Gynecological tumors in patients with Peutz-Jeghers syndrome (PJS)

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ABSTRACT

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by the development of hamartomatous polyposis in the gastrointestinal tract and melanin-pigmented macules on the skin mucosa. The responsible gene is a tumor suppressor, *STK*11/*LKB*1, on chromosome 19p13.3. PJS complicates with benign and malignant tumors in various organs. In gynecology, there has been a particular focus on complications of PJS with sex cord tumor with annular tubules (SCTAT) and minimal deviation adenocarcinoma (MDA), which are rare diseases. Approximately 36% of patients with SCTAT are complicated with PJS and these patients are characterized by multifocal, bilateral, small and benign lesions that develop into tumors with mucinous to serous ratios of 8:1. In addition, 10% of cases of MDA are complicated with PJS and mutation of *STK*11, the gene responsible for PJS, has a major effect on onset and prognosis. The disease concept of lobular endocervical glandular hyperplasia (LEGH) has recently been proposed and LEGH is thought to be a potential premalignant lesion of MDA, however, the relationship between PJS and LEGH remains unclear. Several case reports of PJS patients complicated with gynecological tumors have been published and further studies are needed to determine the underlying causes.

Keywords: Gynecologic Tumor; Minimal Deviation Adenocarcinoma; Peutz-Jeghers Syndrome; Sex Cord Tumor; *STK*11/*LKB*1

1. INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by the development of hamartomatous polyposis in the gastrointestinal tract from the stomach to the large intestine and melanin-pigmented macules on the skin mucosa, including the oral mucosa, lips, nasal wings and interdigits. Clinical manifestations of PJS include increased numbers of or enlarged polyps in the gastrointestinal tract and abdominal symptoms such as abdominal pain, bowel obstruction and gastrointestinal bleeding. PJS is the second most common hereditary gastrointestinal polyposis, after familial adenomatous polyposis, and has an incidence of 1 in 60,000 to 300,000 births. The responsible gene has been shown to be a tumor suppressor gene, *STK*11/*LKB*1, on chromosome 19p13.3. *STK*11 is thought to be involved in cellular energy metabolism, cell proliferation, cell polarity, p53-dependent apoptosis, vascular endothelial growth factor (VEGF) regulation, and Wnt signaling. The pathogenic mechanism of PJS is assumed to involve loss of heterozygosity (LOH), a loss of one allele of a gene in which the other allele is already mutated, in the *STK*11 gene of germline cells, leading to the appearance of gastrointestinal polyposis and malignant transformation in other organs. PJS also complicates with benign and malignant tumors in various organs. In gynecology, considerable attention has been paid to complications of PJS with sex cord tumor with annular tubules (SCTAT) and minimal deviation adenocarcinoma (MDA). In this article, we review recent findings for PJS and these associated gynecological tumors.

2. CLINICAL MANIFESTATION OF PEUTZ-JEGHERS SYNDROME

PJS was first described by Hutchinson in 1896 and further detailed descriptions were given by Peutz in 1921 and Jeghers *et al.* in 1949 [1,2].

In pathology, polyps of PJS are non-neoplastic and hamartomatous. Histology shows a structure similar to the normal mucosa, although a PJS lesion shows irregular hyperplasia of the crypt epithelium. However, polyps in PJS have different forms from common hyperplastic polyps, with epithelial/mucosal hyperplasia expanding

ducts outward and leading to duct opening, and muscle fibers overgrowing dendritically along epithelia. These changes suggest that epithelial hyperplasia occurs first and that adjacent muscularis mucosae are then inflected and fused, resulting in the characteristic form. Small lesions often remain as hyperplastic changes.

PJS complicates with benign and malignant tumors and approximately half of patients have a malignant tumor by the age of 57 years old. The incidence of malignant gastrointestinal tumors is highest in the large intestine, followed by the stomach, small intestine, duodenum and pancreas, and the incidence of malignant tumors in other organs is highest in the uterine cervix, followed by the ovary and lung [3] (**Table 1**). In the gynecological field, the relationship of PJS with cervical tumors such as SCTAT and MDA is of particular interest.

Table 1. Cancer cases reported in patients with Peutz-Jeghers Syndrome.

Gastrointestinal	
Esophagus	1
Stomach	16
Small intestine	22
Large intestine	26
Pancreas	8
Extraintestinal	
Breast	17
Uterine cervix	10
Ovary	7
Uterus	2
Fallopian tube	1
Testis	1
Prostate	1
Lung	9
Thyroid	2
Leiomyosarcoma	2
Gall bladder	1
Liver	1
Basal cell	1
Osteosarcoma	1
Multiple myeloma	1

3. RESPONSIBLE GENE IN PEUTZ-JEGHERS SYNDROME

The responsible gene in PJS is a tumor suppressor gene, *STK*11/*LKB*1, that is located on the short arm of chromosome 19 (19p13.3) [4]. *STK*11/*LKB*1 is a 23-kb gene that encodes a serine-threonine kinase of 432-amino-acid protein and consists of 9 coding exons and 1 non-coding exon [4].

In 1997, Hemminki *et al.* first found significant evidence that the gene region responsible for PJS was on the short arm of chromosome 19 [5]. This was subsequently confirmed by Amos *et al.* [6] and further studies then identified the *STK*11 gene on chromosome 19 [7,8]. Yoon *et al.* investigated *STK*11 mutations in 10 PJS patients using PCR-SSCP [9] and found missense mutations, frameshift mutations, a stop codon caused by a single nucleotide mutation, a splicing site mutation in an intron, and mutations in germ cells in 5 of the patients. Tseng *et al.* analyzed mRNAs by RT-PCR in twin sisters with PJS who had a homoallele and found complete loss of *STK*11 gene expression in both patients [10]. These findings suggest that mutation or downregulation of *STK*11 is the cause of PJS.

In contrast with this conclusion, some sporadic PJS patients have no mutation in the *STK*11/*LKB*1 gene and no family history of this mutation. Furthermore, Yoon *et al.* detected germ cell mutations in only 5 of 10 PJS patients, suggesting that another pathogenic mechanism may be present in the remaining 5 patients. A sporadic mutation in *STK*11 gene may account for sporadic PJS and mutation of other genes may also be involved in the onset of PJS. PJS-related genes other than *STK*11 were identified by Papp *et al.* in an examination of 21 patients of 13 families with PJS, of whom 8 (62%) of 13 PJS probands had a family history and 5 (38%) had de novo mutations [4]. Germline mutation screening in the 21 patients detected 13 pathogenic mutations, including 3 frameshifts, 3 nonsense mutations, 2 splicing site mutations, and 5 knockouts in exons 1 to 7 of *STK*11. Several knockouts were frequently detected in 5 of the 13 families, and certain knockouts affected 2 genes, *SBNO*2 and *GPX*4, upstream of *STK*11. *SBNO*2 and *GPX*4 also modified the actions of *STK*11. These results suggest that mutation of a gene that modifies *STK*11 behavior can cause onset of PJS, without a mutation in *STK*11 itself.

About somatic mutation in *STK*11/*LKB*1, many investigators has reported. Aviziente *et al.* studied a set of colonic, testicular, cervical, and lung cancers, as well as sarcoma and myeloma and melanoma cell lines. One missense mutation was found in a testicular cancer as well as in a lung cancer, and one mutation leading frameshift and truncating protein product was detected in an adenocarcinoma of the uterine cervix [11,12]. Wang *et al.*

[13] reported the absence of *STK*11/*LKB*1 mutations in colorectal and ovarian cancers. Most reports thus far have found little evidence of somatic mutational inactivation of *STK*11/*LKB*1, although clearly in few tumor cases somatic inactivation of *STK*11/*LKB*1 has been seen.

4. PEUTZ-JEGHERS SYNDROME AND SEX CORD TUMOR WITH ANNULAR TUBULES (SCTAT)

SCTAT is an ovary tumor with histological characteristics intermediate between granulosa cell tumor and Sertoli cell tumor. SCTAT is characterized by annular growth of sex cord cells that produces vitreous bodies around the nucleus. SCTAT includes ovarian Sertoli cell tumor, serous and mucinous epithelial ovarian tumor, and ovarian mature teratoma. Scully *et al*. proposed the hypothesis that SCTAT occurred in ovarian granulosa cells and grew in a pattern specific to Sertoli cells [14]. An alternative hypothesis suggests that SCTAT consists of sex cord-derived unmature cells with the potential for differentiating to granulosa and Sertoli cells. In immunohistochemistry, testosterone and estradiol stain positively in SCTAT tissue, and SCTAT is commonly diagnosed based on clinical symptoms associated with the endocrine system, such as menstrual irregularity manifesting as precocious puberty, amenorrhea, hypermenorrhea and postmenopausal bleeding.

SCTAT is a common complication in PJS patients and approximately 36% of cases of SCTAT are considered to be related to PJS [15]. The clinical manifestations of SCTAT differ between patients with and without PJS [15]. Young *et al.* conducted a comparative study in 21 SCTAT patients with PJS and 47 SCTAT patients without PJS, and found that SCTAT complicated with PJS is commonly multifocal, bilateral, small (detected microscopically), and calcified in >50% of cases, and has a good prognosis. In contrast, SCTAT without PJS is unilateral, large (palpable), calcified in 12% of cases, and has a poor prognosis in 20%. These tumors also differ in histology, with ratios of mucinous ovarian tumors to serous tumors of 8:1 and 1:3 in cases of SCTAT with and without PJS, respectively [15].

5. PEUTZ-JEGHERS SYNDROME AND MINIMAL DEVIATION ADENOCARCINOMA (MDA)

MDA was proposed as a new disease concept by Silverberg and Hurt in 1975 and named adenoma malignum [16]. MDA is a subtype of adenocarcinoma, but is well-differentiated and difficult to distinguish from normal endocervical glands. Some cases of MDA have a good prognosis, and Nucci *et al.* proposed the disease concept of lobular endocervical glandular hyperplasia (LEGH) in

1999 [17]. LEGH was suggested to be a potential premalignant lesion of MDA, but a definitive conclusion on this issue has yet to be established.

MDA is a well known gynecological tumor that commonly occurs as a complication in PJS. The incidence of MDA is estimated to be 15% - 30% in PJS patients, while approximately 10% of MDA patients complicate with PJS. The mean age of MDA patients with PJS is younger than that of MDA patients without PJS, with one report finding mean ages of 33 and 55 years old, respectively [18]. MDA complicated with PJS may have the worst prognosis among gynecological tumors.

Analyses of mutations in *STK*11, the main gene responsible for PJS, and LOH in chromosome 19p13.3, in which *STK*11 is located, revealed LOH in chromosome 19p13.3 in approximately 50% of MDA patients complicated without PJS [19,20]. Allelic loss of ≥3.5 Mb was also detected in chromosome 19p13.3 in 9 MDA patients without PJS [21]. Connolly *et al*. [18] analyzed 8 MDA patients without PJS to elucidate the relationship between *STK*11 mutation and LOH in chromosome 19p13.3, and found no mutations in the *STK*11 coding region in somatic cells in any of the patients. However, LOH in chromosome 19p13.3 was found in 3 patients. Thus, LOH in chromosome 19p13.3 was observed but mutation of *STK*11 was not present in MDA patients without PJS. These findings suggest that a tumor suppressor gene other than *STK*11 may be present on chromosome 19p13.3.

In contrast, Kuragaki *et al*. [20] found *STK*11 mutations in 6 of 11 mucinous MDA patients without PJS, and also detected LOH in all 6 patients with the *STK*11 mutation. Of these 6 patients, 3 had the mutation in exon 1. These results suggest that onset of MDA may be related to mutations of *STK*11 on chromosome 19p13.3.

With regard to the finding that mutations of *STK*11 were detected only in 6 of 11 mucinous MDA patients, Kuragaki *et al*. also suggested that onset of mucinous MDA may be associated with defective expression or posttranslational modification of *STK*11 protein, perhaps with involvement of a gene other than *STK*11. Lee *et al*. also detected LOH in chromosome 19p13.3 in 9 MDA patients without PJS [21], including proximal to *STK*11 in 6 patients and 190 Kb distant from *STK*11 in 2 patients. These results suggest that a tumor suppressor gene related to onset of MDA is present on chromosome 19p13.3, in addition to *STK*11. Furthermore, since these patients developed MDA but not PJS, it is possible that mutations in *STK*11 do not always cause PJS, but lead to MDA alone.

Since *STK*11 has 9 coding exons, the exon responsible for PJS upon mutation may differ from that for MDA. Nakagawa *et al*. found mutations in exon 6 of germ cell

*STK*11 in 5 of 10 PJS patients [22], Connolly *et al*. detected mutation in exons 4 and 6 in 2 SCTAT patients complicated with PJS [18], and Hemminki *et al.* found mutations in exon 1 in 7 of 12 PJS patients [23]. These results suggest that mutations in exons 1, 4 and 6 in *STK*11 are essential for PJS. Recentry, Hirasawa *et al.* has reported germline frameshift mutation (4-bp deletion) in exon 6 in LEGH patient with PJS [24]. This is the first report about the mutation of LEGH patient with PJS.

Prognosis of MDA varies from extremely poor [25] to almost similar to that for well-differentiated cervical adenocarcinoma in the same stage [26]. Kuragaki *et al.* [20] examined the relationship between *STK*11 mutation and prognosis in 11 MDA patients without PJS: 6 patients with a *STK*11 mutation, including 5 in Stage 1b and 1 in Stage 2b, and 5 patients without a *STK*11 mutation, including 4 in Stage 1b and 1 in Stage 2b. There was no difference in clinical stage between patients with and without a *STK*11 mutation. However, of the 6 patients with a *STK*11 mutation, 4 died within 24 months after the first surgery and one had recurrence, whereas all 5 patients without a *STK*11 mutation survived for 50 months or more after the first surgery. Thus, MDA patients with a *STK*11 mutation had a poorer prognosis than those without a *STK*11 mutation ($p = 0.039$). Many studies have also shown a poor prognosis of PJS patients complicated with MDA. This is consistent with the findings in Kuragaki *et al.*, since MDA patients with PJS are more likely to have a *STK*11 mutation compared to MDA patients without PJS.

6. CONCLUSIONS

PJS patients are likely to develop benign and malignant tumors in various organs including the gastrointestinal tract, mammary gland, ovary and uterus, with the risk for these tumors increasing 10- to 18-fold compared to persons without PJS [27]. The risk of tumors as complications of PJS is particularly high in women, by approximately 20-fold compared to women without PJS. This may be due to an increased incidence in breast cancer and gynecological malignant tumors such as SCTAT and MDA in women with PJS [18]. Complication of PJS with gynecological tumors is rare, but women with PJS complicated with microscopic ovarian SCTAT, cervical MDA, borderline ovarian malignant serous/mucinous mixed cystadenoma, and mucinous metaplasia in the tubal mucosa have been reported, as discussed by Mangili *et al.* [28].

There is considerable evidence showing that *STK*11 on chromosome 19p13.3 is the main gene responsible for both MDA and PJS. Another tumor suppressor gene related to onset of PJS and MDA may also be present on chromosome 19p13.3, however, this gene has yet to be identified. Genetic analyses of PJS and MDA have been conducted with consideration of these entities as a single disease, but MDA complicated with PJS has only been described in case reports and no comparative study or genetic analysis of the link between the diseases has been conducted. There are few case reports of complication of PJS with LEGH, a potential premalignant lesion of MDA, in part because there are no international criteria for diagnosis of LEGH and MDA. Thus, establishment of appropriate criteria is needed to examine the relationship between PJS and MDA/LEGH. The pathogenic mechanisms of PJS, MDA and SCTAT also require studies at the genetic level to elucidate the relationships among these conditions. However, PJS is a rare disease and there are only a few patients with PJS complicated with SCTAT and MDA. Therefore, multicenter studies will be needed for collection of a sufficient number of cases for genetic analysis. Elucidation of the pathogenic mechanism of SCTAT and MDA at the genetic level may help with understanding of the pathogenesis of cervical adenocarcinoma and that of development of gynecological tumors in PJS patients.

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