CASE REPORT

Recurrent ovarian Sertoli–Leydig cell tumor in a child with Peutz–Jeghers syndrome

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Abstract

We present a female child with Peutz–Jeghers syndrome (PJS) with a recurrent ovarian Sertoli–Leydig cell tumor (SLCT). SLCTs are relatively rare sex cord neoplasms that can occur in PJS. The patient was an African-American female who first presented at the age of 3 years with precocious puberty, and then at the age of 17 years with abdominal pain and irregular menses. In each case, she had resection of the mass, which included oophorectomy. To our knowledge, this is the first reported case in a child with PJS to have a recurrent ovarian SLCT.

INTRODUCTION

Peutz–Jeghers syndrome (PJS) is an autosomal dominant condition characterized primarily by mucocutaneous pigmentation and intestinal polyposis [1]. Sertoli–Leydig cell tumors (SLCTs) are sex cord neoplasms that can occur in patients with PJS. However, SLCTs are rare, making up to 1% of all ovarian tumors [2]. Recurrent ovarian SLCT in a pediatric-aged patient has yet to be documented.

CASE REPORT

A 3-year-old African-American female with a strong paternal history of PJS and associated polyposis presented with gonadotropin-independent isosexual precocious puberty and vaginal bleeding. Her laboratory studies revealed undetectable serum luteinizing hormone (LH) and follicle stimulating hormone (FSH), elevated testosterone 78 ng/dl (0–9.9) and estradiol 210 pg/ml (0–55)—consistent with peripheral etiology of her pubertal signs. Oncologic workup included CA-125 54 U/ml (0–35), often elevated in ovarian neoplasm, but with negative alpha-fetoprotein and beta-human chorionic gonadotropin (β-HCG) tumor markers. Abdominal computed tomography demonstrated a large pelvic mass involving the right ovary and a prominent thick-walled uterus. She underwent mass resection with right salpingo-oophorectomy. Pathology results demonstrated an SLCT limited to the ovary with confirmatory positive cytokeratin, vimentin and inhibin staining. Uterine bleeding ceased 6 days after the surgery, with decrease in breast size and pubic hair over the following months. Her bone age was 8 years at the chronological age of 4 years at follow-up. She underwent menarche at the age of 11.5 years with a bone age concordant with her chronological age at that time.

Although she had been followed until the age of 13 years without tumor recurrence, she was lost to follow-up until the age of 17 years when she presented with 1-year history of intermittent stabbing abdominal pain, daytime fatigue and irregular menses. She had no clinical signs of hyperandrogenemia and no palpable mass on abdominal examination. Laboratory studies revealed appropriately post-pubertal serum FSH 1.9 IU/l (3.4–10),

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testosterone 53 ng/dl (11–62) and estradiol 201 pg/ml (2–259). However, she demonstrated an unusually elevated serum LH 48 IU/l (2.1–10.9), concerning for impending ovarian failure, which prompted further workup.

Abdominal magnetic resonance imaging (MRI) demonstrated a left adnexal complex cystic mass extending to the midline (Fig. 1). An extremely high inhibin B level suggested a likely recurrence of SLCT. It also explained why in the presence of ovarian failure, FSH was decreased, as inhibin provides negative feedback on FSH secretion. She underwent mass excision with left salpingo-oophorectomy and cervical biopsy. Pathology results again demonstrated an SLCT limited to the ovary (Fig. 2). Immunohistochemical stains were positive for vimentin, inhibin (Fig. 3), as well as WT1, calretinin, CAM 5.2 and estrogen receptors. Additionally, 30% of the lesion demonstrated heterologous annular features, known as sex cord tumor with annular tubules (SCTATs) (Fig. 4). Lab results are summarized in Table 1.

Six months after her surgery, she developed hot flashes, at which point she was started on low-dose estrogen replacement. She continues to be followed by gynecology and gastrointestinal (GI) services for cancer surveillance. The recurrent mass was very likely a new primary lesion due to its differences in histological, biochemical and clinical properties when compared with the original neoplasm.

DISCUSSION

PJS is an autosomal dominant condition that has a clinical diagnosis that includes two or more histologically confirmed PJS...
Table 1: Summary of laboratory workup.

|                     | 2002 (3 years) | 2014 (17 years) | 2015 (6 months post-resection) |
|---------------------|----------------|-----------------|-------------------------------|
| LH (IU/l)           | <0.2           | 48 (2.1–10.9)   | 33                            |
| FSH (IU/l)          | <0.2           | 1.9 (3.4–10)    | 65                            |
| Testosterone (ng/dl)| 78 (0–9.9)     | 53 (11–62)      | 14                            |
| Estradiol (pg/ml)   | 210 (0–55)     | 201 (2–259)     | 3.0                           |
| CA-125 (U/ml)       | 54 (0–35)      | 18 (0–35)       | –                             |
| Inhibin B (pg/ml)   | –              | >5000 (0–360)   | <10                           |
| AFP                 | Negative       | Negative        | –                             |
| β-HCG               | Negative       | Negative        | –                             |

At the age of 3 years, the patient’s estradiol and testosterone were elevated with undetectable gonadotropins, consistent with peripheral precocious puberty. At the age of 17 years, there was an elevated LII likely due to ovarian failure secondary to tumor infiltration. Elevated inhibin from the Sertoli cell tumor component explains the FSH suppression. At 6 months post-resection, the biochemical profile is consistent with a bilateral oophorectomy.

polyps, any number of PJS, mucocutaneous pigmentation in someone with a family history of PJS, or any number of PJS polyps in an individual who also has characteristic mucocutaneous pigmentation [5]. Additionally, it is associated with other malignancies of the GI tract, pancreas, lung, breasts and cervix [3]. In fact, the cumulative risk of a patient diagnosed with PJS developing a malignancy between the ages of 15 and 64 years is 93% [3]. The genetic etiology in more than 90% of those meeting the clinical criteria is a germline mutation in STK11, a serine–threonine kinase gene within a region on chromosome 19p13.3, whose product functions as a tumor suppressor [4].

Sertoli–Leydig cell tumors are a type of sex cord stromal tumors (SCSTs), which make up to <7% of ovarian tumors but with a cumulatively increased risk of up to 20% in PJS [2, 5]. SCSTs may present with symptoms similar to those of other ovarian tumors such as abdominal pain and distention, isosexual precocity, primary or secondary amenorrhea and/or virilization [2]. Histopathologic diagnosis is based on characteristic stains, which include inhibin, cytokeratin and vimentin [2].

The patient’s recurrent mass included heterologous elements, known as SCTATs. This type of neoplasm, first described in patients with PJS, is a rare subtype of SLCT [6]. SCTAT is considered a variant of either pure Sertoli or Granulosa cell tumor and observed in ~20% of SLCTs [7]. Microscopically, the neoplasm differs in its ring arrangement of tubules and frequent presence of calcification. When occurring in patients with PJS, SCTAT is typically bilateral, multifocal, 3 cm and benign [8]. It has also been known to secrete estrogen and/or progesterone, which can present clinically as precocious puberty and menstrual irregularities [8]. However, in our patient, estrogen was not elevated. It is possible that either the small focus of the SCTAT or the interaction of the surrounding SLCT prevented sufficient differentiation for secretion of sex steroid hormones. It remains unclear the prognostic implication of a neoplasm with both SLCT and SCTAT features. Owing to the neoplasm’s focality in both instances, surgical resection with oophorectomy and ipsilateral pelvic lymphadenectomy were performed. Metastatic SCTAT, however, can be treated via resection with adjuvant radiation therapy [9].

This case demonstrates two vastly different presentations of the same neoplasm due to its presence at different time points in the child’s age and development. Guidelines recommend cancer surveillance to begin at the age of 8 years [1]. However, this case emphasizes the importance of screening at any age when there is suspicion of malignancy in a patient with PJS or family history of PJS. Furthermore, due to the high risk of malignancy recurrence in patients with PJS, regular cancer surveillance is critical to minimize morbidity and mortality. A patient who is lost to follow-up presents a dangerous risk for cancer progression; thus, extra care must be taken to maintain continuity of care.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

Not applicable.

CONSENT

Written consent was obtained from the patient.

GUARANTOR

E.J.B. is the guarantor of this article.

REFERENCES

1. Beggs AD, Latchford AR, Vasen HFA, Moslein JG, Alonso A, Aretz S, et al. Peutz-Jeghers syndrome: a systematic review and recommendations for management. Gut 2010;59:975–86.
2. Schultz KAP, Schneider DT, Pashankar F, Ross J, Frazier L. Management of ovarian and testicular sex cord-stromal tumors in children and adolescents. J Pediatr Hematol Oncol 2012;34:555–63.
3. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447–53.
4. Aretz S, Stienen D, Uhlhaas S, Loff S, Back W, Pagenstecher C, et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. Hum Mutat 2005;26:513–9.
5. van Lier MG, Wagner A, Mathus-Vliegen EM, Kuipers EJ, Steyerberg EW, van Leerdam ME. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenrol 2010;105:1258–64.
6. Momim YA, Kulkarni MP, Pandav AB, Sulhyan KR. Non Peutz-Jeghers syndrome associated malignant sex cord stromal tumor with annular tubules. Int J Appl Basic Med Res 2013;3:126–8.
7. Tandon R, Goel P, Saha P. A rare ovarian tumor – Sertoli-Leydig cell tumor with heterologous element. MedGenMed 2007;9:44–51.

8. Young RH, Welch WR, Dickersin GR, Scully RE. Ovarian sex cord tumor with annular tubules: review of 74 cases including 27 with Peutz-Jeghers syndrome and four with adenoma malignum of the cervix. Cancer 1982;50:1384–402.

9. Shen K, Wu PC, Lang JH, Huang RL, Tang MT, Lian LJ. Ovarian sex cord tumor with annular tubules: a report of six cases. Gynecol Oncol 1993;48:180–4.