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Massive Hemorrhagic Ascites at Stage 1A Juvenile Granulosa Cell Tumor in a 5 Years Child: A Case Report and Review of the Literature

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Abstract

Background: Juvenile granulosa cell tumor is a sex cord-stromal tumor, which is the leading cause of precocious puberty. Massive hemorrhagic ascites at early stage was rarely reported.

Case report: Here we report a rare case of Stage 1A juvenile granulosa cell tumor with massive hemorrhagic ascites in a 5 years old Eritrean child. She presented with breast enlargment and vaginal bleeding followed by progressive abdominal distention of four months period. She was emaciated and mild respiratory distress. Breasts developed to Tanner stage 3 with scant axillary hair. The abdomen was grossly distended, with positive fluid trill, and a firm, mobile, abdomino-pelvic mass identified. She had mild anemia and estradiol level was 1259 ng/dl. Magnetic resonance imaging showed a solid 13cm x 14cm x 8cm size mass. Parecentesis was performed for symptomatic relief before laparotomy and its analysis revealed chronic inflammatory cells on hemorrhagic background. Fertility-sparing surgery with full staging was performed and three kg left ovarian mass was completely resected. Histopathology analysis revealed a stage 1A, Juvenile granulosa cell tumor confined to the left ovary. Her postoperative period was uneventful, estradiol level dropped to <5 ng/dl in two weeks. Chemotherapy was not initiated and during her follow up she investigated with different imaging modalities for possible recurrence but all are of normal study.

Conclusion: Fertility preserving surgery can be favored even in patients with giant masses of juvenile granulosa cell tumor and massive hemorrhagic ascites without malignant cells.

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Introduction

Granulosa Cell Tumors (GCTs) are sex cord-stromal tumors comprising 2-5% of all ovarian neoplasms and approximately 70% of malignant sex-cord stromal tumors [1,2]. GCTs are divided into Adult GCT (AGCT) and Juvenile GCOT (JGCT) [3,4]. Juvenile Granulosa Cell Tumor (JGCT) accounts for 5% of GCTs and commonly, it occurs in premenarchal girls or women less than 30 years age [1,4-6]. These tumors are the most common ovarian tumors to cause precocious puberty in prepubertal females [7,8]. Clinically, they present with manifestations of hyperestrogenism and excess inhibins including precocious puberty in younger females, early pigmentation in the areola, breast enlargement, increased pubic hair, vaginal discharge, vaginal bleeding, palpable abdominal mass, and nonspecific abdominal pain [2,5,8-10].

Juvenile granulosa cell tumor is a hormone-producing tumor and serum estradiol level is almost always elevated, though there are reports of pseudopuberty even with normal or low estradiol concentrations [11]. Confirmatory diagnosis of JGCT is based on histomorphology assisted by immunohistochemistry. In a microscopic examination, granulosa cells can show several different characteristics and call-exner body and coffee bean nuclei, which are mostly seen in the adult type, are not very common in the juvenile type [4,9]. The detection of serum Anti-Mullerian Hormone (AMH), inhibin B, and sex hormone levels also contributes to the diagnosis of GCOT. The primary treatment of GCT is standard staging surgery; Fertility-Sparing Surgery (FSS) is acceptable in patients who wish to preserve fertility when the tumor is confined to the ovary [12].

Case presentation

This 5-year-old Eritrean female child came to Orotta national referral hospital with a complaint of abnormal breast enlargement, pubic hair growth and vaginal bleeding of four month period. The child experienced two episodes of vaginal bleeding each lasting for three days and family changed two pads per day. This was accompanied with occasional non-odors yellowish vaginal discharge. Later, she developed progressive abdominal distension accompanied by diffuse abdominal pain which limited the child's normal activity. She had also a history of shortness of breath, loss of appetite, and unquantified weight loss. Family denies any history cough, fever, or alteration in bowel habits. She was the second child of her three siblings and the caregivers denies any similar problem in their family.

On physical examination, she was sick-looking with a blood pressure of 90/50 mmHg, pulse rate of 118 beats/minute, respiratory rate of 56 breaths per minute, and temperature of 36.8^{0}C. She had a slightly pale conjunctiva and non-icteric sclera, and her chest was clear to auscultation with good air entry bilaterally. Breasts enlarged with clearly formed areola at tanner stage 3 with tiny hair growth in axilla. The abdomen was grossly distended with mild tenderness and a firm, mobile, globular 14 cm x 10 cm size abdomino-pelvic mass (See Figure 2a). Fluid trill was positive and she had normal external genitalia with pubic hair growth at tanner stage 2.

Paracentesis of 2 liters of hemorrhagic fluid was performed for symptomatic relief at interval of 48 hours. She was investigated with locally available investigative modalities and inhibin was not available (See Table 1). And ascetic analysis revealed inflammatory cells with no evidence of malignancy in hemorrhagic background. MRI and abdomino-pelvic ultrasound showed a large, irregular, fairly circumscribed solid mass with internal cystic spaces measuring 13cm x 14cm x 8cm with ascites and no evidence of contralateral ovarian or lymph node involvement (Figure 1 b, c, d).

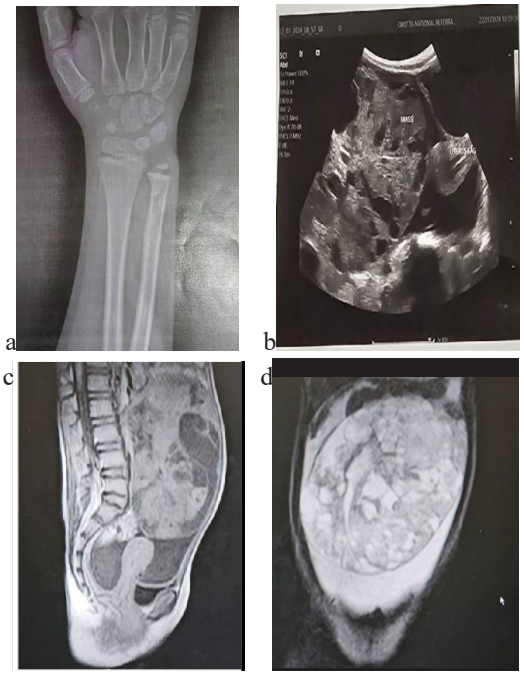

Figure 1: Imaging results **(a)** Wrist x-ray for age determination, corresponding to 8 years **(b)** Trans-abdominal USG showing huge abdomino-pelvic solid with multiple cystic components measuring 17cm x 10cm with massive ascites. **(c,d)** MRI displayed a large, irregular, fairly circumscribed solid mass with internal cystic spaces measuring 13cm x 14cm x 8cm with ascites and a normal uterus big for her age.

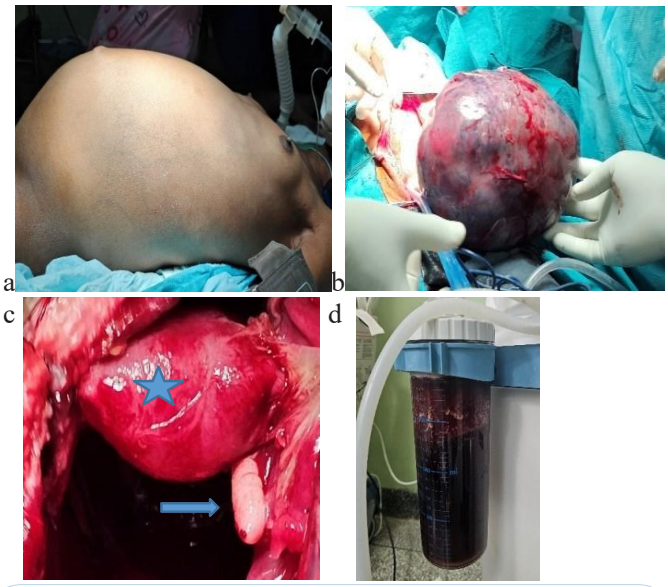

Figure 2(a): Grossly distended abdomen with enlarged breasts and formed areola **(b)** 18cm x 15cm left ovarian mass, weighing 3kg during resection. **(c)** Macroscopically healthy-looking contralateral ovary (arrow) and enlarged uterus after fertility-sparing surgery (star). **(d)** Hemorrhagic ascites sacked intraoperatively.

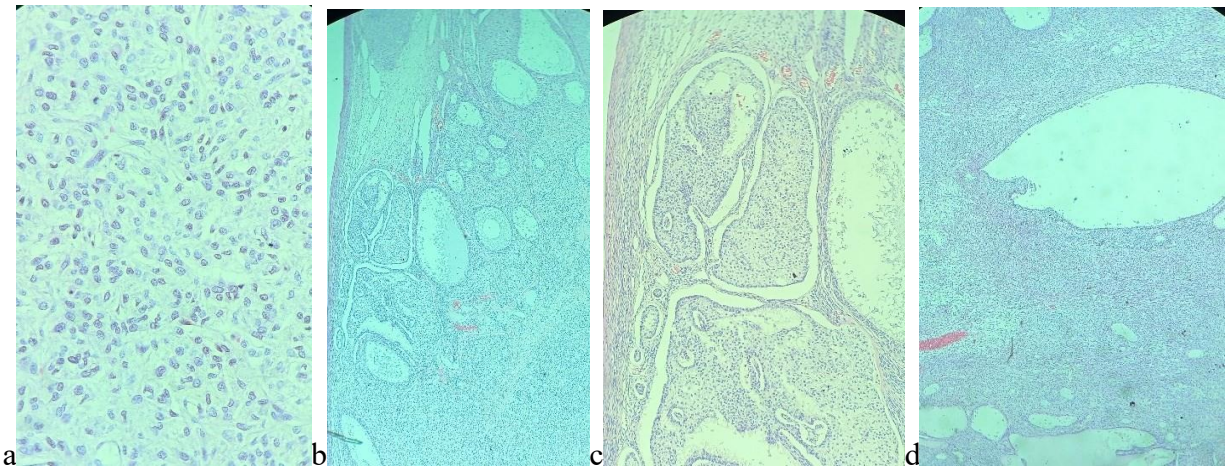

Figure 3(a-d): Diffuse macro follicular with mild to moderate pleomorphism mitotic activity (6 figures/10HPF), marked luteinization with very few cells with nuclear growth.

Table 1: CBC, Blood chemistry, Hormone analysis, and tumor markers of patient [16].

Investigation	Result	Reference range	Investigation	Result	Reference range
Complete blood count			**Hormone analysis before surgery**		
Hemoglobin	9g/dl	12-16g/dl	Estradiol	1259 pg/ml	<20-53 pg/ml
hematocrit	27.2	36-47%	FSH	<0.30mIU/ml	<0.1-7 mIU/ml
Platelet	$344\times10^3/mm^3$	$150\text{-}450\times10^3/mm^3$	LH	0.45 mIU/ml	<0.1-3.3 /ml
Blood chemistry			Progesterone	2.91 ng/ml	<1ng/ml
Albumin	2.9	3.4-4.8g/dL	Prolactin	17.7 ng/ml	<26 ng/mL
ALT	7	0-31 U/L	Testosterone	30.2	5-70ng/dl
AST	28	0-31 U/L	**Hormone analysis 2 weeks after surgery**		
ALPO4	142	39-117 U/L	Estradiol	<5.00 pg/ml	<20-53 pg/ml
Creatinine	0.2	0.5-1.2 mg/dL	FSH	0.86 mIU/ml	<0.1-7 mIU/ml
BUN	7	6-20 mg/dl	LH	0.12 mIU/ml	<0.1-3.3 /ml
Calcium	9	8.8-10.2 mg/dL	Progesterone	0.07	**<1ng/ml**
Tumor markers			Prolactin	40.73	<26 ng/mL
CEA	<0.75	0 - 3.0	Testosterone	<2.5	5-70ng/dl
AFP	<0.20	0 - 39	**Thyroid panel**		
CA 19-9	7.16	0 - 8.1	T uptake	1.19 TBI	0.80 - 1.30 TBI
LDH28	529	94-250 U/L	TSH	0.75Uiu/ml	0.27-4.20 iu/ml
CA-125 &	N/A	<35 U/ml	T4	13.3ug/dl	5.13-14.06 ug/dl

Preoperatively she was transfused with two units of packed red blood cells and fertility sparing surgery was planned with an impression of juvenile granulosa cell tumor. Under general anesthesia midline incision was performed for adequate exposure and full staging procedure. After entering to peritoneum another two liters of hemorrhagic ascetic fluid was sacked. An oval purple mass originating from left ovary was identified and the contralateral ovary and uterus inspected for any gross lesion and were looking healthy. A fertility-sparing surgery was performed in which three kilograms left ovarian mass was completely resected (Figure 2 b, d, c). Infra-colic omentectomy was done followed by complete staging, were samples taken from sub diaphragmatically, paracolic gutters bilaterally, the right and left pelvis, and the anterior and posterior cul-de-sac.

The histopathology results were consistent with juvenile granulosa cell tumor and microscopically, cells have mild to moderate pleomorphic with mitotic activity 6 figures/10HPF (Figure 3 a, b, d, c). Section from the omentum and different sites of peritoneum didn't show tumor involvement. The patient was staged as 1A and the postoperative period was uneventful despite having hormone withdrawal vaginal bleeding after one week. She was not started on chemotherapy because of the stage of disease and her hormone analysis dropped to normal. During her follow up she investigated with different imaging modalities and hormone analysis for possible recurrence but all are of normal study.

Discussion

In the pediatric population, ovarian tumors are unusual with an estimated incidence of 2.6 cases per 100.000 girls per year [13]. Juvenile granulosa cell ovarian tumor is non-epithelial ovarian tumor that occurs usually in premenarchal girls with a mean age at diagnosis of 13 years [3,11,12]. Precocious pseudopuberty is related to hormonal changes and is divided as Central Precocious Puberty (CPP) which results from premature activation of the hypothalamus-pituitary-gonadal axis, and Peripheral Precocious Puberty (PPP) which results from sex steroid expo-

sure which starts with breast enlargement [13]. Our case presented with symptoms of precocious puberty which start with breast enlargement followed by abnormal pubic hair growth and menstrual blood flow respectively.

The unique finding in our patient was the massive hemorrhagic ascites leading to gross abdominal distention embarrassing her respiratory effort at early stage of the disease. Repeated paracentesis was required to resolve symptoms during preoperative preparation. Comparatively advanced bone age and accelerated height velocity were seen due to tumor-derived estradiol and commonly, these tumors are diagnosed in the early stage due to hormonal-related prompt symptomatic manifestation [7,9]. Similarly, our patient's age determination using wrist X-rays corresponds to 8 years with overall duration of the symptoms was four months.

The final diagnosis of JGCT is based on histopathologic analysis assisted by immunohistochemistry and detection of serum AMH, inhibin B, and sex hormone [12]. Inhibin is released from the granulosa cells which are the best tumor markers used in monitoring the course of the disease, and serum gonadotropins, and gonadotropin releasing hormone levels in JGCT patients are very low due to elevated inhibin levels [9]. In our patient, the sex hormone levels had a similar picture to most reported cases, but; the inhibin level was not determined as it was not available in our setting for this reason she was sent abroad for disease surveillance. Imaging is nonspecific and estrogenic effect may result in uterine enlargement or increased uterine size and endometrial thickening likewise to of our patient finding [9].

Management of JGCT depends on the age of the patient and the stage of the disease [13]. Surgery is the mainstay of management of JGCT, as it is helpful for histopathology analysis, staging, and debulking procedure [1,14]. Laparotomy should comprises a mass resection with full staging procedure and lymphadenectomy can be omitted unless lymph node metastasis is suspected based on radiographic evidence or intraoperative examination [9,12]. In young women, the optimal treatment is less clear but fertility-sparing surgery with unilateral salpingo-oophorectomy is an acceptable option [15]. In the some way, our patient underwent fertility-sparing surgery as the preoperative ascetic fluid analysis revealed only inflammatory cells with no malignant cell though frozen section was not feasible. Caregivers were satisfied by the fertility preserving surgery and dramatic improvement after the procedure. In addition, the MRI finding didn't suggest any lymph node or contralateral ovarian involvement and reasonable lymph node dissection was deferred and fertility-sparing surgery was carried out.

There is no standard protocol for adjuvant chemotherapy because of the rarity of the disease. A worse prognosis and early recurrence should be expected in the case of an advanced disease [3]. Besides, unfavorable prognostic outcomes tend to occur if the tumor size is large (10-15cm), tumor rupture, nuclear atypia, high mitotic rate, and extra-capsular extension of the tumor within the ovary [10,13]. In our case, the tumor size was large with low mitotic rate, at early stage. For the bigger size of the mass there was a fear of recurrence and dilemma about the initiation of chemotherapy. Fortunately during follow up the child showed dramatic improvement and all the investigations performed did suggest any disease recurrence.

Conclusion

Juvenile granulosa cell tumors diagnosed in early stages due to hormonal-related prompt symptomatic manifestation. Fertility-preserving surgery can be performed even in patients presenting with giant mass and massive hemorrhagic ascites at stage 1A. Beside with close monitoring of the course of the disease after surgery, chemotherapy can be deferred to mitigated drug related adverse effects.

Declaration

Ethical approval: Not applicable

Informed consent: Informed consent was obtained from the parents to publish her anonymized personal details and accompanying images in an international journal.

Availability of data and material: All the available information is included in the manuscript.

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Author Contribution:

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Surgical Intervention: Dawit Sereke, Rami Yassin, Okbu Frezgi, and Selam Menghisteab,

Writing - Original Draft: Okbu Frezgi

Writing - Review & Editing: Okbu Frezgi, Dawit Sereke, Berhe Tesfai, Rami Yassin, Mahmud Mohammed.

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