Metachronous Breast and Lung Cancers in a Middle-Aged Woman with Peutz-Jeghers Syndrome

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Abstract: We report the case of a middle-aged woman with Peutz-Jeghers syndrome who developed metachronous breast and lung cancers, because lung cancer is infrequently associated with PJS, especially for women with this disorder. At the age of 12 years, the patient was diagnosed with Peutz-Jeghers syndrome owing to the presence of multiple hamartomatous polyps in the gastrointestinal tract and mucocutaneous melanin pigmentation. She developed breast cancer and underwent curative mastectomy and postoperative adjuvant chemotherapy at 48 years of age. Five years later, computed tomography showed multiple lung nodules. The pathological diagnosis of the lung lesion was a mucinous adenocarcinoma, which differed from that of the resected breast cancer. She then received cisplatin/ pemetrexed therapy combined with pembrolizumab for non-small cell lung cancer, which reduced the size of the lung tumors. However, the disease eventually progressed, and she underwent a gene panel test because of the refractoriness to pharmacotherapy, which demonstrated a germline *STK11* pathogenic variant.

Keywords: Peutz-Jeghers syndrome, *SKT11* pathogenic variant, lung cancer, breast cancer, metachronous primary cancers, hamartomatous polyp.

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant disorder, characterized by mucocutaneous pigmentation, hamartomatous polyps in the gastrointestinal tract, and an elevated risk of malignancies [1, 2]. The first descriptions of PJS date back to the late 1800s by Dr. Conner and later in the 1920s by Dr. Peutz. A combination of intestinal polyposis and mucocutaneous pigmentation was first described by Dr. Jeghers in 1949 [3]. Mutations in the tumor suppressor gene serine threonine kinase 11 (*STK11*) are common in patients with PJS [4]. As a result, PJS is associated with an increased risk of malignancies resulting in significant morbidity and mortality [2, 3]. Gastrointestinal cancer is the most common malignancy in patients with PJS, accounting for up to two thirds of all malignancies in this population. Breast cancer is the second most common malignancy associated with the PJS [5]. Although among 240 patients with *STK11* mutations, a 7% risk of lung cancer by the age of 60 was observed, lung cancer is relatively rare, especially in women [6]. In addition, the incidence of multiple primary cancers is approximately 10% even in patients with hereditary cancer syndromes.

Herein, we present the case of a middle-aged woman carrying a germline *STK11* pathogenic variant with metachronous breast cancer and inoperable lung cancer.

CASE REPORT

A woman with PJS became conscious of bloody lactation from her left breast at the age of 48. At 12 years of age, she complained of abdominal pain and was referred to a university hospital. Due to the presence of multiple hamartomatous polyps in the gastrointestinal tract and pigmentation in the oral lips, hands, and feet, a clinical diagnosis of PJS was made at that time. Since then, she has undergone periodic follow-up total colonoscopies. She consulted department of breast surgery. She was diagnosed with left breast cancer and underwent sentinel lymph node biopsy, followed by simple mastectomy. Histological examination of the resected specimen revealed ductal carcinoma (stage 1: pT1b, Ly0, V0, pN0, M0) (Figure **1**). Because invasion of the scirrhous-type cancer was found, she eventually underwent postoperative adjuvant chemotherapy (four cycles of docetaxel/ cyclophosphamide therapy). During follow-up, the patient was hospitalized for small bowel obstruction due to intussusception and underwent resection of the small intestine at 51 years of age (Figure **2**). The large polyp was histologically diagnosed as a hamartoma. She had no siblings or marital history (gravidity 0), and no family history of hamartomatous polyps in the

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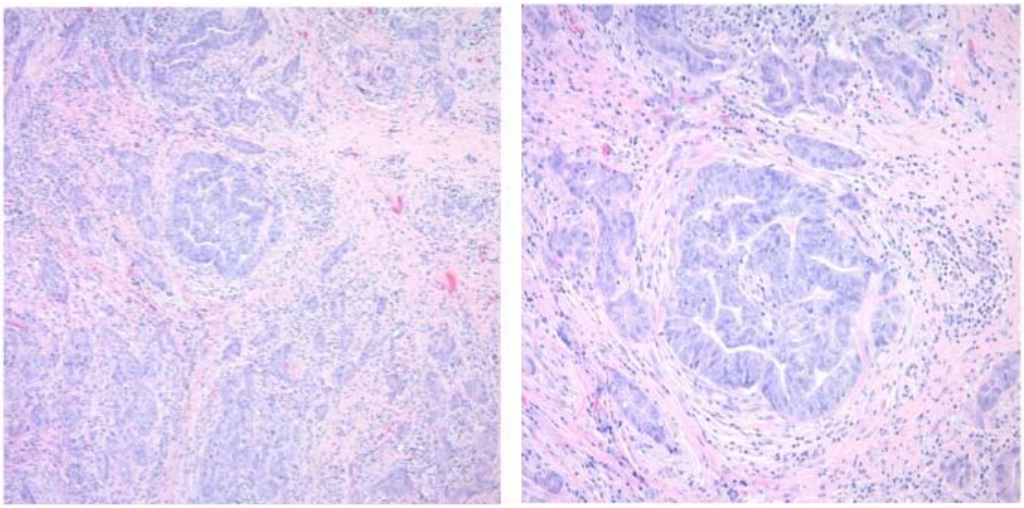
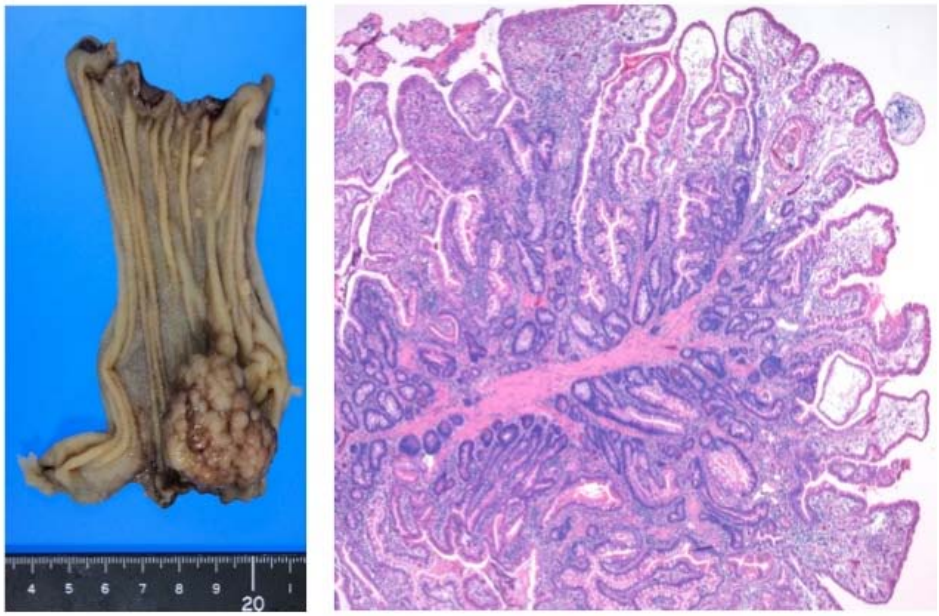


A **B**

Figure 1: Histological examination of the resected specimen revealed ductal carcinoma (stage 1: pT1b, Ly0, V0, pN0, and M0) with scirrhous-type cancer invasion.

A. Hematoxylin-eosin staining (HE) x40.

B. HE x100.



A **B**

Figure 2: A. Macroscopic findings of resected small bowel.

B. Microscopic findings showing hamartomatous polyp (Hematoxylin-eosin staining x20).

gastrointestinal tract or mucocutaneous pigmentation. The detailed pedigree is presented in Figure **3**.

Five years after curative resection of the breast cancer, computed tomography revealed multiple bilateral lung lesions. The histological diagnosis of the biopsy specimens obtained from the pulmonary nodules revealed a mucinous adenocarcinoma (Figure **4**). Immunohistochemically, the tumor cells were positive for CK-7 (Figure **4B**) and negative for CK20 and Thyroid Transcription Factor-1 (Figure **4C**). Based on the pathological diagnosis, chemo-immunotherapy was initiated for the treatment of non-small cell lung cancer (NSCLC). After 4 cycles of cisplatin/pemetrexed therapy combined with pembrolizumab, the size of her lung tumors decreased; however, re-exacerbation eventually occurred. The patient then underwent a gene panel test (GenMineTop; KONICA MINOLTA) to determine the course of treatment, which revealed a germline *STK11* pathogenic variant.

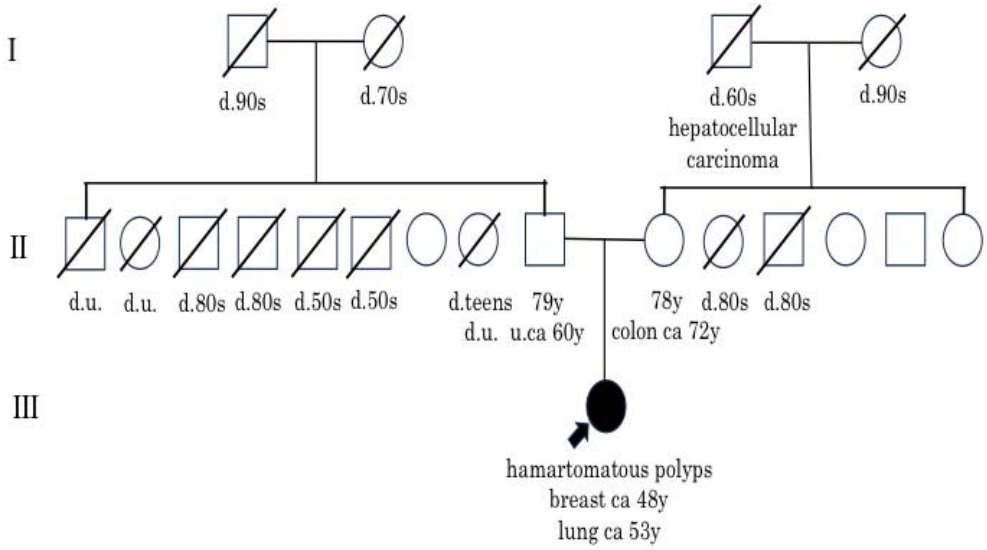


Figure 3: Detailed family pedigree.

d.: died, d.u.: details unknown, u.ca: urothelial carcinoma.

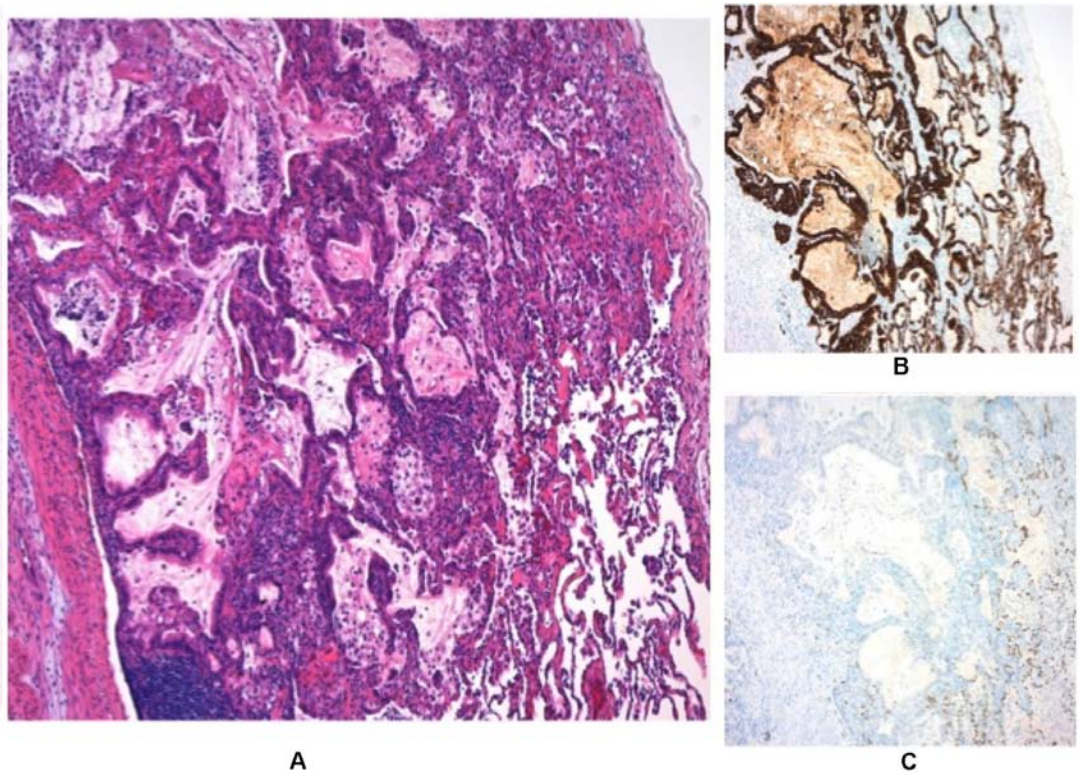


Figure 4: Microscopic findings of lung biopsy showed mucinous adenocarcinoma, which differs from the pathological findings of breast cancer.

A. Hematoxylin-eosin staining (HE) x40.

B. Immunostaining with CK-7 x40.

C. Immunostaining with Thyroid Transcription Factor-1 x40.

DISCUSSION

The estimated incidence of PJS ranges from 1: 50,000 to 1: 200,000 births with no sex or racial predilection [6]. Patients with PJS have a 15- to 18-fold increased risk of malignancy compared to the general population [7]. Among the various cancer types, gastrointestinal and breast cancers are the most

common in Western countries. The risk of gastrointestinal cancer is estimated to be 15% by the age of 50 years and 57% by the age of 70 years. In women with PJS, the risk of breast cancer is estimated to be 8% at 40 years of age and 31% at 60 years of age. In contrast, among female Japanese and Chinese patients with PJS, the incidence of gynecological cancers is higher than that of breast cancer [8, 9].

Lung cancer is included in the tumor spectrum associated with PJS but is relatively uncommon. By the age of 60 years, the risk of lung cancer diagnosis is estimated at 13% for men and 1% for women with PJS [6]. There are several case reports of patients with PJS who developed lung cancer [10-15]. Due to the rarity of lung cancer among the patients with PJS, pulmonary lesions in this population are usually discovered incidentally or when performed during a metastatic work-up. Most of these patients were already in advanced stage lung cancer at the time of diagnosis and their prognosis was very poor. Because PJS should be regarded as a general cancer predisposition syndrome, surveillance program is needed to decrease the morbidity and mortality. Lung cancer has been known to be a tumor type mostly associated with environmental factors such as tobacco smoking [16]. In addition to the establishment of cancer surveillance guidelines, the individuals with PJS should be encouraged to lead as healthy lifestyle as possible; to avoid tabacco use, limit exposure to tabacco smoke, and avoid excess sun exposure. This patient was a never-smoker; however, had a history of receiving anticancer agents as postoperative adjuvant therapy for breast cancer.

Germline pathogenic *STK11* variants were first identified as causal mutations in PJS [17]. Most germline *STK11* mutations result in truncation of the protein, leading to its dysfunction; thus, the *STK11* gene, also known as *LKB1* gene, has been considered to act as a tumor suppressor in PJS. The *STK11* gene is implicated in the regulation of multiple biological processes, including cell cycle arrest, p53-mediated apoptosis, and induction of cell polarity [18]. Genetic alterations of *STK11* in patients with lung cancer are commonly detected in males and smokers, indicating a correlation between the occurrence of genetic alterations and tobacco exposure [18]. Some cases with a *KRAS* mutation, which is considered to be also relevant to smoking, were reported to carry *STK11* genetic alterations. Lung cancer patients with coexistence of *STK11* genetic alterations and *KRAS* mutations have significantly shorter overall survival, when compared to patients having *KRAS* mutations only [15, 19]. Our case has somatic *KRAS* mutations along with a germline *STK11* pathogenic variant. On the other hand, there were no tumors carrying both *STK11* genetic alterations and *EGFR* mutations. *EGFR* mutations occur frequently in NSCLC of females and nonsmokers and lung cancers with *STK11* genetic alterations are likely to be a different subset from those with *EGFR* mutations. It might be correlated with the findings that lung cancer with a germline *STK11* pathogenic variant is less common in women. In patients with NSCLC who received immunotherapy combined with chemotherapy, the presence of *STK11* pathogenic variants has been associated with worse clinical outcomes in terms of survival and response rates [20].

Multiple primaries were defined as the presence of more than one synchronous or metachronous cancer in the same individual [21]. The prevalence of multiple primary cancers among patients will increase based on a combination of factors such as diagnosis, treatment, and demographics. Cancer survivors may be susceptible to developing secondary primary malignancies due to various factors, including environmental exposure, late effects of chemotherapy, or cancer predisposition syndromes [22]. Epidemiological studies have reported the frequency of multiple primaries to be the range 2-17%. In patients with breast cancer, the incidence of multiple primaries has been reported in the range of 4.1% to 16.4%. The median time to a second malignancy was 5-8 years. Certain patient populations are at a higher risk of developing multiple primaries, including patients with a history of smoking or alcoholism, and those with hereditary cancer syndromes such as Li-Fraumeni syndrome, hereditary breast and ovarian cancer syndrome, and PJS. Hearle *et al*. reported that among 419 patients with PJS, 96 malignancies were detected (gastrointestinal cancer, 40; breast cancer, 17; pancreatic cancer, 11; gynecologic cancer, 9; and lung cancer, 8) and 11 individuals developed second primary cancers [5]. Among 583 Japanese patients with PJS, 186 malignancies were found (gastrointestinal cancer, 40; breast cancer, 17; pancreatic cancer, 11; gynecologic cancer, 9; lung cancer, 8), and 25 patients developed multiple cancers [8]. The Surveillance Epidemiology and End Results (SEER) recommends a two-month period to distinguish between synchronous and metachronous multiple primaries.

In conclusion, we encountered the case of a middle-aged woman with germline *STK11* pathogenic variants who had a history of curative resection of breast cancer and then developed lung cancer 5 years later. PJS is a rare genetic disorder characterized by the development of gastrointestinal polyps, mucocutaneous pigmentation, and an increased risk of various type of cancer. Given the proper management measures, we can reduce the chance of cancer development and improve the prognosis. Surveillance for breast cancer includes monthly self-examinations starting at 18 years of age, semi-annual clinical evaluation, and the annual mammography beginning at 25years of age, as strongly recommended by NCCN; however, no definite guidelines exist to manage this population. Since the prevalence of lung cancer is much smaller than that of breast cancer, surveillance protocols for lung cancer are not yet established for patients with PJS.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHOR CONTRIBUTIONS

KI and YK contributed to the study conception and design. MM, TK, KE, and TF provided medical care. KI and MM drafted the manuscript. MM and TN interpreted radiological and pathological findings. All the authors have read and approved the final version of the manuscript.

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