Peutz-Jeghers syndrome with small intestinal malignancy and cervical carcinoma

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Author contributions: Wu BP performed the endoscopic examination and the polypectomy; Li LJ and Wang ZQ collected the data; Li LJ wrote the paper.

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Received: October 5, 2008 Revised: November 23, 2008 Accepted: November 30, 2008 Published online: December 28, 2008

Abstract

We report a case of a 30-year-old woman with Peutz-Jeghers syndrome (PJS). Because of small intestinal obstruction, she received the small intestinal polypectomy in 2001, and the pathological diagnosis was Peutz-Jeghers polyp canceration (mucinous adenocarcinoma, infiltrating full-thickness of the intestine). The patient did not feel uncomfortable after 6 mo of chemotherapy and other management. We kept a follow-up study on her and found that she suffered from cervical cancer in 2007, with a pathological diagnosis of cervical adenosquamous carcinoma. The patient presented with typical features of PJS, but without a family history. The PJS accompanied with both small intestinal and cervical malignancies has not been reported so far in the world.

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Key words: Peutz-Jeghers syndrome; Polypectomy; Small intestine malignancy; Cervix cancer; Multiple organ neoplasms

Peer reviewer: Francis Seow-Choen, Professor, Seow-Choen Colorectal Centre, Mt Elizabeth Medical Centre, Singapore, 3 Mt Elizabeth Medical Centre #09-10, 228510, Singapore

LI LJ, Wang ZQ, Wu BP. Peutz-Jeghers syndrome with small intestinal malignancy and cervical carcinoma. World J Gastroenterol 2008; 14(48): 7397-7399 Available from: URL: http://www.wjgnet.com/1007-9327/14/7397.asp DOI: http://dx.doi.org/10.3748/wjg.14.7397

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is an autosomal dominant disease characterized by hamartomatous polyps in the gastrointestinal tract and mucocutaneous melanin pigmentation. Patients with PJS are at increased risk for common and unusual types of gastrointestinal and extra-gastrointestinal tumors. This report describes the clinicopathological characteristics of PJS complicating multiple organ neoplasms. It provides evidence not only for the risk of malignancy in this disorder, but also for a hamartoma-adenoma-carcinoma sequence.

CASE REPORT

We report here a case of a 30-year old woman who suffered from multiple organ neoplasms with PJS. The melanin pigmentation around lips appeared when she was 3 mo old, after that, melanin pigmentation increased and also appeared on the palm and planta. She presented with iterative abdominal pain and vomit in 1997, and was found having multiple polyps in colon by colonoscopy. Most of the polyps were resected several times, but the symptoms still existed.

The patient presented to us in April 2001. Physical examination revealed the pigmentation on the oral lips, the buccal mucosa (Figure 1A), and the hands and feet (Figure 1B), about 1-3 mm in diameter. Endoscopy and gastrointestinal tract contrast examination revealed multiple polyps in sinus ventriculi, small intestine and colon. Most of the polyps were resected and demonstrated hamartomatous polyps, some of which showed adenomatous changes (Figure 2A), and the one in small intestine revealed carcinomatous changes (mucinous adenocarcinoma, infiltrating full-thickness of the intestine) (Figure 2B). The patient received FOLFOX4 chemotherapy after surgery. Tumor markers and routine blood tests were mainly normal during the treatment. The patient gradually recovered, then we kept follow-up visit on her.

In November 2007, the patient complained of abnormal vaginal discharge for 2 mo, without vaginal
bleeding and abdominal pain. Gynecological B-mode ultrasonography found occupying lesion located between inferior segment of cervix and vagina. Gynecologic examination revealed thick cervix, and cervical scraping smear confirmed cervical adenocarcinoma. After neoadjuvant chemotherapy (Paclitaxel 120 mg/dL, Carboplatin 350 mg/dL, one day per wk for 6 wk), total hysterectomy was performed in February 2008. Final pathological diagnosis was cervical adenosquamous carcinoma (Figure 3), and cancerometastasis of lymph nodes in left external iliac (1/1). The patient also received pelvic radiotherapy after surgery (50 GY in total).

The tumor markers (CA125, CA19-9, CEA) were normal when the patient paid a return visit in May 2008. She was found to have multiple polyps in her stomach, terminal ileum and sigmoid colon by endoscopy (Figure 4), polyps were resected and pathology still confirmed hamartomatous polyps. In addition, none of her lineal relations has the symptoms and physical signs of PJS, and no tumor patient was found in her family history.

DISCUSSION

PJS patients have an increased risk for several malignancies including small intestine, stomach, pancreas, colon, esophagus, ovary, uterus, lung, and breast cancer. PJS is associated with a markedly increased risk of malignancy that is not confined to the gastrointestinal tract. A metaanalysis found that,
compared with the general population, patients with PJS have a relative risk (RR) of 15 times higher than for developing many kinds of cancer. And the cumulative risk for all cancers was 93% from age 15 to 64. Very high RR's for the development of cancer were observed in the small intestine (520), stomach (213), pancreas (132), colon (84) and esophagus (57), and RR's are greater than 10 for the development of breast, lung and ovarian cancer. Several gonadal malignancies occur in PJS patients. In female patients, sex cord tumors with annular tubes (SCTAT) are found in the ovaries of many individuals examined. Patients with these tumors can present with menoxenia, hyperestrogenism or sexual precocity. Minimal deviation of cervical adenocarcinoma has been reported in PJS patients. Presenting symptoms include abnormal vaginal bleeding or a mucoid vaginal discharge. It is an extremely well differentiated adenocarcinoma of the cervix. It usually shows poor malignant behavior and poor prognosis with mucinous type of adenocarcinoma.

\textit{STK11/LKB1} was identified strongly relative to the PJS, which is a tumor-suppressor involved in intracellular signal transduction and cellular polarity. Some studies provided molecular evidences of a hamartoma-adenoma-carcinoma sequence in PJS. The second hit in \textit{LKB1} causing loss of heterozygosity (LOH) in adenomatous and carcinomatous lesions in PJS polyps was noted by several investigators. In addition, LOH of \textit{p53}, \textit{K-Ras} and \textit{beta-catenin} mutations were found in adenomas developing in hamartomatous polyps, indicating that molecular alterations in these genes drive carcinogenesis in PJS as well. However, the precise frequency of LOH of \textit{LKB1} in PJS polyps in human remains unclear, and studies in mice showed that loss of the wild-type \textit{LKB1} allele is not a prerequisite for the formation of hamartomatous polyps. Therefore, the need for the second-hit in \textit{LKB1} during polyp development in PJS, and the role of \textit{LKB1} as a typical ‘Knudson’ two-hit tumor-suppressor gene, is questioned. One theory suggests mucosal prolapse as a pathogenic mechanism underlying the development of typical hamartomatous polyps in PJS. In this hypothesis, PJS hamartomatous polyps represent an epiphenomenon to the cancer-prone condition and the hamartoma-adenoma-carcinoma sequence as such does not exist. The important role of \textit{LKB1} in cellular polarity may provide new insights into the molecular mechanism of polyp and carcinoma development in PJS. Loss of polarity function may also affect asymmetric stem cell division in PJS and lead to expansion of the stem cell pool. It could contribute to polyp formation and explain the increased cancer risk as well. A recent study found \textit{STK11}-deficient mesenchymal cells produced less TGF-\(\beta\), and defective TGF-\(\beta\) signaling to epithelial cells coincided with epithelial proliferation. TGF-\(\beta\) signaling defects in polyps of individuals with PJS, suggesting that the identified stromal-derived mechanism of tumor suppression is also relevant to PJS.

We report the unique case of a patient with the Peutz-Jeghers syndrome who developed intestinal malignancy and cervical cancer in 7 years. As far as we know, no similar case has been reported to date. The pathological changes of polyps would support the development of hamartoma-adenoma-carcinoma; and the carcinomatous change of cervix would add the risk of extra-gastrointestinal tumors in this disorder. However, the pathogenetic mechanism of these changes is still unknown. It should be studied progressively on whether germline mutation of \textit{STK11/LKB1} exists or other factors participate in the process of malignant changes. We also suggest that the patient and her family members should be followed up with endoscopy.

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S-Editor Tian L  L-Editor Ma JY  E-Editor Zheng XM