt. His mental status was normal, and asterixis was not present.

Admission laboratory studies included a bilirubin of 7.7 mg/dl, AST 3414 IU/liter, ALT 2760 IU/liter, alkaline phosphatase 397 IU/liter, albumin 3.4 g/dl, cholesterol 133 mg/dl, BUN 4 mg/dl, creatinine 0.4 mg/dl, prothrombin time prolonged 6 sec, white blood cell count 5200 cells/mm^3 with 6% eosinophils, hemoglobin 13.2 g/dl, and platelet count 400,000 cells/mm^3. There was no evidence of bile duct dilatation on ultrasonographic examination. Anti-HB_s was detected. HB_sAg and anti-HB_c were both negative.

Asterixis, lethargy, and an arterial blood ammonia level of 190 μM/liter were noted on the twelfth hospital day. During the several subsequent days the patient's transaminase levels slowly fell, but the encephalopathy persisted and the prothrombin time continued to climb despite administration of exogenous clotting factors. On the seventeenth hospital day the patient required five units of blood to replace losses due to bleeding from stress ulcerations of the stomach. On the eighteenth hospital day, the patient had grand mal seizures. On the thirty-second hospital day, the patient's bilirubin was 20 mg/dl, alkaline phosphatase 174 IU/liter, AST 94 IU/liter, ALT 40 IU/liter, albumin 2.2 g/dl, cholesterol 27 mg/dl, and prothrombin time 26 sec with control of 11 sec. The patient died on the thirty-sixth hospital day. The postmortem liver weighed 750 g and showed massive hepatic necrosis with focal nodules of regenerating parenchyma (Figure 2).

DISCUSSION

Jaundice has been associated with parenteral gold therapy since its first use in clinical medicine in the 1920s. The incidence of jaundice reported in the early clinical trials of crysotherapy ranged from 0.25% (7) to as high as 9.4% (8). In addition, there were a number of early reports of fatal hepatitis in patients receiving gold (1–4). A single case of severe hepatocellular necrosis has been reported recently (5) in a patient who had been receiving gold injections for longer than six months. All other recent reports of idiosyncratic liver reactions to gold have stressed the cholestatic and benign nature of the condition. Of these 16 cases reported since 1970 (9–19), all patients became jaundiced within the first 12 weeks of treatment. Total gold doses ranged from as low as 10 mg (13) to as high as 600 mg (15), and thiomalate (9–11, 13, 15, 16, 18, 19), thiopropanol (11), and thioglucose (14, 17) gold salt preparations have been implicated. Most of the patients reported were only mildly symptomatic. Fever, rash, and eosinophilia were frequently, but not invariably, present. The reported biochemical parameters and histologic features were predominantly those of an intrahepatic cholestasis, and serum transaminase levels greater than 10 times the upper limit of normal were reported in only one patient (12). Resolution of jaundice was generally prolonged but eventually all but a single patient (18) recovered. This patient, however, died of pneumonia and, at autopsy, histologic evaluation of the liver revealed only "mild centrizonal congestion, necrosis and bile stasis" (18).

The two patients presented in this report do not fit the clinical pattern of gold hepatitis as recently reported. On admission to the hospital and prior to any evidence of hemodynamic instability, each patient had serum transaminase elevations that exceeded 70 times the upper limit of normal. In each patient, the liver injury proved to be fatal.

It is not possible to establish a direct causal relationship between parenteral gold and the fatal hepatitis reported here even though each patient had recently begun treatment with this agent. In addition to gold, each patient was using a medication which has occasionally been reported to cause hepatitis (20, 21). Thus, drug-induced hepatitis due to indomethacin and ibuprofen is possible. In addition, in neither case could non-A, non-B viral hepatitis be completely excluded, as there is no reliable serologic marker for this condition; however, neither patient had a history of recent dental work, blood transfusions, homosexuality, or illicit drug use.

Despite these reservations, the striking similarity of these two cases, seen at different institutions, and their similarity to the older reports of fatal

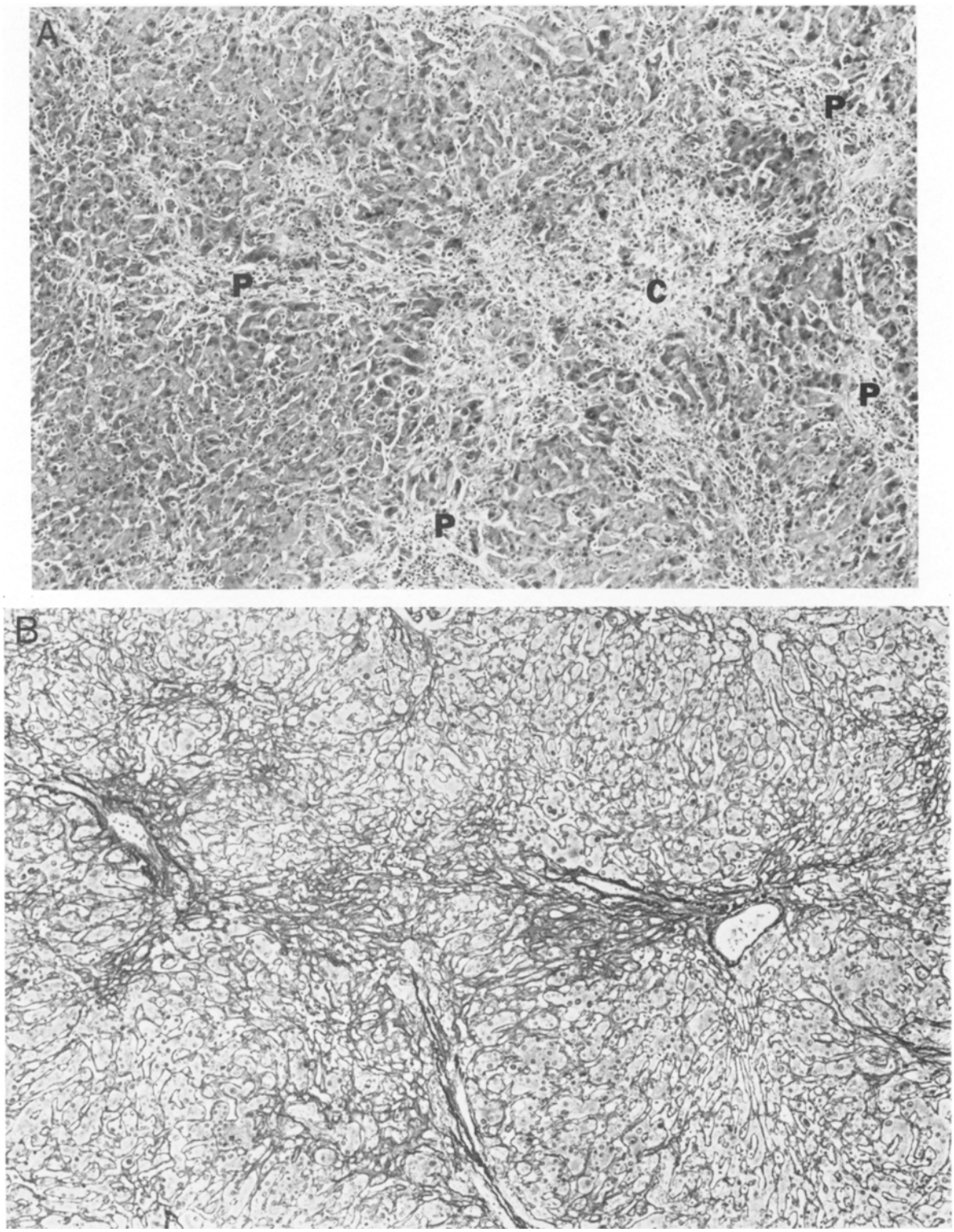

Fig 1. Case 1, liver: (A) There is complete drop-out of hepatocytes in the centrizonal region of the lobule with portal–central bridging necrosis. Lymphocytes are scattered throughout the lobule. C, central; P, portal (H&E, 25×). (B) Bridging necrosis is highlighted by reticulin collapse (Wilder's reticulin, 25×).

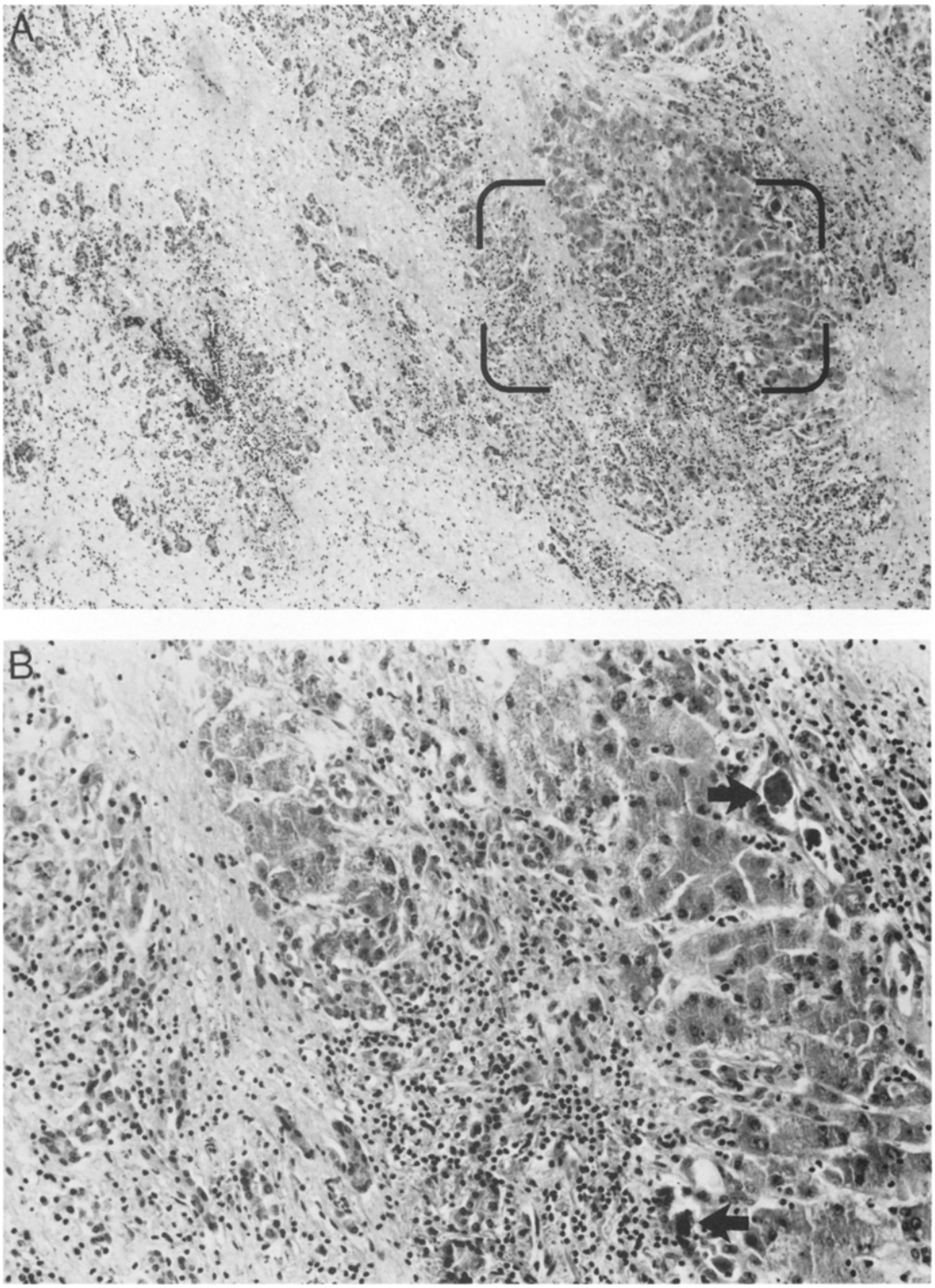

Fig 2. Case 2, liver: (A) There is panlobular necrosis with haphazardly scattered islands of viable hepatocytes. Pseudoductular proliferation is prominent in areas of necrosis. The field bracketed is seen at higher magnification in B (H&E, 25×). (B) Clusters of viable hepatocytes are surrounded by a mixed inflammatory infiltrate composed largely of lymphocytes. Occasional bile plugs (arrows) are present (H&E, 100×).

hepatitis following the institution of gold therapy raise concern that they may represent severe idiosyncratic reactions to gold. It has been estimated that seven million people suffer from rheumatoid arthritis in the United States alone (22). Oral gold preparations have recently been approved by the Food and Drug Administration, and it is expected that this will result in a great increase in the use of gold in this patient population (23). Awareness of the possibility of severe hepatocellular injury resulting from the use of gold preparations alone or in combination with nonsteroidal antiinflammatory drugs may become increasingly important.

SUMMARY

Two young black male patients with seronegative rheumatoid arthritis and treated with nonsteroidal antiinflammatory agents developed fulminant hepatic necrosis following the institution of parenteral gold therapy. These cases, reported from different institutions, may represent a severe form of idiosyncratic gold hepatonecrosis. Awareness of the possible association between gold therapy and severe hepatic injury may become increasingly important as oral gold preparations become widely available.

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