Case report

Fulminant Hepatitis secondary to anti-tuberculosisdruginducedhepatotoxicity.How whatwecan do to preventthis complication ?– A Case report.

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

Presentation of case :case: We report the case of a young 34-year-old patient treated for pleural tuberculosis in whom fulminant hepatitis appeared after four months of treatment with a fatal outcome.

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

Conclusion:Actually, pPrevention of hepatotoxicity starts withofidentifying 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. It is an infectious disease caused by the bacteria Mycobacterium tuberculosis. Treatment is based on a combination of anti-tuberculosis drugs. this This treatment may leads to hepatotoxicity of varying severity. Fulminant hepatitis following anti-tuberculosis treatment is a rare but fatal phenomenon outside of liver transplantation. Recognizing and managing signs of hepatotoxicity is important to avoid this type of complication.

2. PRESENTATION OF CASE

Anadult 34 year oldadult, male, single who lived in a military community, was.Aadmitted 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).

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'A Case Report of Fulminant HepatitisSecondary to Anti-tuberculosis Drug-InducedHepatotoxicityComplication - itsPreventionStrategies and Management'

OR

'Fulminant HepatitisSecondary to Anti-tuberculosis Drug-InducedHepatotoxicityComplication, itsPreventionStrategies and Management: A Case Report.'

OR

'Preventionand Management of Fulminant HepatitisSecondary to Anti-tuberculosis Drug-InducedHepatotoxicityComplication: A Case Report.

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The patient benefited from regular follow-up in pulmonologydepartmnent. The ~~treatment~~ drugs~~was~~ werewell tolerated in the first four months of treatment. During this period there was no blood transfusion, no intak~~eing~~ of paracetamol or other medications, no ~~taking~~ drinking ofalcohol or staying in a malaria endemic area. The patient has never been operated on and no known hereditary illness in the family ~~is known~~.

Twelve days before admission to intensive care unit (ICU), cutaneous jaundice appeared and gradually intensified. He was moved to ~~Arrived at~~ the emergency room on day 6 of jaundice. The patient was conscious without fever. ~~the~~ The laboratory assessment found a prothrombin level at 45%, transaminases at five times normal, total bilirubin was at 52µ/L~~U/L~~, alkaline phosphatases at 160 U/L, gammglutamyl transferase at 75µ/L~~U/L~~. 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.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, ~~R~~respiratory frequency~~at~~ was18, 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 (FIGURE 1) and magnetic resonance (FIGURE 2) did not find any abnormalities.

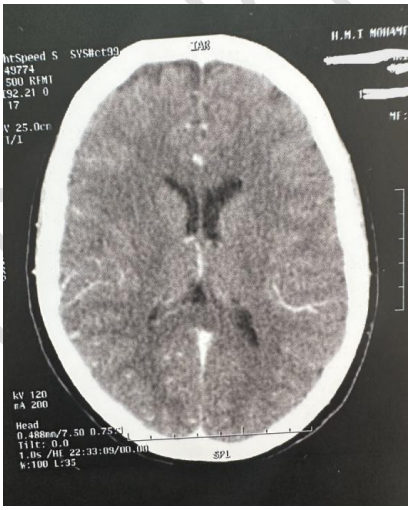

Figure 1 : CerebralTomographyshowing no abnormalities

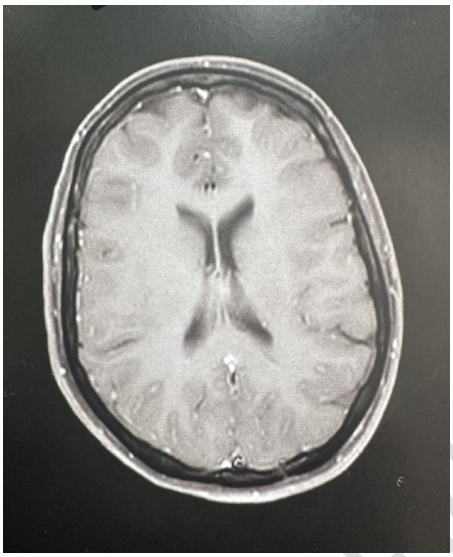

Figure 2: Cerebral MRI showing no abnormalities

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 (628µ/L~~U/L~~), AST at 20 times the normal N (600µ/L~~U/L~~), high total bilirubin (BT at 396 mg/l) predominantly conjugated, alkaline phosphatase PAL at 2 times normal (228U/L) and gammaglutamyl transferase (GGT L) at 4 times normal (140µ/L~~U /L~~). Lipase was normal. Hemoglobin was at 14 g/dl, Platelets at 230,000 elements/mm^3. White blood cells: 7500 elements/mm^3 and CRP at 11 mg/l. kidney functions were normal. The thyroid panel was correct and the albumin level was 25g/L.

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).
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.

The evolution was marked by the onset of a shock state with hypoperfusion of peripheral extremeties and Oliguria (200cc/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/mm^3 CRP at 42 mg/l and Procalcitonin at 0.6 ng/ml). Infectious samples found coagulase negative Staphylococcus,~~A~~ ablood 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 [1]. In Morocco,~~In 2020,~~ 29,018 cases were recorded in 2020, of which 240 were co-infected with the human immunodeficiency virus (HIV) [2] The national authorities consider the fight against tuberculosis a

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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 ~~are~~ all increase the risk of hepatotoxicity when used together [3,4].
The frequency of hepatotoxicity during anti-tuberculosis treatment varies according to the studies, 12% [5], 27% [6], and 11.7% [7].

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[8].
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 oxidizedby cytochrome P4502E1 (CYP2E1) to form hydroxylamines, which are intermediates in the formation of ~~hapatotoxic~~ hepatotoxic metabolites. Genetic variants of enzymes can explain high variability of patient response during treatment [9]. Slow acetylides are the most predisposed to causing hepatic toxicity.

The impact on the patient varies from simple asymptomatic biological hepatitis to moderate toxic hepathopathy, 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% [10]. It ~~R~~remains fatal if left untreated (mortality of 60 to 95%)[10].

Demographic data of FH secondary to anti-tuberculosis drugs illustrates the lack of knowledge of this entity [10, 11].
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) [5,8].
Combined Strategy to ~~identifing~~identifying slow acetylors with pharmacogenetics analysis and therapeutic drug monitoring by ~~mesureament~~measurement of plasmatic ~~concentraion~~concentration levels of isoniazid and rifampicin can be ~~usufull~~useful to predict ~~pharmakokinetic~~pharmacokinetic variability and leads to optimizing treatment[7]. Among 1152 ~~moroccan~~ Moroccan patients at therapeutic dose, 57.8% ~~of~~ had plasma concentrations of isoniazid above the therapeutic range [7].

However, the cost necessary for such a strategy would be significant to adopt it on a collective level.
Treatment protocols requires 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.Other liver damage affections can ~~occure~~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~~a liver ultrasound which helps to rule out tumor pathology, portal vein thrombosis or biliary obstruction, and ~~.~~ Viral serologies to rule out viral hepatitis. The management in intensive care 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 [10,12].
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 ~~occur~~happen at any phase of anti-tuberculosis treatment. Fulminant hepatitis is a serious complication even if it is rare. Prevention starts with ~~identifing~~identifying risk factors, application ~~of personnalized~~personalized strategy of genetic analysis and pharmacological drug monitoring to ~~optimise~~optimize treatment. Treatment protocol (drugs

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combined and duration) is not subject of debate actually given the objective to fight against bacterial resistance. ~~r~~Regular clinical and biological monitoring of patients can reduce hepatotoxicity impact and avoid severe forms.

ETHICAL CONSIDERATION

REFERENCES

1. World HealthOrganization. Global tuberculosis Report 2023. Available : www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023
2. ~~2.~~ Chahboune M, Barkaoui M, Iderdar Y, Alwachami N, Mourajid Y, Ifleh M, Boumendil K, Bachar K, El Madani S. Epidemiological profile, diagnostic and evolutionary aspects of tuberculosis patients at the center for diagnosis of tuberculosis and diseases respiratoires de Settat, Morocco [Epidemiological profile and diagnosis and evolutionaryfeatures of TB patients at the Diagnostic Center for Tuberculosis and RespiratoryDiseases in Settat, Morocco]. Pan Afr Med J. 2022 Jul7;42:185. French. doi: 10.11604/pamj.2022.42.185.35250. PMID: 36212926; PMCID: PMC9508374.
3. ~~3.~~ 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 AntituberculosisTherapySubcommittee. An official ATS statement:hepatotoxicity of antituberculosistherapy. Am J RespirCrit Care Med. 2006 Oct15;174(8):935-52. doi: 10.1164/rccm.200510-1666ST. PMID: 17021358.
4. ~~[PubMed] 4.~~ Yew WW, Leung CC. Antituberculosisdrugs and hepatotoxicity. Respirology. 2006 Nov;11(6):699-707. doi: 10.1111/j.1440–1843.2006.00941.x. PMID: 17052297.
5. ~~5.~~ Shu CC, Lee CH, Lee MC, Wang JY, Yu CJ, Lee LN. Hepatotoxicity due to first-line anti-tuberculosisdrugs: a five-yearexperience in a Taiwan medical center. Int J Tuberc Lung Dis. 2013 Jul;17(7):934-9. doi: 10.5588/ijtld.12.0782. PMID: 23743313.
6. ~~6.~~ 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.
7. El Bouazzi, O., Belabbes, S et al. Suivi Thérapeutique Pharmacologique Des Antituberculeux: Quinze Ans d'Expérience. European Scientific Journal, 2016 ; 12(21).
8. Bouchentouf, R., El jastimi, S., Benjelloun, A., &Aitbenasser, M. A. Hepatotoxicity of antituberculosistherapy:epidemiology, mechanism, and patient management. Journal Africain d'Hépato-Gastroentérologie, 2011 ;5 :168-173.
9. Chen B, Zhang WX, Cai WM. The influence of variousgenotypes on the metabolicactivity 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.
10. Ichai P, Samuel D. Etiology and prognosis of fulminant hepatitis in adults. LiverTranspl. 2008 Oct;14 Suppl 2:S67-79. doi: 10.1002/lt.21612. PMID: 18825677.
11. 11. Aouam K, Chaabane A, Loussaïef C, Ben Romdhane F, Boughattas NA, Chakroun M. Adverse effects of antituberculardrugs:epidemiology, mechanisms, and patient management]. Med Mal Infect. 2007 May;37(5):253-61. French. doi: 10.1016/j.medmal.2006.12.006. Epub 2007 Mar 1. PMID: 17336011.
12. Gotthardt D, Riediger C, Heinz Weiss K et al. Fulminant HepaticFailure:Etiology and Indications for Liver Transplantation. Nephrol Dial Transplant 2007; 22 [Suppl 8]: viii5–viii8.

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