Clinical and Experimental HEPATOLOGY

Clin Exp HEPATOL 2019; 5, 1: 60–64
DOI: https://doi.org/10.5114/ceh.2019.83158
Received: 06.08.2018; **Accepted:** 07.10.2018, **Published:** 20.02.2019

Original paper

Extra-abdominal involvement is associated with antitubercular therapy-related hepatitis in patients treated for abdominal tuberculosis

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Abstract

Aim of the study: Incidence and predictors of antitubercular therapy (ATT)-related hepatitis in abdominal tuberculosis are not known. The aim of the study was to identify the incidence and predictors of ATT-induced hepatitis in abdominal tuberculosis.

Material and methods: A retrospective analysis of patients who received ATT for suspected abdominal tuberculosis with complete follow-up was done. We excluded patients with underlying chronic or acute liver disease necessitating an alteration in the usual ATT at start. We recorded the occurrence of ATT-induced hepatitis and compared patients with and without ATT hepatitis for any predictors of ATT-induced hepatitis.

Results: Of 163 patients, 22 were excluded (17 missing information, 5 chronic liver disease). One hundred and forty-one patients (mean age: 34.33 ±15.18 years, males: 72) were included. The Mantoux test was positive in 78; 1 had HIV and 32 had an abnormal chest X-ray. Six patients had an alternative diagnosis and 11 needed surgery. Forty-nine (34.8%) had extra-abdominal involvement. Ten patients (7.1%) developed ATT-induced hepatitis. Patients with extra-abdominal tubercular involvement had a greater risk of developing ATT-induced hepatitis (*p*-value 0.003). None of the other parameters including hematological tests, liver function tests and biochemical parameters were different between the two groups.

Conclusions: Seven percent of patients treated for abdominal tuberculosis developed ATT hepatitis. Presence of extra-abdominal involvement was associated with ATT hepatitis.

Key words: tuberculosis, drug-induced liver injury, peritoneal tuberculosis, intestinal tuberculosis, hepatitis.

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Introduction

Tuberculosis is an important global health concern and has afflicted humans since time immemorial. In India, tuberculosis is a major public health problem with the country harboring one fourth of the world's tuberculosis burden. The advent of the directly observed treatment strategy has increased the cure rates in these patients with improvement in the outcomes [1]. The current antitubercular therapy (ATT) usually consists of four drugs – rifampin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) – used in the initiation phase for 2 months followed by three drugs (HRE) in the continuation phase for four months [2]. At least three of these four drugs are recognized to be hepatotoxic and the use of these drugs in combination enhances the risk of hepatotoxicity [3]. Abundant literature is available regarding the incidence, risk factors and outcomes of ATT-related hepatitis in pulmonary tuberculosis [4, 5]. ATT-induced liver injury can have protean manifestations ranging from asymptomatic liver enzyme elevation to acute liver failure. While ATT-induced hepatitis in patients with pulmonary tuberculosis has been well studied in the literature, similar studies in patients presenting primarily with abdominal tuberculosis are limited.

Extrapulmonary tuberculosis represents 15-20% of all newly diagnosed tuberculosis cases in human immunodeficiency virus (HIV) negative patients and 40-50% of patients with HIV coinfection [6]. Abdominal tuberculosis, as per a recent report, constitutes 11% of all cases of extrapulmonary tuberculosis and six months of therapy is recommended for abdominal tuberculosis [2, 7]. Since the incidence of ATT-induced hepatitis in abdominal tuberculosis is less well studied, we did an analysis of our database of patients treated for abdominal tuberculosis to define the incidence of ATT hepatitis and analyze possible factors which could predispose to occurrence of ATT hepatitis.

Material and methods

The present report is a retrospective analysis of a prospectively recorded database of patients with abdominal tuberculosis treated at a gastroenterology unit of a large tertiary care hospital in North India. We routinely collect data of patients who are initiated on antitubercular therapy for confirmed or probable abdominal tuberculosis. All patients who were treated for possible diagnosis of abdominal tuberculosis (including intestinal, peritoneal, abdominal lymph-nodal) were considered for inclusion. We excluded patients where complete details of follow-up were not available, or those with evidence of underlying chronic liver disease at presentation. The study was approved by the institute ethics committee and the need for informed consent was waived in view of the retrospective nature of the study.

The type of case of abdominal tuberculosis was defined as either confirmed tuberculosis (acid fast bacilli positivity on stain, culture or polymerase chain reaction based tests or presence of caseating granulomas on tissue fine needle aspiration or biopsy) or probable abdominal tuberculosis (granulomas without caseation, elevated adenosine deaminase (> 32 U/l) in ascitic fluid or clinic-radiological picture consistent with tuberculosis and with demonstration of response to therapy, i.e. mucosal healing or ascites resolution) [8, 9]. Some of the patients who received ATT for a presumed diagnosis of abdominal tuberculosis had eventually been found to have an alternative diagnosis and were included in the analysis as 'alternative diagnosis'.

Clinical history of all patients presenting with a presumptive diagnosis of abdominal tuberculosis was taken and they underwent clinical examination, baseline investigations including complete blood count, biochemical evaluation (liver and kidney function tests), inflammatory markers (C-reactive protein), Mantoux test, serum electrolytes and chest roentgenogram. Abdominal ultrasound (USG) or computed tomography and ascitic fluid evaluation (for peritoneal tuberculosis), colonoscopy and biopsy (intestinal tuberculosis) and USG-guided fine needle aspiration for abdominal lymph-adenopathy were done as indicated. Any invasive procedure was done only after obtaining informed consent. All patients diagnosed with abdominal tuberculosis were started on standard first line ATT (HRZE). The patients were initially followed up fortnightly for the first month and then monthly.

We defined ATT hepatitis as per previous definitions including any of the following features and exclusion of other differential diagnoses such as acute viral hepatitis (using viral markers IgM anti-HAV, IgM anti-HEV and IgM anti-HBc, HBsAg and anti-HCV) [10]:

- five-fold elevation in alanine aminotransferase (ALT) level in absence of symptoms of ATT hepatitis such as abdominal pain, vomiting, jaundice, etc.,
- three-fold elevation in aspartate aminotransferase (AST) or ALT level in presence of symptoms of ATT hepatitis,
- a rise in the level of serum total bilirubin to 2 mg/dl or more.

We calculated the incidence of ATT hepatitis and noted the follow-up strategy in these patients, which was based on the clinician's discretion. We also compared the baseline parameters such as clinical presentation, laboratory parameters and extent of disease, underlying alternate diagnosis, etc., and also the outcomes amongst patients with and without ATT hepatitis.

Statistical analysis

The data were analyzed using SPSS software (version 23.0, IBM). Data were explored for any outliers, errors and missing values. Quantitative or numerical variable were represented with measures of central location, i.e. the mean or median (if non-parametric), with measures of dispersion, i.e. standard deviation or interquartile range. Categorical variables were compared between groups using the chi-square test. Comparison of means between the groups was done with Student's *t* test or the Mann-Whitney test depending on the normality of distribution of data. The normality of data was assessed with the Kolmogorov-Smirnov test. We planned to do a multivariate analysis of variables which were significant in univariate analysis to predict the occurrence of ATT hepatitis. The *p* value of less than 0.05 was statistically significant.

Results

Of the total of 163 patients with abdominal tuberculosis who were seen, complete information and

follow-up were available for 141 patients. Twenty-two patients were excluded because of either incomplete information (17 patients) or underlying chronic liver disease (5 patients) which required modification of the ATT at the time of initiation.

A total of 141 patients presenting with a clinical and/or radiological picture consistent with abdominal tuberculosis and who received ATT were eventually included in the analysis. Of these, 34 cases (24.1%) had confirmed diagnosis, while 107 cases (75.9%) were treated empirically with probable diagnosis of abdominal tuberculosis. Of these, 101 patients had probable tuberculosis, while 6 (4.3%) patients had an alternative diagnosis (5 had Crohn's disease and 1 had NSAID enteropathy). The mean age of the study group was 34.3 ±15.1 years (13-80 years). Overall 72 (51%) patients were male. Forty-nine (34.8%) patients had associated extra-abdominal tuberculosis. This included 29 cases of pulmonary involvement on chest roentgenogram/computed tomography, 15 cases of pleural effusion, 5 cases with mediastinal lymphadenopathy, 2 cases each of genitourinary and neurological involvement and 1 case with pericardial involvement. Only 1 patient had HIV infection while 36 patients had other comorbidities. The other comorbidities were diabetes mellitus (7 patients), thyroid disorder (6), hypertension (6), neurological diseases (5), gallstones (4), coronary artery disease (3), chronic obstructive lung disease (4), kidney diseases in 3 (chronic kidney disease and nephrotic syndrome), and chronic pancreatitis, prostatic hypertrophy and extra-hepatic portal venous obstruction in 1 patient each. The clinical presentation of the patients was due to abdominal pain or discomfort (129, 91.5%), intestinal obstruction (45, 31.9%), loss of weight (114, 80.9%), loss of appetite (103, 79%), fever (78, 55.3%), diarrhea (19, 13.5%), abdominal lump/mass (15, 7.8%) and bleeding per rectum (6, 4.3%).

Overall, 6 patients underwent endoscopic dilatation for relief of obstructive symptoms and the sites were ileocecal area (3), ascending colon (2), and multifocal (1). Eleven patients (7.8%) underwent surgery during the course of treatment. The reasons for surgery were recurrent subacute intestinal obstruction in 10 patients (strictures – 7, mass forming lesion – 2, abdominal cocoon – 1) and gastrointestinal bleeding during the initial week in 1 patient. A total of 10 patients (7.1%) developed ATT-induced hepatitis. We then compared the group of patients developing ATT hepatitis with those who did not develop ATT hepatitis (Tables 1 and 2). Table 1 shows the comparison of the baseline characteristics in the two groups. Various hematological and biochemical investigations and also the clinical presentations were similar in the two groups. However, the patients who had a higher frequency of extensive disease with evidence of extra-abdominal involvement had a significantly higher risk of developing ATT-induced hepatitis (p value 0.003). Clinical outcomes including the need for surgery, dilatation and occurrence of mortality were not different between the two groups. Only 1 patient died and the death was in the ATT-induced hepatitis group.

Of the 10 patients who developed ATT-induced hepatitis, 1 died of associated sepsis and another had acute liver failure (ALF) but improved. The median time to onset of ATT hepatitis was 13 days (range: 5-56 days). This patient with ALF was reintroduced with rifampin and isoniazid without further worsening but pyrazinamide was not reintroduced. In rest of the patients reintroduction was done in a phased manner with rifampin followed by isoniazid and pyrazinamide. Only 2 patients developed ATT hepatitis on re-challenge and the drugs implicated were rifampin and isoniazid in 1 case each. These were replaced with oral levofloxacin.

Discussion

Drug-induced liver injury (DILI) is one of the most important side effects of tuberculosis treatment. A plethora of reports have been published about the frequency and risk factors of ATT-induced hepatitis in patients with pulmonary tuberculosis. In pulmonary tuberculosis the reported frequency of ATT hepatitis varies across different countries from 1 to 3.3% in Western countries to 8 to 10% in developing countries [6, 11]. This increased incidence in the developing world has been attributed to a number of factors: higher prevalence of viral hepatitis, poor hygienic conditions causing intestinal parasitism, indiscriminate use of drugs, and poor health infrastructure, among others [12]. Studies from India have reported extrapulmonary tuberculosis to be an independent risk factor for developing druginduced hepatitis [13]. Abdominal tuberculosis with its protean manifestations accounts for around 11% of all cases of extrapulmonary tuberculosis [7]. Studies highlighting the specific risk factors associated with ATT-induced hepatitis in this subset have not been reported in the medical literature. This subgroup is important because the yield of microbiological and histological tests is low and often the therapy has to be initiated empirically. Indeed a small subset of patients started on therapy on the basis of 'probable abdominal tuberculosis' in the present study had an alternative diagnosis.

The previous reports regarding predictors of ATT-induced hepatitis have suggested that older age, lower body mass index, hypoalbuminemia, female gen-

Table 1. Differences between the two groups in baseline characteristics

Factor	ATT-induced hepatitis (10)	No hepatitis (131)	*p* value
Male gender	4	68	0.527
Type of cases			0.061
Confirmed	5	29	
Probable	5	86	
Alternative	0	6	
Comorbid illness	4	32	0.277
Extra-abdominal tuberculosis	8	41	**0.003**
Pain	8	121	0.203
Diarrhea	1	18	1.000
Intestinal obstruction	2	43	0.502
Fever	5	73	0.752
Loss of weight	6	108	0.099
Loss of appetite	6	97	0.459
Hematochezia	0	6	1.000
Lump abdomen	0	15	0.600
Comorbidity	4	32	0.277
HIV positive	0	1	1.000
Age (years)	33 (4.3)	29.5 (25.8)	0.585*
Hemoglobin (gm/dl)	11.1 ±2.0	10.8 ±2.1	0.636
Total leucocyte count (/mm^3)	8850 (8825)	6750 (4350)	0.910*
Platelet count (× 10^5/mm^3)	4.54 (2.25)	2.90 (1.76)	0.346*
Serum bilirubin (mg/dl)	0.5 (0.5)	0.6 (0.52)	0.425*
Alanine aminotransferase (U/l)	66 (90.5)	23.5 (11.5)	0.092*
Aspartate aminotransferase (U/l)	67.5 (98)	17 (13.3)	0.068*
Alkaline phosphatase (IU/l)	111 (130.5)	90.5 (40)	0.337*
Serum albumin (gm/dl)	3.675 (3.15)	3.7 (2.07)	0.752*
Serum globulin (gm/dl)	3.8 (0.52)	3.45 (0.9)	0.779*
Serum calcium (mg/dl)	8.95 (2.42)	8.725 (1.45)	0.656*
Serum phosphorous (mg/dl)	2.81 ±0.9	3.30 ±0.8	0.210
Initial weight (kg)	55 (39)	49 (17)	0.387*

**Non-parametric distribution Mann-Whitney U test; in cases where non-parametric test is used the value is for median (interquartile range); otherwise it is provided as mean ± standard deviation.*

der, extensive disease (extrapulmonary disease), and viral hepatitis may predispose to occurrence of DILI [14-16]. While a few earlier studies have reported increased incidence of ATT-induced hepatitis in the age group over 50 years, we did not find any such correlation [16, 17]. Studies from developing countries have indicated low nutritional status to be one of the contributing factors to high incidence of ATT-induced hepatitis [14-16]. No such correlation has been found in our study and the two groups were similar in the initial weight and baseline serum albumin levels. However, the subgroup of patients having extra-abdominal involvement were found to have a significantly higher risk of development of hepatitis in our study. The presence of extrapulmonary tuberculosis itself has been found to be an important risk factor for drug-induced

Table 2. Differences in outcomes of the two groups

	ATT-induced hepatitis (10)	No hepatitis (131)	*p* value
Surgery	1	10	0.569
Dilatation	0	6	1.000
Mortality	1	0	0.071

hepatitis in other studies. The presence of an alternative diagnosis did not seem to impact the occurrence of ATT hepatitis. This is important because possibly this subgroup of patients did not warrant ATT. However, since discrimination of intestinal tuberculosis and Crohn's disease is often difficult, clinicians often have to resort to empirical ATT in such cases [9]. The frequency of ATT hepatitis in our subgroup of patients with abdominal tuberculosis was at least similar to some of the studies on pulmonary tuberculosis. The inferences of our paper are limited by the retrospective study design, lack of evaluation of genetic factors and polymorphisms. However, the present series is a fairly large series of patients with abdominal tuberculosis and the data have been recorded in a prospective database.

To conclude, the frequency of ATT hepatitis in patients with abdominal tuberculosis is around 7% and presence of extra-abdominal disease may increase the risk of occurrence of ATT-induced hepatotoxicity.

Disclosure

Authors report no conflict of interest.

References

1. Chetty S, Ramesh M, Singh-Pillay A, Soliman ME. Recent advancements in the development of anti-tuberculosis drugs. Bioorg Med Chem Lett 2017; 27: 370-386.
2. Sharma SK, Ryan H, Khaparde S, et al. Index-TB guidelines: Guidelines on extra pulmonary tuberculosis for India. Indian J Med Res 2017; 145: 448-463.
3. Ramappa V, Aithal GP. Hepatotoxicity related to anti-tuberculosis drugs: mechanisms and management. J Clin Exp Hepatol 2013; 3: 37-49.
4. Abbara A, Chitty S, Roe JK, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. BMC Infect Dis 2017; 17: 231.
5. Kar P, Karna R, Ruttala R, et al. Clinical and molecular risk factors of anti-tubercular therapy induced hepatitis. J Clin Exp hepatol. DOI: https://doi.org/10.1016/j.jceh.2018.06.012
6. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res 2004; 120: 316-353.
7. Cherian JJ, Lobo I, Sukhlecha A, et al. Treatment outcome of extrapulmonary tuberculosis under Revised National Tuberculosis Control Programme. Indian J Tuberc 2017; 64: 104-108.
8. Sharma V, Mandavdhare HS, Lamoria S, et al. Serial C-reactive protein measurements in patients treated for suspected abdominal tuberculosis. Dig Liver Dis 2018; 50: 559-562.
9. Sharma V, Mandavdhare HS, Dutta U. Letter: mucosal response in discriminating intestinal tuberculosis from Crohn's disease-when to look for it? Aliment Pharmacol Ther 2018; 47: 859-860.
10. Saukkonen JJ, Cohn DL, Jasmer RM, et al; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 2006; 174: 935-952.
11. Rathi P, Gambhire P. Abdominal tuberculosis. J Assoc Physicians India 2016; 64: 38-47.
12. Gangadharam PR. Isoniazid, rifampin, and hepatotoxicity. Am Rev Respir Dis 1986; 133: 963-965.
13. Parthasarathy R, Sarma GR, Janardhanam B, et al. Hepatic toxicity in South Indian patients during treatment of tuberculosis with short-course regimens containing isoniazid, rifampicin and pyrazinamide. Tubercle 1986; 67: 99-108.
14. Singh J, Arora A, Garg PK, et al. Antituberculosistreatment-induced hepatotoxicity: role of predictive factors. Postgrad Med J 1995; 71: 359-362.
15. Sharma SK, Balamurugan A, Saha PK, et al. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. Am J Respir Crit Care Med 2002; 166: 916-919.
16. Tostmann A, Boeree MJ, Aarnoutse RE, et al. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. Gastroenterol Hepatol 2008; 23: 192-202.
17. Dhiman RK, Saraswat VA, Rajekar H, et al. A guide to the management of tuberculosis in patients with chronic liver disease. J Clin Exp Hepatol 2012; 2: 260-270.