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Terbinafine-induced cholestatic hepatitis treated with ursodeoxycholic acid: a case report

Ursodeoksikolik asit ile tedavi edilen tebinafine bağlı gelişen kolestatik hepatit: olgu sunumu

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Abstract

Terbinafine is a synthetic antifungal agent commonly used for dermatophytosis, is generally well tolerated, with few adverse effects. Hepatobiliary dysfunction associated with terbinafine has been reported infrequently. We here report a patient who developed severe cholestatic hepatitis following the use of terbinafine. Pruritic symptoms and cholestatic findings of our case were resolved within six weeks after addition of Ursodeoksycholic acid (UDCA). From the review of published cases, predominant pattern of terbinafine-induced hepatic injury has been cholestatic hepatitis whereas the mechanism of hepatic injury still remains unknown. In summary; physicians should remember terbinafine as a causative agent when a patient presents cholestatic symptoms, and UDCA can be a reasonable choice to treat this type of drug-induced hepatitis.

Keywords: Cholestasis, hepatitis, terbinafine, ursodeoxycholic acid

Özet

Terbinafin, dermatofitozda sık kullanılan, yan etkileri az ve genellikle iyi tolere edilen sentetik bir antifungal ajandır. Terbinafine bağlı hepatobiliyer patoloji nadir görülmektedir. Burada terbinafin kullanımından sonra ciddi kolestatik hepatit gelişen bir hasta rapor edilmiştir. Vakamızda kaşıntı şikayetleri ve kolestatik bulgular, ursodeoksikolik asitin (UDCA) tedaviye eklenmesinden sonraki altı hafta içinde düzelmiştir. Tam olarak mekanizması bilinmese de, önceki yayınlanmış vakalar incelendiğinde terbinafine bağlı hepatik hasarın genellikle kolestatik tipte olduğu görülmektedir. Sonuç olarak kolestatik semptomlarla bir hasta başvurduğunda hekimler, bunun terbinafine bağlı olabileceğini ve UDCA'nın bu tip ilaca bağlı hepatitte iyi bir tedavi seçeneği olabileceğini düşünmelidirler.

Anahtar sözcükler: Kolestaz, hepatit, terbinafin, ursodeoxycholic acid

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Introduction

Terbinafine is a synthetic antifungal agent of the allylamine class administered orally or topically, and is effective for the treatment of onycomycosis and dermatophystosis [1]. The drug is generally well tolerated, with few adverse effects [2]. Hepatobiliary dysfunction associated with terbinafine has been reported infrequently [3]. We report a male patient who developed severe cholestatic hepatitis following the use of terbinafine.

Case report

A previously healthy 58 year-old-man was admitted to our clinic because of jaundice and pruritus for two weeks. He was started on terbinafine for tinea corporis about seven weeks before admission. Immediately after concluding one month course of terbinafine treatment he began to experience lassitude, anorexia, nausea-vomiting and dark urine and subsequently developed jaundice and pruritus. He also complained of weight loss. Liver function tests (LFT) before terbinafine treatment were in normal range. When he applied to a local hospital two weeks after cessation of therapy; laboratory tests were as follows: Total serum bilirubin 11.6 mg/dL (conjugated 7.1 mg/dL); serum alanine aminotransferase: 68 U/L; serum aspartate aminotransferase: 58 U/L. Abdominal ultrasound at that hospital showed no abnormality. He had no history of liver disease, risk factors for viral hepatitis, alcohol use or hematological disorders.

On admission to our hospital, the patient did not have encephalopathy and had normal vital signs. He had markedly icteric sclerae but had no stigmata of chronic liver disease. He had neither ascites nor splenomegaly. Laboratory tests (3 weeks after terbinafine discontinuation) showed bilirubin 18.7 mg/dL (conjugated 12.8 mg/dL), alkaline phosphatase (ALP) 488 U/L, AST 58 U/L, ALT 68 U/L, GGT 145 U/L, serum albumin:3.9 g/dL haemoglobin: 13.7 g/dL; white cell count 6000 /mm3 (with no rise in eosinophils); platelet count 332 000/mm3 and prothrombin time (PT) 15.9 s. Serologic tests for viral hepatitis were only positive for antihepatitis A IgG. Tests for acute cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infections were also negative. Anti-smooth muscle antibody and antimitochondrial antibody were negative. Abdominal ultrasound showed neither bile duct dilatation nor any other abnormality. He was given cholestyramine for pruritus. One week later, he was treated with vitamine K for 5 days as his PT was 17.2 s. He did not show prolonged PT after that. However, his bilirubin progressively increased to reach the peak value of 27.5 mg/dL 5 weeks after terbinafine discontinuation. Two weeks later he appealed to another institution and underwent a liver biopsy. Histological analysis showed perivenular cholestasis and active portoparenchymal inflammation. The presence of eosinophils in the portal spaces was also noted. Use of the Naranjo probability scale indicated a probable relationship between terbinafine and cholestatic hepatitis in this patient. Ursodeoksycholic acid (UDCA) and pantoprazole were added to his medication 8 weeks after terbinafine discontinuation. Three weeks later when the patient was admitted to our clinic again, we observed that the patient's pruritus had resolved fully and bilirubin level had decreased to 3 mg/dl. Now, 18 weeks after cessation of terbinafine therapy, bilirubin returned to the normal range whereas ALT level was 49 U/ml, GGT 111 U/L, and ALP 434 U/L. The laboratory parameters in the follow-up period are represented in Table 1.

Table 1. Liver function test values during follow-up period.

Parameters	Weeks after terbinafine discontinuation							
	3rd	4th	5th	6th	7th*	11th	14th	18th
AST (<37 U/L)	58	50	60	69	71	94	40	34
ALT (<40 U/L)	68	53	61	69	77	130	59	49
ALP(<270 U/L)	488	444	508	544		580	699	434
Total bilirubin (<1,2 mg/dL)	18,7	22,5	27,5	24,9	23,3	3	1,35	0,65
Albumin (g/dL)	3,9	3,7	3,7	3,2	3,2	4	4,2	4,4
PT (second)	15,9	17,2	11,7	12,4		12,6		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; PT=prothrombin time; *UDCA was introduced one week after this time, which fits to 8 weeks after terbinafine discontinuation.

Discussion

Terbinafine has the potential to induce cholestatic or mixed cholestatic liver disease and it

may also cause hepatic failure [4]. The mechanism of terbinafine induced hepatic injury remains unknown. Chambers et al [5] reported a case of terbinafine induced cholestatic hepatitis in 2001 and reviewed 16 previous cases. According to this report and another comprehensive review by Ajit et al. [3] most patients with terbinafine associated hepatotoxicity developed symptoms after several weeks of terbinafine administration (the average time of 27 days). Symptoms and LFT's returned to normal after cessation of terbinafine, generally within one to six months. Liver biopsy findings have often included mononuclear cells and eosinophilic inflammatory infiltrates of the portal tracts, and variable cholestatic changes [3,5,6]. Features of our case were consistent with previous reports. Agca et al. [7] reported a case of terbinafine-induced cholestatic hepatitis treated successfully with UDCA. Similar to that case, pruritic symptoms and cholestatic findings of our case were resolved within six weeks after addition of UDCA. In conclusion; terbinafine may cause cholestatic hepatic injury and, UDCA can be a reasonable choice to treat this type of drug-induced hepatitis.

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