CASE REPORT

Prepubertal gynecomastia in Peutz-Jeghers syndrome: incomplete penetrance in a familial case and management with an aromatase inhibitor

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Abstract

Background: Peutz-Jeghers syndrome (PJS) is a rare autosomal-dominant disorder characterized by multiple gastrointestinal hamartomatous polyps, mucocutaneous pigmentation and increased predisposition to various neoplasms. Endocrine manifestations in PJS include gynecomastia due to calcified Sertoli cell testicular tumors usually referred to as large-cell calcifying Sertoli cell tumors (LSCT).

Objective: To evaluate the value of endocrine markers and aromatase inhibitor treatment in children with PJS and LSCT.

Design and setting: Familial cases, followed in a tertiary care center.

Patients: Two male siblings aged 7 and 9 years with PJS and LSCT.

Intervention: Third generation aromatase inhibitor (anastrozole) in one of the patients.

Main outcome measures: Longitudinal measurements of sex-steroids, gonadotropins, Sertoli cell markers and auxological evaluation.

Results: The two male siblings with PJS had similar bilateral multifocal testicular calcifications and biochemical evidence of Sertoli cell dysfunction manifested by elevated plasma inhibin- α levels. Only one sibling had gynecomastia. Estradiol levels were normal in both. During treatment with anastrozole, estradiol levels, growth and skeletal maturation, as well as Sertoli cell markers (inhibin B, inhibin- α and anti-Müllerian hormone) decreased.

Conclusions: Inhibin- α may be considered as a marker for LSCT in children with PJS, pointing to a specific defect in inhibin regulation in this condition. Moreover, the decrease in Sertoli cell markers during aromatase inhibitor treatment suggests that increased estrogen production is a primary event regulating downstream production of Sertoli cell peptides. Anastrozole is efficient in controlling the clinical features of the disease and should be proposed as an alternative to bilateral orchidectomy, which is often performed in this condition.

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Introduction

The Peutz-Jeghers syndrome (PJS) is a rare autosomal-dominant disorder classically characterized by the association of multiple gastrointestinal hamartomatous polyps, mucocutaneous pigmentation and increased predisposition to various neoplasms (1, 2). Inactivating germline mutations of the LKB1/STK11 gene, which encodes a serine/threonine kinase have been found in patients with PJS (3). Endocrine manifestations of PJS include gynecomastia due to estrogen production by calcified Sertoli cell testicular

tumors, often bilateral and multifocal, usually referred to as large-cell calcifying Sertoli cell tumors (LSCT) (4, 5).

We report two male siblings with PJS and bilateral multifocal testicular calcifications. Although biochemical evidence of Sertoli cell dysfunction was similar in both patients, clinical expression was different and only one of them had gynecomastia. He was treated with an aromatase inhibitor to reduce skeletal maturation. Their father also had PJS, but no gynecomastia or testicular calcification, further emphasizing the phenotypic variability of the disease.

Patients and methods

Laboratory assays

Radioimmunoassays were used to measure serum concentrations of testosterone (CisBio International, Gif-sur-Yvette, France), dehydroepiandrosterone sulfate (CisBio International), and estradiol (DiaSorin, Antony, France). The detection limit for plasma estradiol was 2 pg/ml. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by time-resolved immunofluorometric assay (Delfia, Wallac, Turku, Finland). Inhibin B was measured by a solid phase sandwich assay (Serotec, Oxford, Oxon, UK). Anti-Müllerian hormone (AMH) was measured with a solid phase sandwich assay (DSL-France, Cergy-Pontoise, France). Details of the assays used and their precision profiles have been described previously (6, 7). Immunoreactive inhibin- α was measured by RIA using antiserum 1989 raised against purified 31 kDa bovine inhibin, kindly donated by D M de Kretzer (Monash University, Clayton, Australia) (8). Purified bovine 31 kDa inhibin iodinated by the lactoperoxidase method was used as a tracer. Diluted human follicular fluid was used as a standard. Its bioactivity was 280 U/ml as assessed by *in vitro* bioassay with dispersed

rat pituitary cells. The sensitivity was 28 U/l. Longitudinal assessment of hormonal values was performed in a single assay using stored frozen samples.

DNA sequencing

Exons 1 to 9 of LKB1/STK11 were directly sequenced after PCR amplification using an Applied Biosystems (Foster City, CA, USA) model 377 sequencer (9).

The subjects and their family gave informed consent for the study and were informed of the investigative nature of the treatment that was used in patient IV₅.

Case reports

Patient IV₅, a 7-year-old male member of a family with PJS presented with progressive gynecomastia that had developed over the course of 2 years. Physical examination revealed a healthy boy with pigmented lesions of the lips and bilateral gynecomastia, 5 cm in diameter, corresponding to a female Tanner B3 stage (Fig. 1). His testicular volume was 4 ml bilaterally. The penis was infantile and there was no pubic or axillary hair. Height was 134 cm (+3 standard deviation score

Figure 1 Gynecomastia (A) and testicular calcifications on ultrasound (B) in patient IV₅ at initial evaluation at the age of 7 years. A normal testis from an age-matched individual is shown for comparison (N).

(SDS)), with a growth velocity of 9 cm/year (+4 SDS for age) and normal weight for height (Fig. 2). Target height was 179 cm (+1 SDS). Bone age was 10 years (10). There was no familial history of gynecomastia, in particular among family members with PJS (Fig. 3). An abdominal computed tomography scan to exclude

an estrogen producing adrenal tumor, showed normal sized adrenal glands. Testicular ultrasound examination revealed bilateral multifocal calcifications of 0.5 to 1 mm and a testicular size of 2.5 cm × 1.5 cm bilaterally (Fig. 1). Given the context and the testicular aspect on ultrasound examination, a likely diagnosis of LSCT was made.

Patient IV₄, the older brother of patient IV₅, was systematically evaluated at 9 years of age. Physical examination revealed melanin spots on the lips and no gynecomastia. Testicular volume was 4 ml bilaterally, with a normal sized penis, and P2 pubic hair development. Height was 143 cm (+2.5 SDS), growth velocity was 6 cm/year (+1 SDS for age) and bone age was 10 years. Similar to his brother, bilateral calcifications (0.8 to 1 mm) were observed on testicular ultrasound. Testicular size was 2 × 1.5 cm bilaterally.

Patient III₄, the father of patients IV₅ and IV₄, was a 54-year-old man with PJS, with intestinal polyps and characteristic mucosal lesions. His height was 182 cm. He had no history of, or current gynecomastia. Testicular size was 5 × 3 cm bilaterally, with no calcifications on ultrasound.

Results

Direct sequencing of the LKB1 gene showed a mutation at codon 279 in exon 6, leading to a translational frameshift in all 3 affected family members analyzed. Endocrine investigations in patients IV₅ and IV₄ (Table 1) showed normal prepubertal serum concentrations of testosterone, estradiol, AMH, inhibin B,

Figure 2 Auxology and hormonal evolution in patient IV₅ during treatment with anastrozole. (A) Growth velocity (GV) and difference between bone age and chronological age (BA-CA). (B) Estradiol (E2), testosterone (T) and luteinizing hormone (LH) levels. (C) Inhibin B and follicle-stimulating hormone (FSH) levels. (D) Inhibin-α and anti-Müllerian hormone (AMH) levels. Shaded areas correspond to anastrozole treatment.

Figure 3 Pedigree of the family with Peutz-Jeghers syndrome and LKB1/STK11 mutation. Shaded symbols correspond to affected family members; the genotype (mutation at codon 279, 6th exon, leading to a translational frameshift) was determined in patients III₄, IV₃, IV₄, IV₅; the proband with gynecomastia is indicated by an arrow.

Table 1 Endocrine evaluation in male relatives with Peutz-Jeghers syndrome.

	Patient IV ₅ (age 7.3 yr)	Patient IV ₄ (age 9 yr)	Normal age-matched range of values	Patient III ₄ (age 54 yr)	Normal age-matched range of values
Testosterone (ng/ml) ^a	0.02	0.11	0.05–0.3	5.2	3–10
Estradiol (pg/ml) ^b	9.3	6.3	<2–17	23.7	10–40
DHAS (ng/ml) ^c	238	399	20–260	—	—
Δ4 (ng/ml) ^d	0.24	0.59	0.05–0.3	—	—
FSH (UI/l)	0.12	1	0.3–2.5	2.4	1–6
LH (UI/l)	0.03	0.5	0.3–1.6	1.8	0.8–6
AMH (pmol/l)	570	470	96–965	47	11–84
Inhibin B (pg/ml)	130	110	10–220	178	135–150
Inhibin-α (UI/l)	215	349	10–150	219	330–710

^{a–d}To convert to SI units multiply by 3.46^a, 3.67^b, 2.71^c, 3.49^d.

DHAS, dehydroepiandrosterone sulfate; Δ4, Delta4-androstenedione.

FSH and LH. In contrast, plasma inhibin-α concentrations were markedly increased. The father (patient III₄) had normal hormonal results.

In order to reduce gynecomastia and delay skeletal maturation, patient IV₅ was treated with an aromatase inhibitor, anastrozole (Arimidex, Astra-Zeneca), 1 mg orally, once daily, from the age of 7.3 years. Clinical and biological parameters were followed (Fig. 2). During this first treatment period, growth velocity decreased from 9 cm to 6 cm/year and gynecomastia from 5 cm to 3 cm in diameter. Serum estradiol, inhibin B and inhibin-α declined and gonadotropins did not change. At 4 months on treatment, anastrozole was stopped because of asthenia and severe hot flushes. During the off-treatment period, estradiol and inhibin B concentrations increased and gynecomastia worsened leading to bilateral mastectomy. Eighteen months after anastrozole discontinuation, at age 8.7 years, bone age was 14 years and had therefore advanced by 4 years in 18 months with an adult height prognosis of 165 cm. Anastrozole treatment was resumed and well tolerated. It is still currently used at age 13.7 years with a current height prognosis of 183 cm. Testicular volume increased from the age of 12 years reaching 10 ml at last examination at the age of 13.7 years. Testicular ultrasound was undertaken yearly and showed no change in the size, number or characteristics of the calcifications.

Estradiol levels decreased when treatment was instituted and remained low on treatment. LH did not increase until the age of 11 years while FSH increased progressively from 10 years. Both inhibin B and inhibin-α decreased on treatment and increased at the time of puberty. AMH decreased on treatment and decreased later in puberty, when testosterone levels reached mid-pubertal ranges.

Discussion

Testicular tumors are extremely rare in prepubertal males and only 5% of these tumors are of Sertoli

cell origin (11). PJS is characterized by an increased risk of gonadal sex cord tumors among other malignancies. Twenty-two patients with PJS and testicular tumors have previously been described (Table 2). Gynecomastia was the presenting symptom in most cases and calcifications varied from minimal to massive. All tumors appeared to be of Sertoli cell origin after biopsy or orchidectomy. Increased estrogen production and aromatase expression in Sertoli cells has been demonstrated in PJS LSCT (12–14). In view of the clinical manifestations of increased estrogen action in patient IV₅, one might question why serum estradiol concentrations remained in the normal prepubertal range. This suggests that small amounts of estrogen may be sufficient to induce breast enlargement and promote skeletal maturation. Alternatively, increased bioavailability, local tissular biosynthesis or tissue responsiveness might be involved (15). In this context, it is noteworthy that patient IV₄ had similar findings by testicular ultrasonography, only slightly lower estradiol levels but absent gynecomastia and normal skeletal maturation. The frequency of asymptomatic LSCT in PJS remains to be established through prospective familial screening since all but one of the patients with PJS and LSCT reported to date presented with gynecomastia.

The Sertoli cell origin of LSCT prompted us to measure plasma inhibins and AMH. Inhibin B is usually the main form of inhibin found in the male circulation and is involved in the regulation of FSH secretion. It is a dimer of disulfide-linked α and β-B subunits, primarily secreted by Sertoli cells (16). The α subunit is predominantly expressed in Sertoli cells but also in Leydig cells (17). In our two patients, inhibin B levels were at the upper normal range of prepubertal boy values, while inhibin-α levels were markedly elevated. Few studies have examined inhibin subunits in human testicular tumors, but they appear to be a marker of Sertoli cell tumors (18). Mechanisms for the discordance between α and β-B subunit levels are poorly known and our observation suggests that such dissociation can occur in tumoral Sertoli cells in

Table 2 Summary of the published literature on LSCT in boys with PJS.

Reference	Age at diagnosis (yr)	Gynecomastia (Y/N)	Plasma estradiol (pg/ml) ^a	Testicular calcifications on ultrasound	Testicular management	Management of gynecomastia
23	1.6	Y	27	Bilateral	Bilateral orchidectomy	NA
5	3	Y	47	Unilateral	Unilateral orchidectomy	NA
24	3	Y	30	Bilateral	NA	Mastectomy
13	3.5	Y	98	Bilateral	Bilateral orchidectomy	Mastectomy
14	3.5	Y	97	NA	Bilateral orchidectomy	NA
25	4	Y	NA	Bilateral	Follow-up	NA
12	4.5	Y	39	Bilateral	NA	Testolactone, mastectomy
13	5.5	Y	45	Bilateral	Bilateral orchidectomy	Mastectomy
26	5.5	Y	23	Bilateral	Loss of follow-up	NA
27	6	Y	High	Absent	Unilateral orchidectomy	NA
28	6	Y	27	Absent	Bilateral orchidectomy	NA
14	7	Y	25	NA	Bilateral orchidectomy	Mastectomy
29	7	Y	<2	Bilateral	NA	Bilateral mastectomy
20	7.5	Y	<2	Bilateral	NA	Testolactone
14	8	Y	5	NA	NA	Mastectomy
30	8	Y	NA	Bilateral	Bilateral orchidectomy	NA
31	8	Y	NA	Bilateral	Follow-up	NA
31	8.5	Y	—	Bilateral	Follow-up	NA
32	11	N	NA	Bilateral	Bilateral orchidectomy	NA
31	11	Y	NA	Bilateral	Follow-up	NA
33	13	Y	Normal	Bilateral	Bilateral orchidectomy	NA
31	14	Y	NA	Bilateral	Follow-up	NA

^aNormal prepubertal values: 5–17 pg/ml. To convert to SI units multiply by 3.67. NA, information not available.

LSCT. We propose that serum inhibin- α subunit is a marker of Sertoli cell testicular tumors (and in particular LSCT) in prepubertal boys.

The management of LSCT and the evaluation of its malignant potential is an important part of the discussion. In at least 9 of 22 reported patients (Table 2) a bilateral orchidectomy was performed (14). We decided on a conservative medical treatment on account of the low risk of malignant transformation of sex cord tumors (2), taking the option of a careful follow-up, allowing sperm preservation if an orchidectomy was decided upon after sexual maturation. Therefore, medical treatment was warranted to reduce the effects of increased estrogens on the breast and skeleton. Aromatase inhibitors are currently the best option to achieve this goal (19) and testolactone has been used previously (12, 20). We used anastrozole, an effective third generation inhibitor of estrogen synthesis. Interestingly, initiation of the treatment was associated with 'menopausal-like symptoms', as observed with gonadotropin-releasing hormone agonists. Symptoms might have been amplified by the psychological distress of the family with several severely affected members. Overall, anastrozole was clinically efficient and decreased breast development and growth velocity and delayed bone maturation. Serum estradiol concentrations decreased, but LH and testosterone did not increase, as opposed to the observations made with aromatase inhibitors in early pubertal boys (21). The decrease in inhibin B, inhibin- α and AMH levels on treatment was unexpected since these markers are believed to reflect Sertoli cell activation by the mutated STK11 serine/threonine kinase. Our observation suggests that increased estrogen production might be a primary event, regulating downstream production of Sertoli cell peptides. A further argument for the role of estrogen signaling in Sertoli cell tumorigenesis comes from observations made in male mice with inhibin- α knockout mice who develop Sertoli cell tumors that are prevented by estrogen receptor α and β knockouts (22).

In conclusion, LSCT, revealed by testicular calcifications, can occur in prepubertal boys with PJS in the absence of gynecomastia. Inhibin- α seems to be an interesting marker for these tumors. Anastrozole is efficient in controlling the clinical manifestations of LSCT and should be proposed as an alternative to orchidectomy, which is often performed in this condition.

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