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Norethisteron Induced Cholestasis: A Case Report

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ABSTRACT

Norethisteron is a progesterone-only oral contraceptive (OCS) that is widely used in some gynecological disorders. The side effects of the drug are nausea, vomiting, thromboembolia and hypertension, however rarely do these lead to cholestasis. We present a 42-year-old female patient admitted with fatigue, jaundice, dark urine, itching subsequent to use of norethisteron for amenorrhea. Due to sustained elevation of bilirubin and cholestasis enzymes, the patient underwent a liver biopsy. Histopathologic examination revealed canalicular cholestasis which is usually observed subsequent to administration of steroidal drugs. The patient responded well to steroid administration, and clinical and biochemical recovery were achieved on the 6th month of therapy.

Key words: cholestasis, norethisterone, prednisolone

NORETHİSTERONA BAĞLI KOLESTAZ: BİR OLGU SUNUMU

ÖZET

Norethisteron bazı jinekolojik hastalıklarda kullanılan sadece progesteron içeren bir oral kontraseptiftir. Genellikle bulantı, kusma, tromboemboli ve hipertansiyona yol açmakla birlikte nadiren kolestaz tablosuna neden olur. Bu yazıda 42 yaşında amenore nedeniyle norethisteron kullanımına bağlı halsizlik, sarılık, koyu renkli idrar ve kaşıntı şikayeti ile başvuran bir kadın hasta sunulmuştur. Kolestaz enzimlerinde ve bilirubin düzeyinde yüksekliğin devam etmesi üzerine hastaya karaciğer biyopsisi yapıldı. Histopatolojik incelemesinde steroid grubu ilaçlarda görülebilecek kanaliküler kolestaz bulguları saptandı. Ampirik oral prednizolon tedavisi başlanan hastanın 6 ay içerisinde kliniğinde ve laboratuvar değerlerinde iyileşme görüldü.

Anahtar kelimeler: kolestaz, norethisteron, prednizolon

The incidence of cholestasis due to oral contraceptives (OCS) is approximately 1:10 000 in Western Europe, but as high as 1:4000 in Chile and Scandinavia (1). The oestrogenic component of the combined oral contraceptive pills is believed to be responsible for intrahepatic cholestasis (2). Norethisterone 19 is a synthetic progesterone derivate which is usually prescribed against abnormal uterine bleeding in women of reproductive age. Synthetic progesterones usually engage to enterohepatic cycle, and in contrast to the natural progesterones, they are more slowly metabolized in the liver and less strongly bound to plasma proteins (3,4). The mechanism of progestogen induced cholestasis remains unclear (2). In this report, we present a case of progesterone-induced intrahepatic cholestasis and briefly discussed the management of drug induced cholestasis.

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Case report

A 42-year-old female patient was admitted with fatigue, jaundice, dark urine, itching. She had been suffering from amenorhea and receiving norethisterone tablets for 2 months. Her complaints had started at the 1st month of progesteron therapy and had gradually increased. Laboratory examination revealed mild anemia (hemoglobin: 11.8 g / dl, hematocrit: 37.8%, mean corpuscular volume (MCV) 76 fl), elevated liver function tests (AST: 178

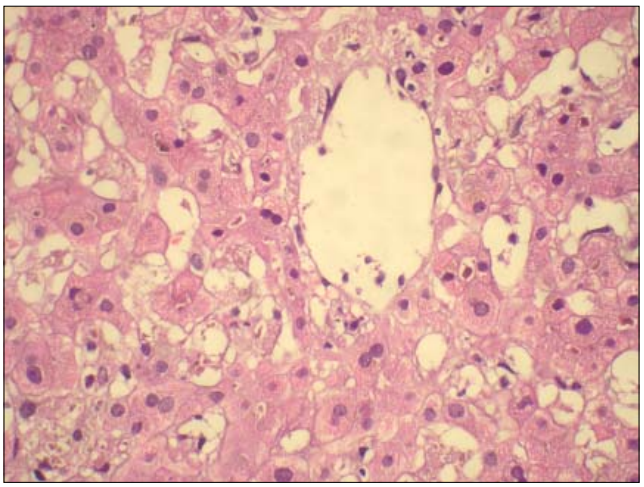

Figure 1. Centrilobular sinusal dilatation, cytolytic nekrobiozis, acute hepatocellular damage and intracanalicular cholestasis

U / L, ALT: 503 U / L, ALP: 224U / L, LDH: 222 U / L) and severe hyperbilirubinemia (total bilirubin: 19.8 mg / dl, direct bilirubin 9.9 mg / dl). Viral hepatitis markers including HBsAg, anti-HCV and AntiHAV IgM were negative. She had no history of chronic drug use except norethisterone and alcohol intake history den sonraya gelecek:She had no history of alcohol intake or chronic drug use except norethisterone. On physical examination, she had icteric scleras and scratch marks all over the body. Peripheral blood smear examination revealed hypochromic, microcytic erythrocytes, anisocytosis and poikilocytosis. On the second week of hospitalization, total bilirubin reached to 41.3 mg/dl, direct bilirubin was 20.7 mg / dl, indirect bilirubin was 20.6 mg / dl, ALP was: 344 U / L, GGT was 66 U / L, LDH was 252 U / L, ALT: was 16 U / L, AST: was 21 U / L. Itching did not respond to antihistaminics, cholestyramine, and ursodeoxycholic acid treatment. Serologic tests (cytomegalovirus, Epstein-Barr virus and herpes simplex type 2 IgM), and markers of autoimmune liver disease (antinuclear antibody, smooth muscle antibody, antimitochondrial, anti liver kidney microsomal antibody) were negative. The thyroid stimulating hormone, alpha-1 antitrypsin, and ceruloplasmin levels were within normal range. There was no sign of Keischer-Fleischer ring on opthalmic examination. No abnormality was observed in the ultrasonographic and tomographic examination of abdomen. The Ultrasound-guided percutaneous liver biopsy indicated centrilobular sinusal dilatation, cytolytic nekrobiosis, acute hepatocellular damage and intracanalicular cholestasis (Figure 1). Steroid therapy (prednisolone 32 mg/day) was initiated. The patient made a complete recovery and serial serum biochemical examinations showed complete normalisation of liver parameters at the 3rd week of prednisolone therapy. At the 6th month of follow-up, she has no clinical or biochemical sign of cholestasis.

Discussion

The side effects of OCS's on the gastrointestinal tract, liver and pancreas are rare but potentially serious (5). The oestrogenic component of combined oral contraceptive is usually accused of the development of intrahepatic cholestasis. Oestrogen-induced cholestasis can occur in women with previous obstetric cholestasis, and has also been described in other family members, suggesting the role of genetic susceptibility. Experimental animal studies suggest that canalicular bile transporters, particularly multidrug resistant protein 2 responsible for biliary secretion of several organic anions including bilirubin glucuronides, may be implicated in oestrogen-induced cholestasis (6). By lowering bile canalicular Na-K-ATPase activity, ethinyl oestradiol decreases bile acid transport independent of bile flow. In contrast, progestogens are not typically implicated in cholestasis (2). However, there are reports of intrahepatic cholestasis when high doses of the progesterones; norethisterone or megestrol acetate have been used to treat women with breast cancer. In rats, norethisterone can induce hepatic cholestasis associated with bile staining of hepatocytes (7,8,9). Symptoms include pruritus with anorexia, asthenia, vomiting, and weight loss without fever, rash or abdominal pain. The syndrome of OCS related jaundice is usually mild, with rapid resolution upon withdrawal of the drug (5, 10). Anabolic and contraceptive steroids typically produce this expression of hepatotoxicity (11). In the present case the liver biopsy showed cholestasis and dilatated biliary canaliculi with bile plugs, but with little or no inflammation and necrosis.

Steroids have rarely been associated with hepatotoxicity; morever, they are the treatment of choice for severe hepatitis (12). In a study from Korea, prednisolone treatment achieved response in eight days in three patients with prolonged hyperbilirubinemia and jaundice (13). Within 3 weeks of treatment with oral prednisolone, our patient showed complete clinic and biochemical improvement.

As a result, jaundice due to oral contraceptives is usually benign however, may be serious and long-lasting that well responds to prednisolone therapy.

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