Digestive Diseases and Sciences, Vol. 32, No. 5 (May 1987), pp. 554–557

CASE REPORT

Carbamazepine-Induced Acute Cholangitis

DOMINIQUE LARREY, MD, ANTOINE HADENGUE, MD, DOMINIQUE PESSAYRE, MD, LAURENCE CHOUDAT, MD, CLAUDE DEGOTT, MD, and JEAN-PIERRE BENHAMOU, MD

KEY WORDS: carbamazepine; drug-induced cholangitis; carbamazepine-induced cholangitis; carbamazepine hepatotoxicity.

Carbamazepine, a drug used mainly in the treatment of seizures and trigeminal neuralgia, can induce several adverse reactions including nervous, gastrointestinal, cardiovascular, and skin disorders (1). Carbamazepine has been mainly implicated in two types of liver injury: granulomas and hepatocellular necrosis (2–9). In two reports, granulomas were associated with another type of liver lesion, mild cholangitis (4, 5). In this report, we describe the case of a patient in whom carbamazepine caused severe acute cholangitis without granuloma or hepatocellular necrosis. This liver lesion was associated with marked hypereosinophilia.

CASE REPORT

On June 25, 1984, a 79-year-old woman was admitted for jaundice. She had never received a blood transfusion. She was taking vincamine for several years. From May 2, she was given clobazepam and carbamazepine, 200 mg daily, for facial neuralgia. On June 2, she started complaining of itching. On June 24, she was jaundiced.

On admission, clinical examination was normal, except for jaundice and mild fever. The liver span was 10 cm on the right midclavicular line. Serum bilirubin was 113 μmol/liter; serum alanine aminotransferase, 91 units (normal, 5–45); serum gammaglutamyltransferase, 390 units (normal, 10–40); serum alkaline phosphatase, 25 units (normal, 2–5); white blood cell count, 14 700/mm^3, with 54% eosinophils; HB_s antigen, anti-HB_s, anti-HB_c, and anti-HAV IgM, absent; antibodies to mitochondria, smooth muscle, and endoplasmic reticulum, absent; antibody to nuclei, present at 1:100; serological tests for fascioliasis and echinococcosis, negative. The liver and biliary tract were normal at ultrasonography.

Manuscript received May 2, 1985; revised manuscript received January 23, 1986; accepted April 2, 1986.

From the Unité de Recherches de Physiopathologie Hépatique (INSERM), Service d'Hépatologie, and Service d'Anatomie et de Cytologie Pathologiques, Hôpital Beaujon, Clichy, France.

Address for reprint requests: Dr. D. Larrey, INSERM U 24, Hôpital Beaujon, 92118 Clichy, France.

A percutaneous liver biopsy was performed. Histologic examination showed normal lobular architecture. The lesions predominated in the portal tracts which were infiltrated with abundant mononuclear and polymorphonuclear cells (Figure 1). Ductular proliferation was present in all the portal spaces (Figure 1). The interlobular bile ducts were markedly abnormal; several of them were dilated and/or surrounded with fibrosis; the epithelium of the bile ducts was infiltrated with inflammatory cells; numerous epithelial cells were swollen or necrotic (Figure 2). Marked cholestasis was seen in the centrilobular areas. There were mild lobular inflammatory infiltration and scarce necrotic hepatocytes. Examination of multiple sections at different levels of the liver specimen did not show granuloma.

On the day of admission, all the drugs were interrupted. The clinical manifestations disappeared within two weeks. The liver function tests and blood eosinophils returned to normal within three months (Figure 3). Readministration of vincamine and clobazepam did not interfere with recovery. In December 1985, one year after recovery, there was no evidence of biliary tract disease.

DISCUSSION

Cholestatic jaundice affecting our patient can be ascribed to carbamazepine: (1) There was no past history of disease of the liver or biliary tract. (2) There was no circumstantial or serological argument for viral hepatitis. (3) Test for antimitochondrial antibodies was negative. (4) There was no evidence for fascioliasis or echinococcosis. (5) Obstruction of the common bile duct was improbable: ultrasonography was normal and no disorder suggestive of biliary tract obstruction was observed within the year following the disappearance of jaundice. (6) Vincamine and clobazepam were unlikely to be responsible for liver injury in our patient, since these drugs are not known to be hepatotoxic (10) and their readmission was not followed by a recurrence of jaundice or abnormal liver tests. (7) Jaundice developed eight weeks after the onset of

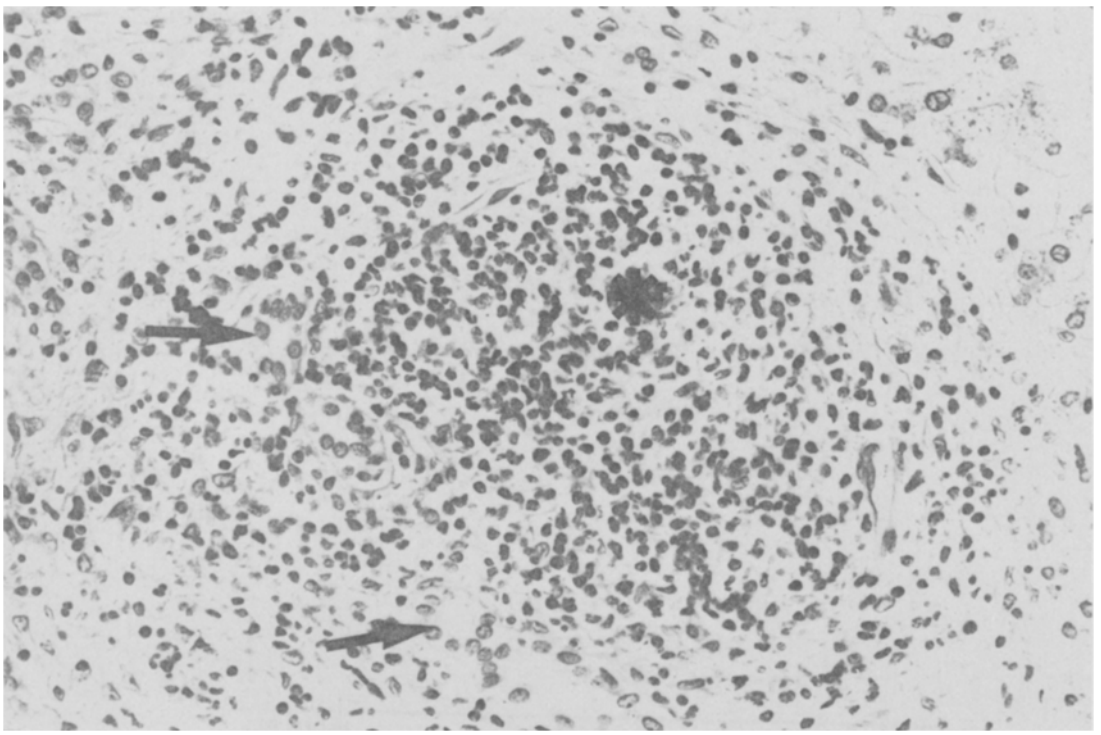

Fig 1. Enlarged portal tract with abundant inflammatory cells (asterisk) and ductular proliferation (arrows). (Hematoxylin and eosin; original magnification, ×650).

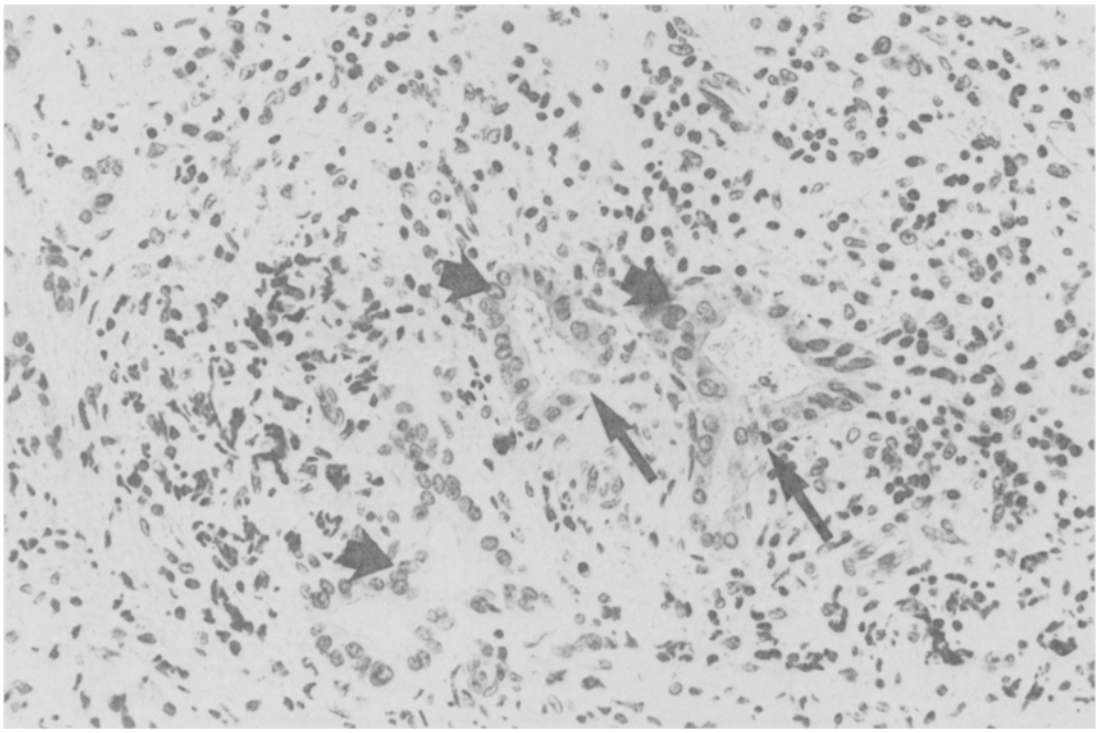

Fig 2. Dilated interlobular bile ducts (large arrows) surrounded with abundant inflammatory cells. Some cells of the biliary epithelium are necrotic (small arrows).

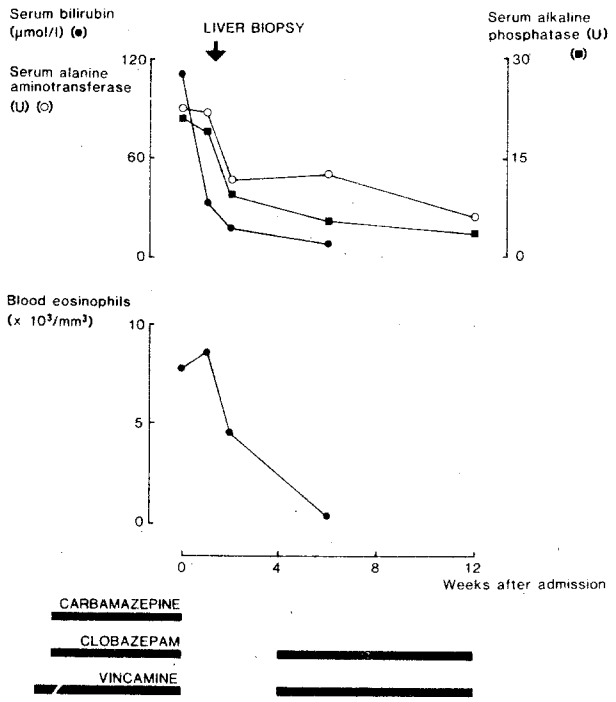

Fig 3. Serum bilirubin, serum alanine aminotransferase (normal, 5–45), serum alkaline phosphatase (normal, 2–5), and blood eosinophils.

carbamazepine administration and promptly disappeared after the withdrawal of the drug.

In the previously reported cases of carbamazepine-induced liver injury, the lesion has consisted of granuloma (2–5), sometimes associated with mild cholangitis (4, 5), or of hepatocellular necrosis (6–9). In our patient, carbamazepine has induced severe acute cholangitis, with scarce necrotic hepatocytes and without granuloma. Drug-induced cholangitis is uncommon and has been described after administration of imipramine (11), phenothiazines (12), haloperidol (13), barbiturates (14), tolbutamide (15), phenytoin (16), and ajmaline (17). It is noteworthy that carbamazepine, imipramine, and phenothiazines have in common a tricyclic ring that might be involved in the toxicity of these drugs to the liver in general and to the intrahepatic small bile ducts in particular.

Hypereosinophilia associated with drug-induced liver injury is usually mild. However, in our patient, blood eosinophils reached 8500/mm^3 and accounted for more than 50% of the blood white cells, a level comparable to that observed in parasitic diseases of the liver (18). This observation suggests that acute cholangitis induced by carbamazepine is caused by an immunoallergic mechanism. This view is further supported by the early recurrence of liver injury after readministration of the drug (2–9).

SUMMARY

We report the case of a patient with carbamazepine-induced cholestasis in whom histologic examination showed acute cholangitis. This type of lesion broadens the spectrum of carbamazepine-induced liver injury which also includes granuloma and hepatocellular necrosis. Its association with marked hypereosinophilia suggests that carbamazepine may cause acute cholangitis through an immunoallergic mechanism.

REFERENCES

1. Rall TW, Schleifer LS: Drugs effective in the therapy of the epilepsies. *In* The Pharmacological Basis of Therapeutics. AG Gilman, LS Goodman, A Gilman (eds). New York, Macmillan, 1980, pp 448–474
2. Knudsen L, Jensen KB: En oversit-og et tilfaelde udlost of carbamazepin (Tegretol). Ugeskr Laeger 141:3160–3163, 1979
3. Levander HG: Granulomatous hepatitis in a patient receiving carbamazepine. Acta Med Scand 208:333–335, 1980
4. Levy M, Goodman MW, Van Dyne BJ, Sumner HW: Granulomatous hepatitis secondary to carbamazepine. Ann Intern Med 95:64–65, 1981
5. Mitchell MC, Boitnott JK, Arregui A, Maddrey WC: Granulomatous hepatitis associated with carbamazepine therapy. Am J Med 71:733–735, 1981
6. Hopen G, Nesthus I, Laerum OD: Fatal carbamazepine-associated hepatitis. Report of two cases. Acta Med Scand 210:333–335, 1981
7. Davion T, Capron JP, Andrejak M, Geoffroy P, Capron-Chivrac D, Quénum C: Hépatite aiguë due à la carbamazépine (Tégrétol). Etude d'un cas et revue de la littérature. Gastroenterol Clin Biol 8:52–56, 1984
8. Zucker P, Daum F, Cohen MI: Fatal carbamazepine hepatitis. J Pediatr 91:667–668, 1977
9. Rigau-Canardo J, Bruguera M, Sese J, Morlans G: Hépatite aiguë cholestatique due à la carbamazépine. Gastroenterol Clin Biol 8:769–770, 1984
10. Zimmerman HJ: Hepatotoxicity. New York, Appleton-Century-Crofts, 1978
11. Short MH, Burns JM, Harris ME: Cholestatic jaundice during imipramine therapy. JAMA 206:1791–1792, 1968
12. Ishak KG, Irey NS: Hepatic injury associated with the phenothiazines. Clinicopathologic and follow-up study of 36 patients. Arch Pathol 93:283–304, 1972
13. Dincsoy HP, Saelinger DA: Haloperidol-induced chronic cholestatic liver disease. Gastroenterology 83:694–700, 1982
14. Pagliaro L, Campesi G, Aguglia F: Barbiturate jaundice. Report of a case due to a barbital-containing drug, with positive rechallenge to phenobarbital. Gastroenterology 56:938–943, 1969
15. Gregory DH, Zaki GF, Sarcosi GA, Carey JB: Chronic

cholestasis following prolonged tolbutamide administration. Associated with destructive cholangitis and cholangiolitis. Arch Pathol 84:194–201, 1967
16. Spechler SJ, Sperber H, Doos WG, Koff RS: Cholestasis and toxic epidermal necrolysis associated with phenytoin sodium ingestion: The role of bile duct injury. Ann Intern Med 95:455–456, 1981
17. Rotmensch HH, Leiser A, Dan M, Klejman A, Livni E, Ilie B, Messer G, Kadish U, Liron M: Evaluation of prajmalium-induced cholestasis by immunologic tests. Arch Intern Med 141:1797–1801, 1981
18. Marcial-Rojas RA, Ramirez-Ronda CH: Parasitic diseases of the liver. *In* Diseases of the Liver. L Schiff, ER Schiff (eds). Philadelphia, Lippincott, 1982, pp 1165–1198