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RESEARCH ARTICLE

ACUTE SUB FULMINANT HEPATITISINDUCED BY ANTI-TUBERCULOSIS DRUGS

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Abstract

Introduction : Hepatotoxicity is a prominent adverse effect of anti-tuberculosis drugs, with a frequency of up to 20%, but it is often reversible on cessation of treatment, and fatal outcome is exceptional. We report an observation of acute subfulminant hepatitis induced by antituberculosis treatment.

Observation : A 60-year-old patient with a three-year history of insulin-dependent diabetes was started on anti-tuberculosis treatment for smear-positive pulmonary tuberculosis. After two months of treatment, the patient complained of asthenia, epigastric pain, and conjunctival jaundice. Physical examination revealed only jaundice, with no signs of chronic liver disease. Laboratory tests showed hepatic cytolysis (transaminases 10 times the upper limit of normal), associated with cholestasis (alkaline phosphatase 2 times the upper limit of normal, total bilirubin 98 µmol/L), and hepatic insufficiency (prothrombin time = 53%). Despite adjustment of anti-tuberculous drug doses based on serum concentrations, the decision was made to discontinue anti-tuberculosis treatment and admit the patient to the hospital. During the etiological work-up, viral serologies (hepatitis B, C, and HIV) were all negative, as was the autoimmune screening. There was no inflammatory syndrome or hyper eosinophilia. The patient denied alcohol consumption, and no potentially hepatotoxic medications were identified on medication review. Abdominal ultrasound and CT showed normal hepatic and biliary structures with the presence of ascites. Paracentesis revealed transudative fluid, attributed to hypoalbuminemia of 12 mg/L. Liver biopsy was deferred due to clinical and biochemical deterioration (total bilirubin elevated to 288 µmol/L) and worsening hepatic failure (prothrombin time at 7%, unresponsive to vitamin K supplementation). The patient died from grade III hepatic encephalopathy 35 days after discontinuation of treatment.

Discussion et Conclusion: In the light of this observation, we emphasise the role of screening and early diagnosis of toxic hepatitis, and we reiterate the importance of monitoring patients on anti-tuberculosis drugs to avoid a severe and fatal course due to adverse liver reactions.

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Introduction:-

Tuberculosis (TB) is a preventable and usually curable disease, yet in 2022, TB was the world's second leading cause of death from a single infectious agent, after coronavirus disease (COVID-19), and caused almost twice as many deaths as HIV/AIDS, More than 10 million people develop tuberculosis (TB) annually [1] and require anti-tuberculous treatment,which, although effective, is prolonged and combines several potentially hepatotoxic medications.

Hepatotoxicity is a prominent adverse effect of anti-tuberculosis drugs, with a frequency of up to 20%, but it is often reversible on discontinuation of treatment, and fatal outcome is exceptional. We report an observation of acute fulminant hepatitis induced by antituberculosis treatment.

Observation:-

A 60-year-old patient, chronic smoker, with a three-year history of well-controlled insulin-dependent diabetes, started an anti-tuberculosis treatment for smear-positive pulmonary tuberculosis.

After two months of treatment, the patient complained of asthenia, nausea, and epigastric pain, accompanied by conjunctival jaundice with progressively worsening pruritus.

Physical examination revealed only jaundice, with no signs of chronic liver disease. Laboratory tests showed hepatic cytolysis (transaminases 10 times the upper limit of normal), associated with cholestasis (serum gamma-glutamyl transferase and alkaline phosphatase levels 2 times the upper limit of normal, total bilirubin 98 μmol/L), and hepatic insufficiency (prothrombin time = 53%). Based on these findings, the decision was made to discontinue anti-tuberculosis treatment and admit the patient to the hospital.

During the etiological work-up, viral serologies (hepatitis B, C, and HIV) were all negative, as was the autoimmune screening. Renal function and complete blood count were normal, with no evidence of inflammatory syndrome. There was no history of alcohol use, potentially hepatotoxic medications, or prolonged exposure to hepatotoxic chemicals. The patient's nutritional status was adequate.

Abdominal ultrasound revealed a liver with homogeneous echotexture and normal-caliber intra- and extrahepatic bile ducts. The gallbladder contained no stones, and there was a small amount of ascites. CT scan confirmed the absence of bile duct dilation. No thrombosis of the hepatic veins suggestive of Budd-Chiari syndrome was identified. Paracentesis yielded a citrine yellow transudative fluid. Cardiac ultrasound showed no abnormalities, and both renal function and 24-hour proteinuria were normal. Protein electrophoresis revealed hypoalbuminemia of 12 mg/L, explaining the recurrent ascites.

Liver biopsy was deferred due to clinical and biochemical deterioration (total bilirubin elevated to 288 μmol/L) and worsening hepatic failure (prothrombin time = 7%, unresponsive to vitamin K supplementation). The patient died following the onset of hepatic encephalopathy.

Disussion:-

Tuberculosis remains a major public health issue worldwide. The treatment strategy is well standardised, using four major antibiotics: isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB). Anti-tuberculosis drugs are responsible for frequent and potentially serious side-effects, requiring precautions to be taken when initiating treatment and monitoring to be carried out when treatment is continued.

Hepatotoxicity is a prominent adverse effect of anti-tuberculosis drugs, with a frequency of up to 20%. Isoniazid and pyrazinamide are the drugs most likely to cause liver damage, followed by rifampicin; ethambutol is exceptionally hepatotoxic. Various studies have highlighted the association between CYP2E1*1A/*1A and NAT2 genotypes and the risk of hepatotoxicity associated with INH use [2,3].

A meta-analysisof nine studies taking into account various genetic factors (NAT2, CYP2E1, GST) concluded that the following genotypes were responsible for the increased risk of liver toxicity associated with INH use in tuberculosis patients: NAT2 mt/mt (OR = 2.52), CYP2E*1A/*1A (OR = 2.22), GSTM1 null/null (OR = 2.62). [3]

The most severe cases of toxic hepatitis appear early, but according to the ATS account for only 0.023% of cases, and fatal forms or forms requiring liver transplantation have been described within the first week of treatment [2,3]. Cases of fatal fulminant hepatitis have been reported when latent tuberculosis infections have been treated with RMP-PZA.

The clinical manifestations of hepatitis are not very specific. They may include anorexia, asthenia, abdominal pain, diarrhoea, jaundice and fever before neurological signs appear.

Drug-induced hepatitis is an exclusiondiagnosis of, and a complete etiological work-up must be performed before establishing this diagnosis. Particular attention must be paid during patient history-taking to identify any exposure to medications or toxic substances. The role of transjugular liver biopsy in fulminant hepatitis remains controversial. Although its performance may be challenging in this context, in some cases it can establish the diagnosis of treatable liver diseases (such as autoimmune hepatitis or Wilson's disease), exclude underlying chronic conditions, or rule out contraindications to transplantation (such as tumorous liver infiltration) [4,5].

The severity of hepatitis is determined by the degree of hepatic insufficiency (defined as prothrombin time < 50% or International Normalized Ratio (INR) > 1.5) and the presence of neurological manifestations. When the interval between the onset of jaundice and the development of hepatic encephalopathy is less than 15 days, the hepatitis is classified as fulminant; if the interval is between 15 days and 3 months, it is classified as subfulminant hepatitis [4].

Hepatic encephalopathy is graded according to the Trey and Davidson classification, Grade 1: Psychomotor slowing, Grade 2: Asterixis (flapping tremor), Grade 3: Confusion, Grade 4: Coma.

The spontaneous prognosis of fulminant hepatitis is poor, with mortality rates ranging from 50-80% [4,5]. Therefore, when a patient meets established criteria, the decision regarding transplantation should be made promptly.

Total bilirubinand ALTat admission were the prognostic factors, and the progression to hepatic encephalopathy IV stage or hypoalbuminemiaduring hospitalization represented the significant factors for a poor prognosis[6].

Fulminant hepatitis represents a medical emergency requiring urgent action. Within hours, clinicians must:Identify the underlying cause (although in 15-20% of cases, the aetiology remains undetermined), exclude contraindications to liver transplantation, establish whether transplantation is indicated, prevent and/or treat complications of hepatic failure.

Conclusion:-

In the light of this observation, we emphasise the role of screening and early diagnosis of toxic hepatitis, and reiterate the importance of monitoring patients on anti-tuberculosis drugs to avoid a severe and fatal course due to adverse liver reactions.

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