TUBERCULOSIS IN LIVER CIRRHOSIS

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About one-third of the world’s population is infected with *Mycobacterium tuberculosis*. In India, 40-50% of the adult population is infected, although only 5% of these may develop active disease during first year or two and another 2-5% will develop disease later on in life. The estimated incidence of tuberculosis in India is 1.96 million new cases annually and the estimated prevalence is 3.8 million cases. Certain medical conditions increase the risk of latent TB infection progressing to active disease e.g. HIV infection, injection drug use, history of organ transplant, immunosuppressive therapy (including steroids and anti-TNF alpha drugs), diabetes mellitus, and chronic renal failure. The progression from latent infection to active disease depends on a number of factors, of which the most important is immunodeficient state.¹

Cirrhosis of liver is also a relatively common condition. Although the exact prevalence in India is unknown, the autopsy studies in USA showed a prevalence of 5-10%. In addition to Hepatitis B and C, there has been a massive increase in alcoholism in India contributing to an increase in chronic liver disease including cirrhosis. This leads to an immunodeficient state and along with malnutrition which is commonly present in such patients, may increase the risk of tuberculosis.

When discussing tuberculosis in liver cirrhosis, the following issues need to be addressed:

1. Is there a higher prevalence of tuberculosis in liver cirrhosis?
2. If yes, then whether it is pulmonary or extra pulmonary?
3. Diagnostic difficulties in presence of cirrhosis and how to overcome?
4. What are the treatment guidelines (esp. regarding use of hepatotoxic drugs)
5. What is the outcome?

INCIDENCE & PREVALENCE

A number of studies have been conducted worldwide to evaluate the prevalence of tuberculosis in patients with liver cirrhosis. Evidence suggests a higher prevalence of tuberculosis in cirrhotics as compared to the general population. In a cohort study of patients with liver cirrhosis done in Denmark (1977 to 1993), the incidence rate of tuberculosis was found to be 168.6 per 1,000,000 and it was highest in men over 65 years of age, with an incidence rate of 246 per 1,000,000.² Another study conducted in western India showed the prevalence rate to be 15 times higher than in the general population and was significantly higher in alcoholics.³

PULMONARY VS EXTRAPULMONARY TUBERCULOSIS

In the general population, pulmonary tuberculosis accounts for more than 80-85% of all cases.⁴ However, in patients with cirrhosis, extra pulmonary tuberculosis is more common. In a Korean study, 31% cirrhotics had extrapulmonary tuberculosis as compared to 12% in the non-cirrhotic control group with predominance of peritoneal tuberculosis.⁵ Ascites due to peritoneal tuberculosis may be difficult to diagnose in the setting of liver cirrhosis where portal hypertensive ascites is common.⁶
Tuberculosis in Liver Cirrhosis

DIAGNOSTIC ISSUES

Patients with liver cirrhosis generally have impaired cellular immunity. These patients demonstrate impaired delayed type of hypersensitivity; hence there is a higher likelihood of false negative tuberculin test. In addition, abdominal tuberculosis is a paucibacillary disease and AFB smears are generally negative in such patients. The diagnosis of tuberculosis in cirrhotics otherwise, is similar as compared to the disease in general population.

A specific diagnostic problem occurs where peritoneal tuberculosis is suspected in a patient with hepatic cirrhosis since both conditions can present with ascites. Tubercular ascites should be suspected in the clinical setting of a new ascites in a patient with stable compensated hepatic cirrhosis or where increasing or resistant ascites occurs despite diuretic treatment in cirrhotic ascites, esp. when there is background of constitutional symptoms such as anorexia, fever, weight loss etc. A high index of suspicion is required to exclude tubercular ascites and ascitic fluid examination should be done in all such cases. Tubercular ascites in the setting of cirrhosis reveals a high SAAG, high protein ascites with a lymphocytic predominant high cell count fluid. The ADA levels are usually more than 40 U/L. PCR for MTB may be positive. The ascitic fluid characteristics which can help in making the diagnosis is shown in Table 1.

TREATMENT GUIDELINES

The need for critical review of treatment of tuberculosis in cirrhotics arises because 3 of the 5 first line anti-tubercular drugs are potentially hepatotoxic. The administration of these drugs can lead to worsening LFT with decompensation of stable cirrhotics and sometimes cause fulminant hepatic failure with a high mortality.

Current guidelines take a broad perspective regarding treatment of tuberculosis in liver cirrhosis. Broadly, the more advanced the liver disease the less the number of hepatotoxic drug should be used. It must be remembered that pyrazinamide has the highest hepatotoxicity followed by rifampin and isoniazid. Safer anti tubercular drugs are Ethambutol, quinolones, aminoglycosides and cycloserine.7

There are broadly two categories of treatment:

A. Cirrhotic patients with essentially normal baseline liver function tests (Childs A Cirrhosis)

Such patients may be treated with standard 4 drug regime for 2 months followed by 2 drugs for remaining 4 months (total 6 month treatment). Since Pyrazinamide is potentially the most hepatotoxic drug, it may be completely avoided and a 9 month 3 drug regime may be used. Regular monitoring of LFT is recommended.

B. Cirrhotics patients altered baseline liver function tests (Childs B & C)

According to 2010 WHO guidelines,8 depending on the severity of the disease and degree of decompensation, the following regimen can be used, by altering the number of hepatotoxic drugs.

One or two hepatotoxic drugs may be used in moderately severe disease (e.g., Child B cirrhosis) whereas hepatotoxic drugs are completely avoided in decompensated Child C cirrhosis.

- Two hepatotoxic drugs
  - 9 months of Isoniazid, Rifampin and Ethambutol (until or unless isoniazid susceptibility is documented)
  - 2 months of Isoniazid, Rifampin, Ethambutol and Streptomycin followed by 6 months of Isoniazid and Rifampin

- One hepatotoxic drug
  - 2 months of Isoniazid, Ethambutol & Streptomycin followed by 10 months of Isoniazid and Ethambutol

- No hepatotoxic drugs
  - 18-24 months of Streptomycin, Ethambutol and Quinolones

Regular LFT monitoring should be done in all cirrhotic patients receiving anti-tubercular treatment and drug therapy may be stopped /altered as per the LFT reports.

Hepatotoxicity due to antitubercular treatment is more commonly observed in patients with hepatic cirrhosis. In the general population, the criteria for stopping anti tubercular treatment is

- AST / ALT > 3times upper limit of normal and symptomatic
- AST / ALT > 5times upper limit of normal even if asymptomatic.
• Raised bilirubin

No clear guidelines are available for patients with cirrhosis. However, as a general principle a rising trend of liver abnormalities on 2 consecutive testing may be an indication for stopping treatment. The absolute level of transaminases cannot be used as the sole criteria in cirrhotics. Any rise in S Bilirubin should be treated with great caution and hepatotoxic drug treatment stopped immediately.

Treatment should be stopped and re-started after serum bilirubin and transaminase return to near normal. Drugs are re-started in a sequential fashion starting with rifampin first followed by isoniazid and lastly pyrazinamide which may be avoided altogether.

However, these guidelines have to be modified according to individual needs and regular liver function test has to be done during entire treatment.

PROGNOSIS

The prognosis of patients with hepatic cirrhosis depends on the stage of disease and associated complications. Overall, the 1 year mortality is 34% whereas patients with complications admitted in ICU have 1yr mortality rate of 69%. The mortality rate in patients with tuberculosis who have not received treatment (or delayed treatment) is >50%. In a US study done in 2007, 554 deaths occurred out of 13,280 cases in patients treated for TB (case fatality rate of 4.2%).

The prognosis in patients of liver cirrhosis who develop tuberculosis is poorer compared to either disease alone. The 30 day case fatality rate was found to be 27.3% and one year case fatality rate was found to be 47.7% as compared to controls in Danish population study.

REFERENCES