

# Skin and Lung Tuberculosis and Anti Tuberculosis Drug Liver Injury (ATLI)

I Ketut Kwartantaya Winaya<sup>1</sup>, I Made Suma Wirawan<sup>2</sup>

<sup>1</sup>Postgraduate Student of Doctoral Program, of Udayana University, Denpasar, Bali, Indonesia

<sup>2</sup>Postgraduate Student of Doctoral Program, of Udayana University, Denpasar, Bali, Indonesia

**Abstract:** *Female, 57 years old with tuberculosis on the lung and skin lesion, came to hospital with chief of complaint nausea, and vomiting after taking an oral antituberculosis for one month. Patient with lung tuberculosis and extrapulmonary (skin tuberculosis) but unknown liver cirrhotic before oral antituberculosis treatment. Laboratory results revealed increased AST, ALT, total bilirubin and decreased liver function. Patient diagnosed with skin and lung tuberculosis and anti Tuberculosis drug Liver Injury (ATLI). We do reintroducing of antituberculosis as protocol with observation of liver function test carefully.*

**Keywords:** antituberculosis, liver injury, ATLI, extrapulmonary tuberculosis

## 1. Background

Indonesia included as number two in six countries accounted for 60% of the global total between India, China, Nigeria, Pakistan, and South Africa. The total TB incidence in Indonesia is 395 (255 – 564) /100,000 with mortality rate of 40 (26-57) / 100.000 in HIV-negative TB group and 10 (7.6 – 13) / 100.000 in HIV-positive TB group.<sup>1</sup>Cutaneous tuberculosis was a major public health problem in the nineteenth and early twentieth centuries. With the improvement of hygiene habits in the general population, the improvement of living standards, the use of the BCG vaccine, and the introduction of effective chemotherapy, there was a significant decrease in the number of cases. From the midtwentieth century onwards, there was a resurgence of the disease with the main causes being the increased incidence of HIV-positive patients, the emergence of multidrug-resistant tuberculosis and the growing number of patients receiving immunosuppressive treatment. About 14% of the affected, corresponding to just over 10,000 patients, present extra-pulmonary forms. When it is assumed that 1-2% of those with extra-pulmonary forms have cutaneous involvement, one can estimate about 100 to 200 new cases of cutaneous tuberculosis per year in Brazil.<sup>2</sup> As with TB of other organs, treatment of cutaneous tuberculosis (CTB) requires a 4 drug chemotherapeutic regimen that usually consist of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), and Streptomycin (S) as the first line anti TB drug. Despite of the effectiveness of these drugs, they are known to induce various side effects, including liver injury, skin reactions, gastrointestinal, and neurological disorders.<sup>2</sup> The incidence of anti tuberculosis drug liver injury (ATLI) during standard multi-drug TB treatment has been reported varying from 3.0% - 34.14%.<sup>3-4</sup> ATLI incidence in Saiful Anwar Hospital Malang, Indonesia reported in 5.4% patients.<sup>3-5</sup>

Patient with liver cirrhosis have immune dysfunction with relative derangements of cell mediated immunity. There is reticuloendothelial system dysfunction, with reduced monocyte spreading, chemotaxis, bacterial phagocytosis, and bacterial killing.<sup>6</sup>Baijalet *al* found that the prevalence of tuberculosis in patients with liver cirrhosis was fifteen times

higher than in the general population in Mumbai, Western India.<sup>7</sup>

In this case, we report a case of liver function derangement caused by drug induced in skin and lung TB patient admitted in Wangaya General Hospital Denpasar, Bali.

## 2. Case Presentation

A 55 years old, female, admitted in Wangaya General Hospital with complains of nausea, vomiting, fatigue, yellowish skin since 5 days prior to admission. Loss of appetite was also complained. She had dark urine and pale stools within 3 days. Fever, muscle aches, or any history of melena were denied. She had loss of weight in one last month about 15 kilograms. Past history of jaundice is denied. There is no seizure and focal neurological deficit. She diagnosed with pulmonary tuberculosis so he was on the first month of intensive phase of antituberculosis treatment (ATT) in fixed drug combination form (Isoniazid (INH) 300 mg, Rifampicin (RIF) 600 mg, Pirazinamid (PZA) 1600 mg, and Ethambutol (EMB) 1100 mg).

On physical examination, she has shortened attention span, hypersomnia, lack of awareness, mild confusion, and looked very weak. Vital signs were in normal range. Her body was thin and malnourished with yellowish coloured skin. Both of sclera and anterior part of tongue were icteric. He felt pain on palpation on right hypochondriac and epigastric area of abdomen. There was slight hepatomegaly, but no splenomegaly is found. Cardiac and pulmonary examination were sound. Peripheral edema and asterixis were absent.

Laboratory examination revealed derangement of liver function test with high level of alanine transferase (ALT) and aspartate transferase (AST), 300 U/L and 154U/L, respectively. But normal alkaline phosphatase (ALP) 94 U/dL, and gamma glutamyl transferase (GGT) 50 U/L. Total bilirubin is high (20.15 mg/dL) with direct bilirubin predominant (14 mg/dL). Total protein was low (4.7 gr/dL) with low albumin 1.0 gr/dL. Prolonged prothrombine time (PT) 20.2 seconds (INR 2.09) and APTT 51.7 seconds. The

patient also had low random blood glucose 99 mg/dL. Serological tests of HBsAg and Anti HCV Ig were negative.

Abdominal ultrasonography revealed coarseness in echotexture of liver parenchym, signs of cholecystitis with minimal ascites.



**Figure 1:** Patient ultrasonography, coarseness in echotexture of liver parenchym



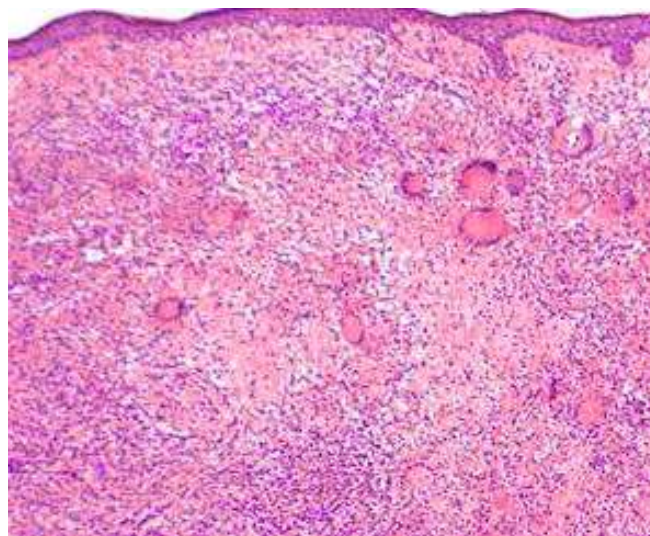
**Figure 2:** Chest X ray photo showed infiltrates at the right apex of lung

Chest x-ray showed infiltrates at right apex and confirm with pulmonary tuberculosis. Assessment of Child-Pugh score is 14, so he had Child-Turcotte-PughGrade C. Treatment was done by halt the ATT regimen with planning of reintroducing ATT when patient is clinically stable and serial liver function tests become normal.

### 3. Discussion

The presentation of cutaneous tuberculosis depends on the pathogenicity of the mycobacteria, route of infection, and level of cell-mediated immunity (CMI) of the host. Following infection, the mycobacteria are phagocytosed by presenting cells and interact with T lymphocytes. Memory T lymphocytes are generated during initial sensitisation within three to ten weeks and circulate in the blood and internal organs.

The tubercle consists of a collection of epithelioid cells at the centre with a variable number of Langhans giant cells surrounded by a rim of lymphocytes. As the inflammation progresses, the centre of the granuloma undergoes caseation necrosis, which is a distinctive feature of tuberculous infection.



The immune response in tuberculosis occurs basically via Th1 pathway, with little or no involvement of Th2 pathway. After the mycobacteria are inhaled, alveolar macrophages are activated, the infectious agents are internalized and the bactericidal apparatus, such as the generation of intermediate nitrogen compounds, is triggered in an attempt to eliminate the bacilli at that point. ZUNIGA

Cutaneous tuberculosis can be acquired from hematogenous or lymphatic dissemination of a pulmonary focus or by direct inoculation. However whenever there is a new accretion of bacilli, the entire immunologic cascade will start again and continue until the formation of granulomas. FUKAMACHI

**Table 1.** The classification of cutaneous tuberculosis

Route	Disease	Immunity
I. Inoculation tuberculosis (exogenous source)	• Lupus vulgaris	• Present
	• Tuberculosis verrucosa cutis	• Present
	• Primary inoculation tuberculosis	• Absent
II. Secondary tuberculosis (endogenous)	• Scrofuloderma	• Equivocal
	• Orificial tuberculosis	• Absent
III. Haematogenous tuberculosis	• Acute miliary tuberculosis (AMT)	• Absent
	• Tuberculous gumma	• Absent
	• Some cases of lupus vulgaris	• Present
IV. Tuberculids Micropapular Papular Nodular	• Papulonecrotic tuberculid	
	• Lichen scrofulosorum	
	• Erythema induratum	

## HO

Cutaneous TB is rare despite the high prevalence of TB worldwide. The highest incidence of CTB is in underdeveloped, resource-poor countries. With some exceptions, lupus vulgaris (LV) is the most common form. Cutaneous TB manifests a wide spectrum of clinical presentations, and current classification systems are based on the route of transmission and the immunologic state of the host. The exogenous (or primary) form of CTB occurs via traumatic direct inoculation of *M. tuberculosis* into the skin or mucous membranes leading to primary cutaneous TB, TB verrucosa cutis, and rarely LV. The endogenous (or secondary) form of CTB occurs through lymphatic, hematogenous, or contiguous spread of *M. tuberculosis* to the skin from an internal focus leading to the development of LV, scrofuloderma, TB cutis orificialis, miliary TB, and metastatic TB abscesses. Tuberculids are another form of CTB resulting from a hypersensitivity reaction to an internal source of *M. tuberculosis* antigens. Diagnosis can be made based on history, morphologic features, and histopathologic characteristics but can be complicated and substantially delayed because of the resemblance to other dermatologic conditions. Furthermore, skin biopsy and/or acid-fast bacilli staining and culture may fail to reveal the presence of *M. tuberculosis*.

This case illustrates about antituberculosis induced liver injury in cirrhosis patient. To best of our knowledge there rarity of data in describing hepatotoxicity in patient with cirrhosis especially in Indonesia. Shang P *et al* found the cumulative incidence of ATLI in China was 2.55% (2.04%-3.06%, CI 95%). Incidence of ATLI related hepatitis in United Kingdom over 30 years reported as 3%.<sup>3</sup> But there's more number in incidence of ATLI in chronic liver disease patient. Sharma *et al* found that DILI occurred in 35 % of cohort cirrhosis patients in India.<sup>8</sup>

Risk factor associated with this potentially fatal complication include co-infection with HIV, hepatitis B or C, pre-existing chronic liver disease, high alcohol intake, malnutrition, advanced age (>35 years old), female sex, and slow acetylators.<sup>4,9</sup> In our patient, there were risk factors such as, old age (55 years old), malnutrition (thin body and loss of 10 kg body weight), and pre-existing chronic liver disease (liver cirrhosis). Patients over 35 years old have 4 fold increased possibility of developing ATLI.<sup>4</sup> Clinical symptoms of ATLI in United Kingdom reported by Abbara *et al* are nausea and vomiting (54.3%), abdominal pain (18.1%), skin complaints (17.1%), and clinical jaundice (12.4%).<sup>10</sup> Shang *et al* showed that nausea (41.51%) and vomiting (39.62%) also being the most common symptom in ATLI followed by anorexia, dizziness, abdominal symptoms, rash/pruritus, fatigue, jaundice, and dark urine. Although nausea, anorexia, and vomiting are not specific to ATLI diagnosis, they might help clinician be more cautious about ATLI. On the other hand, there was 33.02% of ATLI patients who had asymptomatic transaminase elevation. Liver injury could be fatal when it is not recognized early or therapy is not interrupted in time.<sup>2</sup> In our patient, he had nausea, fatigue, jaundice, loss of appetite, dark urine, and pale stools within three days before admission. These symptoms are consistent with clinical data above.

Liver injury occurred in our patient when he was on the first month of ATT treatment. The first line ATT regimen (HRZE) was used. Reported in a population based prospective study in China, 71.59 % of ATLI cases were identified within 2 months after starting anti-TB treatment. The median interval between the initiation of TB treatment and the detection of ATLI was 52.5 (IQR 30, 63).<sup>2</sup> Shorter median time of onset of DILI was 12 days (4-34 days). This has been observed in cirrhosis patient with ATT regimen in India.<sup>8</sup> Vigilant clinical and biochemical monitoring are mandatory to improve the outcomes of cirrhosis patients with ATT therapy. Liver function test showed high ALT (107 U/L) and high AST (144 U/L), high total bilirubin (18.15 mg/dL) with direct bilirubin (10 mg/dL) predominantly. However, level of ALP and GGT were normal. These results fulfilled the diagnostic criteria of ATLI by US DILI network.<sup>11,12</sup> Low serum protein (4.8 gr/dL) with low albumin (1.5 gr/dL), prolonged prothrombine time (PT; 22.2 seconds) and INR (2.09), and hypoglycemia indicated that there was liver production capacity impairment in liver cirrhosis. Our patient was assessed as Child-Turcotte-Pugh (CTP) grade C (score 12).

There remains ongoing debate as to an adequate definition of drug induced liver injury (DILI). Diagnostic criteria of DILI by US DILI network are elevation of ALT/AST more than five times ULN, or more than three times ULN with jaundice.<sup>11</sup> Deparbhavi *et al* used other but similar criteria for DILI, i.e. (i) Documented exposure to anti-tuberculous drugs, isoniazid, rifampin, pyrazinamide, ethambutol resulting in hepatotoxicity, defined as recent onset abnormalities in liver tests (rise in bilirubin of at least 2 mg/dL, or AST or ALT > 3x ULN) or ALP > 2x ULN and (ii) Exclusion of other competing cause such as acute hepatitis A, B, C and E, autoimmune hepatitis and bile duct obstruction.<sup>12</sup> ALP based criteria potentially being affected by TB infection related cholestasis and hence may not be indicative of true DILI.<sup>10</sup> Sharma *et al* reported similar findings with our patient, median and range value in patients with cirrhosis and tuberculosis as followed: ALT (61±42 U/L), AST (76±54 U/L), total bilirubin (4.8±6.1 mg/dL), INR (1.8±0.7), CTP score (8.5±1.5).<sup>8</sup> The phenomenon of liver adaptation or tolerance with mild liver transaminases increases remaining below the threshold values of liver injury is commonly observed during treatment with drugs such as statin and antituberculous medications, especially isoniazid. Despite drug continuation, liver transaminases remain stable or return to normal range, and this should not exclude the drug as likely cause of acute liver injury.<sup>13</sup>

Diagnosis of ATLI in cirrhotic patient is difficult because it requires the ruling out of other possibilities such as viral hepatitis or other possible causes of hepatotoxicity, elevated enzymes and bilirubin at baseline and fluctuations in enzymes level caused by underlying liver diseases may confound the diagnosis.<sup>2,8</sup> As these drugs are metabolized in the liver, there is a theoretical risk of increased hepatotoxicity in patients with underlying chronic liver disease (CLD). ATT constitutes an important acute precipitating event in decompensation of underlying known or unknown liver disease in India.<sup>8,14</sup> Our patient had no alcoholic drinking habit, no history of injecting drug abuse or blood transfusion recipient. Serological tests of HBsAg and

Anti HCV IG were negative. Due to our laboratory limitation, we did not test for autoantibody marker and other serological markers. Diagnostic problems of DILI may therefore be solved in patients with pre-existing infections by hepatotropic viruses, since assessment of the viral load could indicate hepatitis flares rather than DILI.<sup>15</sup> The implicated ATDs should be restarted one at a time after the AST concentration has returned to less than two times the upper limit of normal. After ALT returns to less than two times the ULN, RIF may be restarted with or without EMB. RIF should be restarted first because it is much less likely to cause hepatotoxicity than INH and is a highly effective agent. ATD should be reintroduced in lower doses than were used in the initial therapy, e.g., INH 50 mg and RIF 150 mg and then stepped up (e.g., 50–100 mg for INH and 150 mg for RIF) every 3–4 days gradually to the recommended therapeutic doses. We do not recommend the reintroduction of PZA and should be permanently discontinued. If symptoms recur or ALT increases, the last drug added should be stopped. In patients with elevated baseline ALT from preexisting liver disease, drugs should be restarted when the ALT returns to near baseline levels in the manner described above.<sup>16</sup>

#### 4. Conclusions

Anti tuberculosis therapy should be given cautiously in patient with pre-existing liver disease. Liver function derangement usually occurred in the first and second month of ATT as initial phase. Symptoms are not specific but most of patients complain nausea, anorexia, and vomiting. Comprehensive laboratory studies are needed as to exclude other possible causalities. Drugs cessation and monitoring of clinical symptoms and liver function profiles is recommended. Re-introduction and continuing ATT could be done with close supervision.

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