Turk J Gastroenterol 2004; 15 (3): 123-125

EDITORIAL

Drug-induced hepatitis, drug-induced autoimmunity or classical autoimmune hepatitis: How can we differentiate ?

İlaca bağlı hepatit, ilaca bağlı otoimmunite veya klasik otoimmun hepatit: Nasıl ayırabiliriz?

Dydrogesterone-induced hepatitis and autoimmune hemolytic anemia

E. ALTINTAŞ[1], D. OĞUZ[2], S. KAÇAR[3], Y. ÖZDERİN[2], O. SEZGİN[1], N. İ. ZENGİN[3]

Mersin University, School of Medicine, Division of Gastroenterology[1], Mersin

Türkiye Yüksek ihtisas Hospital, Gastroenterology Department[2], Pathology Department[3], Ankara

Dydrogesterone, similar to women's natural progesterone, has been used in a wide range ofgynecological conditions. Despite its widespread use, dydrogesterone-induced hepatotoxicity and dydrogesterone-induced hemolytic anemia have, to the best of our knowledge, never been reported previously. We describe a case of hepatitis and warm antibody hemolytic anemia due to dydrogesterone. ***Turk J Gastroenterol 2004; 15 (1): 49-52***

Dydrogesterone is a widely used agent for various gynaecologic diseases because of the similarity to natural progesterone. Altintas et al. reported a case diagnosed with dydrogesterone induced autoimmune hepatitis and Coombs positive haemolytic anemia on March 2004 issue of the *Journal* (1).

This case was a 26 years old female. She had suffered from jaundice, arthalgia and myalgia on 1997. Aminotransferase levels were high, and she was diagnosed as acute hepatitis A. Her clinical signs and symptoms were improved in one and half months. She was admitted to hospital again with same complaints on February 1999. Portal hypertension signs were detected at that time. 1/40 titer of antinuclear antibody (ANA) seropositivity was found. Liver biopsy was revealed mild hepatocellular damage. Her complaints regressed again within a few months. After 2 years, she had another attack with similar complaints on December 2000. Jaundice and splenomegaly were detected when she was hospitalized. Although esophagogastric varices and hypersplenism were not found, abdominal ultrasonography revealed portal hypertension findings (splenomegaly and dilated portal vein). Aminotransferases levels [aspartat aminotransferase level (AST) > alanine aminotransferase level (ALT)] were very high suggesting acute hepatitis. Erythrocyte sedimentation rate was very high, ANA (1/40 titer) was positive. Liver biopsy showed a submassive necrosis with both rare eosinophils and dense polymorphonuclear cells infiltration. Although there was no manifest anemia, she was diagnosed autoimmune haemolytic anemia by direct and indirect Coombs positivity, erythrocyte morphology on peripheral smear, indirect hyperbilirubinemia, reticulocytosis and low haptoglobulin levels. She had received dydrogesterone in a short period before these every 3 acute hepatitic attacks within 4 years. Because of this history, acute hepatitis and haemolytic anemia accompanied by the last attack were thought to be related to dydrogesterone. Clinical symptoms and signs were regressed after 2 months of drug discontinuation.

Drugs are one of the most common causes of liver injury. However, making the diagnosis sometimes can be difficult, ignoring the possibility of underlying disease. Drug related hepatic injury can be seen in all forms of acute and chronic liver diseases. But, usually it is presented with acute hepatitis or cholestasis. Drugs such as halothane, tienilic acid, dihydralazine, and anticonvulsants trigger a hepatitic reaction. Drugs including chlorpromazine, erythromycins, amoxicillin-clavulanic acid, sulfonamides and sulindac may induce cholestatic or mixed reaction. Unstable metabolites of the drug may bind to cellular proteins or macromolecules, leading to a direct toxic effect on hepatocytes. Protein molecules produced in the metabolism of the drug may be recognized by the immune system as neoantigens. Immunological activation may then generate autoantibodies and cellular immune responses, which in turn damage the liver (2).

Estrogen, androgen and anabolic steroids are well known sex steroids that induce liver injury. Up to date, there is no reported hepatotoxicity with

dydrogesterone. Consequently, is this paper a historical certificate that firstly reports dydrogesterone hepatotoxicity? Acute hepatitic attack in this patient correspons the criteria of CIOMS consensus meeting of diagnosis drug related liver disease (3). But, although she was diagnosed as acute hepatitis A on 1997, this attack has been related with dydrogesterone. After 2 years of this attack, sudden development of portal hypertension was detected during another attack. Sometimes, transient portal hypertension can accompany by serious acute hepatitis (4). Portal hypertension signs of this patient were persistent, because they persisted through the last attack on 2000.

Briefly, we are facing a chronic liver disease patient who has portal hypertension. Liver biopsy performed during the last attack revealed mixed cellular infiltration included eosinophils giving the possibility of drug related liver disease. Submassive necrosis is a histopathological sign of serious liver injury. It can develop by all causes of acute hepatitic. In this patient, there was some defects in both history and laboratory results. In retrospective evaluation of her history, it is not convincing that she had taken dydrogesterone before each hepatitic attacks. Most probably, she used dydrogesterone from time to time. Are dydrogesterone and hepatitis A virus both responsible for the first attack? Is it synergistic effect, or is it wrong diagnosis? If she had used this drug from time to time, why did no acute hepatitic attacks develop in other times? Or did it cause to develop insidious asymptomatic chronic hepatitis? Many speculations can be made.

Wilson's disease must be excluded in all patients presenting acute hepatitic attacks with haemolysis. Serum ceruloplasmin and copper levels were analyzed in this patient. But, the most valuable screening test for Wilson's disease is serum ceruloplasmin and 24-hour urinary copper excretion (5). Free serum copper levels can be used instead of total serum copper for following-up the Wilson's disease and dosage of copper-chelating agents. Haemolysis which is seen in Wilson's disease is a Coombs-negative haemolytic anemia and it may occur during the Wilsonian crisis which has a very high mortality. Presence of Coombs positive haemolytic anemia and spontaneous regression of this condition excludes Wilson's disease. Likewise, urinary copper excretion in 24 hours can increase in acute hepatitic attacks. In spite of all these findings, Kayser-Fleischer rings and 24-hour urinary copper excretion should be tested in this patient.

If, this patient is evaluated according to the criteria of autoimmune hepatitis which is accepted in 1999 Chicago international meeting, she takes 11 points and diagnosed as probable autoimmune hepatitis (6). High erythrocyte sedimentation rate and amenorrhea increase the probability. Delayed menarche or amenorrhea can be seen in 80% of woman with autoimmune hepatitis. Recurrent acute hepatitic attacks are the features of autoimmune hepatitis. 10% of autoimmune hepatitis patients present acute hepatitic attacks (7, 8). Spontaneous remission can occur in some patients during the course of the disease. In literature, there are some case reports that have recurrent acute hepatitic attacks and spontaneous remission (9). In the light of these results, clinical features and course of the disease in this patient are compatible with autoimmune hepatitis. Methods used for analyzing of autoantibodies have not been explained in this paper. ANA positivity at a titer of 1/80 is more valuable in adults, but positivity at titers of 1/40 is also acceptable. The other autoantibodies (antibody to soluble liver antigen, perinuclear antineutrophil cytoplasmic antibody,...) related with autoimmune hepatitis should tested (10). Also, we did not know gammaglobulin and IgG levels in this patient. It seems to be that the reason of higher AST level than ALT level is the presence of haemolysis.

Is there any triggering factor for autoimmune hepatitis? Viral infections and drugs are the main triggering factors for autoimmune hepatitis. We know that autoimmune hepatitis can develop during the acute hepatitis A virus (HAV) infection (11). If the history is right, first attack can accepted as acute hepatitis A in this patient. Asymptomatic autoimmune hepatitis triggered by HAV may progress and portal hypertension can be found during the second attack. In literature, reported cases usually had a grave progress, but obtained remission by immunosuppressive therapy.

Most hepatotoxic events associated with drugs are unpredictable, and they have intermediate (1 to 8 weeks) or long latency (up to 12 months) periods characteristic of hypersensitivity reactions. Immune-mediated drug-induced liver disease nearly always disappears or becomes quiescent when the drug is stopped. Methyldopa, minocycline, and nitrofurantoin can produce a chronic hepatitis resembling AIH if the drug is continued. Clometacine, methyldopa, minocycline, nitrofurantoin, oxyphenisatin, benzarone, diclofenac, ectasy, fenofibrate, papaverine and propylthiouracil may cause a syndrome resembling autoimmune hepatitis type 1. Dihydralazine, tienilic acid and halothane

may cause a syndrome resembling autoimmune hepatitis type 2 or acute hepatitis. Seronegative chronic hepatitis may develop after using drugs like lisinopril, etretinate, sulphonamide and trazadone (12). Can dydrogesterone be a triggering factor for autoimmune hepatitis? This is a possibility. On the other hand, hepatotoxicity with progesterone derivatives has not been reported yet and moreover medroxyprogesterone uses as a stimulative agent of protein synthesis in liver failure (13). Possibility of dydrogesterone hepatotoxicity is not clear with this knowledge.

As a conclusion, there is a serious defect in a history, follow-up and laboratory tests in this patient. Even if we suppose all attacks produced by dydrogesterone; still we can not accept this situation as a drug induced acute hepatitis. Because she had portal hypertension in second and third attacks, there must be a continuing chronic hepatitis that is not improved after first attack. Or does dydgesterone induce chronic hepatitis which has recurrent acute hepatitic attacks? This condition may be seen only in autoimmune hepatitis triggered by dydrogesterone. Another speculation is that the cause of portal hypertension is defferent. However, the facts are always simple. Diagnosis of this patient is autoimmune hepatitis type 1 with the findings of amenorrhea, high erythrocyte sedimentation rate, recurrent acute hepatitic attacks accompanied by haemolytic anemia and convenient criteria's of international autoimmune study group. Truth of other speculations should be evaluated with taking a reliable history and complete laboratory results.

REFERENCES

1. Altintas E, Oğuz D, Kaçar S, et al. Dydrogesterone-induced hepatitis and autoimmune hemolytic anemia. Turk J Gastroenterol 2004 Mar; 15: 49-52.
2. Liu ZX, Kaplowitz N. Immune-mediated drug-induced liver disease. Clin Liver Dis 2002; 6: 467-86.
3. Standardization of definitions and criteria of causality assessment of adverse drug reactions. Drug-induced liver disorders: report of international concencus meeting. Int J Clin Pharmacol Ther Toxicol 1990; 28: 317-22.
4. Tai D, Changchien CS, Chen CJ, et al. Sequential evaluation of portal venous hemodynamics by Doppler ultrasound in patients with severe acute hepatitis. Am J Gastroenterol 1996; 91: 545-50.
5. Ferenci P. Review article: diagnosis and current therapy of Wilson's disease. Aliment Pharmacol Ther 2004; 19: 157-65.
6. Alvarez F, Berg PA, Bianchi FB, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929-38.
7. Kessler WR, Cummings OW, Eckert G, et al. Fulminant hepatic failure as the initial presentation of acute autoimmune hepatitis. Clin Gastroenterol Hepatol. 2004 Jul; 2(7): 625-31.
8. Kaymakoglu S, Cakaloglu Y, Demir K, et al. Is severe cryptogenic chronic hepatitis similar to autoimmune hepatitis? J Hepatol 1998; 28: 78-83.
9. Lohse AW, Kogel M, Meyer zum Buschenfelde KH. Evidence for spontaneous immunosuppression in autoimmune hepatitis. Hepatology 1995; 22: 381-8.
10. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. Hepatology 2002; 36: 479-97.
11. Urganci N, Akyildiz B, Yildirmak Y, et al. A case of autoimmune hepatitis and autoimmune hemolytic anemia following hepatitis A infection. Turk J Gastroenterol 2003; 14: 204-7.
12. Zimmerman HJ, Ihsak KG. Hepatic injury due to drugs and toxins. In: MacSween RNM, Burt AD, Portmann BC, Ishak KG, Scheuer PJ, Anthony PP (eds). Pathology of the Liver. IV. Ed. Churchill Livinstone. London. 2002; 621-709.
13. Saarni HU, Stengard J, Karki NT, et al. Medroxyprogesterone acetate improvement of the hepatic drug-metabolizing enzyme system in rats after chemical liver injury. Biochem Pharmacol 1983; 32: 1075-81.

Sabahattin KAYMAKOĞLU

Istanbul Medical Faculty Dept of Gastroenterohepatology
Çapa, Istanbul, Turkey

E-mail: kaymakoglus@hotmail.com