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■ REVIEW ■

# Peutz-Jeghers Syndrome: A New Understanding

Peutz-Jeghers syndrome is an autosomal dominant inherited disorder characterized by hamartomatous polyps in the small bowel and mucocutaneous pigmentation. Patients with Peutz-Jeghers syndrome often present as surgical emergencies with complications of the polyps, such as intussusception, bowel obstruction and bleeding. Furthermore, repeated operations may be needed in some patients, which may result in short bowel syndrome. Although early reports did not demonstrate a predisposition to cancer in patients with this syndrome, more recent studies have described an increased risk for both gastrointestinal and extra-gastrointestinal cancers. Women with the Peutz-Jeghers syndrome have the extremely high risk for breast and gynecologic cancer. Recently, Peutz-Jeghers syndrome susceptibility gene, encoding the serine threonine kinase *STK11* (also called *LKB1*), was identified in families with Peutz-Jeghers syndrome. The identifications of germline mutations in families with Peutz-Jeghers syndrome could be a turning point in the management of Peutz-Jeghers syndrome.

Key Words : *Peutz-Jeghers syndrome; Hamartomat; Germ-line mutation; Gene, STK-11*

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## INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a disease of autosomal dominant inheritance, which is characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. PJS is a relatively rare disease entity; approximately 1 in 8,000 to 30,000 live births, or about one-tenth as frequent as the familial adenomatous polyposis coli. Although hamartomatous polyps, melanin pigmentation and family history are typical features of PJS, some patients do not present the full spectrum of the disease. The unusual combination of clinical features often makes a clear diagnosis difficult. Definition of this syndrome, proposed by Giardiello et al. requires histopathologic confirmation of hamartomatous gastrointestinal polyps and two of the following three features: 1) small bowel polyposis, 2) family history of PJS, 3) pigmented macules of the buccal mucosa, lips, fingers, and toes (1).

Although early reports did not demonstrate a predisposition to cancer in patients with this syndrome, more recent studies have described an increased risk for both gastrointestinal and extra-gastrointestinal cancer.

In this review we will deal with clinical features of PJS with a special emphasis on the high risk of various cancers. Finally, we will describe recent developments in the study of the *STK-11* gene, the mutation that causes susceptibility to PJS.

## PHENOTYPE

### Pigmentation

One of the typical features of PJS is mucocutaneous melanin pigmentation, which is seen in more than 90% of patients. It consists of freckle-like pigmented macules that vary in size (from 0.1 cm to 1.2 cm) and number (Fig. 1). The melanotic spots have varied hues of brown or black. They are found on the lips, around and inside the mouth, on fingers and toes and, less commonly on hands, feet and in the mucosa of the nose, conjunctiva and rectum. They are usually noted in infancy and those on the skin tend to gradually fade after puberty.

### Gastrointestinal polyps

Hamartomatous polyps in the gastrointestinal tract are found in nearly all patients with PJS. They may be found in the stomach to the rectum. The small intestine, especially, the jejunum, is the most common site of polyps. The total numbers of polyps vary from only a few to several hundreds, but they usually do not exceed 100. One third of patients have symptoms before the age of ten years and one half of patients before the age of 20 (2, 3). Patients most commonly present obstruction or abdominal pain related to intus-

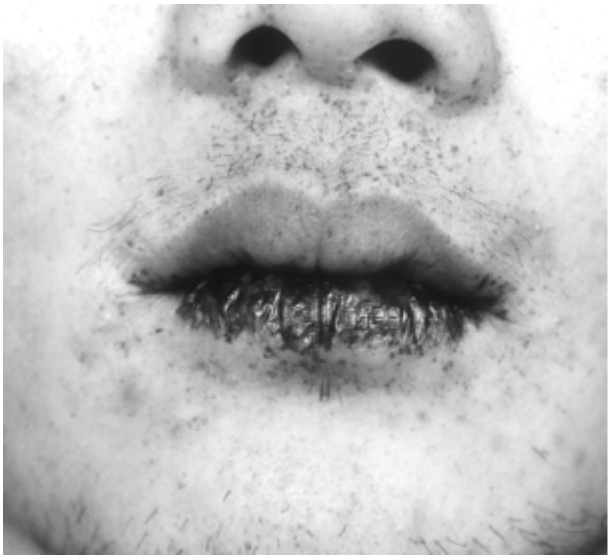

Fig. 1. Typical Peutz-Jeghers pigmentation of the lip.

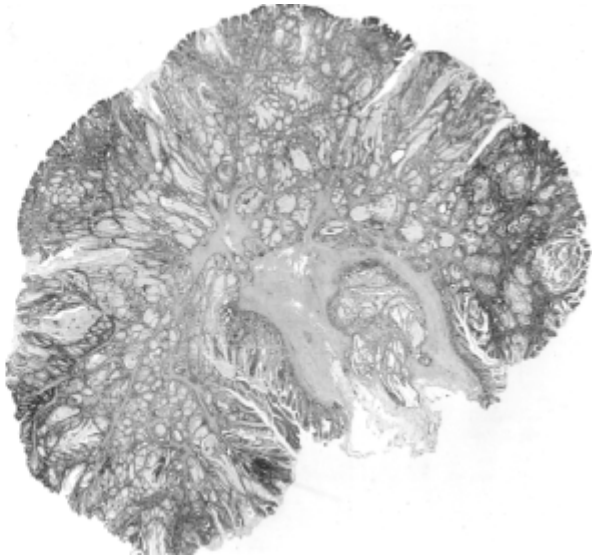

Fig. 2. A typical Peutz-Jeghers polyp resected from small intestine. Hamartomatous polyp showing ramifying central stalk containing muscle bundle (original magnification ×4).

susception induced by polyps. Intestinal bleeding from the polyps is the second most common intestinal symptom.

It is sometimes difficult to make a differential diagnosis between hamartomatous polyps and adenomatous polyps by gross inspection. Thus, microscopic examination is required for an accurate diagnosis. Polyps in PJS are hamartomas that are derived from glandular epithelium together with stroma that includes a branching muscular framework from muscularis mucosa. Histologically, the polyps in PJS consist of a non-neoplastic hamartomatous proliferation of normal epithelium and smooth muscle. Prominent branching of the smooth muscle bundle in the core of the polyps, is a characteristic finding of small intestinal polyp (Fig. 2). Within the colon, interlacing bands of smooth muscle are less frequent than in the small bowel polyps. Sometimes, mucosal epithelium is displaced into a polyp, which may be mistaken for invasion (4). This phenomenon may account for a sizable portion of the earlier reports describing carcinoma arising in PJS polyp (5). Thus, extra caution is required in the interpretation of the microscopic findings of PJS polyps. In the pseudoinvasive areas, the glandular structures are lined by cytologically benign cells having the appearance of the normal cell population of the involved organ.

### Natural history of patients

Most patients with PJS have a characteristic clinical course of recurrent episodes of polyp induced bowel obstruction and bleeding. The major cause of the intestinal obstruction is intussusception of the small bowel, which requires repeated laparotomies. Many patients undergo several operations in their lifetime. According to our data, 43 percent of the patients received two or more laparotomies, and one patient received laparotomy five times (6). Surgical interventions began at a young age (average age of 21, range 5 to 56 years old). Complications induced by polyps, especially intussusception, were major causes of the laparotomies. A review of the literature shows a sizable percentage of short bowel syndromes resulting from the repeated bowel resection (7). In order to prevent short bowel syndrome, many authors recommend polypectomy rather than segmental resection of the bowel, unless evidence of malignancy is present. Recently, intraoperative endoscopy and endoscopic polypectomies have been used to avoid unnecessary enterotomy (8, 9). In order to reduce the number of laparotomies resulting from obstruction of the bowel, periodic endoscopic screening and polypectomy are advocated. Burt et al. (10), recommended endoscopic investigation of the upper and lower gastrointestinal tract every three to five years, in addition to radiography of the small bowel (Fig. 3). However, recently some authors have recommended more frequent screening, especially in connection with the possibility of the polyps changing malignantly. The surveillance problem in connection with cancer will be discussed further later in this article.

## INCREASED RISK FOR CANCER

Patients with PJS have a substantially greater risk of dying of cancer at a relatively young age than does the general population. Common cancers such as those of the

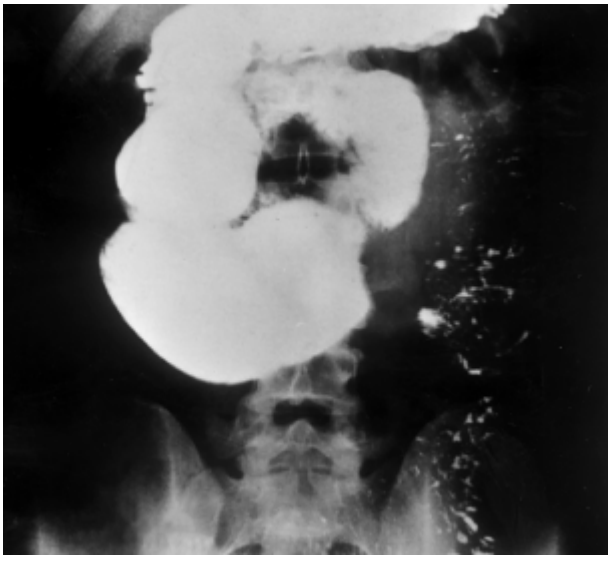

Fig. 3. Multiple polyps are seen in the small bowel series.

Table 1. Literature review of cancer development in patients with PJS.

| Authors | No of patients | G-I cancer | Non G-I cancer |
|---|---|---|---|
| Giardiello et al. (1) | 31 | 4 | 11 |
| Utsunomiya et al. (3) | 102 | 12 | 5 |
| Foley et al. (7) | 12 | 2 | 0 |
| Spigelman (17) | 72 | 10 | 7 |
| Linos et al. (11) | 27 | 1 | 3 |
| Hizawa (20) | 8 | 3 | 1 |
| Boardman et al. (18) | 34 | 10 | 16 |
| Total | 286 | 42 | 43 |

breast, pancreas and colon appear at an earlier age in patients with PJS than in the general population, and several rare cancers also are more frequent (Table 1). In Korea, there are only a few reports analyzing the risk of cancer in patients with PJS except several reports on one or two cases of PJS patients with cancer (6, 14, 15, 16) (Table 2). Whether PJS predisposes patients to cancers of the gastrointestinal tract has been debated for a long time (11). According to early investigators, the risk of gastrointestinal cancer of PJS was reported to be high as 20% to 25% (12, 13). However, these authors commented that the evidence for truly malignant transformation in the polyps was not convincing since metastasis of the cancer was not observed in any of the cases. The high malignancy rate in these reports may well be due to histologic misinterpretation of the presence of non-neoplastic glands within smooth muscle fibers as neoplastic invasion.

The prevailing belief in the early period was that the hamartomatous polyps had little or no malignant potential since there were no reports on death from metastasis. Subsequently, however, this belief was reversed by an array of long-term follow-up reports of large families with PJS (3). Most of these reports have showed that patients with PJS have a far greater risk of developing cancers. However, the descriptions of cancer risks in individual reports are heterogenic depending on the period of follow-up, as is the criteria for selecting patients.

Table 2. Literature review of cancer development in korean patients with PJS

| Authors | No of patients | G-I cancer | Non G-I cancer |
|---|---|---|---|
| Park et al. (14) | 18 | 2 | 0 |
| Lee et al.(15) | 11 | 1 | 0 |
| Chang et al. (16) | 35 | 1* | Not specified |
| Choi et al. (6) | 31 | 4 | 1 |

* One additional case showed carcinomatous change within the polyp, but not included as a genuine malignancy

According to Spigelman et al. 16 of 72 patients developed cancer during the follow-up period. Ten of these cancers from nine patients originated from the gastrointestinal tract (one patient had two cancer), and seven cancers developed outside the gastrointestinal tract. The relative risk of death from gastrointestinal cancer was estimated to be 13 (95% confidence interval(CI) 2.7-38.1), and the relative risk of a non-gastrointestinal tumor was 9 (CI 4.2-17.3). By the age of 57, the chance of dying of cancer was 48% and the chance of dying of any causes was 57% (17).

The relative risk for cancer was reported to be different for men and women; 18.5 (95% CI, 8.5-35.2) in women with PJS, and 6.2 (CI, 2.5-12.8) in men with the syndrome. In women, the relative risk for breast and gynecologic cancer was 20.3 (CI, 7.4-44.2) (18).

In addition to this high prevalence of cancer in patients with PJS, survival of patients with PJS was also reported to be impaired, with the risk of mortality from cancer approaching 40 % by 40 years of age (17).

Moreover, several authors (17, 19, 20) have documented the transformation of some portion of hamartomatous polyps into adenomatous components and consequent carcinoma, which suggest the presence of a hamartoma-adenoma-carcinoma sequence in the carcinogenesis mechanism of intestinal cancer in patients with PJS. However, histologic review of all of the PJS-related polyps recorded in the St. Marks polyposis registry did not come up with any cases of epithelial dysplasia among the almost 500 polyps examined, suggesting that malignant change in these polyps is rare (5). Malignant tumors may also arise de novo or from coexisting adenomas. According to Eniinus et al. *K-ras* mutation in dysplastic adenomatous component was very rare, in contrast to colorectal adenoma (21). Thus, a different carcinogenesis pathway is suggested from that of colorectal cancer. The relative importance of hamartomas and these other mechanisms in intestinal carcinogenesis remains to be

determined. As in most cancers in hereditary diseases, patient at the time of diagnosis of cancer in PJS was younger than that of the general population, regardless of whether the cancers were gastrointestinal or non-gastrointestinal in origin. Most reports indicated that the mean age of cancer patients is less than 50 years. Furthermore, some indicated frequent cancer development even in those below the age of 30. The development of cancer at a young age is a well-known feature of cancer related to hereditary diseases.

## Non-gastrointestinal cancer

There have been many case reports of cancers occurring at various sites in patients with PJS. Some tumors, especially those occurring in young patients with PJS with typical phenotypes, should be considered to have a genuine association with PJS. Extra-gastrointestinal tumors likely to be genuinely associated with PJS are those of the ovary, cervix, and testis. Bilateral breast cancer, pancreatic cancer and cancer of the Fallopian tubes may also be genuinely associated with PJS.

According to a recent report (18), 26 noncutaneous cancers developed in 18 of 34 PJS patients. Among them, only ten was the gastrointestinal cancers. The remaining cancers were extra-gastrointestinal in origin and included six breast cancers. This result indicates that extra-gastrointestinal cancers associated with PJS may be at least as frequent as gastrointestinal cancers. Consequently, extreme attention should be paid to the extra-gastrointestinal organs, including the breast, pancreas and reproductive organs when following PJS patient.

A wide range of benign and malignant ovarian tumors, including cystadenoma, granular cell tumors and sex cord tumors, has been reported in patients with PJS (22, 23). Of these, the sex cord tumor with annular tubules (SCTAT) is now considered a characteristic of PJS. SCTAT was considered rare in the past, but it is now thought to present in almost all patients with PJS (24, 25). These tumors are typically multifocal and bilateral, and usually benign. However, malignant sex cord tumors have also been found in patients with PJS (25).

## Surveillance strategy

The optimal screening strategy for PJS has not yet been determined. Clinicians will need to revise their screening strategy as additional information is gained about the tumor spectrum and the risks associated with PJS. After reviewing the PJS literature, Tomlinson and Houlston have offered the following surveillance plan for those with known PJS (26); 1) upper gastrointestinal endoscopy every other year from age 10, sooner if clinically indicated, 2) colonoscopy every third year from age 25, sooner if clinically indicated, and removal of any polyp large than 1mm, 3) small bowel follow-up screening from age ten, 4) breast surveillance from age 25, with mammography beginning at age 35, 5) annual abdominal and pelvic ultrasound from age 25 and 6) cervical smear every other year. The Mayo Familial Cancer Program recommends a more strict strategy (27). In addition to the above, it recommends regular breast and gynecologic screening for affected women or those at risk, pelvic ultrasound from age of 20, regular testicular examination and periodic colonoscopy from age 35.

As in the screening strategy there is still debate on the management strategy for known polyps. Generally, surgery has been recommended for the removal of symptomatic small bowel polyps or small bowel polyps larger than 1.5cm. Some have advised intra-operative small bowel endoscopy, when laparatomy is necessary, to remove all possible polyps. Substantial morbidity arises from short bowel syndrome, which is the usual result of repeated bowel resection. Thus, simple polypectomy, whether it is open or endoscopic, is preferred to bowel resection, if possible.

## Peutz-Jeghers syndrome genes

PJS has a well-known hereditary pattern and a relatively apparent phenotype. Thus, there have been many attempts to map the locus of the disease-causing gene. But it has taken longer than expected, probably due to the rarity of the disease, and the lack of large families which are essential to linkage analysis.

There have been several reports on the possible site of the candidate for PJS gene. Markie et al. reported a pericentric inversion of chromosome 6 in a patient with PJS (28), but the linkage study failed to find any evidence that the genetic defect in the long arm of chromosome 6 was the site of a PJS locus. Another report suggested chromosome 1p32-34 as a possible site for PJS (multiple lod score 4.0) from a study of two families (29). However, subsequent extension of the pedigrees of the families did not confirm the original linkage, and neither was the evidence for linkage found in different sets of families (30).

The problems with linkage analysis were circumvented by the use of comparative genomic hybridization (CGH) in multiple polyps from a single PJS patient (31). The study relied on several assumptions; 1) that the PJS locus is a tumor suppressor gene, 2) that the wild type allele is deleted in the early stage of tumorigenesis, 3) that intestinal carcinoma arises from hamartomatous polyps and 4) that the amount of stromal tissue in the polyps does not obscure the result of deletion in neoplastic component. Despite these potential problems, the result of CGH combined with LOH clearly showed the deletion in the short arm of chromosome 19 (19p13.3). Subsequent linkage analysis demonstrated the presence of a high-penetrance locus in distal 19p

with a multipoint lod score of 7.00 at marker D19S886 without evidence of genetic heterogeneity. The candidate location of the PJS gene was further supported by a subsequent study investigating five families with a multiple lod score of 7.52 at D19S886 (32). Here, D19S886 defined the proximal border of the candidate region. In the above two studies, no recombinations were observed at marker D19S8 86, indicating that a susceptibility gene was located in the vicinity of this locus.

After the mapping of the candidate locus of PJS, two groups succeeded in cloning the PJS susceptibility gene and identified the germline mutations in PJS patients with a family history nearly at the same time (33, 34). The gene was a novel human gene, encoding the serine threonine kinase STK11 (also called LKB1) which consisted of ten exons spanning 23 kb. As of now, several reports on germline mutation on *STK11* have been published (35, 36). According to these reports, most of the PJS patients had the mutation in the *STK11* gene. Frequent type of mutations were frame shift, nonsense, deletion and splice site mutations. Missence type mutation was relatively infrequent. We recently detected germline mutations of *STK11* gene from 4 Korean PJS families. Three families had missense type mutations and one family had frameshift type mutation (37). Thus, our impression is that missense type mutations are also frequent in patients with PJS.

Knowledge of the causative gene in a certain hereditary disease has important implications for management of patients with the disease. The most immediate of these is accurate and pre-symptomatic diagnosis of patients through genetic testing. It can also provide important tools in management of familial members of the disease. However, further accumulation of the data on germline mutation is needed to delineate such important issues in PJS, regarding the phenotype-genotype correlation, the most frequent mutation types, and the guidelines for deciding which patients should be candidates for the gene test.

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