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Case Report

The patients with Peutz-Jeghers syndrome have a high risk of developing cancer

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ABSTRACT

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by mucocutaneous hyperpigmentation, and intestinal and extraintestinal multiple hamartomatous polyps. Development of gastrointestinal and extragastrointestinal cancer risk is markedly increased in patients with Peutz-Jeghers syndrome. We analyzed five patients from two families diagnosed with Peutz-Jeghers syndrome between 1999 and 2012. This study confirms the actual malignancy potency of PJS. Therefore, we suggest a close follow-up of patients with Peutz-Jeghers syndrome for the risk of malignancy.

Keywords: Peutz-Jeghers syndrome, hamartomatous polyp, intussusception

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INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder that is characterized by mucocutaneous hyperpigmentation, and intestinal and extraintestinal multiple hamartomatous polyps. It usually occurs in infancy and late adolescence. Although most of the polyps are encountered in the jejunum, they can occur in any other part of digestive system. Development of gastrointestinal and extragastrointestinal cancer risk is markedly increased in patients with PJS (1, 2). We analyzed five patients from two families diagnosed with PJS between 1999 and 2012. There were three male and two female patients, and their ages at the initial diagnosis ranged from 2 to 38 years. At the time of diagnosis, all patients had characteristic mucocutaneous hyperpigmentations and multiple polyps in the digestive system. Gastrointestinal cancer occurred in four of the five patients, three of whom developed colon cancer and one of whom developed small intestinal cancer at 32 years of age. One female patient with colon cancer also developed bilateral breast cancer. Three of these patients died within one month to one year after being diagnosed with colorectal cancer. Thus, we aim to present some new clinical features of PJS that have not previously been described in the literature and to discuss again the relationship between PJS and the development of cancer.

CASE PRESENTATIONS

Case 1: The male patient was born in 1970. He was 32 years old when colon cancer was first diagnosed. His father had been diagnosed with colon cancer at 54 years of age, and he died two years later. The patient had four siblings, two of whom were males at 14 and 22 years of age who do not show any signs or symptoms of PJS. The other two siblings described below, one male and one female, had PJS. The patient had undergone partial jejunectomy due to jejunal intussusception at the age of 17. He was admitted to our hospital in 2004 with subileus complaints and apparent perioral and oral hyperpigmentations on inspection. Detailed analysis revealed small intestinal intussusception at two locations and concomitant rectum cancer. The patient then underwent polyp excision (a total of 13 polyps were excised) and Miles operation in the same session. Histopathological examination of the resected specimen revealed signet ring carcinoma, regional lymph node metastasis (27/28), perinodal infiltration, and 13 hamartomatous pedunculated polyps with small intestinal localization, two of which contained adenocarcinoma. Postoperatively, the patient received chemotherapy; however, he died from progressive cancer metastasis one month after surgery.

Case 2: The female patient was born in 1972. She was 32 years old when the colon cancer was first diagnosed. She was the sister of the abovementioned patient. The patient underwent a left hemicolectomy in 1999 due to obstructive left colon cancer. Several small-sized hamartomatous polyps were detected in the small intestine. Histopathological examination revealed mucinous carcinoma. Polypectomy was performed in 2005 to excise adenomatous polyps localized in the colon. The polypectomy was followed by right and left mastectomy in 2007 and 2010, respectively, due to breast cancer. The patient has been healthy since then and has no medical problems in follow-up examinations.

Case 3: The male patient was born in 1980, and was the third affected sibling in the family above (Cases 1 and 2). He was 32 years old when colon cancer was first diagnosed. He was admitted to our hospital with severe abdominal pain, vomiting, and abdominal distention. On inspection, mucocutaneous hyperpigmentation

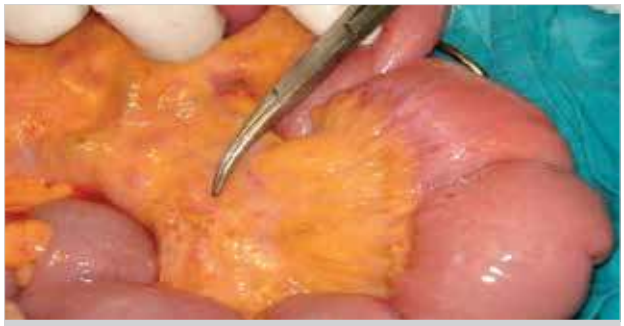

Figure 1. Melanin pigment deposits on mesentery of the small intestine

was detected in the hands, feet, and perioral and oral mucosa. Physical examination revealed a mass on the right side of the umbilicus. A computed tomography scan revealed jejunojejunal intussusceptions. During laparotomy, a small bowel intussusception was detected. Multiple polyps were palpated from the stomach to the colon. Numerous melanin pigment deposits were observed in the mesenteries of both the small intestine and the colon (Figure 1). In addition, a tumoral mass was detected in the duodenum at the level of Treitz. He underwent duodenojejunal resection and side-to-side jejunoduodenostomy. Histopathological examination revealed adenosquamous carcinoma and multiple hamartomatous polyps. This patient was discharged on the 11th day postoperatively and started receiving cancer chemotherapy. However, systemic metastasis was detected one month after the operation, and he died two months later.

Case 4: The male patient was born in 1965. He was 38 years old when colon cancer was first diagnosed. The patient did not display typical PJS symptoms initially. However, he had diffuse vitiligo and hypospadias on inspection. He underwent rectal polyp excision twice in 1985 and 1986 at different healthcare centers, intussusception operation in 1986, and undescended testicle surgery in 1996. PJS was diagnosed in one of his two daughters, but his son, who was 2 years old, did not display any signs or symptoms of the disease. The patient underwent surgery due to multiple colon polyps following his admission on April 30, 2003 due to polyp protrusion from the anus. The patient underwent total colectomy, loop ileostomy, and J-pouch ileoanal anastomosis. Histopathological examination revealed moderately differentiated adenocarcinoma and regional lymph node metastasis accompanied by multiple tubular, villous, and tubulovillous adenomas in the colon. The patient died due to diffuse liver and lung metastases, despite systemic cancer chemotherapy, one year after surgery.

Case 5: The female patient was born in 1993, and she was just 2 years old at the time of diagnosis of PJS. She is the daughter of the abovementioned patient (Case 4). She underwent endoscopic polyp resection several times on detection of large-sized polyps localized throughout the whole gastrointestinal system from the stomach to the colon. In addition, she underwent partial small intestinal resection in 2010 due to jejunal intussusception. The patient is now healthy and under periodic follow-up.

All the patients in this study were informed about the procedures in detail and signed the informed consent form. Necessary consents were obtained from the patients to perform scientific work.

DISCUSSION

Peutz-Jeghers syndrome is an autosomal dominant disorder with familial occurrence of gastrointestinal hamartomatous polyps in association with mucocutaneous hyperpigmentation and occurs in approximately 1 in 8300 to 280,000 live births (1, 2). The cause of PJS is a mutant gene named STK1, also known as LKB1. This gene is localized at 19p34-p36 and is a serine/threonine kinase that controls growth regulation. Aretz et al. (3) studied large STK11 deletions in 56 patients with PJS using the combination of sequence analysis to detect point mutations and multiplex ligation-dependent probe amplification (MLPA). They found that the STK11 mutation detection rate was 94%. Further, other authors reported that mutations could be observed in all patients with PJS (4, 5). We were unable to perform genetic analyses in our patients due to technical and financial reasons. The earliest symptom of PJS is mucocutaneous pigmentations that occur in the first year of life in about 95% of patients. The melanotic pigmented macules are dark brown or bluish brown in color and 1-5 mm in size; these lesions can occur at many sites on the body in children, while in adults, the characteristic buccal lesions are most evident. They can be located on the vermilion border of the lips (94% of patients), buccal mucosa (66%), hands (74%), feet (62%), lips, eyes, nostrils, and perianal area (6). Histological examination of the pigmented macula reveals increased melanin in basal cells. We detected 10 to 30 circle- or ovoid-shaped melanin pigment deposits of 1-3-mm diameter that we named "sprinkled black pepper" in the mesentery of the intestines in one patient with PJS; this symptom has not been reported in the literature to date.

The Peutz-Jeghers polyp is a true hamartoma with unique histopathological characteristics that consist of a branching structure of connective tissue and smooth muscles lined by normal intestinal epithelium. The hamartomatous polyps in the gastrointestinal system can lead to complications, such as bleeding, obstruction, anal protrusion, and intussusception, which have also been observed in our cases, during the first three decades of life. Although polyps are detected throughout the gastrointestinal tract other than the mouth, the jejunum is the most affected intestinal segment. One of the most commonly observed complications of these polyps is intussusception. Gastrointestinal bleeding may accompany PJS and causes anemia. Bleeding might occur on the surface of the polyp, and considerable attention must be paid as malignancy may also cause anemia. Anemia had developed in all our cases.

The fourth patient, who had vitiligo, hypospadias, undescended testicles, and multiple intestinal and colonic polyps, was operated on due to malignant transformation of these polyps. The small intestinal polyps were hamartomatous in nature. This patient's daughter developed all characteristic lesions of PJS. Therefore, we suggest that this disease belongs to a family of hamartomatous polyposis syndromes including PJS, juvenile polyposis, and Cowden syndrome.

The relation between gastrointestinal carcinoma and PJS has been discussed for many years. It is commonly accepted that the incidence of cancers within the gastrointestinal tract as well as in other organs increases in patients with PJS. Perzin et al. (7) described adenoma and *in situ* carcinoma in a PJS patient who developed polyps for the first time in 1982. In 1987, Giardiello et al. (8) reported that 31 patients with PJS in the United States had a

higher frequency of cancer (48%) and confirmed an excessive risk of gastrointestinal malignancy. In addition, they found an excess of malignancies at a number of other sites. It has been well known that breast cancer, ovarian sex cord tumors, cervical cancer, and feminizing Sertoli cell testicular tumors in prepubertal boys can develop in patients with PJS. Although cancer is uncommon before the age of 30, the risk of development of malignancy becomes important in later years. It has been reported that over 90% of patients with PJS are likely to develop at least one malignancy, either gastrointestinal or elsewhere in the body, by the age of 65 years (9). Of all tumors associated with PJS, breast cancer poses the greatest risk, affecting 32%-54% of patients. Giardiello et al. (10) have determined that the relative risk for gynecological and breast cancers in women increased by 20.3% and that for gastrointestinal cancers increased by 50.3%in PJS patients. Spigelman et al. (6) reported that the relative risks of death from gastrointestinal cancer and death from overall cancer in patients with PJS were 13% and 9%, respectively. The age of onset for many PJS-associated cancers was very young, similar to our series. Particularly, we want to emphasize the importance of regular cancer screening in all patients with PJS who have a first-degree family history of cancer. We use and recommend NCCN surveillance guidelines for screening methods and interval time for patients with PJS (9). Many other polyps may also develop in patients with PJS; polyps showing adenomatous changes frequently emerge in the colon and may be confused with familial adenomatous polyposis.

The risk of small bowel cancer development in PJS patients is low (approximately 12% lifetime risk). The most common gastrointestinal malignancies in PJS patients are seen in colon, pancreas, and stomach. Cancer was localized to the colon in three out of four patients in our series, while the other one was localized to the duodenum. Among non-gastrointestinal cancers (breast, ovary, thyroid gland, lung, and endometrium), the most common is breast cancer (greater than 50% lifetime risk). Although gastrointestinal cancer was seen in four out of five patients in our series, extragastrointestinal cancer (bilateral breast cancer) was seen in one patient. In the present study, which included a relatively small number of patients, malignant neoplasms were found in all patients except one. The patient age at the time of diagnosis of cancer was younger than 50 years in all patients. The development of cancer in such young patients is in good accord with previous reports (10-12). Thus, once a patient, even at a young age, is diagnosed with PJS, it should be kept in mind that the patient might already have cancer or that cancer may develop in the near future. Our study reports that malignancy developed in four out of five patients who were members of two different families. Two different types of rapidly growing malignancies with different histopathological features were detected in two male members of the first family and died within one month of diagnosis, despite radical surgery accompanied by adjuvant chemotherapy. Despite colon cancer and subsequent bilateral breast cancer, the third patient (female) in the same family is still alive. In light of the findings that cancer occurred in the third decade of life on average in the two families reported in our study, it might be hypothesized that members of some families with PJS have a greater risk and/or tendency to show malignant transformation. Therefore, we consider that further studies are required for the genetic screening of patients with PJS who have close relatives with a history of cancer. In conclusion, gastrointestinal or extragastrointestinal cancers were found in four out of five patients with PJS, and three of these patients died due to cancer metastasis. Patients with PJS require close follow-up immediately after the time of diagnosis. In order to reduce the rates of mortality and morbidity in patients with PJS, we suggest that patients must be screened periodically with endoscopy.

CONCLUSION

We conclude that PJS is a precancerous syndrome with a marked predisposition for both gastrointestinal and extragastrointestinal cancers. Additional intensive and systemic evaluations may be required in patients with PJS, especially in young patients with symptomatic disease, and they must be closely followed up due to the risk of development of malignancy.

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