Chlorpromazine-induced Vanishing Bile Duct Syndrome Leading to Biliary Cirrhosis

DARIUS MORADPOUR,1* JOSEF ALTORFER,1,4 RENATA FLURY,2 PETER GREMINGER,1 CHRISTA MEYENBERGER,1 RENÉ JOST1 AND MARTIN SCHMID2

Departments of 1 Internal Medicine and 2 Pathology, University Hospital Zurich, CH-8091 Zurich, Switzerland

We describe a 33-yr-old pregnant woman in whom a primary biliary cirrhosis-like syndrome developed after 2 wk of chlorpromazine therapy. The clinical course was characterized by severe jaundice lasting 22 mo, intense pruritus, fever, steatorrhea, high alkaline phosphatase levels and hypercholesterolemia. Jaundice resolved with initiation of ursodeoxycholic acid therapy, but subclinical cholestasis and low-level inflammatory activity persisted and ultimately evolved into biliary cirrhosis. The pathological substrate of this severe and prolonged cholestatic reaction was found to be the vanishing bile duct syndrome with a marked transient pseudoxanthomatosis. (HEPATOLOGY 1994;20:1437-1441.)

Cholestatic jaundice is a well-recognized complication of chlorpromazine therapy. It is observed in about 1% of patients who receive the drug and usually resolves without sequelae 2 to 8 wk after cessation of chlorpromazine administration (1-3). On rare occasions, however, jaundice may persist despite discontinuation of the drug. Thirty patients with severe and prolonged courses of chronic chlorpromazine jaundice resembling PBC have been reported in the literature (4-19). In general, the prognosis of this condition has been regarded as favorable, with jaundice ultimately clearing in most patients. However, progression to cirrhosis has been reported in two cases (13, 19). In this report, we describe a patient with chronic chlorpromazine jaundice in whom biliary cirrhosis developed, with the VBDS being the underlying pathological substrate.

CASE REPORT

A previously healthy 33-yr-old white woman became pregnant for the first time in December 1988. During the sixth week of pregnancy severe vomiting developed that resisted various therapeutic trials. Finally, early in February 1989, she was given chlorpromazine at a dose of 25 mg twice daily. After 2 wk the patient noted dark urine and light-colored stools, and a few days later generalized jaundice developed, accompanied by intense pruritus. Chlorpromazine therapy was stopped after a total dose of 1,000 mg. Laboratory investigations revealed a marked increase of bilirubin, alkaline phosphatase and GGT, whereas the transaminase levels were only moderately increased. Abdominal ultrasound examination showed no abnormalities of the liver or bile ducts. Jaundice persisted throughout the pregnancy. Because of premature labor, pregnancy was terminated in the 28th wk by cesarean section, with birth of female twins. A first liver biopsy was performed at the time of the cesarean section. The specimen showed severe perivenular and midzonal cholestasis with bile plugs and pseudoglands, minimal lymphohistiocytic portal inflammation and infiltration of small bile ducts and minor hepatocellular degenerative changes. Most striking was a severe reduction in the number of bile ducts (Fig. 1). Only 1 of 10 portal tracts contained a bile duct. In addition, we noted marked cholestasis and pseudoxanthomatous transformation of ductular epithelia and hepatocytes in the region of the limiting plate. (Pseudoxanthomatosis relates to the xanthomatosus transformation of epithelial cells, whereas xanthomatosis relates to the xanthomatosus transformation of phagocytes [20].)

Jaundice persisted after delivery, and several therapeutic trials including various types of topical treatments, cholestyrmine, S-adenosylmethionine and phototherapy sessions failed to relieve the pruritus. Concomitant with the administration of prednisone (50 mg daily for 1 wk, then gradual tapering over 3 wk) in August/September 1989, cholestasic laboratory parameters reached a peak, with an alkaline phosphatase level of 4,128 U/L (normal, <32 U/L), GGT of 2,385 U/L (normal, <32 U/L) and cholesterol of 23.1 mmol/L (893 mg/dl).

In October 1989, the patient was referred to our hospital for further investigation and therapeutic evaluation. On admission, we found a deeply jaundiced and emaciated 34-yr-old woman with tormenting pruritus, intermittent fever of more than 39°C, fatigue and steatorrhea. She reported a weight loss of 10 kg since the onset of jaundice. The liver was palpated 3 cm below the right and the spleen 2 cm below the left costal margin. Physical examination otherwise was normal. Erythrocyte sedimentation rate was 100 mm in the first hour and
C-reactive protein 47 mg/L (normal, < 5 mg/L). We detected normochromic anemia of 102 gm/L. The leukocyte count was 16,900/μl without eosinophilia, and the platelet count was 550,000/μl. Total bilirubin was 559 μmol/L (32.7 mg/dl), direct bilirubin 365 μmol/L (21.5 mg/dl), alkaline phosphatase 2,502 U/L (normal, < 115 U/L), GGT 1,116 U/L (normal, < 32 U/L), AST 186 U/L (normal, < 60 U/L), ALT 184 U/L (normal, < 60 U/L) and cholesterol 14.4 mmol/L (557 mg/dl). Prothrombin time, total serum protein, albumin and γ-globulins were normal. Urine was positive for bilirubin and negative for urobilinogen. α1-Antitrypsin and ceruloplasmin levels were mildly increased (7.36 gm/L [normal, 1.90 to 3.50 gm/L] and 727 mg/L [normal, 150 to 600) mg/L]). Antinuclear, anti-native DNA, antimitochondrial and anti-smooth muscle antibodies were not detected. The level of soluble interleukin-2 receptors was increased to 8,880 U/ml (normal, < 477 U/ml). Several blood cultures were negative. Serological tests for hepatitis A and B were positive for anti-hepatitis A virus IgG and HBs antibody as a result of earlier vaccination. Assays for hepatitis C virus antibodies were negative. IgG antibodies against cytomegalovirus and Epstein-Barr virus were detected; IgM antibodies were not. Abdominal ultrasonography revealed an enlarged liver with slightly increased echogenicity. The intrahepatic and extrahepatic bile ducts appeared normal. The spleen was enlarged to 18 cm. Flow in the portal vein was hepatopetal. Endoscopic retrograde cholangiopancreatography showed a normal biliary tree.

A second liver biopsy specimen, obtained 8 mo after the onset of jaundice, revealed increased cholestasis and more pronounced pseudoxanthomatosis, with biliary piecemeal necrosis and incipient perportal fibrosis. Pseudoxanthomatous hepatocytes and xanthomatously transformed Kupffer cells
lined the sinusoids. Bile ducts and ductules were still drastically reduced in number, and ductular proliferation was absent (Fig. 2). Of eight portal tracts, only two contained bile ducts. Clusters of eosinophils were found in several sinusoids.

On the basis of history, laboratory findings and liver biopsy specimens, we diagnosed chronic chlorpromazine jaundice. A medium-chain triglyceride diet and supplementation of fat-soluble vitamins were prescribed. The pruritus proved refractory to various antihistaminics, phenobarbital and six cycles of plasmapheresis. Finally, at the end of March 1990, we initiated a treatment with UDCA, at a dose of 900 mg/day.

In April 1990, 14 mo after the onset of jaundice, a third liver biopsy specimen was obtained. Paucity of bile ducts was still the predominant feature. Bile ducts were detectable in only 3 of 16 portal tracts. Most were transformed into strands of pseudoxanthomatous cells (Fig. 3). These pseudoxanthomatous ductular and liver cell cords were accompanied by marked fibrosis. The lobar architecture was disturbed by periportal fibrosis and incomplete septa formation. We noted an inflammatory infiltrate composed of lymphocytes, histiocytes and eosinophils around pseudoxanthomatous cords and in the portal tracts.

In the ensuing months the laboratory signs of cholestasis gradually decreased, jaundice cleared and the patient regained normal weight. By the end of 1990, she had completely recovered clinically (Fig. 4).

Follow-up examinations revealed persistently increased alkaline phosphatase levels between 150 and 400 U/L (normal, < 115 U/L), levels of transaminases ranging from 40 to 160 U/L (normal, < 60 U/L) and bilirubin values fluctuating around the upper normal limit. Erythrocyte sedimentation rate, C-reactive protein, blood counts and cholesterol returned to normal, but soluble interleukin-2 receptors remained increased in the range of 1,500 to 2,000 U/ml (normal, < 477 U/ml). Prothrombin time, albumin and γ-globulins remained normal throughout the entire observation period. Immunological and serological investigations were repeatedly negative. Hepatomegaly resolved by the end of 1991.

In December 1992, ultrasound examination revealed an irregular liver surface and an inhomogeneous parenchyma, suggestive of cirrhosis. At the same time (i.e., 46 mo after the onset of jaundice and 24 mo after jaundice had ceased), a fourth liver biopsy was performed. The specimen was characterized by fully developed cirrhosis (Fig. 5). Only 5 of 12 portal tracts contained bile ducts. Some degree of ductular proliferation was observed in these portal tracts. Cholestasis was restricted to a few pseudolobules, and pseudoxanthomas were replaced by fibrous connective tissue. The portal tracts were loosely infiltrated by lymphocytes and histiocytes.

**DISCUSSION**

The clinical course of 14 patients with chlorpromazine-induced jaundice lasting more than 6 mo was summarized by Read, Harrison and Sherlock (15). Review of the literature revealed another 16 cases of chronic chlorpromazine jaundice (2, 4-6, 8-12, 14, 16, 17, 19). The similarity of the clinical, laboratory and histological features of these 30 patients suggests chronic chlorpromazine jaundice to be a distinct clinical entity closely resembling PBC.

In the reported cases of chronic chlorpromazine jaundice, jaundice lasted from 6 to 76 mo. The onset most commonly occurred around day 14 of therapy. The reaction did not appear to be dose related. Many patients reported nonspecific prodromal symptoms. Jaundice was accompanied by intense pruritus, which was uniformly reported as the most disturbing symptom. Hepatomegaly was described in most and splenomegaly occurred in many patients. Steatorrhea, pronounced weight loss and xanthomatous skin changes are additional characteristic features of chronic chlorpromazine jaundice. In our patient, fever and the increase of humoral inflammatory parameters were more pronounced than in any other reported patient.

The laboratory findings were highlighted by markedly increased alkaline phosphatase levels and striking hypercholesterolemia, whereas levels of transaminases were only mildly increased.

Liver biopsy specimens revealed the changes reflecting long-lasting cholestasis. Hepatocellular injury was only minor in degree. In the typical case, there was minimal to moderate portal inflammatory infiltrate composed of lymphocytes, polymorphonuclear and some eosinophilic leukocytes. Xanthomatous and pseudoxanthomatous changes, as well as some degree of fibrosis, were often reported with disease progression. A loss of bile ducts was found by Read, Harrison and Sherlock in one of their patients and by Ishak and Irey in their four patients with chronic chlorpromazine jaundice (2, 15). Chlorpromazine hepatotoxicity, therefore, must be considered one of the causes of the VBDS. The VBDS has recently been described as the pathological substrate in several cases of prolonged cholestasis induced by other drugs (21, 22).
The differential diagnosis includes intrahepatic cholestatic syndromes such as PBC, primary sclerosing cholangitis and intrahepatic cholestasis of pregnancy. The onset of chlorpromazine jaundice is more acute (with high initial bilirubin levels) than the more insidious onset of PBC. In the typical case, portal infiltration with lymphocytes and plasma cells, as well as evidence of hepatocellular injury, is more pronounced in PBC (2, 15). Epitheloid cell granulomas, if present, argue in favor of PBC. However, the histopathological differentiation of these two entities can be difficult, and a distinction may only be possible with the presence of antimitochondrial antibodies in over 90% of patients with PBC. Primary sclerosing cholangitis can be ruled out by endoscopic retrograde cholangiopancreatography. The patient with intrahepatic cholestasis of pregnancy is typically seen with increasing pruritus in the third trimester of pregnancy, and in only a few patients does jaundice actually develop. Pruritus usually subsides 1 to 2 days after delivery, whereas jaundice may take 1 to 2 wk to clear (23, 24).

Treatment with steroids was tried in most of the reported cases but did not affect the clinical course in any patient. In our patient, improvement of pruritus and of the biochemical changes reflecting cholestasis, as well as the gradual resolution of jaundice, took place after initiation of a UDCA therapy. However, although the clinical course suggests a causal relationship, temporal coincidence with a spontaneous resolution of jaundice cannot be ruled out.

Read, Harrison and Sherlock suggested that complete clinical recovery ultimately follows in chronic chlorpromazine jaundice and that there is no progression to biliary cirrhosis (15). Indeed, as far as is known, the patients reported in this series recovered completely (Sherlock S, Personal communication, 1994). However, Walker and Combes described a patient who died after
bleeding from esophageal varices after 76 mo of persistent jaundice. Autopsy and earlier needle biopsy of the liver revealed fully developed cirrhosis (19). Also, in a patient described by Myers, cirrhosis developed 5 yr later (13, 19). Unfortunately, information on the ultimate outcome is not available in most other cases. Critical reappraisal of the published cases of chronic chlorpromazine jaundice indicates that even when jaundice cleared, laboratory evidence of continuing liver abnormalities persisted in most. In addition, in most cases there was an inflammatory infiltrate, and some degree of fibrosis persisted in the last biopsy specimen.

Four other patients with chronic chlorpromazine jaundice were pregnant (7, 8, 15, 18), suggesting increased susceptibility to chlorpromazine toxicity during pregnancy.

In conclusion, our clinical observation and sequential histopathological examinations indicate that chlorpromazine can induce a VBDS and ultimately lead to biliary cirrhosis. We therefore believe that the prognosis of chronic chlorpromazine jaundice should be considered more serious than previously thought.

Acknowledgments: We gratefully acknowledge Dr. Hubert E. Blum and Dr. Burton Combes for helpful discussions and critical review of the manuscript.

REFERENCES
