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Case Report

Bone metastasis in gastrointestinal stromal tumors preferentially occurs in patients with original tumors in sites other than the stomach

Takahiko Nakajima[1], Toshiro Sugiyama[2], Hayato Baba[1], Hideki Hatta[1], Takeshi Nishida[1], Shigeharu Miwa[1], Shinichi Hayashi[1], Koichi Tsuneyama[3], Johji Imura[1]

Departments of [1]Diagnostic Pathology, [2]Gastroenterology and Hematology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan; [3]Department of Molecular and Environmental Pathology, Institute of Health Biosciences, University of Tokushima *Graduate School, 3-8-15 Kuramotomachi,* Tokushima 770-8503*, Japan*

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Abstract: Bone metastases are rare in gastrointestinal stromal tumors (GISTs) and data on the clinicopathological profiles are lacking. The purpose of this report was to identify the clinicopathological profiles of this rare clinical setting by evaluating 23 cases, four of which were our own and the additional 19 were from the relevant English literature. In 18 cases, the primary GISTs occurred in sites other than the stomach, although a high proportion of these tumors do arise in the stomach. All tumors at the disease presentation had more than a low risk of recurrence, with most tumors either at a high risk or initially malignant with liver metastasis. In four cases, bone metastasis was the primary metastatic manifestation. Although rare in GISTs, bone metastasis should be considered in patients with primary tumors at a high risk for recurrence or in initially malignant tumors with liver metastasis, especially with primary tumors in sites other than the stomach.

Keywords: GIST, bone metastasis, risk classification

Introduction

Gastrointestinal stromal tumors (GIST) are rare mesenchymal tumors of the gastrointestinal tract that account for 1%-3% of all malignant gastrointestinal tumors [1, 2]. The most frequent site of occurrence is the stomach (60%), followed by the small bowel (35%) and other sites (colon, rectum, and esophagus < 5%) [1, 2]. The liver is the most common site of metastasis at both presentation and relapse [3, 4]. The peritoneum is the second most common site of metastasis, whereas bone metastasis is rare [3, 4].

We present four cases of GISTs with bone metastasis. The purpose of this report was to identify the clinicopathological characteristics for this rare clinical setting through our cases and the cases from the literature.

Case report

Case 1

A 76-year-old man presented with hematochezia due to bleeding from a rectal GIST. The resected tumor was 10 cm in size. Histology revealed a pure spindle cell tumor and the mitotic count was 20 per 50 high-power fields (HPF). In 49 months after the surgery, multiple lesions were detected in the thoracic vertebrae on follow-up computed tomography (CT) examinations. Percutaneous needle biopsy revealed metastatic GIST. Imatinib therapy was initiated and the patient had disease stability until he died of pneumonia 152 months after presentation of the primary disease.

Case 2

A 43-year-old man presented with melena due to bleeding from a jejunual GIST. The resected

Table 1. The four current cases and previously published cases with bone metastasis

Case Number	Age (year)/Sex	Site	Risk-modified NIH	Risk AFIP	Time association between liver and bone metastases	Reference
1	76/M	Rectum	High	High	Bone first	Present study
2	43/M	Jejunum	High	High	Synchronous	Present study
3	50/M	Rectum	High	High	Synchronous	Present study
4	50/M	Jejunum	Malignant	Malignant	Liver first	Present study
5	58/M	Jejunum	High	High	Synchronous	[6]
6	57/F	Jejunum	High	Moderate	Liver first	[7]
7	81/M	Rectum	NA	High	Synchronous	[8]
8	53/M	Esophagus	Malignant	Malignant	Bone first	[9]
9	57/M	Rectum	Malignant	Malignant	Synchronous	[10]
10	55/M	Mesentery	High	high	Synchronous	[11]
11	54/M	Rectum	Malignant	Malignant	Liver first	[12]
12	26/M	Duodenum	Malignant	Malignant	Liver first	[13]
13	37/M	Duodenum	NA	NA	Synchronous	[14]
14	60/M	Small intestine	NA	NA	Liver first	[15]
15	65/M	Rectum	Malignant	Malignant	Synchronous	[16]
16	68/M	Ileum	Malignant	Malignant	Synchronous	[17]
17	62/M	Ileum	Malignant	Malignant	Synchronous	[18]
18	54/F	Duodenum	High	High	Liver first	[18]
19	82/F	Stomach	Malignant	Malignant	Synchronous	[18]
20	73/M	Stomach	NA	NA	synchronous	[19]
21	62/M	Stomach	NA	NA	Bone first	[20]
22	38/M	Stomach	Malignant	Malignant	Liver first	[21]
23	62/M	Stomach	Intermediate	Moderate	Bone first	[22]

NA, not available NIH, National Institutes of Health AFIP, Armed Forces Institute of Pathology.

tumor was 8 cm in size. Histology revealed a pure spindle cell tumor and the mitotic count was 19 per 50 HPF. Imatinib therapy was initiated after multiple metastases were detected in the liver 39 months after surgical resection. The patient had clinical benefit and disease stability for 42 months on imatinib therapy when multiple metastases in the cervical and lumbar vertebrae were detected on a follow-up CT. The metastases were confirmed by fluorine-18 fluorodeoxyglucose (FDG) positron-emission tomography (PET) activity. The patient is now under consideration for sunitinib therapy as a second-line regimen 118 months after primary disease presentation.

Case 3

A 50-year-old man presented with hematochezia due to bleeding from a rectal GIST. The resected tumor was 4.5 cm in size. Histology revealed a pure spindle cell tumor and the mitotic count was 15 per 50 HPF. At 108 months after the surgery, the follow-up FDG PET/CT revealed multiple metastases in the liver, cervical vertebrae, and rib bones. Imatinib therapy was initiated and the patient had disease stability for 62 months when regrowth of the hepatic tumor as well as a new tumor in the right kidney were detected. The metastatic tumors in the liver and kidney were excised. The patient is now under imatinib therapy for imatinib-sensitive lesions in the bone 187 months after the primary surgery.

Case 4

A 50-year-old man presented with a jejunual GIST with liver metastasis. Partial jejunectomy and hepatectomy were performed. The jejunal tumor was 8 cm in size. Histology revealed a spindle cell tumor and the mitotic count was 15 per 50 HPF. He was followed up without any adjuvant therapy. At 27 months after the pri-

mary surgery, he presented with multiple metastases of the liver and peritoneum and imatinib therapy was initiated. The patient had clinical benefit and disease stability for 77 months on the imatinib and subsequent sunitinib therapies when he complained of back pain. CT revealed multiple metastases in the thoracic and lumbar vertebrae and the patient soon developed paralysis of the lower limbs because of spinal cord compression. The patient had an unfavorable clinical course and died 83 months after primary disease presentation.

Discussion

In GIST, the incidence of bone metastases among different metastatic locations has been estimated to be roughly 5% or less [5]. With this background, the number of cases at a single institution with this disease may be limited. In order to accurately assess this rare clinical setting, this study was conducted using the data of the four presented cases and of an additional 19 cases retrieved from a review of the English literature [6-22]. A total of 23 cases are summarized in **Table 1**.

There were 20 male and three female patients with an age range of 26-82 years (mean, 57.5 years). Ten tumors originated from the small bowel and duodenum, six from the rectum, five from the stomach, one from the esophagus, and one from the mesentery. Of note, tumors with bone metastasis preferentially originated in sites other than the stomach (18 of 23 cases; 78%), although approximately 60% of all GIST tumors arise in the stomach in general [1, 2]. This seems to reflect the more aggressive biological behavior of intestinal GISTs compared with gastric tumors [23]. In addition, a much higher proportion of tumors originated in the rectum (six of 23 cases; 26%) compared with the very infrequent rectal occurrence (< 5%) of all GISTs in general [1, 2]. The hematogeneous spread via nonportal vein drainage from the rectum may explain the high occurrence of rectal tumors among patients with GISTs with bone metastasis. Furthermore, the high incidence of synchronous or previous liver metastasis in patients with bone metastasis (19 of 23 cases; 83%) may also be a result of hematogeneous spread via hepatic vein drainage from the metastatic tumors in the liver. Therefore, a higher incidence of rectal origin and a high frequency of concurrent liver metastasis in patients with GISTs with bone metastasis may be explained by hematogeneous spread.

Other than the 10 tumors that were initially malignant, the initially local tumors with a description of the size, site, and mitotic counts were evaluated for recurrence risk. Based on the modified National Institutes of Health consensus criteria, seven tumors were classified as high risk for recurrence and one was as an intermediate risk [24]. However, according to the Armed Forces Institute of Pathology criteria, seven were classified as high risk and two as moderate risk [23]. Therefore, all tumors with bone metastasis were classified as either high or intermediate risk for recurrence in both classification schemes, with most tumors as high risk or malignant. These findings suggest that the tumors at a low or a very low risk for recurrence should rarely be considered for bone metastasis.

The clinical survey for recurrence after complete resection of the primary tumor is focused on the liver or peritoneum and is usually performed using abdominal CT. Because it is unknown how much consideration should be given to delayed bone metastasis in the follow-up survey, we have evaluated the time relationship between bone and liver metastases. Bone metastasis preceded liver metastasis in four of the 23 cases (17%). Three of the four cases had bone metastasis as the primary or the only metastatic manifestation and one case had synchronous pulmonary metastasis. Although the optimal method or interval for the detection of bone metastasis requires clarification, bone metastasis can sometimes be the primary metastatic manifestation.

In summary, although rare in GISTs, bone metastases preferentially occur in patients with primary tumors in sites other than the stomach. Most patients with bone metastasis initially have local tumors that are at a high risk for recurrence or malignant tumors with liver metastasis.

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Disclosure of conflict of interest

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Address correspondence to: Dr. Takahiko Nakajima, Department of Diagnostic Pathology, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama 930-0194, Japan. Tel: 81-76-434-2281; Fax: 81-76-434-5016; E-mail: tnkjm@med.u-toyama.ac.jp

References

[1] Miettinen M, Sobin LH and Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005; 29: 52-68.

[2] Miettinen M, Makhlouf H, Sobin LH and Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol 2006; 30: 477-489.

[3] DeMatteo RP, Lewis JJ, Leung D, Mudan SS, Woodruff JM and Brennan MF. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000; 231: 51-58.

[4] Burkill GJ, Badran M, Al-Muderis O, Meirion Thomas J, Judson IR, Fisher C and Moskovic EC. Malignant gastrointestinal stromal tumor: distribution, imaging features, and pattern of metastatic spread. Radiology 2003; 226: 527-532.

[5] Jati A, Tatli S, Morgan JA, Glickman JN, Demetri GD, Van den Abbele A and Silverman SG. Imaging features of bone metastases in patients with gastrointestinal stromal tumors. Diagn Interv Radiol 2012; 18: 391-396.

[6] Feki J, Bouzguenda R, Ayedi L, Bradi M, Boudawara T, Daoud J and Frikha M. Bone metastases from gastrointestinal stromal tumor: a case report. Case Rep Oncol Med 2012; 2012: 509845.

[7] Abuzakhm SM, Acre-Lara CE, Zhao W, Hitchcock C, Mohamed N, Arbogast D and Shah MH. Unusual metastases of gastrointestinal stromal tumor and genotypic correlates: Case report and review of the literature. J Gastrointest Oncol 2011; 2: 45-49.

[8] Tezcan Y and Koç M. Gastrointestinal stromal tumor of the rectum with bone and liver metastasis: a case study. Med Oncol 2011; 28: 204-206.

[9] Ozan E, Oztekin O, Alacacioğlu A, Aykaş A, Postaci H and Adibelli Z. Esophageal gastrointestinal stromal tumor with pulmonary and bone metastases. Diagn Interv Radiol 2010; 16: 217-220.

[10] Barrière J, Thariat J, Vandenbos F, Bondiau PY, Peyrottes I and Peyrade F. Diplopia as the first symptom of an aggressive metastatic rectal stromal tumor. Onkologie 2009; 32: 345-347.

[11] Jain A, Dubashi B, Mangaladevi, Chandra SS and Halanaik D. Mesenteric gastrointestinal stromal tumor with bone metastases. Indian J Cancer 2011; 48: 383-384.

[12] Selcukbiricik F, Tural D, Ozturk MA, Dervisoglu S, Sager S, Hız M and Mandel NM. Gastrointestinal stromal tumor of the rectum with scapular metastasis: a case report. J Med Case Rep 2012; 6: 145.

[13] Li LF, Tse YH, Ho SL, Yan KW and Lui WM. Duodenal GIST metastasized to skull and orbit managed by surgery: a case report. Asian J Surg 2011; 34: 181-184.

[14] Slimack NP, Liu JC, Koski T, McClendon J Jr and O'Shaughnessy BA. Metastatic gastrointestinal stromal tumor to the thoracic and lumbar spine: first reported case and surgical treatment. Spine J 2012; 12: e7-12.

[15] Akiyama K, Numaga J, Kagaya F, Takazawa Y, Suzuki S, Koseki N, Kato S, Kaburaki T and Kawashima H. Case of optic nerve involvement in metastasis of a gastrointestinal stromal tumor. Jpn J Ophthalmol 2004; 48: 166-168.

[16] Gil-Arnaiz I, Martínez-Trufero J, Pazo-Cid RA, Felipo F, Lecumberri MJ and Calderero V. Skull metastasis from rectal gastrointestinal stromal tumors. Clin Transl Oncol 2009; 11: 625-627.

[17] Lutz JC, El-Bouihi M, Vidal N, Fricain JC, Robert M, Deminière C and Zwetyenga N. Mandibular metastases from an ileum stromal tumor. Rev Stomatol Chir Maxillofac 2008; 109: 399-402.

[18] Di Scioscio V, Greco L, Pallotti MC, Pantaleo MA, Maleddu A, Nannini M, Bazzocchi A, Di Battista M, Mandrioli A, Lolli C, Saponara M, Giorgio G, Biasco G and Zompatori M. Three cases of bone metastases in patients with gastrointestinal stromal tumors. Rare Tumors 2011; 3: 51-53.

[19] ChuTYC and Wong CS. Bone metastases from gastrointestinal stromal tumour: correlation with positron emission tomography-computed tomography. J HK Coll Radiol 2009; 11: 172-175.

[20] Zheng CK, Kan WS and Li P. A case report of a metastatic gastrointestinal stromal tumor occurring in femur. Case Rep Gastrointest Med 2011; 2011:926-179.

[21] Romero-Rojas AE, Mesa-Botero OA, Melo-Uribe MA, Chinchilla-Olaya SI and Barajas-Solano PA.

Gastric gastrointestinal stromal tumor with unusual skull metastasis. Rev Col Gastroenterol 2011; 26: 303-307.

[22] Sahin E, Yetişyiğit T, Oznur M and Elboğa U. Gastric gastrointestinal stromal tumor with bone metastases - case report and review of the literature. Klin Onkol 2014; 27: 56-59.

[23] Miettinen M and Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23: 70-83.

[24] Joensuu H, Vehtari A, Riihimäki J, Nishida T, Steigen SE, Brabec P, Plank L, Nilsson B, Cirilli C, Braconi C, Bordoni A, Magnusson MK, Linke Z, Sufliarsky J, Federico M, Jonasson JG, Dei Tos AP and Rutkowski P. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012; 13: 265-274.