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Case Report

Large incidental gastrointestinal stromal tumors in a patient presenting with acutely symptomatic nephrolithiasis: A case report

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal neoplasms, representing approximately 1%-2% of all primary gastrointestinal malignancies. Incidental GISTs are often less than 1 cm when discovered and have been reported predominantly in obese patients undergoing surgery for other medical indications. We present the rare case of a large incidental GIST in a nonobese patient with acutely symptomatic nephrolithiasis. Large GISTs may be treated with neoadjuvant imatinib mesylate to reduce tumor size prior to surgery, though some tumors may experience little change in size despite effective treatment. Treatment response for GISTs can be monitored via imaging studies, such as computed tomography or magnetic resonance imaging, but computed tomography is generally preferred over magnetic resonance imaging.

This study was conducted at Cooper University Hospital, Department of Radiology at 1 Cooper Plaza, Camden, NJ 08103, USA.
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Introduction

Many incidental findings during imaging studies, such as radiographs, computed tomography (CT), and magnetic resonance imaging (MRI), are clinically irrelevant. Occasionally, incidental findings may be concerning and warrant further workup to rule out serious diseases or anomalies. Gastrointestinal stromal tumors (GISTs) are the most common primary mesenchymal neoplasms occurring in the gastrointestinal (GI) tract, comprising 1%-2% of all primary GI tumors. Periodically, GISTs have been reported to be found incidentally during workup of other abdominal complaints through either imaging studies, laparotomies, or autopsies [1,2]. They originate from the interstitial cells of Cajal and predominantly arise in the stomach or small bowel, although they may occur anywhere along the gastrointestinal tract [3–5]. Approximately 80%-90% of these tumors contain a mutant form of transmembrane tyrosine kinase receptor (KIT) or platelet-derived growth factor receptor alpha (PDGFRa), both of which are receptor tyrosine kinases [6]. GISTs present most commonly during the seventh decade of life with a median age of diagnosis of 60 years old. Presenting symptoms include GI bleeding, which may manifest as anemia, or findings due to mass effect, such as vague abdominal discomfort, early satiety, and a palpable mass [7]. Around 30% of GISTs have been reported to be found incidentally, 10% of which were discovered during autopsy [8]. Treatment of GISTs consists of surgery for localized and nonmetastatic tumors, with surgery and adjuvant imatinib mesylate, a tyrosine kinase inhibitor (TKI), reserved for large, invasive, and/or metastatic tumors [9–11]. Most incidental GISTs are noted during gastric surgery in obese patients or in patients with other coexisting GI tumors [12]. We report the incidental finding of a large, high grade GIST tumor in a patient undergoing workup for unilateral flank pain with associated hematuria.

Case report

A 57-year-old man presented to the emergency room with complaints of intermittent left flank pain with radiation to the left groin for 5 days. Preliminary urinalysis was significant for hematuria. At the time, his medical history was significant only for chronic back pain. On physical exam, his body mass index (BMI) was 26.62. A CT scan of the abdomen and pelvis showed a 0.3 cm nonobstructing left renal calculus (Fig. 1), along with an incidental $13 \times 5 \times 10.5$ cm mass in the left upper quadrant of the peritoneal cavity. The mass was contiguous with the anterior border of the stomach and the left lobe of the liver. Due to the small size of the renal calculus, the patient was managed supportively. A bolus of intravenous (IV) normal saline was administered for hydration, and an IV injection of ketorolac was given for pain control. He was later discharged with a short course of oral oxycodone and passed the stone spontaneously with no issues. For his incidental mass, fine needle aspiration was performed, and subsequent cytology revealed spindle cells that stained positively for c-KIT, CD34, and vimentin, findings consistent with a GIST. The Ki-67 proliferative index was low at 2%.

The patient was then started on a course of neoadjuvant chemotherapy consisting of imatinib mesylate 400 mg daily, which was eventually reduced to 300 mg due to significant adverse effects, including bleeding mouth ulcers, loose stools, and light headedness. After 90 days of treatment, a repeat CT of the abdomen and pelvis showed minimal change in the size of the GIST. In addition, the demarcation between the tumor and the stomach was less conspicuous than previously reported.

The mass was resected with a partial gastrectomy. There were no perioperative complications, and the patient tolerated the procedure well. Gastric margins showed no involvement by the GIST, and 8 lymph nodes were without evidence of

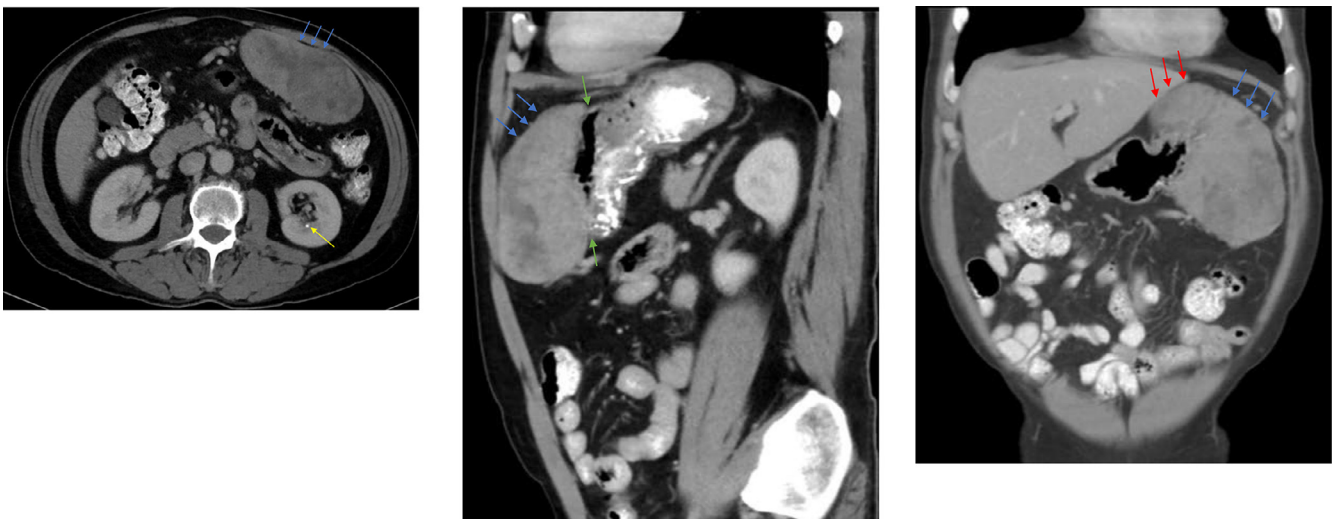

Fig. 1 – Axial, sagittal and coronal CT images of the abdomen demonstrate a 13 x 5 x 10.5 cm heterogeneously enhancing mass (blue arrows) abutting anterior wall of the stomach (green arrows) and the left hepatic lobe (red arrows) and a 0.3 cm nonobstructing left renal calculus (yellow arrow). (Color version of figure is available online.)

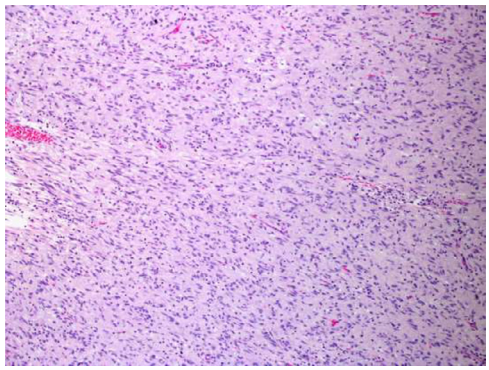

Fig. 2 – Gastrointestinal stromal tumor, spindle cell type. The tumor is moderately cellular and composed of uniform spindle cells in a hyalinized matrix (H&E, ×100).

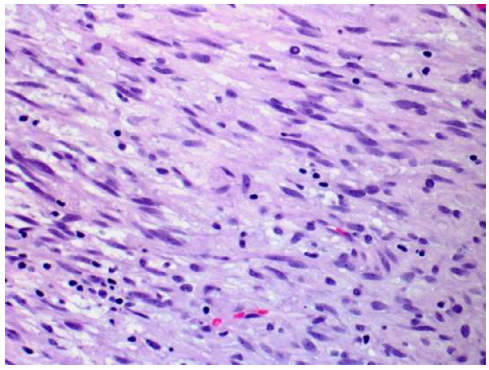

Fig. 3 – Gastrointestinal stromal tumor, spindle cell type. Higher magnification shows spindle cells with elongated nuclei, inconspicuous nucleoli and a moderate amount of eosinophilic cytoplasm (H&E, ×400).

metastatic disease. Surgical pathology showed uniform spindle cells with elongated nuclei, inconspicuous nucleoli, and a moderate amount of eosinophilic cytoplasm in a hyalinized matrix, giving final confirmation of disease (Figs. 2-3). Further analysis revealed a PDGFRa mutation with no c-KIT mutation, as well as a specified mitotic rate of 5 per 50 high powered fields.

Discussion

Many GISTs are clinically asymptomatic at presentation, but when present, symptoms are often nonspecific, including early satiety and abdominal fullness, or obstructive depending on the tumor size and location [13,14]. Not surprisingly, our patient reported no symptoms relating to his GIST prior to its incidental discovery. What is remarkable, however, is the nature of his presentation, especially in the context of such a large tumor. To our knowledge, this is the first case report of a patient presenting with acutely symptomatic nephrolithiasis found to have a large incidental GIST. The size of a GIST is particularly important when trying to establish a prognosis. The Fletcher model uses tumor size and mitotic activity to determine the metastatic potential of GISTs, with any tumor greater than 10 cm considered high risk regardless of the number of mitoses per high-power field [15]. Miettinen et al modified the Fletcher model by including tumor site as an additional prognostic factor, with gastric GISTs having overall more favorable outcomes than small intestinal tumors of the same size and mitotic rate [13,14]. Using the Fletcher model, our patient's tumor would be considered high risk due to its size, but with application of the Miettinen model, his tumor was determined to be intermediate risk. GISTs which are found incidentally usually have very low to low risk of malignant potential [12,16,17].

Incidental GISTs have been reported predominantly in obese patients during laparotomies or autopsies [1,2]. Mean tumor size for incidental GISTs during obesity surgery has been reported as 0.8 cm [18], while those found incidentally during resection of other upper GI neoplasms were found to be close to 0.5 cm in size [19]. GISTs discovered during laparoscopic surgery have also been small at the time of discovery, measuring less than 1 cm [20]. Historically, incidental GISTs have been small at the time of presentation. However, they have the capacity to grow into remarkably large tumors, ultimately presenting with typical abdominal symptoms. One study reported a large 20 cm × 20 cm GIST, but the patient presented with abdominal and constitutional symptoms, including fatigue and vomiting likely due to mass effect [21]. The largest reported GIST to date was 42 cm in a 65-year-old man who presented with significant weight loss, early satiety, dyspnea, and progressive abdominal distention for 1 year [22]. Our patient who presented with acutely symptomatic nephrolithiasis was found to have an incidental 13 cm GIST, which is much larger than the reported size of other incidental GISTs. Additionally, the discovery of the GIST during workup for flank pain and hematuria in our nonobese patient is also unique compared to prior literature on incidental GISTs. Overall, this case differs from previous reported cases of incidental GISTs in that the patient was not obese, was asymptomatic and only diagnosed because of imaging done to identify potential nephrolithiasis, yet the tumor was much larger than typical incidentally found GISTs.

For localized nonmetastatic GISTs, surgical resection with clear margins remains the most definitive form of treatment. Preoperative localization of the tumor using endoscopy or CT is crucial, as this will determine the surgical approach, but precise localization may be challenging in patients with GISTs >10 cm [20]. Gastric GISTs are commonly treated by wedge resection rather than conventional gastrectomy [23]. For tumors originating from the small bowel or colon, segmental bowel resection is performed, though duodenal involvement may require a pancreaticoduodenectomy [24]. Due to decreased surgical trauma, pain, blood loss, and recovery time, minimally invasive procedures are gaining popularity across many surgical specialties. Studies have shown that laparoscopic resection is safe and effective for GISTs up to 12 cm without evidence of local invasion on imaging or endoscopy [23,25–27]. When considering laparoscopic management of large GISTs, primary concerns include tumor rupture and feasibility of obtaining clear margins [23]. For these reasons, open surgical resection is generally preferred over laparoscopy for large GISTs.

Postsurgical pathologic analysis is important for diagnostic confirmation of GISTs, particularly in patients for whom fine needle aspiration is not possible or has been unsuccessful. Most GISTs are well-circumscribed lesions arising within the wall of the stomach or intestine. Large tumors may ulcerate the overlying mucosa. On gross cut section, GISTs vary from fleshy tan-white to pink-tan and may show areas of hemorrhage, necrosis, or cystic change [28]. The histomorphology is variable and includes pure spindle cell (70%), pure epithelioid cell (20%) and mixed spindle, and epithelioid cell types (10%) [15]. GISTs of all types usually have a monotonous appearance with minimal cytologic atypia or mitotic activity [28]. Spindle cell GISTs are composed of intersecting fascicles of uniform, elongated cells that have nuclei with fine chromatin, inconspicuous nucleoli and moderate amounts of pale to eosinophilic cytoplasm. There are several histologic variants of spindle cell GISTs. Sclerosing spindle cell GISTs are paucicellular contain abundant collagenous matrix and often have calcifications. The palisaded-vacuolated type displays a spindle cell pattern with rhythmic nuclear palisading and variably prominent perinuclear vacuolization. Hypercellular spindle cell GISTs contain crowded sheets of spindle cells, and sarcomatous spindle cell GISTs show significant nuclear atypia and mitotic activity [13]. Epithelioid GISTs are composed of nests or sheets of rounded cells with abundant cytoplasm and may show sclerosing, dyscohesive, hypercellular, and sarcomatous subtypes [13]. Several immunohistochemical markers are useful in the evaluation of a potential GIST. KIT (CD117) is expressed diffusely and strongly in as many as 95% of GISTs and is relatively restricted to GISTs among sarcomas and other tumors [29]. Anoctamin-1 (Ano1), also known as “Discovered on GIST 1” (DOG1) is immunoreactive in GISTs and has a sensitivity similar to that of KIT. Moreover, DOG1 is positive in most KIT-negative GISTs [30,31]. However, although DOG1 is highly specific for GIST, DOG1 positivity has been identified in some smooth muscle tumors and occasional synovial sarcomas [30,31]. CD34 is expressed in most spindle cell GISTs but is less consistently expressed in epithelioid GISTs, and it is not a specific marker for GISTs [13]. Approximately 70% of GISTs express CD34, 30%-40% of GISTs are positive for smooth muscle actin, 5% express S100 protein, and 1-2% are positive for desmin or keratin [15,28,29].

Surgery, both open and laparoscopic, may be limited for large GISTs with involvement of adjacent tissue, extensive abdominal adhesions, or distant spread. For these nonresectable and metastatic tumors, imatinib mesylate, a TKI, is considered effective and improves overall survival [32]. Imatinib can also be used as adjuvant or neoadjuvant therapy for potential surgical candidates, and although our patient was unable to tolerate it, 400 mg/day is generally accepted as a standard dose for preoperative treatment [33]. Despite the high response rate of imatinib in many patients, some GISTs may be imatinib resistant. This highlights the importance of mutational studies when choosing treatment options. Imatinib is effective against most common KIT mutations, namely the exon 11 mutation, as well as some PDGFRa mutations [24]. For wild-type GISTs, with no KIT or PDGFRa mutations, other TKIs may be used; these include sunitinib and regorafenib [24].

Treatment response can be characterized by applying the Response Criteria in Solid Tumors. Before using this technique, up to 5 unique and consistent target lesions must be identified either within an involved organ or in other involved organs, with an imposed limit of 2 target lesions per organ [34]. These representative lesions are used to objectively measure tumor response throughout treatment. Several tools, including imaging, endoscopy, and cytology, are available for monitoring changes in these target lesions, but CT and MRI are considered the best methods to measure treatment response. In certain types of tumors, especially GISTs, there may be little decrease in size of the tumor despite histologic response to treatment. A decrease in attenuation of the mass as measured in Hounsfield units on CT is indicative of treatment response. On CT, the cellular components of GISTs often appear cystic after treatment, and the mean attenuation may approach that of water. This is measured by the Choi criteria, which employs changes in tumor size, density, and vascularization as observed on CT to monitor treatment response during imatinib therapy [35]. In addition, some GISTs may experience an increase in size due to myxoid degeneration as well as intratumoral hemorrhage and necrosis [35]. Using a combination of Choi and Response Criteria in Solid Tumors criteria, tumor response may be categorized as complete, partial, stable, or progressive [34]. Although our patient did not undergo an MRI during his treatment course, GISTs have been described to have distinct MRI features depending on their size. According to the literature, large tumors commonly demonstrate mild gradual inhomogeneous enhancement, intratumoral cystic change, and mucosal ulceration [36]. However, despite providing more information on the tumor components of the GIST, MRI signal intensities have been shown to be unreliable in assessing GIST treatment response compared to Hounsfield units with CT [37].

Conclusion

Incidental GISTs are commonly low risk and occur in obese patients or those undergoing surgical resection for other gastrointestinal tumors. GISTs are typically asymptomatic, but when present, symptoms are often nonspecific, including gastrointestinal bleeding, anemia, abdominal pain and discomfort, and a palpable mass on exam. We report the rare case of a large, intermediate risk GIST found incidentally in a nonobese patient presenting with acutely symptomatic nephrolithiasis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.radcr.2019.02.005.

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