



A Rare Case of a Metastatic Gastrointestinal Stromal Tumor (GIST): a Case Report and Review of the Literature

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Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of gastrointestinal (GI) tract, accounting for less than 1% of all GI tumors. The incidence of GIST is estimated to be approximately 10–20 per million people, per year [1]. GISTs are typically seen in the stomach (50–60%), followed by small intestine (30–35%), colon and rectum (5%), and esophagus (<1%) [2, 3]. There are only 38 cases of GISTs with metastasis to the bone that have been reported in the English literature [4–28].

Case Presentation

We present a case of a 62-year-old Filipino man with past history of hypertension, hyperlipidemia, and benign prostatic hyperplasia who presented with a severe dull neck pain and stiffness. Pain started 2 weeks prior to presentation and was not relieved with neither over the counter non-steroidal anti-inflammatory drugs nor opioids. He denied neck weakness, numbness, paresthesia, recent trauma, fever, chills, or recent weight loss. On close reviewing of the patient's records, he

was evaluated 3 months prior to this presentation for rectal pain, tenesmus, and bleeding per rectum. Further investigation at that time with colonoscopy showed internal hemorrhoids and rectal polyps that were hyperplastic on histopathology. He was prescribed supportive treatment with only mild improvement of symptoms. On this presentation, his vital signs were within the normal range. Examination of the neck revealed tenderness over the left trapezius and para-cervical muscles, associated with reduced range of motion of neck to the left side due to pain. Rectal exam showed normal tone of anal sphincter with no masses. Complete blood count and complete metabolic panel were normal. Magnetic resonance imaging (MRI) of the cervical spine (Fig. 1) showed an enhancing mass, about 5 cm in size, within the left subarticular zone extending along the 2nd, 3rd, and 4th cervical vertebrae. Computed tomography (CT) of the abdomen and pelvis revealed an enhancing mass within the recto-vesical pouch (Fig. 2), measuring up to 7.6 cm, and multiple hepatic lesions, with the largest lesion measuring 8.6 cm in diameter (Fig. 3). Ultrasound-guided percutaneous FNA of the liver lesion was performed. The rapid on-site evaluation (ROSE) of the air-dried cytology smears with a rapid Romanowsky stain revealed neoplastic cells with elongated hyperchromatic nuclei

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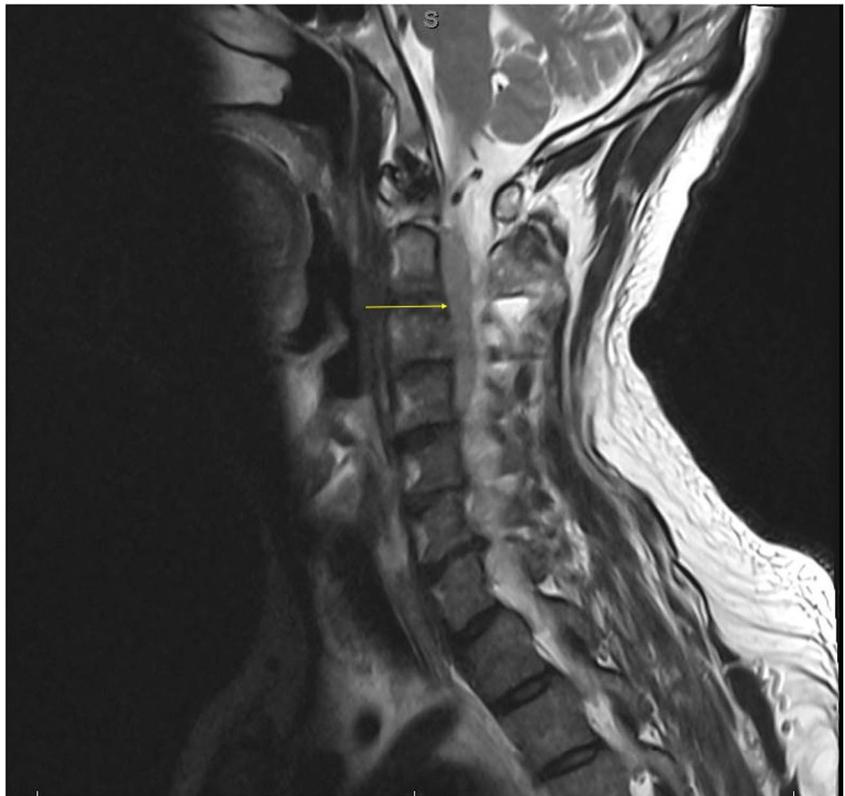
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Fig. 1 MRI of cervical spine is showing an enhancing mass, about 5 cm in size, within the left subarticular zone extending along the 2nd, 3rd, and 4th cervical vertebrae



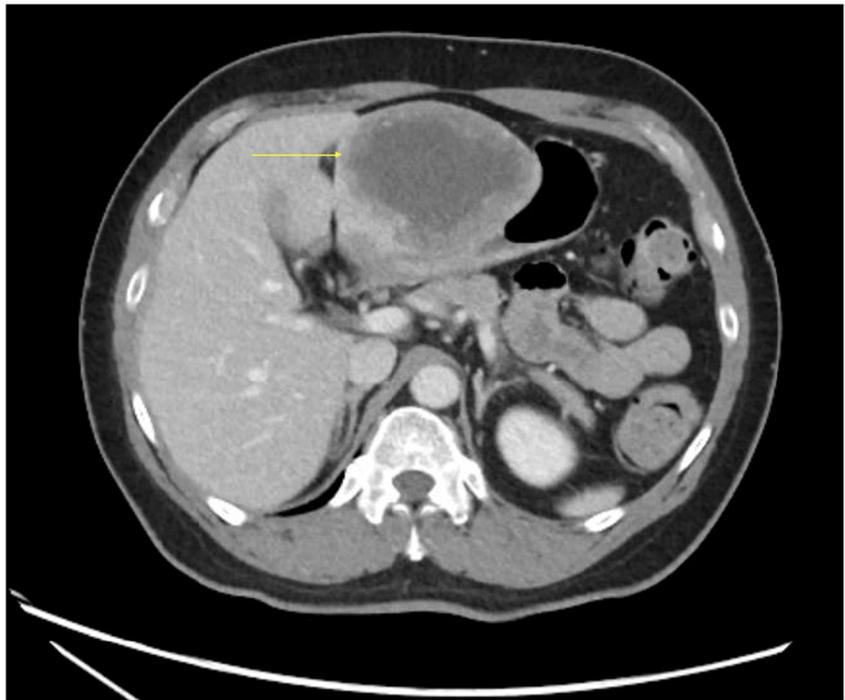
(Fig. 4). The differential diagnosis at that point was metastatic colorectal adenocarcinoma versus metastatic spindle cell neoplasm. A core biopsy was obtained. A Papanicolaou stain also visualized neoplastic cells with elongated hyperchromatic nuclei (Fig. 5). The core biopsy of the liver mass showed a cellular spindle cell neoplasm with a mitotic index of more than 2–5 per 50 high-power field (HPF) (Fig. 6) with the following immunohistochemical profile: immune-negative for pankeratin (AE1/3), smooth muscle actin (SMA), desmin, and S-100, ruling out carcinoma, sarcoma, leiomyoma, and

melanoma, respectively. The core biopsy was immune-reactive for c-KIT-CD117 (Fig. 7) and DOG1 (Fig. 8) immune markers, confirming the diagnosis of gastrointestinal stromal tumor (GIST). Given the presence of multiple liver lesions, along with a high mitotic index (0–2 mitosis per high-power field), a diagnosis of metastatic malignant gastrointestinal stromal tumor (GIST) was rendered. Bone scintigraphy revealed increased uptake in the humerus, scapula, pelvis, and sternum as well as the cervical and lumbar spine. Neurosurgery was consulted for possible surgical resection

Fig. 2 CT of the pelvis is revealing an enhancing mass within the recto-vesical pouch measuring up to 7.6 cm



Fig. 3 CT of the abdomen is revealing multiple hepatic lesions, with the largest lesion measuring 8.6 cm in diameter



of the cervical mass. However, the tumor was deemed to be unresectable at that time with recommendation to treat medically. The patient was started on targeted therapy imatinib, a tyrosine kinase inhibitor (TKI), 400 mg daily. Two months through treatment, he reported a dramatic improvement of the initial neck pain. Repeat cervical MRI showed a dramatic decrease in the size of the neck mass (Fig. 9). Repeated imaging showed a decrease in the size of the rectal mass from 7.3 to 5.5 cm (Fig. 10), and decrease in the size of the hepatic mass from 8.6 to 5.1 cm (Fig. 11). Follow-up bone scintigraphy

revealed only mild improvement in bony lesions. Patient is still receiving imatinib treatment.

Discussion

GISTs are the most common mesenchymal neoplasms of GI tract, accounting for less than 1% of all GI tumors [1]. They originate from interstitial cells of Cajal—intestinal pacemaker cells that arise from the muscularis propria of the GI tract wall

Fig. 4 The rapid on-site evaluation (ROSE) of the cytology smears that were fixed with a rapid Romanowsky stain revealed neoplastic cells with elongated hyperchromatic nuclei (Romanowsky stain, $\times 400$ magnification)

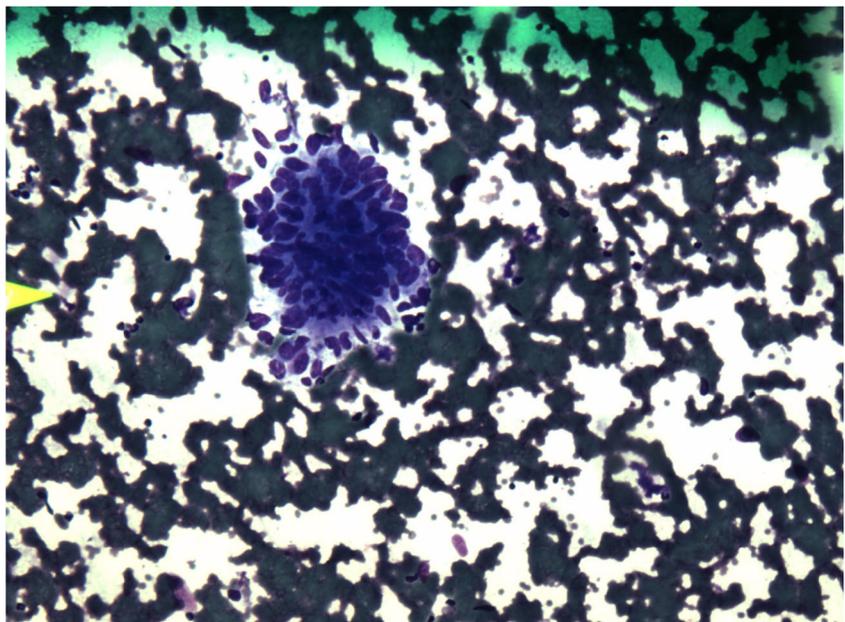
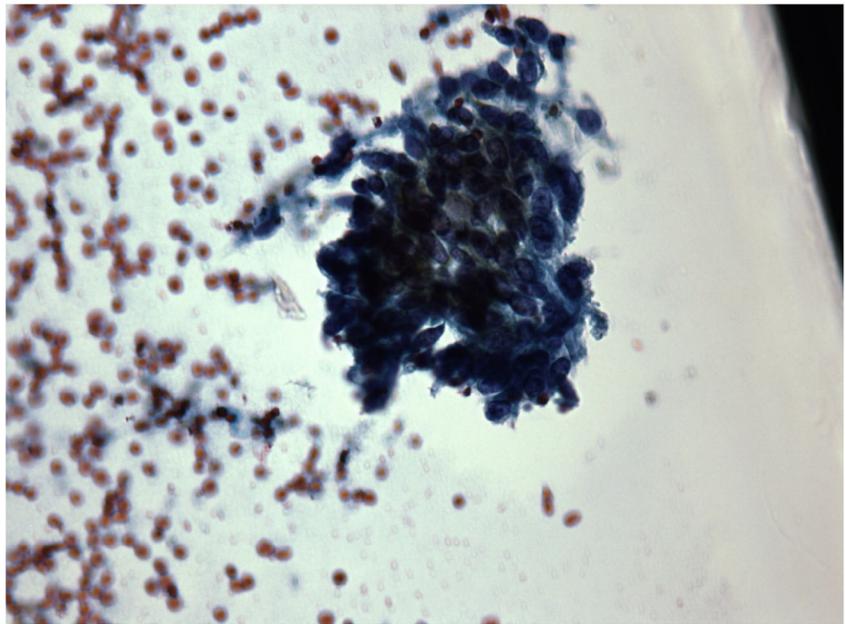


Fig. 5 Cytology smears fixed with Papanicolaou stain revealed neoplastic cells with elongated hyperchromatic nuclei (Papanicolaou stain, $\times 400$ magnification)



[13]. They are characterized by mutations in exons of KIT genes (stem cell growth factor receptor, CD 117) or exons of platelet-derived growth factor receptor- α (PDGFRA) genes [2]. However, approximately 10 to 15% of GISTs lack the mutations in KIT and PDGFRA, and those are referred to as wild-type GISTs [29].

Typically, GIST arise in older individuals, mostly ranging 50s to 60s and are marginally more common in males compared to females [30]. Although they are most commonly seen in the alimentary tract (95%), few cases of GISTs were diagnosed outside it, usually in the omentum, mesentery, retroperitoneum, urinary bladder, ureter, uterus, pancreas, and gall bladder. This type of GIST is referred to as an

extra-gastrointestinal stromal tumor (EGIST) [2, 31]. In this case, our patient's primary tumor is believed to be originated from the recto-vesical pouch which is extremely rare [3].

The clinical presentation of GIST is unpredictable; only 70% of patients are symptomatic, while 20% are asymptomatic and almost 10% of cases are detected at autopsy [1]. Presentation varies from an incidental radiological finding to cases of intestinal obstruction and life-threatening upper or lower GI bleeding [32]. Our patient presented with an initial complaint of neck pain which is an extremely rare presentation. On a thorough literature review, we could identify only one similar case described by Ishi et al. of a metastatic GIST in the craniovertebral

Fig. 6 Ultrasound-guided core biopsy of the liver mass showed a spindle cell neoplasm with mitotic figures as pointed by arrow and arrowhead (hematoxylin and eosin stain, $\times 400$ magnification)

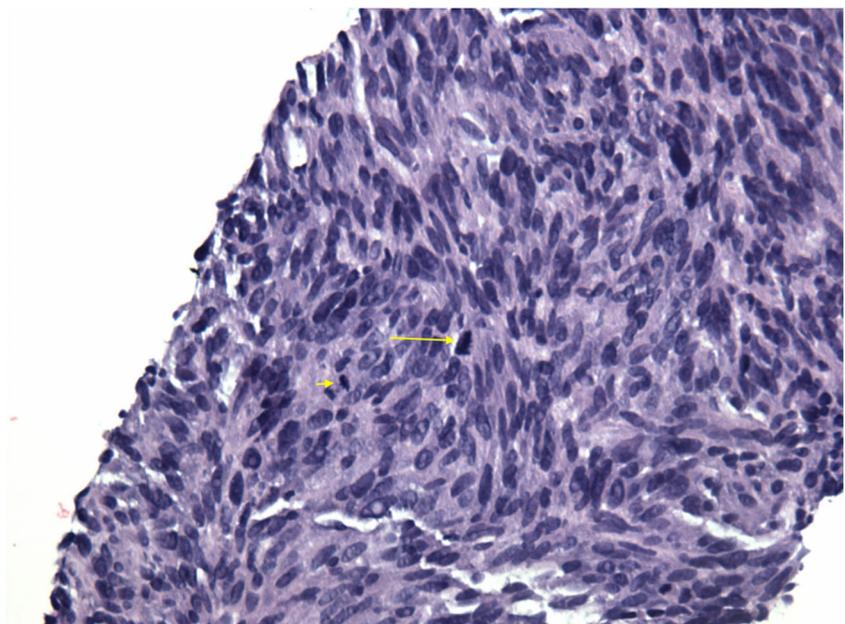
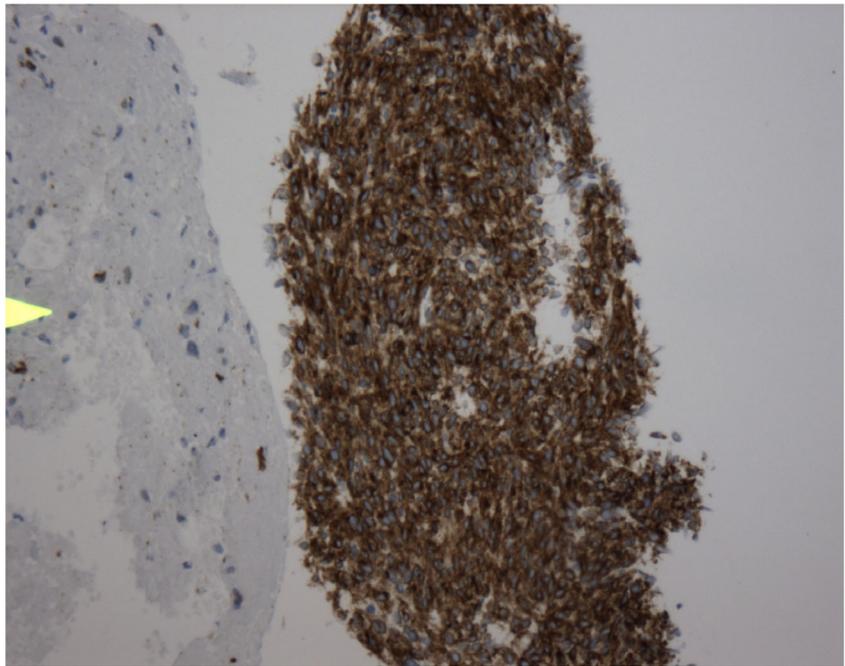


Fig. 7 The core biopsy of the liver mass showed a spindle cell neoplasm that is positive for c-KIT protein after it was immunohistochemically stained using anti-CD117 antibody (C-KIT stain, $\times 100$ magnification)



junction that presented with neck pain and was managed successfully with surgical resection [33].

Upon reviewing the most recent date of the Journal of the National Comprehensive Cancer Network (JNCCN) in 2007 [34], the prognosis of gastrointestinal stromal tumor (GIST) depends on both the size and the mitotic index of the primary tumor as well as the location. Our patient has presumed rectal GIST that has a size of 7.6 cm and mitotic index of more than 2–5 per 50 high-power field (HPF). Based on this presentation, there is currently insufficient data to risk stratify his tumor. However, given the presence of multiple liver lesions as well as bone

lesions, a diagnosis of metastatic malignant gastrointestinal stromal tumor (GIST) was rendered.

GISTs usually metastasize to the omentum, liver, less frequently to the lymph-nodes, lungs, and very rarely to the bones [1]. At the time of our patient's presentation, bone scintigraphy visualized metastasis to both axial and peripheral skeleton, involving the humerus, scapula, pelvis, sternum, and cervical and lumbar spine. To our best knowledge, there are only 38 cases of GISTs with metastasis to the bone that have been reported in the English literature prior to this case [4–28]. Further analysis of previous cases reveals a close association between liver and bone involvement in metastatic GIST disease, with 26 out of 39

Fig. 8 The core biopsy showed a spindle cell neoplasm that is immune-reactive to the DOG 1 stain (DOG1 stain, $\times 100$ magnification)

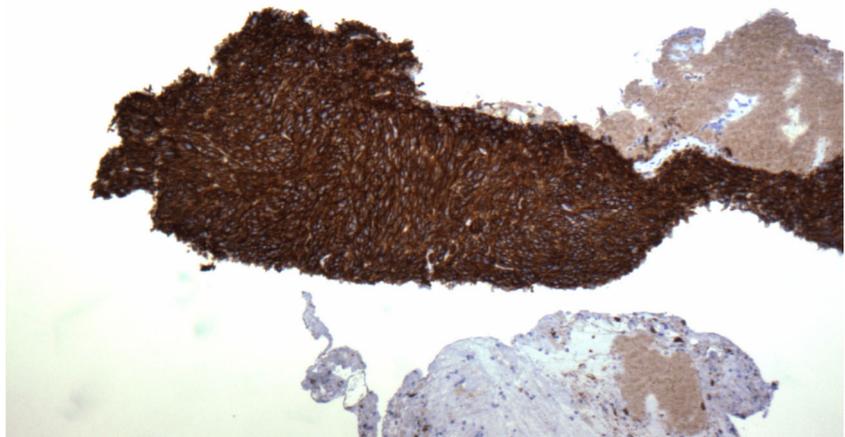


Fig. 9 Two month after treatment initiation, repeat cervical MRI showed a dramatic decrease in the size of the neck mass



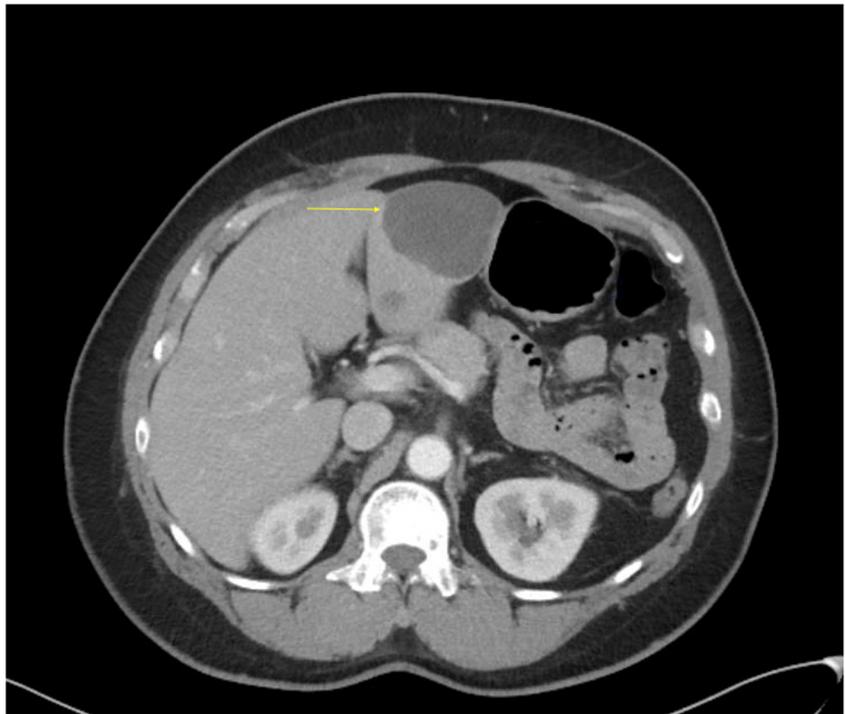
patients suffering of both liver and bone metastases. Almost 80% of patient who suffered from bone metastasis are males [4]. Moreover, although the most common location of primary GIST is the stomach [1], only 34% (13/39) of patients with

bone metastasis presented with a primary gastric GIST. This finding was initially discussed by Nakajima et al. [12] and would indicate that an extra-gastric GIST per se would raise a concern for metastatic bone disease.

Fig. 10 Two months after treatment initiation, a follow-up CT of the pelvis showed a decrease in the rectal mass size from 7.3 to 5.5 cm



Fig. 11 Two months after treatment initiation, a follow-up CT of the abdomen showed a decrease in the size of the hepatic mass from 8.6 to 5.1 cm



Management of GISTs depends upon the extent of the disease. Prior to the discovery of KIT and PDGFRA genes mutation, surgery was the only available treatment for GIST, with recurrence rate in those undergoing surgery approaching 50%, irrespective of margins' negativity [35]. Dematteo et al. could prove in a 200-patient prospective study that those with primary disease who underwent complete resection had a median survival of 66 months, compared with 22 months in those who had an incomplete resection of an unresectable tumor [36]. Conventional adjuvant chemotherapy and radiotherapy have not proven to be effective. Median survival for GIST patient treated with cytotoxic chemotherapy is approximately 12 months [35]. In correlation with this, surgical resection of the tumor is the gold standard treatment for localized disease. The goal of surgical treatment is to achieve complete gross resection (i.e., negative microscopic margins and intact pseudo capsule without tumor rupture). Resection with wide margins has not shown any better outcomes [35]. TKIs remain the 1st-line agents for those with unresectable primary disease or metastatic disease. TKIs have proven to be useful in the neoadjuvant setting as well. Current NHCC guidelines recommend the use of neoadjuvant TKIs in both large tumors and poorly positioned GISTs that are considered marginally resectable.

In those with metastatic disease, up to 80% of patients attain a partial or complete response to imatinib [37]. Although a higher dose of imatinib has been associated with a progression-free survival, overall survival is actually unchanged with higher doses [35]. Despite that clinical trials for patients with advanced GISTs treated with imatinib reveal a median time for objective response to be about 13 weeks,

our patient showed a dramatic response both clinically and radiologically in less than 8 weeks.

In conclusion, skeleton is a rare and yet a possible site of GIST metastasis. Presentation can be deceptive and late. A low threshold for clinical suspicion should always be in mind, especially with remote gastrointestinal symptoms. Currently, TKIs play an important role in controlling tumor progression in metastatic GIST. Optimum timing of surgical intervention is still unclear and further studies are needed to investigate the best timing of operative management in patients with metastatic GIST disease.

Authors' Contributions H Sarairoh and O Tayyem wrote the manuscript and reviewed the literature. R Nawgiri helped in writing the manuscript and providing the cytology smears and histopathology slides. H Sarairoh, O Al Asad, and I Alawin critically revised the manuscript for important intellectual content. H Sarairoh, R Nawgiri, and I Alawin supervised the process and approved the final draft. H Sarairoh is the corresponding author and is the article guarantor.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Consent Consent was obtained from patient.

Disclosure Statement This case was presented as a poster at the 2017 American College of Physician (ACP) National meeting: March 29–April 1, 2017, San Diego, California. All the co-authors consent to submit the manuscript to the Journal of Gastrointestinal Cancer. All the co-authors confirm that the content of the manuscript has not been published or submitted for publication elsewhere.

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