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CASE REPORT

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Bile ductopenia following therapy with sulpiride

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Abstract We report a case of ductopenia associated with cholestatic hepatitis in a 59-year-old woman treated for 41 years for temporal epilepsy. The patient developed jaundice, without any clinical or biochemical features of hypersensitivity, 10 months after the beginning of treatment with sulpiride. Liver biopsy showed ballooning and acidophilic degeneration of the hepatocytes, macrophages packed with lipofuscin, biliary pigment in Kupffer cells, some biliary plugs, confluent necrosis and absence of biliary ducts in all the portal tracts. These features and the presence of foci of cholangiolitis suggest a destructive cholangitis as the pathogenetic mechanism causing ductopenia. Other causes of ductopenia were excluded. Sulpiride is known to produce severe cholestatic jaundice, which we believe is due to ductopenia. The absence of hypersensitivity and the 10-month latency suggest that sulpiride may cause liver damage through a toxic mechanism in genetically susceptible subjects.

Key words Bile duct lesions · Drug · Sulpiride

Introduction

"Ductopenia" defines an hepatic lesion characterized by a decreased number of interlobular and septal bile ducts [10]. It may be caused by immunological, infectious, vascular diseases or may be a congenital malformation [16]. However, a number of cases have been reported which suggest that the disappearance of biliary structures may be induced by drugs, including antibiotics and neuro-psychotropic drugs, but also methyltestosterone, azathioprine and glycyrrhizin [1, 2, 4–9, 11]. Most of these drugs provoke a destructive cholangitis with consequent ductopenia, and in some cases there is progression to biliary cirrhosis [2, 7].

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Recently a case of severe cholestatic jaundice related to therapy with sulpiride (a dibenzodiazepine usually used as an antidepressant and gastrointestinal sedative) was reported, but the liver histology of this patient was not described [12]. Here we describe a case of ductopenia, associated with a pattern of mixed hepatocellular and cholestatic injury, observed in the liver biopsy specimen of a patient who developed jaundice during treatment with sulpiride.

Case report

In December 1993 a 59-year-old woman was admitted to our hospital because of jaundice. The patient had no fever or skin rash. She had no past history of liver or biliary tract diseases, blood transfusions or surgery, and she denied alcohol abuse. From 1952 to December 1992 she had been treated with phenytoin (50 mg/day), phenobarbitone (100 mg/day) and valpromide (600 mg/day) because of temporal epilepsy. From January 1993 the therapy was partially changed by the psychiatrist who prescribed, in addition to phenytoin, sulpiride (100 mg/day) and clordemetyldiazepam (4 mg/day) instead of valpromide and phenobarbitone.

Clinical examination of the patient at admission revealed moderate hepatomegaly and jaundice. Liver biochemistry showed abnormal levels of the following function tests: total bilirubin=18.3 mg/dl (normal 0.20–1 mg/dl), conjugated bilirubin= 10.3 mg/dl (normal 0.1–0.3 mg/dl), aspartate aminotransferase=140 U/l (normal 10–42 U/l), alanine aminotransferase=105 U/l (normal 10–50 U/l), gammaglutamyltranspeptidase=443 U/l (normal 10–50 U/l), alkaline phosphatase=597 U/l (normal 39–117 U/l), lactic dehydrogenase=563 U/l (normal 150–460 U/l), cholesterol=651 mg/dl (normal 130–250 mg/dl). Hepatic protein synthetic activity was normal, as shown by the normal values of serum protein electrophoresis, pseudocholinesterase and prothrombin. Red and white blood cells and platelet counts did not show any abnormality. The level of serum immunoglobulins (IgG, IgA, IgM) was normal. Autoantibodies to mitochondria, nucleus, smooth muscle and microsomes were absent. The patient was negative for serum markers of hepatitis A, B and C viruses (HAV, HBV and HCV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV) tested using standardized commercial kits. The absence of HCV infection was confirmed by failure to detect viral RNA through nested polymerase chain reaction [3].

On ultrasonography the liver of the patient was moderately enlarged and the biliary tract was normal. CT of the abdomen re-

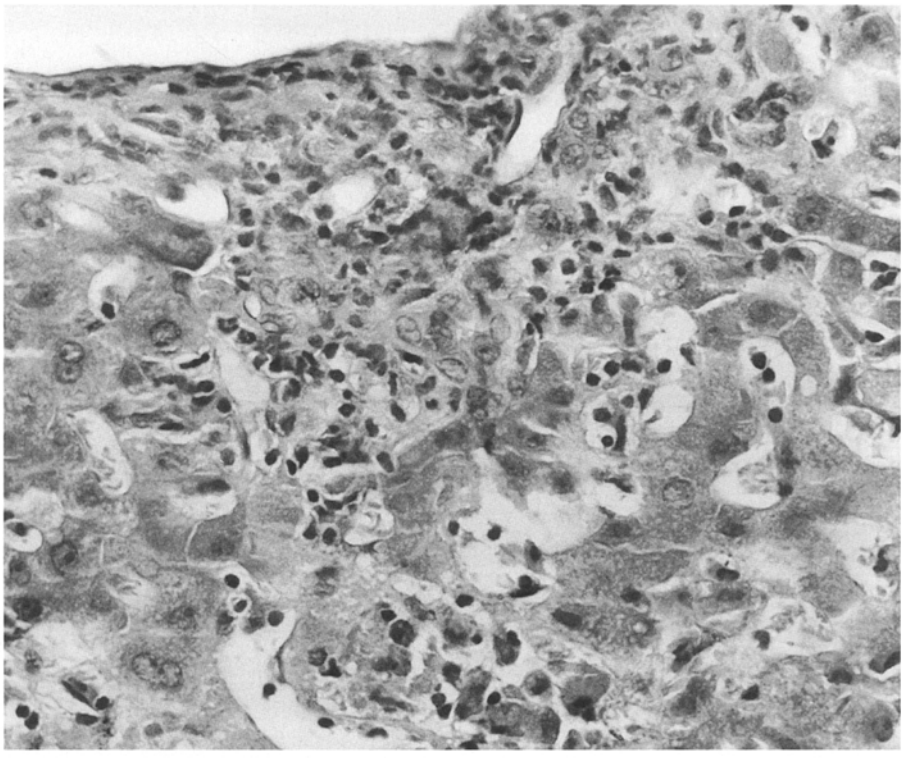

Fig. 1 Neutrophils are intermingled with hepatocytes of zone 1 revealing foci of cholangiolitis. H-E stain, ×500

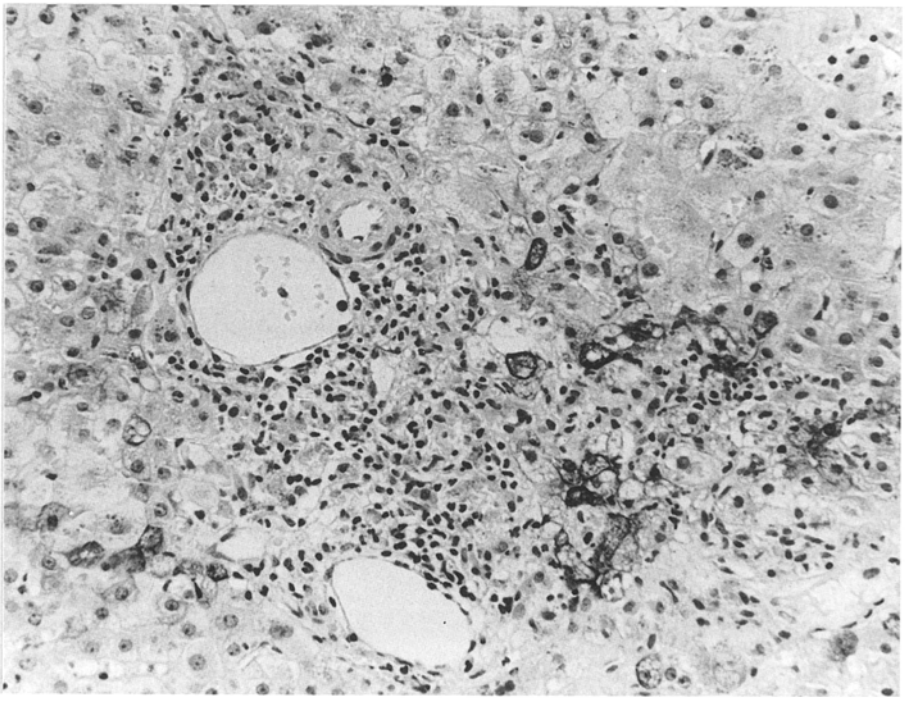

Fig. 2 Immunostaining for cytokeratin 7 reveals the presence of bile duct cells, without any ductular arrangement, at the periphery of the portal tract. Cytokeratin 7, B-SA-AP method, ×170

vealed neither focal lesions in the liver nor strictures or dilatation of bile ducts. Endoscopic retrograde cholangiopancreatography did not show any abnormality.

A percutaneous needle liver biopsy was performed 2 months after the appearance of jaundice (on 10 February 1994). At the histological examination 13 portal tracts were found in the liver specimen and all of them contained many macrophages packed with lipofuscin pigment and a moderate number of eosinophils. A number of neutrophils were observed intermingled with hepatocytes of limiting plate revealing foci of cholangiolitis (Fig. 1). Minimal periportal fibrosis was observed. Few portal tracts were brought closer to centrilobular veins, as the result of previous confluent necrosis. The hepatocytes of zone 1 showed ballooning and acidophilic degeneration. Few acidophilic bodies were present. The same features were also noticed in zone 3 of the acinus, where ballooning of the hepatocytes was evident, associated with accu-

mulation of biliary pigments and lipofuscin in Kupffer cells and some biliary plugs. Immunostaining for cytokeratin 7, a specific marker for bile duct cells [13], revealed the presence of a few positive cells at the periphery of portal tracts without any ductular arrangement (Fig. 2). Therefore, either bile duct or ductular proliferation was absent in all the portal tracts. The content of copper was very low and it appeared only in some periportal hepatocytes, as revealed by the rubeanic acid method.

The clinical-histological data and the exclusion of known aetiological causes of ductopenia led us to make a diagnosis of drug-induced cholestasis. Consequently, the neurological therapy was suspended with the exception of phenobarbitone treatment (100 mg/day). Moreover, therapy with cholestyramine (12 g/day), vitamin K (70 mg/day) and vitamin D (0.25 μg/day) was started. Nevertheless, the jaundice persisted, although the serum bilirubin level slowly decreased to 10 mg/dl.

The patient was discharged from hospital in March 1994 and 6 weeks later, when she came to our outpatient department, she still presented jaundice (serum bilirubin level of 10.6 mg/dl) and reported itching episodes. After 6 more months of follow-up serum bilirubin values reached the level of 19.4 mg/dl, with a level of conjugated bilirubin of 17.0 mg/dl. At the same time the values of serum alkaline phosphatase and gammaglutamyltranspeptidase were also elevated (587 and 344 U/l, respectively), while hepatic protein synthetic activity had not changed. At present the patient is under evaluation for orthotopic liver transplantation.

Discussion

The diagnosis of ductopenia can be made when interlobular and septal bile ducts are absent in at least 50% of the portal tracts examined, according to Ludwig et al. [10]. This percentage is considered meaningful when about 20 portal tracts are observed in one surgical liver biopsy or multiple consecutive needle biopsy specimens [10]. However, we believe that the total absence of bile ducts in 13 portal tracts can be considered sufficient to propose this diagnosis in the case we are reporting. Moreover, ductopenia appears to be confirmed by the observation that cytokeratin 7, which is considered to be a specific marker for duct epithelium [13], was found only in sporadic cells showing no ductular arrangement. In addition, examination of the liver specimen revealed the presence of residual foci of cholangiolitis, suggesting that a destructive cholangitis was responsible for the disappearance of bile ducts. The unexpected failure to detect ductular proliferation could depend on the time when the needle liver biopsy was performed, namely after the destruction of biliary ducts and before the beginning of regenerative events.

Several points have to be considered concerning the aetiology of the ductopenia in our patient. She had no history of liver or biliary tract diseases, primitive biliary cirrhosis was excluded because the test for antimitochondrial antibodies was negative, the level of IgM was normal and no granulomatous cholangitis was observed. There was a normal biliary tract on retrograde cholangiography and absence of concentric fibrosis around bile ducts ruled out the diagnosis of primary sclerosing cholangitis.A diagnosis of "idiopathic adulthood ductopenia" is usually formulated in cases of young adults that have not taken drugs or any other hepatotoxic substances [10], while our patient was a postmenopausal 59-year-old woman with a history of exposure to hepatotoxic drug. Viral infections were excluded because of the negativity of serum markers of all known hepatitis viruses, EBV, CMV and HIV. There were no lesions of the arterial vessels of the bile ducts, which may cause ischaemic necrosis and disappearance of the bile ducts; these are usually consequent to abdominal surgery such as cholecystectomy [16] and the patient had no history of surgery.

These considerations led us to suggest that the ductopenia was a drug-induced event. When jaundice developed, the patient was treated with phenytoin, sulpiride and clordemetyldiazepam. Both phenytoin and sulpiride are known to be capable of inducing severe cholestatic jaundice [7, 12], which has never been reported to be provoked by clordemetyldiazepam. However, long-term therapy with phenytoin cannot be considered the cause of the liver disease in our patient because a latency time of 41 years would be too long for an immunoallergic or toxic mechanism [2, 7, 14]. Consequently, we believe that the 10-month period of treatment with sulpiride was responsible for ductopenia in this case, and this is therefore the first report concerning the type of liver damage induced by such a drug. Nevertheless, the pathogenesis of the bile duct lesions is obscure. Our patient did not show any manifestation of hypersensitivity such as skin rash, eosinophilia, lymphadenopathy, fever or exfoliative dermatitis. Immunoallergic mechanisms can thus be excluded [6, 14, 15]. We suggest that the liver damage was due to a toxic effect consequent to a constitutional inability to normally metabolize sulpiride with accumulation of the drug or formation of toxic metabolites. However, we have to underline that the pathogenetic mechanisms responsible for most of the previously reported cases of drug-induced ductopenia are also unknown. We believe that this case provides evidence that sulpiride may be a hepatotoxic drug able to induce a severe cholestatic jaundice through the destruction of bile ducts.

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