Case Report

Virilization in a Girl Caused by an Ovarian Yolk Sac Tumor: A Case Report

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A B S T R A C T

Background: Yolk sac tumors (YSTs) are rare malignancies that originate from germ cells and rarely present with endocrine symptoms. We report a case of a 13-year-old girl with a YST manifesting as virilization.
Case: A 13-year-old girl was diagnosed with a YST with endocrine symptoms because of Leydig cells in the stroma, which were identified using hematoxylin and eosin staining and immunohistochemistry.
Summary and Conclusion: This case suggests that clinicians should consider the possibility of YST when encountering patients with symptoms of virilization. When a YST is found to have endocrine function, a functioning stroma could present. Immunohistochemistry is useful for identifying stromal cells and performing a differential diagnosis.
Key Words: Virilization, Yolk sac tumor, Leydig cells

Introduction

Ovarian yolk sac tumors (OYSTs) are rare malignant germ cell neoplasms that originate from multipotent embryonic stem cells. Most patients complain of abdominal pain and enlargement, and rarely present with endocrine symptoms. In contrast, ovarian sex-cord stromal cell tumors, which also arise from ovarian follicles, are well documented ovarian tumors that are more commonly associated with endocrine symptoms.[1,2] However, endocrine symptoms associated with an ovarian mass are more consistent with sex-cord stromal tissue. One exception is malignant or benign teratomas, which can present with functional endocrine tissue. To our knowledge, only a few studies[3–6] have described the combination with functioning stomal cells of OYSTs causing virilization. Because of its unusual occurrence, we report a case of OYST with a mixture of Leydig cells manifesting as virilization in a 13-year-old girl.

Case

Clinical Findings

A 13-year-old girl presented with deepening of the voice and amenorrhea for approximately 3 months. She was born at full term without perinatal complications and had no previous health problems. Menarche occurred at the age of 12 years with a duration of 7 days, and menstruation occurred at irregular intervals. Her body weight was 49.0 kg (50th-75th percentile), her height was 160.0 cm (75th percentile), and her body mass index was 19.1. Her blood pressure was normal. A physical examination revealed acne on her face and back, prominent bumps, enlargement of the clitoris, and extended hirsutism of the mons pubis, with a score of 4 according to the Ferriman-Gallwey scale. A hard mass was palpated in her lower abdomen. Her breasts were Tanner stage 2. Her bone age was equal to her chronological age, which was 13 years (Fig. 1A).

Laboratory investigation revealed a normal blood count. Her liver and renal functions were within the normal range. Hormone evaluation revealed an increased plasma total testosterone level (3.12 ng/mL, reference range, $<$0.1-0.75 ng/mL). Her serum chorionic gonadotrophin, plasma adrenocorticotrophic hormone, and plasma cortisol levels were normal. Her α-fetoprotein (AFP) level was very high at $>$1210 ng/mL, and her carcinoma antigen 125 level (45.65 U/mL; reference range, 0-35 U/mL) was also mildly increased. Her chromosomes were normal (46XX).

Abdominal ultrasound and magnetic resonance imaging showed a 14.3 $\times$ 14.5 $\times$ 8.0 cm mass displacing the front of the uterus (Fig. 1C and D). She was then transferred to the gynecology ward, and a unilateral salpingo-oophorectomy and a partial omentectomy were performed. Her serum AFP level decreased to 629.5 ng/mL, and testosterone returned to normal levels. After surgery, she received 4 courses of bleomycin, etoposide, and cisplatin chemotherapy. To date, 2 years after surgery, the patient is still alive. No clinical evidence suggests recurrence or metastasis.

Gross Findings

The resected tumor measured 15 $\times$ 15 $\times$ 8.0 cm on the left ovary (Fig. 1B). The cut section showed a pattern of solid

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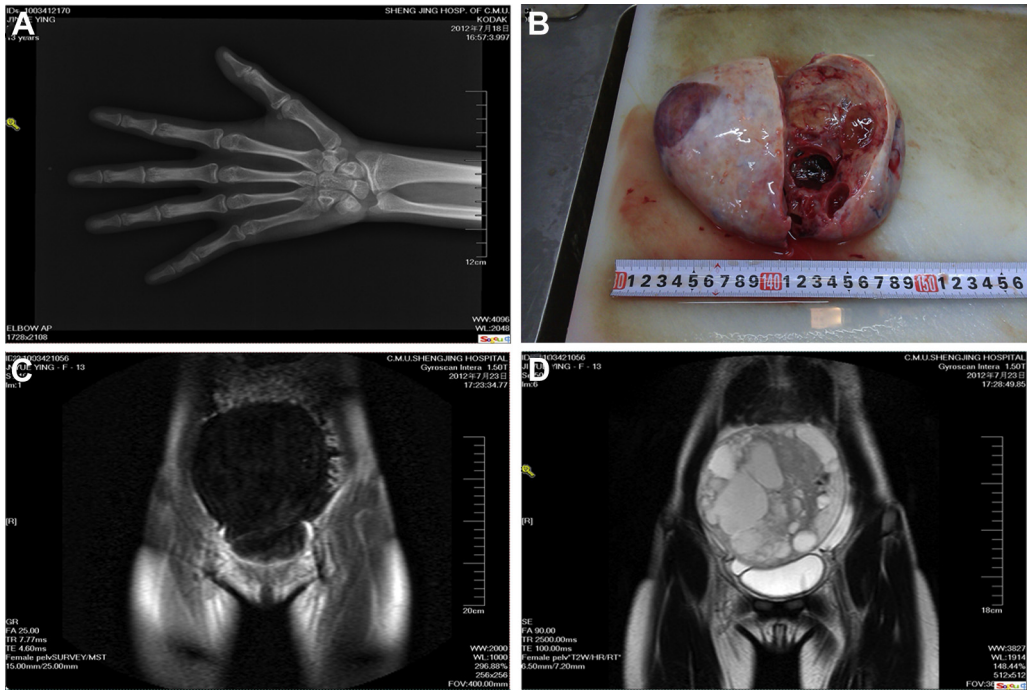

Fig. 1. (A) An X-ray of the left palm showed the bone age. (B) Gross findings of the resected tumor: a well demarcated, large mass; the cut surface of the resected tumor shows necrotic and hemorrhagic regions. (C and D) Magnetic resonance images: the large tumor was hypointense on (C) T1-weighted images and hyperintense on (D) T2-weighted images.

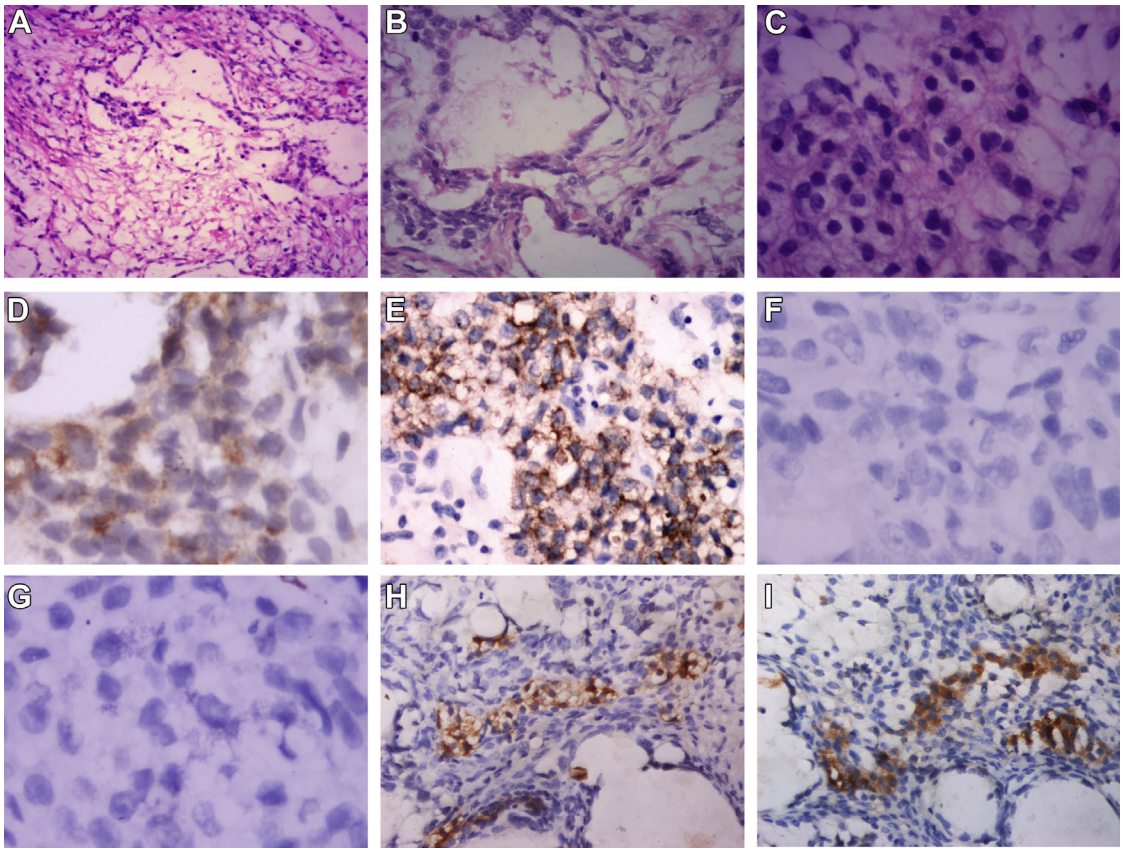

Fig. 2. (A) Microscopic image of the yolk sac tumor (×100); (B) the Schiller Duval body (×200); (C) hematoxylin and eosin staining of the Leydig cells (×400); (D) the tumor cells were positive for α-fetoprotein (×400); (E) the tumor cells were positive for cytokeratin (400×); (F) the tumor cells were negative for vimentin (×400); (G) the tumor cells were negative for CD30 (×400); (H) the tumor cells were positive for inhibin α subunit (×400); and (I) the tumor cells were positive for testosterone (×400).

and cystic areas with regions of mucus and hemorrhagic fluid that was yellowish white and pink-white in color. The surface was smooth.

Pathologic Findings

Microscopically, the hematoxylin and eosin-stained sections exhibited a histology typical of a yolk sac tumor (YST), including a glandular pattern, reticular pattern, and Schiller Duval bodies (Fig. 2A-C). Immunohistochemistry showed that the tumor cells were positive for AFP and cytokeratin but negative for vimentin and CD30 (Fig. 2D-G). Hematoxylin and eosin staining showed Leydig cells with distinct cell borders and nuclei that were uniformly round. The cells were arranged in clusters and cords. Immunohistochemistry was used to identify Leydig cells via the α subunit of inhibin and testosterone in the cytoplasm (Fig. 2H and I).

Discussion

OYSTs are extremely rare accompanying with endocrine symptoms. Only a few studies[3–6] have reported OYSTs manifesting virilization with highly elevated testosterone levels for the admixture of functioning stroma; in contrast, elevated testosterone level is more commonly associated with Leydig cell tumors.[1–7] Therefore, it is important to differentiate such OYSTs from Leydig cell tumors. Many features are helpful in making this distinction. Elevated serum AFP level is a useful tumor marker for the diagnosis of OYSTs because almost all YSTs present with this characteristic, whereas it is absent in Leydig cell tumors. Leydig cells are consistently positive for vimentin and negative for cytokeratin, and in the present case, this pattern allowed a clear distinction from the cells of the YST. Marked histologic variability patterns other than microcystic or solid are also helpful. Relatively uniform nuclei and low mitotic activity strongly favor a diagnosis of a Leydig cell tumor over a YST.

OYSTs with functional stromal cells are associated with endocrine functions, including estrogenic, androgenic, or rarely progesterogenic functions. The manifestation of excess estrogen is not clinically overt and often presents with abnormal vaginal bleeding or thickening of the endometrium.[8] The appearance of virilization is due to the excessive production of androgen.

The patient in the present study was a 13-year-old girl with a 2-month history of virilization. We found 4 cases in the literature describing OYSTs associated with virilization and their clinical features are described in Table 1. The ages of the patients ranged from 15 to 22 years, with a median of 19 years. Patients complained of abdominal pain or enlargement as the presenting symptoms as well as androgenic manifestations. The signs of virilization included menstrual disruption, deepening of the voice, hirsutism, acne, and clitoromegaly. The duration of symptoms was brief, with a history of several months. Serum testosterone and AFP levels were markedly elevated. Serum chorionic gonadotrophin and carcinoma antigen 125 levels were generally normal. Ovarian tumors often presented as a

Table 1
Clinical and Pathologic Features of Four Ovarian Yolk Sac Tumors Associated With Virilization

Number	Study	Age	Duration of Symptoms	Abdominal Pain	Virilization Characteristics			T	Serum AFP, ng/mL	Tumor Size, cm	Functioning Stroma
					Deepened Voice	Hirsutism	Clitoromegaly				
1	Stewart et al[3]	20	6 Months	Pos	Neg	Pos	Pos	220 (N: 14-80)	Pos	23 × 18 × 10	Luteinized cells
2	Prat et al[4]	15	1 Month	Neg	Pos	Pos	Neg	2.29 (N: 0.3-1.2)	Pos	-	Luteinized cells
3	Arima et al[5]	22	-	-	Pos	Neg	Pos	35.7	127,444	20 × 20.5	Leydig cells
4	Horiuchi et al[6]	19	-	Pos	Pos	Neg	Neg	6.47	177,510	17 × 10 × 10	Luteinized cells

AFP, α-fetoprotein; T, testosterone; Pos, positive; Neg, negative; -, not mention.

large and rapidly enlarging mass with foci of hemorrhage and necrosis on cut sections. Microscopically, the typical histopathological features of YST were present; furthermore, stromal cells could be found via light and electron microscopy. The 4 cases of YST with virilization reported luteinized cells or Leydig cells as the functioning stroma. Leydig cells with distinct cell borders were also found in the present study, and the nuclei were uniformly round with little pleomorphism and few mitotic figures. Immunohistochemistry confirmed that the cells were positive for inhibin α subunit and testosterone. The level of testosterone significantly decreased after surgery. Obviously, Leydig cells are a tumor component and are part of the functioning stroma.

In conclusion, we report a very rare case of a YST associated with virilization due to the presence of Leydig cells in the stroma. This case suggests that the clinician should consider the possibility of a YST when encountering patients with symptoms of virilization. Furthermore, if a YST with endocrine function is found, a functioning stroma could be present. Immunohistochemistry is useful for identifying stromal cells and performing a differential diagnosis.

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