Enlargement of Multiple Cavernous Hemangioma of the Liver in Association with Pregnancy

Tomohiro Saegusa, Kazuki Ito, Noriuki Oba*, Masayuki Matsuda, Koichi Kojima, Kazushige Tohyama*, Miyuki Matsumoto**, Katsutoshi Miura** and Harumi Suzuki**

Four cavernous hemangiomas were found in a 34-year-old woman after the first delivery. All four hemangiomas became enlarged after the second delivery. Due to complaints of symptoms of compression, and to rule out malignancy, surgical intervention was employed. Histologically, the tumors were typical cavernous hemangiomas. Although a relationship between enlargement of hemangiomas and estrogen was suggested, estrogen receptors were not detected in the tumors.

Key words: induction of ovulation, estrogen, surgical treatment, estrogen receptor

Introduction

Cavernous hemangiomas are encountered more often in women (1–4). Enlargement of these tumors after estrogen replacement therapy (5, 6) or during pregnancy (4, 7–9) has been reported, thus the relationship between hemangiomas and estrogen has been suggested. The tumors sometimes appear as multiple nodules (4, 10), but there have been no reports of simultaneous enlargement of multiple nodules. Here, we report a case of multiple cavernous hemangioma of the liver which were found after the first delivery and were enlarged on CT films after the second delivery.

Case Report

A 34-year-old woman was admitted to the hospital for examination of multiple liver tumors. The patient had married when she was 23 years old, but had been infertile. Her menses tended to be prolonged. In 1984, at the age of 26, she consulted a doctor because she wanted to become pregnant. The doctor made the diagnosis of ovarian insufficiency and began induction of ovulation using clomiphene. Four months later, she became pregnant, but aborted spontaneously in the 11th week. Although clomiphene therapy was continued, she remained infertile for the subsequent 6 months. In 1986, the regimen was changed to cyclic gonadotropins, using human menopausal gonadotropin and human chorionic gonadotropin. She became pregnant a second time. However, in the 30th week, the fetus died. The same induction regimen was re-instituted. In 1988, the third pregnancy culminated in a delivery by cesarean section.

Two months after delivery, in 1989, at the age of 31, she felt a mass in the right lateral region of the abdomen and consulted the same doctor. Computed tomography of the abdomen (Figs. 1A–D) revealed four tumors of the liver, all with diameters of less than 50 mm. A diagnosis of multiple cavernous hemangioma of the liver was made. She did not visit the doctor again after that diagnosis because he said that the tumors would not be a problem.

In 1991, at the age of 33, she still had oligomenorrhea, but the patient spontaneously became pregnant a fourth time. The fetus was delivered by cesarean section. Six months later, she experienced right hypochondrial discomfort and noticed enlargement of the mass. She consulted another clinic and multiple liver tumors were noted. The patient was referred to our hospital for further evaluation.

Her family history provided no pertinent findings. At the age of 24, she underwent an operation for congenital dislocation of a hip, but no blood transfusion was given. There was no history of alcohol intake or smoking. On physical examination, she appeared healthy. Her body temperature was 36.2°C, and her pulse was 72. The blood pressure was 120/60 mmHg. There were no eruptions on the skin. Neither pallor nor icterus were observed. The head, neck, lungs and heart were normal. Two fist-sized elastic tumors, which had smooth surfaces, were palpated in the epigastrium and right hypochondrium. They showed respiratory mobility. The tumors were not tender and no bruit was heard. Neurologic examination was negative.

From the Department of Hepato-gastroenterology, *the Department of Surgery and **the Department of Pathology, Shizuoka General Hospital, Shizuoka
Received for publication June 13, 1994; Accepted for publication November 18, 1994
Reprint requests should be addressed to Dr. Tomohiro Saegusa, the Department of Hepato-gastroenterology, Shizuoka General Hospital, Kita-Ando 4-27-1, Shizuoka 420
Urinalysis was normal. The hematocrit was 40.8%. The white cell count was 3,300 and the platelet count was 235,000 per cubic millimeter. The aspartate aminotransferase level was 22 IU per liter, the alanine aminotransferase level was 17 IU per liter, the alkaline phosphatase level was 136 IU per liter and the lactate dehydrogenase level was 274 IU per liter. The protein, bilirubin, urea nitrogen, creatinine and electrolytes were normal. The alpha-fetoprotein level was 5.6 ng per milliliter, and
Enlargement of Multiple Hemangioma

Fig. 2. Bloodpool scintigram of liver. Multiple hot nodules are seen in the liver.

the carcinoembryonic antigen was not detected. HBs antigen and anti-HCV antibody were negative.

The chest radiogram showed a normal appearance. Computed tomography of the abdomen showed multiple low-density tumors with a well-defined margin in the liver. They showed early peripheral opacification after contrast enhancement (Figs. 1E-H). Each tumor was enlarged, compared with previous CT films at the age of 31 (Figs. 1A–D). The tumor in segment 3 (defined by Couinaud) (11) had grown in diameter from 23 mm to 45 mm, in segment 4, from 46 to 61 mm, in segment 6, from 27 to 45 mm, and in segment 8, from 35 to 61 mm. There were also some new lesions (Figs. 1A and E).

Multiple hot nodules were consistently observed on blood pool scintigrams with 99mTc-labeled red blood cells (Fig. 2). A hepatic arteriogram showed cotton wool-like patchy pooling in each of the liver tumors in the late arterial phase (Fig. 3). A diagnosis of multiple cavernous hemangioma of the liver was made.

Because each tumor had obviously become enlarged over the 3 years, malignancy had to be ruled out. The patient had been suffering from symptoms of compression during the last several months. Therefore, we decided to remove the tumors surgically.

Upon laparotomy (Fig. 4), four giant soft dark-red tumors were observed on the hepatic surface, accompanied by some small nodules showing the same characteristics. Partial resection of the liver was performed to remove the four largest tumors, but some residual nodules were left.

Gross examination of the resected specimens revealed that the tumors were easily visible from the external surface, and the borders of the tumors were well defined. Histologic examination (Fig. 5A) revealed cavernous vascular spaces incompletely separated by septa, which were composed of fibrous tissue and covered with endothelial cells. Some small hemangiomas were observed in the macroscopically normal liver tissue surrounding the larger tumors (Fig. 5B). These findings proved that the tumors were typical cavernous hemangiomas. There was no evidence of malignancy in any of the tumors or nodules. The tumor tissues were negative for estrogen receptors and progesterone receptors, as measured by the multiple-point dextran-coated charcoal assay (12).

The patient was healthy and her menstrual cycle was normal one year after the operation. CT films taken at that time showed some residual nodules, but they had not increased in size.

Discussion

The patient had multiple cavernous hemangiomas of the
Figs. 5A and B. Microscopic sections. A) The hemangioma is clearly separated from the liver parenchyma (Elastica van Gieson stain ×25). B) Small hemangiomas are seen in macroscopically normal liver tissue (Elastica van Gieson stain, ×25).

liver, which were found after induction of ovulation and the first delivery. Three years later, after the second delivery, enlargement of the tumors was discovered. Because the tumors were symptomatic and due to the possibility of malignancy based on their marked enlargement, we performed surgical excision of the tumors. The diagnosis of cavernous hemangiomas was histologically proven in the resected specimens.

Cavernous hemangiomas are detected in 2.3% of autopsy series (10). They are the most common benign tumor of the liver (13, 14). The tumors are multiple in 9–22% of patients (4, 10). Symptoms due to hemangioma include the sensation of an abdominal mass, abdominal pain, abdominal discomfort, digestive difficulty and abdominal distention. However, the tumors are asymptomatic in most patients. According to Schwartz and Husser (4), about half of the patients whose tumors are larger than 4 cm have symptoms. Adam et al (14) defined hemangiomas whose diameter exceeded 4 cm as “giant hemangiomas”.

Resection is generally performed for symptomatic hemangioma (15). Other indications for operation include rapid growth, marked thrombocytopenia and rupture with intraperitoneal bleeding (4). There have been some reports of spontaneous rupture of a hemangioma (7, 14, 16). However, Schwartz and Husser (4) stated that the risk of rupture is not an indication for excision, because the potential for rupture is minimal and rupture is not necessarily fatal. Baer et al (15) reported six cases, that had a confident preoperative diagnosis of hemangioma, which upon operation were found to be malignant tumors. Thus, they proposed that surgery should be indicated when malignancy cannot be ruled out, even in cases of asymptomatic hemangiomas. Because the present patient complained of compression and progression of the tumors suggested malignancy, we performed a surgical removal.

The present patient had been administered clomiphene and gonadotropins, and she experienced enlargement of the hemangiomas after delivery. Although she had been diagnosed as having ovarian insufficiency, she seemed to have developed a hyperestrogenic state at those times. Some reports have suggested a relationship between hemangiomas and estrogen. Conter and Longmire (6) reported four cases of recurrent hemangiomas after resection or radiation therapy. In their series, three of the four recurrent cases were in patients who had received estrogen replacement therapy. There have been some reports of enlargement of tumors during pregnancy (4, 7–9). In addition, Sewell and Weiss reported a case of spontaneous rupture in the fourth month of pregnancy (7).

As mentioned above, cavernous hemangiomas sometimes show progression, but the mechanism of enlargement is not clear. Conter and Longmire (6) observed recurrence after complete resection and suggested that the recurrence was the result of growth of true neoplasm. In the present case, the growth of the tumors seemed to be in association with pregnancy. About 80% of all breast cancer cases have estrogen receptors or progesterone receptors in the tumor tissue (17), and the cancer shows progression in association with hormone status. There have been no reports of estrogen receptors in cavernous hemangiomas. Progression of hemangiomas in the present case may not have been a direct effect of estrogen, because estrogen receptors were not detected in the tumors. Many kinds of cytokine such as fibroblast growth factor are produced in fetus-placenta complex (18). Some of them may be related to progression of cavernous hemangiomas, because they can induce angiogenesis, but there have been no reports to document this.

Trastek et al (2) suggested that the enlargement is due to dilatation of existing channels rather than to new growth. Considering the small hemangiomas in the macroscopically normal liver tissue of the present case, their hypothesis seems feasible. Winkler and Poulsen (19) reported that oral contraceptives, which are estrogen analogs, might induce periportal congestion. The hemodynamic status in pregnant women is different from that of non-pregnant women. The renin-angiotensin-aldosterone system is activated in pregnant women, because estrogen stimulates the synthesis of angiotensinogen and the secretion of renin (20). The levels in plasma of deoxycortico-
sterone (DOC) also increase during pregnancy because proges-
terone in plasma, which is increased in pregnant women, is
converted to DOC (21). High levels of mineralocorticoid con-
tribute to the increase in blood volume in pregnant women. In
spite of the increased levels of angiotensin II, most pregnant
women are not hypertensive. Everett et al (22) suggested that
prostaglandin mediates the refractoriness of pregnant women to
the pressor effects of angiotensin II. These findings suggest that
the mechanism of enlargement of hemangiomas in pregnant
women may be ectasia of preexisting tissue due to a change in
the hemodynamics such as the increase in blood volume and
prostaglandin (i.e. indirect effects of estrogen and pregnancy).

References

1) Henson SW Jr, Gray HK, Dockerty MB. Benign tumors of the liver. Surg
2) Trastek VF, van Heerden JA, Sheedy PF II, Adson MA. Cavernous
3) Kawarada Y, Mizumoto R. Surgical treatment of giant hemangioma of
4) Schwartz SI, Husser WC. Cavernous hemangioma of the liver: A single
5) Morley JE, Myers JB, Sack FS, Kalk F, Epstein J. Enlargement of
cavernous haemangioma associated with exogenous administra-
6) Conter RL, Longmire WP Jr. Recurrent hepatic hemangiomas: Possible
7) Sewell JH, Weiss K. Spontaneous rupture of hemangioma of the liver.
with combined use of laparoscopy and hepatic arteriography. Am J Surg
9) Creasy GW, Flickinger F, Kraus RE. Maternal liver hemangioma in
10) Ochsner JL, Halpert B. Cavernous hemangioma of the liver. Surgery 43:
577, 1958.
11) Couinaud C. Lobes et segments hepatiques. Note sur l’architecture
12) Thibodeau SN, Freeman L, Jiang NS. Simultaneous measurement of
estrogen and progesterone receptors in tumor cytosols with use of 125I-
13) Henson SW Jr, Gray HK, Dockerty MB. Benign tumors of the liver. Surg
14) Adam YG, Huvos AG, Fortner JG. Giant hemangiomas of the liver.
15) Baer HU, Dennison AR, Mouton W, Stain SC, Zimmermann A, Blumgart
LH. Enucleation of giant hemangiomas of the liver: Technical and
17) Wintliff JL. Steroid-hormone receptors in breast cancer. Cancer 53: 630,
1984.
Fibroblast growth factor in the human placenta. Biochem Biophys Res
19) Winkler K, Poulsen H. Liver disease with periportal sinusoidal dilatation:
A possible complication to contraceptive steroids. Scand J Gastroenterol
20) Casey ML, MacDonald PC, Simpson ER. Endocrinological changes of
pregnancy, in: Williams Textbook of Endocrinology, Wilson JD, Foster
21) Winkel CA, Milewicz L, Parker CR Jr, Gant NF, Simpson ER, MacDonald
PC. Conversion of plasma progesterone to deoxycorticosterone in men,
nonpregnant and pregnant women, and adrenalectomized subjects: evi-
dence for steroid 21-hydroxylase activity in nonadrenal tissues. J Clin
22) Everett RB, Worley RJ, MacDonald PC, Gant NF. Effect of prostaglandin
synthetase inhibitors on pressor response to angiotensin II in human