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Small intestine adenocarcinoma associated with Peutz-Jeghers syndrome: a report of 5 cases and literature review

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Abstract Peutz-Jeghers syndrome (PJS) is a rare autosomal dominant inherited disorder, manifested as multiple hamartomatous polyps of gastrointestinal tract, mucocutaneous pigmentations and increased risk of cancers. In this manuscript, we reported five cases of small intestinal carcinoma associated with the PJS. All the five patients have a history of PJS and postoperative pathological examination confirmed the diagnosis of small intestinal carcinoma. Histopathological features and recommended surveillance were additionally discussed.

Key words small intestine adenocarcinoma; Peutz-Jeghers syndrome (PJS); histopathology; clinical surveillance

Peutz-Jeghers syndrome (PJS) is an autosomal dominant inherited syndrome characterized by mucocutaneous pigmentation and gastrointestinal hamartomatous polyps. Considerable evidence has indicated that PJS is a cancer-susceptibility syndrome, which is associated with a substantial risk for the development of gastrointestinal carcinomas and extraintestinal malignancies [1, 2]. Primary small intestinal carcinoma is a relative rare disease and usually of unknown cause. In this manuscript, we report five cases of PJS in which small intestinal carcinomas were developed, with emphasis on histopathological features and recommended surveillance.

Clinical data

From January 2008 to March 2014, a total of 170 patients were diagnosed as PJS in our hospital (General Hospital of Air Force, PLA, China), among which five cases were found with small intestinal carcinoma. The clinical features were summarized in Table 1. Three of the five cases underwent intestinal segment resection and the other two cases received exploratory laparotomy. Postoperative pathological examination confirmed the diagnosis of adenocarcinoma in all five patients.

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Typical case 1

Case 1 was a 21-year-old male patient with PJS who had no family history. He was admitted to our hospital for melena and upper abdominal pain of half month duration. Physical examination revealed mucocutaneous pigmentation over the lips, buccal mucosa and fingers. The serum levels of CA19-9 and CA125 were evaluated as > 300 U/mL (normal 0–30 U/mL) and 192.05 U/L (normal 0–35 U/mL), respectively. Peroral enteroscopy revealed multiple polyps in the duodenum and proximal jejunum, among which some of the polyps showed surface erosion and active bleeding. Pathological examination using biopsy specimens confirmed hamartomatous polyps but no carcinoma or atypical hyperplasia was found. Intestinal segment resection was performed in this patient. During surgery, metastases to abdominal cavity were observed. Postoperative pathological results revealed the adenocarcinoma in a hamartomatous polyp located at the horizontal part of duodenum (Fig. 1). For economic reason, the patient refused further treatment and died two months later.

Typical case 2

Case 2 was a 42-year-old male patient with a family history of PJS. He was first admitted to our hospital in 2006 for abdominal pain. Before that, he had undergone twice segmental intestinal resection for small intestinal invagination. Since 2006, he received three rounds of

Table 1 Clinical features of the five cases

Case No.	1	2	3	4	5
Gender	Male	Male	Male	Male	Female
Age (years)	21	42	27	49	39
Family history	No	Yes	Yes	No	No
Symptom	Melena and upper abdominal pain	None	None	Abdominal pain	Abdominal pain
Serum tumor markers	CA19-9↑, CA125↑	Normal	Normal	CA125↑	Normal
Tumor site	Horizontal part of duodenum	Descending part of duodenum	Proximal jejunum	Horizontal part of duodenum	Descending part of duodenum
Pathological results	Mucinous adenocarcinoma	Mucinous adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Mucinous adenocarcinoma
Metastasis	Abdominal cavity	None	Liver	Abdominal cavity	None
Treatment	Intestinal segment resection	Intestinal segment resection	Exploratory laparotomy	Exploratory laparotomy	Intestinal segment resection
Recurrence	–	none	–	–	yes
Follow-up	2 months	12 months (still under follow-up)	5 months	3 months	23 months

endoscopic polypectomy including by enteroscopy, per 2–3 years. At 2013, in the third round of endoscopic polypectomy, a huge polyp with diameter about 4 cm was observed near the duodenal papilla. Considering the high possible of papillary damage associated with polypectomy, this patient was transferred to department of hepatobiliary surgery and received intestinal segment resection. Postoperative pathological examination revealed that this polyp had developed a focal invasive adenocarcinoma (Fig. 2).

Discussion

PJS is the first cancer-susceptibility syndrome to be identified that is due to inactivating mutations in protein kinase STK11 (serine/threonine kinase 11, also called LKB1) [3, 4]. Although the mechanism of carcinogenesis remains further debatable, PJS patients carry a considerably increased risk for the development of both gastrointestinal and extra-gastrointestinal malignancies. According to the reports of Giardiello and van Lier *et al* individuals with PJS have a lifetime risk of developing cancers as high as 37% to 93%, with relative risks up to 4.8 to 18 compared to the general population [5, 6].

The most common cancers appeared in PJS patients were gastrointestinal in origin. As developmental anomalies, hamartomatous polyps in PJS are benign; however, occasional neoplastic change may occur. Examples of adenocarcinomas arising in the hamartomatous polyps in patients with PJS have been described several times [7, 8]. However, some researchers suggested that the carcinomas in PJS patients may arise from coincidental adenomatous polyps. Other researchers suggested the existence of a hamartoma-adenoma-carcinoma sequence, similar to the adenoma-carcinoma sequence in sporadic colorectal cancer [9]. In the past years, near 1000 resected PJ polyps were performed histopathological examination in our hospital, but very few adenomatous changes could be observed in the hamartomatous polyps. In the five reported cases of PJS patients who had developed adenocarcinomas, also no adenomatous changes could be observed in the resected tissues, indicating that adenoma may not be the necessary stage for the carcinogenesis of PJ polyp.

Because the cancer risks in PJS patients are very high and come close to other high-risk conditions such as breast cancer mutation for breast cancer, surveillance has been recommended [10]. Van Lier MG *et al* proposed a surveillance strategy which recommends small intestinal surveillance starting at a young age [5]. Video capsule endoscopy and/or MRI-enteroclysis are suggested for PJS patients from the age of 10 per 2–3 years. For the polyps > 1 cm in diameter, enteroscopy with polypectomy is indicated. The age of the two patients presented here is 21 and 42 years old, respectively. The 21-year old patient was newly diagnosed as PJS when he was admitted in our hospital for melena and upper abdominal pain. Unfortunately, he was found already having carcinoma and metastasis to abdominal cavity during surgery and died soon after. The 42-years old patient has been diagnosed as PJS for over twenty years and has undergone surgery and enteroscopy with polypectomy several times. At this time, both surgery and enteroscopic polypectomy were performed and postoperative pathological examination revealed the malignant alteration of a hamartomatous polyp. At present, this patient is still under follow up, with no signs of recurrence and metastasis. In the remaining three cases, surgery and enteroscopic polypectomy for these hamartomatous polyps were also previous performed. However, the time intervals are all over five

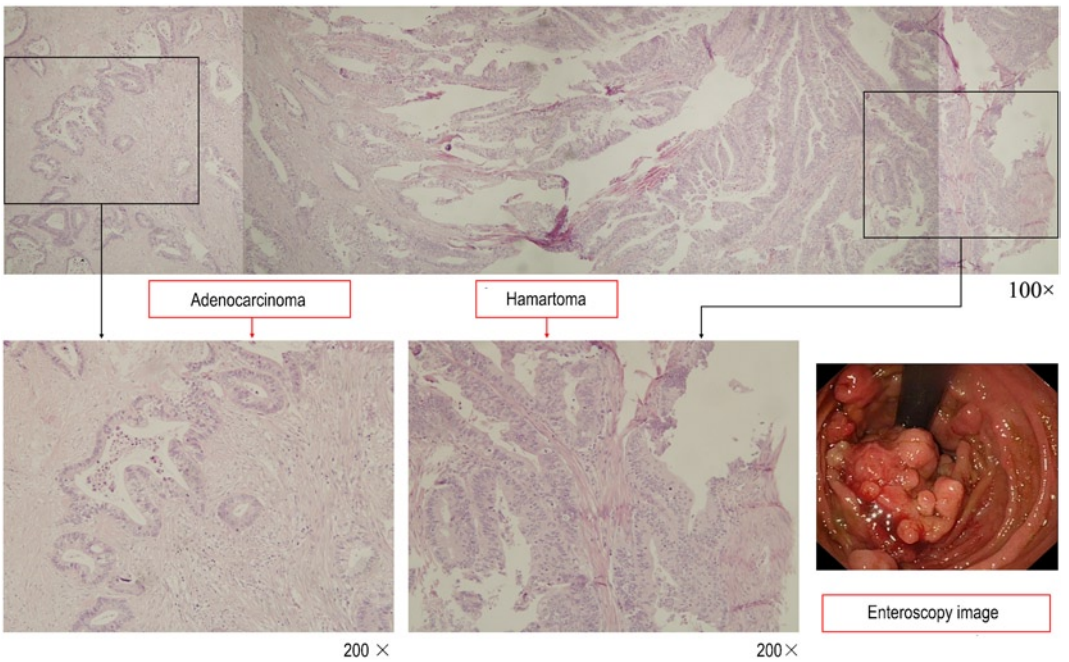

Fig. 1 Case 1. The duodenal tumor was a middle-differentiated invasive adenocarcinoma, partly mucinous. Hamartomatous structure (branching bundles of smooth muscle fibers covered by hyperplastic duodenal mucosa) could be observed in adjacent tissue. Enteroscopy showed surface erosion and active bleeding in the hamartomatous polyp

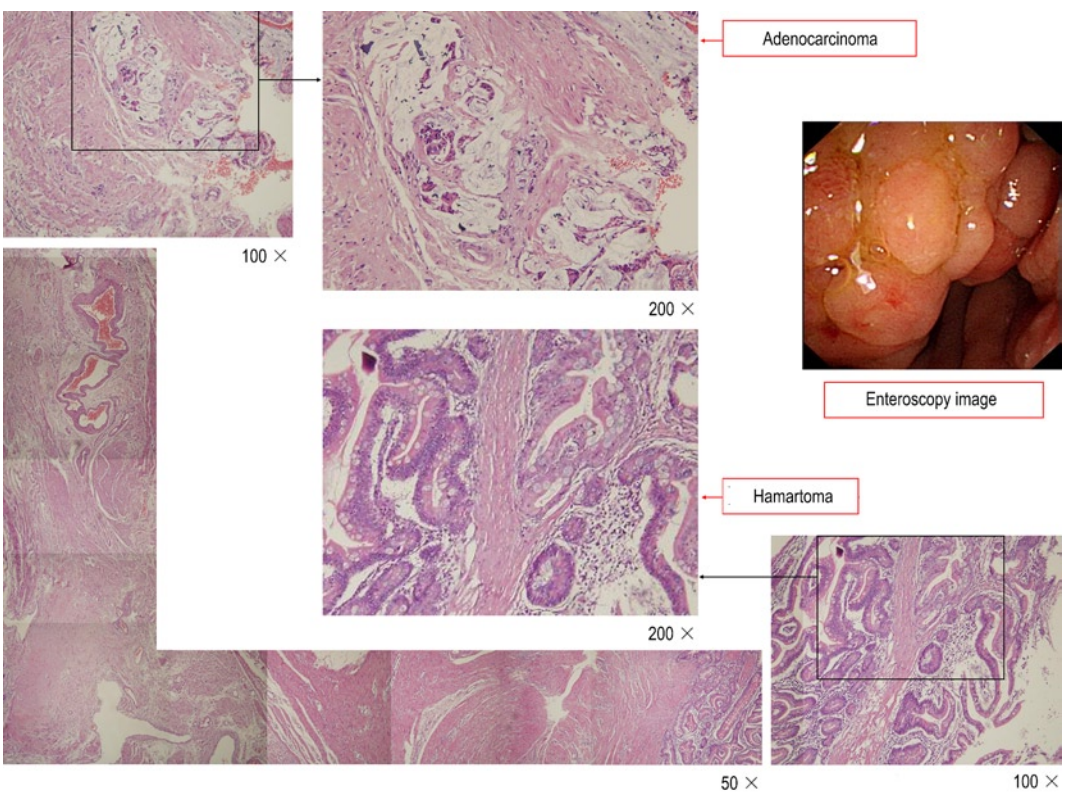

Fig. 2 Case 2. One focal mucinous adenocarcinoma was discovered within the smooth muscle tissue of the resected hamartomatous polyp. Enteroscopic view showed no obvious surface erosion in this polyp

years before the diagnosis of carcinoma, suggesting the value of removing the hamartomatous polyps in a relative short time interval such as per 2–3 years.

In conclusion, this manuscript presented five cases of PJS patients who had developed small intestine adenocarcinoma, and analyzed the histopathological features. In addition, based on our observation, it is suggested that polyp removal per 2–3 years may be of important value for the prevention of neoplastic transformation of these hamartomatous polyps.

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