Neoplastic Transformation Arising in Peutz-Jeghers Polyposis

Kazuoki Hizawa, M.D.,* Mitsuo Iida, M.D.,* Takayuki Matsumoto, M.D.,* Norio Kohrogi, M.D.,* Takashi Yao, M.D.,† Masatoshi Fujishima, M.D.*

*From the * Second Department of Internal Medicine and the † Second Department of Pathology, Faculty of Medicine, Kyushu University, Fukuoka, Japan*

PURPOSE AND METHODS: To clarify the potential for malignancy of Peutz-Jeghers polyposis, we investigated 75 gastrointestinal polyps resected surgically or endoscopically from seven patients with this syndrome. RESULTS: There were 19 polyps in the stomach, 18 in the duodenum, 22 in the small intestine, and 16 in the large intestine, and these were histologically composed of 1 pyogenic granuloma, 1 cancer in adenoma, 2 adenomas, and 71 Peutz-Jeghers polyps. Nine of these Peutz-Jeghers polyps were accompanied by an adenomatous component, and, in addition, two of these showed a cancerous transformation with stalk invasion. A total of 12 neoplastic polyps (16 percent) were found in three relatively young patients (aged 20, 25, and 43 years), all of which were pedunculated and located either in the duodenum or in the jejunum. There was no statistical significance in size between the neoplastic polyps (mean ± SD, 20.1 ± 10.8 mm) and the completely hamartomatous polyps (mean ± SD, 15.8 ± 9.0 mm). Moreover, the configuration of these types of polyps seemed similar. CONCLUSION: Neoplastic transformation is not a rare event, and our results may indicate evidence of a hamartoma-adenoma-carcinoma sequence in Peutz-Jeghers polyposis. [Key words: Peutz-Jeghers syndrome; Hamartomatous polyp; Cancer]

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Peutz-Jeghers syndrome has been recognized as manifesting mucocutaneous pigmentations and gastrointestinal hamartomatous polyps,[1,2] characterized by cores of smooth muscle fibers in a tree-like pattern with hyperplasia of the epithelium.[3] Hamartoma in itself is considered to be a disturbance of superfluous tissue, not a malignancy, however, it has been recently reported that more than 10 percent of the patients with Peutz-Jeghers syndrome were found to later develop gastrointestinal cancer during the long periods of follow-up studies.[4–7] To clarify whether Peutz-Jeghers polyposis has the potenial to bring about the development of gastrointestinal cancer, we investigated 75 polyps resected surgically or endoscopically from seven patients with syndrome.

Address reprint requests to Dr. Hizawa: Second Department of Internal Medicine, Faculty of Medicine, Kyushu University, Maidashi 3–1–1, Fukuoka 812, Japan.

MATERIALS AND METHODS

Between March 1976 and January 1992, seven patients were diagnosed as suffering from Peutz-Jeghers syndrome at our institute. The diagnosis was based upon a demonstration of polyposis of the gastrointestinal tract by endoscopy and radiography and by confirmation of the histologic characteristics of Peutz-Jeghers polyps. There were four males and three females, and the ages of the patients at the time of diagnosis ranged from 17 to 60 (mean ± SD, 31.1 ± 15.3) years. All of the patients manifested mucocutaneous pigmentations in the lip, buccal mucosa, and extremities, which were compatible with the diagnosis. A family history of gastrointestinal polyposis was confirmed in six of the seven patients.

Gastric, duodenal, and colonic polyps in these patients, which were indicative of endoscopic polypectomy, were excised endoscopically using an electrocautery snare. In patients with multiple and large pedunculated polyps in the small intestine demonstrated by preceding small bowel radiology, the polyps were removed under intraoperative endoscopy. One submucosal tumor and two large sessile polyps in the ileum were resected surgically. In addition, four small polyps in a segment of the small intestine in one patient, which was removed because of adhesive ileus, were also included in this study.

The sizes of the resected polyps were measured after they were fixed in formalin for two days. Histologic findings in the resected polyps obtained after hematoxylin and eosin staining were carefully reviewed by a pathologist. When any neoplastic changes were observed microscopically, they were classified according to the criteria described by Morson *et al.*[8]

We reviewed the location, gross configuration, and size of the polyps, and compared them with the histologic findings. Wilcoxon's rank-sum test and Fisher's exact probability test were used for

statistical analysis. A probability of <0.05 was considered significant.

RESULTS

A total of 75 polyps were removed from the patients, and these were fully investigated. All of the polyps were pedunculated or semipedunculated, except for one submucosal tumor in the ileum in a 26-year-old female patient.

Table 1 summarizes the histologic diagnosis of the polyps. Seventy-one of the 75 polyps were consistent with the histologic features of Peutz-Jeghers polyps, characterized by cores of smooth muscle fibers in a tree-like pattern with hyperplasia of the epithelium. Of the 71 Peutz-Jeghers polyps, 9 were accompanied by an adenomatous component. In addition, in two of these nine polyps, definite foci of well-differentiated adenocarcinoma were further confirmed. Three of the remaining four polyps, one of which showed evidence of a cancerous area, were adenomas conserving the branching structure of smooth muscle. The remaining one submucosal tumor was histologically diagnosed as a pyogenic granuloma.

In the nine Peutz-Jeghers polyps with adenoma, the adenomatous involvement varied from tiny spots (Fig. 1) to a massive area. Cancerous transformation was observed in the surface of the two Peutz-Jeghers polyps which were surrounded with an adenomatous component (Fig. 2), and adenoma in one (Fig. 3). Furthermore, in two of the polyps, the carcinoma invaded the stalk with additional venous invasion (Fig. 4). Pseudoinvasion[9,10] of the hamartoma through the subserosa without any atypia was observed in 3 of the 22 Peutz-Jeghers polyps in the small intestine.

Table 1.
Histologic Classification of 75 Polyps Resected from Patients with Peutz-Jeghers Syndrome

Histologic Findings	Number (%)
Peutz-Jeghers polyp	71 (95)
Pure Peutz-Jeghers polyp	62 (83)
With adenoma	7 (9)
With carcinoma in adenoma	2 (3)
Adenoma	2 (3)
Carcinoma in adenoma	1 (1)
Pyogenic granuloma	1 (1)

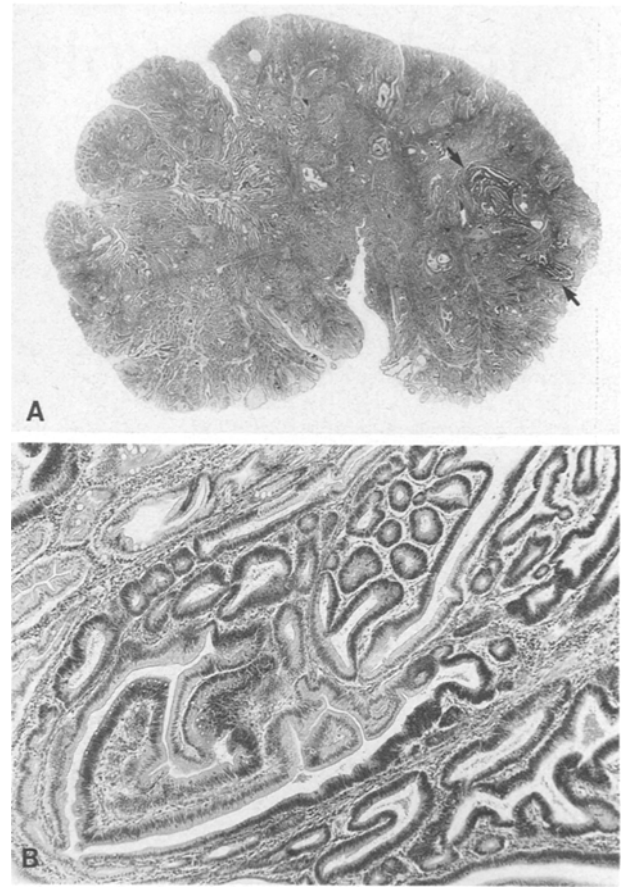

Figure 1. A. Low-power view of the jejunal polyp that demonstrates distinguished branching of the smooth muscle consistent with the features of Peutz-Jeghers polyp. A small focus of neoplastic glands (arrows) is also present (hematoxylin & eosin; original magnification ×6.5). B. High-power view of the neoplastic glands reveals tubular adenoma with moderate atypia (hematoxylin & eosin; original magnification ×96).

There was a total of 12 neoplastic polyps, all of which were pedunculated and located in the duodenum or jejunum in three patients (aged 20, 25, and 43 years). Table 2 indicates the correlation between the incidence of neoplastic polyps in all of the polyps and the location or the size of the polyps. Neoplastic polyps were more frequently found in the duodenum than in other sites of the gastrointestinal tract. Although there were no neoplastic polyps less than 10 mm, the incidence of neoplastic polyps more than 10 mm was 23 percent while for polyps more than 20 mm, it was 17 percent. However, there was no significant difference in size between the neoplastic polyps (mean ± SD, 20.1 ± 10.8 mm) and the completely hamartomatous polyps (mean ± SD, 15.8 ± 9.0 mm).

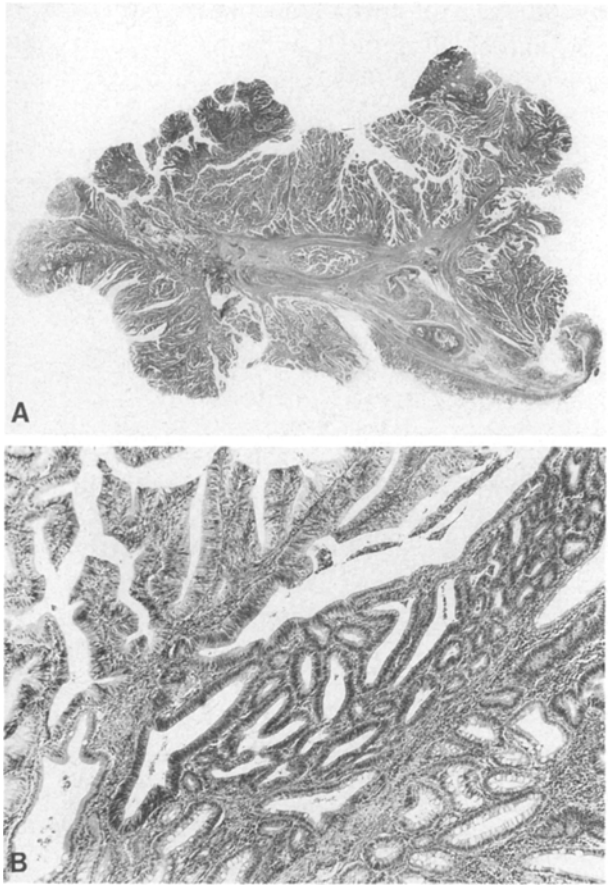

Figure 2. A. Low-power view of the duodenal polyp shows a massive neoplastic area in Peutz-Jeghers polyp ((hematoxylin & eosin; original magnification ×5). B. Cancerous, adenomatous, and non-neoplastic components are simultaneously recognized in the left, middle, and right corner of the photomicrograph, respectively ((hematoxylin & eosin; original magnification x96).

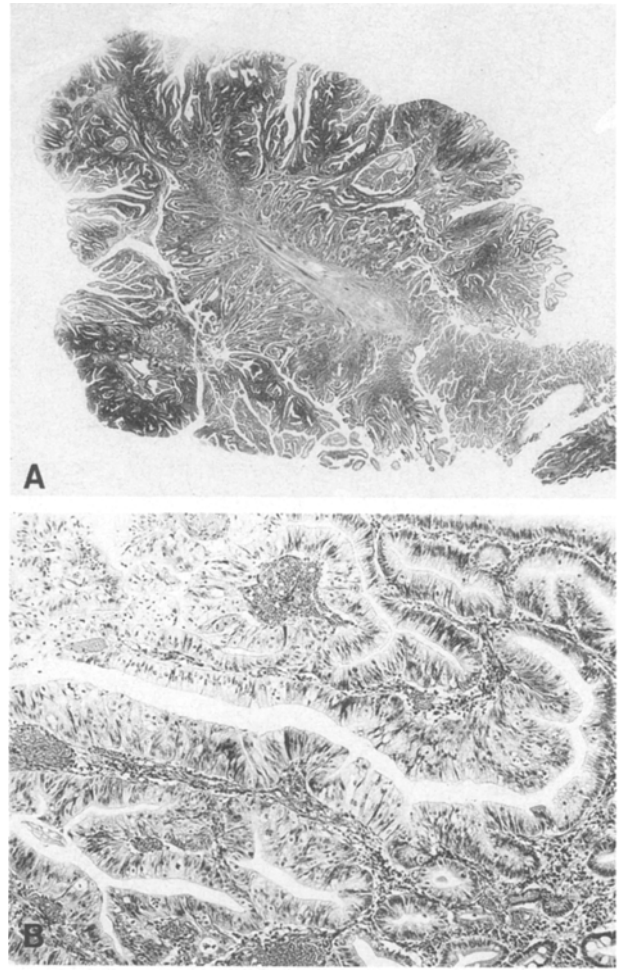

Figure 3. A. Low-power view of the duodenal polyp appears to be replaced entirely by neoplastic glands, conserving the branching structure of smooth muscle ((hematoxylin & eosin; original magnification ×6.5). B. High-power view of the polyp demonstrates cancerous focus in tubular adenoma (hematoxylin & eosin; original magnification ×110).

DISCUSSION

There have been many reports describing the association between Peutz-Jeghers syndrome and gastrointestinal cancer. Recently, several investigators have reported that gastrointestinal cancers occur more frequently[4–7,11–17] than described previously,[18,19] and the incidence has been reported to be more than 10 percent by Giardiello *et al.*[5] and by Spigelman *et al.*[7] Although most of these reports have been based on the overall incidence of advanced cancer occurring with this syndrome, Narita *et al.*[16] investigated the incidence of neoplasia within the colonic polyps in a patient with Peutz-Jeghers syndrome. In this study, we evaluated 75 polyps in seven patients with Peutz-Jeghers syndrome and found 12 neoplastic polyps, 3 of which contained carcinoma.

When investigating the neoplastic changes within Peutz-Jeghers polyps, pseudoinvasion, which is an apparent invasion of the epithelium without any atypia into the submucosal layer,[9] and which is speculated as being induced mechanically by intussusception of the polyp, especially in the small intestine,[10] should be carefully ruled out. In this study, 3 of 22 polyps in the small intestine showed pseudoinvasion. The incidence and the locations of the polyps with this phenomenon seem similar to those reported previously by Shepherd *et al.*[10]

The neoplastic polyps, either adenomas or carcinomas in adenoma, that were found in this study were characterized by their predominant occur-

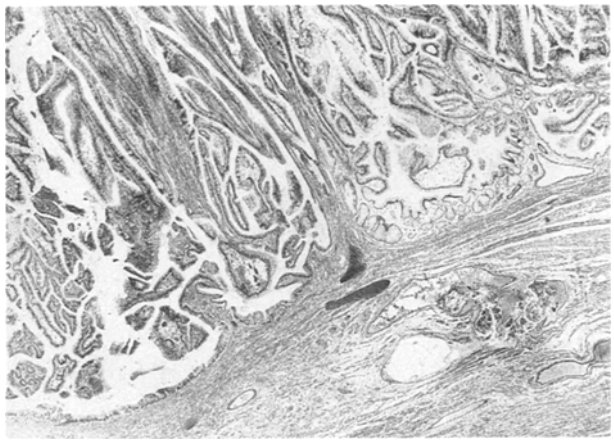

Figure 4. Photomicrograph shows cancerous glands invade the stalk with venous invasion ((hematoxylin & eosin; original magnification ×30).

Table 2.
Location and Size of 75 Polyps Resected from Patients with Peutz-Jeghers Syndrome

Location	Size (mm)			Total
	<10	10–19	20–	
Stomach	10	2	7	19
Duodenum	0	14 (7)	4 (4)	18 (11)
Small intestine	1	10	11 (1)	22 (1)
Large intestine	3	5	8	16
Total	14	31 (7)	30 (5)	75 (12)

Numbers in parentheses indicate neoplastic polyps.

rence in the duodenum and by the relatively younger ages of the patients (aged 20, 25, and 43 years). The distribution of the polyps and the age of the patients confirmed a previous review by Konishi *et al.*[15] of 23 cases of cancer arising in Peutz-Jeghers polyps. However, endoscopy was insufficient for differentiating these polyps from other non-neoplastic polyps. The size was similar between the neoplastic and non-neoplastic polyps, although this could perhaps be explained by the fact that we did not include small polyps which were not excised.

There still remains the controversy as to whether gastrointestinal cancer in the Peutz-Jeghers syndrome arises from the Peutz-Jeghers polyps themselves, or *de novo*. While Estrada and Spjut[20] emphasized the genetic predisposition to develop cancer in patients with this syndrome, regardless of the existence of hamartomas, a hamartoma-adenoma-carcinoma sequence has been suggested in the pathogenesis of gastrointestinal cancers.[13] In this study, 3 of the 12 neoplastic polyps were carcinomas, all three carcinomas were accompanied by an adenomatous area and, in addition, histologic features compatible with Peutz-Jeghers polyps were identified in 2 of the 3 polyps. These results, along with previous reports fully describing histologic findings in which 7 of 10 cancers in Peutz-Jeghers polyps were accompanied by adenomas,[6,11–17] seem to support the hamartoma-adenoma-carcinoma sequence.

CONCLUSION

Our results indicated that neoplastic change within the polyps, especially in the duodenum, is not a rare event in Peutz-Jeghers syndrome and suggests the necessity for removal of the polyps, not only as a treatment for clinical symptoms, such as bleeding and intussusception, but also from the aspect of cancer prevention. Even though the hamartoma-adenoma-carcinoma sequence seemed to be confirmed in this study, a further study is mandatory because neoplastic polyps were frequently found in the duodenum in our patients, whereas invasive cancer is known to occur anywhere within the gastrointestinal tract in patients with Peutz-Jeghers syndrome.[15]

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