Iran J Public Health, Vol. 45, No.4, Apr 2016, pp.540-541

Letter to the Editor

Drug Induced Autoimmune Hepatitis by Amoxicillin-Clavulanate

*Ufuk BARIŞ KUZU [1], Erkin ÖZTAŞ [1], Mustafa KAPLAN [1], Nuretdin SUNA [1], Tülay TEMUÇİN KEKLİK [2], Meral AKDOĞAN [1]

1. Dept. of Gastroenterology, Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey
2. Dept. of Pathology, Yuksek Ihtisas Training and Research Hospital, Ankara,Turkey

***Corresponding Author:** Email: ubarisk@gmail.com

(Received 09 Oct 2015; accepted 21 Nov 2015)

Dear Editor-in-Chief

Drug induced liver injury (DILI) is a disease caused by xenobiotics (drugs, herbal or diet products) and diagnosed by exclusion of other causes. Some drugs that cause DILI can also cause drug induced autoimmune hepatitis (DI-AIH) by triggering the immune response against liver proteins (1, 2).

A 24- yr old male patient in 2015, was admitted to Turkiye Yuksek Ihtisas Hospital, gastroenterology clinic with complaints of 3 days of vomiting, weakness joint pain and jaundice. In his laboratory analysis the results were as followes: alanine aminotransferase: 3388 U/L (<33), aspartate transaminase: 3319 U/L (<32), alkaline phosphatase: 176 U/L (33-105), total bilirubin: 19.5 mg/dL (<1.2), direct bilirubin: 11.3 mg/dL (<0.3), albumin: 4.4 mg/dL (3.5-5.2), INR 1.4, immunoglobulin-G (IgG): 18.4g /L (6-16) respectively and complete blood count was within normal limits. Viral serological tests for hepatitis A, hepatitis B and hepatitis C were negative. Screening for other diseases such as Wilson and hemacromotosis diseases that can cause liver failure were also negative. Written informed consent was obtained from the patient.

The patient was hospitalized due to fulminant hepatitis. Amoxicillin-clavulanate had been prescribed because of tooth abscess 15 days ago. In his previous history there was not any disease, alcohol consumption or smoking. Patient's score for Council for International Organization of Medical Science was 7 (probable), and hepatocellular type damage pattern was present (3). Antinuclear antibody (ANA) was positive by 1/1000 ratio (immunofluorescence assay). At the seventh day of hospitalization, liver biopsy was performed. In histopathologic examination of liver biopsy revealed interface hepatitis, lymphoplasmacytic cell infiltration in portal area, emperipolesis and hepatic rosette formation which supporting autoimmune hepatitis. Confluent necrosis in lobular area and eosinophilic infiltration were seen (Fig. 1).

One mg kg/d prednisone therapy was started with the diagnosis of amoxicillin-clavulanate induced autoimmune hepatitis by using simplified autoimmune hepatitis scoring system (6 points: probable autoimmune hepatitis) (4). Patient whose transaminases and bilirubin levels declined rapidly after steroid treatment was discharged with maintenance treatment.

DILI accounts for 5-10% of patients with new jaundice and 25-50% of patients with acute liver failure. Damage can be due to dose dependent (intrinsic) or idiosyncratic reaction (5). The most common agent causing idiosyncratic DILI are antimicrobial agents, especially amoxicillin-clavulanate. There are publications about agents such as

minocycline, nitrofrontain, statins or non-steroidal anti-inflammatory drugs which cause DI-AIH. However there is not a case about amoxicillin-clavulanate induced DI-AIH (5, 6).

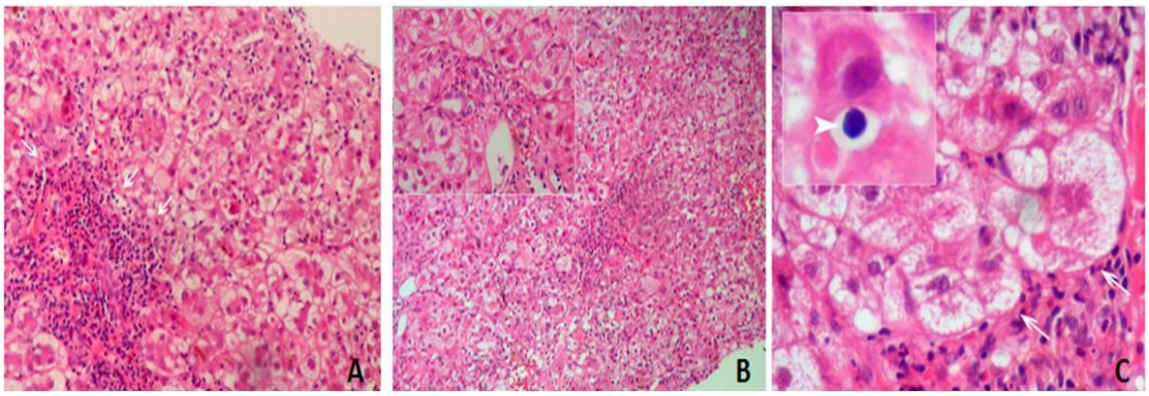

Fig. 1: DI-AIH due to amoxicillin-clavulanate use show typical aspects of classic-AIH. A; Interface hepatitis (white arrows) (Hematoxylin-eosin stain (HE), x200). B; Eosinophil and lymphoplasmacytic-cell inflammation in portal area (HE, x200). C; Emperipolesis (white arrowhead) and hepatic rosette formation (white arrows) (HE, x400)

DI-AIH is an inflammatory-immunmediated process which directly affects liver cells. Pathophysiological mechanism is based on the hypothesis that liver proteins which drugs and metabolites binded is defined as neoantigens by the immune system and antibody response occurs. Like in classical autoimmune hepatitis female predominance is more common. Marked transaminase and Ig-G increase compared to cholestatic enzyme changes are in the foreground in laboratory analysis. The most common autoantibodies are ANA and smooth muscle antibody (2,7). By histology may show characteristics which remind of classic autoimmune hepatitis (4,7). Due to the mentioned reasons above and lack of a standart diagnostic test, separation of the two clinical practice is difficult. However acute onset, the absence of the histopathological chronicity, well response to steroids and a short recovery period suggest the diagnosis of DI-AIH as in our case (5,6).

As a result, also DI-AIH may be seen in males and with drugs that was not mentioned before, it must be considered in differential diagnosis.

Acknowledgement

The authors declare that there is no conflict of interests.

References

1. Björnsson ES, Bergmann OM (2015). Drug-induced liver injury: an overview over the most critical compounds. *Arch Toxicol*, 89(3): 327-34.
2. Robin MA, Le Roy M, Descatoire V (1997). Plasma membrane cytochromes P450 as neoantigens and autoimmune targets in drug-induced hepatitis. *J Hepatol*, 26(1): 23-30
3. Danan G, Benichou C (1993). Causality assessment of adverse reactions to drugs — I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries . *J Clin Epidemiol*, 46(11):1323 -30 .
4. Hennes EM, Zeniya M, Czaja AJ (2008). International Autoimmune Hepatitis Group. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*, 48(1): 169-76.
5. Czaja AJ (2011). Drug-induced autoimmune-like hepatitis. *Dig Dis Sci*, 56(4): 958-76.
6. Bjornsson E, Talwalkar J, Treeprasertsuk S et al. (2010). Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology*, 51: 2040-8.
7. Lewis JH, Zimmerman HJ (1998). *Drug-induced autoimmune liver disease. Autoimmune Liver Diseases.* 2nd ed. Elsevier, Amsterdam, pp.: 627-49.