Case Report

Enhanced Growth of Hepatic Hemangiomatosis in Two Adults after Postmenopausal Estrogen Replacement Therapy

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OZAKYOL, A. and KEBAPCI, M. Enhanced Growth of Hepatic Hemangiomatosis in Two Adults after Postmenopausal Estrogen Replacement Therapy. Tohoku J. Exp. Med., 2006, 210 (3), 257-261 — Liver hemangiomatosis is defined as extensive hemangioma in the liver. Although hemangioma is the most common hepatic tumor, diffuse hepatic hemangiomatosis is very rare. Most cases of hepatic hemangiomatosis are seen in infancy, but it is extremely rare in adults. This is the first report, showing the enhanced growth of diffuse hepatic hemangiomatosis after hormone replacement therapy. We report herein two unrelated women, 47 and 42 year-old, from different regions of Turkey, who admitted to hospital because of right abdominal pain with diffuse hepatic hemangiomatosis, developed after hormone replacement therapy for menopause. The patients were healthy, except for hemangiomatosis, and their physical examination, routine laboratory tests, and tumor marker levels were within normal limits. It should be noted that their abdominal ultrasonography was normal before hormone therapy, but ultrasonography on admission revealed numerous, ill defined, diffusely located liver nodules in both patients. Dynamic magnetic resonance imaging and scintigraphy have revealed that these lesions are compatible with hemangiomatosis. These results suggest that hepatic hemangiomatosis was induced by estrogen therapy. Consequently, hormone replacement therapy was discontinued, and the patients were followed up for 3 years. Their physical examination and blood chemistry, including liver enzymes, remained within normal range, and the follow-up examination with ultrasonography showed no changes in size of lesions. Because of the possible association of hemangioma with estrogen administration, decisions should be made carefully about estrogen therapy for patients who already have hemangioma, and the periodic ultrasonography examination should be planned to detect possible new growth of liver hemangiomatosis. —— hepatic hemangioma; hepatic hemangiomatosis; estrogen; hormone replacement therapy

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Hemangioma is a mesenchymal tumor and is defined as abnormal proliferation of blood vessels that may occur in any vascularized tissue. Hepatic hemangiomas are usually asymptomatic and often discovered incidentally. It is the most common hepatic tumor and makes up 54% of the
benign tumors of the liver (Reddy et al. 2001). Incidence of the liver hemangioma is approximately 2% in population with the predilection of female sex (Ochsner and Halpert 1958; Porayko and Choudhary 2001; Reddy et al. 2001). It is usually solitary but can be multiple in some cases. Liver hemangiomatosis is defined as extensive hemangioma of the liver and it is a very rare condition. Most cases of hemangiomatosis were reported in infancy (Starrte et al. 1996; Balaci et al. 1999) and, in adults, it is rare and only limited number of cases were presented in literature (Feurle 1990; Lehmann et al. 1999; Jayanti et al. 2000; Moon et al. 2000; Langner et al. 2001).

Although etiology of hemangioma is not completely understood, estrogen administration is a debated issue. Development of hepatic hemangiomas after estrogen medication was reported (Conter and Longmire 1988). However, estrogen administration has not been described in the published cases of hemangiomatosis (Feurle 1990; Lehmann et al. 1999; Jayanti et al. 2000; Moon et al. 2000).

We herein present two cases that developed diffuse hepatic hemangiomatosis after estrogen administration as a hormone replacement therapy for menopause. As far as we know, this report is the first one declaring growth of hepatic hemangiomas after hormone replacement therapy. Also, formulation of this report was concurred by both patients and Eskisehir Osmangazi University Ethics Committee.

**CASE REPORTS**

Forty-seven and 42 year-old unrelated women, who came from different regions of Turkey, were admitted to hospital with right upper abdominal pain and dullness. Their medical histories were unremarkable, except that both patients were menopausal and receiving oral conjugated estrogen. First patient, 47 year-old, had total abdominal hysterectomy and bilateral salpingo-oopherectomy because of profuse bleeding due to uterine myoma, four years ago, and she was put on oral conjugated equine estrogen (0.625 mg/day, 21/28 day) treatment. Second patient, 42 year-old, had irregular menstruation (she had not had her menstruation for three months) as well as vasomotor symptoms two years ago. At that time, she showed follicle stimulating hormone (48 IU/ml), luteinizing hormone (36 IU/ml) and estradiol (13 pg/ml), and was diagnosed as having menopause. Second patient was given oral conjugated equine estrogen (0.625 mg/day, 21/28 day) and medroxyprogesterone acetate (5 mg/day, 12/21 day).

Abdominal ultrasonography was performed in the two patients during diagnosis of menopause, showing no pathological findings. No liver nodules were observed at that time. First patient had been treated with estrogen for 4 years, and second patient for 2 years. Their physical examination and routine laboratory tests, including liver enzymes, were within normal limits. Tumor marker levels (carcinoembryonic antigen, alpha pheto protein, cancer antigen 19-9, cancer antigen-125, and cancer antigen 15-3) were also normal. Abdominal ultrasonography revealed similar findings in both patients: Numerous (more than 20), well-defined, hyper-hypo echoic, various sized (0.5-4 cm) nodules were diffusely located in both lobes of the liver (Fig. 1). On magnetic resonance imaging (MRI), all tumors showed low signal intensity on axial T1 weighted (spin echo) images, and high signal intensity on axial T2 weighted images (turbo spin echo) (Fig. 2A).

![Fig. 1. Axial ultrasonography image of the liver of First Patient after hormone therapy.](image)
Patients, also, underwent dynamic turbo fast low-angle shot MR examination. Dynamic gradient echo images were obtained before and after intravenous injection of contrast bolus of gadolinium. All tumors showed peripheral nodular enhancement on the arterial phase (Fig. 2B). During the delayed phase, all tumors showed progressive centripedal filling (Fig. 2C). These findings were typical for hemangioma. Also, red blood cell tagged technetium-99m scintigraphy of the liver was performed and showed the same result.

Finally, imaging methods and clinical features indicated hepatic hemangiomatosis. There were no complications (high-output heart failure, liver failure, and thrombocytopenia) due to hemangiomatosis. Surgery was not performed. Hormone replacement therapy was discontinued, and the patients were put on followed-up. During 3 years of follow-up, although they complained from mild right hypocondrium dullness from time to time, their quality of life was well. Their physical examination, and blood chemistry, including liver

Fig. 2. MRI of the liver of Second Patient after hormone therapy.
A: MRI demonstrating lesions with high signal intensities (arrows) in the right and left lobes of the liver on T2 weighted image.
B: MRI demonstrating lesions with peripheral nodular enhancement (arrows) on the arterial phase after gadolinium injection.
C: MRI demonstrating lesions with progressive centripedal filling (arrows) on the delayed phase after gadolinium injection.
enzymes, remained within normal range. After hormone cessation, the follow-up with periodic ultrasonography did not show any reduction or increase in size of hemangioma in each patient. Complications did not develop.

**DISCUSSION**

Even though hemangioma is the most common benign hepatic tumor, hemangiomatosis is extremely rare in adults. Hepatic hemangiomatosis is a condition of extensive hemangioma in the liver. We believe that estrogen therapy played a contributory role in the development of hepatic hemangiomatosis in our patients. Liver ultrasonographies of our patients were normal during diagnosis of menopause, and revealed lesions after hormone therapy. Abdominal ultrasonography is the primary imaging modality in the study of liver parenchymal lesions. Its sensitivity is high for hepatic hemangioma, even for lesions below 2 cm (Falappa et al. 1983). It is reasonable to think that ultrasonography, depending on operators’ competence, might miss detection of small lesions, but our cases had very large, as big as 4 cm in dia., lesions and would be very difficult to miss their detection during ultrasonographic examination performed prior to estrogen therapy. However, specificity of ultrasonography for hemangioma is not so high. Both red blood cell tagged technetium-99m scintigraphy and magnetic resonance imaging (MRI) has a high specificity for the diagnosis of hemangioma. McFarland et al. (1994) indicate that MRI accuracy rate for hemangiomas is 97%. For that reason, after determination of lesions, post-estrogen therapy, we have performed red blood cell tagged technetium-99m scintigraphy and MRI of the liver, and confirmed that lesions were indeed hemangiomatosis. Etiology of hemangiomas is not well defined, but the affects of female sex hormones are debated. Hepatic hemangioma is seen 5-6 times more frequently in women than men in adults (Ochsner and Halpert 1958; Poraloko and Choudhry 2001; Reddy et al. 2001). In addition, female patients often develop larger and multiple tumors than men (Reddy et al. 2001), and rapid enlargement of hemangioma during pregnancy are also reported (Saegusa et al. 1995). Growth of hemangioma after hormone replacement therapy is observed not only in the liver, in several other organs as well, such as breast (Mesurolle et al. 2003). In another report, increased frequency and severity of liver hemangioma was seen in estrogen treated mice, whereas, tamoxifen, an estrogen antagonist, significantly reduced the frequency and severity of liver hemangioma (El-Hashemite et al. 2005). All these data have proposed a relationship of hemangioma and female sex hormones. Besides hemangioma, benign hepatic tumors such as adenoma, focal nodular hyperplasia and hamartomas in women receiving estrogen therapy are also reported (Christopherson et al. 1975). Glinkova et al. (2004) evaluated the impact of female sex hormones on the natural history of liver hemangiomas and reported that hepatic hemangioma enlargement of the tumor were more frequent in hormone treatment exposed women than control group even though enlargement is not significant in size. Alternatively, Gemer et al. (2004) reported that presence of liver hemangiomas was not associated with menstrual, reproductive and oral contraception use history. The exact role of estrogens in the pathogenesis of hemangioma was investigated in several studies. Lehmann et al. (1999) suggested that liver hemangiomatosis was an angiogenesis-dependent condition with phases of activation and regression. Estrogen augments endothelial cell proliferation, migration and organization into capillary like structures (Schaper et al. 1996). It, in vitro, can promote the proliferation of hemangioma vascular endothelial cells (Xiao et al. 2004), and works in synergistic manner with vascular endothelial growth factor (Xiao et al. 2004). Sex steroid receptor positivity, especially estrogen, is found in hemangioma tissue, and this data suggests that hemangiomas are target tissues of estrogen (Lui et al. 1997).

Herman et al. (2005) followed-up hepatic hemangiomas and reported that they have a benign course with no complication. However, in their study, patients with hemangioma were not receiving estrogen during follow-up period. We have stopped estrogen treatment when we diag-
nosed hemangiomatosis. Although there are case reports, and the exception of Glinkova’s research, to the best of our knowledge, there exists no research which examines long term effect of estrogen therapy in patients with preexisting hemangiomas or hemangiomatosis. Experimental research shows that estrogen causes proliferation of hemangioma cells (Lui et al. 1997; Xiao et al. 1999, 2004). Furthermore, hemangiomatosis presents a higher risk to the patient than hemangioma. There is no specific therapy for hemangiomatosis, but in the presence of complications such as rupture, biliary obstruction of mass, cardiac failure due to arteriovenous shunting, and consumption coagulopathy, surgery is the preferred treatment. Although we lack sufficient data for the long-term prognosis of hemangiomatosis, because it is extremely rare, we think it is in the interest of patients who have hemangioma-tosis not to stay on estrogen replacement therapy. Risk–benefit analysis should be made for administration of estrogen to patients with preexisting hemangioma, and ultrasonographic follow-up is necessary. In addition, newly developing liver nodules in patients receiving estrogen should bring to mind the growth of liver hemangiomatosis.

References


