Case Report

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

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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 jejunal GIST. The resected
Bone metastasis in GIST

<table>
<thead>
<tr>
<th>Case Number</th>
<th>Age (year)/Sex</th>
<th>Site</th>
<th>Risk-modified NIH</th>
<th>Risk AFIP</th>
<th>Time association between liver and bone metastases</th>
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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 jejunal 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-
Bone metastasis in GIST

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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

None.

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Bone metastasis in GIST


