CASE REPORT

Reviewing the Compounding Risks for Tuberculosis Drug-Induced Liver Injury in a Patient with Transfusion Dependent Thalassaemia

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ABSTRACT

A patient presents with jaundice three weeks into commencement of anti-tuberculosis therapy (ATT). Tuberculosis drug-induced liver injury (TB-DILI) is a main concern in patients commencing ATT. Studies have reported various risk factors associated with TB-DILI, urging vigilance in monitoring liver enzymes in these patients. We aim to review the causes of jaundice in a patient with transfusion dependent thalassaemia commenced on ATT and highlight the risk factors associated with TB-DILI.
Malaysian Journal of Medicine and Health Sciences (2023) 19(4):365-367. doi:10.47836/mjmhs19.4.51

Keywords: Antitubercular agents, Case report, Drug-induced liver injury, Tuberculosis, Thalassaemia major

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INTRODUCTION

Tuberculosis drug-induced liver injury (TB-DILI) is a well-known adverse effect of anti-tuberculosis therapy (ATT) recommending close monitoring of liver enzymes upon commencement. Transfusion-dependent thalassaemia (TDT) is associated with complications including contracting blood-borne viruses such as hepatitis B, C, and HIV from unscreened blood products, and chronic iron overload increasing the risk of chronic liver disease. We present the following case in accordance with the CARE reporting checklist detailing the importance of screening for chronic liver disease and highlighting risk factors associated with TB-DILI in a patient with beta-thalassaemia major.

CASE REPORT

A 45-year-old man was seen in the chest clinic 3 weeks following commencement of anti-TB therapy (ATT). He had symptoms of shortness of breath on exertion and abdominal distension for a week. On examination, he looked cachectic, his BMI was 16.8kg/m2. He was deeply jaundiced, had moderate ascites and left pleural effusion but had no other signs of chronic liver disease. He had a prolonged hospital stay due to disseminated Klebsiella pneumoniae resulting in intra-abdominal abscesses and left empyema. Pleural fluid adenosine deaminase (ADA) was high 133 (reference range <25 U/L in pleural/pericardial/ascitic fluid) consistent with pleural TB. In addition to exposure to antibiotics including intravenous amoxicillin/clavulanate, tazobactam/piperacillin, meropenem and oral cefuroxime, he was started on a 4-drug fixed-dose combination ATT (isoniazid 75mg, rifampicin 150mg, ethambutol 275mg, pyrazinamide 400mg per tablet) 3 tablets a day. He did not consume alcohol, take herbal or non-prescribed medications.

He has beta thalassaemia major diagnosed at the age of eight and is transfusion dependent. A few years prior, he was commenced on direct acting antivirals (DAA) Sofosbuvir and Daclatasvir for chronic hepatitis C infection. He only completed 2 out of the prescribed 12 week-course. His regular medications include deferiprone 3 tablets three times daily and penicillin prophylaxis post-splenectomy.

Blood investigations taken at baseline and 3 weeks post-commencement of ATT are listed in Table I. Viral hepatitis screen performed at baseline including Hepatitis B surface antigen and HIV were negative but hepatitis C antibody was positive.

Abdominal ultrasound showed coarse liver echotexture

Table I: Blood test results taken at baseline prior to commencement of anti-tuberculosis therapy on the 27th of December 2021 and 3 weeks post-commencement of therapy on the 20th of January 2022

	Baseline	3 weeks post commencement of ATT	Reference range
Hb, g/dL	8.2	9.0	13.5-17.4
WBC, x10^9/L	17.8	16.5	4.1-11.4
Neutrophil, x10^9/L	13.0	12.1	3.9-7.1
Platelet, x10^9/L	668	289	142-350
Albumin, g/L	22	19	40-49
Bilirubin, µmol/L	47	89	<24
ALT, U/L	18	19	<42
ALP, U/L	61	62	40-129
APTT, seconds	43.1	53.5	32.36-42.00
INR	1.8	2.7	0.94-1.07

Hb: Haemoglobin, WBC: White blood cells, ALT: alanine aminotransferase, ALP: alkaline phosphatase, APTT: activated partial thromboplastin clotting time, INR: international normalized ratio

and an irregular liver margin suspicious of liver cirrhosis, no portal vein thrombosis or biliary duct dilatation. CT showed presence of uncomplicated cholelithiasis and ascites.

His peak bilirubin in hospital was 150 (111 conjugated bilirubin; reference range <24 µmol/L), ALP 98 (reference range 40-129 U/L), INR 3.4 (reference range 0.94-1.07), but his ALT remained normal 19 (reference range <42 U/L). Due to worsening jaundice, coagulation studies and ascites during his hospital stay his ATT was stopped. At discharge 2 weeks after his admission, his serum bilirubin level improved to 58µmol/L.

DISCUSSION

DILI remains a diagnosis of exclusion and is defined when any one of the following criteria is met 1) ALT ≥ 5x upper limit of normal (ULN), 2) ALP ≥ 2x ULN (especially with a high GGT or after excluding bone disease), 3) ALT ≥3x ULN plus total bilirubin >2x ULN (1). The American Thoracic Society however defines TB-DILI differently: 1) ALT >3x ULN in the presence of typical hepatitis symptoms or 2) an ALT >5x ULN or 3) an elevated total bilirubin >2x ULN regardless of symptoms in the absence of an alternative cause (2).

Our patient had marked elevation of bilirubin with a peak of 150µmol/L (more than 6 times the ULN with majority being conjugated bilirubin) on treatment. Hepatic transaminases and alkaline phosphatase levels however had remained normal. There were a few explanations for isolated hyperbilirubinaemia in our patient. It is known that rifampicin inhibits the major bile salt exporter pump (BSEP) and organic anion transporting polypeptide (OATP1B1) transport protein causing an accumulation in bilirubin. Occurrence of this is early, often within the first two weeks of treatment and is higher in patients with pre-existing liver disease (3).

Hepatic TB was a concern; however our patient's ALP was normal and CT showed no liver nodules. Other differential diagnosis included obstructive jaundice as his CT showed cholelithiasis, but there was no evidence of biliary dilatation on imaging. Haemolytic screen showed a positive direct antiglobulin test (DAT), but his LDH was normal, no increase in reticulocyte count nor changes of haemolysis on peripheral blood film examination and his conjugated bilirubin level was 111µmol/L. A week's course of amoxicillin/clavulanate could have contributed to cholestatic jaundice, however other liver enzymes remained normal.

Several TB-DILI risk factors have been reported, including age, presence of chronic liver disease, viral hepatitis B, C and HIV infection, malnutrition, cytochrome P450 polymorphisms, slow acetylator status, Asian ethnicity, high aminotransferases and a low albumin level pre-treatment (4). Drug regimens especially fixed-dose combination regimens and longer duration of ATT increase the likelihood of TB-DILI.

Our patient had a number of risk factors. He had a vulnerable liver due to a history of hepatitis C infection and chronic iron overload with his most recent ferritin level being 2858 (reference range 30-400 ug/L). However, we could not confirm as to whether our patient has active hepatitis C infection due to financial implications of performing confirmatory tests. Based on his previous records, he had HCV genotype 3a infection without liver cirrhosis. Transient elastography was not available to assess for liver fibrosis prior to commencing DAA. Having said that, reports suggest that patients with HCV genotype 3 had an increased risk of progression to liver cirrhosis (5).

We retrospectively calculated his liver fibrosis score prior to commencement of ATT. His AST to platelet ratio index (APRI) and FIB-4 scores were 0.523 (<1.5) and 2.21 (<3.25) respectively, consistent with no significant fibrosis or cirrhosis.

Prior to commencement of ATT, investigations at baseline including liver enzymes, platelet count, creatinine, HIV, HBV, HCV serology and diabetes screening tests are recommended. Evidence on routine monitoring of liver enzymes on treatment is inconclusive due to cost efficiency, liver enzyme thresholds for discontinuation of ATT, and the difficulty in differentiating hepatic adaptation to significant liver injury. However, patients at risk of developing TB-DILI should be closely monitored for symptoms suggestive of hepatitis as well as regular monitoring of liver enzymes starting at 2 weeks from commencement of ATT.

CONCLUSION

In conclusion, clinicians should remain vigilant in identifying risk factors for TB-DILI prior to commencement of ATT and continue close regimented monitoring as suggested by international guidelines.

ACKNOWLEDGEMENT

The authors would like to thank the patient for his permission to publish this case report.

REFERENCES

1. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, Hunt CM, Wilke RA, Avigan M, Kaplowitz N, Bjornsson E, Daly AK. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther. 2011 Jun;89(6):806-15. doi: 10.1038/clpt.2011.58.
2. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006;174(8):935–52. doi: 10.1164/rccm.200510-1666ST.
3. Capelle P, Dhumeaux D, Mora M, Feldmann G, Berthelot P. Effect of rifampicin on liver function in man. Gut. 1972;13(5):366–71. doi: 10.1136/gut.13.5.366.
4. Patterson B, Abbara A, Collin S, Henderson M, Shehata M, Gorgui-Naguib H, et al. Predicting drug-induced liver injury from anti-tuberculous medications by early monitoring of liver tests. Journal of Infection. 2021;82(2):240–4. doi: 10.1016/j.jinf.2020.09.038
5. Bochud PY, Cai T, Overbeck K, Bochud M, Dufour JF, Mьllhaupt B, et al. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. J Hepatol. 2009 Oct;51(4):655–66. doi: 10.1016/j.jhep.2009.05.016