

Yonago Acta medica 2002;45:117–120

A Case of Malignant Gastrointestinal Stromal Tumor of the Transverse Colon: Evaluation of Proliferation Activity

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Here, we report a colonic gastrointestinal stromal tumor (GIST) in a middle-aged man above 40. A histologically similar second tumor was detected 2 years after initial surgery. The primary GIST, measuring 5.5×6.0 cm, consisted of spindle tumor cells with a higher number of mitoses and Ki67 labeling index (about 20%) than those of the second tumor, implying a *de novo* GIST. These markers might be useful in evaluating malignant potential, as well as to differentiate between a *de novo* and a recurrent tumor in the colonic GIST.

Key words: colon; gastrointestinal stromal tumor; Ki67; mitosis

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. They are defined as c-kit (CD117, stem cell factor receptor)-positive mesenchymal spindle or epithelioid tumor cells in the GI tract. GISTs are most common in the stomach (60–70%), followed by the small intestine (20–25%). Colorectal GISTs are relatively rare, frequency being reported at approximately 5% (Miettinen and Lasota, 2001). Moreover, the pathobiological features of malignant GISTs of the colon remain unclear. Here, we report a case of malignant GISTs which developed in the transverse colon and the ascending colon, the latter being detected 2 years after initial surgery. We analyzed the number of mitoses and Ki67 labeling cells in the primary and second GISTs.

Patient Report

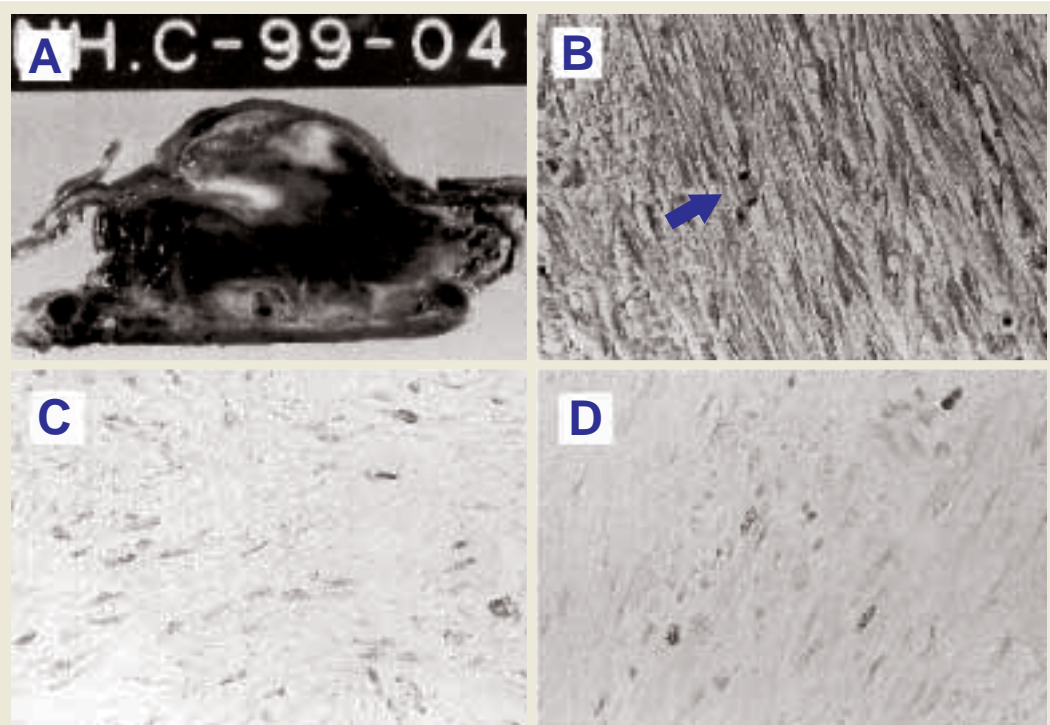
The patient was a man in his mid-40's who noticed an abdominal tumor without abdominal pain about 4 years ago. Abdominal ultrasonog-

raphy did not reveal significant findings at that time. A colonic tumor was detected by a barium contrast enema in February 1999. The tumor was surgically removed with partial resection of the transverse colon. Two years after surgery, computed tomography revealed the presence of another tumor in the ascending colon. The patient underwent surgery again. The postoperative course was uneventful and there has been no clinical evidence of tumor recurrence since.

Pathological findings

The primary tumor was 5.5×6.0 cm found in the transverse colon, whereas the second tumor was 3.0×5.3 cm found in the ascending colon. Grossly, the primary tumor showed irregular surfaces with areas of hemorrhage but without ulceration or necrosis (Fig. 1A). Histologically, the tumor, from the muscularis propria to the serosa, consisted predominantly of spindle shaped cells with an eosinophilic cytoplasm and mild nuclear atypia. No skeinoid fibers or epithelioid cells were observed. In addition, the

Abbreviations: EMA, epithelial membrane antigen; HPF, high power field; GI, gastrointestinal; GIST, gastrointestinal stromal tumor; NSE, neuron specific enolase



Figs. 1A–D.

- A:** Gastrointestinal stromal tumor. Tumor is brownish and well circumscribed, and located from the muscularis to the serosa of the transverse colon.
- B:** Gastrointestinal stromal tumor. Formalin-fixed, paraffin-embedded tissue section of the tumor in the transverse colon shows spindle cells possessing mild nuclear atypia and clear nucleoli. Mitotic figure is noted (arrow) (hematoxylin and eosin stain; original magnification $\times 100$).
- C:** Immunohistochemistry for CD117. CD117 immunoreactivity is shown in the cytoplasm of tumor cells (hematoxylin counterstain; original magnification $\times 200$).
- D:** Immunohistochemistry for Ki67. Tumor cells show nuclear immunoreactivity for Ki67 (hematoxylin counterstain; original magnification $\times 200$).

tumor did not show metastases to the regional lymph nodes nor lymphatic invasion. The second tumor showed similar pathological findings. Mitotic figures were relatively frequent [5/50 high power fields (HPFs)] in the primary tumor (Fig. 1B), but less frequent in the second tumor.

Immunohistochemically, most tumor cells in both lesions were positive for CD117 (Fig. 1C) and vimentin, in contrast to no immunoreactivity for CD34, human muscle actin, α -smooth muscle actin, desmin, S100 protein, neuron specific enolase (NSE) or epithelial membrane antigen (EMA). Both tumors were

diagnosed as GIST from the point of histopathological and immunohistochemical findings. In the primary tumor, nuclear immunoreactivity for Ki67 was observed in approximately 20% of tumor cells (Fig. 1D). On the other hand, only 5% of tumor cells were positive in the second tumor, which showed similar pathological findings with the primary, except for tumor size, mitotic figures and the Ki67 labeling index.

Discussion

Here, we describe a case of GIST in the transverse colon, followed by a second tumor in the ascending colon 2 years after initial surgery. The second GIST was smaller in size, and had a lower number of Ki67 labeling cells and mitoses than the primary tumor, implying a more static nature and lower malignant potential in the former than in the latter. These pathological findings promptly raised the question of whether the tumor localized in the ascending colon was truly recurrent or *de novo* developed GIST. It is well known that the most common sites for metastases of malignant GISTs are in the liver and peritoneum. These metastases can develop for as long as 30 years after the removal of GISTs as well as gastrointestinal leiomyosarcomas (Salmela, 1968; Ng et al., 1992; Rosai, 1996). In this case, the primary tumor did not show metastases to the regional lymph nodes nor lymphatic invasion. In addition, the observed pathological findings were similar, and the term until the clinical detection of the second tumor was relatively short, which suggested that the tumor might be *de novo*.

Rosai (1996) classified GISTs in the following 4 categories; (i) smooth muscle, (ii) neural, (iii) combined and (iv) uncommitted. The present case showed neither smooth muscle nor neural differentiation by immunohistochemistry. Therefore, the primary and second tumors were classified as the uncommitted type. Although GIST is a mesenchymal tumor of the GI tract, colorectal GISTs are relatively uncommon (Miettinen et al., 1995; Miettinen and Losota, 2001). Miettinen et al. (2000) reported 37 GISTs of the colon, of which 11 cases showed recurrence or metastasis. In these 11 cases, the mean age was 59.2, and the descending colon was the most frequent site, followed by the sigmoid colon and the cecum. In 4 cases out of the 11, extremely frequent mitotic figures, more than 100 in 50 HPFs, were observed. Moreover, liver metastasis was noted in 6 cases. Recurrence in the colon was not reported. On the other hand, the present case differs from the

report on a few points. The GIST was located in the transverse colon and occurred in a middle-aged man.

Previous studies indicated that the proliferative index evaluated by Ki67 antigen in the nuclei of the tumor cells was the most important predictor of clinical behavior in GISTs (Carrillo et al., 1997; Seidal and Edvardsson, 1999). However, GISTs of the transverse colon have not been evaluated enough. We confirmed that about 20% of tumor cells showed Ki67 expression in the primary tumor, suggesting that primary GIST might have possessed high proliferative activity compared to the second tumor. Similar to Ki67 expression, high mitotic figures and tumor size might be also considered to be aggressive factors in GISTs (Amin et al., 1993; Rosai, 1996). According to Amin et al. (1993), malignant gastric stromal tumors were greater than 5/50 HPFs in mitotic count and more than 5 cm in size. Moreover, previous studies demonstrated a significant correlation between the mitotic count and proliferative nuclear antigen index or Ki67 index (Amin et al., 1993; Seidal and Edvardsson, 1999). The present case showed a higher number of mitotic figures (5/50 HPFs) and Ki67 labeling tumor cells in the primary GIST. These factors might also be applicable to GISTs of the transverse colon and useful in evaluating malignant potentials.

In summary, we described a case of malignant GIST of the transverse colon and compared it with a second tumor from a pathobiological viewpoint. The primary GIST showed a larger size and consisted of spindle tumor cells with a higher number of mitoses and Ki67 labeling index than those of the second tumor, implying a *de novo* development.

Acknowledgments: The authors thank Mr. N. Itaki and Miss M. Kajimura for their technical support.

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Received October 7, 2002; accepted October 28, 2002

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