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Case Report

Complete androgen insensitivity syndrome with accelerated onset of puberty due to a Sertoli cell tumor

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Abstract. Complete androgen insensitivity syndrome (CAIS) is caused by mutations in the androgen receptor gene. Patients with this syndrome have a 46,XY karyotype, male gonads, and normal female external genitalia. While the pre-pubertal risk of developing gonadal tumors is low in these patients, it increases with age. Most gonadal tumors arise from germ cells; stromal cell tumors are uncommon. Herein, we report a CAIS patient with a feminizing Sertoli cell tumor. The patient presented at 8 yr of age with breast enlargement and growth acceleration, concomitant with elevated serum estradiol levels and suppressed serum gonadotropin levels; these findings were inconsistent with CAIS. The patient underwent gonadectomy at 10 yr of age, and histology demonstrated presence of a non-malignant Sertoli cell tumor in the right gonad. We conclude that this is the first reported case of CAIS with accelerated onset of puberty resulting from a Sertoli cell tumor.

Key words: complete androgen insensitivity syndrome, androgen receptor gene, disorders of sex development, Sertoli cell tumor, feminizing tumor

Introduction

Androgen insensitivity syndrome (AIS) is an X-linked disorder of sex development (DSD) caused by mutations in the androgen receptor (AR) gene (OMIM:313700). Patients with the complete form (CAIS) have a 46,XY karyotype, male gonads, absent Müllerian structures, and normal female external genitalia resulting from normal anti- Müllerian hormone (AMH) action and insensitivity to circulating androgens. Patients with CAIS are typically assigned to the female sex, and can undergo spontaneous breast tissue development and growth acceleration at the typical age of onset of puberty if gonadectomy is not performed. However, patients exhibit scant or absent pubic and axillary hair as well as primary amenorrhea.

Patients with 46,XY DSD (including AIS) exhibit an increased frequency of gonadal tumors and most tumors arise from germ cells. However, the pre-pubertal risk in CAIS patients of developing a germ cell tumor is low, approximately 0.8–2.0% (1). Abnormal testicular position and high gonadotropin levels due to androgen insensitivity may lead to pathological testicular changes, which likely account for the increasing risk of malignancy with age (1–8).

Gonadal stromal (Sertoli or Leydig) cell tumors are rarer than germ cell tumors (1–3). Sertoli cell tumors account for only 0.4–1.5% of testicular tumors, and the average age of presentation is 45 yr. The most common presenting sign of a Sertoli cell tumor is a painless scrotal mass; signs of hyperestrogenism are present in 20–30% of cases (8–14).

To the best of our knowledge, only 6 cases of Sertoli cell tumors in CAIS patients have been described (3, 7, 8, 15, 16). All patients presented post-pubertally (16–73 yr), without signs of hyperestrogenism. Herein, we report the first case of a CAIS patient with a Sertoli cell tumor resulting in early-onset puberty.

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Case Report

A girl aged 8 yr and 9 mo presented to our hospital with a 9-mo history of bilateral breast enlargement. She was born at term to non-consanguineous parents and exhibited average weight (3,496 g) and length (52 cm). She was believed to be of female sex based on normal female external genitalia. No noteworthy medical events occurred during the perinatal period, and psychosocial development was normal. There was no known family history of DSD. Following examination at a different hospital at 6 mo of age for bilateral inguinal hernia, CAIS was clinically diagnosed based on the presence of male gonads and a Y chromosome. In order to acquire spontaneous secondary sexual characteristics, gonadectomy was not performed at that time.

At presentation to our hospital, the patient's height and weight were 136.9 cm (+ 1.38 SD for normal Japanese girl) and 29.8 kg (+ 0.3 SD for normal Japanese girl), respectively. She had been experiencing growth acceleration for the preceding 9 mo (**Fig. 1**) (17). Skeletal maturity estimated from left hand and wrist radiographs, using the Tanner-Whitehouse 2 method for Japanese populations, was 8 yr and 9 mo. Physical examination confirmed breast development and pubic hair consistent with Tanner stages 3 and 2, respectively. However, axillary hair was absent. External genitalia was normal female type (including absence of clitoral enlargement), and no masses were palpable.

Karyotype analysis revealed 46,XY,inv(9)(p12q13). Chromosome 9 inversion is a common human variation, and the diagnosis of CAIS was confirmed by the presence of a hemizygous missense mutation (p.Pro893Leu) in the AR gene (18). As shown in **Table 1**, serum LH and FSH levels were suppressed to undetectable levels, and the estradiol level (88.9 pg/mL) was relatively high, considering the testosterone level (48.7 ng/dL). Such findings were inconsistent with typical laboratory findings for CAIS patients. Ultrasonographic (US) imaging of the abdomen and inguinal regions demonstrated the absence of ovaries and Müllerian structures, presence of a testis-consistent mass (1.34 × 1.33 × 2.59 cm) in

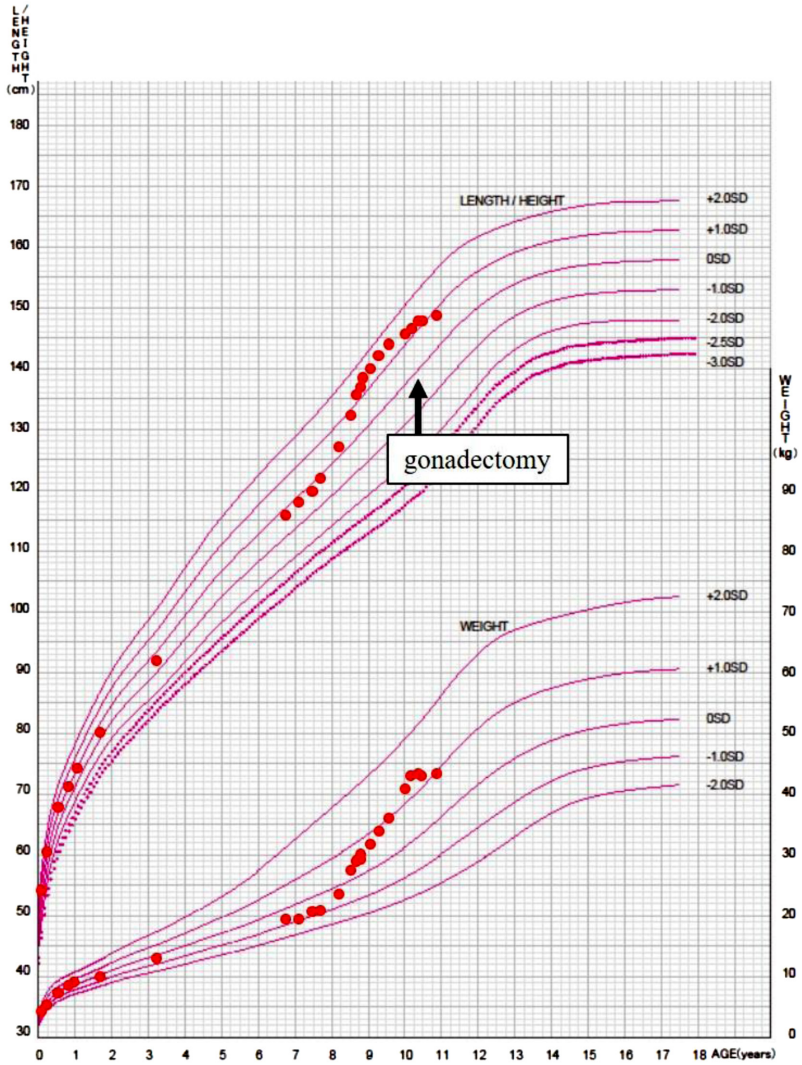

Fig. 1. Growth chart of the patient according to the cross-sectional growth chart for Japanese girls (17). Growth acceleration began at 8 yr of age.

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the left inguinal area and presence of a solid mass (2.74 × 1.64 × 3.09 cm) with small cystic components in the right intra-abdominal area, suggestive of a dysgenetic testis (**Fig. 2A**).

The atypical right gonad was followed up for 19 mo until the patient's parents provided consent for extirpation. During this interval, serum LH and FSH levels remained below 0.1 mIU/mL, and estradiol levels increased to remarkably high levels (218.6–338.8 pg/mL) (**Table 2**), concomitant with enlargement of the right intra-abdominal mass (2.70 × 3.03 × 4.33 cm) (**Fig. 2B**). Tumor markers remained within the normal range (**Table 1**).

Following bilateral gonadectomy at the age of 10 yr and 4 mo, estradiol rapidly fell below the detectable level (**Table 2**). Grossly, the excised right gonad demonstrated a solid tumor with a smooth capsule, and the cut surface was soft and yellow (**Figs. 3A and 3B**). Microscopically, encapsulated tumor lesions were present within the testicular tissue. The tumor was composed of tubules formed by enlarged Sertoli cells with eosinophilic cytoplasm and oval nuclei (**Fig. 3C**). Immunohistochemistry demonstrated the presence of inhibin, vimentin, and cytokeratin 8 and 18 (the latter detected using anti-cytokeratin monoclonal antibody CAM5.2), and the absence of epithelial membrane antigen (EMA), S-100, c-kit, and octamer-binding transcription factor-3/4 (Oct-3/4) (**Fig. 3D**). Such

Table 1. Endocrinology data at age 8 yr and 9 mo

LH	< 0.1 mIU/ml	TSH	1.394 μIU/ml
FSH	< 0.1 mIU/ml	Free T_3	4.19 pg/ml
Estradiol	88.9 pg/ml	Free T_4	0.78 ng/dl
Testosterone	48.7 ng/dl	IGF-I	283 ng/ml
AMH	305 ng/ml	ACTH	24.3 pg/ml
HCGß	< 0.1 ng/ml	Cortisol	7.38 μg/dl
AFP	2.3 ng/ml	DHEA-S	134 ng/ml
CEA	0.4 ng/ml		

AMH, anti-Müllerian hormone (5–95% level of prepubertal boy younger than 9 yr: 44.9–170.5) (19); HCGß, beta-human chorionic gonadotropin (normal range: 0–0.1); AFP, alpha fetoprotein (normal range: 0–10.0); CEA, carcinoembryogenic antigen (normal range: 0–5.0), DHEA-S, dehydroepiandrosterone-sulfate.

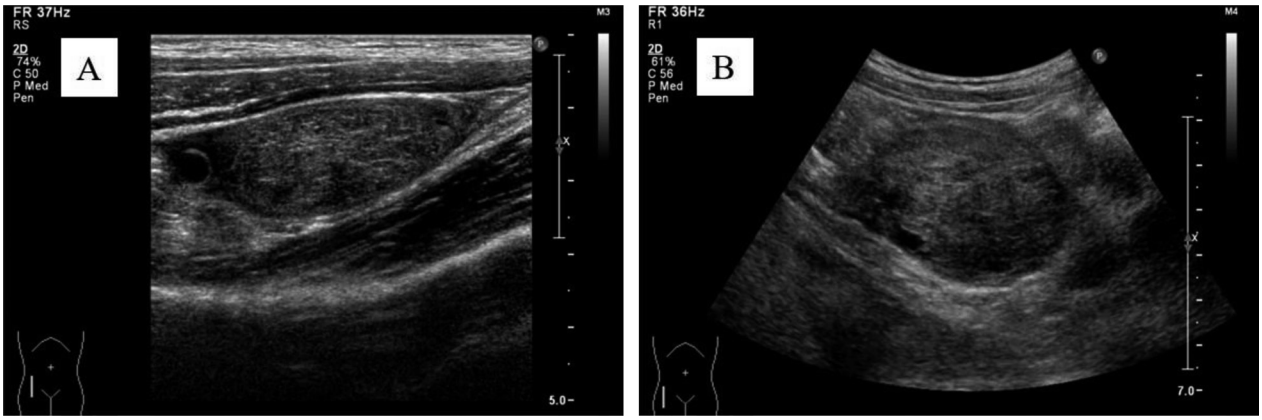

Fig. 2. Ultrasonographic imaging of the right gonad. (A) Age: 8 yr and 9 mo. Heterogeneous solid mass (2.74 × 1.64 × 3.09 cm) including small cystic components. (B) Age: 10 yr. The mass had enlarged (2.70 × 3.03 × 4.33 cm) during the 15 mo.

Table 2. Gonadotropin and estradiol dynamics

Gonadectomy

	at age of				1 d post-resection	16 d
	8 yr 9 mo	9 yr 5 mo	10 yr 0 mo	10 yr 4 mo		
LH (mIU/ml)	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	3.2
FSH (mIU/ml)	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	27.5
Estradiol (pg/ml)	88.9	218.6	307	338.8	< 5.0	<5.0

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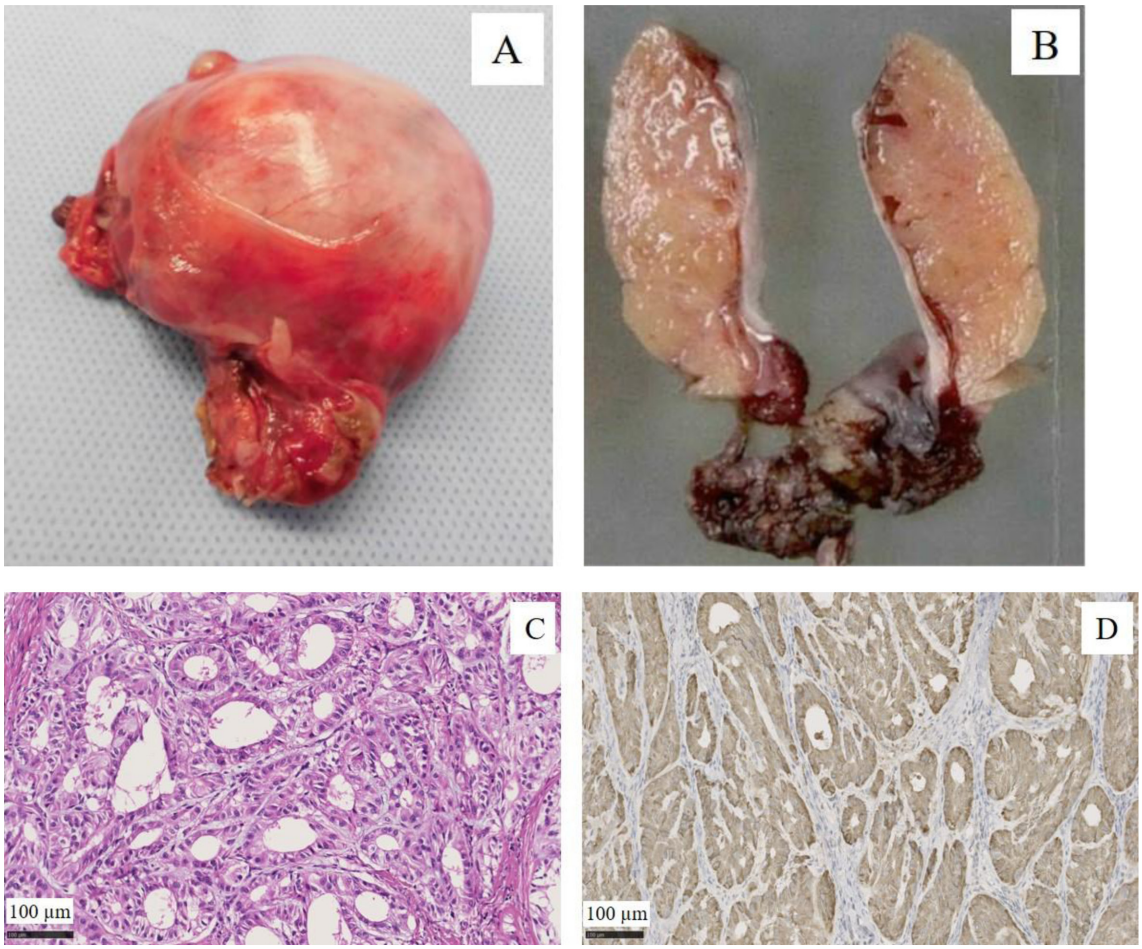

Fig. 3. (A), (B) Gross appearance of the excised right gonad containing a solid tumor. (C) Photomicrograph of a hematoxylin and eosin stained tumor section. The tumor was composed of tubules consisting of enlarged Sertoli cells. (D) Tumor cell immunohistochemistry demonstrating the presence of inhibin.

findings are consistent with Sertoli cell tumors. The excised left gonad exhibited immature seminiferous tubules consisting largely of Sertoli cells, with germ cells present in only a few tubules. Such findings are consistent with the abnormal testicular development characteristic of AIS. Neither gonad exhibited findings suggestive of malignancy.

The patient's parents opposed full disclosure of the condition to the patient prior to the surgery. Therefore, stepwise information was provided to the patient as the case progressed.

This case report was approved by the Institutional Ethical Review Board of Aichi Children's Health and Medical Center (No.2020052).

Discussion

A unique case of CAIS is reported, representing the youngest documented patient with a Sertoli cell tumor, and the first documented case with accelerated onset of puberty resulting from the tumor. Patients with CAIS who do not undergo gonad extirpation may begin developing secondary sexual characteristics at approximately the typical age of onset of puberty, due to conversion of excess testosterone into estradiol (1, 2). The patient reported herein began experiencing breast tissue development and growth acceleration (suggesting onset of puberty) at an early age (8 yr), concomitant with suppressed gonadotropin levels. Following tumor resection, the rapid fall in estradiol levels suggested that the tumor was responsible for both elevated estradiol levels and secondary sexual characteristic development, which are inconsistent with the typical course of CAIS.

Malignancy occurs in approximately 17% of patients with Sertoli cell tumors, but is rare in younger patients (9, 10, 12, 20). Moreover, benign forms are not typically hormonally active, and up to 60% of malignant forms are feminizing (20). In the present case, despite the diagnosis of CAIS being made during infancy, the patient's parents elected to delay gonadectomy until they were able to obtain informed consent from their daughter. Therefore, her parents did not agree to extirpate the tumor accompanying her gonads immediately. We carefully followed up the tumor development for 19 mo, while no pathological malignant findings were observed in the tumor.

In the present case, clinical suspicion of a Sertoli cell tumor was informed by early-onset apparent puberty

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and laboratory data were atypical of CAIS (elevated estradiol and suppressed gonadotropin levels). The incidence of pre-pubertal testicular tumors is 0.5–2 per 100,000 children, and Sertoli cell tumors accounts for only 2–3% of these. The most common presenting sign of Sertoli cell tumors among male patients is a painless scrotal mass. Gynecomastia and other signs of hyperestrogenism are present in 20–30% of cases (8–14). In females with CAIS, breast enlargement can be the first sign of hyperestrogenism, as observed in the present case; this may be difficult to recognize as an abnormality in post-pubertal cases.

The enzyme aromatase converts androgens to estrogens. Excessive estrogen production can result from an increase in aromatase activity, aromatase substrate levels, or both. Coen *et al*. demonstrated elevated estrogen levels and gynecomastia due to increased aromatase activity in the presence of a gonadal tumor (21). In contrast, elevated serum estradiol levels are not typically observed in patients with feminizing Sertoli cell tumors (10, 11, 21), unlike the present case, suggesting that small amounts of estrogen are sufficient to induce gynecomastia (11, 21). In males, only 15–25% of serum estradiol is produced by the testis (1); a substantial increase in testicular estradiol production may not significantly affect total serum estradiol concentrations, especially pre-pubertally (21). It was initially assumed that the extremely elevated estradiol level observed in the present case may have been due to excess aromatase substance (due to androgen insensitivity), in addition to increased aromatase activity within the tumor.

Conclusion

In conclusion, we report a case of CAIS with a feminizing Sertoli cell tumor diagnosed at an early pubertal age. It is rare for gonadal tumors to occur in CAIS patients at an early age, and Sertoli cell tumors are rarer than germ cell tumors, but do occasionally occur. Similarly, benign Sertoli cell tumors produce feminization more rarely than malignant forms. As illustrated by the present case, feminizing Sertoli cell tumor should be suspected, especially when secondary sexual characteristics begin to develop prior to reaching the typical age of onset of puberty.

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References

1. Achermann JC, Hughes IA. Pediatric disorders of sex development. Philadelphia: Williams Textbook of Endocrinology 13th edition; 2016.p.932-6.
2. Fagouri H, Moussaoui DR, Kouach J, Babahabib A, Oukabli M, Ameur A, *et al*. Complete androgen insensitivity syndrome with a Sertoli-Leydig cell tumor. J Pediatr Adolesc Gynecol 2014;27: e113–5. [Medline] [CrossRef]
3. Lin MH, Shamszadeh M, Pitukcheewanont P. Sertoli cell tumor and intratubular germ cell neoplasia located in separate gonads in an adolescent patient with complete androgen insensitivity: a case report and review of literature. J Pediatr Endocrinol Metab 2012;25: 547–51. [Medline] [CrossRef]
4. Jarzabek K, Philibert P, Koda M, Sulkowski S, Kotula-Balak M, Bilinska B, *et al*. Primary amenorrhea in a young Polish woman with complete androgen insensitivity syndrome and Sertoli-Leydig cell tumor: identification of a new androgen receptor gene mutation and evidence of aromatase hyperactivity and apoptosis dysregulation within the tumor. Gynecol Endocrinol 2007;23: 499–504. [Medline] [CrossRef]
5. Nakhal RS, Hall-Craggs M, Freeman A, Kirkham A, Conway GS, Arora R, *et al*. Evaluation of retained testes in adolescent girls and women with complete androgen insensitivity syndrome. Radiology 2013;268: 153–60. [Medline] [CrossRef]
6. Hannema SE, Scott IS, Rajpert-De Meyts E, Skakkebaek NE, Coleman N, Hughes IA. Testicular development in the complete androgen insensitivity syndrome. J Pathol 2006;208: 518–27. [Medline] [CrossRef]
7. Wysocka B, Serkies K, Debniak J, Jassem J, Limon J. Sertoli cell tumor in androgen insensitivity syndrome– a case report. Gynecol Oncol 1999;75: 480–3. [Medline] [CrossRef]
8. Fleckenstein GH, Gunawan B, Brinck U, Wuttke W, Emons G. Simultaneous sertoli cell tumor and adenocarcinoma of the tunica vaginalis testis in a patient with testicular feminization. Gynecol Oncol 2002;84: 460–3. [Medline] [CrossRef]
9. Fernando A, Ferrer MD. Pediatric Urologic Oncology: Bladder and testis. Philadelphia: Campbell-Walsh Urology 11th edition; 2015.p.3590-91.
10. Dursun F, Su Dur ŞM, Şahin C, Kırmızıbekmez H, Karabulut MH, Yörük A. A rare cause of prepubertal gynecomastia: Sertoli cell tumor. Case Rep Pediatr 2015;2015: 439239. [Medline]
11. Alikasifoglu A, Gonc EN, Akcoren Z, Kale G, Ciftci AO, Senocak ME, *et al*. Feminizing Sertoli cell tumor associated with Peutz-Jeghers syndrome. J Pediatr Endocrinol Metab 2002;15: 449–52. [Medline] [CrossRef]
12. Crocker MK, Gourgari E, Lodish M, Stratakis CA. Use of aromatase inhibitors in large cell calcifying sertoli cell tumors: effects on gynecomastia, growth velocity, and bone age. J Clin Endocrinol Metab 2014;99: E2673–80. [Medline] [CrossRef]
13. Young S, Gooneratne S, Straus FH 2nd, Zeller WP, Bulun SE, Rosenthal IM. Feminizing Sertoli cell tumors in boys with Peutz-Jeghers syndrome. Am J Surg Pathol 1995;19: 50–8. [Medline] [CrossRef]
14. Armijo B, Bocklage T, Heideman R. Intratubular large cell hyalinizing Sertoli cell tumor of the testes in a 4-year-old male with Peutz-Jeghers Syndrome. J Pediatr Hematol Oncol 2015;37: e184–7. [Medline] [CrossRef]
15. Knoke I, Jakubiczka S, Ottersen T, Göppinger A, Wieacker P. A(870)E mutation of the androgen receptor gene in a patient

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with complete androgen insensitivity syndrome and Sertoli cell tumor. Cancer Genet Cytogenet 1997;98: 139–41. [Medline] [CrossRef]
16. Takekawa Y, Kimura M, Sakakibara M, Yoshii R, Ato M, Nemoto N, *et al*. Immunohistochemical study of Sertoli-stromal cell tumor; comparison between the tumor arising from the gonad of a testicular feminization syndrome bearing patient and from ovaries of non-bearing patients. Rinsho Byori 1999;47: 1070–4 (in Japanese). [Medline]
17. The Japanese Society for Pediatric Endocrinology. The 2000 National Growth Survey on Preschool Children and School Health Statistics Research. http://jspe.umin.jp/medical/chart_dl.html (accessed 2021/01/11).
18. The androgen receptor gene mutations database world wide web server. Montreal: androgendb.mcgill.ca/.
19. Aksglaede L, Sørensen K, Boas M, Mouritsen A, Hagen CP, Jensen RB, *et al*. Changes in anti-Müllerian hormone (AMH) throughout the life span: a population-based study of 1027 healthy males from birth (cord blood) to the age of 69 years. J Clin Endocrinol Metab 2010;95: 5357–64. [Medline] [CrossRef]
20. Masiakos PT, Flynn CE, Donahoe PK. Masculinizing and feminizing syndromes caused by functioning tumors. Semin Pediatr Surg 1997;6: 147–55. [Medline]
21. Coen P, Kulin H, Ballantine T, Zaino R, Frauenhoffer E, Boal D, *et al*. An aromatase-producing sex-cord tumor resulting in prepubertal gynecomastia. N Engl J Med 1991;324: 317–22. [Medline] [CrossRef]