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Case Report

Juvenile granulosa cell tumor with massive ascites: A case report and immunohistochemical study of ascites formation

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Summary

Juvenile granulosa cell tumors (JGCTs) are rare tumors, representing 5% of all granulosa cell tumors (GCTs) that occurs in premenarchal girls and young women. Clinical signs in Juvenile granulosa cell tumor after adolescence are menstrual irregularities or amenorrhea in most cases. We describe here a rare case of 23-year-old nulliparous woman with Juvenile granulosa cell tumor, whose only clinical manifestation was abdominal distention due to massive ascites. The patient underwent mass resection with salpingo-oophorectomy. No metastatic implants were noted in the peritoneal cavity, and cytology of ascitic fluid was negative for malignancy. Immunohistochemically, the staining for vascular endothelial growth factor (VEGF) was observed diffusely in the cytoplasm of tumor cells and partly in the endothelial cells, together with marked tumor microvessel density visualized by staining with blood endothelial marker CD34. These results suggest that vascular endothelial growth factor-driven angiogenesis and increased vascular permeability in Juvenile granulosa cell tumor may cause massive ascites production from the tumor itself.

Key words: Juvenile granulosa cell tumor (JGCT); massive ascites; vascular endothelial growth factor (VEGF).

Introduction

Granulosa cell tumors are a group of estrogen producing sex cord stromal tumors of the ovary. They occur in 95% of the cases in adults, and only about 5% of the cases which differ in histologic characteristics, are of juvenile type [1]. In a study comprising of 125 cases of juvenile granulosa cell tumor, 44% of the tumors occurred before the first decade of life and only 3% developed after the third decade [2]. Clinical signs in juvenile granulosa cell tumor after adolescence are menstrual irregularities or amenorrhea in most cases.

We report here a rare case of 23-year-old nulliparous woman with juvenile granulosa cell tumor, whose only clinical manifestation was a sudden onset of abdominal distention due to massive ascites. We also include the immunohistochemical analysis of ascites formation with respect to possible relationship between the expression of vascular endothelial growth factor and angiogenesis.

Case

A 23-year-old nulliparous woman presented with a progressive abdominal distention for about two weeks. She did not experience any menstrual irregularities previously. Physical examination revealed shifting dullness on a very distended abdomen. Abdominopelvic magnetic resonance imaging showed a multilocular cystic component and solid areas arising from the right ovary with large aggregates of ascites (Figure 1). Preoperative tumor markers and hormone levels were as follows: CA-125 244 U/ml (normal range, $<$ 35 U/ml); alpha-fetoprotein (AFP) $<$ 0.7 ng/ml (normal range, $<$ 5.0 ng/ml); CEA 2.0 ng/ml (normal range, $<$ 5.0 ng/ml); CA19-9 0.6 U/ml (normal range, $<$ 37 U/ml); estradiol 2760 pg/ml; FSH $<$ 0.10 U/ml; LH $<$ 0.10 U/ml; testosterone 0.76 ng/ml (normal range, 0.1 to 0.9 ng/ml).

During explorative laparotomy a large mass originating from the right ovary was found. The dark reddish tumor was encapsulated yet so edematous and fragile that it was ruptured during the procedures (Figure 2). No metastatic implants were noted in the peritoneal cavity. The liver, spleen, bilateral paracolic gutters, bowel, and the space beneath the diaphragm were all free of tumor. Tumor resection with right salpingo-oophorectomy and partial omentectomy was performed through which about 5 liters of transudate ascites fluid was evacuated from the abdomen. Cytology of ascites fluid was negative for malignancy. In macroscopic analysis the tumor appeared necrotic and hemorrhagic. Microscopic examination also showed granulosa cells surrounding the microfollicules with hyperchromatic nuclei. In immunohistochemical staining these tumor cells were strongly positive for calretinin and alfa-inhibin (INHA). Nuclear mitotic figures were frequent, and Call-Exner bodies could not be found (Figure 3). These findings supported the diagnosis of juvenile granulosa cell tumor of the ovary. To analyze tumor angiogenesis and visualize the tumor microvessels, paraffin-embedded sections were immunostained with vascular endothelial growth factor (VEGF) and vascular endothelial marker, CD34. The staining of VEGF was dif-

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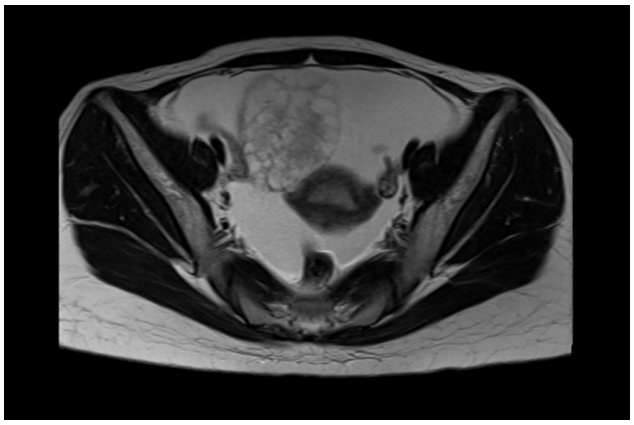

Figure 1. Abdominopelvic CT scan shows a multilocular cystic component and solid areas arising from the right ovary with large amounts of ascites.

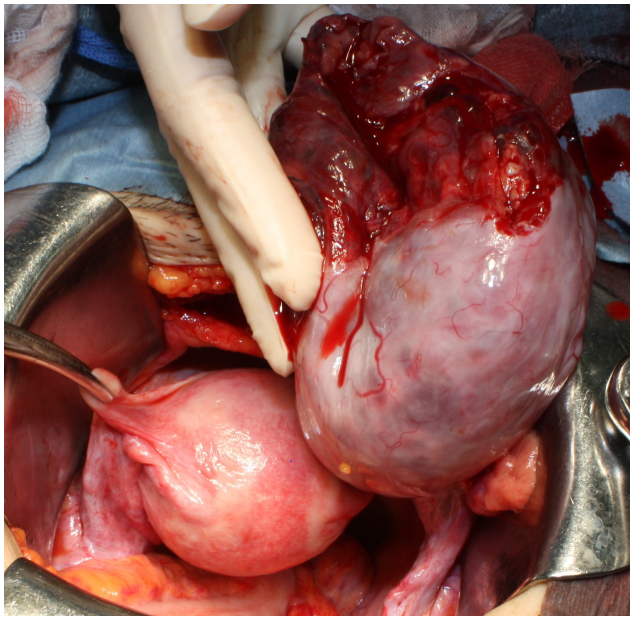

Figure 2. A dark reddish tumor originating from the right ovary is encapsulated, but partly so congestive and fragile that it was ruptured during the procedures.

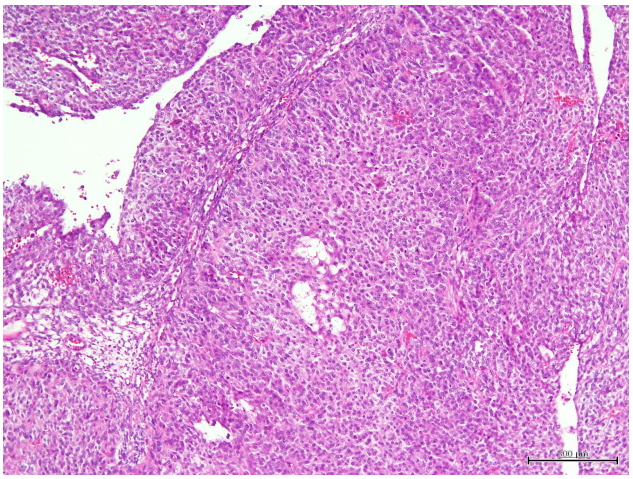

Figure 3. Microscopic examination shows granulosa cells surrounded the microfolliculars with hyperchromatic nuclei. Nuclear mitotic figures are frequent and Call-Exner bodies are not found.

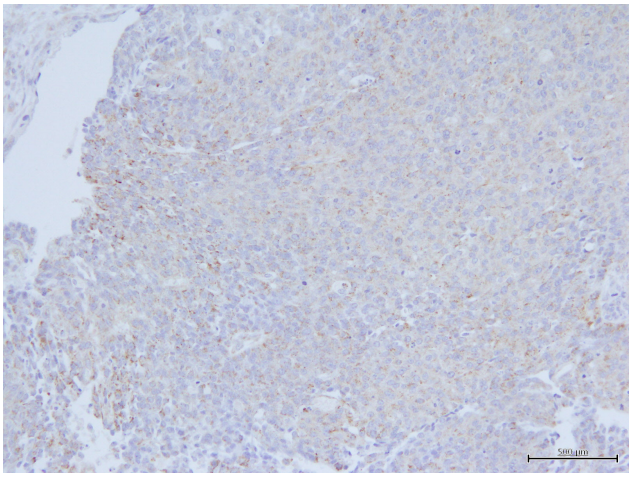

Figure 4. The staining for VEGF is diffusely observed in the cytoplasm of tumor cells.

fusely positive in the cytoplasm of tumor cells (Figure 4), and partially in the endothelial cells. Marked tumor microvessel density (MVD) visualized by CD34 demonstrated more than 60 vessels per visual field (Figure 5).

After the surgery, the ascites disappeared rapidly, and the levels of CA-125 and estradiol were decreased whereas the levels of LH and FSH were increased. No recurrence has been found 12 months post-surgery.

Discussion

Granulosa cell tumors are derived from the granulosa cells and hormonally active neoplasms secreting high level of estrogen. Symptoms related to hyperestrogenism occurs in all ages. In prepubertal age group, precocious puberty with breast development, increased pubic hair, vaginal bleeding [3] and increased growth is observed. In the reproductive age group, altered menstrual patterns like menorrhagia, intermenstrual bleeding or amenorrhea may manifest [4]. Postmenopausal bleeding is the most common finding in the postmenopausal age group. The present case is unique because the patient was free of such symptoms and her presentation was mainly massive ascites leading to sudden enlargement of the abdomen.

The reason often given as to why massive amounts of ascites fluid accumulate in cases of borderline ovarian tumors such as granulosa cell tumor is that the fluid is the product of peritoneal tumor implants. However, the case presented was stage I tumor with massive ascites without metastatic implants. Interestingly the cytodiagnosis of the ascites was negative for tumor cells. Moreover, the ascites was serous

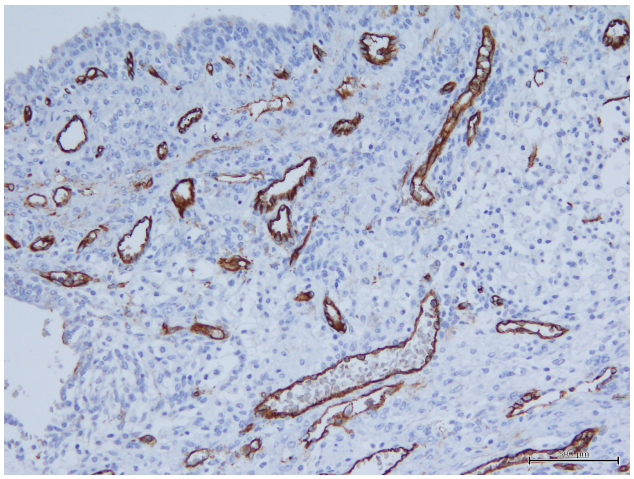

Figure 5. Marked tumor microvessel density visualized by CD34 is demonstrated.

(clear), so it was not due to the rupture of a tumor cyst. The pathophysiology of ascites in ovarian tumors in general remains hypothetical. Miyoshi *et al* [5] have reviewed several proposed theories concerning the source of ascites namely, production of ascites fluid from the tumor, lymphatic obstruction, hormonal stimulation, release of inflammatory mediators, or tumor torsion. It is noteworthy that the ascites disappeared completely after resection of the mass, and that there was no recurrence of disease. This strongly suggests that the ovarian tumor had either produced or induced the ascites. Rubinstein *et al*. [6] suggested that the ascites formation results from a discrepancy between the arterial supply to a large tumor mass tissue and the venous and lymphatic drainage of the same mass, leading to stromal edema and transudation. This mechanism might contribute to rapid ascites formation in the present case because the tumor was edematous and congestive. In addition, the immunohistological analysis demonstrated the diffuse staining of VEGF in the cytoplasm of tumor cells and marked tumor angiogenesis.

VEGF is a member of the family of heparin binding proteins that act directly on endothelial cells to induce proliferation and angiogenesis, and it is expressed in the granulosa cells of preovulatory and ovulatory follicles and most abundantly in the granulosalutein cells of the highly vascularized corpus luteum [7]. VEGF is also known to be the main factor contributing towards ovarian hyperpermeability and abdominal ascites, mechanism by which HCG triggers vascular permeability in iatrogenic ovarian hyperstimulation syndrome (OHSS) patients [8].

Based on the existing literature and from our results, it might be speculated that VEGF-driven angiogenesis and increased capillary permeability in the tumor and its vasculature plays an important role in ascites formation in juvenile granulosa cell tumors without peritoneal implants.

Conflict of Interest

The authors have no conflicts of interest in connection with submitted material.

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