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LETTERS TO THE EDITOR

EDİTÖRE MEKTUPLAR

Terbinafine induced prolonged cholestasis: Case report and review of the literature

Terbinafine bağlı uzamış kolestaz: Olgu sunumu ve literatürün gözden geçirilmesi

To the Editor,

Terbinafine is a synthetic antimycotic agent of the allylamine class that exhibits potent fungicidal activity and is effective in the treatment of onychomycosis and chronic cutaneous mycosis resistant to other treatments (1). Adverse effects of this drug are infrequent and include mostly mild gastrointestinal symptoms, transient neutropenia, reversible agueusia, and skin reactions, with rare instances of severe erythrodermia (2,3). Terbinafine-induced cholestasis is uncommon. Nine cases of self-limited liver injury (4-12) and a case in whom fulminant hepatic failure developed (13) have been reported to date. We recently observed a case of cholestatic hepatitis induced by terbinafine and which was characterized by a prolonged course.

A 30-year old female patient was admitted to our hospital with jaundice and pruritus in May 1999. She had been prescribed 250 mg oral terbinafine daily for five weeks for the treatment of onychomycosis. She had no history of chronic alcoholism, blood transfusion, recent travel, other medications or previous liver or biliary tract disease. Her physical examination was normal apart from jaundice. Laboratory tests showed the following values: total serum bilirubin: 3.2 mg/dL (conjugated 2.5 mg/dl) (N < 1.0), serum alanine aminotransferase (ALT): 211 IU/L (N <40 IU/L), serum aspartate aminotransferase (AST): 68 IU/L (N < 40 IU/L), gamma-glutamyl-transpeptidase (GGT): 96 IU/L (N < 50 IU/L), alkaline phosphatase: 392 IU/L (N < 279 IU/L). The eosinophil count (200/ mm^3) and prothrombin time were normal. Terbinafine was discontinued. Serologic tests for hepatitis B surface antigen, anti-hepatitis B core IgM, anti-hepatitis B surface antibody, anti-hepatitis A virus IgM, anti-hepatitis C virus antibody, anti-hepatitis E virus antibody, anti-CMV IgM, anti-EBV IgM and anti-HSV 1 and 2 antibodies were negative. Serum HCV RNA detected by polymerase chain reaction was negative, there were no antibodies against mitochondria, microsome, smooth muscle and DNA in the patient's serum and serum ceruloplasmine and alpha-1 antitrypsin values were normal. Abdominal ultrasonography and ERCP were also normal. She became more pruritic and the serum bilirubin value peaked at 20.6 mg/dl during the fifth week after the withdrawal of the drug. A liver biopsy was performed and the liver architecture was found to be intact with hepatocellular and canalicular cholestasis. Portal tracts were marked by mild , mixed cellular infiltrate, including rare eosinophils. Although biliary duct epithelia were reactive, there was no ductopenia. In particular, the centrilobular zone was marked by canalicular

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and intrahepatocytic cholestasis, minimal hepatocyte necrosis and Kupffer cell hyperplasia. There was no periportal or pericellular fibrosis. The cause of liver function abnormalities was considered to be due to terbinafine. Ursedeoxycholic acid (750 mg per day) treatment was commenced for intractable pruritus. Seven weeks after the withdrawal of terbinafine, the patients symptoms began to diminish. Hyperbilirubinemia and liver tests returned to normal values at the 13th and 15th week respectively (Figure 1).

This report describes a case of terbinafine-induced prolonged cholestatic hepatitis. Evidence that terbinafine was the offending agent is as follows: (1) the onset of jaundice five weeks after institution of terbinafine therapy is compatible with drug-induced liver injury; (2) normalization of serum bilirubin and other liver tests within three months of drug withdrawal and (3) exclusion of other causes of liver disease.

Clinically significant hepatotoxicity caused by terbinafine is rare. Trivial elevations of ALT, AST and bilirubin (<1.2 X upper limits of normal) occur in less than 10 % of patients. Elevation of GGT occurs more frequently, but the magnitude of increase is less than 1.5 times the upper limit of normal (2). Our patient represents the tenth reported case of terbinafine induced icteric hepatitis. It was considered that the idiosyncratic effect played a role in the pathogenesis of the terbinafine induced liver injury because of the rarity of these cases. When terbinafine is used at a standard dose (250 mg per day), there is no interaction with cytochrome p-450 system and steroid metabolism (2).

When all cases in the literature were evaluated; jaundice had appeared between weeks two and six of therapy and total serum bilirubin values peaked up to 30 mg/dL three-five weeks later despite discontinuation of therapy. Normalization of liver function tests had taken between two and 12 months. The histopathologic examinations of liver biopsies had shown mostly mixed type hepatitis, both cholestatic and hepatocellular, particularly centrilobular cholestasis (4-12). The paucity of interlobular bile ducts had been reported in only one case (11). Histologic examination of explanted liver revealed panacinar submassive necrosis and nearly complete hepatocyte disapperance with no evidence of chronic liver disease (13). In conclusion, terbinafine-induced toxic hepatitis must be considered in the differential diagnosis of cholestatic hepatitis, despite its rare occurrence.

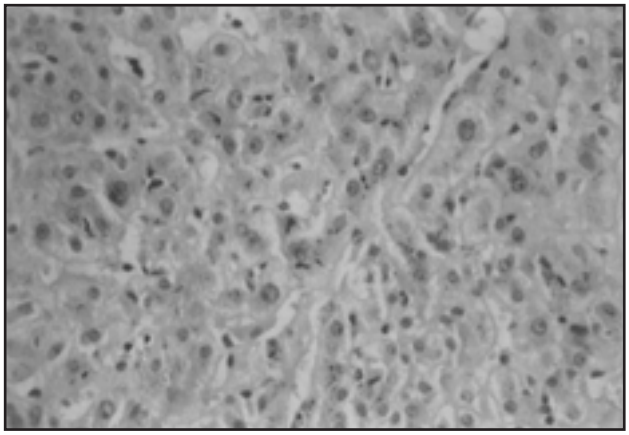

Figure 1. Time course of serum bilirubin, alkaline phosphatase, ALT levels.

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