Case Report

Antituberculosis Drug-Induced Liver Injury with Autoimmune Features: Facing Diagnostic and Treatment Challenges

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The authors present a case report of antituberculosis drug-induced liver injury that offered diagnostic challenges (namely, the possibility of drug-induced autoimmune hepatitis) and treatment difficulties.

1. Introduction

Drug-induced liver injury (DILI) is a well-established concern in the treatment of tuberculosis infection and can vary widely from a transient hepatic adaptation to acute hepatitis and hepatocellular injury [1, 2]. It can seriously contribute to nonadherence, eventually contributing to treatment failure, relapse, or the emergence of drug resistance.

2. Case Report

Seventeen-year-old girl, Guinea native, living in Portugal, was screened for tuberculosis after pulmonary tuberculosis was diagnosed in a girl living in the same school residence. She had a positive tuberculin skin-test and interferon-gamma release assay, and a nodular image on the chest X-ray. Mycobacterium tuberculosis was isolated on the sputum, susceptible to all first-line antituberculosis drugs. Treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) was started, with daily-observed administration, achieving negative sputum cultures in the first month of treatment.

Three weeks after starting treatment, elevation of Alanine Aminotransferase (ALT) and aspartate aminotransferase (AST), 136 and 89 UI/L, respectively, and palmoplantar desquamation was first detected, with further increase (ALT 281 UI/L and AST 186 UI/L) by the 5th week of treatment, leading to the interruption of the classic scheme and initiation of a second-line one with amikacin, levofloxacin, and ethambutol.

By the third month of treatment, maintaining changes on serum transaminases, despite the changes on treatment, without jaundice, cholestasis, or liver dysfunction, she was referred and admitted by the first time to our hospital. At this point, she had 31 doses of HRZE, 9 days without treatment followed by 34 doses of amikacin, levofloxacin, and ethambutol.

With a suspected DILI, withdraw of the antituberculosis drugs was determined and other causes of liver injury were excluded, such as viral hepatitis, concomitant HIV
of hypergammaglobulinaemia, and negative autoantibodies. A dose of 5mg/day of prednisolone was reached, showing clinical improvement, with no signs of liver cytolysis, normalization of hypergammaglobulinaemia, and negative autoantibodies. While still under treatment, 5 mg in alternate days was tried but liver enzymes slightly increased (ALT 42 U/L and AST 52 U/L), so she maintained 5 mg/day until 18th months of TB treatment was completed, with no side effects of steroids. After that gradually reduction of prednisolone dose to complete suspension was accomplished, maintaining normal liver enzymes and with no relapses.

3. Discussion

As mentioned earlier, DILI can vary from a mild transient elevation of ALT and AST, usually asymptomatic, to acute hepatitis or even liver failure [1]. The risk of hepatotoxicity ranges from 2 to as high as 33% in some studies, and it is influenced by multiple cofactors, such as drug regimen, age, alcohol consumption, malnutrition, concomitant HIV, and hepatitis B or C chronic infection [1, 2].

Towards 3 to 5 times' increase in serum transaminases, hepatotoxic drugs should be stopped, other causes ruled out, and a rechallenge made [1]. In this particular case, rechallenge was unsuccessful since symptoms rapidly relapsed (by the 12th day). Palmoplantar desquamation was interpreted as a possible immune-mediated reaction and not just a metabolic idiosyncratic reaction to drugs [4]. Investigation pointed out a possible delayed hypersensitivity reaction to rifampicin [5]. Since it was not possible to use the first-line drugs, namely, HRE, and because of the fast and severe relapse on the first rechallenge, a slower reintroduction of a complete alternative scheme was attempted. The second-line drugs are often used in special conditions like resistance to first-line therapy, extensively drug-resistant tuberculosis (XDR-TB), and have not been tested systematically. These include (1) aminoglycosides such as amikacin and kanamycin; (2) polypeptides such as capreomycin, viomycin, and enniacin; (3) fluoroquinolones such as ciprofloxacin, levofloxacin, and moxifloxacin; (4) thioamides such as ethionamide and prothionamide; (5) cycloserine; and (6) terizidone [6]. Expert opinion suggests that a regimen of this sort should be given for at least 18–24 months [6–8].

The success of a TB treatment plan will depend on combining an appropriate number of drugs (usually at least four) and selecting one with the ability to kill M. tuberculosis in its various stages of growth. Among second-line drugs, only the fluoroquinolones (especially new-generation) and injectables have good bactericidal activity, followed by the thioamides. It is possible that the new fluoroquinolones will also have a sterilising capacity on these bacilli [9]. Hence, although fluoroquinolones are sometimes associated with mild, transient elevations in aminotransferase levels [10], the patient started a second-line treatment with levofloxacin plus other hepatic-safer drugs, with no elevation on serum transaminases, palmoplantar desquamation getting progressively better, and no other symptoms.

Two months later, nevertheless, she again developed symptoms associated with serum transaminases elevation, the same liver injury phenotype from previous DILI, but, at this time, with hypergammaglobulinaemia and positive autoantibodies, namely, ANA, ASMA, pANCA, and F-actin, raising the hypothesis of drug-induced autoimmune hepatitis [11, 12]. A second episode of DILI in the same patient is extremely rare (~1.2% of patients) and the probability of
likely diagnosis. With normal liver enzymes afterwards, IM-DILI is the more likely scenario, since patient remained asymptomatic and its diagnostic challenges. Although susceptible to all first-line antituberculosis drugs and with excellent response to treatment (negative cultures in the first month of treatment and normal chest X-ray), these side effects required the use of second-line regimens, which are longer in duration and usually associated with the use of an injectable drug. The associated morbidity can severely compromise the adherence to treatment.

Competing Interests

The authors declare that they have no competing interests.

Additional Points

Summary. This case report illustrates a hepatotoxic reaction developing during treatment of TB very difficult to manage and its diagnostic challenges. Although susceptible to all first-line antituberculosis drugs and with excellent response to treatment (negative cultures in the first month of treatment and normal chest X-ray), these side effects required the use of second-line regimens, which are longer in duration and usually associated with the use of an injectable drug. The associated morbidity can severely compromise the adherence to treatment.

Table 1: Classification of drug-induced autoimmune liver disease.

| Diagnosis | Summary |
|-----------|---------|
| AIH with DILI | Patients with known AIH, AIH quiescent: the drug may be the trigger of a new bout, AIH under IS or corticosteroids treatment: reactivation of a known AIH upon intro of a new drug (very difficult to demonstrate a causal relationship as it might be coincidental), Often advanced fibrosis on histology |
| DI-AIH | Patient with a low-grade disease not diagnosed before or predisposition to AIH, Drug produce an immune reaction that lead to a chronic process: perpetuating the AIH, Permanent need of IS |
| IM-DILI (Autoimmune hypersensitivity) | Fever, eosinophilia, lymphadenopathy, rash, Indistinguishable from true AIH: mandatory IS treatment, Frequently spontaneous remission after drug cessation, Usually complete response to treatment and sustained remission without relapse |

AHI: autoimmune hepatitis; DILI: drug-induced liver injury; IS: immunosuppressants; IM-DILI: immunomodulated DILI; DIAILD: drug-induced autoimmune liver disease; HLA: human leukocyte antigen.

Authors’ Contributions

All authors contributed to the patient treatment and management, as to manuscript righting.

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