

## Case Report

# Gastrointestinal stromal tumor with multiple bone, liver, lung and abdominopelvic cavity metastases: significant clinicopathologic characteristics of an unusual case

Qiuyu Liu<sup>1</sup>, Yunzhen Kan<sup>1</sup>, Tingyi Sun<sup>1</sup>, Hui He<sup>1</sup>, Mengyang Zhang<sup>1</sup>, Ziguang Xu<sup>1</sup>, Fangfang Fu<sup>2</sup>, Lingfei Kong<sup>1</sup>, Huanzhou Xue<sup>3</sup>

Departments of <sup>1</sup>Pathology, <sup>2</sup>Image, <sup>3</sup>Liver-Gallbladder-Pancrease Surgery, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, Zhengzhou, China

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**Abstract:** Gastrointestinal stromal tumors (GISTs) are the common neoplasms of the gastrointestinal (GI) tract. The tumor often spreads to the liver and peritoneum, but bone metastasis is relatively rare. We present an unusual case of an intestine GIST with multiple bone (thoracic vertebrae and right cervical rib), liver, lung and abdominopelvic cavity metastases, including a review of the literature. Histopathological features showed a hypercellular tumor with epithelioid cells and multifocal coagulation necrosis. Part of the cellular figures presented rhabdoid morphology. The same mutation of KIT exon 11 was found in the bone metastasis and initial intestine lesion. The patient received complete resection of thoracic vertebrae lesion and was taken the targeted therapy of imatinib, without progression of disease and drug resistant at present. The patient remains alive 2 years after the initial diagnosis. We believe that this is the first report involving in comparison of genetic variation between the primary and metastatic bone lesion in the native place.

**Keywords:** Gastrointestinal stromal tumor, bone metastasis, surgery, imatinib

## Introduction

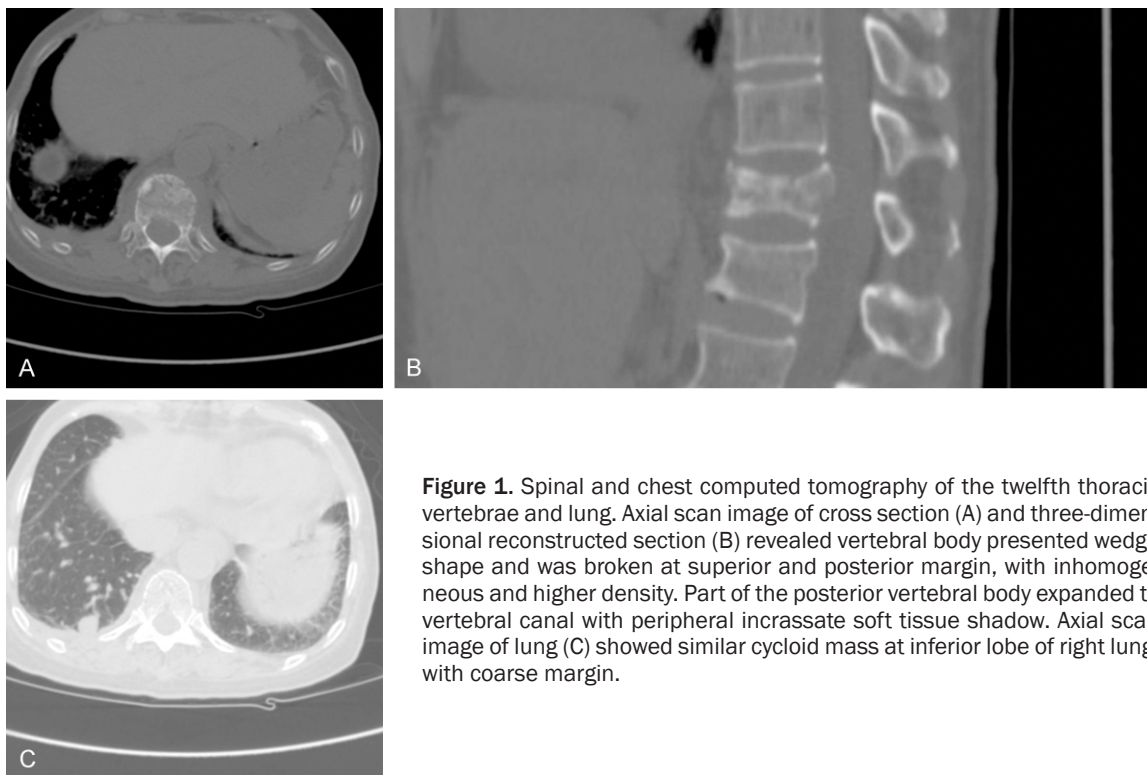
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract, and were misdiagnosed as leiomyoma in the past. It is now known that GISTs arise from interstitial cells of Cajal (ICC) or ICC precursor cells. GISTs can occur along the entire length of the digestive tract but are most common in the stomach (60%), jejunum and ileum (30%), duodenum (5%), and colon and rectum (less than 5%). GISTs also rarely involve the esophagus [1], appendix, and gall bladder. GISTs have a characteristic pattern of metastasis. The distribution of metastases is predictable, with the liver and peritoneum the most common sites [2, 3]. Metastases to other sites, such as bone and lung and so on [1-6], are relatively rare. Although a few numbers of studies have reported bone metastases originating from GISTs, the true prevalence remains unknown. The present study describes a rare case of multiple bone

metastases in a first Chinese patient with GIST and reviews the relevant literature.

## Case report

A 71-year-old woman, with 10 years of history of rheumatic heart disease (RHD), atrial fibrillation and chronic cardiac failure (CCF), had previously undergone surgical removal of an intestine GIST in 2013. The patient was treated with imatinib (400 mg, daily) after operation. However, metastatic liver and abdominopelvic cavity lesions were identified subsequently about six months later. And then, the patient felt low back pain for three months in 2014. The pain showed inconsecutive dull pain from few minutes to hours. Specialized examination discovered the tenderness and fall-off of superficial sensation nearby the twelfth thoracic and first lumbar vertebrae. Spinal, chest and abdominopelvic cavity computed tomography (CT) suggested metastatic lesions at the twelfth thoracic vertebrae and inferior lobe of right lung, and another mass

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**Figure 1.** Spinal and chest computed tomography of the twelfth thoracic vertebrae and lung. Axial scan image of cross section (A) and three-dimensional reconstructed section (B) revealed vertebral body presented wedge shape and was broken at superior and posterior margin, with inhomogeneous and higher density. Part of the posterior vertebral body expanded to vertebral canal with peripheral incompressible soft tissue shadow. Axial scan image of lung (C) showed similar cycloid mass at inferior lobe of right lung, with coarse margin.

at right lower quadrant, measuring about 4.8 cm \* 3.4 cm, with multiple mild intumescent lymph nodes at cavitas pelvis and pelvic wall (**Figure 1**). Nuclear medicine examination revealed three metastatic bone lesions at the right fifth and sixth rib and the twelfth thoracic vertebrae (**Figure 2**). The vertebrae lesion was completely resected in April 2014 at our hospital, to relieve low back pain, and reconstructed using a nanometer bone for tumor prosthesis (**Figure 3**). Then the patient was administered imatinib (800 mg, daily) continuously.

Grossly, the resected tumor of the twelfth thoracic vertebrae was fleshy with cystiform degeneration and hemorrhage on the cross section. Histopathology examination revealed hypercellular epithelioid cell morphology. The tumor cells had ovoid nuclei with dark chromatin and conspicuous nucleoli, and a moderate amount of eosinophilic cytoplasm. Part of the cellular figures presented rhabdoid morphology that was a harbinger of high-grade or dedifferentiated component. The epithelioid cells arranged in a sheet-like or nested growth pattern with multifocal coagulation necrosis. Myeloid tissue was infiltrated which was associated with aggressive clinical behavior. The tumor stroma was relatively rarefactive. Mitotic

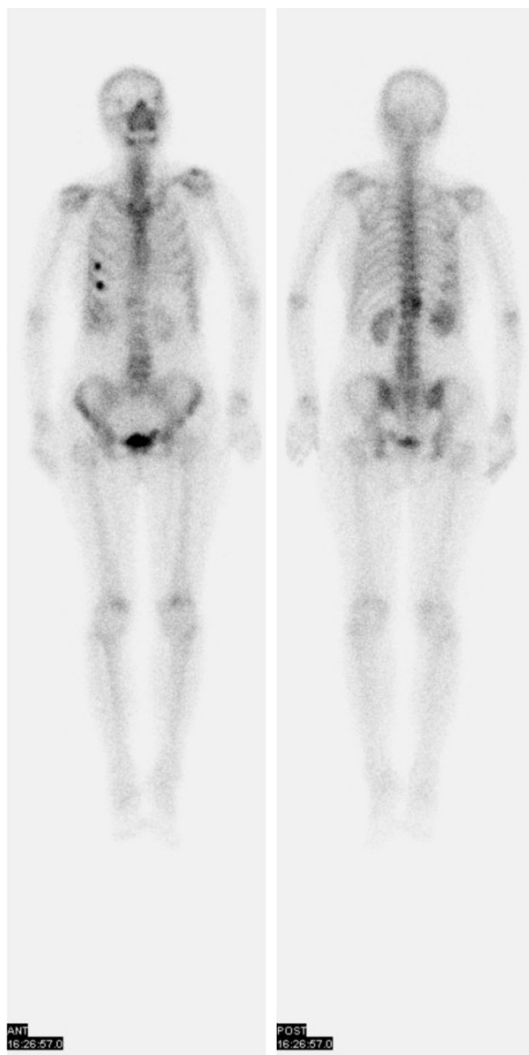
index was about 40 per 50 high-power fields, without lymphovascular invasion and lymph node metastasis (**Figure 4**).

Immunohistochemically, the tumor cells were positive for KIT and DOG1, but negative for CD34, S-100, SMA, Desmin and cytokeratin protein. KIT exon 11 mutation was found in the bone metastasis and the initial intestine lesion. Type of mutation was missense. The thoracic vertebrae lesion showed immunohistochemical and molecular features in common with the primary tumor, during targeted therapy. The patient remains alive for 2 years after the initial diagnosis.

### Discussion

GISTs show many morphologic, immunohistochemical, and molecular features in common with ICC. The tumors can have predominantly epithelioid (20%) or spindle cell cytomorphology (70%) or a combination of both epithelioid and spindle cell morphology (10%), and range from hypocellular to densely cellular lesions. And immunohistochemically GISTs express KIT protein, DOG1, and in the majority of cases, CD34. The identification of KIT gene mutations in the majority of GISTs has given GISTs added impor-

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**Figure 2.** Nuclear medicine examination revealed three metastatic bone lesions in the right fifth and sixth rib and the twelfth thoracic vertebrae.

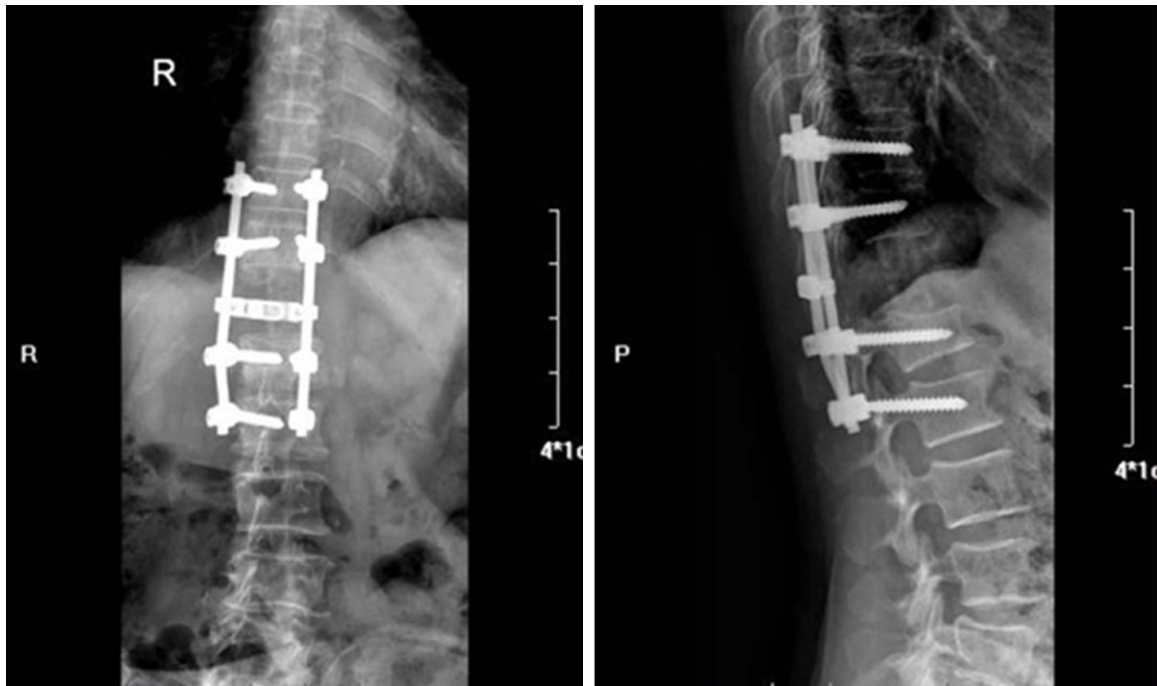
tance because it has become a paradigm for targeted therapy of oncogenic proteins/oncogene addiction in solid tumors. However the gold standard of therapy for GISTs is complete resection of the local mass. And for the tumors with high or intermediate risk of recurrence, based on the modified National Institutes of Health consensus criteria, the administration of imatinib markedly improve the rate of progression-free and overall survival [7]. Despite this, GISTs still have a high risk of metastatic relapse.

Unlike epithelial neoplasms of the gut, except in SDH deficient GISTs, they do not metastasize to lymph nodes. However, they metastasize to

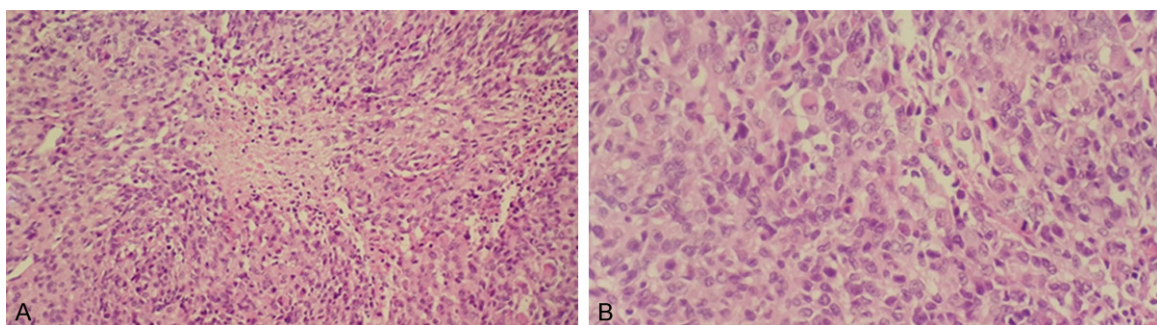
the liver or disseminate throughout the peritoneal cavity as numerous metastatic nodules. It is unusual for GISTs to metastasize outside of the abdomen, but dermal/subcutaneous, bone, brain, and lung metastases occur rarely. Most GISTs with rare metastatic sites were presented by case reports. In a series of reports concerning metastatic GISTs, the incidence of bone metastasis was about 3%-5.5% [2-4]. But the specific characteristics of patients with bone metastasis have not yet been identified. Suzuki K et al. [3] showed that the bone and liver metastases usually exhibited at the same time, and the most common site of bone metastasis was the spine, but the time between initial diagnosis and the development of bone metastasis varied. However, Nakajima T et al. [2] discovered that bone metastasis could be the primary metastatic manifestation in very rare cases. They also found primary tumors in sites other than the stomach especially developed bone metastasis, which also should be considered in patients with primary tumors at a high risk for recurrence or in initially malignant tumors with liver metastasis. Our present case developed the clinical recurrence on the liver, lung and abdominopelvic cavity using CT scan, after complete resection of the primary intestine tumor with high risk for recurrence. Though administration of the imatinib, the bone metastasis followed liver metastasis about less 1 year after the initial diagnosis, which suggested a malignant biological behavior.

The diagnosis of bone metastasis originating from a GIST should be often based upon clinical findings, bone fractures or pain. Imaging especially PET-CT or nuclear medicine technique is useful for the early diagnosis of bone metastasis. Jati A et al. [8] found the bone lesions are usually characterized by single or multiple lytic lesions with or without soft tissue involvement, and a sclerotic rim may appear around the metastatic lesions in response to treatment. Further, bone metastasis show intense fluorine-18 fluorodeoxyglucose (FDG) uptake. Our case also presented intense uptake on nuclear medicine imaging with multiple lesions of thoracic vertebrae and light cervical rib. Histopathology examination revealed a hypercellular epithelioid cell cytomorphology. Part of the cellular figures presented rhabdoid morphology that was a harbinger of high-grade or dedifferentiated component. Further target-

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**Figure 3.** Radiographical observations following surgery. The metastatic spine lesion was resected completely and reconstructed using a nanometer bone for tumor prosthesis.



**Figure 4.** Histopathological appearance of the bone metastasis. A. The resected mass revealed a hypercellular tumor with epithelioid cells and multifocal coagulation necrosis (hematoxylin and eosin stain,  $\times 200$ ). B. Part of the cellular figures presented rhabdoid morphology. And Mitotic index was about 40 per 50 high-power fields (hematoxylin and eosin stain,  $\times 400$ ).

ed therapy could make the tumor cells present rhabdoid morphology too. Multifocal coagulation necrosis, infiltration and the above morphology features suggested the aggressive clinical behavior. The thoracic vertebrae lesion showed immunohistochemical and molecular features in common with the primary tumor, during targeted therapy.

Due to the low incidence of bone metastasis, acknowledged and optimal therapy methods are not yet reached at present [9, 10]. For an isolated bone lesion, complete resection often

could achieve long term survival in the present study. But bone metastases, especially spinal lesions, are typically unresectable due to the infiltration of surrounding nervous tissue. Imatinib, the revolutionized treatment of advanced GISTs, could enable the long-term survival of patient, but dose escalation should rise to 800 mg/day in the absence of severe adverse drug reactions. Our patient was taken 800 mg/day after resection of bone metastases. In addition to targeted therapy, radiotherapy can be used for palliative purpose.

## Multiple bone metastases of a GIST

In conclusion, bone metastasis originating from GISTs is rare. When liver metastasis exists, the risk of bone metastasis, including lung metastasis, should be considered during long-term follow up, especially for the primary intestinal tract GISTs. And complete resection if possible and adjunctive targeted therapy are necessary.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Huanzhou Xue, Department of Liver-Gallbladder-Pancreas Surgery, People's Hospital of Zhengzhou University, Henan Provincial People's Hospital, 7 Weiwu Road, Zhengzhou 450003, China. Tel: +86-371-65580256; Fax: +86-371-65580256; E-mail: xuehuanzhou@sina.com

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