

Peutz-Jegher Syndrome in Gynecologic Pathology

Ozlen Saglam*

Assistant Professor, Department of Pathology, Yale University, USA

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder characterized by melanotic macules, intestinal polyps, and an increased cancer risk [1]. There are diverse pathologic manifestations of the syndrome in females. These can present from early infancy to late adulthood either concomitantly or subsequently. There is no consensus or guidelines for cancer surveillance in PJS patients. There are occasions when the pathologist's awareness and interpretation of the microscopic findings can contribute to the overall clinical managements of these cases.

PJS is caused by mutations in the serine/threonine kinase 11 gene (LKB1, STK11) in a majority of cases [2]. Up to 25-30% of PJS patients carry a mutation in an unidentified gene that confers high susceptibility to cancer development. These patients probably have large rearrangements of LKB1, including deletions, duplications, and inversions of areas larger than an exon [3].

In addition to gynecologic neoplasms, PJS patients have an increased risk for cancers of the colon, stomach, small intestine, pancreas, breast, and other organs [4,5,6]. The cumulative cancer risk for a PJS patient was 85% by age 70 (control population risk 18%). Thirteen percent to 15% of PJS patients will develop with two cancers [7].

According to Surveillance, Epidemiology, and End Results data for comparison, the relative risk for cancer is 18 in women with the PJS and 6.2 in men with the syndrome [8]. The risk of developing cancer among women with PJS is more than three times higher than that of men with PJS. This higher risk is attributed to the added relative risk of breast and gynecologic cancers, which is around 20.3.

The two well-known gynecologic lesions related to PJS are cervical minimal deviation adenocarcinomas (MDA), also called adenoma malignum (ADM), and a rare lesion of the ovary known as sex cord tumor with annular tubules (SCTATs).

Histologically, the cervical adenocarcinomas closely resemble normal endocervical glands and for this reason it is referred to as minimal deviation adenocarcinoma. There are enlarged, irregular glands lined by mucin-containing columnar epithelial cells with basal nuclei. The glands are typically large and have markedly abnormal branching shapes. They deeply invade the cervical stroma and incite a stromal reaction. The morphologic features of MDA are same whether or not associated with PJS [9].

The prognosis of MDA is controversial in the literature. In some series, despite the radical treatment in most cases, the prognosis was poor compared to the patients with other histologic types of cervical adenocarcinoma [10]. In two other small series, (13 and 6 cases), the prognosis was found similar to the other types of cervical adenocarcinomas [11,12]. Srivatsa et al. [13] reported poorer prognosis of MDAs when they are related to PJS.

The recurrences are usually intrapelvic or intraabdominal even though MDA can spread to pelvic lymph nodes. The cases with at least one ovary persevered during the time of initial surgery had subsequent recurrent mucinous tumor of the ovaries in four of ten cases in one series [9]. This indicates a risk of subsequent carcinomas associated with ovarian conservation in these cases. Ovarian conservation is associated with a relatively worse prognosis compared those cases

without ovarian preservation. In another case study, a simultaneous occurrence of MDA, SCTAT and mucinous metaplasia of fallopian tube was reported [14]. The mucinous lesions of fallopian tubes are rare and they may be associated with PJS [15].

Multiple independent mucinous neoplasms of the female genital tract are extremely rare [16]. The simultaneous involvement of multiple loci within the female genital tract such as uterine cervix, ovaries and the fallopian tubes by mucinous lesions may represent a direct spread from a solitary primary rather than independent lesions. This possibility was discussed in the previous studies [9,15]. Considering the fact that pseudomyxoma peritonei is a locally aggressive lesion despite a morphologically bland appearances, this possibility deserves some further investigation. In current practice, it would be prudent to rule out PJS syndrome in these cases.

Most female PJS patients of reproductive age have ovarian cysts. It is unclear how many of these represent physiological cysts versus stable SCTATs. Hearle et al. [7] estimated 10% of female PJS patients will develop SCTATs that require surgery and about one third of patients with SCTATs have PJS.

Histologically, SCTATs are either simple or complex tubules lined by cells with peripherally placed nuclei that surround a hyaline-filled lumen. PJS-associated SCTATs are bilateral, multifocal, often microscopic, and contain focal calcifications. Sporadic SCTATs are large and unilateral [17,18].

PJS-associated SCTATs have a low malignant potential and a good prognosis.

In a review of 74 cases of SCTAT, including 27 patients with concurrent PJS, none of the 27 patients with both PJS and SCTAT exhibited tumor recurrence or metastasis in reported follow-up intervals ranging from 6 months to 11 years [18]. Only a few cases of malignant SCTATs have been reported in PJS patients [19, 20].

The malignant potential of the tumor cannot be reliably predicted by the microscopic examination only. A high mitotic activity (7-10 per 10 high power field) and tumor emboli in lymphovascular spaces were identified in these rare cases [21]. There is a further reported case of a poorly differentiated Sertoli-Leydig cell tumor associated with an ovarian SCTAT in a woman with PJS [22].

MDA and SCTATs sometimes occur in association with one another [13]. Therefore, patients presenting with either SCTATs or MDA should be carefully followed for development of the other. There

*Corresponding author: Ozlen Saglam, Assistant Professor, Department of Pathology, Yale University, USA, Tel: 203-735-6010; Fax: 203-737-2922, E-mail: ozlen.saglam@yale.edu

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are other rare forms of ovarian tumors also associated with PJS. These include lipid-rich and oophilic variants of Sertoli cell tumor [23,24].

PJS patients with SCTATs usually present with an asymptomatic adnexal cyst or mass identified by cancer surveillance testing. SCTATs sometimes produce estrogen, causing precocious puberty. Most PJS patients with SCTATs are young. In this age group, precocious puberty secondary to a functioning sertoli or sertoli-leydig cell tumor is the presenting symptom [25,26].

For all children or women of reproductive age who desire fertility, every attempt at surgical conservation should be made to preserve ovarian tissue. This requires a management team including a gynecologic oncologist, reproductive endocrinologist, and pediatric surgeon, enabling clinicians to design a treatment plan that will not only appropriately treat the medical situation but also provide the patient with the greatest opportunity for the preservation of ovarian function and fertility [27].

Establishing a surveillance program is difficult for malignancies occurring in patients with PJS. Metaanalysis has showed around 20% lifetime risk of ovarian cancer in patients with PJS with most occurring during the fourth and fifth decades of life. Ovarian screening with transvaginal ultrasound and serum CA-125 level is recommended beginning at the age 25 years [28,29].

The rare case presentations in early infancy illustrate the importance of considering early screening, along with close clinical review and patient/parent education, for detection of life threatening neoplasms and complications [25,26].

Establishing the diagnosis of MDA can also be difficult in patients with PJS. The approximate lifetime risk for cervical carcinoma is around 10% among women with PJS (29). They may present with a watery vaginal discharge or vaginal bleeding. On pelvic examination, the cervix has alternatively been described as being normal or having a firm or nodular appearance. Imaging studies show multiple cervical cysts [30]. Surveillance for ADM should include annual gynecological examination with Papanicolaou smear and pelvic ultrasound.

PJS patients have an increased risk of cancer in multiple organ systems. In gynecologic pathology, the spectrum of manifestations varies in different age groups and they can present as single or multiple lesions. These lesions will remain challenging given their rarity and unusual morphology.

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