CHRONIC CHLORPROMAZINE CHOLANGIOLITIC HEPATITIS

Report of a case with immunofluorescent studies

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Chronic chlorpromazine hepatitis may simulate a syndrome clinically indistinguishable from xanthomatous biliary cirrhosis, but progression to a true cirrhosis is exceptional. The purpose of this report is to describe a patient observed for 16 months with chlorpromazine-induced jaundice showing persistent pericholangiolitic hepatitis, pruritus, xanthomatosis, abnormal lipid metabolism, and steatorrhea. Although these features mimic the syndrome of primary biliary cirrhosis, immunopathological studies in this patient differed from those described in primary biliary cirrhosis.

Case Report

A 20-year-old Caucasian man was given 200 mg of chlorpromazine daily, from December 13 through December 21, 1963, because of increasing emotional instability. On December 26 he noted the onset of epigastric distress, nausea, vomiting, dark urine, and on the following day, generalized icterus and pruritus.

When examined on January 5, 1964, the patient was jaundiced and afebrile. The liver, spleen and lymph nodes were not enlarged. The leukocyte count was 14,400/µm³ with 55% neutrophils, 23% lymphocytes and 11% eosinophils; 4 days later the leukocyte count was 10,700/µm³ with only 1% eosinophils, and thereafter remained within normal limits. Bile was present in the urine. Results of the serum cholesterol and abnormal liver function studies on January 6, and for the next 16 months, are shown in figure 1. Other liver function tests, including cephalin flocculation, thymol turbidity, total serum proteins, and prothrombin time, remained normal throughout the period of observation. Serum γ-globulin, determined by acetate strip electrophoresis, ranged from 1.2 to 1.4 g/100 ml of serum on four occasions over the 16-month period, and concomitantly, mean lipid phosphorus was 56 mg/100 ml, with a range of 34 to 75 mg/100 ml (normal value, 9 to 16 mg/100 ml); mean total glycerides were 198 mg/100 ml, with a range of 147 to 237 mg/100 ml (normal value, 30 to 120 mg/100 ml); and mean plasma nonesterified fatty acids were 927 μEq/liter with a range of 600 to 1020 μEq/liter (normal value, 500 to 800 μEq/liter). Total serum lipids averaged 1929 mg/100 ml (normal value, 450 to 850 mg/100 ml). Cardiolipin microflocculation and latex fixation tests were negative on five separate examinations.

Esophagoscopy and gastroscopy, performed at 10 and 14 months, showed no evidence of varices. Studies with 14C-labeled Bengal rose dye, after 4 months, showed a delayed rate of blood clearance with delayed excretion of dye into the intestine. Dark green gall bladder bile was obtained by duodenal drainage at 9 months. Transhepatic percutaneous cholangiography and oral cholecystography were normal at 9 and 14 months, respectively.

Seven-day pooled fecal fat studies were performed consecutively between 10 and 13 months, while the patient was on a measured 100-g oral intake of fat. Constant steatorrhea was demonstrated, with a range of 10.2 to 16.8 g of stool...
fat per 24 hr. Small bowel biopsies and aspirations of secretions, obtained as previously reported at 10, 11, and 13 months with a Crosby capsule, showed normal upper jejunal mucosa and sterile cultures. Other studies for malabsorbtion, including urine p-xylose tests, glucose tolerance tests, serum carotene, vitamin A, calcium, and radiographic studies of the gastrointestinal tract and long bones, were normal. Serum amylase and lipase levels were normal.

The patient complained of pruritus for 14 months. Xanthomas of the finger creases, elbows, and buttocks, first noted during the 6th month of his illness, began to fade at 13 months, concomitant with diminution of the jaundice, but those of the palmar creases persisted (fig. 2). The patient was ambulatory after the 1st month of hospitalization. Steroids were not used because of their failure to alter the clinical course in previous patients and because of the negative immunological findings described below.

Liver biopsies. The first biopsy demonstrated moderate centrilobular biliary retention, with intracanalicular bile plugging, accumulation of bile in the parenchymal and Kupffer cells, and focal hepatocellular necrosis (fig. 3). The portal tracts showed moderate infiltration of lymphocytes, histiocytes, occasional eosinophils, and rare plasma cells, consistent with chlorpromazine
hepatitis. Subsequent biopsies revealed progressive intrahepatic bile stasis and enlargement of the periportal spaces with edema, granulocytic infiltration, and stellate fibrosis. Bile duct epithelium remained intact. After 6 months, the portal fibrotic reaction was most marked, with loss of the limiting plates, entrapment of small islands of parenchyma within periportal septa, and many triad-triad bridges with condensation of the reticulum (fig. 4). This biopsy was characteristic of chronic pericholangiolitic hepatitis. Thereafter, bile retention and portal inflammation gradually decreased. Some bridging persisted between portal areas by small delicate strands of fibrous tissue (fig. 5). The last biopsy, at 14½ months, showed a resolving pericholangiolitic hepatitis.

**Immunohistological studies.** A modification of the method of Coons et al. was used for the demonstration of bound globulin. Cryostat tissue sections of liver and small bowel were fixed in acetone and washed for 10 min in Bacto-FA phosphate buffer (Difco Laboratories, Detroit, Mich.), pH 7.2. The sections were covered with fluorescein isothiocyanate-conjugated antisera, washed four times in phosphate buffer, and examined for fluorescence under the ultraviolet microscope. The following antisera (Antibodies Incorporated, Davis, Calif.), conjugated with fluorescein isothiocyanate, were employed: sheep antihuman γ,M-globulin (19 S macroglobulin), rabbit antihuman γ-globulin (7 S γ-globulin), rabbit antihuman fibrinogen (absorbed with human serum), and rabbit antihuman serum albumin. Immunological specificity of the antisera was checked with agar double diffusion and micromethods previously described. In an attempt to demonstrate tissue-specific or antinuclear antibodies,
or both, the patient’s own serum was applied to frozen tissue, followed by fluorescent antihuman γ-globulin. Tissue sections and sera obtained from patients with lupus erythematosus, rheumatoid arthritis, and chronic glomerulonephritis, as well as patients with Laënnec’s cirrhosis, served as positive and negative controls, respectively, with the same technique and identical batches of antisera as utilized in our patient. The fourth and sixth liver biopsy specimens were stained with the aforementioned fluorescein-labeled antisera, and failed to show fluorescence in either the hepatic cytoplasm or nuclei. The patient’s second jejunal mucosal biopsy was similar to control jejunal biopsies, obtained from healthy volunteers, and showed no fluorescence except for a few plasma cells within the lamina propria, normally found in the intestinal mucosa.

Discussion

Although hepatic dysfunction is commonly observed with chlorpromazine therapy, the patient herein presented is only the 11th reported case of chronic chlorpromazine jaundice with xanthomatosis. Since one of these patients developed true cirrhosis, and jaundice had not completely cleared in a number of others at the time of the reports, the prognosis must remain somewhat guarded. Recent immunological studies in primary biliary cirrhosis have demonstrated alterations in the immune mechanism, as manifested by both mitochondrial and cytoplasmic antibodies. The failure to demonstrate bound γ2-globulin (7 S γ-globulin) or γ1M-globulin (19 S macroglobulin) in the liver, and the inability to show elevations of these globulins, antinuclear substances, or rheumatoid factor in the serum of this patient, suggest that an immunological mechanism may not be involved in the pathogenesis of chronic chlorpromazine hepatitis. This conclusion reinforces the observations of Walker et al. who likewise obtained negative immunofluorescent results in three patients with chlorpromazine jaundice of 2 to 14 months’ duration. The
Fig. 4 (top). Third liver biopsy specimen taken 6 months after onset of jaundice. Portal triads show a marked fibrotic reaction, irregular edges with loss of the limiting plate, triad-triad bridging, and extension into adjacent liver lobules. Note intact central vein (arrow) (Masson, × 58).

Fig. 5 (bottom). Fourth liver biopsy specimen taken during 10th month. Portal tracts have become less enlarged but delicate areas of bridging persist (arrow) (Masson, × 70).
absence of an immunohistological mechanism in this disorder is further supported by the rarity of plasma cells in the liver. If this patient’s clinical course remains chronic, it is conceivable that subsequent restudy might demonstrate evidence of altered immune reactivity previously described in primary biliary cirrhosis.

The 6-day period following cessation of chlorpromazine therapy may suggest that acute viral hepatitis was a precipitating factor in the causation of jaundice in our patient. The subsequent clinical and biochemical course makes this possibility exceedingly remote, despite the presence of hepatocellular necrosis with acidophilic bodies, which has also been documented in chlorpromazine hepatitis.\textsuperscript{12, 13}

It is of interest that multiple small bowel biopsies and cultures, performed for the first time in this condition, were normal on the basis of light microscopic, immunohistochemical, and microbiological studies.

**Summary**

A case of chlorpromazine-induced chronic pericholangiolitic hepatitis, simulating the clinical syndrome of xanthomatous biliary cirrhosis, was observed over a 16-month period. Hepatic biopsy tissue tested by immunofluorescence for bound globulin and studies of the patient’s serum for tissue-specific circulating binding substances were negative. Although some cases of primary biliary cirrhosis may be causally related to chlorpromazine, this study suggests that dissimilar mechanisms are probably involved in the pathogenesis of these two diseases.

**REFERENCES**


