

Adverse reactions to antituberculosis drugs presenting as DRESS syndrome and acute liver failure

Reacciones adversas a los fármacos antituberculosos que se presentan como síndrome DRESS e insuficiencia hepática aguda

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Recibido: 01/04/2022 - Aprobado: 20/06/2022

ABSTRACT

Drug induced liver injury (DILI) can be triggered by many medications including antituberculosis drugs. We present the case of a 37-year-old woman with a smear-positive pulmonary tuberculosis who started treatment with first-line antituberculosis drugs and 4 weeks later presented jaundice, somnolence and a morbilliform generalized rash with progressive neurologic deterioration which had a fatal outcome. Antituberculosis drugs can cause DILI in 2 to 28% of patients and drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) in 1.2%. Acute liver failure (ALF) can occur in 35% of patients with DILI with an overall mortality of 9.7%. If the ALF is unresponsive to medical treatment, liver transplantation has shown promising results and can avoid progression of complications. DILI can be a serious medical condition in patients receiving antituberculosis drugs. If ALF develops and is unresponsive to medical treatment, liver transplantation should be considered as the treatment of choice.

Keywords: Drug hypersensitivity syndrome; Antibiotics, antitubercular; Liver failure, acute (source: MeSH NLM).

RESUMEN

La injuria hepática inducida por fármacos (IHIF) puede ser desencadenado por varios medicamentos incluyendo fármacos anti tuberculosos. Presentamos el caso de una paciente mujer de 37 años con un frotis positivo para tuberculosis pulmonar quien inició tratamiento de primera línea y 4 semanas después, presentó ictericia, somnolencia y un exantema generalizado de tipo morbiliforme con deterioro neurológico progresivo y un desenlace fatal. Los fármacos anti tuberculosos pueden producir injuria inducida por fármacos en 2 a 28% de pacientes y síndrome de DRESS (reacción de sensibilidad a medicamentos con eosinofilia y síntomas sistémicos) en 1,2%. La falla hepática aguda (FHA) en pacientes con injuria hepática inducida por fármacos, puede presentarse en un 35% con una mortalidad del 9,7%. Si la FHA no responde a tratamiento médico, el trasplante hepático ha mostrado resultados positivos y evita la progresión de complicaciones. La IHIF puede ser una condición médica grave en pacientes que reciben medicamentos antituberculosos. Si se desencadena una FHA y no responde a tratamiento médico, debe considerarse con urgencia la posibilidad de trasplante hepático.

Palabras clave: Síndrome de hipersensibilidad a medicamentos; Antibióticos antituberculosos; Fallo hepático agudo (fuente: DeCS Bireme).

INTRODUCTION

Drug induced liver injury (DILI) can be triggered by many medications including herbal medicines and dietary supplements⁽¹⁾. Antituberculosis drugs can cause DILI in many clinical presentations ranging from asymptomatic forms, drug reaction with eosinophilia and systemic symptoms (DRESS) and acute liver failure (ALF) following to death in some cases⁽²⁾.

We present the case of a 37-year-old woman with a smear-positive pulmonary tuberculosis who started treatment with first-line regimen of antituberculosis drugs and 4 weeks later presented jaundice, somnolence

and a morbilliform generalized rash with progressive neurologic deterioration which had a fatal outcome.

CASE REPORT

A 37-year-old woman with a smear-positive pulmonary tuberculosis, started treatment with the first-line regimen consisting on Isoniazid 5 mg/kg, Rifampicin 10 mg/kg, Ethambutol 15 mg/kg and Pyrazinamide 25 mg/kg. On the third week of treatment, she presented general malaise, right upper quadrant abdominal pain and fever. A week later, she developed generalized jaundice, somnolence and a morbilliform rash that began on the chest and upper limbs and spread through

Citar como: Carlin Ronquillo A, Alvizuri Gómez C, García-Encinas C. Adverse reactions to antituberculosis drugs presenting as DRESS syndrome and acute liver failure. Rev Gastroenterol Peru. 2022;42(2):136-8. doi: 10.47892/rgp.2022.422.1344



Figure 1. Morbilliform rash on chest, abdomen, and upper extremities.

the entire body (Figure 1). On admission, the patient was tachycardic (110/min), febrile (38.6°C), hypotensive (86/60 mmHg), somnolent (Glasgow Coma Scale 14/15) and presented right upper quadrant abdominal tenderness with a hepatic span of 16 centimeters.

Laboratory exams were abnormal as follows: leukocytes $20,400 \times 10^9/L$ (eosinophils $1,500 \times 10^9/L$), platelets $246,000 \times 10^9/L$, glucose 36 mg/dL, prothrombin time of 76 s (INR 5.98), AST 2553 U/L, ALT 1,635 U/L, alkaline phosphatase 161 U/L and total bilirubin 8.1 mg/dL with a direct predominance of 6.4 mg/dL. Serological tests for HIV, HAV, HBV, HCV, were all negative. Abdominal ultrasound revealed mild hepatomegaly with no focal liver lesions.

DRESS syndrome and ALF due to antituberculosis drugs was highly suspected. Initial general measurements were admission to intensive care unit, suspension of the drugs, corticoids, antihistamines and N-acetylcysteine administration. On the third day of hospitalization, the neurological condition worsened and the patient had a fatal outcome.

DISCUSSION

DILI is caused by intrinsic dose-dependent or idiosyncratic reactions; by immune reaction or by a metabolite, with latency periods ranging from days to months. Our case corresponds to an idiosyncratic reaction ⁽¹⁾.

It is considered that an antituberculosis drug induces liver injury if it meets one of the following criteria: 1) Aminotransferases > 3 times upper limit of normal (ULN) and alkaline phosphatase > 2 times, without symptoms; 2) Aminotransferases > 5 times ULN, with or without symptoms; and 3) Bilirubin > 2 times the normal value ⁽¹⁻³⁾. In our case, there was hepatocellular involvement with a Ratio (R) > 10 and aminotransferase levels > 20 times the ULN.

Likewise, our patient meets the criteria for severe DRESS syndrome: cutaneous rash, eosinophilia and systemic involvement with liver compromise ⁽⁴⁾. It is usually difficult to establish its relationship with a certain drug and, therefore, its probability is objectified using the European Registry System RegiSCAR (severe cutaneous adverse reaction). The patient obtained 5 points for which she was classified as a probable case, having also ruled out other causes of acute liver failure ⁽⁵⁾.

Antituberculosis drugs can cause DRESS syndrome in 1.2% of patients receiving these medicines. In a 4-year retrospective study, Ethambutol was associated with the majority of the events in up to 53.5%, followed by Rifampicin with 26.7% and isoniazid with 6.7% ⁽⁶⁾. On the other hand, ALF can occur in 35% of patients with DILI with an overall mortality of 9.7%. Most of these patients developed DILI within the first month of treatment and the ALF occurred in the first 2 months ⁽⁷⁾.

Early recognition of the syndrome and withdrawal of the precipitating drug is essential. In most cases is reversible but some can progress to a fatal outcome. Is very difficult to identify the responsible drug because all of them can produce this clinical picture. In ALF due to anti-tubercular drugs unresponsive to medical treatment, liver transplantation is the treatment of choice. Bartoletti *et al* described two successful cases of liver transplantation during anti tuberculous treatment that prevented progressive complications in a 14-year-old boy and a 50-year-old woman with pulmonary tuberculosis ⁽⁸⁾.

In our country, liver transplantation is not yet a universal health practice, which is why our patient could not access to this option. Given this, it is essential to strengthen pharmacovigilance for early detection and early management.

Contribution: CRA, AGC drafted the initial manuscript. GEC edited and provided final approval of manuscript.

No financial supports were needed for this report.

No prior presentation of this case has been done before.

Conflict of interest statement: The authors have no conflicts to declare.

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