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Morphological Features of Metastatic Gastrointestinal Stromal Tumors after Gleevec Treatment
– Two Cases Report –

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We report two patients with metastatic gastrointestinal stromal tumors (GISTs) with a focus on the morphological features related to Gleevec treatment. In case 1, a 50-year-old woman presented with a 1.8 cm metastatic GIST in the liver after resection of a gastric GIST. Majority of the metastatic tumor showed fibrosis and hyalinization after 8 weeks of Gleevec treatment. CD117-positive cells were present in approximately 1% of the overall tumor. In case 2, a 2 cm and 14 cm metastatic liver masses were found in a 54-year-old man who had a rectal GIST. After 4 weeks of Gleevec treatment, metastatic tumors showed a decrease in size on CT scan. The metastatic tumors showed a decrease in number of tumor cells. The hemorrhage, cystic changes, necrosis, and fibrosis made up approximately 90% of the tumor. The morphological features related to Gleevec treatment are important for correct diagnosis and evaluation of tumor response and prognosis.

Key Words : Gastrointestinal stromal tumor; Gleevec; Liver; Metastasis; Morphology

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. GISTs occur predominantly in middle-aged and older adults. Approximately 50-60% of GISTs arise in the stomach, while 20-30% occurs in the small intestine, 10% occurs in the large bowel, 5% occurs in the esophagus, and 5% occurs elsewhere in the abdominal cavity.[1] The liver and peritoneum are the most frequent metastatic sites in patients with GISTs. Imatinib mesylate (Gleevec; Novartis, Basel, Switzerland), an inhibitor of tyrosine kinase activity of the KIT receptor, has been shown to be an effective treatment in metastatic or unresectable disease.[2] The morphological findings such as cystic changes, hemorrhage, myxoid degeneration, or a decrease in the number of tumor cells have been demonstrated in metastatic GISTs after Gleevec treatment.[2-8] However, the morphological features attributed to Gleevec ingestion have not been well characterized. Metastatic GISTs after Gleevec treatment mimic reactive lesions, epithelioid or spindle cell tumors. Therefore the correct diagnosis is important. Herein, we show the morphological features of hepatic metastases from two patients with GISTs who were treated with Gleevec.

CASE REPORTS

Case 1

A 50-year-old woman presented with a submucosal mass in the gastric fundus. It was incidentally found on gastroscopic examination during a health screening examination. Wedge resection was performed. The gastric tumor measured 4.5 cm at its greatest dimension. The cut surface was relatively circumscribed, gray-white, and rubbery soft. The gastric mucosa was intact. Histologically, the tumor was composed of spindle-shaped cells. The tumor cells were uniform and arranged in fascicles. On immunohistochemical staining, the tumor cells were diffusely positive for CD117 and focally positive for CD34, and negative for S-100

protein, smooth muscle actin, and desmin. The mitotic activity was 39 per 50 high power fields (HPFs). According to a consensus approach to predict behavior of GISTs,[1] the tumor was considered to be in the high risk category. Mutational analysis of *c-kit* gene using DNA extracted from the gastric tumor tissue showed a *c-kit* gene exon 11 deletion and insertion (c.1656-1676 del GTATGAAGTACAGTGGAAGGT; ins ATATAA), but no mutation in exons 9, 13, and 17. A follow-up abdominal CT scan showed a metastatic lesion in segment 4 of the liver at 8 months after surgery. Wedge resection was performed after 8 weeks of treatment with Gleevec (400 mg daily). Grossly, a 1.8 cm well-demarcated, gray-white nodule was noted in the liver (Fig. 1A). On microscopic examination, the lesion showed fibrosis and hyalinization (Fig. 1B, C). The central area of the nodule was more fibrotic compared to the peripheral area. Myxoid and cystic degeneration were found in the peripheral area. Lymphoplasmacytic cells infiltration was present in some areas. Hemosiderin pigments were present (Fig. 1D). The extent of viable tumor was approximately 5% of the overall tumor. CD117-positive cells were noted in approximately 5% of the overall tumor. The spindle cells were positive for CD34 and negative for smooth muscle actin, desmin, and S-100 protein. The metastatic tumor showed no change of immunophenotypes. Some residual tumor cells had pyknotic nuclei and a reduced amount of cytoplasm. Mitotic figures were not noted. Forty-two months after surgery, multiple new metastatic lesions developed in the liver. Gleevec was continuously administered, and 50 months after hepatic resection, the patient remains alive.

Case 2

A 54-year-old man has presented with a rectal mass and bleeding for several years. A transanal excision of the rectal mass was done. The tumor measured 6.0 cm at its greatest dimension. The

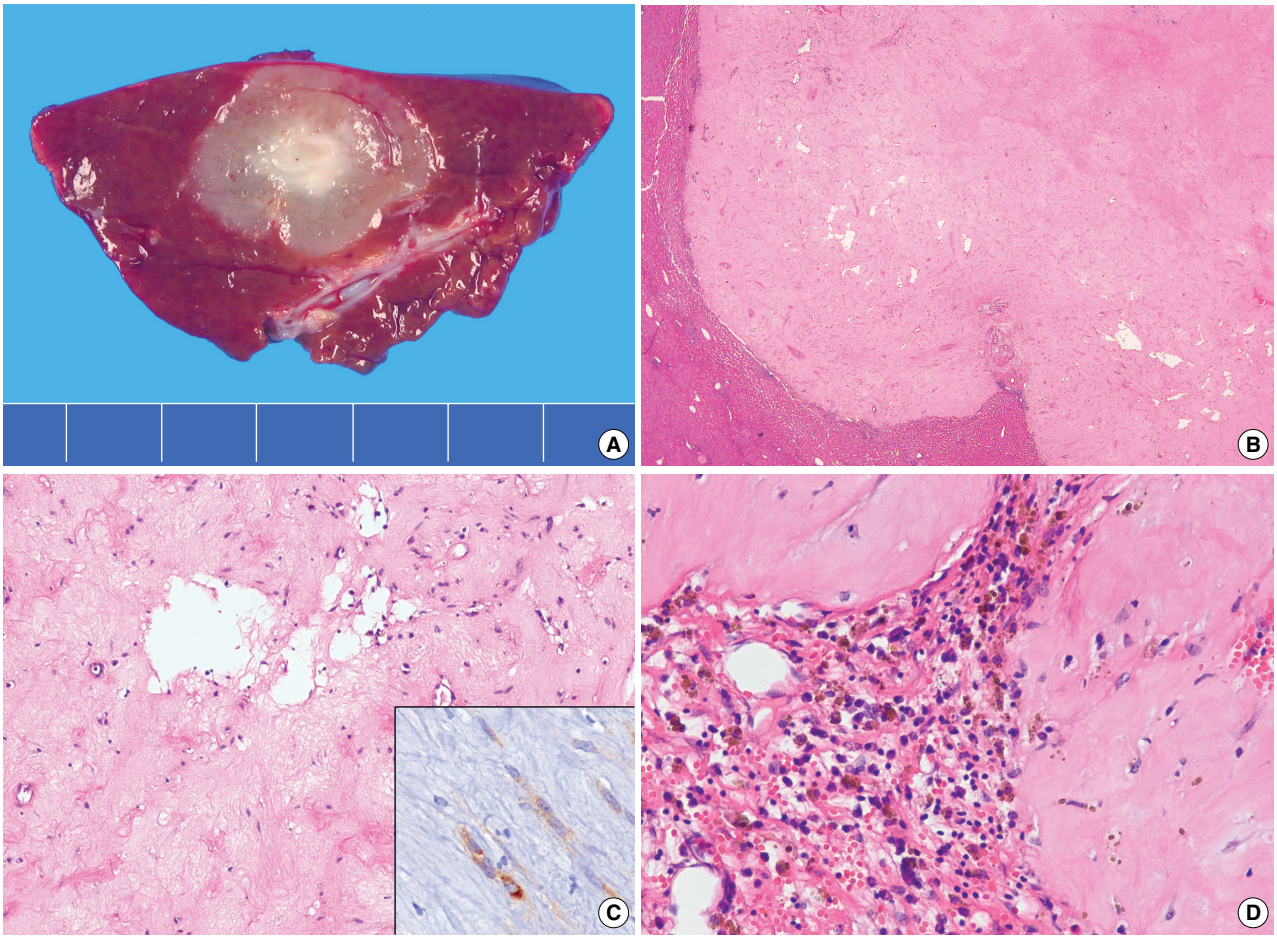

Fig. 1. Case 1. Gross and microscopic findings of hepatic metastasis. (A) The liver shows an 1.8 cm, well-demarcated, gray-white nodule. (B) Marked fibrosis and hyalinization are present. (C) Myxoid and cystic degeneration are present. (Insect) CD117-positive tumor cells are sparsely present. (D) Lymphoplasmacytic infiltration and hemosiderin pigments are present.

cut surface was yellow-gray, lobulated, and rubbery soft. The colonic mucosa was intact. Microscopic examination showed spindle-shaped tumor cells proliferation with a fascicular arrangement. Mitotic counts were 6 per 50 HPFs. The tumor cells were diffusely positive for CD117 and focally positive for CD34, and negative for smooth muscle actin, desmin, and S-100 protein. Ki-67 labeling index was 18.3%. According to a consensus approach,[1] the rectal tumor was considered to be a GIST in the high risk category. Mutational analysis of *c-kit* gene exons 9, 11, 13, and 17, was done from the rectal tumor tissue. There was a *c-kit* gene exon 13 point mutation p.Gly658Glu (c.1973 G>A), but no mutation in exons 9, 11, and 17. Follow-up abdominal CT scan showed two hepatic metastatic lesions 34 months after excision of the rectal mass. After 4 weeks of treatment with Gleevec (400 mg daily), a follow-up CT revealed that the metastatic lesions had decreased in size. A left lateral segmentectomy and wedge resection were done. Grossly, a 14.0 cm mass in segments 2, 3, and 4 showed extensive hemorrhage and cystic changes (Fig. 2A). A 2.0 cm lesion in segment 7 was well-circumscribed, hemorrhagic, and cystic, with soft-to-friable consistency. Histologically, the large metastatic lesion showed hemorrhage, necrosis and cystic change (Fig. 2B). Fibrosis and hyalinization were noted, with loss of tumor cells. Viable tumor cells were noted in the peripheral area of the lesion (Fig. 2C). The extent of viable tumor was approximately 10% of the overall tumor. The small metastatic lesion showed necrosis and hemorrhage. The tumor cells had pyknotic nuclei. Some tumor cells showed nuclear atypia. There were lymphocytes, plasma cells, foamy histiocytes, and fibroblasts in some areas (Fig. 2D). Hemosiderin-laden macrophages were noted. Multinucleated foreign-body type giant cells were occasionally seen. On immunohistochemical stain, viable tumor cells were positive for CD117 and CD34, and negative for smooth muscle actin and desmin, S-100 protein, and cytokeratin (AE1/AE3). No change of immunophenotypes was found in the

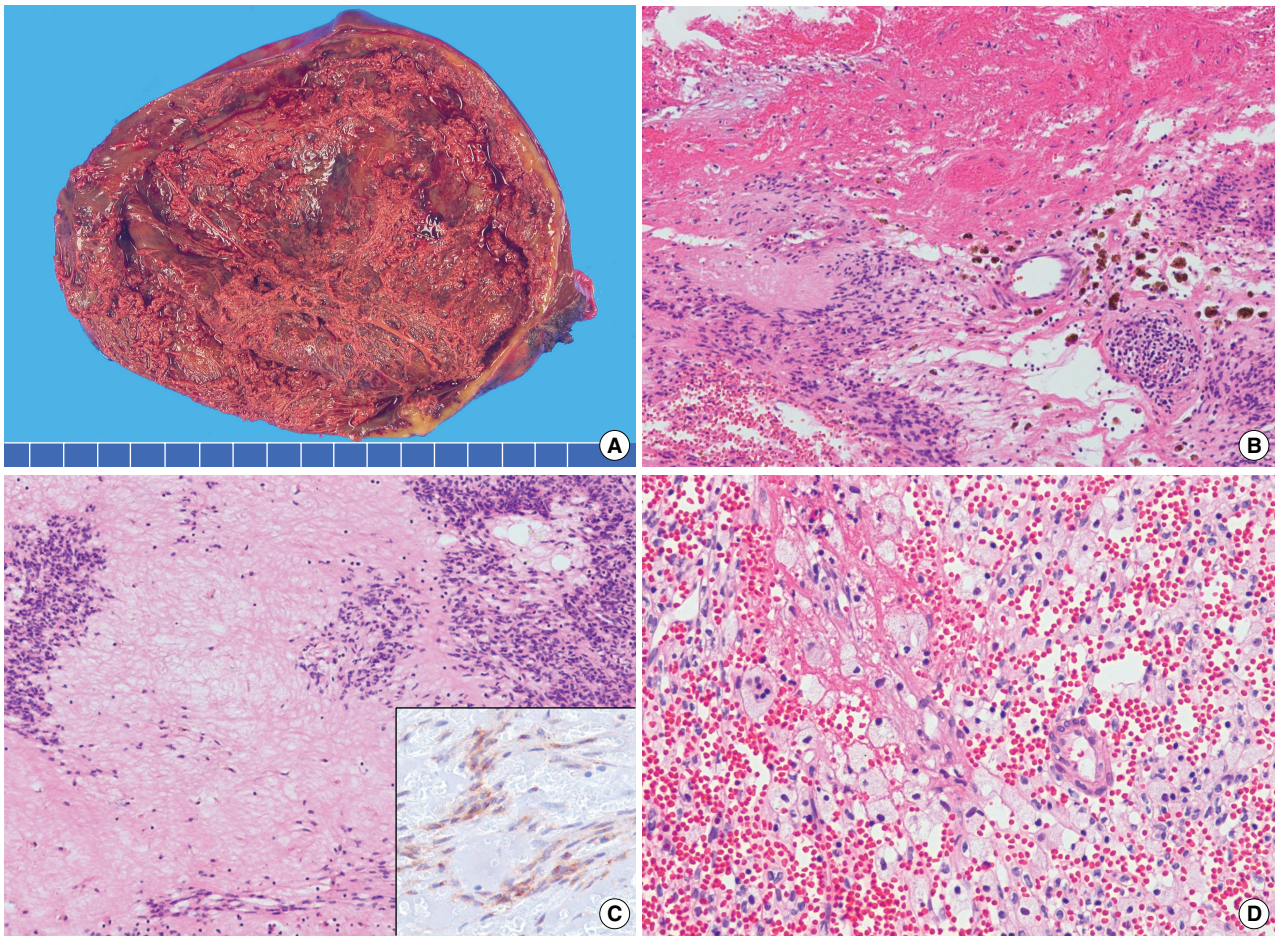

Fig. 2. Case 2. Gross and microscopic findings of hepatic metastasis. (A) A 14.0 cm, hepatic mass shows extensive hemorrhage and cystic changes. (B) Hemorrhage, necrosis and cystic change are present. (C) Fibrosis and hyalinization are present. Foci of viable tumor cells are noted. (Insect) CD117-positive tumor cells are present. (D) Foamy histiocytes are present.

metastatic tumors. Ki-67 labeling index was 0.2%. There was a decrease of Ki-67 labeling index in the metastatic tumors as compared to the primary rectal tumor. The average mitotic count was 1 per 50 HPFs. Newly developed, multiple hepatic metastatic lesions were found in segments five and six 21 months after hepatic resection. Treatment with Gleevec was continued. After 50 months from the hepatic resection, the patient still remains alive.

DISCUSSION

GISTs are distinctive tumors that arise from, or show differentiation towards, the interstitial cells of Cajal (ICC), the gut pacemaker cells. In recent years, there has been a rapid evolution in the tumorigenesis and management of GISTs. C-kit is a transmembrane receptor tyrosine kinase, which is physiologically activated by a growth factor termed stem-cell factor. It is though that the proliferation of most GISTs is mediated by the ligand-independent activation of the *c-kit* receptors which in turn activates tyrosine kinase causing uncontrolled cell proliferation.[9] Imatinib mesylate (Gleevec; Novratis) was originally developed as an inhibitor of the BCR-ABL fusion protein of chronic myelogenous leukemia and shown to inhibit mutant KIT oncoproteins in GISTs. Gleevec is currently the standard of care for first-line treatment for unresectable or metastatic GISTs.[10,11]

A summary of the morphological findings of metastatic GIST after Gleevec treatment is shown in Table 1.[2-8] Gleevec-treated hepatic metastatic lesions show a variety of histological findings. Pyknotic nuclei in an eosinophilic myxoid background with a decrease in the density of the tumor cells, myxoid degeneration, and scarring have been documented. In addition, large bizarre cells with large nuclei and prominent nucleoli are found. Complete remission in patients with metastatic GISTs has been documented.[6,8] In case 1, the metastatic tumor was replaced by fibrosis and hyalinization which is similar to the findings described in previously reported cases. Sparsely CD117-positive tumor cells were noted. The loss of tumor cells, fibrosis and hyalinization are considered as one pattern of tumor regression.

In case 2, a follow-up CT after Gleevec treatment showed that metastatic tumors had decreased in size. The resected lesion showed extensive hemorrhage and cystic changes. A study had demonstrated that the hepatic and peritoneal metastases from GISTs treated with Gleevec showed cystic structures partly lined by a simple squamous epithelium.[4] In the present case, the cystic lining epithelium was not found. The mechanism that induces cystic change after Gleevec treatment is uncertain. The cystic change is considered an effective regression in response to Gleevec administration. In addition, reduction in the Ki-67 labeling index and an absence or decrease in the mitotic count may be associated with suppression of tumor progression by Gleevec administration.

It has been shown that blockage of the KIT signaling pathway induced transdifferentiation of ICC to a smooth muscle phenotype.[12] GIST specimen from patients on therapy showed complete loss of CD117 immunoreactivity and the progression was accompanied by desmin expression.[7] Gleevec treatment can undergo immunophenotypic changes when compared to the original tumors. Therefore, the differential diagnosis is difficult, particularly in the case of new lesions, which appear during treat-

Table 1. Summary of the morphologic findings of metastatic GISTs after Gleevec treatment

Reference	Gross findings	Microscopic findings	Response
Joensuu[2]	Cyst-like appearance	Decrease in density of tumor cells, myxoid degeneration, scarring, few pyknotic tumor cells	Partial
Chen[3]	Decreased tumor size, cystic changes	NA	Partial
Bechtold[4]	Cystic changes	Small tumor cells, large bizarre cells, reactive multinucleate giant cells, sparsely cellular fibromyxoid tissue	Partial
Colecchia[5]	NA	Sclerohyalinized nodule, hyperchromatic nuclei, chronic inflammatory cells, fibroblasts	Partial
Högenauer[6]	Reduced tumor size, fewer metastatic nodules	No viable tumor cells, myxoid degeneration, few macrophages	Complete
Pauwels[7]	NA	Loss of KIT expression, gain of desmin expression in recurrent tumor	Partial
Suzuki[8]	Necrosis, hemorrhage, cystic changes	No viable tumor cells, hyaline degenerative tissue	Complete
Present case	Cystic changes, hemorrhage, necrosis, decreased tumor size	Reduced numbers of tumor cells, pyknotic nuclei, reduced cytoplasmic volume, myxoid, hyalinization, fibrosis	Partial

GIST, gastrointestinal stromal tumor; NA, not available.

ment. *KIT* mutational analysis seems to be indispensable for the accurate diagnosis of newly appearing lesions that do not express KIT or show an unexpected immunohistochemical profile in the context of an unusual morphology.[7] Liegl *et al.*[13] described rhabdomyosarcomatous differentiation in gastrointestinal stromal tumors after tyrosine kinase inhibitor therapy and loss of KIT expression in the rhabdomyoblastic component. Areas with classic GIST morphology expressed KIT. The overexpression of genes involved in muscle differentiation may be associated with the change of immunophenotype. In the present two cases, the change of immunophenotypes was not found between the primary tumors and metastatic tumors. We guess that no change of immunophenotypes may be associated with the duration and dosage of Gleevec treatment and mutational status of the primary tumor. However, the mechanism remains to be determined.

A recent study had demonstrated that the mutational status of *c-kit* gene could predict the clinical response to Gleevec.[14] GISTs with exon 11 *c-kit* mutations are more likely to respond to Gleevec than GISTs with exon 9 or no detected mutations. Case 1 showed a *c-kit* exon 11 point mutation and case 2 showed a *c-kit* exon 13 deletion and insertion. In case 1 and 2, a follow-up radiologic study showed newly developed metastatic nodules in the liver. Therefore, it suggests that these patients presented herein were resistant to Gleevec. Although Gleevec achieves a partial response or stable disease in the majority of GIST patients, complete and lasting responses are rare.[15]

The differential diagnosis of metastatic GISTs after Gleevec treatment includes reactive pseudosarcomatous spindle cell lesions, smooth muscle tumors, solitary fibrous tumors, inflammatory myofibroblastic tumors, malignant melanomas, and metastatic carcinomas.[16,17] Reactive pseudosarcomatous spindle cell lesions tend to have a prominent inflammatory component and can be separated from GIST on the basis of clinical features and CD117 negativity. In smooth muscle tumors, tumor cells have vesicular blunted nuclei arranged in a fascicular pattern and show extensive positivity for smooth muscle actin. In solitary fibrous tumors, tumor cells are bland oval, fusiform, or spindle cells in whorled or patternless arrangement. The characteristic alternating hypercellularity and hypocellularity and hemangiopericytomalike vessels are seen in solitary fibrous tumors. Inflammatory myofibroblastic tumors show myofibroblasts, fibroblasts, and inflammatory infiltrate rich in plasma cells. The frequent location in the mesentery and omentum and the younger age of patients provide important clues to the diagnosis of inflammatory myofibroblastic tumors. Malignant melanomas show spindled and epithelioid cells and immunoreactivity for S100 protein, HMB-45, and Melan-A. Metastatic carcinomas can occasionally assume a spindle cell morphology mimicking GISTs. The degree of nuclear pleomorphism seen in spindle cell carcinomas usually exceeds that of GISTs. Immunohistochemical stain for cytokeratins can be helpful in confirming the diagnosis. However, carcinomas may rarely show immunoreactivity for CD117.[17]

In conclusion, patients with metastatic GISTs receiving Gleevec treatment showed loss of tumor cells, fibrosis, hyalinization, cystic changes, and necrosis. The pathologist should be aware that the morphological features may occur in metastatic GISTs after Gleevec treatment. These morphological features may mimic other hepatic lesions. Immunohistochemical studies, mutational analysis, and clinical correlation are helpful to establish the correct diagnosis.

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