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Asymptomatic ovarian hemangioma in a postmenopausal patient with elevated estrogen

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Summary

Ovarian hemangiomas are rare. Here, the authors report an asymptomatic ovarian hemangioma in a postmenopausal patient. Ultrasound revealed a left ovarian cyst measuring 2.06×1.74×2.11 cm in a 57-year-old postmenopausal female. On preoperative examination, estrogen and carbohydrate antigen 72-4 (CA72-4) were 131 pmol/L and 7.88 U/mL, respectively. The results of intraoperative frozen section examination and final histopathology were indicative of an ovarian hemangioma. This rare case of asymptomatic ovarian hemangioma with elevated estrogen might demonstrate a possible relationship between estrogen levels and ovarian hemangioma.

Key words: Ovarian hemangioma; Estrogen; CA72-4; Asymptomatic.

Introduction

Ovarian hemangiomas are rare and benign tumors. Since they were first described by Payne in 1869 [1], only 60 or so cases have been sporadically reported in the literature. Although the incidence is low and ovarian hemangioma pathogenesis is unclear, it is important to learn more about this condition as it can be confused with ovarian cancer. Here the authors describe a rare, asymptomatic ovarian hemangioma in a postmenopausal patient who presented with elevated levels of estrogen and carbohydrate antigen 72-4 (CA72-4).

Case Report

A 57-year-old Chinese female was diagnosed with an ovarian tumor following a routine medical check-up in June 2014. She had experienced menopause seven years earlier. Her clinical history was negative for abdominal pain, vaginal bleeding, and other gynecologic complaints. A physical examination showed normal appearing external genitalia with cervical atrophy. A transvaginal ultrasound scan revealed a middle echo in the left ovary measuring about 2.06×1.74×2.11 cm. The boundaries were clear with star-point color blood flow around the lesion. A CT scan confirmed irregular soft tissue shadows measuring about 3.4×2.4 cm in the left ovary; 45 HU on normal CT, which increased to 59 HU with enhancement. The serum levels of tumor markers CA12-5 and CA19-9 were within normal limits, but CA72-4 was 7.88 U/mL (normal range, 0-6.9 U/mL). Her serum estrogen was 131 pmol/L (normal range for postmenopausal females, 73.4-110 pmol/L). Serum levels of testosterone, luteinizing hormone, and follicle-stimulating hormone were within normal ranges.

An estrogen-secreting tumor of the ovary, possibly a granulosa or theca cell tumor, was suspected clinically. The patient underwent a laparoscopic hysterectomy and a bilateral salpingo-oophorectomy. Her serum estrogen and CA72-4 levels decreased to within normal limits one week after surgery.

Gross intraoperative examination revealed that the left ovary was enlarged and plump with a smooth outer surface. The uterus and right ovary appeared normal. The endometrium was thin and smooth. Cut sections of the left ovary revealed a brownish-red, honeycombed cyst mass measuring 2.5×1.5×1 cm in the medulla with relatively clear boundaries. Kermesinus blood was visible in the multilocular spaces. Intraoperative frozen section consultation yielded a diagnosis of ovarian hemangioma.

Microscopically, the mass was composed of multiple irregular dilated vessels with thin and thick walls. The vessel lumens were filled with red blood cells, and the endothelial layer was composed of a single layer of endothelial cells without nuclear atypia. Stromal luteinization was not seen in the peripheral stroma. The cells lining the vascular spaces were immunoreactive for endothelial markers, including CD31 (Figure 1) and CD34 (Figure 2). Immunohistochemistry revealed the intensely vascular nature of the lesion, confirming an ovarian cavernous hemangioma. Estrogen receptor (ER) and progesterone receptor (PR) were negative in the endothelial cells (Figure 3), but ER was expressed in the stromal cells around the hemangioma.

Discussion

A true ovarian hemangioma is a mass of vascular channels of variable sizes with minimal stroma, which is reasonably circumscribed and distinct from the remaining ovary or involving the ovary almost entirely [2]. Hemangiomas are divided into capillary and cavernous types based on blood vessel caliber. Most ovarian hemangiomas are cavernous, but some are mixed cavernous-capillary, or

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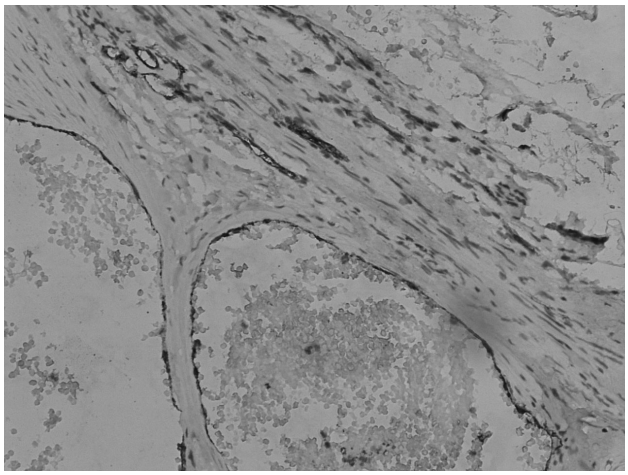

Figure 1. — Immunohistochemical staining for CD31 is positive in the nucleus of endometrial cells (original magnification, ×200).

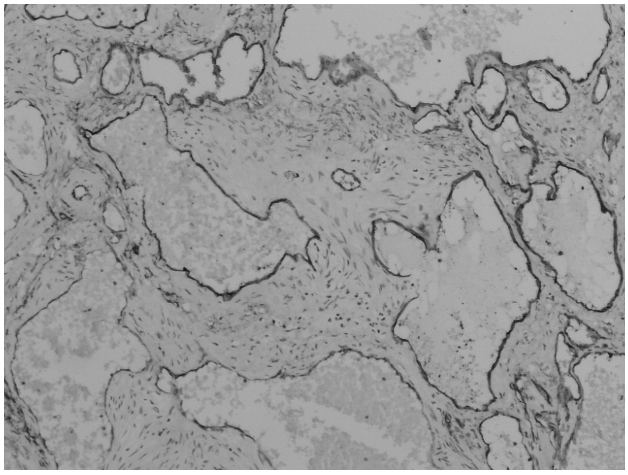

Figure 2. — Immunohistochemical staining for CD34 is positive in the nucleus of endometrial cells (original magnification, ×100).

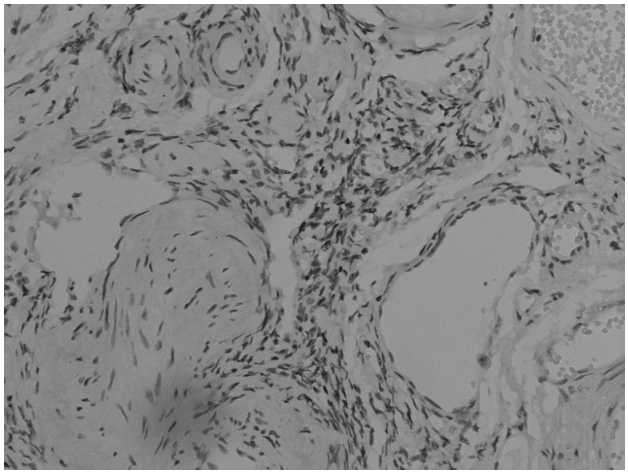

Figure 3. — Immunohistochemical staining for estrogen receptor (ER) is positive in the stromal cells surrounding the hemangioma, whereas it is negative in the endometrial cells of the hemangioma (original magnification, ×200).

pure capillary. Ovarian hemangiomas are usually unilateral, and most often in the medulla and hilus.

Most ovarian hemangiomas are incidentally identified intraoperatively or during work-up for another unrelated disease. However, some patients present with an adnexal mass, abdominal pain, calcification, pseudo-Meigs', or even elevated CA-125, and ascites, mimicking ovarian carcinoma [3, 4].

The origin of ovarian hemangioma is controversial. Several cases of ovarian teratoma with a massive hemangiomatous proliferation have been reported, and it has been proposed that hemangiomas may originate from germ cells as part of a teratoma [5]. On the other hand, ovarian teratomas with a prominent vascular component are distinct from teratomatous areas and can be distinguished from pure hemangioma by the presence of typical dermoid elements such as skin, hair, and cartilage [5]. On the other hand, Prus *et al.* used molecular genetic analysis using simple sequence repeat (SSR) polymorphic markers to show that ovarian vascular tumors can arise from ovarian somatic cells rather than germ cells [6]. Comunoglu *et al.* reported a case of ovarian cavernous hemangioma with concomitant contralateral mature cystic teratoma in an 81-year-old patient, indicating that these two tumors can independently coexist [7].

Several cases of ovarian hemangioma with stromal luteinization have been reported [2, 3, 8-12]. Stromal luteinization is most frequently seen in pregnancy but also occurs as a reactive phenomenon to the presence of expansile ovarian lesions. Several hypotheses have been suggested to account for stromal luteinization in non-pregnant patients. One theory is that the expanding tumor mass produces a mechanical effect on the adjacent tissue, mimicking the effect of the expanding follicle [13]. Another is that stroma-stimulating substances secreted by neoplastic cells cause stromal luteinization [3].

Some authors have considered stromal luteinization around ovarian hemagiomas to be the result of mechanical action [2]. Androgens produced by luteinized stromal cells are mainly converted to estrogen in the adipose tissue, which can result in both hyperandrogenism and hyperestrogenism [11]. The end results are endometrial hyperplasia and endometrial carcinoma [8, 9, 11]. However, there are several issues that are not explained by this hypothesis: 1) besides the affected ovary, stromal luteinization was also observed in the normal contralateral ovary [8, 9]; 2) stromal luteinization is proportional to the volume of tumor in contact with the stroma, but not all cases have stroma reactions [13]. Stromal luteinization might appear around smaller ovarian hemagiomas [2, 8], but not larger lesions [14]. This cannot be explained by mechanical action. In the present case, the patient's serum estrogen was elevated, but stromal luteinization was not observed.

Hormones are thought to play a crucial role in hemangioma development [9, 10] although the effect of estrogen is not well-defined. Clinical and laboratory evidence indicates that estrogen increases the number of endothelial pro-

genitor cells (EPCs) and angiogenic factors such as matrix metalloproteinase 9, vascular endothelial growth factor, nitric oxide, and other related factors to promote hemangioma formation [15]. As estrogen stimulates vascular growth, some authors hypothesize that hyperestrogenism resulting from stromal luteinization or hyperthecosis stimulates ovarian hemangioma development [9, 10]. Miliars *et al.* found that endothelial cell nuclei in ovarian hemangioma in one patient were positive for ER and PR [10]; however, some of the endothelial cells were ER negative [2, 11, 14]. In the present case, the ovarian stroma adjacent to the hemangioma was positive for ER, while the hemangioma endothelium was not, similar to previous case reports [11, 14].

In the ovarian hemangioma cases described so far, few authors have mentioned serum estrogen. To the present authors' knowledge, this is the first report of asymptomatic ovarian hemangioma with only elevated serum estrogen in a postmenopausal female. The elevated estrogen level is presumably related to the ovarian hemangioma because the patient was postmenopausal. While it has been proposed that ovarian tumor cells directly secrete hormones, no direct proof has been found to support this [13]. In the present case, there was no stromal luteinization associated with the elevated serum estrogen, and the authors propose that ovarian hemagiomas may promote the secretion of endocrinologically active substances from vascular endothelial cells. This speculation may even explain the symptom of ascites in patients with ovarian hemangiomas. Several publications have reported ovarian hemangioma combined with massive ascites; these cases were clinically suspected to be ovarian malignancies, and the ascites disappeared postoperatively [3, 4]. Although the mechanism of ascites in ovarian hemangioma remains unclear, vascular disturbance may play a role.

Here, the authors describe an asymptomatic ovarian cavernous hemangioma in a postmenopausal female with elevated estrogen. The relationship between hemangiomas and estrogen and stromal luteinization is still unclear and should be clarified.

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