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An Antitubercular Therapy Induced-Hepatotoxicity Case with Diffuse Ascites

Antitüberküloz Tedaviye Bağlı, Yaygın Assit Gelişimiyle Seyreden Hepatotoksisite Olgusu

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Abstract / Özet

Hepatic abnormalities are the most common side effects seen in patients taking standard antitubercular (isoniazid, rifampicin, ethambutol and pyrazinamide) therapy. These abnormalities can range from liver enzyme abnormalities to fulminant hepatic failure.The drug itself or its metabolites can cause this damage with a direct toxic effect or immunologic mechanisms. Underlying liver disease, alcohol intake, malnutrition or presence of other systemic diseases can facilitate the liver damage as well as enhancing the severity and worsen the progress. Here, we will discuss a female patient who developed hepatotoxicity with a sudden onset of serious ascites at the end of the first month of antitubercular treatment.

Key Words: Antitubercular therapy, hepatotoxicity, diffuse ascites

Karaciğer anomalilikleri standart antitüberküloz (isoniazid, rifampisin, etambutol ve prazinamid) tedavi alan hastalarda en sık rastlanılan yan etkilerdir. Bu anomaliler karaciğer enzim yüksekliği olabildiği gibi ağır karaciğer yetersizliği yapan tablolara kadar olabilmektedir. İlacın kendisi veya metabolitleri direkt toksik etki ile ya da immunolojik mekanizmalarla bu hasara yol açabilmektedir. Altta karaciğer hastalığının bulunması alkol alımı malnutrisyon ve başka sistemik hastalıkların varlığı karaciğer hasarınını kolaylaştırdığı gibi hastalığın seyrini ve şiddetini de artırmaktadır. Burada diyabeti olan kadın hastada; antitüberküloz tedavinin birinci ayında, ani başlangıçlı ve şiddetli asitle seyreden hepatotoksisite vakası tartışılacaktır.

Anahtar Kelimeler: Antitüberküloz tedavi, hepatotoksisite, difüz assit

Introduction

Tuberculosis is a severe chronic disease which has been a growing health problem in our society recently. It seems to be spreading easily and its incidence is increasing rapidly. As it has to be treated with multidrugs and for a long time, various side effects are possible and these side effects are added to the burden of the disease itself. Here, we introduce a case with hepatotoxicity due to antitubercular therapy aiming to call attention to tuberculosis and the expected side effects of its treatment.

Case Report

A forty-seven year old female patient was admitted to the internal medicine outpatient clinic with fatigue, jaundice of sclera and skin, abdominal pain and distention. She had been to a community hospital with a right side located pain and fever where she was found to have right pleural effusion and referred to a chest diseases hospital. There she was diagnosed with tubercular pleurisy and started on 4-drug-antitubercular treatment, (Isoniazid+rifampicin+pyrazinamide+streptom ycin). Her past medical history was remarkable for type 2 diabetes and she had been using oral antidiabetics for 10 years. In the first evaluation of the patient presenting with the above complaints, her skin and sclera were icteric, the breath sounds were reduced bilaterally at the basal regions of the lungs, and distended abdomen and diffuse ascites were also present.

Her initial labs were as following:
Glucose: 203 mg/dL AST:1172 U/L ALT:1050 U/L GGT:193U/L ALP:125U/L LDH:378U/L T otal bilirubin 14.8 mg/dL Direct bilirubin 11.1 Total protein 4.9 g/dL Albumin 2.2 g/dL PT.16.3sn APTT: 35.6 INR 1.37 WBC:13.2 PLT:200 hgb:13.2 gr/dL HCT:41%

Her chest x-ray showed homogenous density reaching the middle lung zones bilaterally and consisted of pleural effusion. Her abdominal ultrasound showed hepatomegaly (178 mm in the long axes) with smooth edges and a normal ecogenity.

Intrahepatic bile ducts, vasculature,choleduct and bile duct were normal. Massive effusion was detected intraabdominally between solid organs and intestinal ansae.

The patient was given treatment with the diagnosis of hepatotoxicity and liver failure with these clinical and laboratory findings. Her antitubercular therapy was discontinued and supportive

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therapy was started. Her liver enzyme levels decreased beginning on the second day of her admittance to hospital. At day fourteen the patient, whose liver enzymes normalized and ascites regressed and was clinically stabilized, was discharged from the hospital to be followed from the outpatient clinic.

Discussion

Different side effects might be seen due to drugs used for antitubercular treatment. The most important and frequently seen side effect is hepatotoxicity. Hepatotoxicity can range from a mild liver enzyme elevation to fulminant liver failure. Mild liver enzyme elevation can (<X5; less than five-fold the upper limit of normal levels) be detected in 6-11% of the patients taking antitubercular treatment, whereas hepatotoxicity is seen in 1.5-16% of these patients (1-3). The wide variation of the hepatotoxicity state depends on the differences in patient features, use of different treatment regimens and different hepatotoxicity criteria (4).

Possible risk factors predisposing towards hepatoxicity include alcohol intake, usage of nonprescribed drugs, pre-existent hepatic disease, malnutrition and related hypoalbuminemia, advanced age, diabetes mellitus, dissemination of tuberculosis infection and HbsAg positivity (5, 6). These risk factors are not definitely proved but it is obvious that the patients who have these risk factors should be determined and monitored closely. Nevertheless, most hepatotoxicity cases are independent of these risk factors.

Isoniazid, rifampicin and pyrazinamide are antitubercular drugs most frequently responsible for hepatotoxicity. They can be toxic either combined or with single use. Toxicity usually occurs within 15-60 days with different mechanisms. The drugs can be toxic directly or via their metabolites. The drugs can elevate ALT, acting like hapten that leads to allergic reactions with immunologic mechanisms. Sharma and colleagues showed that the absence of HLA-DQA1-0102 and presence of HLA-DQB1-0201 is related to hepatotoxicity seen in antitubercular drug treatment. This can also explain the hepatotoxicity and lupus like syndrome via an immunologic mechanism seen in isoniazid treatment (7).

Congenital defect, low activity or inhibition of enzymes needed for drug metabolism in hepatic microsomes causes the toxicity of the drug itself or its metabolites (8).

Rifampicin; which is one of the hepatotoxic drugs, has good dissemination to all body tissues and inflamed meninges. Its main excretion route is through the bile and enterohepatic circulation and 30-40% is through the kidneys. It inducts hepatic microsomes in the liver to enhance the metabolism and clearance of drugs. Isoniazid is metabolised in the liver by acetylation and hydrolysis and its metabolites are excreted renally. Its metabolite acehydrazide might be toxic via hypersensitivity. Acehydrazide is more toxic when there is alcohol abuse, malnutrition or pre-existent liver disease. The toxic effect of pyrazinamid is usually dose-dependent and rarely causes hepatotoxicity at treatment doses. Liver enzymes return to normal within 2 weeks from the onset of hepatoxicity (9).

Several studies showed that the hepatoxicity risk is increased with advanced age (10, 11). Especially, an increased risk is mentioned above 50 years old. This situation is related to decrease in cytochrome p450 activity and renal functions which cause enhanced drug half life (5, 12). On the contrary, Shakya and colleagues declared that hepatotoxicity incidence is higher in young patients (13).

Hepatototoxicity rate has been shown to be higher in women than men (14-16). Probably women are more sensitive to drug side effects because of low acetylation and changes in drug pharmacokinetics (17).

Diabetes mellitus is a risk factor for tuberculosis (18, 19). The worldwide increase in diabetes prevalance will also produce an increase in new tuberculosis cases. However, the effects of diabetes on the extent of tuberculosis are not known completely. In some studies, no differences in symptoms are found, whereas in a study in Mexico Texas fever, hemoptysis and weight loss are found to be more frequent among diabetics. Diabetes also has negative effects on tuberculosis treatment (20-23). This is considered to be related to the change in antituberculosis drug pharmacokinetics in diabetic patients. In a study by Ruslami and colleagues, it was observed that there was no difference between diabetic and non-diabetic patients in rifampicin, pyrazinamid and ethambutol pharmacokinetics in the intensive phase of treatment; but in the continued phase of treatment, pharmacokinetics of rifampicin were changed and its blood concentration was decreased (24-26). Although this can be explained by weight gain and other possible causes, further studies are needed. In another study, diabetes is showed to enhance the tuberculosis symptoms but not the severity of the disease. The change of drug pharmacokinetics can cause low bacterial response, facilitating resistance to the drug (24).

Patients should be monitored closely for drug toxicity during tuberculosis treatment. Upper abdominal pain, loss of appetite and dark urine should be an alarm indicator for hepatitis. In this case, at the time of presentation, there was ascites charactarized as a transudate, normal PT and INR and a mild decrease in albumin level. The patient did not give consent to a liver biopsy. After discontinuation of antitubercular treatment, clinical and biochemical recovery was seen within 48 hours.

There are major differences between clinical approaches to hepatotoxicity. International guidelines issued by the American Thoracic Society and British Thoracic Society state that liver function tests should be carried out before the initiation of tuberculosis treatment and baseline values should be known. Also, the patients should be informed about all possible side effects.

Conclusion

During antitubercular therapy, biochemical monitorization is not recommended for all patients. It is recommended for patients whose baseline liver function tests are high, who have pre-existent liver disease or alcohol abuse and for the elderly (8). When abnormal liver function tests are found, it is recommended that therapy is continued unless there is presence of icterus or hepatitis, but if liver function tests exceed five times the upper level of normal or bilirubin level elevation occurs; it is suggested that all medications are discontinued and wait until the liver enzyme levels return to normal (13, 23).

Conflict of Interest
No conflict of interest was declared by the authors.

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Author Contributions

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