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Terbinafine induced fulminant hepatic failure and patient death

MohD Ibrahim
ETSU

Omer sheikh
ETSU

Pratyksha Sankhyan
ETSU

Ayah Al Qaryoute
University of North Texas Health Science Center at Fort Worth

Abdulrahman Ibrahim
University of Jordan

See next page for additional authors

Author Names

MohD Ibrahim, Omer sheikh, Pratyksha Sankhyan, Ayah Al Qaryoute, Abdulrahman Ibrahim, Akilesh Mahajan, Nilesh Mahajan, Mohsen Pourmoteza, and Jason Mckinney

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Ibrahim, M[1], Al Sheikh[1], O, Sankhyan, P[1], Mahajan, N[3], Mahajan, A[1], Al Qaryoute,A[4], Pourmorteza, M[5], Mickenny, J[5]

[1] Internal Medicine Department, ETSU, Johnson City, TN

[3] BJ Medical School, Pune, India

[4] University of North Texas, Denton, TX

[5] Division of Gastroenterology, Department of Internal Medicine, Johnson City, TN

Introduction

Fulminant hepatic failure (also called acute hepatic failure) is a disease characterized with acute liver injury, hepatic encephalopathy and elevated prothrombic time/ international normalized ratio (INR). It has a dismal prognosis if left untreated and mandated early clinical intervention and potential liver transplantation in some cases. Among the most common etiologies are infection (e.g. Viral hepatitis), and drug induced (e.g. Acetaminophen). Drug induced liver injury (DILI) is the most common cause of acute liver injury in the United States with higher incidence in women. It can come with various clinical presentation including hepatocellular, cholestatic and mixed ones. Terbinafine is a drug used to treat skin and nails superficial fungal infections. DILI following terbinafine present clinically with hypersensitivity signs including rash, fever and eosinophilia. Here we are presenting a case of a patient with fulminant hepatic failure with patient death.

Case Report

A 72 year-old-patient without known past medical history presented to the hospital with worsening cough, dyspnea on exertion, decreased appetite, weight loss for two months. Prior to admission, he was treated with a 10- day course of levofloxacin and prednisone as a case of bronchitis with minimal improvement. Then he started to develop red urine with marked changes in mental status. On physical examination, the patient had notifiable scleral icterus, confusion and abdominal tenderness in the right upper quadrant.

On admission his labs were significant for alkaline phosphatase 541, aspartate transaminase 557, alanine transaminase 94, total bilirubin 8.6, lactate 11.7.

CT scan of abdomen showed hepatosplenomegaly, mild ascites and trace bilateral pleural effusion. Work up with Viral hepatitis serology, cryptococcal antigen, histoplasma antigen, respiratory virus panel, Epstein Barr virus tests were negative. Anti-nuclear antibodies (ANA) and anti-mitochondrial antibody were also negative. Blood level of amylase, lipase, acetaminophen and alcohol were negative at admission too. The patient was started initially on broad spectrum antibiotics, N-acetyl cysteine empirically and aggressive intravenous fluid hydration. Patient condition rapidly worsened and he developed profound shock requiring mechanical ventilation and started on stress dose steroid and pressor support. Upon further investigation, patient was noted to take terbinafine for toe onychomycosis (day 112). Ferritin level was elevated to 1596 with 93% iron saturation. Ceruloplasmin level was normal. Patient was not a transplant candidate due to multiple organ failure. As per family request, patient was palliatively extubated and died.

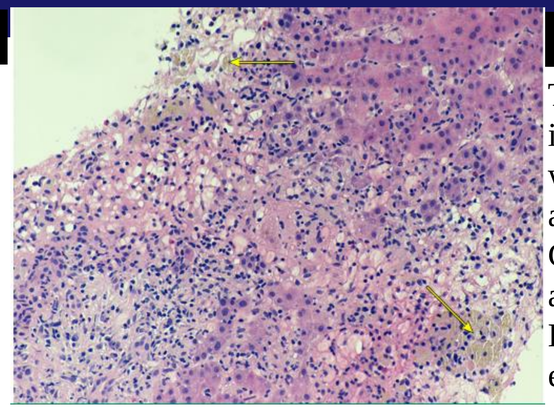
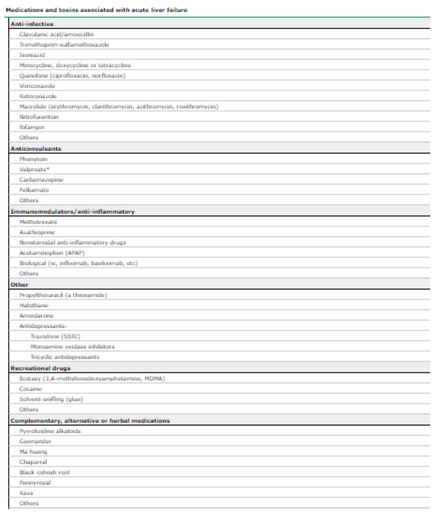


Figure 1: Acute liver failure from DILI. Most of the parenchyma has been destroyed and collapsed (confluent necrosis) with only a few viable hepatocytes remaining. There is a mild infiltrate of inflammatory cells in the areas of necrosis. Arrows point to ceroid-containing macrophages. Source: Uptodate.com



Medications and toxins associated with acute liver failure
Anti-infective
Clavulanic acid/amoxicillin
Trimethoprim-sulfamethoxazole
Isoniazid
Minocycline, doxycycline or tetracycline
Quinolone (ciprofloxacin, norfloxacin)
Voriconazole
Ketoconazole
Macrolide (erythromycin, clarithromycin, azithromycin, roxithromycin)
Nitrofurantoin
Rifampin
Others
Anticonvulsants
Phenytoin
Valproate*
Carbamazepine
Felbamate
Others
Immunomodulators/anti-inflammatory
Methotrexate
Azathioprine
Nonsteroidal anti-inflammatory drugs
Acetaminophen (APAP)
Biological (ie, infliximab, basiliximab, etc)
Others
Other
Propylthiouracil (a thioamide)
Halothane
Amiodarone
Antidepressants:
Trazodone (SSRI)
Monoamine oxidase inhibitors
Tricyclic antidepressants
Recreational drugs
Ecstasy (3,4-methylenedioxyamphetamine, MDMA)
Cocaine
Solvent-sniffing (glue)
Others
Complementary, alternative or herbal medications
Pyrrolizidine alkaloids
Germander
Ma huang
Chaparral
Black cohosh root
Pennyroyal
Kava
Others

Figure 2: Medications associated with acute liver failure. Source: uptodate.com

Discussion

Terbinafine is a fungicidal drug with activity against dermatophytes including Epidermophyton flccosum and trichophyton rubrum. It works by inhibition of squalene epoxidase with a resultant accumulation of squalene in the fungal cell and killing it as a result. Commonly used orally to treat onychomycosis and other fingernails and toenails infections. Shortly after its introduction to the market, DILI had been reported with elevation with serum aminotransferases elevation that was usually self-limited. Usually presents within first 6 weeks of therapy with either hepatocellular or cholestatic initially with sings of hypersensitivity. Mechanism of injury entails hypersensitivity reaction, though the full pathogenesis was not elucidated yet, but genetic polymorphism is implicated in the variable presentation especially among HLA-A 33:01 allele carriers. Terbinafine DILI resolves usually within 6 months of stopping the medication but can lead to death or need liver transplantation in some cases.

Conclusions

DILI is among the most common causes of DILI in the USA and high index of suspicion should be followed when cholestatic features or liver enzymes level start to elevate. Terbinafine DILI is usually self-limited and resolves with minimal sequel but in our case, the patient developed fulminant hepatic failure and died in a short course. Antifungals can be lifesaving but with dangerous side effect profile sometimes. The presence of hemochromatosis in this patient predisposed him to mortality.

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