CLINICOPATHOLOGICAL FEATURES OF JUVENILE GRANULOSA CELL TUMOR WITH AN EXTENSIVE MUCINOUS COMPONENT. CASE REPORT

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CLINICOPATHOLOGICAL FEATURES OF JUVENILE GRANULOSA CELL TUMOR WITH AN EXTENSIVE MUCINOUS COMPONENT. CASE REPORT (Abstract): Granulosa cell tumors (GCTs) are a rare type of ovarian neoplasm accounting for only 2-3% and their mix with mucinous elements is uncommon. Despite their favorable natural course, correct diagnosis is imperative for proper management to prevent metastatic spread and local recurrences. We herein report a case of a 34-year-old female patient presenting to our clinic with a pelvic mass which required surgical removal. Her past medical history was peculiar: she was diagnosed with a right ovarian tumor for which she underwent total hysterectomy with bilateral salpingo-oophorectomy. Histological features of the specimen suggested the diagnosis of mucinous ovarian carcinoma. Seven years later, she underwent a right hemicolectomy for a tumor recurrence involving the ascending colon, followed by the same histological diagnosis. After another eight years, a computed tomography scan showed a pelvic tumor which was removed and after histological evaluation with extensive immunohistochemical staining the diagnosis was clarified: juvenile granulosa cell tumor with extensive mucinous component. Our case report emphasizes the necessity of immunohistochemical staining for accurate diagnosis, especially when clinical features do not correlate with histology findings. Moreover, due to the rarity of these types of tumors, further reports and studies are encouraged to standardize their diagnosis and treatment. **Keywords:** JUVENILE GRANULOSA CELL TUMOR; IMMUNOHISTOCHEMISTRY; OVARIAN CARCINOMA.

Granulosa Cell Tumors (GCTs) are a type of malignant sex cord-stromal tumors and account for only 2-3% of all ovarian neoplasms (1). They present as slow-growing masses with an indolent natural course. Two types of GCTs are described based on their histologic appearance: adult and juvenile GCTs. Adult type is the most common occurring in perimenopausal women, while juvenile GCTs are rare, accounting for roughly 5%, and arise in young females (2). Imaging findings vary

from well-defined solid masses with internal cysts to pure cystic lesions (3). Macroscopically they appear as encapsulated lesions with a smooth surface resembling cystadenoma. The classic microscopic features found in GCTs are Call-Exner bodies which are amorphous, eosinophilic, fluid-filled spaces formed by secretions from neighboring granulosa cells; however, Call-Exner bodies are found only in the adult-type GCT thus their absence cannot exclude a juvenile GCT. Immunohistochemistry (IHC) is the only tool to provide a specific diagnosis. Inhibin, calretinin, FOXL2 and SF-1 are specific positive markers, while epithelial markers such as CK7, EMA are negative markers (4, 5). Due to their rarity and favorable prognosis, standard treatment protocols are yet to be implemented. However, current management is multimodal. Surgery is the first step. Stage I tumors are candidates for fertility-sparing surgery, while advanced stages require total hysterectomy with bilateral salpingo-oophorectomy and, if needed, cytoreductive procedures. Adjuvant therapy consists of chemotherapy, radiation therapy and hormone therapy. Follow-up regimens are hardly adopted, however GCTs are prone to late recurrence therefore, imaging follow-up is needed to early depict tumor relapse (6, 7). Our aim is to present the clinical course of a rare recurrent GCT with mucinous infiltration initially misdiagnosed as mucinous ovarian carcinoma. GCTs can present in many different facets and have a tendency to behave unpredictably with late relapses demanding a high degree of expertise for accurate clinical and pathological diagnosis. Our target is to include this entity in the differential diagnosis of ovarian masses, to support immunohistochemical staining in inconclusive cases and by reporting them, prospective studies may be conducted to standardize GCT diagnosis, optimal treatment and follow-up, considering their recurrence rate.

CASE REPORT

A 34-year-old female patient was admitted to our clinic after being diagnosed on a follow-up computed tomography (CT) scan with a pelvic tumor. Physical examination revealed an abdominal mass in the hypogastrium, painful on palpation. The abdomen showed signs of collateral venous circulation, while lower extremities showed signs of bilateral deep vein thrombosis (DVT). Laboratory results were insignificant except for an iron-deficiency anemia and slightly elevated CA125 (37.8 U/mL).

In her past medical history, we found some prominent features. She was diagnosed with mucinous ovarian carcinoma, based on the immunohistochemical findings (tab. I), for which she underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. Despite the confirmed results, the patient refused chemotherapy.

TABLE I

Immunohistochemical analysis of specimen suggestive for mucinous ovarian carcinoma

Marker	CK7	ER	CEA	S100	Vimentin	CK20	P53	PCNA
Result	Focally +	60% +	-	-	+	-	-	30%

Seven years later the patient was diagnosed with a tumor recurrence involving the ascending colon. A right colectomy was performed as the tumor was adherent

to the cecum. Specimen analysis revealed the diagnosis of mucinous ovarian carcinoma. Noteworthy is that IHC was not performed. The patient received six cycles of chemotherapy with carboplatin and paclitaxel.

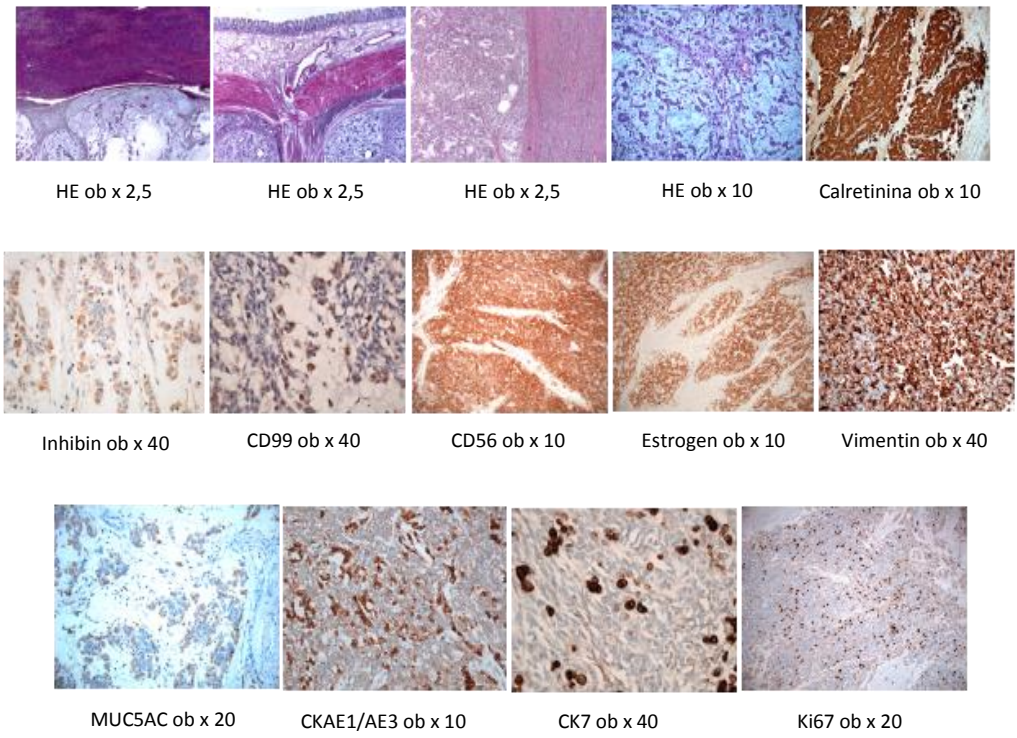

Fig. 1. IHC panel. Hematoxylin Eosin (HE) staining can be observed in the first four images. The next ten images show the presence of different IHC markers

Eight years later she was diagnosed in our clinic with an abdominopelvic tumor, the CT scan revealing a well-defined interhepatorenal tumor measuring 162/143/160 mm with direct invasion of the liver segment 6, right kidney, adrenal gland, and right diaphragmatic pillar. The mass had a compressive effect on the psoas muscle, caudate lobe, hepatic hilum, gallbladder and inferior vena cava (fig.1). Beside this mass, two other tumors were identified with the same features. One at the mesenteric root measuring 89/127/90 mm and another in the left pelvic area in direct contact with the sigmoid colon and bladder. In addition, multiple enlarged lymph nodes suggestive of metastatic spread were found in the paraaortic and external iliac regions, obturator fossa and mesentery. Intraoperatively, three tumors were identified. One measuring 120/15 mm located on the greater omentum, another measuring 80/100 mm attached to the mezosigmoid, and an infiltrative multilobulated mass in the right iliac fossa extending to the right upper quadrant and retroperitoneum. The masses were

removed along with the resection of the greater omentum, marginal hepatectomy, partial diaphragmatic peritonectomy, right nephrectomy and adrenalectomy, sigmoid colectomy and aortocaval lymph node dissection.

On receipt of the specimens, multiloculated, encapsulated masses were found. Cut section of the lesions showed a grey to white appearance with areas of hemorrhage, large cystic degeneration and mucinous content. Histopathological examination revealed round and fusiform cells with rich eosinophilic cytoplasm arranged in a lax architecture surrounded by mucus and rare Call-Exner bodies. Mitotic figures were 10/10 high power field. IHC testing was conducted and based on the expanded panel of markers (tab. II) the diagnosis was clarified: juvenile granulosa cell tumor with extensive mucinous component. Postoperative chemotherapy was initiated as soon as possible with cisplatin and etoposide.

TABLE II

IHC panel for the retrieved specimens

Marker	Result
CD 10	negative
EMA	negative
WT1	negative
CDx2	negative
CK20	negative
Podoplanin	negative
Inhibin A	focal positive
Calretinin	diffuse positive
ER	intense positive
CD 99	focal positive
CD 56	positive
MUC 2 and MUC 5 AC	low positive
Vimentin	positive
Cytokeratin AE1/AE3	positive and negative alternation
CK 7	focal positive
Ki 67	18% positive

DISCUSSION

Firstly, described by Rokitansky in 1885 (8), GCTs are sex cord tumors which can originate not only from granulosa cells, but also from interstitial cells, fibroblasts or techa cells explaining their occurrence in men. Morphologically, they are divided into two groups: adult GCT and juvenile GCT. This classification is based on their histological features, not on their epidemiology, thus adult GCT is indeed more frequent in postmenopausal women, but not exclusively. Adult granulosa cells show a solid organoid-like architectural pattern, with frequent pathognomonic Call-Exner bodies. In contrast, juvenile granulosa cells organize in nodular patterns, have a high mitotic index (and a worse prognostic), wide cytoplasm and rare Call-Exner bodies. Both types are usually unilateral, and both can differentiate into hormone-producing tumors. Juvenile GCTs are more frequent in younger patients, 90% of them being diagnosed at less than 30 years of age (3, 4, 5, 9, 10, 11).

Typically, GCTs present as slow-growing masses with a low malignant potential and favorable prognosis in comparison to epithelial ovarian cancers; however, they are at risk of early and late local recurrence, so a follow-up scheme is recommended including CT scans and tumor marker determinations. In these tumors the prognostic value of CA-125 is poor. Serum inhibin determination is a good choice for monitoring GCTs. Surgical removal followed by chemotherapy in recurrent cases is the mainstay of treatment. Radiation therapy has limited efficacy and hormone therapy is an option for hormone-producing tumors (12, 13, 14). Long-term follow-up including pelvic and abdominal examination, CT scan and tumor marker determina-

tion is recommended as delayed recurrences are characteristic for this disease.

Our case had a clinical presentation as a mucinous ovarian tumor with late relapses which required a high degree of suspicion for pathological diagnosis. We emphasize the importance of a complete immunohistochemical panel in differentiating ovarian masses. GCT cells usually stain positive for inhibin, calretinin, CD99, CD56, vimentin, estrogen and progesterone receptors. They are negative for CK7 and epithelial membrane antigen (EMA). After the first surgical excision of the ovarian tumor, the condition was mistaken for mucinous ovarian carcinoma. This confusion was possible precisely because the whole immunohistochemistry panel was not performed, in our case missing the determinations of inhibin, calretinin, CD 99, CD 56 and EMA. Next, after the removal of the right iliac fossa mass, immunohistochemical staining was not performed, supported by the previous histological exam, and a chemotherapy regimen for mucinous ovarian carcinoma was initiated. The recurrences were diagnosed each time in a locally advanced stage with adjacent visceral invasion because a follow-up sequence was not maintained since the patient did not stick to monitoring. Once the panel of immunohistochemistry markers is accomplished, a correct diagnosis can be made. The direct implications are connected to the appropriate adjuvant therapy and the necessity to track it in the long term. All these highlight the importance of identifying the whole immunohistochemistry panel in the case of patients with ovarian neoplasm, especially in the case of the young patients and when the tumor relapses over long periods of time.

CONCLUSIONS

We here presented a rare case of juvenile granulosa cell tumor misdiagnosed as mucinous ovarian carcinoma, emphasizing the necessity of performing a complete panel of immunochemistry markers. The rarity of these tumors as well as the lack of guidelines for the diagnosis and monitoring requires more insight into studying this disease.

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NEWS

FOLIC ACID AND RISK OF POSTPARTUM DEPRESSION

Postpartum depression, as a common complication of childbearing, is defined as an obvious depressive symptom or a typical depressive episode within 1 to 12 months after delivery. A cohort study aimed to assess the association between duration of folic acid supplementation during pregnancy and the onset of PPD in Chinese women. A total of 1592 participants were recruited, and data collected between July 2015 and March 2017 in Tianjin, China. Participants' baseline data were collected regarding socio-demographic and lifestyle characteristics, obstetric history, and folic acid supplementation during pregnancy. The Self-Rating Depression Scale, Chinese version was used to assess depressive symptoms at 6-12 weeks postpartum, and the prevalence of PPD in participants was 29.4%. Pregnant women who took folic acid supplements for more than 6 months had to lower prevalence of PPD, compared to those who took folic acid for less than 6 months. (Jing Yang, Yuyan Liu, Lujia Cao, Yuzhi Zheng, Wen Li and Guowei Huang. Association between Duration of Folic Acid Supplementation during Pregnancy and Risk of Postpartum Depression. *Nutrients* 2017; 9: 1206)

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