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Case report

Stereotactic ablative radiotherapy for bone metastasis of gastrointestinal stromal tumor: Case report and review of the literature

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. These tumors are rare and only make bone metastases at a rate of 5%.
Case summary: A 31-year-old male with a GIST presented with solitary bone metastasis at the right iliac bone. We performed stereotactic ablative radiotherapy (SABR) and achieved excellent local control. Herein, our case is presented, and a short review of the literature is carried out.
Conclusion: SABR should be considered as a treatment option in GIST with bone metastasis.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract that arise from the interstitial cells of Cajal.[1,2] These tumors are rare, accounting for only 1%–2% of all gastrointestinal malignancies, and they are often located in the stomach or small intestine.[3,4] It is seen with the same frequency in men and women, and more than 75% of patients are older than 50 years.[5]

All GISTs have malignant potential, and the prognosis depends on tumor size, mitotic rate and, tumor location.[6,7] Complete surgical resection with negative margins is considered as the standard treatment. These tumors most commonly carry an oncogenic mutation in the KIT receptor tyrosine kinase gene (CD117 antigen), or platelet derived growth factor receptor alpha (PDGFRA); thus tyrosine kinase inhibitors (TKIs) such as imatinib have a major role in the adjuvant treatment for the high-risk disease.[8,9]

Despite surgery and targeted therapy, many patients with GISTs still experience distant metastasis. The most frequent metastatic sites are reported to be in the liver and peritoneum.[10,11] In the literature, there are limited numbers of publications on bone metastasis of GIST, and they are limited to case reports or small series.[12–23] According to the SEER database, an isolated bone metastasis was found in 0.14% of patients, and the 5-year overall survival (OS) and median survival rates were 33% and 8 months, respectively.[24] Although the role of radiotherapy (RT) in GISTs is controversial, it is recommended, especially in patients with bone metastases to palliate pain. In this report, we present a case of GIST with solitary bone metastasis treated with the combination of TKI and stereotactic ablative radiotherapy (SABR) with an excellent outcome.

2. Case presentation

A 31-year-old male was admitted to the hospital with an incidental abdominal mass in 2015. He underwent surgical excision of the mass. Pathology revealed low-grade GIST (Fig. 1). In immunohistochemical studies, neoplastic cells were diffusely stained with CD117(c-kit), DOG1 and SMA. Desmin, S100, and CD34 were negative. The Ki67 proliferation index was around 5–10%. Local necrosis areas were seen through microscopical evaluation. The tumor was originated from the small intestine, 16 cm in the largest dimension without lymphovascular space invasion or perineural invasion. Mitotic rate was 1 mitosis per 5 mm^2. The serosal margins were positive, and the tumor was staged as pT4 according to the American Joint Committee on Cancer tumor/node/metastasis (TNM) classification for GISTs.[25] There was no lymph node metastasis.

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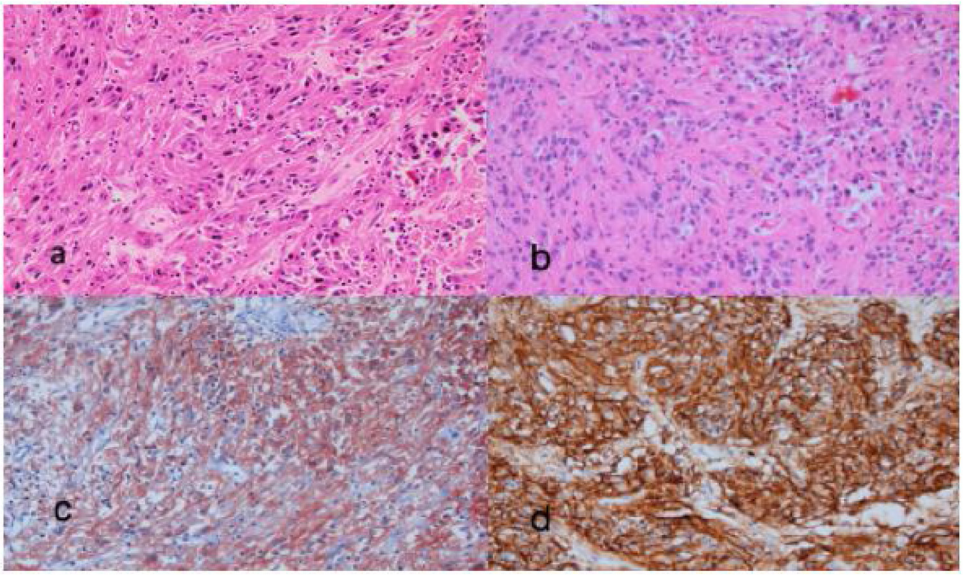

Fig. 1. Histopathology images of GIST, small intestine. (a-b: On hematoxylin-eosin staining, spindle neoplastic cells, c: CD 117 positivity in neoplastic cells, d: DOG1 positiviy in neoplastic cells).

After surgery, the patient is considered to have a high-risk disease. Adjuvant three years imatinib mesylate (400 mg daily) treatment was planned. However, after 2 years of treatment, he was admitted to the hospital with right hip pain. An abdominal computed tomography (CT) scan revealed a lytic lesion in the right iliac bone and positron emission tomography/computed tomography (PET/CT) scan showed 18-fluorodeoxyglucose (FDG) uptake in the same area (Figs. 2 and 3). CT-guided fine needle aspiration biopsy was performed, and pathology confirmed GIST metastasis. After the diagnosis of metastatic disease, imatinib was replaced with sunitinib, and the patient was consulted to our clinic for RT. We performed SABR, 24 Gy in 3 fractions with Novalis®system (BrainLAB AG, Feldkirchen, Germany) (Fig. 4). The patient's metastatic lesion in the right iliac bone was delineated as a gross tumor volume (GTV) as the area of disease seen on CT- and MRI-scan. Also PET avid areas contributed to GTV delineation. Clinical target volume (CTV) was defined as equal to the GTV. To allow for daily set up error, planning target volume (PTV) was created by adding 5 mm to the GTV as an institutional policy. Bowel, sacral plexus, bladder, rectum and hip joints were delineated as organs at risk (OARs) volumes. For target dose planning and delivery, 95% of the PTV had to be covered by at least 95% of the prescribed dose. Dose volume histogram (DVH) of the targets and normal tissues were evaluated. When the DVH parameters were examined, dose details for each OAR were: rectum V50 Gy < 3.5 cc, bladder V20 Gy < 15 cc, bowel V28 Gy < 20 cc, sacral plexus V30 Gy < 5 cc and the right hip joint V30 Gy < 10 cc, respectively.

Three months after SABR, follow up PET/CT showed a complete response in the right iliac bone (Fig. 5). Clinical complete response was also obtained during follow-up. The patient is still in remission at 16 months follow-up after SABR and have not had any acute or chronic side effects during or after SABR, treatment was well tolareted.

3. Discussion

The role of adjuvant RT in GIST is controversial.[4,21,26,27] The risk of toxicity depending on abdominal localization and the need for large RT fields limited the RT application. In addition, these tumors are considered to be "radioresistant", and RT is often used only for palliation in bone metastases.[12–14,18,20–23] However, there are small case series reporting that local RT may be effective in patients with inoperable or residual disease after surgery, or in the treatment of systemic therapy-resistant disease.[22,28] In the only prospective study evaluating the role of RT in progressing GISTs, response was obtained in only 8% of cases with conventional fractionation (1.8–2 Gy/day, 30–40 Gy).[22] Stable or progressive disease was found in 80% and 12% of patients, respectively. Although responses to RT were rarely seen, the median duration of stabilization was 16 months.

In the literature, for patients with bone metastasis, local therapies including surgical excision and/or RT can be used.[29,30] The choice of these methods can be customized according to the characteristics of the patient. There is no clear data regarding RT scheme or dose today. However, better local control rates have been reported with hypofractionated RT.[21,28] In parallel with technological developments, SABR can be applied with limited fields and high fraction dose in a short overall treatment time. In the presence of oligometastatic disease, long-term survival can be achieved with SABR to all metastatic sites in several tumor types.[31] However, a limited number of publications on SABR in GISTs[21,28] are available. In one retrospective study, 15 patients with locally advanced or metastatic disease were mostly treated with palliative RT.[21] Nine tumors in this particular study were treated with SABR with different fractionation and total doses, 6 of them at bone location. Concurrent TKIs were administered in 41% of patients. Partial radiographic response was seen in 35% of tumors and the 6-month local progression-free survival was 57%. Patients treated with SABR (>5 Gy per fraction) had a radiographic response rate of 63%, suggesting that GISTs were not radioresistant and more sensitive to higher radiation dose. In our patient, we used 8 Gy fraction dose (8 Gy in 3 fractions) which may lead to better tumor control.

Patients with GIST who have bone pain should be evaluated for metastasis as we did to our patient. In addition, a biopsy from the suspicious lesion should be performed in order to rule out imatinib-induced bone marrow necrosis.[32,33] Therefore, as in our patient, CT-guided biopsy is required in the confirmation of metastatic disease, especially in patients with a solitary lytic bone lesion.[15]

In 2017, Kosemehmetoglu et al. described the clinical and pathological characteristics of bone metastases in GIST.[15] They analyzed 7 cases and reviewed an additional 17 cases from literature which were published before 2014. In this series, the median age was 61

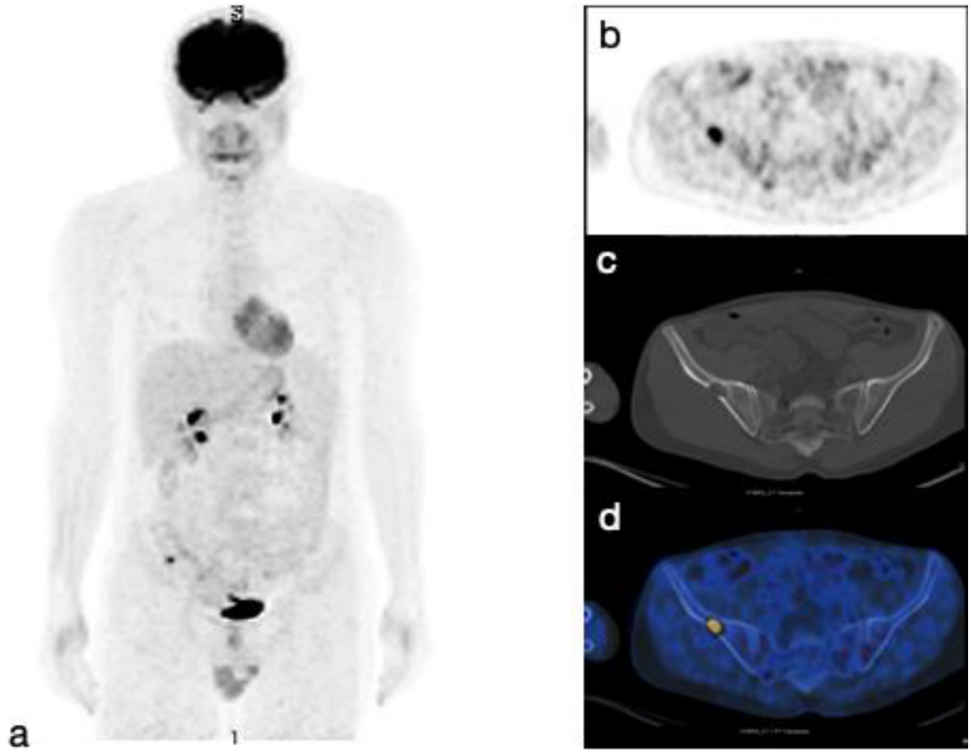

Fig. 2. FDG PET-CT images showed increased uptake in the solitary osteolytic lesion in right iliac bone (a: Maximum intensity projection images (MIP), b-d: FDG PET, CT and fusion images).

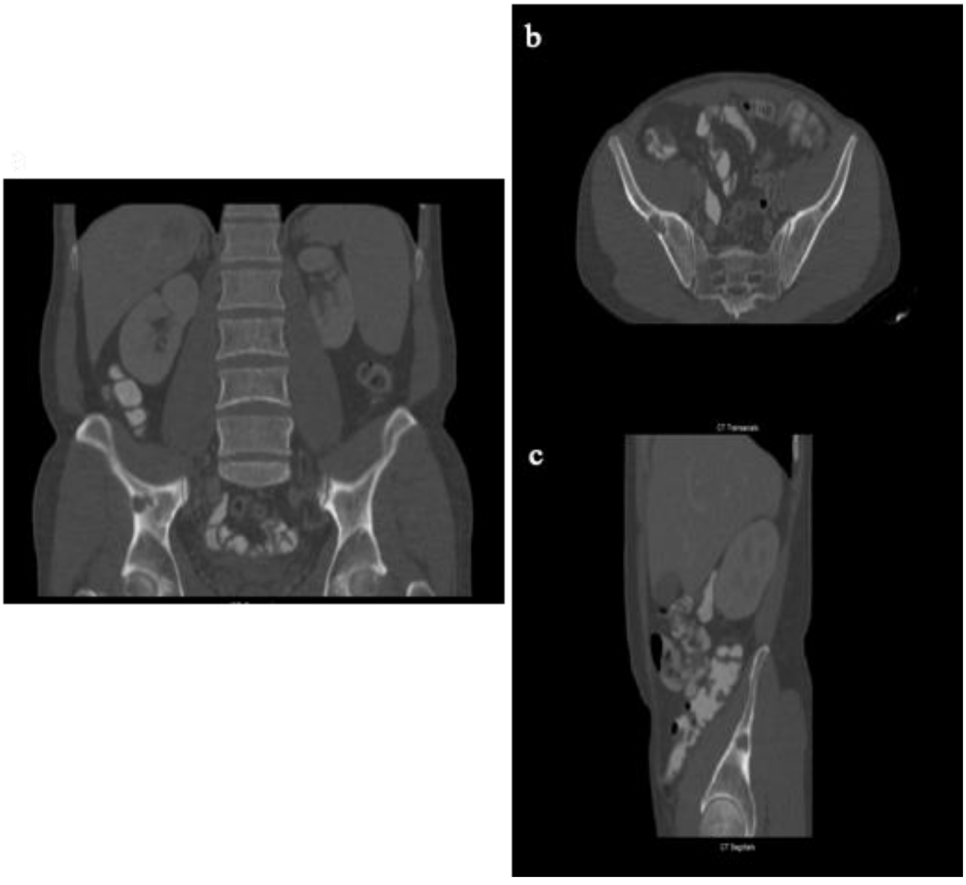

Fig. 3. Contrast-enhanced CT at the bone window showed a lytic bone lesion without any sign of local recurrence (a: coronal,b: axial, and c: sagittal images).

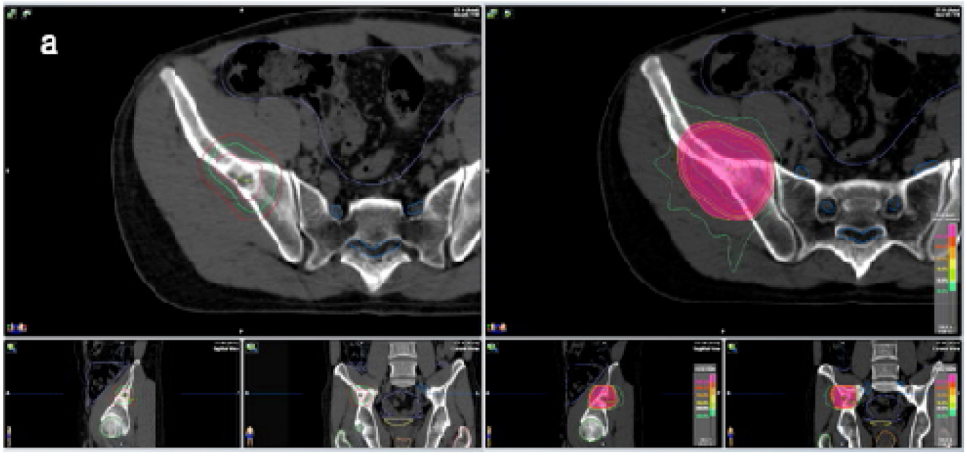

Fig. 4. Radiotherapy treatment plan (a: The stereotactic ablative radiotherapy (SABR) target volume delineations, b: SABR plan showing the lesion covered by the 95% isodose line).

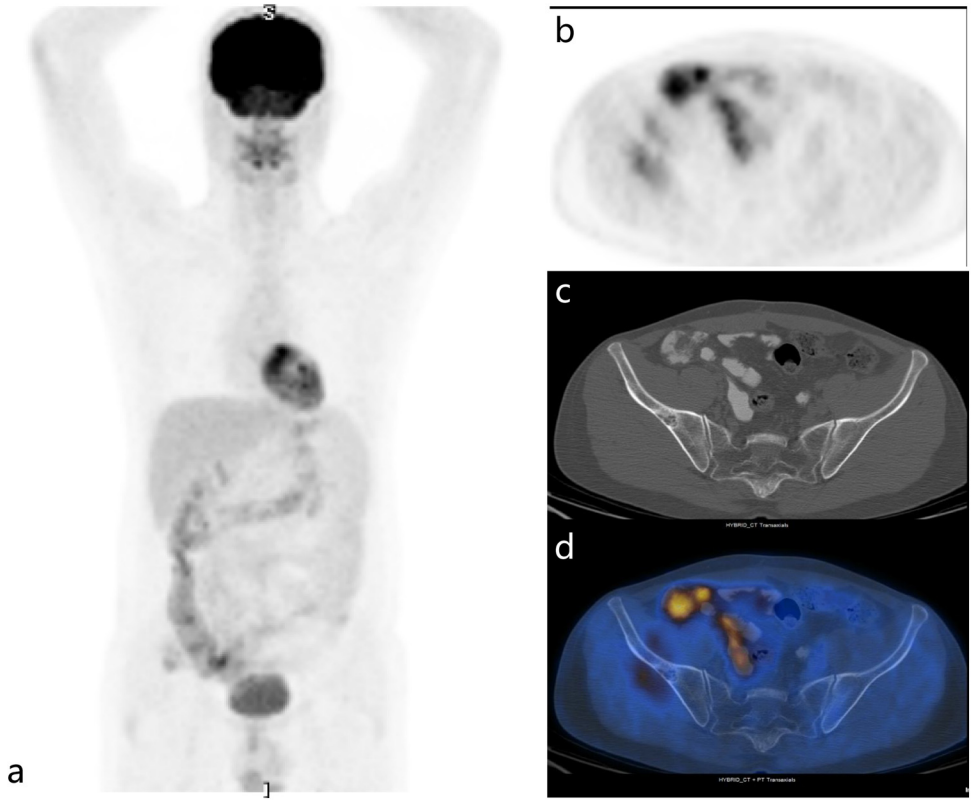

Fig. 5. FDG PET-CT images after SABR, showed disappearance of FDG uptake in the solitary osteolytic lesion in right iliac bone with increased sclerosis compatible with therapy response (a: Maximum intensity projection images (MIP), b-d: FDG PET, CT and fusion images). Mild reactive-inflammatory FDG uptake in peri-lesional muscle was also noted.

years (range, 40–92 years) and the small intestine (29%) and the stomach (25%) were the most common locations. The mean time to metastasis was 4.7 years (range, 0–20 years). Isolated bone metastases were seen in 17% of the cases and were solitary in 58%. When we looked to our patient, he was much younger than the literature. GISTs rarely occur in patients under 40 years. The primary tumor was located in the small intestine and regarding the tumor size, he was considered as high-risk for metastases at diagnosis.

After 2 years of imatinib therapy, our patient developed an isolated solitary bone metastasis which was treated with sunitinib and SABR. Combined treatment was well tolerated, no treatment-related toxicity was observed, and the lesion was resolved completely after 3 months of treatment. However, the effect of local control cannot be attributed to RT alone because our patient is using TKI concurrently with SABR. There are limited numbers of publications in the literature regarding the use of TKIs concurrently with RT.[21] In these studies, TKIs were administered safely in a similar manner as our case and no significant toxicity was observed.

4. Conclusion

SABR should also be considered as a treatment option in GISTs to increase local control in addition to systemic therapy, especially

in oligometastatic disease. Although RT is not effective in these tumors with conventional fractionation, it may have a possible role with hypofractionated stereotactic RT.

Conflict of interest

None declared.

Financial disclosure

None declared.

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