Case report

Duodenal cancer in a patient with Peutz-Jeghers syndrome: molecular analysis

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We experienced an unusual case of duodenal adenocarcinoma associated with Peutz-Jeghers syndrome (PJS). A 34-year-old woman was admitted to our hospital with abdominal pain. She had been diagnosed as having PJS at 21 years of age, based on the presence of mucocutaneous pigmentation of the lip and fingertips, and colonic hamartomatous polyps. Abdominal computed tomography revealed a tumor in the third portion of the duodenum extending into the pancreas head. As the tumor was pathologically determined to be adenocarcinoma at the time of surgery, pylorus-preserving pancreaticoduodenectomy was performed. We carried out molecular analyses of this patient to examine the pathway of carcinogenesis in PJS. The tumor did not show somatic mutation of the APC and K-ras genes, which is a critical step for the adenoma-carcinoma sequence in colon cancer. Importantly, a germline mutation of the STK11 gene was detected at codon 281 delC in exon 6. Moreover, the tumor showed loss of heterozygosity of the 19p marker near STK11 and somatic mutation of the p53 gene. These findings suggest that STK11 is a tumor suppressor gene regulating the development of hamartomas, and that somatic mutation of p53 subsequently promotes gastrointestinal cancer at a later stage in PJS.

Key words: Peutz-Jeghers syndrome, duodenal cancer, STK11

Introduction

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disorder characterized by intestinal hamartomas and melanin pigmentation of the mucocutaneous membrane. This syndrome occurs in approximately 1 in 8300 to 29000 births. Although it was believed that polyps associated with PJS did not have malignant potential, recent studies have revealed that, with this disease, there is an increased risk of the development of carcinoma, including carcinoma of the gastrointestinal tract. Indeed, the relative risk of cancer occurrence in PJS is 18 times as high as that in the general population, and adenocarcinoma has occasionally been identified in hamartomatous polyps in this syndrome.

Hemminki et al., using comparative genomic hybridization to conduct target linkage analysis, have identified a susceptible locus for PJS on 19p13.3. In addition, recent studies have focused on the role of the serine/threonine kinase gene (STK11) in carcinogenesis in various kinds of gastrointestinal tract cancers. However, the actual role of this gene in the pathogenesis of cancer in PJS has not been fully defined. We report here our experience with the occurrence of duodenal cancer in a patient with PJS. Employing molecular analysis of cancer genes, including STK11, we attempted to clarify the pathway of carcinogenesis in PJS.

Case report

A 34-year-old woman with PJS was admitted to our hospital with abdominal pain on November 10, 1998. A tumor in the epigastric region was revealed by abdominal ultrasonography. She had been diagnosed as having PJS at 21 years of age, based on the presence of mucocutaneous pigmentation of the lip and fingertips, and the presence of colonic hamartomatous polyps. Her parents and brother did not have any signs or symptoms relevant to PJS. Abdominal computed tomography showed a tumor in the third portion of the duodenum, invading the pancreas (Fig. 1). Laparotomy was per-
formed on February 3, 1999, with a diagnosis of duodenal malignant tumor. Pylorus-preserving pancreatoduodenectomy was performed, and histopathological examination revealed that the tumor was a well differentiated adenocarcinoma (Fig. 2a,b) arising from the duodenum, with direct invasion to the pancreas. The polypoid portion of the tumor showed a tree-like branching of smooth muscle, which is a characteristic feature of the hamartomatous polyp of Peutz-Jeghers syndrome PJS, and was covered by well differentiated adenocarcinoma cells and, in part, by non-neoplastic intestinal epithelial cells (Fig. 2a,c). At the edge of the tumor, in the portion other than the polypoid portion, intramucosal extension of the carcinoma was rarely observed. It seemed, therefore, that the polypoid lesion did not exhibit incidental de-novo cancer, but that the adenocarcinoma had developed directly from a hamartoma. The postoperative

Fig. 1. Abdominal computed tomography shows duodenal tumor invading the pancreatic head

Fig. 2a–d. Adenocarcinoma arising from a hamartomatous polyp of the duodenum. a the polypoid portion of the tumor shows a branching pattern, which is characteristic of hamartomatous polyp of Peutz-Jeghers syndrome PJS; upper left. Invasion of carcinoma cells is evident in the submucosa and muscularis propria (lower middle-right). b the invasive carcinoma consists of well differentiated components. c The polypoid portion is composed of well differentiated adenocarcinoma cells (left and upper right) and nonneoplastic intestinal epithelial cells (lower middle-right). d Immunostaining of the p53 gene product. The nuclei of the tumor cells stained diffusely with anti-p53 protein with an immuno-peroxidase polymer. a, H&E, ×10; b, H&E, ×50; c, H&E, ×50; d, Immunostaining, ×50