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CLINICAL CASE REPORT

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Liver Transplantation in Antituberculosis Drugs-Induced Fulminant Hepatic Failure

A Case Report and Review of the Literature

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Abstract: The antituberculosis drugs isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) usually expose patients to the risk of fulminant hepatic failure (FHF). This report presents a case of liver transplantation in antituberculosis drugs-induced FHF and reviews the relevant literature. A 39-year-old woman with pelvic and salpinx tuberculosis experienced complex pelvic exenteration. After the operation, she was administrated INH, RMP, PZA, and EMB to prevent tuberculosis. Two months later, examination revealed severe FHF and the antituberculosis therapy regimen was changed to ciprofloxacin and streptomycin. Subsequently, urgent orthotopic liver transplantation was performed. Posttransplantation, her serum transaminases improved gradually, but her total bilirubin level and direct bilirubin level continued to worsen, which may have been related to the rejection. However, irreversible damage from antituberulosis drugs was note excluded. Two liver biopsies and histological examinations were performed. One year after transplantation, she died as a consequence of ischemic cholangitis and pulmonary infection. A literature review revealed 9 other published cases of antituberculosis drugs-associated FHF with liver transplantation.

This report suggests that, in most cases of antituberculosis drugs-induced FHF, discontinuation of toxic drugs and orthotopic liver transplantation are always sufficient treatment.

Editor: Giovanni Tarantino.
Received: July 1, 2015; revised: August 11, 2015; accepted: September 1, 2015.
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This work was supported by the National Natural Science Foundation, China (81200094, 81102022); Natural Science Foundation of Guangdong, China (S2012040006228); Foundation for Distinguished Young Talents in Higher Education of Guangdong, China (2012LYM_0004); Young Teachers Cultivation Foundation of Sun Yat-Sen University, China (13 ykpy 33, 14 ykpy20).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001665

(*Medicine* 94(49):e1665)

Abbreviations: ALT = alanine aminotransferase, APTT = activate part plasma prothrombin time, AST = aspartate aminotransferase, EMB = ethambutol, FHF = fulminant hepatic failure, INH = isoniazid, OLT = orthotopic liver transplantation, PT = prothrombin time, PZA = pyrazinamide, RMP = rifampicin, SM = streptomycin, TB = tuberculosis.

INTRODUCTION

Tuberculosis (TB) is 1 of the major causes of death from a curable infectious disease. The United Nations has estimated there were about 9 million new cases of TB in 2013. Together, India and China account for almost 40% of the world's TB cases.[1] The most effective chemotherapy regimen for TB is a combination of isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM). Frequent adverse effects of treatment include hepatotoxicity, skin reactions, gastrointestinal disorder, and neurological disorder.[2] Hepatotoxicity is 1 of the most serious adverse drug reactions associated with anti-TB drugs. However, INH, RMP, and PZA each have hepatotoxic side effects, which increase when the drugs are combined and may limit their use.[3] Here, we report a case of orthotopic liver transplantation (OLT) for anti-TB drugs-induced fulminant hepatic failure (FHF) in China. We additionally present a review of the literature.

METHOD

This was a case report. The Institutional Review Board of the third affiliated hospital, Sun Yat-Sen University, Guangdong, Guangzhou, approved this study. Informed consent was obtained from the patient.

CASE REPORT

In May 2013, a 39-year-old woman was admitted to our hospital outpatient clinic with a 10-day history of fatigue, anorexia, and jaundice. She had no abdominal pain or fever. Her liver tests revealed an aspartate aminotransferase (AST) level of 1414 U/L (normal range, 13–35 U/L), an alanine aminotransferase (ALT) level of 388 U/L (normal range, 3–35 U/L), a total bilirubin level of 9.6 mg/dL (normal range, 0.23–1.40 mg/dL), a direct bilirubin level of 4.8 mg/dL (normal range, 0.0–0.4 mg/dL), and an indirect bilirubin level of 4.79 mg/dL (normal range, 0.15–1.22 mg/dL; Table 1). The patient had a history of pelvic and salpinx TB and experienced complex pelvic exenteration 3 months before her admission. After the operation, anti-TB therapy was started with INH (200 mg/d), RMP (480 mg/d), and PZA (1200 mg/d) prophylaxis for latent TB infection, per her expected course. The

TABLE 1. Record of the Patient's Liver Function From Day 1 to 15 Months After Her Admission to Our Hospital

Time to Admission	ALT, U/L	AST, U/L	TBILI, mg/dL	DBILI, mg/dL	PT, s
Day 1	1414	388	0.6	0.3	70.9
1 mo later	322	156	20.2	7.4	62.4
2 mo later	126	98	41.1	24.7	50.7
3 mo later	83	39	39.0	23.8	30.9
4 mo later	78	33	30.2	19.4	28.8
5 mo later	160	286	5.6	1.6	13.5
6 mo later	55	65	1.2	0.7	13.1
7 mo later	25	33	2.5	1.7	13.6
8 mo later	210	192	2.8	2.1	11.4
9 mo later	60	55	5.7	4.8	13.6
10 mo later	180	109	13.1	10.6	13.8
11 mo later	64	66	16.4	13.0	12
12 mo later	91	104	16.4	13.2	11.6
13 mo later	81	96	18.8	16.0	12.9
14 mo later	131	144	28.0	22.0	13.7
15 mo later	101	37	44.6	31.6	18.2
Normal range	13–35	3–35	0.23–1.40	0–0.4	9.8–13.2

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DBILI = direct bilirubin, PT = prothrombin time, TBILI = total bilirubin.

patient denied any prior history of chronic liver disease. She did not take any special dietary, herbal, or other supplements and did not drink alcohol. Other laboratory data included ammonia (180 μmol/L; normal range, 0.0–54.0 μmol/L), prothrombin time (PT, 70.9 s; normal range, 11.0–14.5 s), and activate part plasma prothrombin time (APTT, 83.4 s; normal range, 28.0–40.0 s). Serologic markers were negative for acute viral hepatitis, Budd–Chiari syndrome, and autoimmune hepatitis.

All of the anti-TB drugs were discontinued because of presumed anti-TB drugs hepatotoxicity. Abdominal ultrasonography revealed an anechoic mass and computed tomography revealed a mildly irregular liver contour. Two months after her admission, she had developed stage II to stage III hepatic encephalopathy and marked deterioration of synthetic liver functions. Her laboratory tests revealed an AST level of 100 U/L, an ALT level of 56 U/L, a total bilirubin level of 51.3 mg/dL, a direct bilirubin level of 30.4 mg/dL, an indirect bilirubin level of 20.9 mg/dL, a PT of 46.4 s, and an APTT of 68.5 s (Table 1). A liver biopsy specimen demonstrated severe destruction of the liver parenchyma with massive hepatic necrosis (Fig. 1). She was administered packed red blood cells, fresh-frozen plasma, platelets, and cryoprecipitate transfusion to correct her coagulopathy, as well as an artificial liver support system to improve her condition. A diagnostic paracentesis yielded fluid that was consistent with spontaneous bacterial peritonitis, and she was given anti-infection treatment.

Despite these measures, the patient experienced worsening encephalopathy, azotemia, and hepatic synthetic dysfunction. OLT was performed 4 months after admission, and its course was uneventful. Immunosuppression was started with low-dose tacrolimus alone because of the presence of active TB. The anti-TB therapy was continued with EMB, moxifloxacin, and SM. Because her laboratory tests revealed elevated liver enzymes, a second liver biopsy was performed 6 months after admission. Histological examination showed that the liver lobule structure was preserved. Hepatocellular cholestasis and granulocyte infiltration around small bile duct were evident (Fig. 2).

The patient's case was complicated by an acute rejection episode that was treated with the temporary intensification of immunosuppression therapy with methylprednisolone and sirolimus (rapamune). However, her situation became much worse and a severe steroid-resistant rejection episode occurred 7 months after admission, a liver biopsy was performed and showed extensive multiacinar collapse with loss of hepatocytes, portal inflammation, and biliary obstruction (Fig. 3). Laboratory test showed further increases in liver enzymes (Table 1). Fifteen months after admission, she died as a consequence of ischemic cholangitis and pulmonary infection.

DISCUSSION

The liver has a central role in drug metabolism and detoxification and is consequently vulnerable to injury. Drug-induced acute liver failure accounts for approximately 20% of acute liver failure in children and a higher percentage of acute liver failure in adults.[4] INH, RMP, and PZA are all widely

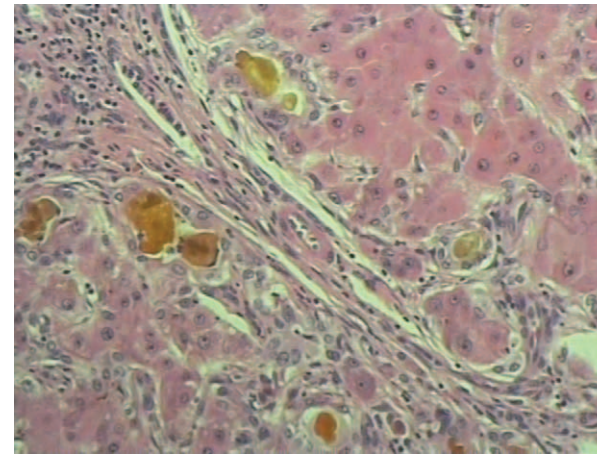

FIGURE 1. Microscopic image of H&E staining for liver tissue demonstrated extensive chronic tissue damage to the liver parenchyma with massive hepatic necrosis, cholestasis, and intrahepatic bile duct proliferation compatible with drug-induced hepatotoxicity (×20).

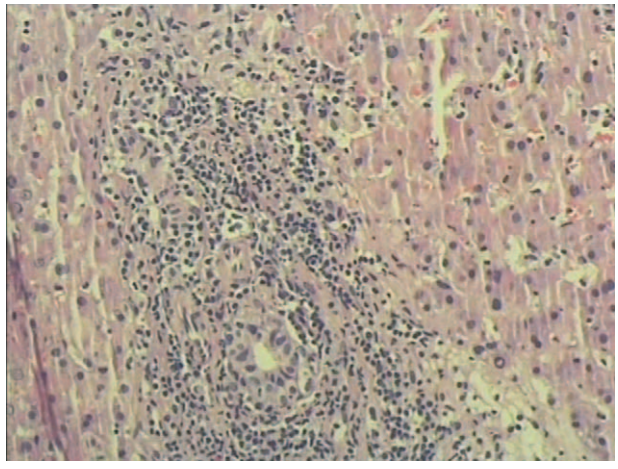

FIGURE 2. Microscopic image of H&E staining for liver tissue demonstrated hepatocyte swelling, cytoplasm rarefaction, spotty necrosis scattering in the hepatic lobule, cholestasis in a small proportion of hepatocytes, and inflammatory cells infiltrating in portal duct areas and the small bile duct (×20).

used as first-line multidrug therapy for TB. Most recent studies have revealed anti-TB INH-induced symptomatic hepatotoxicity with subclinical elevations of serum transaminases rates of 10% to 20%.[4] RMP alone is rarely severely hepatotoxic; however, in combination with INH, its hepatotoxicity occurs earlier and 5% to 8% more frequently than with either medication alone.[5] Although PZA alone is relatively safe, PZA in combination with INH and RMP is significantly associated with higher hepatotoxicity than INH alone.[6] No cases of hepatotoxicity have been described for EMB or SM.[7]

In the present report, we have described a case of acute irreversible FHF following the administration of second-line treatment with anti-TB drugs and OLT, which did not prevent the patient's death. A Medline search of all English-language articles from January 1994 to January 2015 identified 9 reported cases of FHF caused by anti-TB medications in patients who

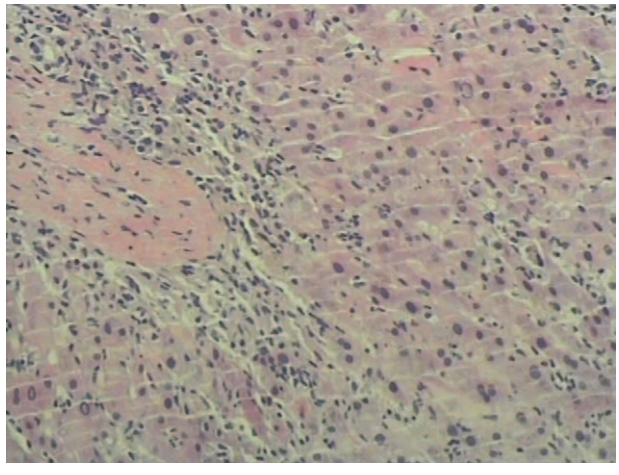

FIGURE 3. Microscopic image of H&E staining for liver tissue demonstrated the hepatic lobule structure and small bile duct were damaged, showing spotty and fragmental necrosis, proliferation of fibrous connective tissue, and inflammatory cells infiltrating in the hepatic sinus and area of tube convergence (×20).

TABLE 2. Clinical Characteristics and Therapeutic Regimen of the 9 Cases Included in the Review

Case	Pretransplant Anti-TB Therapy	Symptoms Leading to SAE Diagnosis	Period to SAE Symptom Onset After Anti-TB Initiation	Posttransplant Anti-TB Therapy	Rejection	Duration of Posttransplant Therapy	Outcome Post transplant
1	INH	Anorexia, epistaxis, jaundice, ascites	4 mo	Not treated	ND	2 y	Survived with liver transplantation
2	INH, RMP, PZA	Laboratory tests	6 wk	SM, EMB, OFX	Cyclosporine and prednisone	4 mo	Survived with liver transplantation
3	INH, RMP, PZA, EMB, CFX	Flu like illness, maculopapular rash, high fevers, nausea, vomiting, dizziness	4 d	Levofloxacin, SM, Amikacin, EMB	Tacrolimus, mycophenolate, and prednisone	4 mo	Survived with liver transplantation
4	EMB, CFX, SM	Jaundice	1 mo	CIP, SM, PZA, EMB	Tacrolimus and mycofenolate	2 y	Survived with liver transplantation
5	INH, RMP, EMB, PZA	Fatigue, malaise, and jaundice	3 d	Cycloserine, CIP, SM, EMB	Tacrolimus and prednisolone	2 y	Survived with liver transplantation
6	INH, RMP, EMB, PZA, CIP, Clarithromycin	Jaundiced	2 wk	Moxifoxacin, SM, EMB	Calcineurin inhibitor, azathioprine, and prednisolone	8 mo	Survived with liver transplantation
7	INH, RMP, PZA	Epigastric pain, weight loss, exhaustion, and mild jaundice with Scleralicterus	1 wk	EMB, CIP, SM	Low-dose tacrolimus, methylprednisolone, antithymocyte globulin, and mycophenolate	18 mo	Survived with liver transplantation
8	INH, RMP, PZA	NA	7 wk	EMB, OFX, SM	Mycophenolate mofetil, tacrolimus, and methylprednisolone	6 mo	Survived with liver transplantation
9	INH	Jaundice, nausea, and fatigue	1 mo	Levofloxacin	Thymoglobulin and tacrolimus	13 d	Survived with liver transplantation

CFX = ciprofloxacin, EMB = ethambutol, INH = isoniazid, NA = not applicable, ND = not done, OFX = ofloxacin, PZA = pyrazinamide, RMP = rifampicin, SAE = serious adverse event, SM = streptomycin, TB = tuberculosis.

received a liver transplant (Table 2).[8–15] Three cases were attributed to INH, RMP, and PZA[9,11,12]; 3 cases were attributed to INH and RMP[8,13,14]; 2 cases were attributed to INH alone[8,15]; and 1 case was attributed to EMB, ciprofloxacin, and SM.[10] The onset of anti-TB induced FHF occurred between 3 days and 4 months after anti-TB treatment. The patients reported prodromes of influenza-like illness, high fevers, anorexia, jaundice, ascites, maculopapular rash, nausea, vomiting, dizziness rash, epistaxis, and abdominal pain, most of which were quickly reversible by withholding the drugs and OLT. The patient described in this manuscript had symptoms of hepatotoxicity 2 months after the initiation of treatment with INH, RMP, PZA, and EMB. The patient's symptoms include fatigue, anorexia, and jaundice. After discontinuing anti-TB drugs and completing OLT, the patient's serum transaminases became normal. Nonetheless, total bilirubin and direct bilirubin levels continues to rise, which may have been related to the rejection, but did not exclude the possibility of irreversible damage from anti-TB drugs.

The exact pathogenesis of the anti-TB induced hepatotoxicity is not well understood. However, some susceptibility of drug-induced liver injury can today be foreseen before drug administration by phenotyping and genotyping studies.[16] Most anti-TB drugs are liposoluble and their elimination requires biotransformation into compounds that are more water soluble. Accordingly, anti-TB drugs-induced hepatotoxicity is not the result of a hypersensitivity or allergic reaction and is most probably caused by toxic metabolites. The hepatic metabolization of INH mainly involves 2 enzymes: N-acetyltransferase 2 (NAT2) and cytochrome P450 2E1. NAT2 acylates INH to acetyl INH, followed by hydrolysation to acetylhydrazine, and cytochrome P450 2E1 contributes to oxidation. Some genetic variants are associated with increased or reduced enzyme activity. Slow acetylators have been associated with a higher risk of anti-TB drugs-induced hepatotoxicity than quick acetylators.[17] Physicians should always consider this adverse effect in the absence of other clear hepatic disease.[16]

The American Thoracic Society, the British Thoracic Society, the Task Force of the European Respiratory Society, the World Health Organization, and the International Union Against Tuberculosis and Lung Disease have all published guidelines for management of drug-induced hepatotoxicity, which remains an exclusion diagnosis based primarily on a detailed history and judicious blood tests, imaging, and liver biopsy. Of the relevant biomarkers, ALT shows the best diagnostic performance for drug-induced hepatotoxicity.[17] The onset of jaundice and the presenting clinical, biochemical, and histological features of anti-TB drugs-induced hepatotoxicity are difficult to distinguish from other forms of hepatitis.[18]

CONCLUSION

For most anti-TB drugs, the relationships between serum concentrations and toxicity had not been established yet. So, monitoring of the anti-TB drugs during treatment is insufficient.[18] Healthcare team members and patients should communicate regularly to help prevent, recognize, and manage drug toxicity.

REFERENCES

1. Elmore K, Nelson R, Gant Z, et al. Data harmonization process for creating the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Atlas. *Public Health Rep.* 2014;129(Suppl 1):63–69.
2. Aziz MA, Wright A. The World Health Organization/International Union Against Tuberculosis and Lung Disease Global Project on Surveillance for Anti-Tuberculosis Drug Resistance: a model for other infectious diseases. *Clin Infect Dis.* 2005;41(Suppl 4):S258–S262.
3. Mitchell I, Wendon J, Fitt S, et al. Anti-tuberculous therapy and acute liver failure. *Lancet.* 1995;345:555–556.
4. Murray KF, Hadzic N, Wirth S, et al. Drug-related hepatotoxicity and acute liver failure. *J Pediatr Gastroenterol Nutr.* 2008;47:395–405.
5. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest.* 1991;99:465–471.
6. Centers for Disease Control and Prevention (CDC), American Thoracic Society. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. *MMWR Morb Mortal Wkly Rep.* 2003;52:735–739.
7. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol.* 2008;23:192–202.
8. Farrell FJ, Keeffe EB, Man KM, et al. Treatment of hepatic failure secondary to isoniazid hepatitis with liver transplantation. *Dig Dis Sci.* 1994;39:2255–2259.
9. Marra F, Cox VC, FitzGerald JM, et al. Successful treatment of multidrug-resistant tuberculosis following drug-induced hepatic necrosis requiring liver transplant. *Int J Tuberc Lung Dis.* 2004;8:905–909.
10. Barcena R, Oton E, Angeles Moreno M, et al. Is liver transplantation advisable for isoniazid fulminant hepatitis in active extrapulmonary tuberculosis? *Am J Transplant.* 2005;5:2796–2798.
11. Idilman R, Ersoz S, Coban S, et al. Antituberculous therapy-induced fulminant hepatic failure: successful treatment with liver transplantation and nonstandard antituberculous therapy. *Liver Transpl.* 2006;12:1427–1430.
12. Nash KL, Yeung TM, Lehner PJ, et al. Orthotopic liver transplantation for subacute hepatic failure following partial treatment of isoniazid-resistant tuberculosis. *Transpl Infect Dis.* 2008;10:272–275.
13. Schneider R, Bercker S, Schubert S, et al. Successful liver transplantation in antituberculosis therapy-induced acute fulminant hepatic failure. *Transplant Proc.* 2009;41:3934–3936.
14. Cramer JP, Lohse AW, Burchard GD, et al. Low N-acetyltransferase 2 activity in isoniazid-associated acute hepatitis requiring liver transplantation. *Transpl Int.* 2010;23:231–233.
15. Sheen E, Huang RJ, Uribe LA, et al. Isoniazid hepatotoxicity requiring liver transplantation. *Dig Dis Sci.* 2014;59:1370–1374.
16. Tarantino GDMM, Capone D. Drug-induced liver injury: is it somehow foreseeable? *World J Gastroenterol.* 2009;15:2817–2833.
17. Bouras T, Pal B, Vaillant F, et al. Notch signaling regulates mammary stem cell function and luminal cell-fate commitment. *Cell Stem Cell.* 2008;3:429–441.
18. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med.* 2006;174:935–952.