CASE REPORT

A curious case of cholestasis: oral terbinafine associated with cholestatic jaundice and subsequent erythema nodosum

Kartik Kumar, Anna Gill, Rachelle Shafei, Janine L Wright

North Middlesex University
Hospital NHS Trust, London,
UK

Correspondence to
Dr Janine L Wright,
janine.wright@nhs.net

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SUMMARY

Terbinafine is a commonly prescribed antifungal agent used in the treatment of trichophytic onychomycosis and chronic cutaneous mycosis that are resistant to other treatments. This case report highlights a rarely documented but important adverse hepatic reaction that was caused by the use of oral terbinafine. A woman in her thirties presented with a 3-week history of jaundice, malaise, itching, nausea, decreased appetite, weight loss, dark orange urine and intermittent non-radiating epigastric pain. She had recently finished a 3-week course of oral terbinafine for a fungal nail infection. Liver biopsy findings were consistent with chronic active hepatitis secondary to a drug reaction. A few days after initial presentation, the patient developed erythema nodosum. Delayed development of erythema nodosum secondary to terbinafine could not be excluded.

BACKGROUND

While it is known that terbinafine may rarely cause cholestasis, this case illustrates an unusual delayed presentation with jaundice following cessation of terbinafine treatment. It emphasises the importance of monitoring liver function tests prior to, during and after treatment with terbinafine. The case also highlights the importance of taking a thorough drug history to identify risk factors for cholestasis.

CASE PRESENTATION

A woman in her 30s presented to the accident and emergency department with a 3-week history of malaise, itching, nausea, decreased appetite, weight loss, dark orange urine and intermittent non-radiating epigastric pain. Her pain was alleviated with paracetamol. Her family had noticed yellowing of her sclerae (figure 1).

The patient did not have any comorbidities or history of gastrointestinal disease. Other than paracetamol, she was not taking any regular medications. Social history revealed that the patient did not drink alcohol and that she had travelled to Pakistan 3 months previously.

On examination, the patient was jaundiced and had slight epigastric tenderness. She had no peripheral stigmata of chronic liver disease: there was no evidence of clubbing, palmar erythema, spider naevi or Dupuytren's contracture. She was initially treated with intravenous fluids, simple analgesia, pantoprazole and vitamin K.

She was admitted by the surgical team and investigated for what appeared to be obstructive

jaundice. An ultrasound scan of her abdomen showed no gallstones and the common bile duct was of normal calibre. The gastroenterology team then reviewed the patient and discovered that she had completed a 3-week course of oral terbinafine (250 mg once daily) to treat a fungal nail infection 3 weeks previously. The possibility of acute hepatitis secondary to terbinafine use was considered, but the symptoms were still thought more likely to be due to obstruction.

Three days after admission the patient developed a maculopapular pruritic rash over her arms, thighs and trunk. This was not thought to be due to her cholestatic jaundice. The patient was reviewed by the dermatology team and was treated with topical betamethasone valerate 0.1% cream and topical urea 5% per lauromacrogols 3% combination cream, which is used in the treatment of dermatitis.

A percutaneous liver biopsy was performed.

INVESTIGATIONS

Key admission blood test results included: haemoglobin 113 g/L, white cell count $7.8 \times 10^9/L$, neutrophils $5.9 \times 10^9/L$, international normalised ratio 1.7, aspartate aminotransferase 101 u/L, alanine transaminase 120 u/L, alkaline phosphatase 463 u/L, total bilirubin 146 $\mu\text{mol/L}$, total protein 75 g/L, albumin 45 g/L and C reactive protein 11 mg/L. γ -Glutamyl transpeptidase was measured when the gastroenterology team took over the patient's care 1 week after admission, at which time the level was 75 u/L; at this time the alkaline phosphatase was 551 u/L and the total bilirubin was 199 $\mu\text{mol/L}$. Unconjugated and conjugated split of bilirubin was not performed; however, there was no anaemia, indicating that haemolysis was unlikely. Fasting serum bile acid analysis was not performed. Urine β

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Figure 1 Patient's eye showing scleral icterus.

human chorionic gonadotropin was negative. Abdominal X-ray was normal. An ultrasound scan of the abdomen showed a normal liver and a gallbladder with increased wall thickness but no gallstones. MR cholangiopancreatography (MRCP) also ruled out gallstones and showed no evidence of acute cholecystitis. The intrahepatic duct, common bile duct and pancreatic duct were normal. There were no intraductal stones. Viral and autoimmune screens of the liver were negative.

Liver biopsy showed mild portal inflammation, interface hepatitis, lobular inflammation and Kuppfer cell hyperplasia. Fibrosis Ishak Score was zero. A mild chronic lymphocytic expansion of the portal tracts without eosinophils and moderate cholestasis was present. There was no steatosis. The bile duct calibre was not diminished and there was no bile duct proliferation. There was no ballooning of hepatocytes. Periodic acid-Schiff staining was not performed. Given the absence of viral and other causes, the impression was one of chronic active hepatitis secondary to a drug reaction.

DIFFERENTIAL DIAGNOSIS

There was no history of alcohol consumption and therefore alcoholic hepatitis was ruled out. Viral hepatitis, autoimmune hepatitis and obstructive jaundice were excluded as the viral hepatitis screen, autoimmune hepatitis screen, abdominal ultrasound scan and MRCP were all negative. The main outstanding differential at this point was drug-induced cholestasis.

TREATMENT

The patient's main symptom was pruritus. To alleviate this, multiple topical agents were used: betamethasone valerate 0.1% cream, urea 5% per lauromacrogols 3% combination cream and calamine lotion. Chlorphenamine and cetirizine were given orally as additional treatment for the itching. Lactulose was given to relieve constipation. As the patient was experiencing very poor sleep due to the pruritus, diazepam was given as a sedative and the patient was discharged home. Diazepam was used because it is not possible to discharge patients from our institution on zopiclone or zolpidem.

OUTCOME AND FOLLOW-UP

Five days following the liver biopsy, the patient re-presented to hospital with discrete erythematous, papular and painful skin lesions over her shins. Skin biopsy of the lesions revealed: (1) underlying inflammation in the form of an abscess; and (2) mild septal panniculitis without vasculitis with occasional mast cells. The appearances were consistent with erythema nodosum but the abscess formation brought in the possibility of sepsis. However, she had no other clinical evidence of sepsis. She was well, not feverish and remained an outpatient during this episode.

A thorough history revealed no symptoms of inflammatory bowel disease: there was no diarrhoea, abdominal pain, rectal bleeding or rectal mucus. There were no extraintestinal manifestations of gastrointestinal disease other than erythema nodosum. The patient had no symptoms of tuberculosis: there was no cough, low grade fever, sputum production, night sweats, haemoptysis or weight loss. She had no family contacts or other close contacts with a history of tuberculosis. She was investigated for sarcoidosis and tuberculosis by performing a chest radiograph, which was normal. Serum ACE level was 70 u/L (normal range 16–85 u/L). Inflammatory markers including C reactive protein and erythrocyte sedimentation rate were entirely normal throughout. To treat the erythema nodosum, the patient was

started on oral prednisolone (initially 40 mg once daily for 7 days; reduced by 5 mg/week until 0 mg).

The patient was subsequently reviewed again in the acute medical unit and had regular outpatient repeat blood tests before being seen in the gastroenterology clinic 6 weeks following her initial presentation. The jaundice, pruritus and skin rash had resolved. Liver function tests had normalised; this was associated with the start of steroid therapy. Outpatient investigations for inflammatory bowel disease were arranged: flexible sigmoidoscopy and random colonic biopsy were normal (F-calprotectin levels were not requested).

DISCUSSION

Terbinafine is a synthetic antimycotic agent that has potent fungicidal activity and is effective in the treatment of trichophytic onychomycosis and chronic cutaneous mycosis resistant to other treatments.¹ However terbinafine has infrequently been incriminated in the occurrence of acute liver injury.²

Six case studies have implicated terbinafine in cholestatic liver dysfunction, one of which was severe enough to require liver transplantation.³ Length of terbinafine course varied from 3.5²–4 to 6 weeks.¹ All had used the standard dose of 250 mg once daily. Patient ages ranged from 'young'¹ to 75 years old.² The typical symptoms of terbinafine-induced hepatotoxicity include marked and progressive pruritus, jaundice, malaise and anorexia.²–4,5 Typically, symptom onset is from weeks 3–6 of therapy but may peak after cessation of terbinafine.¹–2,5

Biochemistry

In the current literature, one case reported a peak bilirubin of 718 µmol/L with alkaline phosphatase at 569 µ/L, alanine aminotransferase at 90 U/L and aspartate aminotransferase at 63 µ/L.⁴ However, patients may become symptomatic even at peak bilirubin levels of 525 µmol/L (30.9 mg/dL).⁵ Notably, some biochemistry results indicate that the effects of terbinafine are not exclusively cholestatic. Some derangement of hepatic liver function tests may be observed.² Furthermore peak bilirubin levels have been found even weeks after the cessation of terbinafine and do not correlate with need for transplantation.⁴ Where the synthetic function of the liver is disturbed, the use of vitamin K does not normalise the prothrombin time.⁴

Biopsy

Biopsy findings consistently show evidence of canalicular or centrilobular cholestasis.²–4,6 Cholestasis, under these circumstances, is secondary to either the binding of drugs to the canalicular membrane transporters, defects in transporter proteins or accumulation of toxic bile acids from canalicular pump failure resulting in a cholestatic drug reaction.⁷ In the long term, biopsy may show discrete portal fibrosis and a reduction in the number of interlobular biliary ducts.²

Prognosis

Liver transplant was required in one case study only. Other reports suggest that most patients can expect a full recovery months after interrupted therapy, without sequelae.¹ The time frame for a full biochemical recovery can vary from between 3⁵ and 15 months.⁴ The time frame for complete resolution differed substantially; in particular, anicteric cholestasis persisted for 3 months after biochemical resolution.²

Even where a prolonged recovery was noted, this did not correlate to transplantation requirement.⁴

The mechanism by which problems are thought to occur is through an allylic aldehyde metabolite, likely to be

concentrating in the bile. The metabolite could cause direct toxicity by binding to hepatobiliary proteins and accumulating in the bile. Alternatively, it may modify canalicular proteins and lead to immune-mediated cholestatic dysfunction.⁸

After confirming normal liver function at the onset of terbinafine therapy,⁹ close monitoring of markers of increased hepatocyte turn-over (eg, alanine transaminase, γ -glutamyl transpeptidase, aspartate transaminase) is recommended during treatment with this drug.¹ Early detection of abnormal hepatic function should prompt immediate discontinuation of the drug along with further evaluation.⁹

Treatment is largely supportive. Cholestyramine or ursodeoxycholic acid are used to alleviate pruritus, with rifampicin and opioid antagonists used as second-line agents.¹⁰ Nutritional support is essential for those with prolonged cholestasis, as they are a subgroup of patients who are at risk of developing biliary cirrhosis and liver failure.¹⁰ This should include supplementation of the fat-soluble vitamins: A, D, E and, especially, K.^{11 12}

The remaining questions

The development of erythema nodosum initially raised suspicions that the patient may have been presenting with early symptoms of inflammatory bowel disease or primary sclerosing cholangitis. However, none of the investigations suggested that she had either of these conditions. Tuberculosis and sarcoidosis were also excluded. The erythema nodosum may have been caused by the terbinafine. This was thought to be the case as the

patient's fungal nail infection was no longer symptomatic but the liver biochemistry abnormalities were still active and unresolved; hence the erythema nodosum was thought to be due to the long-standing effects of the terbinafine. It has previously been documented that there is an association between superficial fungal infections and erythema nodosum.^{13 14} It is possible that the erythema nodosum in this patient may have been secondary to unrecognised fungal infection; however, this seemed less likely. The possibility of developing delayed erythema nodosum secondary to terbinafine could not be excluded.

The patient remains well and will continue to receive follow-up in the gastroenterology clinic.

Contributors All authors were involved in managing the described case. All authors had the idea for the article, drafted the manuscript, revised the manuscript for content and approved the version of the manuscript that was submitted for publication. JIW is the guarantor.

Competing interests None.

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Learning points

- ▶ Terbinafine may cause delayed cholestasis.
- ▶ On confirming normal liver function prior to the onset of terbinafine therapy, close monitoring of markers of increased hepatocyte turn-over should be undertaken during and after treatment with this drug.
- ▶ Viral, autoimmune and other iatrogenic causes of cholestasis should be excluded before cholestasis is deemed to be the result of a specific drug agent.
- ▶ When a patient presents with jaundice, it is important to take a detailed drug history and this should include asking for information about drugs that have been stopped in the recent past.

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