

CASE REPORT

Meropenem-Induced Vanishing Bile Duct Syndrome

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Vanishing bile duct syndrome (VBDS) is a rare and potentially life-threatening disorder in which progressive destruction and disappearance of small intrahepatic bile ducts occur, with resultant cholestasis. The mechanism by which biliary epithelial cells are damaged and intrahepatic bile ducts are lost has not been fully elucidated. However, many etiologies have been reported, and several drugs have been implicated. Meropenem is a widely used, well-tolerated broad-spectrum carbapenem antibiotic indicated for the treatment of intraabdominal infections, complicated skin and skin structure infections, and pediatric bacterial meningitis. We describe what we believe is the first reported case of meropenem-induced VBDS. A 60-year-old woman was diagnosed with VBDS after being treated with meropenem for a left temporal lobe brain abscess. Three weeks after starting the drug, the patient developed mixed hepatocellular and cholestatic liver injury with jaundice and pruritus. Meropenem-induced liver injury was suspected, and the drug was discontinued. Diagnostic tests ruled out other causes of cholestasis, including infectious and immunologic conditions. A liver biopsy, performed due to persistent liver injury, demonstrated an absence of bile ducts, which, in conjunction with the patient's clinical course, was consistent with the diagnosis of VBDS. Several months after the cessation of meropenem, the patient's liver function test results improved. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between the patient's development of VBDS and meropenem therapy. A high index of suspicion is necessary to diagnose VBDS and other types of drug-induced liver injury. Clinicians should consider VBDS as a potential diagnosis in patients receiving meropenem who have prolonged cholestasis, especially after other more probable causes have been excluded.

Key Words: vanishing bile duct syndrome, drug-induced liver injury, cholestasis, meropenem.

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Drug therapy is a frequent cause of hepatic injury. In the United States, more than 50% of acute liver failure cases are secondary to drug-induced liver injury.^{1,2} Hepatocyte damage may occur as a result of a direct toxic effect of the drug or its metabolites in a predictable and dose-related phenomenon. More commonly, however, hepatic injury is unpredictable, idiosyncratic, and independent of dose.¹

Liver injury may be categorized as hepatocellular injury, cholestatic injury, or mixed. With hepatocellular damage, liver enzyme level elevation usually occurs before bilirubin and

alkaline phosphatase levels increase. In cholestatic injury, the bile canicular system is primarily damaged, and increased levels of alkaline phosphatase and bilirubin predominate. Bile is unable to move through the ductal system, leading to accumulation of toxic bile acids, which may result in hepatitis. In one rare type of chronic cholestasis, progressive destruction and subsequent disappearance of the small, intrahepatic bile ducts result in a disorder known as vanishing bile duct syndrome (VBDS).³ The mechanism by which biliary epithelial cells are damaged and intrahepatic bile ducts are lost has

not been fully elucidated. The disorder has several known etiologies, including many pharmacologic agents. We describe what we believe is the first reported case of meropenem-induced VBDS.

Case Report

A 60-year-old woman came to the emergency department after several days of progressive jaundice and pruritus. She denied fever, chills, headache, nausea, vomiting, or abdominal pain. The patient's medical history was significant for type 2 diabetes mellitus, diabetic nephropathy, hypertension, and hyperlipidemia. Her drug therapy consisted of glipizide 5 mg/day, atorvastatin 40 mg/day, telmisartan 80 mg/day, calcium acetate 667 mg 3 times/day, and levetiracetam 250 mg twice/day. She denied taking any herbal or over-the-counter products, and she had no known drug allergies.

Two months earlier, the patient had been hospitalized for a left temporal lobe brain abscess resulting from a complication of otitis media. Levetiracetam had been started for seizure prophylaxis during that hospitalization. Due to negative abscess cultures, a broad-spectrum antibiotic regimen of intravenous vancomycin 1 g twice/day, ceftriaxone 1 g twice/day, and metronidazole 500 mg 3 times/day was initiated. After several weeks, the patient developed presumed antibiotic-induced leukopenia, with a white blood cell count nadir of $2.8 \times 10^3/\text{mm}^3$ (normal range $4\text{--}11 \times 10^3/\text{mm}^3$). At week 5, approximately 3 weeks before the patient developed jaundice and pruritus, the patient's antibiotic regimen was changed to meropenem 1 g twice/day, and the leukopenia resolved over several days. Her cranial surgical site had healed well, and she was discharged, with meropenem to be continued for 4 weeks.

On this visit to the emergency department, the

patient was afebrile and normotensive. Her physical examination was notable for icteric sclera, jaundice, but no hepatosplenomegaly or rash. Initial laboratory data revealed elevated levels of the following: aspartate aminotransferase (AST) 238 I/U (normal range 0–37 U/L), alanine aminotransferase (ALT) 83 U/L (0–40 U/L), alkaline phosphatase 1467 U/L (56–148 U/L), γ -glutamyl transpeptidase (GGT) 230 U/L (7–50 U/L), prothrombin time 15.6 seconds (11.3–14.5 sec), and total and direct bilirubin 11.2 mg/dl (0–1 mg/dl) and 9.9 mg/dl (0–0.3 mg/dl), respectively. In addition, her serum creatinine concentration was elevated but stable at 2.4 mg/dl (0.7–1.5 mg/dl); her complete blood cell count was within normal limits. A hepatic ultrasound revealed a mildly heterogenous liver, with mild intrahepatic biliary ductal dilatation and normal gallbladder. Drug-induced liver injury was suspected, and both meropenem and atorvastatin were discontinued without rechallenge. Cholestyramine 4 g twice/day was started for symptomatic relief of pruritus. The patient remained clinically stable and was discharged after a 3-day hospitalization.

One week later, due to the patient's persistent liver abnormalities, endoscopic retrograde cholangiopancreatography (ERCP) was performed and demonstrated no abnormalities in the bile ducts and gallbladder. A biopsy of the liver was then performed, which showed marked cholestasis, inflammatory cell infiltration of bile ducts, and ductopenia, with the majority of portal tracts having complete absence of bile ducts. The diagnosis of VBDS was made due to the pathologic features on biopsy in combination with negative cholangiographic studies.

Serologic and pathologic evaluation for infectious causes of VBDS including hepatitis B, hepatitis C, cytomegalovirus, and Epstein-Barr virus was negative. In addition, α_1 -antitrypsin deficiency was excluded based on a serum level of 282 mg/dl (normal range 83–199 mg/dl) and a negative genetic screen for α_1 -antitrypsin mutation. Immunologic causes were also excluded, such as primary biliary cirrhosis (negative antimitochondrial antibodies), primary sclerosing cholangitis (lack of characteristic biliary strictures), and autoimmune hepatitis (negative anti-smooth muscle antibodies). Imaging studies were negative for lymphadenopathy or other signs of malignancy. Given the exclusion of other causes of VBDS and the temporal relationship between the start of the antibiotic and the onset of her symptoms, meropenem was

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determined to be the most likely cause.

The patient was treated with ursodiol 900 mg 3 times/day for cholestasis. Her liver function test results gradually improved over several months (Figure 1).

Discussion

Meropenem is an injectable carbapenem antibiotic approved by the United States Food and Drug Administration in 1996 for the treatment of intraabdominal infections, complicated skin and skin structure infections, and pediatric bacterial meningitis. The drug's mechanism of action, like all β -lactam antibiotics, is through inhibition of bacterial cell wall synthesis by binding to penicillin-binding proteins. However, meropenem has superior β -lactamase stability compared with most other β -lactam antibiotics, giving it a broad spectrum of activity. This spectrum includes gram-positive, gram-negative (including susceptible *Pseudomonas aeruginosa*), and anaerobic bacteria.⁴ Meropenem's dosage must be adjusted in patients with renal dysfunction but not in those with impaired liver function. The antibiotic is generally well tolerated, with an adverse-effect profile similar to other β -lactams that includes rash, urticaria, and hypersensitivity reactions.

Several β -lactam antibiotics—amoxicillin-clavulanic acid, ampicillin, and flucloxacillin—have been associated with VBDS,⁵⁻⁷ a severe and potentially life-threatening form of cholestasis;

however, to our knowledge, no reports of meropenem-induced VBDS have been published. Other drugs that have been associated with VBDS include amitriptyline, azathioprine, barbiturates, carbamazepine, chlorothiazide, chlorpromazine, cimetidine, clindamycin, cromolyn sodium, cyproheptadine, diazepam, erythromycin, estradiol, haloperidol, ibuprofen, imipramine, methyltestosterone, norandrostrenolone, phenytoin, prochlorperazine, tetracyclines, thiabendazole, trifluoperazine, tolbutamide, and trimethoprim-sulfamethoxazole.^{3, 8, 9} Non-drug-related causes of VBDS include congenital diseases, neoplastic disorders, and immunologic disorders.

The lack of published reports of carbapenem-induced VBDS may be due to the relatively short duration of time carbapenems have been available compared with older generation β -lactams, which have been in clinical use for several decades. In addition, the increased recognition of VBDS in clinical practice may have contributed to the diagnosis of meropenem-induced VBDS in our patient. Use of the Naranjo adverse drug reaction probability scale indicated a probable relationship (score of 6) between the patient's development of VBDS and meropenem.¹⁰

The patient had received ceftriaxone, a β -lactam antibiotic, during her first hospitalization; however, the drug was used early in the treatment course, discontinued several weeks before the onset of liver enzyme level abnormalities, and has never been associated with VBDS in the

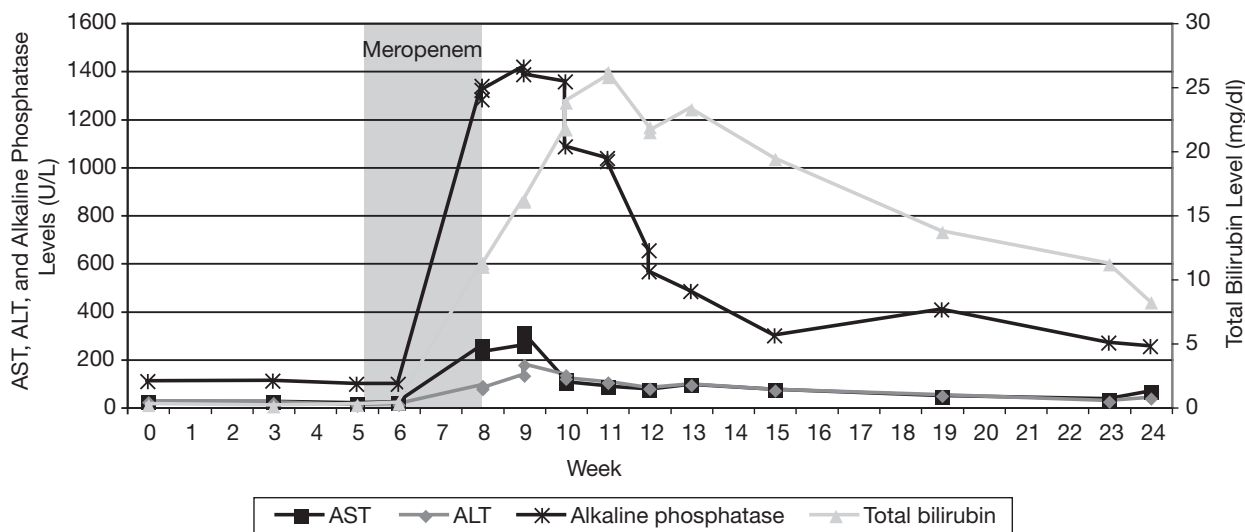


Figure 1. The patient's liver-associated enzyme levels during her hospitalization for brain abscess and 6 months of follow-up. Meropenem was initiated at week 5 and discontinued at week 8 (shaded area). AST = aspartate aminotransferase; ALT = alanine aminotransferase.

literature. In addition, cholestatic liver abnormalities developed shortly after meropenem was started in our patient and gradually improved after cessation of the drug (Figure 1). This is consistent with previous reports of drug-induced liver injury occurring as early as 5 days after initiation of the offending agent.¹ Pathologic evidence of ductopenia, which is the hallmark of VBDS, can be found 10 days after the onset of jaundice.¹¹

Vanishing bile duct syndrome is a diagnosis of exclusion and requires typical pathologic findings by liver biopsy. Extrahepatic biliary obstruction should be ruled out with imaging and/or ERCP. Serologic evaluation should be used to exclude other cholestatic diseases such as primary biliary cirrhosis and primary sclerosing cholangitis. Tests for other causes such as viral and autoimmune hepatitis, sarcoidosis, and malignancy should also be performed. The diagnosis of VBDS is confirmed by liver biopsy when a loss of interlobular or septal bile ducts in greater than 50% of portal tracts is demonstrated.¹²

Patients with VBDS typically present with nausea, jaundice, and pruritus secondary to cholestasis. Constitutional symptoms such as fatigue, weight loss, and abdominal pain have also been reported.⁵ If a drug is suspected, a thorough history of prescription and nonprescription drug exposure is paramount in concordance with cessation of the presumed offending agent. It is important to note, however, that cholestasis and/or bile duct damage may continue despite drug withdrawal, as in our patient. As the patient's condition improves, symptomatic and supportive care should be provided, with serial monitoring of liver function. There is no effective treatment for VBDS; however, cholestyramine and/or anti-histamines may help decrease pruritus secondary to cholestasis.¹³ Ursodeoxycholic acid has been used to provide symptomatic improvement of jaundice, fatigue, pruritus, and hyperbilirubinemia.¹³ There are limited reports using immunosuppressive agents, including corticosteroids, mycophenolate mofetil, and tacrolimus; however, immunosuppression has not been proven effective in treating VBDS and is generally not recommended.^{14, 15}

The prognosis of VBDS is varied, unpredictable, and dependent on the magnitude of bile duct loss and cholestasis as well as on the etiology of the syndrome. Some patients have slow resolution of

biliary epithelial cell damage (regeneration of bile ducts) and cholestasis with clinical recovery over months to years. Some patients may have extensive irreversible bile duct loss, secondary biliary cirrhosis, and hepatic failure, ultimately requiring liver transplantation for survival.¹¹

Conclusion

Vanishing bile duct syndrome is a rare but increasingly recognized disorder involving the progressive destruction of intrahepatic bile ducts. A high index of suspicion is necessary to diagnose VBDS and other types of drug-induced liver injury. Although many drugs, including meropenem and other antibiotics, are generally well tolerated, clinicians should consider the diagnosis of VBDS in patients taking these drugs who have prolonged cholestasis, especially after other more probable causes have been excluded.

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