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Fulminant Hepatitis Secondary to Anti-tuberculosis Drug-induced Hepatotoxicity Complication, Its Prevention Strategies and Management: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. Author SF wrote the manuscript and did literature searches. Author CC involved to care for the patient and literature searches. Author IR was involved to care for the patient and wrote the case report. Author Hicham Bakkali did the literature analyses. Author ND did the literature analyses and managed the manuscript process. Author Hicham Balkhi supervised the manuscript processing. Author AH did literature search and last modifications added last days. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Aim: Tuberculosis remains a public health problem around the world. Hepatotoxicity is a serious side effect of anti-tuberculosis treatment. Fulminant hepatitis is a rare form but considered very

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serious outside of liver transplantation. It can occur several weeks or months after the start of treatment.

Presentation of Case: We report the case of a 34-year-old single male patient treated for pleural tuberculosis in whom fulminant hepatitis appeared after four months of treatment with Isoniazid and Rifampicin. Despite a treatment in intensive care unit He had a fatal outcome because of lack of liver transplantation.

Discussion: Hepatotoxicity varies from biological hepatitis to fulminant hepatitis. Application of personalized strategy of genetic analysis and pharmacological drug monitoring to optimize treatment is the most safe to avoid antituberculosis drug induced hepatotoxicity but not available in all healthcare centers of developing countries. There was any change of anti-tuberculosis protocol because of the risk of bacterial resistance. The protocol includes association between several medicines potentially toxics for a long duration. For some moderate forms of tuberculosis (nodals, pleural), it's necessary to ask if duration of antiviotherapy can be reduced.

Conclusion: Prevention of hepatotoxicity starts with identifying risk factors, regular clinical and biological assessment and informing patients of symptom that can indicate toxicity to react early.

Keywords: Fulminant hepatitis; hepatotoxicity; tuberculosis; isoniazid; pharmacogenetics.

1. INTRODUCTION

Tuberculosis is considered a public health problem in several countries around the world [1]. It is an infectious disease caused by the bacteria Mycobacterium tuberculosis. Treatment is based on a combination of anti-tuberculosis drugs. This treatment may lead to hepatotoxicity of varying severity. Fulminant hepatitis following anti-tuberculosis treatment is a rare but fatal phenomenon outside of liver transplantation. Recognizing risk factors and managing signs of hepatotoxicity is important to avoid this type of complication.

2. PRESENTATION OF CASE

A 34 year old adult, male, single who lived in a military community, was admitted to the intensive care unit (ICU) for the management of a rapidly progressive disorder of coma. The patient was diagnosed with pleural tuberculosis after the appearance of a right pleural effusion. Anti-tuberculosis treatment according to the national protocol was started based on quadruple therapy: Rifampicin, Isoniazid, Pyrazinamide and Ethambutol for two months then dual therapy for another two months with Rifampicin + Isoniazid).

The patient benefited from regular follow-up in pulmonology department. The drugs were well tolerated in the first four months of treatment. During this period there was no blood transfusion, no intake of paracetamol or other medications, no drinking of alcohol or staying in a malaria endemic area. The patient has never been operated on and no known -hereditary illness in family.

Twelve days before admission to intensive care unit (ICU), cutaneous jaundice appeared and gradually intensified. He was moved to the emergency room on day 6 of jaundice. The patient was conscious without fever. The laboratory assessment found a prothrombin level at 45%, transaminases at five times normal, total bilirubin was at 52 µ/L, alkaline phosphatases at 160 U/L, gammglutamyl transferase at 75 µL. Immediate cessation of anti-tuberculosis drugs was recommended.

Six days later, there was a worsening of the intensity of jaundice and the onset of vigilance disorder. The patient was admitted to the ICU and intubated due to a deep coma.

Diagnostic assessment: The clinical examination found an icteric patient, unconscious, the Glasgow score (GCS) was 7/15 (verbal response was 1/4, eyes response was 1 and the motor response was 5), No focalization sign or comitiality, the neck was flexible, brainstem reflexes were normal. Hemodynamically, the patient had normal blood pressure (130/80 mmHg) and heart rate at 85 beats per minute, respiratory frequency was 18, and pulsed oxygen saturation was at 95%. Cardiac and pulmonary auscultation was normal. There was no hepatosplenomegaly, ascites, edema, stellate angioma or palmar erythrosis. Brain imaging by computed tomography (Fig. 1) and magnetic resonance (Fig. 2) did not find any abnormalities.

The electroencephalogram did not reveal any subclinical epileptic seizures. An abdominal ultrasound found a liver, gallbladder, common

bile duct and intrahepatic channels of normal size. The biological assessment found a prothrombin level at 15%, factor V at 11%, elevation of serum transaminase activity with ALT at 18 times normal (628 µ/L), AST at 20 times the normal N (600 µ/L), high total bilirubin (BT at 396 mg/l) predominantly conjugated, alkaline phosphatase PAL at 2 times normal (228U/L) and gammaglutamyl transferase (GGT) at 4 times normal (140 µ/L). Lipase was normal. Hemoglobin was at 14 g/dl, Platelets at 230,000 elements /mm3. White blood cells: 7500 elements/mm3 and CRP at 11 mg/l. kidney functions were normal. The thyroid panel was correct and the albumin level was 25g/L.

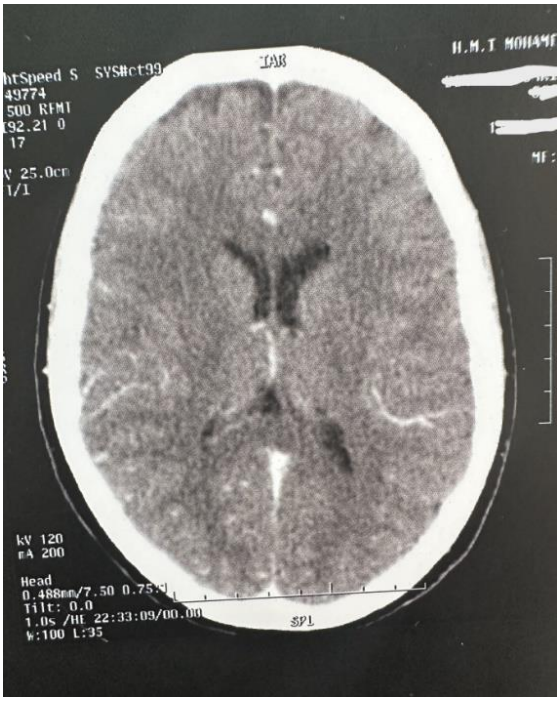

Fig. 1. Cerebral tomography showing no abnormalities

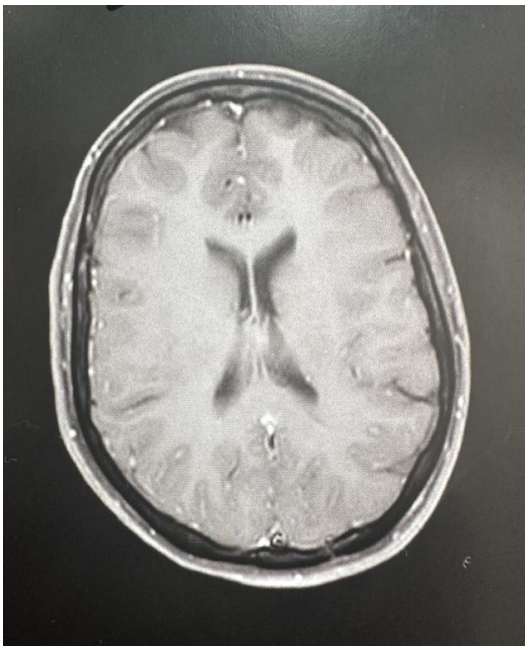

Fig. 2. Cerebral MRI showing no abnormalities

In order to eliminate other causes responsible for acute fulminant hepatitis, an assessment was carried out. Negative HIV serology, HBs antigen, anti-HBc antibody, anti-HAV IgM, anti-HCV IgM, anti-HEV IgM, anti HSV1 and HSV2 IgM, anti-HAV IgM and Anti CMV IgM was negative. The autoimmunity assessment was normal (anti-nuclear antibodies, anti-smooth muscle and anti-LKM1 antibodies).

Therapeutic interventions: Initial treatment was based on intravenous hydration, 10% glucose intake to combat hypoglycemia, an 80 mg lactulose enema per day to have two to three soft stools per day, a treatment with N acetyl cysteine was started, intravenous vitamin K-10 mg/day, gastric protection with omeprazole, and mechanical thrombophylaxis with compression stockings.

Outecomes: The evolution was marked by the onset of a shock state with hypoperfusion of peripheral extremeties and Oliguria (200 cc/24h) and impaired renal function (Creatinine at 15 mg/l). Septic shock was suspected given the increase in infectious parameters (white blood cells at 16,000 elements/mm3 CRP at 42 mg/l and Procalcitonin at 0.6 ng/ml). Infectious samples found coagulase negative Staphylococcus a blood culture bacteremia. Tracheal aspirations and cytobacteriological examination of urine were non-significant. Hydroelectrolytic disorders were subsequently established (hypokalaemia at 2.7 mmol/ without electrical signs, hyponatremia at 128 mmol/l with osmolarity at 266 mmol/l. Management was established based on antibiotic therapy with imipenem and vancomycin, norepinephrine and hydrocortisone hemisuccinate. The outcome was fatal and the patient's death occurred after 5 days of stay in intensive care.

3. DISCUSSION

Tuberculosis is considered by the World health organization (WHO) a major public health problem, an estimated global total of 10.6 million people were infected with tuberculosis in 2022 [2]. In Morocco, 29,018 cases were recorded in 2020, of which 240 were co-infected with the human immunodeficiency virus (HIV) [3] the national authorities consider the fight against tuberculosis a strategic priority. A program has been initiated to this effect for years. The first-line treatment protocol includes isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA). They all increase the risk of hepatotoxicity when used together [4,5].

The frequency of hepatotoxicity during anti-tuberculosis treatment varies according to the studies, 12% [6], 27% [7], and 11.7% [8].

The mechanism leading to toxicity is most often due to the transformation of the drug into a toxic reactive metabolite mainly by cytochrome P450 and its isoenzymes [9].

Isoniazid the most hepatotoxic is converted to acetylisoniazid via phase II enzyme N-acetyltransferase 2 (NAT2), and subsequently to acetylhydrazine through hydrolysis. The latter can be further oxidized by cytochrome P4502E1 (CYP2E1) to form hydroxylamines, wich are intermediates in the formation of hepatotoxic metabolites. Genetic variants of enzymes can explain high variability of patient response during treatment [10]. Slow acetylides are the most predisposed to causing hepatic toxicity.

The impact on the patient varies from simple asymptomatic biological hepatitis to moderate toxic hepatopathy, and finally to severe form which is Fulminant hepatitis (FH) when conscious disorder is installed. The prevalence of FH for medications other than paracetamol, all drug classes combined, remains rare, occurring in 10 to 15% [11]. It remains fatal if left untreated (mortality of 60 to 95%) [11].

Demographic data of FH secondary to anti-tuberculosis drugs illustrates the lack of knowledge of this entity [11,12].

Several risk factors increasing hepatotoxicity during treatment are described in literature: Old age, female sex, autoimmune disease, human immunodeficiency virus infection, pregnancy, Viral hepatitis B, C, Malnutrition, Alcoholism, Disseminated tuberculosis, Genetic factors (slow acetylators) and extrapulmonary tuberculosis [1,6,9].

Combined Strategy to identifying slow acetylors with pharmacogenetics analysis and therapeutic drug monitoring by measureament of plasmatic concentration levels of isoniazid and rifampicin can be useful to predict pharmacokinetic variability and leads to optimizing treatment [8]. Among 1152 Moroccan patients at therapeutic dose, 57.8% had plasma concentrations of isoniazid above the therapeutic range [8]. However, the cost necessary for such a strategy would be significant to adopt it on a collective level.

Treatment protocols require a combination of several drugs and significant duration length. This reduces the risk of bacterial resistance but exposes to a high risk of toxicity. Hepatotoxicity can occur at any phase of treatment [13]. Other liver damage affections can occur in treatment period like bacterial, viral or parasitic affections and medication exposure for other causes. The question of the benefit of the therapeutic protocol in relation to the risk of serious liver toxicity arises for less serious extrapulmonary forms such as pleural or lymph node tuberculosis. Several studies are necessary to answer the question of reducing the duration of anti-tuberculosis treatment for less serious forms and measure benefits of personalizing treatment regimen for certain cases.

During treatment period, the appearance of clinical signs or disturbances in liver biological tests requires a minimal initial assessment including: a history and a clinical examination looking for signs of alcoholism and cardiac liver disease, a liver ultrasound which helps to rule out tumor pathology, portal vein thrombosis or biliary obstruction, and Viral serologies to rule out viral hepatitis. A monitoring every 2 weeks for the first 2 months after starting ATT and every 4 weeks thereafter is an acceptable frequency. For patients without risk factors, the frequency of monitoring can be reduced but should be increased if new nonspecific symptoms appear [13]. The management in intensive care units is that of acute fulminant drug-induced hepatitis combining medical treatment and organ replacement using the organ replacement therapy while awaiting the possibility of a liver transplant. In our case, the patient had an unfavorable outcome, this can be explained a delay in consultation after the occurrence of jaundice and the installation of a septic shock during his stay. Early treatment provided from the onset of jaundice and impaired consciousness optimizes the chances of recovery [11,14].

Prevention of this complication involves informing patients who must recognize jaundice early, not trivialize the crude symptoms and encourage them to consult a physician as soon as possible.

4. CONCLUSION

The occurrence of hepatotoxicity can happen at any phase of anti-tuberculosis treatment. Fulminant hepatitis is a serious complication even if it is rare. Prevention starts with identifying risk factors, application of personalized strategy of genetic analysis and pharmacological drug monitoring to optimize treatment. Treatment protocol (drugs combined and duration) is not subject of debate actually given the objective to fight against bacterial resistance. Regular clinical and biological monitoring of patients can reduce hepatotoxicity impact and avoid severe forms.

CONSENT

As per international standards or university standards, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Djochie RDA, Anto BP, Opare-Addo MNA. Determinants of adverse reactions to first-line antitubercular medicines: A prospective cohort study. J Pharm Policy Pract. 2023 Jun 8;16(1):70.
DOI: 10.1186/s40545-023-00577-6
PMID: 37291618;
PMCID: PMC10249546.
2. World Health Organization. Global Tuberculosis Report ; 2023.
Available:www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023
3. Chahboune M, Barkaoui M, Iderdar Y, Alwachami N, Mourajid Y, Ifleh M, Boumendil K, Bachar K, El Madani S. Profil épidémiologique, aspects diagnostiques et évolutifs des patients tuberculeux au centre de diagnostic de la tuberculose et des maladies respiratoires de Settat, Maroc [Epidemiological profile and diagnostic and evolutionary features of TB patients at the Diagnostic Centre for Tuberculosis and Respiratory Diseases in Settat, Morocco]. Pan Afr Med J. 2022 Jul 7;42:185.
DOI: 10.11604/pamj.2022.42.185.35250
PMID: 36212926;
PMCID: PMC9508374.

4. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, Peloquin CA, Gordin FM, Nunes D, Strader DB, Bernardo J, Venkataramanan R, Sterling TR; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52.
DOI: 10.1164/rccm.200510-1666ST
PMID: 17021358.
5. Yew WW, Leung CC. Antituberculosis drugs and hepatotoxicity. Respirology. 2006 Nov;11(6):699-707.
DOI: 10.1111/j.1440-1843.2006.00941.x
PMID: 17052297.
6. Shu CC, Lee CH, Lee MC, Wang JY, Yu CJ, Lee LN. Hepatotoxicity due to first-line anti-tuberculosis drugs: A five-year experience in a Taiwan Medical centre. Int J Tuberc Lung Dis. 2013 Jul;17(7):934-9.
DOI: 10.5588/ijtld.12.0782
PMID: 23743313.
7. Elkhabbazi H, Sefiani H et al. Evaluation of adverse effects of antituberculosis In El-Idrissi Hospital, Kenitra, Morocco. SR Journal of Pharmacy,2015;5(1):6-11.
8. El Bouazzi O, Belabbes S et al. Suivi therapeutique pharmacologique des antituberculeux: Quinze Ans d'Expérience. European Scientific Journal. 2016;12(21).
9. Bouchentouf R, El jastimi S, Benjelloun A, Aitbenasser MA. Hepatotoxicity of antituberculosis therapy: Epidemiology, mechanism, and patient management. Journal Africain d'Hépato-Gastroentérologie. 2011;5:168-173.
10. Chen B, Zhang WX, Cai WM. The influence of various genotypes on the metabolic activity of NAT2 in a Chinese population. Eur J Clin Pharmacol. 2006 May;62(5):355-9.
DOI: 10.1007/s00228-006-0110-6
Epub 2006 Mar 29.
PMID: 16570187.
11. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. Liver Transpl. 2008 Oct;14 Suppl 2:S67-79.
DOI: 10.1002/lt.21612
PMID: 18825677.
12. Aouam K, Chaabane A, Loussaïef C, Ben Romdhane F, Boughattas NA, Chakroun M. Les effets indésirables des antituberculeux: Epidémiologie, mécanismes et conduite à tenir [Adverse effects of antitubercular drugs: epidemiology, mechanisms, and patient management]. Med Mal Infect. 2007 May; 37(5):253-61.
DOI: 10.1016/j.medmal.2006.12.006
Epub 2007 Mar 1.
PMID: 17336011.
13. Mao Y, Ma S, Liu C, Liu X, Su M, Li D, Li Y, Chen G, Chen J, Chen J, Zhao J, Guo X, Tang J, Zhuge Y, Xie Q, Xie W, Lai R, Cai D, Cai Q, Zhi Y, Li X. Technology committee on dili prevention, management, chinese medical biotechnology association; Study group on drug-induced liver disease, chinese society of hepatology, chinese medical association. Chinese guideline for the diagnosis and treatment of drug-induced liver injury: An update. Hepatol Int; 2024 Feb 24.
DOI: 10.1007/s12072-023-10633-7
Epub ahead of print.
PMID: 38402364.
14. Gotthardt D, Riediger C, Heinz Weiss K et al. Fulminant hepatic failure: Etiology and indications for liver transplantation. Nephrol Dial Transplant. 2007;22 [Suppl 8]:viii5–viii8.

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