Pure Sertoli Cell Tumor of the Ovary, A Rare Cause of Isosexual Pseudoprecocious Puberty in a Two Year Old Girl

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A case of a two and a half year old girl with a 6 month history of isosexual precocious puberty (thelarche: Tanner stage 2 breasts and menarche) secondary to an estrogenizing pure Sertoli cell tumor of the left ovary is presented. Pre-operative tumor markers AFP, βhCG and CA-125 revealed normal results. Transabdominal ultrasound with color flow mapping and Doppler interrogation revealed a solid left ovarian mass probably malignant. The patient underwent exploratory laparotomy, left salpingooophorectomy and frozen section revealing sex cord stromal tumor. Paraffin sections stained with Hematoxylin and Eosin revealed a benign Sertoli cell tumor. Immunostains of the tumor reacted positively for inhibin, calretenin and cytokeratin, but negative for epithelial membrane antigen. Total serum estradiol, prolactin, TSH and LH were elevated prior to surgical operation, with LH and prolactin substantially decreasing four weeks later into the normal prepubertal range. TSH and estradiol levels however have remained very slightly elevated. Serum FSH was at prepubertal levels. Breasts size had likewise regressed to prepubertal size four weeks postoperatively, and the menses never recurred. This is the youngest reported occurrence of this rare sex cord stromal neoplasm in the last 10 years in our institution. The prognosis of this extremely rare tumor presenting at this early juvenile stage is uncertain, and it is recommended to keep a close follow-up and regular endocrinologic investigation until prepubertal values are attained.

Key words: Sertoli cell tumor, isosexual precocious puberty, menarche, thelarche

Introduction

Pure Sertoli cell tumors (SCT) are rare ovarian tumors of the sex-cord stromal cell origin as classified by the World Health Organization. They account for about 0.5 percent of all ovarian neoplasm. They are almost always unilateral, occurring mostly in women 30 years old or younger. Fewer than 10 percent of the patients are over 50 years of age. By definition, pure Sertoli cell tumors lack Leydig cell in the stroma, which is the main source of testosterone in a normal testes. Nonetheless, some authors would report an incidence of as high as 30%-40% virilizing characteristics in some patients with SCT. Immunohistochemical staining of SCT typically shows reactivity for cytokeratin and α-inhibin, and calretenin. Positivity for melan A has also been described as a useful marker. They may be mimicked by many different tumors, some of them more frequent and more serious than Sertoli cell tumors, including mucinous tumors, low grade endometrioid carcinoma, carcinosarcoma, and tubular Krukenberg tumor. Immunohistochemistry may aid in distinguishing between these entities.[1]

Female precocious puberty, defined as the acquisition of sexual maturation prior to 8 years of age, is a common disorder, affecting 1 of every 180 girls in North America.[2] Because it is often distressing to both the child and her parents, precocious puberty can present emotional as well as diagnostic and therapeutic challenges to the primary care physician. The obstetrician-gynecologist is frequently consulted to evaluate this problem and thus must have a

thorough understanding of the physical and hormonal events that characterize normal pubertal development and be able to recognize abnormalities. In addition, as a primary care physician, the obstetrician-gynecologist must be knowledgeable about the numerous causes of precocious puberty and be well-versed in the appropriate evaluation and treatment of this disorder.

Here in our country, we still lack organized data describing these kinds of patients, and so its prevalence in the Philippines is still unknown. In our institution, this is the 2nd reported pseudoprecocious puberty case in the last 10 years.

This paper presents a relevant case of Isosexual Pseudoprecocious Puberty in a 2 year old female patient, who subsequently underwent surgical management of the peripheral estrogen source, with regression of precocious characteristics 4 weeks postoperatively. Immunostaining and various endocrinologic investigations are likewise discussed.

The Case

Patient SB is a 2 and a half year old child from Pampanga, who consulted our outpatient department for vaginal bleeding.

She was born at term to non-consanguineous parents, with an uncomplicated antenatal course. The mother was a 34 year old G2P1 (1001) at the time of conception, had regular prenatal check-ups with an obstetrician-gynecologist, had no history of illnesses, nor intake of any illicit drugs nor prescription medications during pregnancy. Delivery was by emergency low segment cesarean section, at 38 weeks age of gestation, for cephalopelvic disproportion. Birth weight was 4 kg, length 52cm (95th percentile), head circumference 40 cms (>95th percentile). At birth, patient had good suck, cry and activity. Patient's mother claims that the Newborn Screening test was done prior to discharge from hospital, which subsequently revealed negative results. The patient had episodes of febrile seizures (at least twice) between 7 - 9 months. She was bottlefed with formula milk since birth, and started on solid foods at 6 months of age.

Family medical history was unremarkable. BCG, DPT, OPV, MMR and Hepatitis B vaccines were given at the local health center.

The patient's mother is a housewife, and a college undergraduate (BS Education). Her father is a 33 year old tricycle driver, likewise a college undergraduate (BS HRM).

Patient's only sibling is a 5 year old male currently enrolled in a pre-school in Pampanga, apparently with normal physical, mental and psychosocial development.

The following tabulation describes the patient's developmental history.

Category of Activity	Milestones	Age of Patient at Milestone	Average Age of Attainment
Gross Motor Development	Rolls over	7 months	5 months
	Sits without support	1 year old	6 months
	Pulls to stand	2 years old	1 year old
	Walks alone	2 years old	15 months
	Runs around	2 years old (with support)	16 months
Fine Motor Development	Reaches objects	6 months	4 months
	Holds bottle	7 months	4 months
	Transfers objects hand to hand	8 months	5 months
	Scribbles	2 years old	13 months
Receptive Language	Responds to name calling	1 year old	6 months
	Follows one-step command with gesture	1 ½ years old	7 months
	Follows one-step command without gestures	2 years old	10 months
Expressive Language	Monosyllabic babbles "mama", "papa"	1 year old	6 months
	Jargoning	1 ½ years old	15 months

History of present illness started 6 months prior to admission when patient's mother noted enlargement of bilateral breasts. No consult was done nor medications taken. Two months prior to admission, there was onset of cyclic vaginal bleeding initially consuming 1 diaper per day for 2 days, which then progressed to moderate flow on the second episode (after approximately a month), using up 2-3 diapers per day for 3-4 days. This prompted the mother to consult a private pediatrician in their hometown, who coincidentally noted the patient's macrocephalic condition, and immediately referred her to a Pediatric neurologist and endocrinologist. Initial work-ups included a cranial CT scan which revealed essentially normal results,

and a pelvic ultrasound (transabdominal) which revealed a suspicious left adnexal mass. Due to financial constraints, the mother brought the patient for further consult and management to the Philippine General Hospital.

At presentation, the patient's height was 93cm (95th percentile), and weight 15kg (95th percentile). Physical examination revealed an active, alert, mildly irritable child, with a grossly macrocephalic head (head circumference at 53cm ,>+2 SD), a short-webbed neck, a flat nasal bridge, bilaterally-pointed ears and drooping eyelids. No palpable anterior neck mass was noted. Her skin was smooth and supple, with no noted maculopapular lesions nor discolorations. Her face was likewise free of any lesions or acne. The patient had complete dentition with caries, and note of a few small hyperpigmented macules confined to the lower lip. Breast tissue was palpable and the contour of nipples and areolae was equivalent to Tanner stage 2 breast development. Pulmonary and cardiac findings were unremarkable. There was no growth of axillary hair (Figure 1). There was note of simian crease on both palmar areas. Abdomen was globular and soft (AC 53cm, 95th percentile), with normoactive bowel sounds, and no palpable abdominal mass. Inspection of her external genitalia revealed estrogenized vulvar mucosa with a clear viscous discharge, but the clitoris was not grossly enlarged, nor was there any growth of pubic hair noted (Figure 2).

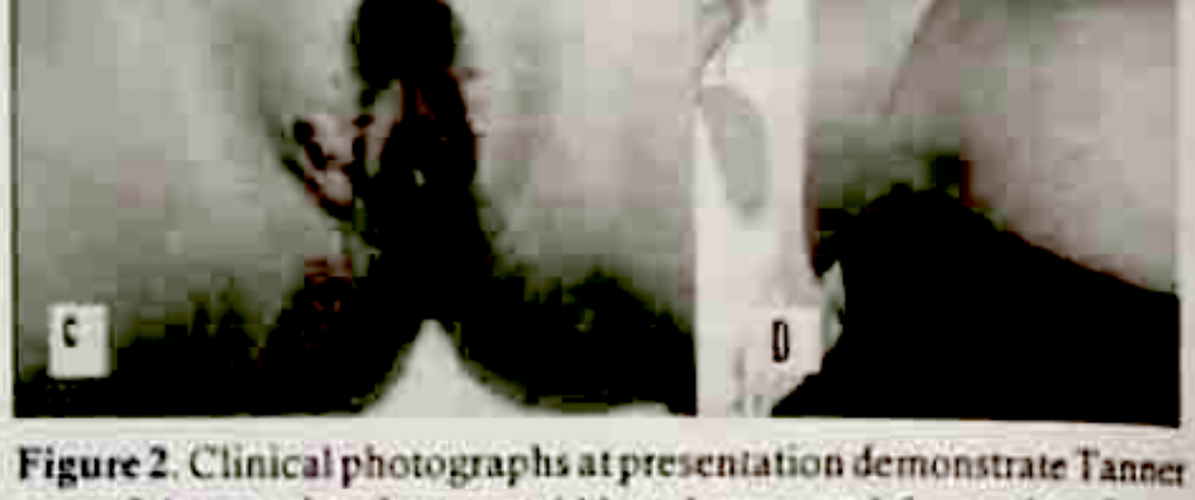

Figure 2. Clinical photographs at presentation demonstrate Tanner stage 2 breast development (A) at 1 year and 6 months of age. Inspection of her external genitalia revealed estrogenized vulvar mucosa with a clear viscous discharge, but the clitoris was not grossly enlarged, nor was there any growth of pubic hair noted (B). External genitalia stained with menstrual blood on day 3 of her menses (C). No growth of axillary hair noted (D).

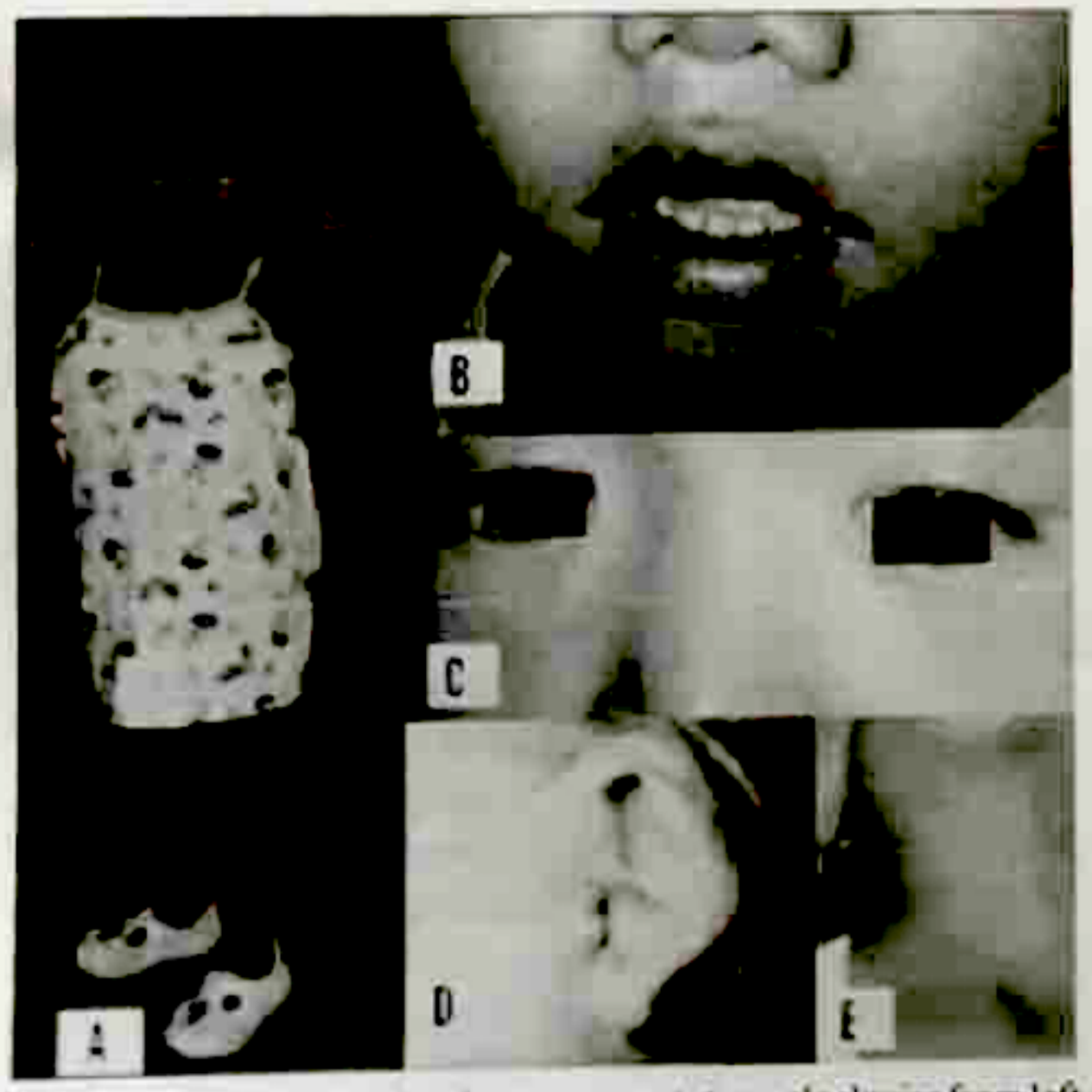

Figure 1. Physical examination on presentation, clockwise from left to right. (A) patient stood at a height of 93 cms (95th percentile); (B) few hyperpigmented brownish macules confined over the lower lip, not crossing the vermillion border; (C)drooping eyelids and flat nasal bridge; (D)slightly-pointed ears (E) short-webbed neck, but no palpable anterior neck mass.

The patient was referred to the section of Developmental Pediatrics. Investigation of the patient's developmental profile at presentation revealed an approximate mental age of 15 to 18 months. Diagnosis was global developmental delay.

Chest X-ray was normal. X-ray examination of her left hand and wrist at a chronological age of 2 years 6 months, revealed a bone age of a 2-3 year old female (based on method of Greulich and Pyle). Skeletal survey revealed macrocephaly, with a cephalic index of 85.64. Cranial CT scan showed essentially normal results, with patent sutures and anterior fontanel, and a craniofacial ratio normal for age. Ultrasonographic investigation of the abdomen revealed a uterus slightly enlarged for age (4.9cm x 2.5cm x 1.7cm) with thin endometrium (0.3cm), normal right ovary, and a left ovarian new growth probably malignant (Sassone 13, Lerner 7), which on color flow mapping and Doppler showed central and peripheral vascularities, and low resistance indices (RI 0.43,PI 0.53) suggestive of malignancy. The rest of the abdominal organs were normal on abdominal ultrasound (Figure 3).

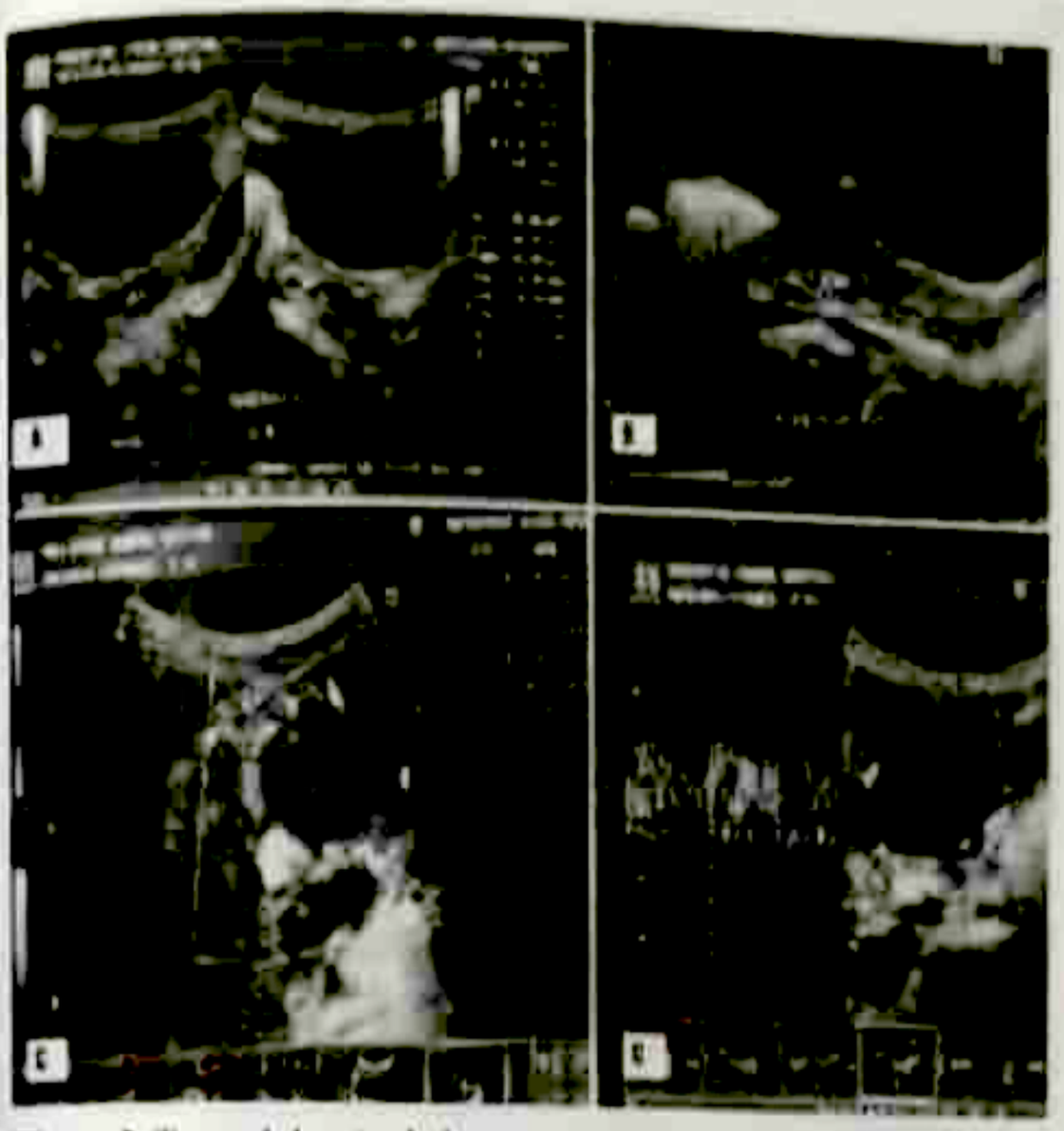

Figure 3. Transabdominal ultrasonographic scan showed (A)the left ovary converted to a heterogenous solid mass measuring 4.9cm x 4.4cm x 3.5cm, (B)The uterus is slightly enlarged for age (4.9cm x 2.5cm x 1.7cm) with thin endometrium (0.3cm) and intact subendometrial halo, (C) On color-flow mapping, the mass has both central and peripheral vascularities, (D) Doppler interrogation revealed low resistance indices (RI 0.43, PI 0.53) suggestive of malignancy.

The patient was likewise referred to the Section of Pediatric Genetics for evaluation. To rule out a chromosomal abnormality, karyotyping was requested, and it revealed a normal female karyotype (46, XX confirmed by gross G banding) (Figure 4).

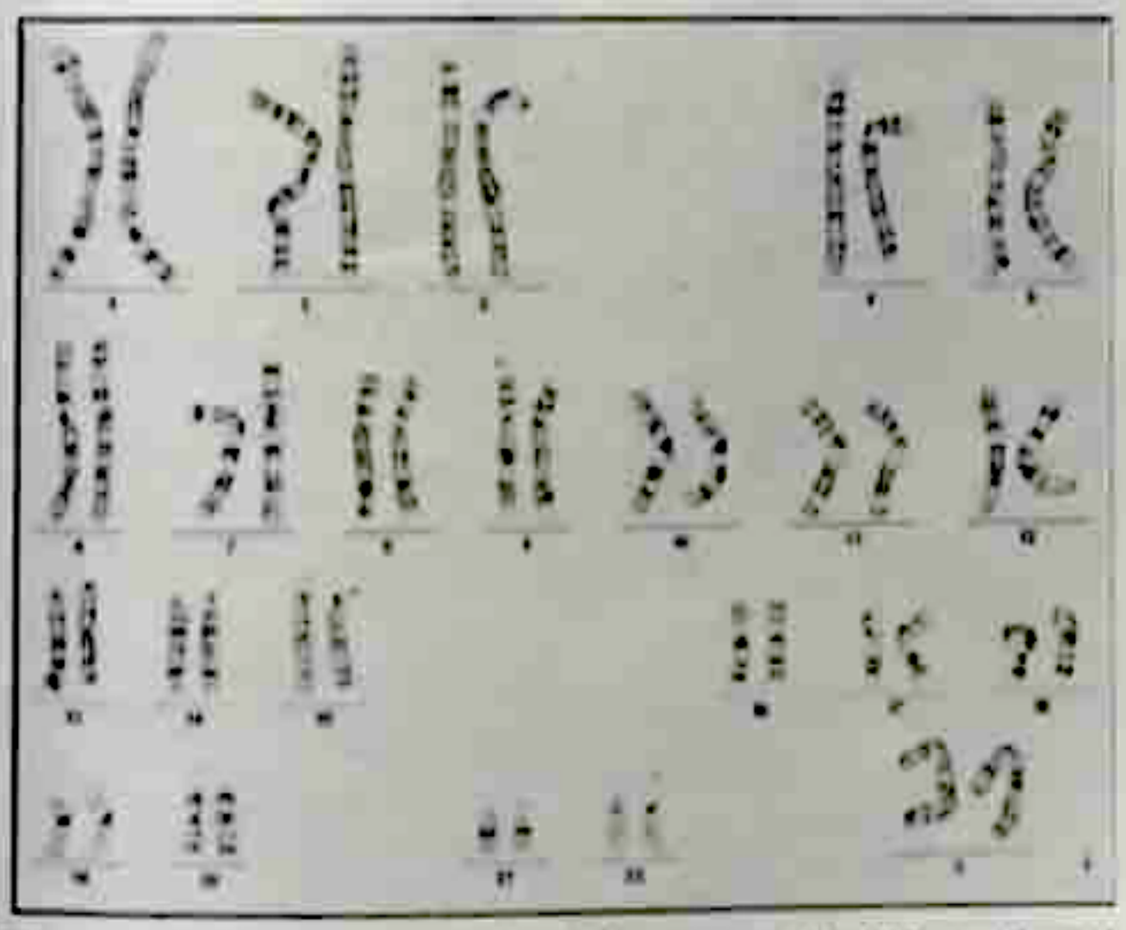

Figure 4. Patient had normal female karyotype (46, XY), confirmed by gross G banding.

The following are the results of the endocrinologic investigation:

Examination	Result	Normal Value
Serum prolactin	783 uIU/ml (↑)	80-500 uIU/ml
FSH IRMA	2.0 (N)	2.2 ± 1.1 IU/L
LH IRMA	0.57 (↑)	0.03 ± 0.03 IU/L
FT4	22.4 (N)	11 - 24 pmol/L
TSH	9.4 mIU/L (↑)	0.3 - 3.8 mIU/L
Estradiol	234 pmol/mL (↑↑)	<20 pmol/mL
DHEAS	0.41 mIU/L (N)	0.34 - 2.16 mIU/L

Tumor markers were likewise investigated with the following results:

Examination	Result	Normal Value
CA-125	26.2 U/ml (N)	0-35 U/ml
AFP	1.28 NG/ml (N)	0.37 - 6.5 NG/ml
βHCG	0.99 MIU/ml (N)	Less than 5 MIU/ml

At exploratory laparotomy, approximately 6 months following initial presentation, a solid ovoid tumor measuring 5cm x 5cm x 4cm, localized to the left ovary was identified. It had a smooth and intact outer capsule, and on cut section showed a smooth, yellowish, firm, non-necrotic, non-hemorrhagic lobulated appearance. The right ovary was grossly normal on inspection and not removed. There were no palpable nor suspicious pelvic nodules. A left salpingooophorectomy was performed and the specimen was immediately sent for frozen section. Frozen section revealed "consistent with sex cord stromal tumor."

Hematoxylin and Eosin staining of paraffin sections favored a Pure Sertoli cell tumor, with advice to test for immunostains Inhibin, Calretenin, Epithelial Membrane Antigen (EMA), Cytokeratin (CK) and Melan-A.

Ovarian Histology

The resected specimen consisted of a left fallopian tube and attached left ovary The ovary measured 5cm x 4cm x 3cm with a smooth external surface that was yellowish-gray in appearance. The cut section revealed a yellow lobulated solid tumor (Figures 5 & 6).

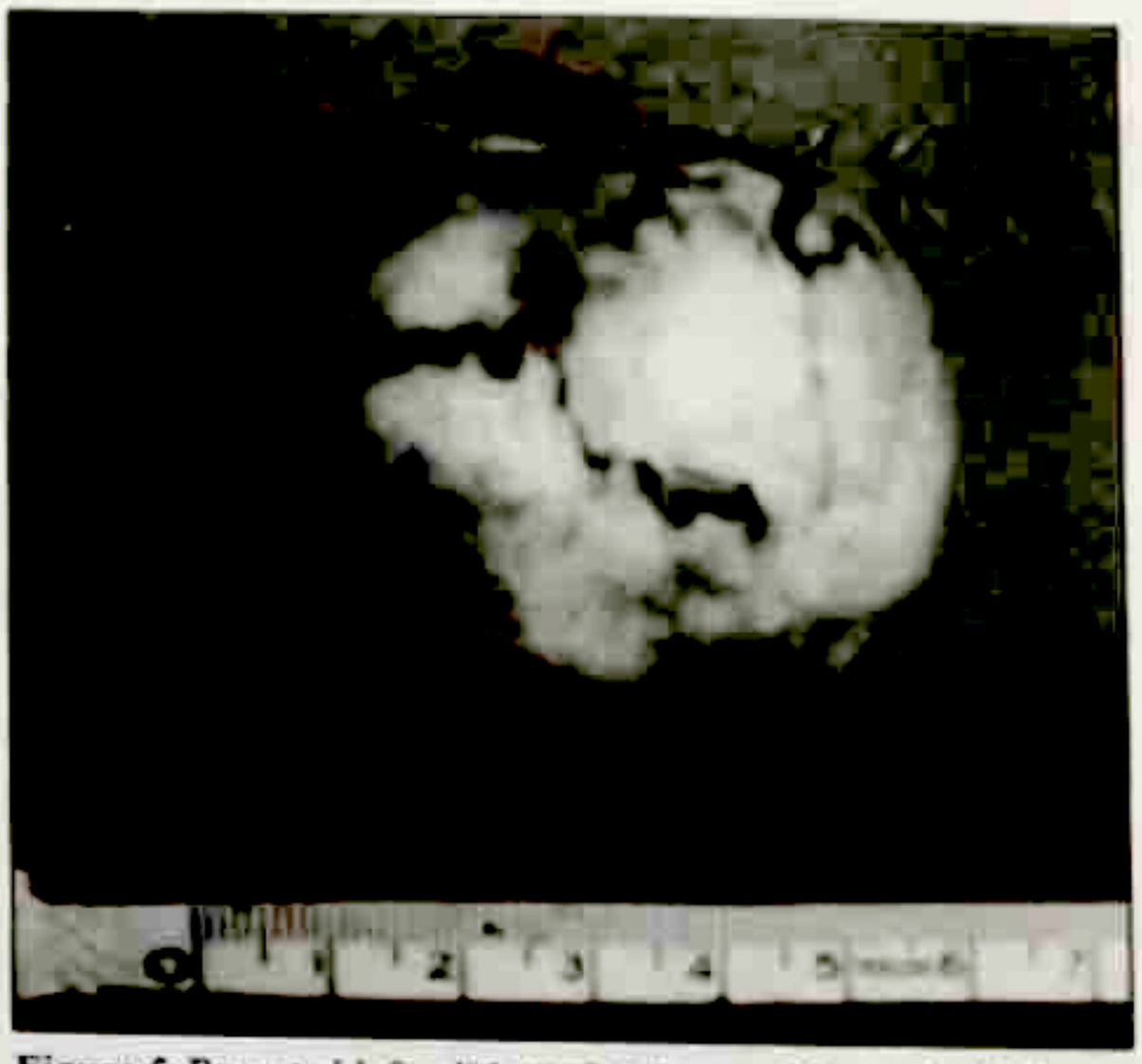

Figure 5. Resected left solid ovarian tumor with attached fallopian tube. External surface of the tumor appears smooth.

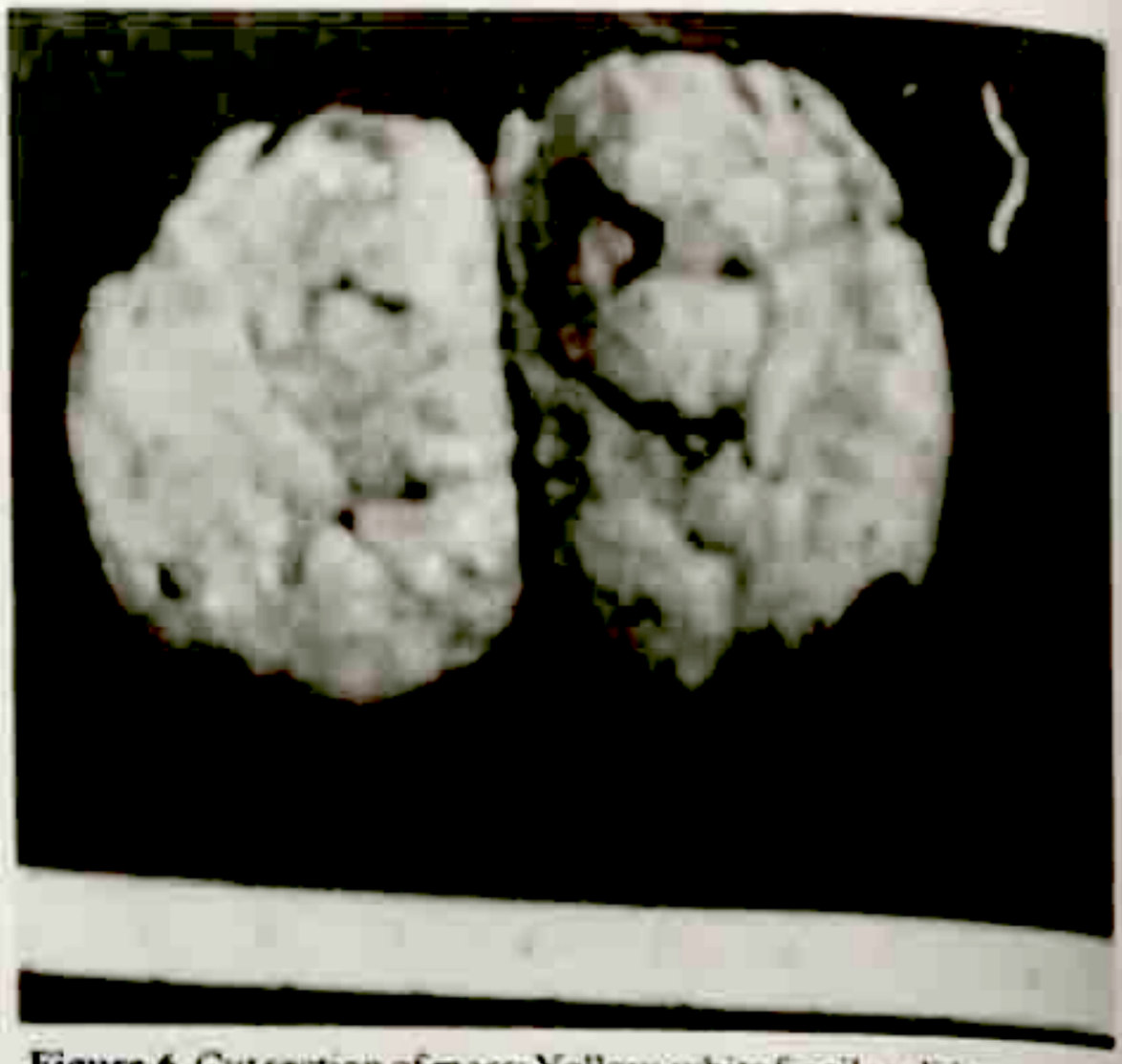

Figure 6. Cut section of mass: Yellow-white fragile solid tumor with lobulated appearance.

Microscopic examination showed that the majority of the ovary was replaced by a vaguely nodular tumor composed of hyalinized stroma containing cells forming in cords and nests. Toward the periphery of the tumor the stroma was somewhat more edematous, and the tumor cells, which were arranged in cord-like structures, showed occasional areas strongly suggestive of poorly formed tubules (Figure 7A).

The high power examination (x400) showed moderately sized cells with mostly clear vacuolated cytoplasm. The nuclei are vesicular with no cytologic atypia or significant pleomorphism (Figure 7B).

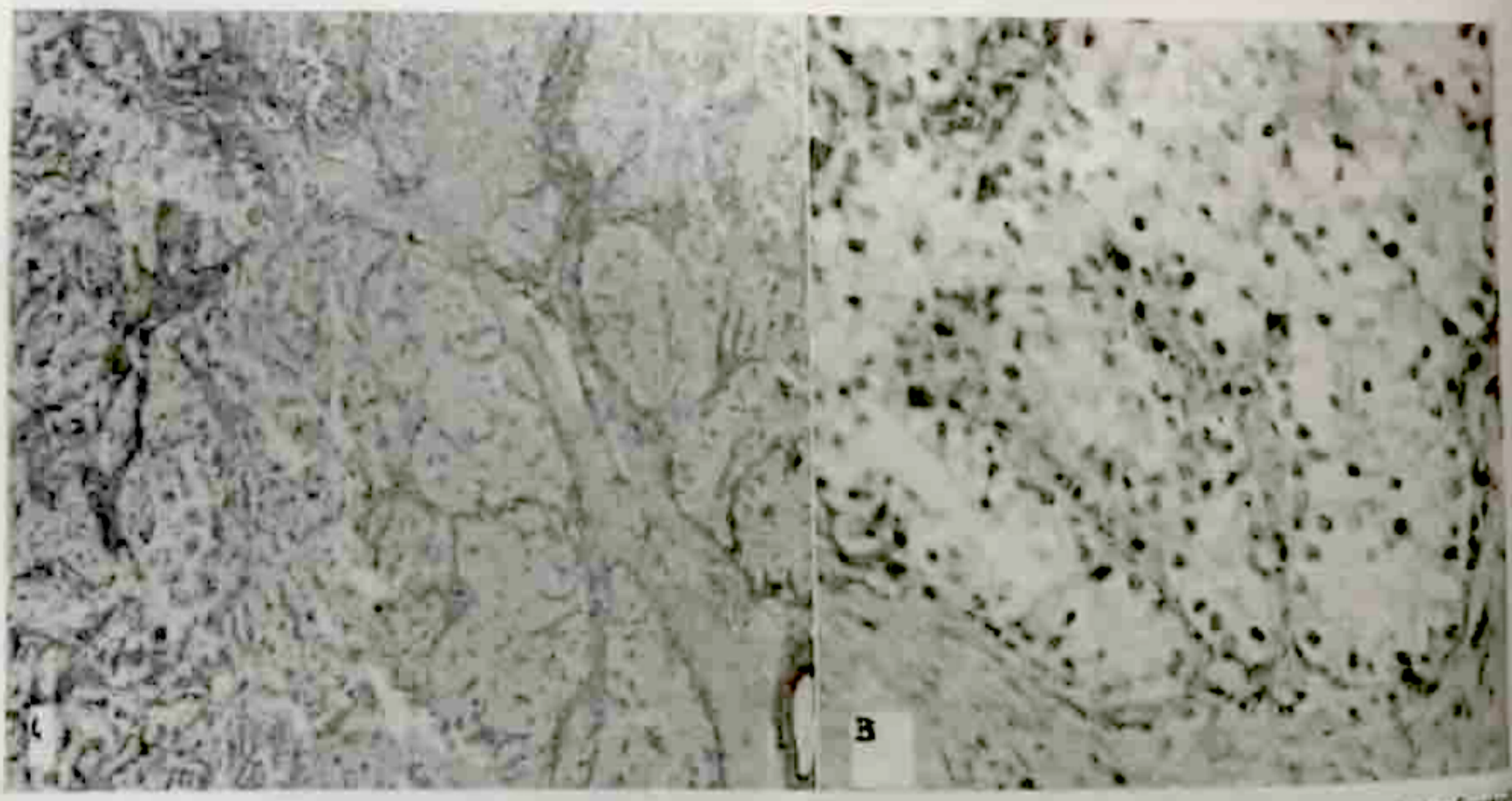

Figure 7. Paraffin sections stained with hematoxylin and eosin stain: Solid tubules separated by thin fibrous bands characteristic of sertoli cell tumor: (A) Scanning view (magnification x20) and (B) HPO (magnification x 400).

Immunostaining yielded the following results:

Immunostain	Result
Inhibin*	Positive
Calretenin*	Positive
CK*	Positive
EMA*	Negative

*Figures 8, 9, 10 and 11

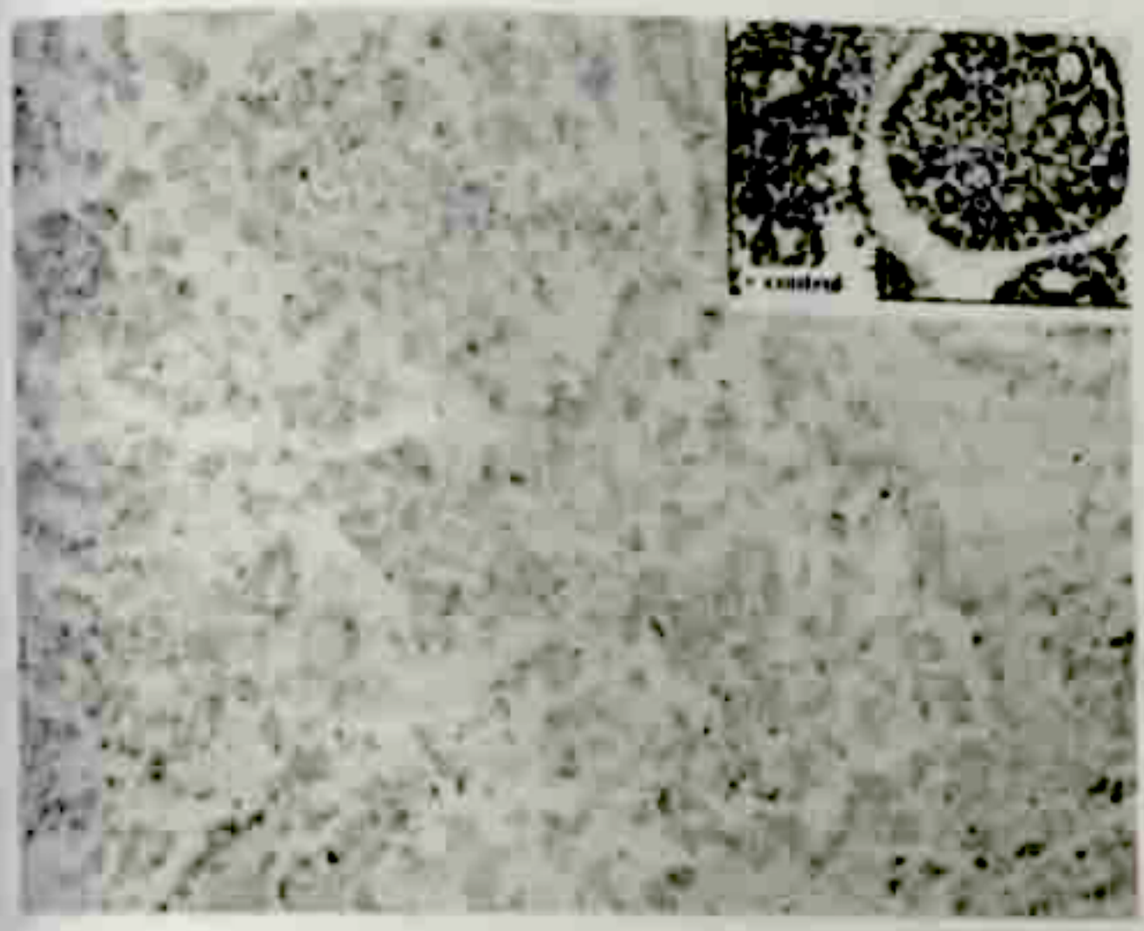

Figure 8. Sertoli cells staining positive for inhibin (magnification x 100).

Figure 9. Sertoli cells staining positive for immunostain cytokeratin (magnification x 100).

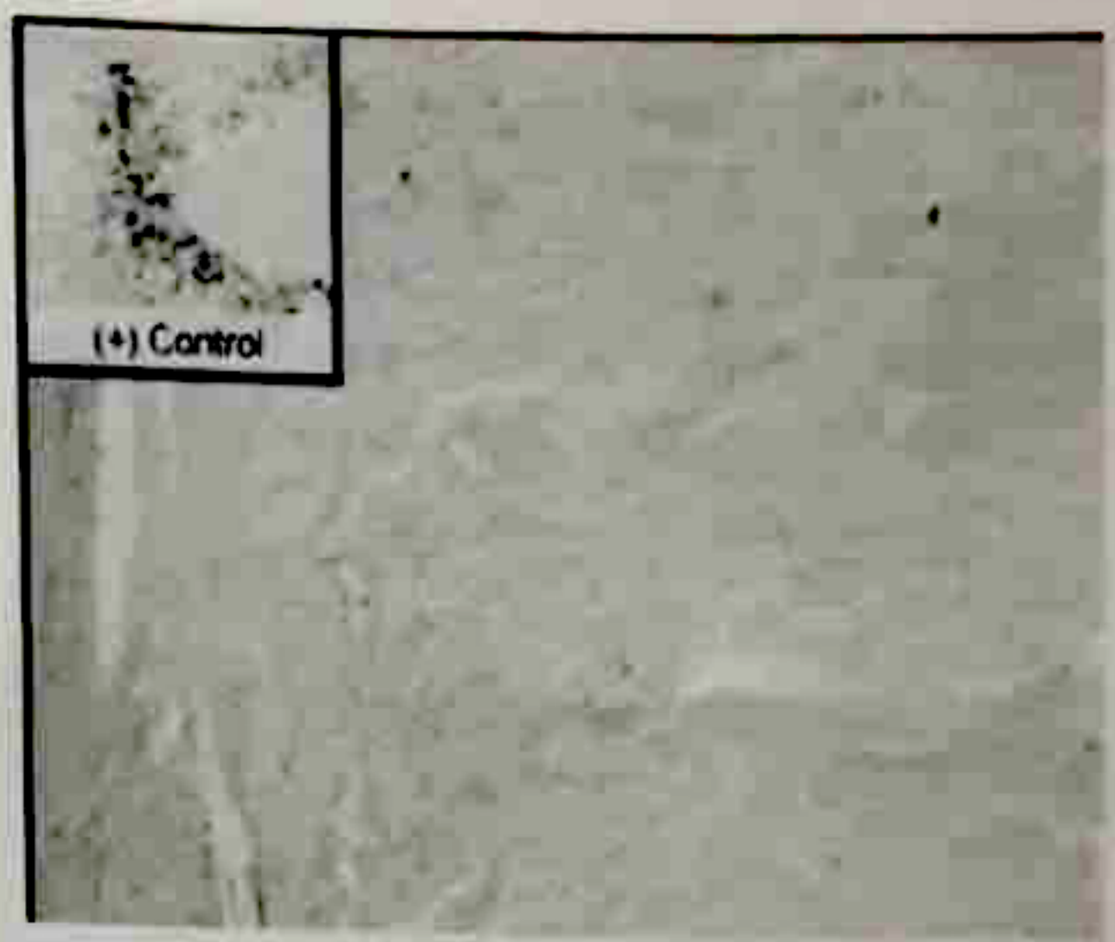

Figure 10. Sertoli cells staining negative to immunostain epithelial membrane antigen (magnification x 100).

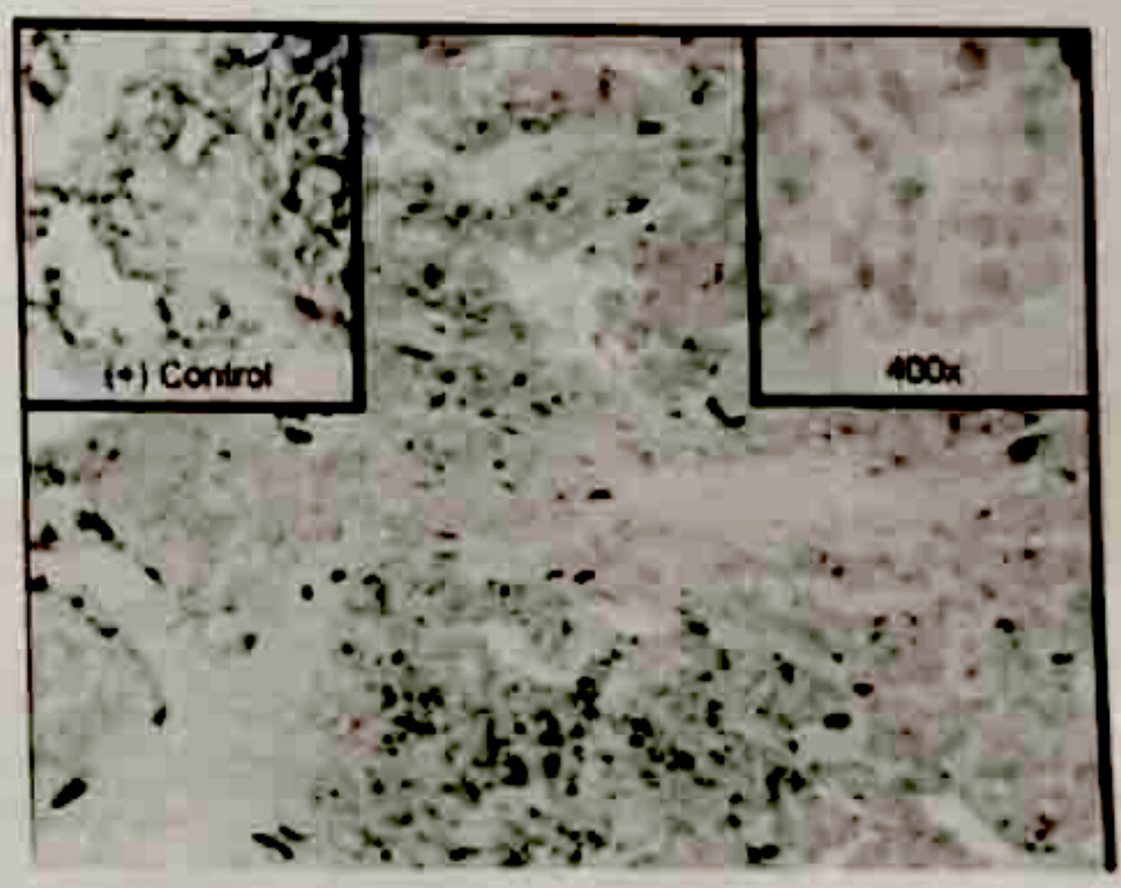

Figure 11. Sertoli cells staining positive to calretenin (magnification x 100).

Postoperative Course and Follow-up

Postoperative course was unremarkable. The patient was discharged on the 4th postoperative day without any complication, and with strict advice on postoperative daily wound care and pain medications, and for follow-up endocrinologic studies. The section of Developmental Pediatrics and Genetics likewise advised close follow-up in their respective clinics.

Four weeks postoperatively, patient's breasts have completely flattened, and the menstruation never recurred. (Figure 12)

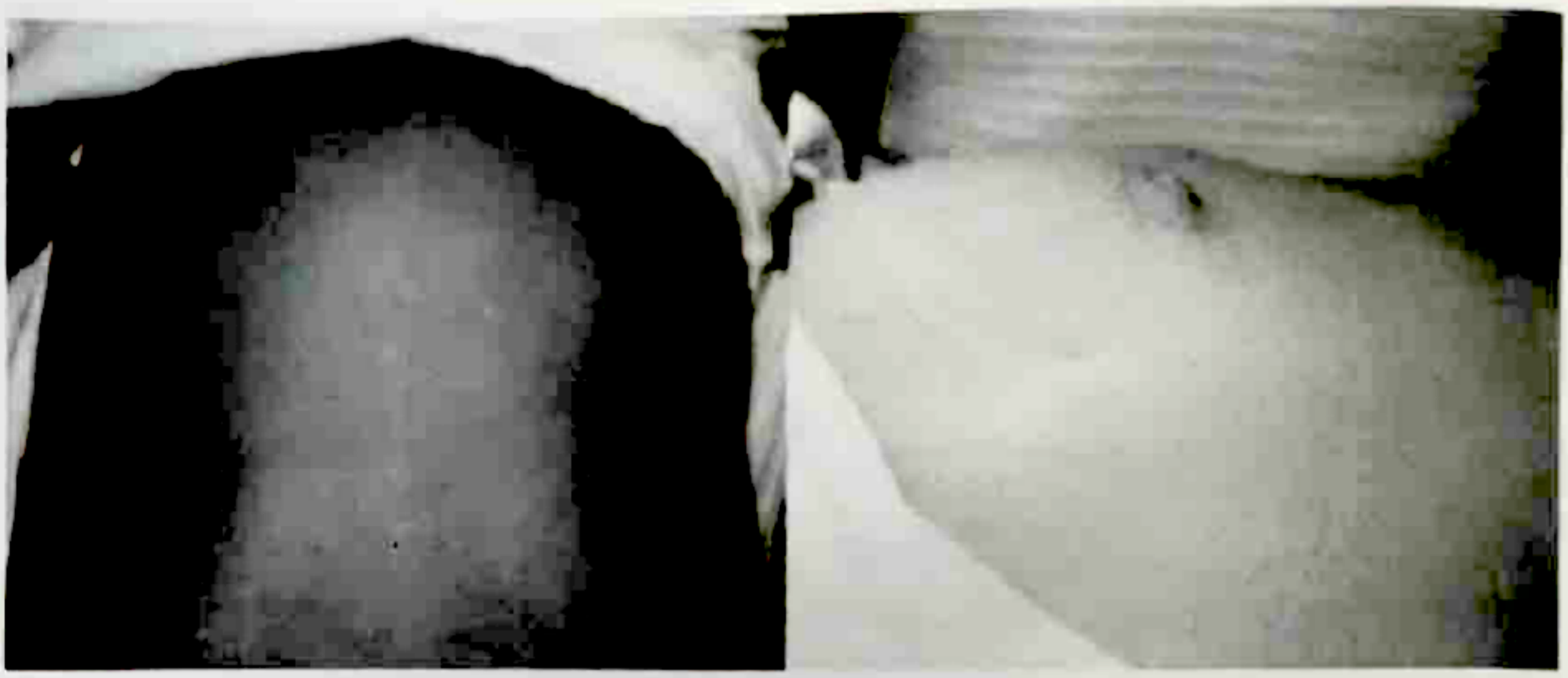

Figure 12. Bilateral breasts have gone back to prepubertal size four weeks postoperatively.

Follow-up (repeat) endocrinologic investigation 1 month postoperatively revealed the following results:

Examination	Preoperative Values	Postoperative Result	Normal Value
Serum prolactin	783 IU/mL	304 IU/mL	80 - 500 IU/mL
FSH IRMA	2.0 IU/L	3.0 IU/L	2.2 + 1.1 IU/L
LH IRMA	0.57 IU/L	0.05 IU/L	0.03 + 0.03 IU/L
FT4	22.4	22.7 pmol/L	11 - 24 pmol/L
TSH	9.4 mIU/L	7.5 mIU/L	0.3 - 3.8 mIU/L
Estradiol	234 pmol/mL	37.3 pmol/mL	<20 pmol/mL

Thyroid scintigraphy 3 months postoperatively revealed a thyroid gland with normal to small dimensions, and depressed uptake function (Figure 13). Section of Pediatric Endocrinology advised against starting any thyroid medication. Close follow-up until thyroid function studies and other endocrinologic markers normalize was recommended instead.

Discussion

Definition of Precocious Puberty

Precocious puberty is the appearance of signs of sexual maturation at an age >3.0 standard deviations below the

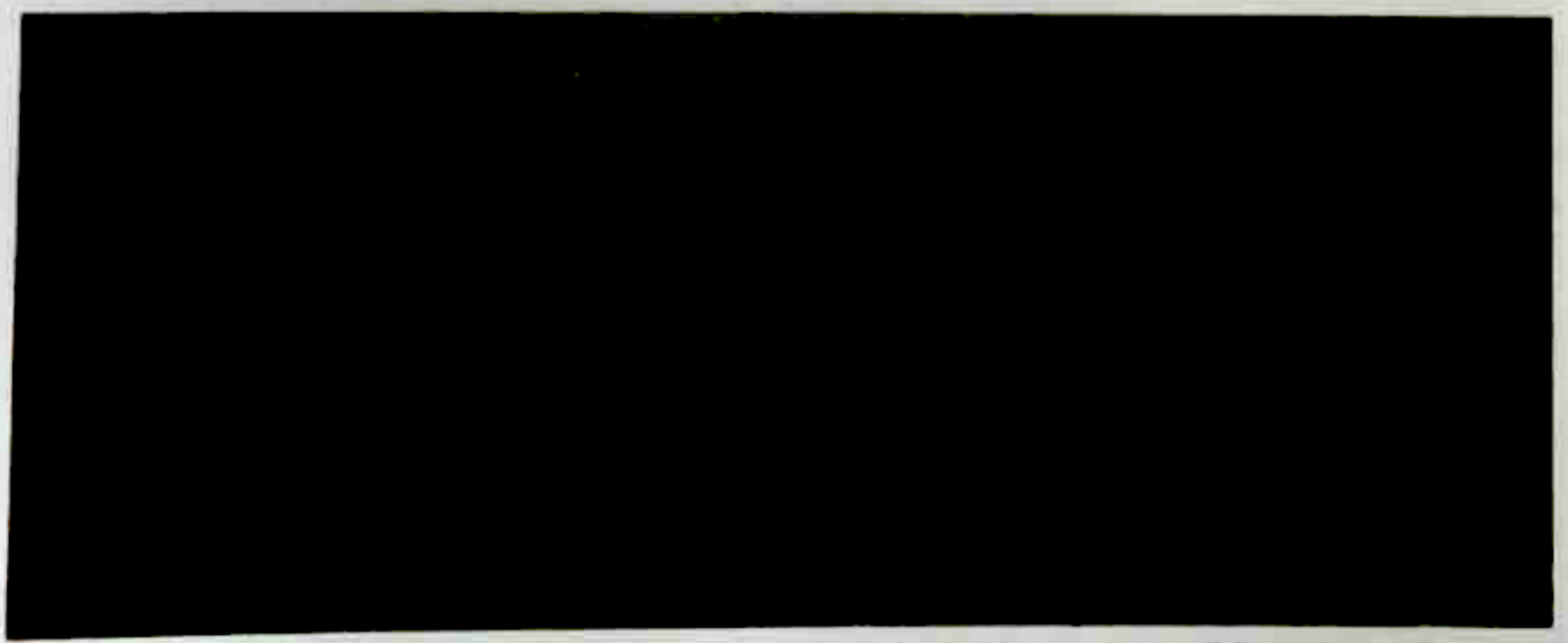

Figure 13. Thyroid scintigraphy 4 weeks postoperatively revealing a thyroid gland with normal to small dimensions and depressed uptake function.

mean. In North America, development of secondary sexual characteristics in girls before 8 years of age is indicative of precocity. Breast and pubic hair development seem to be taking place significantly earlier than current guidelines suggest. The age limit for precocious puberty has been extensively discussed.[1] Definitions included in most textbooks give an age limit of 8 years in girls and 9–9.5 years in boys for the lower limit of normal pubertal development. These age limits were based on earlier longitudinal studies, in particular on the data collected in the London area in the 1960's. However, a prospective evaluation of pubertal development in American boys and girls has led to a different appreciation of the normal variation of age of pubertal onset and to revised criteria proposed by the American Academy of Pediatrics.[2] The proposed age limit used to decide whether girls with pubertal development should be evaluated for precocious puberty is 7 years in girls, although the traditional limit of 8 years is still considered in specific circumstances (rapidly progressive puberty, conditions associated with neurogenic central precocious puberty or poor psychological tolerance to treatment). Both methodological and epidemiological differences between the studies probably explain the apparent discrepancies. The incidence of precocious puberty is approximately 1 in 180 Causasian girls.[3]

The onset of precocious puberty has important physical and psychologic consequences for affected children and induces anxiety in their families. However, not all girls or boys with early signs require treatment. To identify which patients should be referred for therapy, it is necessary to make a rapid, correct diagnosis as well as to form a judgment concerning the progression of the diagnosis as well as to form a judgment concerning the progression of the condition based on a combination of clinical signs, bone age, pelvic echography in girls, and hormonal data as well as follow-up ascertainment as to the state of sexual development. The main aims of therapy of precocious puberty are: 1) to inhibit early pubertal development, 2) to stop and possibly reverse the progression of secondary sex characteristics, 3) to prevent early menarche and early sexual activity, 4) to slow skeletal maturation, 5) to delay epiphyseal closure and consequently to improve final adult height within target range, 6) to treat underlying causes when known, and 7) to improve psychosocial well-being.[4]

Precocious puberty can be categorized as isosexual or heterosexual and as GnRH dependent or GnRH independent (Table 1). In isosexual precocity, there is early development of secondary sexual characteristics that are appropriate for the phenotype (i.e., premature breast budding in a phenotypic female). In heterosexual precocity, the secondary sexual characteristics are discordant with the phenotype (i.e., premature virilization in a phenotypic female). Increased skeletal growth is often the first change in precocious puberty. This is followed by breast development and growth of pubic hair. Early in the course of the disease, affected girls are taller and heavier than their chronologic peers who have not experienced the growth spurt. However, as a result of early epiphyseal fusion from the short growth spurt, eventual short stature results.[5]

Table 1. Classification and relative occurrence of precocious puberty (adapted from Speroff, 2005).

	Female	Male
GnRH-dependent		
Idiopathic	74.0%	41.0%
CNS problem	7.0%	36.0%
GnRH-independent		
Ovarian cyst/tumor	11.0%	—
Testicular	—	10.0%
McCune-Albright syndrome	5.0%	1.0%
Adrenal feminizing	1.0%	0.0%
Adrenal masculinizing	1.0%	22.0%
Ectopic gonadotropin production	0.5%	0.5%

Table 2, in a nutshell, describes differences between GnRH-dependent and GnRH-independent precocious puberty.

The index patient was diagnosed with GnRH-independent precocious puberty based on the following findings: a peripheral estrogen source was positively identified, an unremarkable cranial CT scan result (ruling out a space-occupying lesion in the cranial area), pre-pubertal FSH values, high estradiol levels which dramatically decreased in levels 4 weeks postoperatively, and an LH/FSH ratio < 1.0. Furthermore, the patient's normal statural growth and skeletal maturation at the time of examination support our diagnosis. Most patients with GnRH-dependent precocious puberty have rapid skeletal maturation and a height velocity above the 75th percentile.[6] Secondary sexual characteristics in central precocious puberty tend to occur in a much rapid progression.

The ovarian tumor's characteristic purely sertoli cell component essentially gave rise to the isosexual sexual characteristics found in our index patient.

Table 2. Central vs peripheral precocious puberty (adapted from Hines, 2003).

Characteristics	GnRH-dependent	GnRH-independent
Mechanism of action	Premature activation of HPO axis	Independent of an integrated HPO axis (peripheral estrogen source)
Pubertal development	Secondary sex characteristics, normal menses and ovulation	Secondary sex characteristics, uterine bleeding without ovulation
Estradiol levels	Pubertal	Pubertal to high
FSH levels	Pubertal	Pre-pubertal
LH levels	Pubertal	Pre-pubertal
LH/FSH ratio	>1.0	<1.0
LH response to exogenous GnRH stimulation	Pubertal	Pre-pubertal (no response)
Radiography	Hand-wrist X-ray	Hand-wrist X-ray
	Pelvic ultrasound	Abdominal/Pelvic ultrasound (adrenals/ovaries)
	MRI/CT of the brain	Radionuclide bone scan
Treatment	GnRH agonists	Tumor: surgery McCune Albright: testolactone Hypothyroid: thyroid replacement Iatrogenic: discontinue

GnRH-independent Precocious Puberty

A detailed discussion of gonadotropin-dependent precocious puberty is beyond the scope of this paper.

GnRH-independent precocious puberty is also referred to as incomplete, peripheral, or pseudoprecocious puberty. Premature sexual maturation is independent of the HPO axis and rather from a peripheral estrogen source. There is loss of normal feedback control mechanisms and gonadotropin levels are low with high sex steroid levels. Secondary sexual characteristics develop as a result of the peripheral estrogen source, but the uterine bleeding is irregular, heavy, and nearly always anovulatory. Exposure to sex steroids may lead to central maturation and subsequent secondary gonadotropin-dependent precocious puberty.[4]

Ovarian tumors, affecting 11 percent of all girls with precocious puberty, are the most common cause of GnRH-independent precocious puberty. The most common type is a granulosa cell tumor, accounting for approximately 60 percent of cases. When associated with precocious puberty, these tumors are usually >8 centimeters, and 80 percent can be palpated abdominally. Other less common ovarian tumors associated with precocious puberty include thecomas, luteomas, Sertoli-Leydig tumors, pure Sertoli cell tumors (as in this patient's case), teratomas, benign follicular cysts, and choriocarcinomas. The children demonstrate an absence of gonadotropin pulsations, variable responses to GnRH, and a lack of suppression of puberty by a long-acting GnRH agonist. The cysts may enlarge and involute and then recur so that signs of sexual precocity and vaginal bleeding remit and exacerbate.[4]

Less common causes of GnRH-independent precocious puberty include adrenal neoplasms and hypothyroidism, which each account for about 1 percent of all cases. Adrenal neoplasms can produce either isosexual or heterosexual precocity, but virilizing tumors are more common than feminizing ones. The hypothyroidism associated with precocious puberty is usually due to severe, untreated Hashimoto's thyroiditis. The diminished negative feedback of thyroxine results in an increased production of thyroid-releasing hormone and thyroid-stimulating hormone (TSH). This is associated with an increase in production of gonadotropins and

prolactin. Hypothyroidism can be distinguished from other causes of sexual precocity in that it is the only etiology characterized by growth retardation and delayed skeletal maturation.[2] Plasma levels of TSH are markedly elevated, often greater than 1,000 uU/mL. This massively elevated concentrations of TSH appear to interact with the FSH receptor (specificity spillover), thus inducing FSH-like effects in the absence of LH effects on the gonads. Treatment of hypothyroidism results in a rapid return to normal of the biochemical and clinical manifestations.[3]

For our index patient's case, although TSH levels were slightly higher than normal (both pre and post-operatively), they were not sufficient enough to trigger a cascade of precocious characteristics. It may, instead, be secondary to the increased serum estradiol levels which may have secondarily affected GnRH secretion. Furthermore, a long-standing hypothyroidism would manifest as delayed skeletal maturation and growth, which is not evident in our case. For our index patient, thyroid replacement is deemed unnecessary at this point. Pediatric Endocrinology service recommend repeat/serial thyroid function tests every 3-6 months.

Prolactin concentrations were high, as this hormone and TSH share the same hypothalamic releasing factor, TSH-releasing hormone (TRH). Continuous and high TRH concentrations have been shown to stimulate FSH secretion as well, and this overlap occurs at the level of the pituitary gland.[3]

Although FSH levels, remained within prepubertal levels, as expected for pseudoprecocious puberty cases, LH was elevated (approximately 9-10x above upper limit). Nevertheless, the ratio between LH and FSH was still less than 1.0, which is indicative of a non-central type of precocious puberty, i.e, GnRH-independent.

Moreover, iatrogenic causes of precocious puberty should always be considered. Common sources include oral contraceptives, hormone-containing herbs, and hair or facial creams, all of which were not elicited in this patient.

Pure Sertoli Cell Tumor

Pure Sertoli cell tumors (SCT) are rare ovarian tumors of the sex-cord stromal cell origin as classified by the World Health Organization. They account for about 0.5 percent of all ovarian neoplasms. They are almost always unilateral, occurring in women 30 year old or younger. Fewer than 10 percent of the patients are over 50 years of age. About 30-40 percent of patients show virilization. By definition, pure Sertoli cell tumors lack Leydig cell in the stroma and immature neoplastic stroma. Their origin is unknown, and it is speculated that they arise from ovarian cells that retained the potential to differentiate toward Sertoli cells. Clinical features include isosexual precocity, signs of virilization (in 30% of patients), and menstrual disorders. These tumors are usually unilateral and confined to the ovary, although extra-ovarian spread has been reported. Sertoli cell tumors secrete estrogen, progesterone, testosterone, inhibin, calretenin, vimentin and keratin, all of which can be used as tumor cell markers. Positivity for melan A has also been described as a useful marker. The tumor is typically negative for epithelial membrane antigen, carcinoembryonic antigen, placental alkaline phosphatase and S100. Differential diagnosis of SCT includes mucinous tumors, low grade endometrioid carcinoma, carcinosarcoma when heterologous elements are present, tubular Krukenberg tumor, tubular carcinoid and ovarian tumors of probable Wolffian origin.[4]

Although Sertoli cell tumors usually have a distinctive tubular pattern that facilitates the diagnosis, other patterns may occasionally predominate (e.g., cords or trabeculae, diffuse, pseudopapillary, retiform, islands or alveolar arrangements, and spindled), causing confusion with various other primary and metastatic ovarian tumors. The main neoplasms in the differential diagnosis include endometrioid tumors (including borderline tumor, well-differentiated carcinoma, and the sertoliform variant of endometrioid carcinoma), and carcinoid tumors. Traditional immunohistochemical markers including inhibin, cytokeratin (CK), epithelial membrane antigen (EMA), calretenin, CD99, chromogranin, and synaptophysin are used to make a definitive tissue diagnosis. (Oliva, 2005).

The following table summarizes the immunoreactivity of Sertoli cell tumors:

Immunostain	Immunoreaction
Inhibin	Positive
Calretenin	Positive
EMA	Negative
Melan-A	Negative
Cytokeratin	Negative
CD99	Positive
Chromogranin	Negative
S-100	Positive
Vilmentin	Positive
SMA	Positive
NSE	Positive

Approach to Management of GnRH-independent Precocious Puberty

If a specific etiology for pseudoprecocious puberty is identified, treatment is aimed at curing the underlying disorder. If an ovarian or adrenal tumor is identified, surgical excision is the treatment of choice. In the case of an ovarian tumor, it may be difficult to know whether the tumor is an autonomous source of estrogens or whether its growth is secondary to gonadotropin stimulation. GnRH testing is useful in resolving this question. If multiple bilateral tumors are discovered, these are usually secondary to central gonadotropin secretion. However, if the tumor is solitary and the contralateral ovary appears immature, as in the case of our index patient, then tumor resection is justified.

One of the rules of thumb in the evaluation of precocious puberty in general, is to rule out a central nervous system disorder, most commonly, lesions in the brain. Our index patient presents to us with macrocephaly (presumably from birth). Magnetic resonance imaging (MRI) is now recognised as superior to computerised tomography (CT) in neuroimaging. Use of MRI in children with central precocious puberty has been shown to increase the detection rate of abnormalities in the hypothalamo-pituitary region which might have been missed by previous techniques. However, due to financial constraints, cranial CT scan, instead of the recommended cranial MRI, was done instead.

Ultrasonography permits examination of the intraabdominal and pelvic compartments that is otherwise overlooked in a pediatric patient. It offers an accurate assessment of the pelvic compartment and is less cumbersome than CT scan/MRI and more affordable, especially in under-resourced circumstances.

Prognosis

The prognosis for precocious puberty depends on the underlying cause. Removal of benign ovarian tumors and adrenal tumors carries a good prognosis, while malignant carcinomas often have metastatic disease at the time of presentation, with consequent poor prognosis.

The prognosis of SCT is usually good and correlates with the stage and degree of differentiation of the tumor. Very rarely do SCTs show malignant histological features including high mitotic rate, necrosis, marked cytological and nuclear atypia, and lymphovascular invasion. Adjuvant therapy is considered based on the histological classification and staging of the tumor. Poorly differentiated or metastasic tumors have noted to have a poor prognosis without chemotherapy.

In the current case, SCT was confined to the left ovary, with no malignant cells identified. The tumor showed the typical macroscopic and microscopic features discussed earlier, without any of the features of worse prognosis, thus a benign course would be expected.

As of this paper's writing, the section of Developmental Pediatrics is still working on some other possible syndromes that may explain patient's global developmental delay and other clinical features. It is plausible however, that the patient's developmental delay and congenital macrosomia could indeed be independent of the precocious puberty characteristics, and therefore reassure the parents of a non-neurologic (non-central) cause of the problem at hand. Still, the need for close follow-up and further observation and endocrinologic studies are warranted to keep track of the patient's full recovery, at least towards a more normal sexual development and a better quality of life.

Conclusion

We are presented with the case of a two and a half year old girl with isosexual precocious puberty secondary to a pure Sertoli cell tumor of the left ovary. The patient underwent exploratory laparotomy, left salpingoo-ophorectomy with frozen section revealing sex cord stromal tumor. Paraffin sections stained with Hematoxylin and Eosin revealed a benign sertoli cell tumor. Immunostains of the tumor reacted positively for inhibin, calretenin and cytokeratin, but negative for epithelial membrane antigen. Total serum estradiol, prolactin, TSH and LH were elevated prior to surgical operation, with LH and prolactin decreasing four weeks postoperatively into the normal prepubertal range. Serum FSH was at prepubertal levels. Breasts had regressed to prepubertal size four weeks postoperatively, and the menses never recurred. This is the youngest reported occurrence of this rare sex cord stromal neoplasm in the last 10 years in our institution.

The child with precocious puberty has taught us much about the physiology of adolescence and sexual development. The identified causes of sexual precocity have expanded as our understanding of the mechanisms that regulate sexual development have been identified. This is attributable in large part to the advances in diagnosis afforded by the development of ultrasensitive assays for components of the reproductive endocrine unit. Parallel advances in imaging techniques likewise permit visualization of internal structures heretofore invisible to the most astute clinician. As a primary care physician, the obstetrician gynecologist must be knowledgeable about the numerous causes of precocious puberty and be judicious

in the appropriate evaluation and treatment of this treatable disorder.

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