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Review Article

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DRUG-INDUCED HEPATITIS WITH ANTIBACILLARY DRUGS ASSOCIATED WITH AUTOANTIBODIES MIMICKING PRIMARY BILIARY CHOLANGITIS: APROPOS OF TWO OBSERVATIONS WITH REVIEW OF THE LITERATURE

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INTRODUCTION

Tuberculosis is still endemic in many developing countries. immediate discontinuation of antibacillary drugs,[1] drug-induced liver injury may be associated with an autoimmune phenotype that is poorly defined today, including the differentiation between drug-induced autoimmune hepatitis (HAIM), idiosyncratic autoimmune hepatitis (AIH), and drug-induced hepatitis (HM) with positive autoantibodies is often difficult.[2]

We report two cases of drug-induced hepatitis due to antibacillary drugs with positive autoantibodies mimicking Primary Biliary Cholangitis.

Observation 1

This is a 42-year-old C.O patient, put on antibacillary treatment for breast tuberculosis with antibacillary drugs according to an initial therapeutic regimen 2ERIP/4 RH, after 4 months from the start of treatment, the patient presented with jaundice cholestatic with early postprandial vomiting, without other associated signs.

The initial clinical examination: found a patient conscious, jaundiced, undernourished without signs of hepatic encephalopathy, the abdominal examination was unremarkable, in particular no signs of portal hypertension or cirrhosis

At the biological assessment of admission:

Hemoglobin 13.9 g/dl, Platelets 340,000 elm/mm3, White blood cells 7490 elm/mm3, Lymphocytes 2300 elm/mm3, Eosinophils 500 elm/mm3, GOT 1232 Ui/L i.e. (30*N), GPT 726 Ui/L i.e. (16*N), BT 260 Ui/L, BC 239 Ui/L, GGT 190, PAL at 175 Ui/l, Correct kidney function, PT low at 49%.

After elimination of the obstacle by the abdominal ultrasound which was normal, the patient benefited from a complementary balance sheet objectifying:

Anti HVA type IgM negative, HBs Ag negative, anti HB c type IgM negative, anti-HCV negative, anti CMV type IgG positive and IgM negative, with HSV serology IgG type positive and Ig M negative, Epstein Barr virus type Positive IgG and negative IgM type, negative anti HVE type IgM AC, normal immunoglobulin assays, with normal EPP, in particular no inflammatory syndrome. A supplement by autoimmunity assessment showed negative anti smooth muscle Abs, negative anti LKM1 Abs, positive antinuclear Abs at 1/160, with positive anti M2 Abs.

After stopping the antibacillaitres and putting on Urso desoxycholic acid given the biological cholestasis, the evolution was marked by a progressive improvement in the liver balance sheet with improvement of the TP.

Given the positivity of the autoantibodies and since drug-induced hepatitis is a diagnosis of elimination, a liver biopsy puncture was performed in the patient whose anatomopathological study objectified a polymorphic inflammatory infiltrate, with moderate patchy necrosis associated with septal fibrosis moderate with absence of cholestasis or steatosis concluding with chronic active hepatitis classified (A2, F2) according to the Metavir score without signs in favor of autoimmune hepatitis or in favor of primary biliary cholangitis.

The patient's assessment normalized with a follow-up of 9 months

Observation 2

This is a 57-year-old H.F patient, with a history of pulmonary tuberculosis (TPM+) in 2006 treated and declared cured, with a relapse in the month of 10/2018, hence the resumption of antibacillary treatment ERIP, stopped after 3 months of treatment after the installation of severe acute hepatitis retained on clinical, biological and radiological criteria.

Clinically: the patient presented frank jaundice, with a disturbance of the biological assessment:

Hb 13.7 g/dl, GB 8070elm/mm3, PNN 4810 elm/mm3, PNE 130 elm/mm3, Plq 191000 elm/mm3, Renal function correct, GOT 12N, GPT 9N, GGT 11N, PAL 162, BT 133 ui/l, BD 95ui/l, TP 46%, Na + 134, K+ 3.8, CRP 45.

An abdominal ultrasound supplemented by a CT angiography objectifying a dysmorphic liver with hypertrophy of segment I.

The patient benefited from an additional check-up showing

Ac anti HVA type IgM negative, Ag HBs negative, AC anti HB c type IgM negative, AC anti-HCV Positive with undetectable viral load, AC anti CMV IgG positive and type IgM negative, with HSV serology type IgG positive and Ig M negative, and Epstein Barr virus type IgG positive and type IgM negative, AC anti HVE type IgM negative, assays of normal immunoglobulins, PPE: hypergammaglobulinemia at 1.9N with negative antinuclear antibodies, negative anti-smooth muscle antibodies, negative anti-lkm1 antibodies, and type M2+ anti-mitochondrial antibodies.

The patient was put on UDCA acid given the persistence of cholestasis.

A Hepatic Biopsy Puncture was also made given the diagnostic doubt; objectifying a pan lobular macrovacuolar steatosis estimated at 20%, without signs of autoimmune hepatitis or primary biliary cholangitis.

Fibroscopy did not objectivize esophageal varices

The evolution after one month of stopping the antibacillary was marked by the complete normalization of the hepatic balance sheet and the TP, then a gradual reintroduction of the antibacillary was made without incident with a decline of 6 months.

Discussion and Literature Review

Drug-induced hepatitis accounted for 6% of all recorded drug side effects.[3] The maximum frequency of hepatotoxic side effects of marketed drugs is around 1%.[4]

main examples being the anti-tuberculosis drugs mainly isoniazid, rifampicin and pyrazinamide. Toxicity is most often due to transformation of the drug into a toxic reactive metabolite mainly by cytochrome P450 and its isoenzymes.[5] These reactive metabolites are transformed into non-reactive metabolites by various protection systems, in particular glutathione conjugation and epoxides. When these mechanisms are insufficient, reactive metabolites can bind covalently to certain constituents of hepatocytes and lead to cell death or by triggering immunological reactions leading to the formation of serum autoantibodies. But this toxicity is linked to a constitutional individual susceptibility called idiosyncrasy.[6]

Hepatotoxicity can be favored by different factors

Fasting or undernutrition which decreases detoxification capacities by lowering glutathione,[7] this is the case of the first patient who was undernourished with BMI 16.5, as well as enzymatic induction which can increase the transformation of drugs into metabolites reagents for example rifampicin and isoniazid or chronic alcoholism and paracetamol,[7] as is the case of the two patients whose development of hepatitis was under RH considered as enzyme inducers, hepatitis B and C infections also predispose to drug-induced hepatic toxicities,[7] and this is the case of the second patient who had post-viral C liver disease aggravated by taking antibacillary drugs.

The diagnosis of drug-induced hepatitis is based on chronological, clinical and biological criteria, the symptomatology of which generally appears within the interval of a few days to a few months after taking the drugs on average 3 months later, but can occur 1 year later. 2, in the case of our patients, the symptomatology appeared by means of 3 and a half months after the start of the antibacillary drugs.

There are 3 types of acute drug-induced hepatitis: Cholestatic hepatitis (inflammation of the liver accompanied by a stoppage of the circulation of bile) has a generally favorable course; Cytolytic hepatitis (inflammation with destruction of liver cells) can be severe, even giving rise to fulminant hepatitis (major destruction of the liver); and Mixed hepatitis, both cytolytic and cholestatic, which are the most common,[8] such as our two cases where the hepatitis was mixed. The diagnosis of drug-induced hepatitis is based on the elimination of infectious, immunological and toxic causes of hepatitis. For all our patients, viral serologies of hepatotropic viruses, an immunological assessment and a pharmacovigilance survey were carried out before concluding on the drug origin, except that the positivity of the autoantibodies made the diagnosis difficult, concerning the antinuclear antibodies (AAN) are diagnostic, prognostic and phenotypic markers of systemic autoimmune diseases and autoimmune liver disease but can be detected in other non-autoimmune pathologies Infections, Cancers, But also in patients aged > 60 years and pathologies induced by drugs, among the drugs that can be responsible for an elevation of ANAs we find: Antibiotics: minocycline, isoniazid as is the case of our first patient, Anti-arrhythmics: quinidine, (procainamide) Anti-convulsants: carbamazepine, phenytoins, Anti-hypertensives: β blockers, (hydralazine), captopril, α methyl-dopa, Anti-inflammatories: D penicillamine, sulfasalazine, Anti-psychotics: chlorpromazine, Antithyroid drugs: PTU, Biotherapies : anti-TNF α, IL-2, IFN-α, β, γ. Cholesterol-lowering drugs: fenofibrate, statins, With variable titers and which disappear when treatment is stopped.[9] And

As for AANs, Anti-mitochondrial autoantibodies (AMA) are closely associated with primary biliary cirrhosis, mainly in their specificity anti-M2 (anti-pyruvate dehydrogenase [PDH]). This association was originally described by Walker in 1965. Since then, the specificity of these autoantibodies has been refined and a classification has been proposed, but currently it has been shown that AMA can be positive in other chronic liver diseases such as 'HVC, certain drug-induced hepatitis,[10] this is the case of our patients, the first of which the positivity of AMA is very probably induced by antibacillary drugs and in the second case is mixed secondary to HVC and anti-tuberculosis drugs.

In the situation of hepatitis with positive autoantibodies, a very rigorous approach is necessary to eliminate the non-toxic causes and essentially the liver biopsy puncture to show lesions suggestive of a cause.

drugs when known; and to define the lesions when it comes to drugs of which we did not know hepatotoxicity until proven otherwise, as in our situation the PBH has made it possible to eliminate auto hepatitis -immune and PBC given the absence of suggestive histological signs.

concerning the management of drug-induced hepatitis is essentially based on stopping the drugs in question, the evolution of which is generally favorable.[7]

CONCLUSION

Many toxins, medicinal or not, can be responsible for a Acute liver toxicity whether dose-dependent or idiosyncratic. Apart from a clear exposure to a high dose of a hazardous toxicant, the diagnosis of the toxic origin of cytolytic or cholestatic hepatitis is based on a detailed history, a precise analysis of the anamnesis and essential complementary examinations. to rule out a possible non-toxic cause as in our situation to differentiate drug-induced hepatitis from other autoimmune hepatopathies such as HAI or CBP, and whose etiological management is completely different.

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