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Case Report

Terbinafine hepatotoxicity. A case report and review of literature

Alfonso Javier Zapata Garrido,[1] Alberto Casillas Romo,[1] Francisco Bosques Padilla[2]

Abstract

We report a 53-year old Mexican female who developed liver dysfunction following a seven-day course of treatment with terbinafine for onychomycosis. She presented with jaundice and abdominal pain. Her serum bilirubin levels showed a peak value of 23.2 mg/dL seven weeks after discontinuing the medication. Infectious causes (hepatitis viruses A, B and C) were excluded. Imaging studies of the abdomen did not reveal any abnormalities. Serum iron and ceruloplasmin levels were normal. Autoantibodies were negative. A liver biopsy revealed necrosis and mononuclear infiltration of the parenchyma, mainly along the sinusoids and surrounding the portal spaces and biliary ducts. Eosinophil infiltration of the portal spaces was also noted. Treatment with ursodeoxycholic acid and ademethionine was started. Her liver tests normalized in the sixth months after stopping terbinafine.

Key words: Adverse drug reactions, drug-induced liver disease, hepatitis, terbinafine.

Introduction

Hepatic injury caused by therapeutic medications is an uncommon – but far from rare – occurrence in medical practice. The exact incidence of drug-induced hepatotoxicity is not known, but it has been estimated that serious adverse drug reactions overall are responsible for 4.7% of hospital admissions in the United States. Among all hospitalized patients, 2.1% suffer a serious adverse drug reaction while in hospital, and 0.32% of hospitalized patients (approximately 106,000 in 1994) die because of it, making this the fourth to sixth leading cause of death in hospital.[1] The regulatory drug approval processes of the Food and Drug Administration (FDA) in the United States, and those of similar regulatory agencies in many other countries, keep most highly toxic agents from reaching the market, so that the frequency of hepatotoxicity from any particular drug is generally less than 1% and usually much less. However, there are so many different drugs in use that the aggregate number of cases is significant. Drugs were responsible for 2% to 5% of hospital admissions for jaundice in the United States in the 1970s and for 10% of hospitalized cases of hepatitis in Europe in the 1980s.[2] In New Zealand, over a 21-year period (1974–1994), liver injury represented 4.2% of all reported adverse drug reactions and 7.4% of all fatal drug reactions.[3] In selected groups such as the elderly population, which takes more medications than younger people, this is even more prominent. In patients older than 50 years, drug-induced injury is responsible for more than 40% of cases of acute liver injury,[2] and drug hepatotoxicity causes approximately one half of all cases of fulminant hepatic failure in the United States.[4] Thus, the possibility of drug-induced injury is an important consideration and should be suspected in any patient with unexplained liver disease.

Terbinafine is a synthetic antimycotic agent of the allylamine class that, administered orally, is effective for the treatment of onychomycosis and dermatophytosis.[5] Predominant side effects include gastrointestinal disturbance, mild skin reactions, malaise and lethargy. So far, there have been four reports describing hepatotoxicity associated with the use of this medication.[6] We report a Mexican female who developed liver dysfunction following the use of terbinafine.

Case report

A 53-year old Mexican female was prescribed terbinafine, 250 mg daily, for the treatment of onychomycosis of her toenail. She had no significant past medical history or risk factors for liver disease. At the seventh day of treatment, she presented with constitutional symptoms, progressive jaundice, abdominal pain and dark urine. Initial laboratory evaluation revealed serum γ-glutamyl transferase of 315 IU/L, total bilirubin of 5.8 mg/dL, aspartate aminotransferase of 648 IU/L, alanine aminotransferase of 1272 IU/L and alkaline phosphatase of 154 IU/L. Serolog-

[1] Hospital Christus Muguerza, Monterrey.
[2] Departamento de Medicina Interna y Servicio de Gastroenterología, Hospital Universitario, Universidad Autónoma de Nuevo León. Monterrey, Nuevo León, México.

Address for correspondence:
Francisco Bosques-Padilla MD,
Departamento de Medicina Interna y Servicio de Gastroenterología. Hospital Universitario Dr. J.E. González. UANL. Alejandro Dumas 210, Colinas de San Jerónimo. CP 64630. Monterrey, N.L. México.
E-mail: fbosques58@hotmail.com

Table I. Course of liver function tests after discontinuation of terbinafine.

Day	DB (mg/dL)	IB (mg/dL)	AST (UI/L)	ALT (UI/L)	AP (UI/L)	GGT (UI/L)	PT (sec)	aPTT (sec)
1	3.8	2.0	648.0	1272.0	154.0	315.0		
14	2.9	2.2	575.0	1020.0	146.0		13.6	
21	5.9	3.1	1007.0	1140.0	168.0	416.0	14.8	31.7
24	7.3	4.2	886.0	949.0	135.0	302.0	14.9	35.1
39	11.7	11.5	741.0	520.0	109.0	166.0	13.6	41.0
42	10.0	12.7	517.0	474.0	113.0	166.0	13.0	29.9
45	8.9	6.7	444.0	373.0	101.0	143.0	12.6	31.7
48	5.9	5.4	252.0	263.0	97.0	111.0	14.5	31.7
120	0.2	0.6	40.0	36.0	160.0	26.0		

DB, direct bilirubin; IB, indirect bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; GGT, γ-glutamyl transferase; PT, prothrombin time; aPTT, activated partial thromboplastin time.

ic tests for acute viral hepatitis were only positive for anti-hepatitis A IgG. A computed tomography scan of her abdomen showed no abnormalities. Magnetic resonance imaging of the abdomen was normal. Because of the persistence of symptoms, three weeks after discontinuation of treatment she was admitted to hospital for an ultrasound-guided hepatic biopsy, which revealed histological changes of acute hepatitis, suggestive of a toxic origin. Her laboratory studies on admission are shown in *table I*. A serological test for Epstein-Barr virus was reported as negative. She was voluntarily discharged but was readmitted two weeks later because of progressive jaundice. Serological tests for human immunodeficiency virus, *Toxoplasma* and VDRL were negative. Titers of anti-rubella and anti-cytomegalovirus IgGs were reported as positive and she was referred to our hospital for further management.

On admission, she presented with generalized jaundice and abdominal pain in the upper right quadrant. Magnetic resonance imaging to rule out biliary obstruction showed no abnormalities. Serum iron studies were significant, with a saturation level of 83%. Thyroid function tests were normal. Antinuclear and antimitochondrial antibody tests were negative. IgG antibodies against the Epstein-Barr virus-nuclear antigen and viral capsid were reported as positive. Serum ceruloplasmin level was normal. A detailed examination of the hepatic biopsy revealed significant hepatic damage with a mononuclear inflammatory infiltrate, mainly composed of lymphocytes and plasma cells, along the sinusoids and surrounding the portal spaces and biliary ducts. The presence of eosinophils in the portal spaces was also noted. Neither fibrosis nor a decrease in hepatic glycogen was observed *(Figure 1)*.

Treatment with ursodeoxycholic acid and ademethionine was begun. By the eleventh week after discontinuation of terbinafine, her symptoms showed a marked improvement, with complete normalization of the liver tests by the sixth month.

Discussion

Drug hepatotoxicity can simulate nearly any clinical syndrome or pathologic lesion that can occur in the liver. Consequently, the diagnosis cannot be made on morphologic grounds alone or based on any specific laboratory test. To make a diagnosis of drug-induced liver disease, there must be careful correlation of the history with clinical, laboratory and, if a biopsy has been performed, histologic data. Nevertheless, there are some findings in a liver biopsy that should suggest drug hepatotoxicity and prompt a search for a likely candidate. These include the following: (1) prominent eosinophils in the inflammatory infiltrate; (2) granulomatous hepatitis, with granulomas and hepatitis-like hepatocellular injury; (3) cholestatic hepatitis (i.e., combined hepatocellular and cholestatic injury); (4) severe acute injury with zonal, submassive, or massive hepatic necrosis; and (5) any unusual combination of histologic findings, atypical for any of the common primary liver diseases. None of these findings is specific for drug toxicity, but in a patient having a liver biopsy in a developed country, these are all more frequently seen in drug-induced liver disease than in any other intrinsic inflammatory liver disease.

A complete drug history is of paramount importance, although the fact that the patient was taking a drug does not prove causality. Because injury from any individual agent is uncommon, and because so many drug exposures occur for every actual instance of drug-related injury, every case requires careful analysis before attributing the cause to a specific drug. Several numerical scoring systems have been devised, using combinations of data from the patient's history and laboratory findings to establish the likelihood of a drug-related cause of hepatic injury.[7-11] These scales add or subtract points for important historical items, including issues such as the temporal relationship of the drug exposure to the onset and resolution of injury, the exclusion of other possible causes, the presence of other clinical manifestations, the response to rechallenge (if any) and the presence or absence of a literature precedent. After adding and subtracting points for the various items, a result is obtained; depending on the number of points, the likelihood that the suspected drug was the cause is assessed as definite, probable, possible, unlikely, or excluded. None of these scales, however, uses histologic findings in determining the likelihood of drug-induced hepatotoxicity.

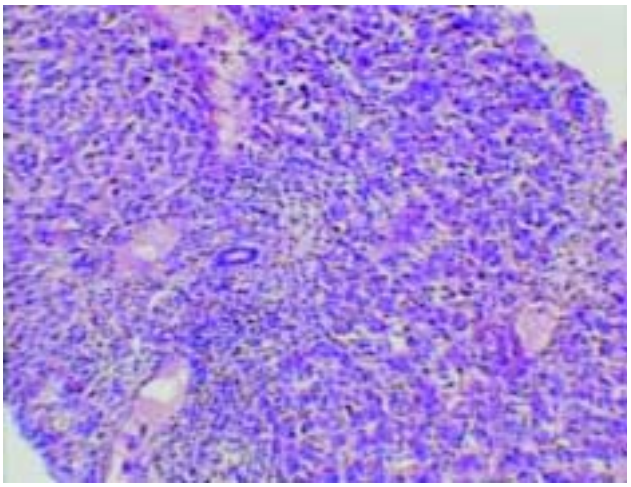

Figure 1A.

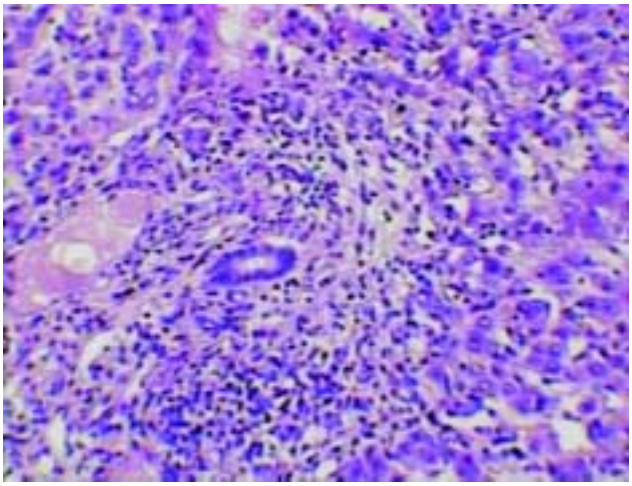

Figure 1B.

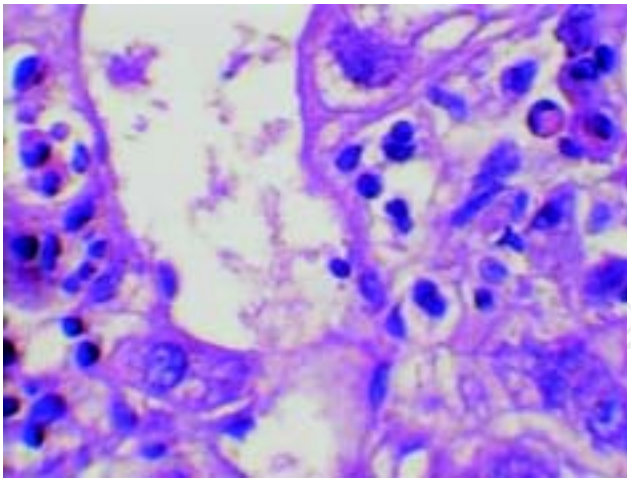

Figure 1C.

Figure 1. Photomicrographs of the liver biopsy. *A.* Photomicrograph showing diffuse hepatocellular and ductal injury, with an inflammatory infiltrate composed mainly of lymphocytes and plasma cells (hematoxylin and eosin, ×5). *B.* Low magnification photomicrograph showing disruption of the hepatic architecture secondary to a lymphocytic infiltrate along the sinusoids and surrounding the portal triad and biliary ducts (hematoxylin and eosin, ×10). *C.* High magnification photomicrograph showing the presence of eosinophils, mainly surrounding the portal space (hematoxylin and eosin, ×40).

This method antedated the clinical scales for more than 20 years. Although it applies many of the same criteria, it has the advantage of incorporating the pattern of tissue injury into the analysis of likelihood of causality. However, because nearly the entire morphologic spectrum of hepatic disorders may be produced by drug administration, evaluation of an adequate clinical history is crucial. The diagnosis can seldom be made by histologic criteria alone. In every instance, the morphologic findings must be correlated with the following:

- A complete drug or chemical history. All exposures must be considered.
- Specific and detailed time-related drug information. It is essential to know exactly when the drug was taken in relation to the signs, symptoms, and laboratory evidence of liver disease.
- The results of the laboratory tests. These are essential in determining the onset, duration, and degree of injury.

Other causes besides the suspected drug need to be carefully considered and excluded if possible. The following should be determined from the history and laboratory studies:

Temporal eligibility. Did the administration of the drug precede the onset of the liver disease by a reasonable time interval (latent period) for that drug? An obvious but often overlooked point is that if the patient was already ill when he or she began taking the suspected drug, then the drug could not have caused the illness. It is also important to recognize that each drug that can cause liver injury does so after a latent period that is characteristic for that drug. In most cases, this period lasts approximately 3 weeks to 3 months, although there are many exceptions. In clinical practice, any drug that has been taken for less than a year should be considered. If a drug has been taken regularly without any problem for years, it is extremely unlikely that it is responsible for a newly recognized injury.

Exclusion of other causes. Other drugs, drug interactions, complications of the underlying disease being treated, or an intercurrent primary liver disease must be excluded by appropriate history and laboratory tests.

Precedent. Any drug that has been in use for sometime will have a record that can be used to assess the likelihood of causality of the suspected injury. Some drugs, like digoxin, have been used for centuries without ever having caused hepatic injury, and others, like hydrochlorothiazide,

have been taken by millions of people with only a few documented cases of hepatotoxicity. Many other drugs are regular causes of liver injury, and, even though the incidence may only be 1 per 1000 exposed individuals (or less), these should be considered as possible causal agents if the patient has a liver injury and the drug is temporally eligible. Also, any newly marketed drugs taken by the patient should be considered, because these will not have a track record. When a list of drugs and dates has been assembled, each drug should be checked for potential hepatotoxicity. The *Physicians' Desk Reference*[14] contains the information required by the FDA described in the product package insert for every drug. It is widely available and has some useful information about many drugs with significant potential for hepatotoxicity; however, for many drugs, abnormal liver tests or "hepatitis" are listed among possible adverse reactions without sufficient elaboration to assess the likelihood of actual causality. Furthermore, drugs that are infrequent causes of liver injury and drugs that have not been marketed for a long time may not be mentioned. Several other more useful books[6,15-17] have lists of drugs and more thorough discussions of their potential hepatotoxicity. Another valuable resource, especially for recent reports and for newly approved drugs, is a search of the Medline-PubMed database of the National Library of Medicine. On the internet browser, type http://www.nchi.nlm.nih.gov/entre2/query.fcgi and click on Medline. From the PubMed search screen, type the name of the drug (generic or brand name), the word "and," and then a term such as "hepatotoxicity," "hepatitis, toxic," or, if these are not productive, simply "liver." You can quickly find whether there are previous case reports of hepatotoxic reactions to any drug.

The pattern of injury produced by each drug tends to be consistent, or at least falls within a defined range. For example, some drugs, such as erythromycin, typically produce cholestatic injury, whereas others, such as isoniazid, are nearly always hepatocellular. The literature search is often helpful in establishing whether the type of injury seen in an individual case is typical or unusual for the suspected drug and will contribute to the assessment of the likelihood of a drug-induced cause.

Dechallenge and rechallenge are very helpful in the final analysis. If the patient recovers after the drug is stopped, the likelihood that the drug was the cause is increased. Lack of recovery does not always exclude the drug, however. In particular, recovery from a cholestatic injury can be very prolonged, sometimes taking a period of months. Deliberate rechallenge is never recommended, because it puts the patient at risk for a more serious injury, but if a drug is inadvertently readministered (eg., before it was suspected as the cause), the prompt return of the injury is an extremely strong evidence that the drug is the causative agent.

Toxicologic analysis of blood, tissue, or other body fluids can establish direct toxicity (overdose or poisoning) in selected cases. However, in most cases, drug hepatotoxicity is caused by idiosyncratic reactions.

After a case has been evaluated in view of the morphology, history, and laboratory studies, it can be classified into one of the following categories, based on the level of certainty that can be achieved:

- Causative. Cases in which toxicologic analysis establishes a drug level in the toxic range.
- Probable. Cases in which the drug is temporally eligible and in which the type of tissue injury is the same as that observed in previous experience with the drug.
- Possible. Cases in which the type of injury can be associated with the drug but in which other factors or possible causes cannot be excluded.
- Coincidental. Cases in which drug-induced disease appears to be most unlikely but cannot be absolutely denied.
- Negative. Cases in which the possibility of a drug injury can be clearly eliminated.

Based on the previous discussion, our conclussion is that this patient had a probable liver injury caused by terbinafine, supported by the following facts:

- The clinical history and laboratory tests could not establish any other cause for the liver injury. The presence of IgG antibodies against hepatitis A virus, rubella virus, citomegalovirus and Epstein-Barr virus only demonstrates previous exposure to these agents, not an active infection.
- There is a consistent temporal elegibility for terbinafine.
- Although reported as rare, hepatotoxicity is an adverse drug reaction of terbinafine.
- The patient showed a cholestatic pattern of liver injury, similar to the drug-related lesions previously reported in the literature.
- Eosinophils were seen in the inflammatory liver infiltrate, a finding consistent with one of the patterns described for drug-related liver injury. Besides, the four patients reported so far showed a similar histological finding, probably related to a hypersensitivity reaction.[5]

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