Mycophenolate mofetil for drug-induced vanishing bile duct syndrome

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CASE REPORT

A 69-year-old man presented with fatigue, upper abdominal discomfort and a pruritic rash involving his torso. He had a history of long-standing and well-controlled polycythemia vera. His medications included aspirin and hydroxyurea, and he drank alcohol sparingly. Three weeks prior to this examination, he had undergone a course of amoxicillin/clavulanate, 875 mg twice daily, for treatment of bronchitis. Physical examination revealed a fine maculopapular rash on his torso. The liver edge was palpable under the costal margin, and was smooth and not tender. No hepatosplenomegaly was noted. Initial laboratory data showed: alkaline phosphatase 624 U/L, aspartate aminotransferase (AST) 89 U/L, alanine aminotransferase (ALT) 82 U/L, total bilirubin 1.6 mg/dL, direct bilirubin 1.0 mg/dL, gamma glutamyl transpeptidase (GGT) 360 U/L, and albumin 3.3 g/dL. Abdominal ultrasound examination showed that the liver had a heterogeneous texture, with normal bile ducts and gallbladder. Over the next 2 weeks, he became jaundiced, with a peak of alkaline phosphatase of 988 U/L, total bilirubin 7.4 mg/dL, direct bilirubin 6.7 mg/dL, AST 235 U/L, and ALT 310 U/L. Prothrombin time (PT) international normalized ratio (INR) remained normal. Autoimmune and viral serologic studies were all negative. Iron studies and alpha-1-antitrypsin levels were within normal ranges. Endoscopic retrograde cholangiography was normal. Liver biopsy, performed 5 mo after

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INTRODUCTION

Acute liver injury caused by amoxicillin/clavulanate occurs in 1.7 cases per 10000 prescriptions written and is mostly of a cholestatic type[3]. Outcomes are usually benign with resolution of cholestasis in 1-4 mo following drug withdrawal[6]. However, some patients develop prolonged drug-induced cholestasis, defined as the persistence of jaundice for more than 6 mo or persistently high alkaline phosphatase and gamma-glutamyl transpeptidase for more than 1 year, despite withdrawal of the causative drug, and in the absence of pre-existing liver or biliary tract disease[3]. Patients who develop progressive destruction of the small interlobular bile ducts (“vanishing bile duct syndrome”) may ultimately require liver transplantation[4,5], given the lack of effective treatment. As an immunological reaction is suspected, corticosteroids have been used empirically[6], although the precise mechanism of amoxicillin/clavulanate-induced cholestatic hepatitis is unknown. We report a case illustrating that mycophenolate mofetil can be a successful and safe alternative to corticosteroids for amoxicillin/clavulanate-induced prolonged cholestasis.

Abstract

Amoxicillin/clavulanate is associated with liver injury, mostly of a cholestatic pattern. While outcomes are usually benign, progression to cirrhosis and death has been reported. The role of immunosuppressive therapy for patients with a protracted course is unclear. We report the case of an elderly patient who developed prolonged cholestasis secondary to amoxicillin/clavulanate. Vanishing bile duct syndrome was confirmed by sequential liver biopsies. The patient responded to prednisone treatment, but could not be weaned off corticosteroids, even when azathioprine was added. Complete withdrawal of both prednisone and azathioprine was possible by using mycophenolate mofetil, an inosine monophosphate dehydrogenase inhibitor. Sustained remission has been maintained for more than 3 years with low-dose mycophenolate mofetil.

Key words: Amoxicillin and clavulanate; Drug-induced cholestasis; Ductopenia; Mycophenolate mofetil; Vanishing bile duct syndrome

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DISCUSSION

About 30 drugs, including amoxicillin/clavulanate, have been reported to cause vanishing bile duct syndrome with protracted clinical courses, the prototype being chlorpromazine\textsuperscript{16}. Ductopenia, when interlobular bile ducts are absent from at least 50\% of the small portal tracts, carries a poor prognosis\textsuperscript{17}. The mechanism of progression from acute liver injury to ductopenia is unclear. However, it is suggested that bile ducts, as complete epithelium-lined tubes, are only rarely reconstructed once they have been completely destroyed\textsuperscript{18}. A patient’s unique immune response likely plays a role in the intensity and duration of injury, as certain HLA haplotypes have been found to be markedly overrepresented in patients who develop drug-induced cholestatic hepatitis\textsuperscript{9,19}.

Our case had the typical characteristics of amoxicillin/clavulanate-induced liver injury. These include advanced age, male sex, a cholestatic pattern of liver injury, delay between cessation of therapy and onset of jaundice, repeatedly negative tests for viral, autoimmune and metabolic diseases, and negative imaging studies\textsuperscript{2,11-14}. Primary biliary cirrhosis and autoimmune cholangiopathy were considered unlikely, given the patient’s age, gender, repeatedly negative serology, and histopathology.

A distinctive feature of our patient was his first liver biopsy that showed destructive cholangiopathy with portal and periportal fibrosis. The second biopsy, obtained 1 year later, revealed persistence of the destructive cholangiopathy but worsening fibrosis, with portoportal bridging and architectural distortion. In our patient, early fibrosis at 5 mo after exposure to amoxicillin/clavulanate may explain the prolonged cholestasis and immunosuppressant dependency. Patients reported complete recovery from prolonged amoxicillin/clavulanate-induced cholestasis did not have fibrosis on liver biopsy\textsuperscript{2,11-14}. By contrast, in Degott’s review of drug-induced cholestasis, all patients with persistent cholestasis had moderate to severe fibrosis\textsuperscript{19}.

Given the small number of patients reported with drug-induced vanishing bile duct syndrome and the unpredictability of its occurrence, there have been no clinical trials of treatment regimens. Short courses of corticosteroids have been used\textsuperscript{16}, based on a suggested immune pathogenesis of drug-induced cholestatic hepatitis. Mycophenolate mofetil, a non-competitive inhibitor of purine synthesis that acts by inhibiting inosine monophosphate dehydrogenase, blocks T- and B-lymphocyte proliferation. Approved for prophylaxis of rejection in solid organ transplantation, it is used against various immune-mediated diseases. Small clinical trials have reported its efficacy as a corticosteroid-sparing agent in autoimmune hepatitis\textsuperscript{16,17}, but it has not been evaluated for use in drug-induced liver disease. Our case illustrates...
that mycophenolate mofetil can be a successful and safe alternative to corticosteroids for drug-induced prolonged cholestasis. Our patient has, at the time of this report, maintained normal liver function for over 3 years on low-dose mycophenolate mofetil, though efforts to withdraw treatment completely resulted in recurrence of mild cholestatic abnormalities.

In summary, we reported a case of severe amoxicillin/clavulanate-induced cholestatic hepatitis that resulted in progressive bile duct destruction and development of bridging fibrosis. Clinical and biochemical resolution was achieved using long-term immunosuppression, initially with prednisone and finally with low-dose mycophenolate mofetil. This suggests that cautious use of immunosuppressive therapy may be of benefit in those rare cases with persistent cholestasis. Further studies are needed to determine if early therapy can prevent irreversible bile duct injury, and to identify patients in whom such therapy is indicated.

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