

## Acute Cytolytic Hepatitis Induced by Allopurinol

S. Elaboudi\*, I. Benelbarhdadi, F-Z Ajana

Medicine "C" Unit, Ibn Sina University Hospital, Mohamed V University, Rabat, Morocco

**\*Corresponding author**

S. Elaboudi

**Article History**

Received: 09.10.2018

Accepted: 17.10.2018

Published: 30.10.2018

**DOI:**

10.36348/sjm.2018.v03i10.006



**Abstract:** Allopurinol is a drug indicated for the treatment of hyperuricemia. Its hepatic toxicity is rare. This is a case report about acute cytolytic hepatitis caused by allopurinol in a 62-year-old.

**Keywords:** Allopurinol, Cytolytic hepatitis, Drug-induced hepatitis, Hepatic toxicity.

**INTRODUCTION**

Allopurinol is an inhibitor of xanthine oxidase, the enzyme responsible for the synthesis of uric acid (urico-synthesis). It is indicated in the treatment of hyperuricemia. It may be responsible for many generalized hypersensitivity reactions, whereas rare cases of asymptomatic elevation of serum hepatic enzymes or even hepatitis, including hepatic necrosis and granulomatous hepatitis, have been reported in the literature [1].

We report a case of acute cytolytic hepatitis probably induced by Allopurinol in a 62-year-old patient.

**CASE REPORT**

A 62-year-old woman, 160 cm tall and weighing 64 kg, was admitted in January 2018, with no history of alcohol intoxication, addiction, or past transfusion. However, she had a medical history of gout, which required the administration of Allopurinol (Zyloric®) at a dose of 200 mg / day.

Fifteen days after the start of treatment, the patient had pain in the right hypochondrium, jaundice without fever, associated with anorexia, asthenia and vomiting.

Biological tests showed cytolysis (7times the upper limit of normal values) with associated cholestasis (3 ULN). Total bilirubinemia was 30mg / L, predominantly conjugated bilirubin. The prothrombin rate, urea and creatinine were normal. There was no biological inflammatory syndrome or abnormal blood count, including no eosinophilia and no hemolysis.

Abdominal ultrasonography was normal. Hepatitis A virus IgM, HBs antigen, anti-HBc antibody, hepatitis C and D anti-virus antibodies were negative. The search for a C viremia by polymerase chain reaction (PCR) was negative. There were no serum anti-nuclear autoantibodies, anti-mitochondria or anti-smooth muscle.

In the absence of any other elements of presumption, Allopurinol was incriminated at the origin of this liver injury and its prescription was suspended. Hepatic biopsy was not performed.

The subsequent evolution after immediate discontinuation of Allopurinol was rapidly favorable

with jaundice regressing in 15 days, associated with an improvement in cytolysis after 30 days and cholestasis after 4 months. The diagnosis of cytolytic drug induced hepatitis, induced by Allopurinol, was strongly suspected. There was no reintroduction of the drug.

**DISCUSSION**

Idiosyncratic drug-induced liver injury (DILI) is a major problem in modern hepatology, which is often underdiagnosed. Yet, it is the most common cause of acute liver failure in the United States [2], and the most common reason for withdrawal of market drug sales [3]. The most common hepatotoxic drugs found in the literature are, after paracetamol, antibiotics, NSAIDs and antiepileptics [4]. Regarding the mechanism of drug-induced liver injury, they may be related to either direct toxicity or an immunoallergic or autoimmune reaction [5-7].

The drug hepatotoxicity, all substances melted (drugs, phytotherapies), oscillates between 1 case / 10 000 and 1 case / 100 000 people exposed [8].

Many mechanisms are involved, such as depletion of ATP or glutathione, covalent bonds with proteins, lipids or nucleic acids [9]. In animal studies, the two initial mechanisms of drug-induced liver injury would be TNF- $\alpha$ -activated cell apoptosis and / or

inhibition of mitochondrial function, producing an excess of free radicals resulting in lipid peroxidation, cell membrane lesions, then cell death [10].

Diabetes mellitus has been reported as an independent risk factor for the severity of drug-induced hepatitis [8], whereas Alcohol consumption is reported to be a negative predictor factor [8]. The latest hypotheses concern the role of genetic factors of the host, environmental and immunological factors in the pathogenesis of drug hepatitis [8, 11].

The first manifestations appear between 5 and 90 days after the beginning of the treatment. They range from no symptoms to acute liver failure, including jaundice [12].

The different attacks can be classified in the following way [13]:

- Hepatocellular type:  $ALT > 2 \times$  the upper limit of the standard or ratio  $ALAT / PA$  (alkaline phosphatase)  $> 5$ ;
- Cholestatic type:  $PA > 2 \times$  the upper limit of the standard or  $ALAT / PA > 2$ ;
- Mixed type:  $ALAT / PA$  between 2 and 5.

The diagnosis of drug-induced liver disease is difficult because the relationship between drug exposure and liver injury is not always obvious. Indeed, polymedication and concomitant liver diseases (alcoholism, NASH, hepatitis C. ...), can make it difficult to identify the responsible agent. Liver biopsy, although nonspecific, is unavoidable in case of diagnostic difficulty, because it strongly directs us to a drug attack and excludes a viral or autoimmune etiology. Despite the absence of specific criteria, there are several scores for attributing toxicity to a drug with objective criteria. The RUCAM score [14] is the most sensitive and specific.

Indeed, several hundred molecules can be the cause of cytolytic damage, as Allopurinol which is an anti-gout agent indicated in the treatment of primary and secondary hyperuricemia. It is thought to be the cause of widespread hypersensitivity reactions, whereas its hepatotoxicity is rare [1].

In our case, it is an acute cytolytic hepatic injury qualified as probable (score of 7) according to the RUCAM score.

Indeed, the reaction appeared within 15 days after introduction of allopurinol (two points), cytolytic fell by more than 50% in less than 30 days after stopping (two points), the subject is older than 55 years (one point), there are no risk factors or suggestive drug intake, nor associated non-drug causes. Hepatotoxicity of the drug is reported in the characteristics of the drug

(two points), finally, the reintroduction of drug has not been tried.

Nevertheless, the diagnosis of drug-induced liver injury remains primarily a diagnosis of exclusion and it is necessary to rule out the other causes of hepatopathy dominated by viral or autoimmune causes (the search for viral RNA from the hepatitis C should be systematic in any subject suspected of drug-induced liver injury [8]. Given the results, a viral etiology, autoimmune, infectious or biliary was excluded in our patient.

Discontinuation of the responsible drug is usually followed by a marked improvement in liver tests in the following weeks and a cure in the following months. The presence of signs of severity (hepatic encephalopathy, drop in coagulation factors synthesized by the liver) requires immediate hospitalization in a specialized unit [5].

When the responsible drug is continued, liver damage may also progress to the development of chronic lesions, with the development of fibrosis or even cirrhosis [15].

The discontinuation of allopurinol in our observation was followed by a clear improvement in liver tests.

## CONCLUSION

The responsibility for allopurinol in this acute regressive cytolytic hepatitis may be considered probable. Indeed, the diagnosis of acute drug hepatitis remains difficult because of the frequent inaccuracy of the history and the lack of specific diagnostic test in the majority of cases.

## REFERENCES

1. Agence française de sécurité sanitaire des produits de santé. (1999). Réactions cutanées et syndromes d'hypersensibilité liés à l'allopurinol.
2. Ostapowicz, G., Fontana, R. J., Schiødt, F. V., Larson, A., Davern, T. J., Han, S. H., ... & Crippin, J. S. (2002). Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Annals of internal medicine*, 137(12), 947-954.
3. Lee, W. M., & Senior, J. R. (2005). Recognizing drug-induced liver injury: current problems, possible solutions. *Toxicologic pathology*, 33(1), 155-164.
4. Chalasani, N., Fontana, R. J., Bonkovsky, H. L., Watkins, P. B., Davern, T., Serrano, J., ... & Drug Induced Liver Injury Network (DILIN). (2008). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*, 135(6), 1924-1934.

5. Mallat, A. (1999). Hépatites médicamenteuses: diagnostic et prise en charge. *Gastroenterol Clin Biol*, 23, 906-914.
6. Mallat, A. (1999). Hépatites médicamenteuses : revue bibliographique. Cahiers FMC. *Gastroenterol Clin Biol*, 23:921-5
7. Pessayre, D. (1995). Mécanisme des hépatites médicamenteuses: Une conséquence de la superposition de deux systèmes xénophobes. *Gastroentérologie clinique et biologique*, 19(5BIS), B47-B56.
8. Watkins, P. B., & Seeff, L. B. (2006). Drug-induced liver injury: summary of a single topic clinical research conference. *Hepatology*, 43(3), 618-631.
9. Tarantino, G., Di Minno, M. N. D., & Capone, D. (2009). Drug-induced liver injury: is it somehow foreseeable?. *World journal of gastroenterology: WJG*, 15(23), 2817.
10. Berson, A., De Beco, V., Lettéron, P., Robin, M. A., Moreau, C., El Kahwaji, J., ... & Pessayre, D. (1998). Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes. *Gastroenterology*, 114(4), 764-774.
11. Chalasani, N., Fontana, R. J., Bonkovsky, H. L., Watkins, P. B., Davern, T., Serrano, J., ... & Drug Induced Liver Injury Network (DILIN). (2008). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology*, 135(6), 1924-1934.
12. Sgro, C., Clinard, F., Ouazir, K., Chanay, H., Allard, C., Guilleminet, C., ... & Hillon, P. (2002). Incidence of drug-induced hepatic injuries: a French population-based study. *Hepatology*, 36(2), 451-455.
13. Andrade, R. J., Robles, M., Fernández-Castañer, A., López-Ortega, S., López-Vega, M. C., & Lucena, M. I. (2007). Assessment of drug-induced hepatotoxicity in clinical practice: a challenge for gastroenterologists. *World journal of gastroenterology: WJG*, 13(3), 329.
14. Lucena, M. I., Camargo, R., Andrade, R. J., Perez-Sanchez, C. J., & De La Cuesta, F. S. (2001). Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology*, 33(1), 123-130.
15. Dhumeaux, D., & Mallat, A. (1993). Hépatites chroniques et cirrhoses d'origine médicamenteuse. *Gastroentérologie clinique et biologique*, 17(5BIS), H31-H35.