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 antituberculosis drugs was not 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.

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. 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. 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. 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, 0.15–1.22 mg/dL; Table 1). Young Teachers Cultivation Foundation of Sun Yat-Sen University, China (13 yky 33, 14 yky20).

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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 388 U/L, a total bilirubin level of 0.6 mg/dL, a direct bilirubin level of 0.3 mg/dL, a PT of 70.9 s, and an APTT of 11.4 s. 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. Imunosuppression 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 ducts 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.3 INH, RMP, and PZA are all widely

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**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        | 12.0 |
| 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.

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**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).
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%. 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. Although PZA alone is relatively safe, PZA in combination with INH or RMP is significantly associated with higher hepatotoxicity than INH alone. No cases of hepatotoxicity have been described for EMB or SM.

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. Table 2 summarizes the clinical characteristics, therapeutic regimens, and outcomes of the 9 cases included in the review.

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

| Case | Pretransplant Anti-TB Therapy | Symptoms Leading to SAE Diagnosis | Period to SAE Symptom Onset | Posttransplant Anti-TB Therapy | Rejection | Duration of Posttransplant Therapy | Outcome Post transplant |
|------|------------------------------|----------------------------------|----------------------------|-------------------------------|-----------|-----------------------------------|------------------------|
| 1    | INH                          | Anorexia, epistaxis, jaundice, acites | 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                       | Levofoxacin, 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 mycophenolate | 2 y                           | Survived with liver transplantation |
| 5    | INH, RMP, EMB, PZA, CIP, Clarithromycin | Fatigue, malaise, and jaundice | 3 d                       | Cyclosporine, CIP, SM, EMB   | Tacrolimus and prednisolone  | 2 y                           | Survived with liver transplantation |
| 6    | INH, RMP, EMB, PZA, CIP, Clarithromycin | Jaundice | 2 wk | Moxifloxacin, SM, EMB | Calcium inhibiter, azathiope, and prednisolone | 8 mo                          | Survived with liver transplantation |
| 7    | INH, RMP, PZA                | Epigastric pain, weight loss, exhaustion, and mild jaundice with Scleroderma | 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, RMP, PZA                | Jaundice, nausea, and fatigue     | 1 mo                      | Levofoxacin                  | 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 PZA9,11,12; 3 cases were attributed to INH and RMP8,13,14; 2 cases were attributed to INH alone8,15; 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, malaculopapular 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 continue 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 hepatoxicity 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 metabolism of INH mainly involves 2 enzymes: N-acetyltransferase 2 (NAT2) and cytochrome P450 2E1. NAT2 acylates INH to acetyl INH, followed by hydrolysisation to acetylhydrazine, and cytochrome P450 2E1 contributes to oxidation. Some genetic variants are associated with increased or reduced enzyme activity. Slow acetylators have been shown to have 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.15 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.16 Healthcare team members and patients should communicate regularly to help prevent, recognize, and manage drug toxicity.

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