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Dydrogesterone-induced hepatitis and autoimmune hemolytic anemia

Didrogesteron'un neden olduğu hepatit ve otoimmün hemolitik anemi

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Dydrogesterone, similar to women's natural progesterone, has been used in a wide range of gynecological 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

Key words: Dydrogesterone, drug-induced liver disease, drug-induced hemolytic anemia

Doğal progesterone benzer olan dydrogesterone çeşitli jinekolojik durumlarda kullanılmaktadır. Yaygın bir şekilde kullanılmasına rağmen; bugüne kadar dydrogesterone'un neden olduğu hepatotoksisite ve otoimmün hemolitik anemi bildirilmemiştir. Dydrogesteron'un yol açtığı hepatit ve sıcak antikor pozitif hemolitik anemili bir olguyu sunduk.

Anahtar kelimeler: Dydrogesterone, ilaç hepatitis, ilaç hemolitik anemisi

INTRODUCTION

Dydrogesterone is one of the leading progestogens in Europe. It is very similar to women's natural progesterone (1). Due to its high selectivity and activity it has fewer side effects than all other progestogens, including progesterone (1). Dydrogesterone is useful in a wide range of gynecological conditions caused by progesterone deficiency, such as endometriosis, premenstrual syndrome, and irregular or absent menstruation (1, 2). In Western Europe, the frequency of sex steroid-induced cholestasis is approximately 1 per 10,000 exposed (3). We herein report a case with dydrogesterone-induced hepatitis and warm antibody autoimmune hemolytic anemia.

CASE

A 26-year-old female patient was sent to our hospital with the diagnosis of acute hepatitis, on 19 December 2000. She had complained of jaundice, pruritus, nausea, vomitus, cough, fever, pain in right upper quadrant of her abdomen, colorless feces and dark urine. The patient had applied to the doctor with similar complaints including jaundice, myalgia, arthralgia and fever in 1997. In the analysis, increased liver enzyme level was detected. Viral hepatitis type A was suspected, and she was prescribed bed-rest. One and a half months later, her complaints and jaundice had resolved.

In February 1999, she admitted to the hospital again, with the same symptoms. Portal hypertension was diagnosed. Viral markers (hepatitis B, hepatitis C, cytomegalovirus, and herpes simplex virus) were determined as negative. While antimitochondrial antibody, anti-smooth muscle antibody and anti-liver kidney microsomal antibody-1 were negative, anti neutrophilic antibody (ANA) was determined as positive in the 1/40 titer. Liver biopsy had been done. In the first liver biopsy, lobular structure was roughly conserved, but mid-level hepatocellular injury was detected. The pati-

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ent took only vitamin B complex, and her jaundice resolved.

In December 2000, her complaints of jaundice, myalgia, arthralgia and fever began again. Abdominal ultrasound showed hepatomegaly, splenomegaly, and portal and splenic venous dilation. Total bilirubin was 31 mg/dl, direct bilirubin was 10 mg/dl, aspartate aminotransferase (AST) was 257 U/L, alanine aminotransferase (ALT) was 204 U/L, and gamma-glutamyltransferase (GGT) was 70 U/L. The patient was sent to our hospital for further examination.

When she admitted to the hospital, vital findings were normal. In physical examination, jaundice, excoriation and slight splenomegaly were observed. Erythrocyte sedimentation rate was 82 mm/h, hemoglobin was 11.3 g/dl, platelets were 273,000/mm^3, and white blood cells were 4900/mm^3. In the peripheral blood, there were obvious anisocytosis, macrocytosis and hypochromia and microcytosis. Prothrombin time was prolonged [17.54 seconds, international normalization ratio (INR) 1.52]. Liver enzymes were high: AST was 831 U/L, ALT 704 U/L, lactic acid dehydrogenase (LDH) 477 U/L, GGT 71 U/L, alkaline phosphatase (ALP) 144 U/L, total bilirubin 51.1 mg/dl, direct bilirubin 19.92 mg/dl, total protein 6.7 g/dl and albumin 3.7 g/dl. She had been married for four years and had received treatment for infertility.

She had used clomiphene six or seven days before admission, and dydrogesterone (10 mg/day) for 15 days. Seven or eight days after using these drugs, her complaints had resurfaced. After investigating her medical history in detail again, it was noted that before the previous icteric features, she had taken 20-day dydrogesterone, 10 mg doses in a day. She said that she had jaundice and itching within two weeks after beginning the medication. Between icteric periods she had taken no medicine. Based on this finding, dydrogesterone-induced hepatitis was suspected.

Viral markers were negative. Abdominal ultrasound revealed diffusely increased parenchyma echo of the liver and splenomegaly. The portal vein measured 17 mm and splenic vein 10 mm. Upper gastrointestinal endoscopy was normal. ANA was determined as positive in the 1/40 titer. Serum iron, iron binding capacity, ferritin, vitamin B12 and folate level, ceruloplasmin, serum copper, free T3, free T4 and thyroid stimulating hormone were normal. In view of indirect bilirubin dominancy, accompanying reticulocytosis (3.4%), gradual decrease in the hemoglobin level, low haptoglobin (less than 0.1 g/L), normal hemoglobin electrophoresis, positive direct Coombs' test [AHG 4(+), IgG 4(+), C3d 1(+)] and indirect Coombs' test [warm 4(+)], warm antibody positive autoimmune hemolytic anemia was suspected. One month later, AST was 184 U/L, ALT 106 U/L, total bilirubin 10.6 mg/dl and direct bilirubin 3.81 mg/dl. Due to prolonged prothrombin time, fresh frozen plasma was administered, and a liver biopsy was done. Microscopic sections of liver biopsy revealed effacement of main acinar structure by confluent necrosis. Hepatocellular damage was severe resulting in submassive necrosis (Fig. 1). Inflammatory cells were mixed type, and rich in neutrophils with occasional eosinophils (Fig. 2). Proliferated bile ductules were located in portal tracts with epithelial damage. Bile pigment was sparse in the cytoplasm of some hepatocytes.

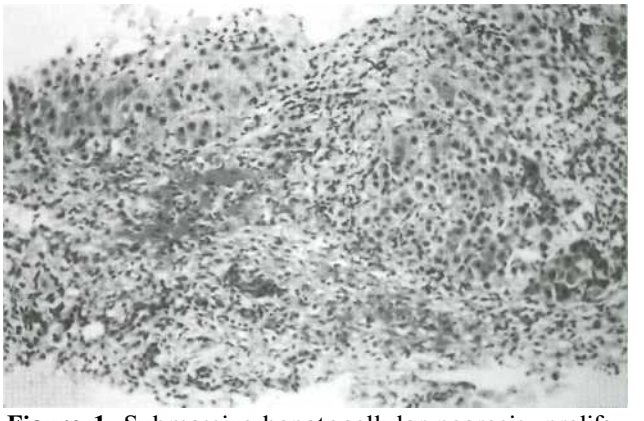

Figure 1. Submassive hepatocellular necrosis, proliferation of interlobular bile ducts and ductules (H&E, x50)

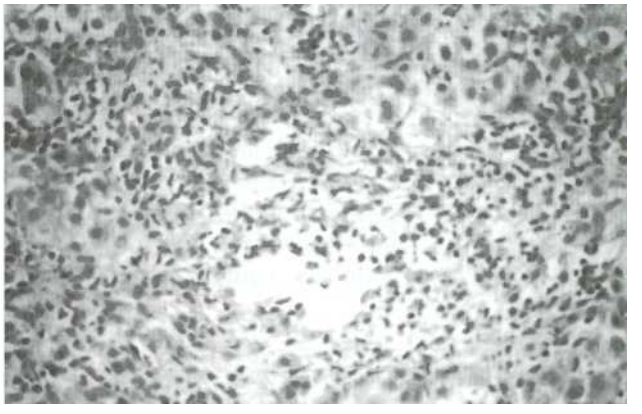

Figure 2. Severe inflammatory cell infiltration type with occasional eosinophils (H&E, xlOO).

When liver enzymes were reduced to half, she was discharged without medication. At one-month follow-up, liver enzymes had returned to normal level, total bilirubin was 2 mg/dl and direct bilirubin 0.3 mg/dl. With the exception of light anemia (hemoglobin 11.2 g/dl), complete blood count and prothrombin time were normal.

DISCUSSION

The close temporal relationship between the first intake of dydrogesterone and liver enzyme elevations, the deterioration under continued dydrogesterone treatment, the considerable decrease in liver enzyme abnormalities after withdrawal of medication, the positive rechallenge and the exclusion of other causes make it highly probable that dydrogesterone was the cause of the initial hepatic injury.

Immune-mediated adverse drug reactions are among the idiosyncratic type of drug reactions (4). They are infrequent, dose independent, unpredictable and not reproducible in experimental animals (4). In addition to hepatocellular injury, there may be coexistent clinical features that specify an acute immune-mediated hypersensitivity response such as fever, a skin rash or eosinophilia (4). Hepatotoxicity can develop abruptly within the first weeks of treatment due to drug-induced hypersensitivity reaction. Constitutional symptoms mentioned above-as in our case- are present typically together with the hepatic dysfunction and can progress to life-threatening complications. Elevated leukocyte counts, blood eosinophilia and increased IgE levels usually indicate the immune-mediated pathogenesis of this clinical presentation (5). Immune-dependent histopathologic features vary and have differing predominance from case to case. They can comprise hepatocellular necrosis, cholestasis, tissue eosinophilia, parenchyma and periportal infiltrates consisting of predominantly lymphocytes and plasma cells (4). The hepatic lesions resolve when the drug is withdrawn. Continued therapy, such as in our case, however, carries a considerable risk of progressing to fulminant hepatic failure. Rechallenge will elicit the same pathology usually within a much shorter interval of time (4). Cytokine release is probably involved considering the fact that constitutional symptoms such as fever or hypotension are frequently present (4). However, it is unclear in this case whether dydrogesterone itself or dydrogesterone's metabolites acted as the triggering antigens.

Such observations both support and challenge the notion that many forms of drug- induced liver disease have an immunologic basis (5). Certainly, the absence of clinical signs of hypersensitivity do not exclude the immune mechanism. For example, autoimmune hepatitis (not related to drugs) clearly has an immunologic basis, but these patients do not generally exhibit clinical signs of hypersensitivity (5).

Interest in immunologic mechanisms has increased since the patients with liver injury due to specific drugs often have circulating antibodies to native or modified liver proteins (5). For example, patients with liver injury associated with several drugs characteristically have circulating antibodies to liver and liver structure (5-9).

It appears that a reactive metabolite formed by these enzymes covalently binds to or otherwise alters the immunogenicity of the enzymes themselves. The presence of an antibody to a specific P450 therefore suggests a role for the enzyme in producing reactive metabolites (8). The detection of anti-P450 antibodies can potentially be useful in establishing the diagnosis of liver injury due to a specific drug (6, 8, 9).

Liver injury, both acute and chronic, is well described in patients receiving methyldopa (10). A positive Coombs' test develops frequently in these patients, and occasionally antinuclear and antismooth muscle antibodies develop (10). The usual onset within several weeks in many of the patients, female predisposition, rapid positive rechallenge, and concomitant development of considerable evidence of disturbed immunoregulation (Coombs' test, antinuclear antibody, hyperglobulinemia) suggest a role of a hypersensitivity reaction (10).

Subacute hepatic necrosis could result from long-term administration of isoniazid or methyldopa and has been described in recipients of cinchophen, propylthiouracil and hydralazine (10).

Warm autoimmune hemolytic anemia is characterized by an accelerated clearance of red blood cells associated with the presence of polyclonal anti-red blood cell immunoglobulin G autoantibodies that optimally bind to erythrocytes at 37°C (11). Anti-red blood cell immunoglobulin G autoantibodies of patients with warm autoimmune hemolytic anemia react with a variety of blood group related red blood cell antigens and other membrane components of autologous and homologous red blood

cells (11). The most common target antigens are the band-3 anion transporter, glycophorin A, and Rh-related proteins (11). In our case we detected warm autoimmune hemolytic anemia characterized by positive direct Coombs' [AHG 4(+), IgG 4(+), C3d 1(+)] and indirect Coombs' [warm 4(+)].

Dydogesterone-induced hepatitis has not been described previously in English literature. The patient presented with signs and symptoms of cholestasis with pruritus and jaundice. There was no history of viral exposure or chronic alcoholism. Her laboratory work-up showed high serum transaminases without any evidence of viral hepatitis, autoantibodies or Wilson's disease. Ultrasound and computerized tomography (CT) scan showed no dilatation of bile ducts, which ruled out extrahepatic cholestasis and main duct obstruction. These findings were supported by serum alkaline phosphatase, which is usually higher than three times the normal value in biliary obstruction.

The diagnosis of dydrogesterone-induced liver disease could have been definitely confirmed by a positive response to rechallenge. However, due to the severity of the reaction, re-administration even at a small dose was not attempted.

Drug-related liver damage is typically idiosyncratic as in this case. Many different mechanisms for idiosyncratic hepatotoxicity have now been elucidated. They include individual genetic variation in the metabolism of drugs, and the development of immune reactions to a drug or its metabolites. With the exception of a few drugs shown to cause liver damage in patients using a particular metabolic pathway, idiosyncratic drug injury is unpredictable in the sense that the susceptibility of individual patients cannot be tested before the drug is given. Timely recognition and drug withdrawal may avoid unnecessary intervention and prevent perpetuation of the hepatic injury. However, often the onset of hepatic injury by drugs may be delayed from days to several months.

The principles of management involve prompt withdrawal of the offending drug and symptomatic therapy to alleviate pruritus. Therapeutic strategies to alleviate pruritus are similar to those for other causes of cholestasis (12). They include cholestyramine and ursodeoxycholic acid, with rifampicin and opiate antagonists as second-line therapies (12). Other methods that have been employed were plasmapheresis, phototherapy, and cascade resin perfusion (12).

In conclusion, the possibility of dydrogesterone-induced cholestatic hepatitis must be borne in mind. It is recommended that dydrogesterone therapy should be discontinued as soon as the monitoring of liver function tests, including parameters indicating cholestasis, reveals marked alterations.

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