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Neurofibromatosis type 1 patient presenting with multiple small bowel gastrointestinal stromal tumors: A case report

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ABSTRACT

Background: Multiple gastrointestinal stromal tumors (GIST) are exceptionally rare. They usually occur in certain syndromes such as neurofibromatosis type 1 (NF1). GIST tumors in NF1 patients behave in a specific manner, which is explained by their distinct molecular biology compared to sporadic GIST. Also, they lack of specific mutations, making them resistant to biological therapy, imatinib. *Case report:* A 62-year-old female, known to have NF1 presented with acute lower gastrointestinal bleeding. Further investigations revealed a bleeding mass in the jejunum. During surgery, two more masses were identified in the terminal ilium and histopathological analysis confirmed 3 GIST tumors. The patient made full recovery and no further treatment was required. *Conclusion:* NF1 GISTs are considered unique in both presentation and management. Further research is required to understand these neoplasms, which will provide better treatment options and improve outcomes for NF1 patients.

Keywords: GIST, NF1, imatinib, case report

1. INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most prevalent mesenchymal neoplasm of the gastrointestinal tract (Søreide et al., 2016). The mean age of diagnosis is the mid-60s with equal male/female distribution. The most common location of incidence is the stomach (55.6%) followed by small intestine (31.8%), colorectal (6.0%), other locations and the esophagus (0.7%). They can rarely occur as primaries outside the GI tract, such as in the omentum, mesentery or retro peritoneum, but most GISTs in these sites are metastases from a gastric or intestinal primary (Miettinen and Lasota, 2003). About 10% to 30% of GISTs are malignant.

The clinical presentation of GIST tumors can vary and are often vague and nonspecific the most common presentations being gastrointestinal bleeding

and abdominal discomfort. Gastrointestinal bleeding account for 30%–40% of symptomatic GIST, abdominal pain 20%–50%, obstruction 10%–30% and GIST can be asymptomatic in 20% of cases (Liu et al., 2018).

GIST tumors arise from the precursor intestinal cell of Cajal and signals KIT tyrosine kinase in the majority of cases. Identifying the mutations in c-KIT and platelet-derived growth factor receptor α (PDGRF-α) can determine their liability of treatment with imatinib, a tyrosine kinase inhibitor targeting these mutations. Imatinib is part of the treatment of metastatic, recurrent disease and as an adjuvant and neo adjuvant agent combined with surgery. This improved understanding of molecular biology has changed GIST to a generally treatable disease (Søreide et al., 2016).

Multiple GIST tumors are very rare. They occur either sporadically or as a part of certain syndromes, including Carney's triad and type I neurofibromatosis (NF1) (Paramythiotis et al., 2022). NF1 is an autosomal dominant disease caused by germline NF1 mutation. There is a well-known association between GISTs and NF1, it is estimated that 7% of the NF1 cases will develop a GIST at some point in their lives and about 28% have GIST at autopsy (Dare et al., 2020). NF1-associated GISTs have certain characteristics, they tend to present in younger patients, they are multiple, generally less aggressive and tend to be located more distally in the digestive tract. They also rarely exhibit classical mutations in c-KIT and PDGFA, which makes their treatment quite different.

2. CASE REPORT

A 62-year-old lady, known case of Neurofibromatosis type 1 and iron deficiency anemia, presented to the emergency with dark stool, dizziness and generalized fatigue. Upon examination, the patient appeared pale and was tachycardic her abdomen was soft and non-tender. Per rectum examination showed a small amount of melena. She had hemoglobin of 4.2, so she was given some blood and was scheduled for urgent gastro colonoscopy. The upper GI endoscopy was unremarkable but before the colonoscopy could be performed, the patient passed fresh blood per rectum, so the procedure was aborted and a sigmoidoscopy was done instead which revealed a bleed coming from a more proximal source. Accordingly, an urgent CT angiogram was arranged which was significant for an enhancing heterogeneous exophytic lesion in the jejunum with central necrosis, which given the patient's history of NF1 was highly suggestive of a gastrointestinal stromal tumor (GIST). The patient was shifted to a surgical high-dependency unit for stabilization and underwent surgery two days later. Intraoperative examination revealed a lesion in the jejunum 7x5 cm (Figure 1), another lesion in the terminal ilium 2x2 cm and a large amount of acetic fluid. The remaining small and large bowels appeared normal. Resection of both lesions followed by re-anastomosis was done, along with an appendectomy. Histopathological examination confirmed a jejunal GIST tumor, a second GIST tumor in the terminal ilium and another one in the appendix. The patient underwent a PET scan, which was negative for metastasis and thus, she required no further treatment.

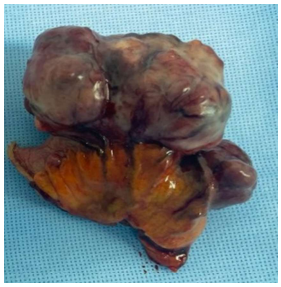

Figure 1 Surgical specimen of the largest GIST excised from the jejunum

3. DISCUSSION

Neurofibromatosis 1 (Recklinghausen disease) is the most common autosomal dominant neoplastic syndrome occurring in about one in every 3000 live births. It is caused by a NF1 gene mutation, leading to negative regulation of RAS proteins and resulting in an increased risk of malignancy. It is associated with a wide range of malignant and benign conditions namely, café au late spots, neurofibromas, malignant peripheral nerve sheath tumors and gliomas. Gastrointestinal manifestations of this disease range from microscopic localized lesions of autonomic nerves and interstitial cells of Cajal and diffuse microscopic ganglio/neuro/fibromatosis to well-formed neurofibromas and gastrointestinal stromal tumors (GIST). In addition, neuroendocrine neoplasms, especially the periampullary duodenum are characteristic of this disease (Agaimy, 2012).

Although NF1-associated GISTs are quite rare (< 1% of all GIST), GIST is the most common gastrointestinal tumor reported in the NF1 population (Dare et al., 2020). These manifestations of NF-1 are not readily recognized because doctors rarely look for them, especially considering the spectrum of pathologies that NF1 comes with. Multiple GISTs are extremely rare, representing only

2% of cases. They can present as spontaneous GISTs but most come as part of certain syndromes, like Carney's triad and NF1. These tumors are interesting because they tend to have distinct phenotypes and behavior.

The Carney triad is syndrome consisting of multiple gastric GISTs, paragangliomas and pulmonary chondroma. The mechanism of tumor genesis includes succinate dehydrogenase C (SDHC) inactivation through hyper methylation. Carney triad associated GISTS lack KIT and PDGFRA mutations (Paramythiotis et al., 2022). Most of NF1 associated GIST are incidental (52.5%) compared to in sporadic GIST (19%) (Dare et al., 2020). They are usually multiple and asymptomatic or mildly symptomatic. They have homogeneous M/F ratio and a mean age of 52.8 (Salvi et al., 2013). Furthermore, these tumors commonly arise in the small intestine unlike sporadic GIST, which favors the stomach.

About 90% of sporadic GIST tumors are positive for KIT and PDGFRA tyrosine-kinase gain of function mutations. This renders these neoplasms susceptible to tyrosine kinase inhibitor imatinib and drastically changed the prognosis of advanced GIST tumors. Although NF1 associated GIST do express KIT and PDGFA receptors (Miettinen et al., 2009), only 8% and 6% possess C-KIT and the PDGFRA mutations respectively (Takazawa et al., 2005). NF1 associated GIST are considered Wild type GIST variant, which is a subtype of GIST accounting for 10% of all GIST tumors. It includes syndromal GIST such as NF1, Carney-Stratakis syndrome (CSS) and Carney triad as well as small percentage of sporadic GIST. In this group of tumors, imatinib therapy is rarely effective (Kays et al., 2018), as the mutations of c-kit and PDGFRA gene play a limited role in the tumorigenesis (Liu et al., 2018).

GIST tumors are typically challenging to diagnose due to their variable locations and nonspecific presenting symptoms. Most of these tumors present with dyspepsia and abdominal discomfort or gastrointestinal bleeding. Chronic GI bleeding can cause longstanding anemia, while acute hemorrhage may cause a life-threatening emergency. Acute GI bleeding may be intraluminal leading to melena/hematochezia or penetrating through the serosa leading to an acute abdomen. Some studies suggest that presenting with GI bleeding immediately worsens the prognosis and increases the malignant potential of the tumor (Liu et al., 2018). Although most GIST tumors are benign, they can still be life-threatening, as this case clearly demonstrates. The diagnosis of GIST tumor in NF1 is similar to sporadic GIST. It begins with imaging using CT scan and CT angiogram to determine site and vascularity of the tumor and roll out bleeding GIST. These tumors usually present as exophytic enhancing mass, most often protruding into the gastric tract, in this case the largest mass originating from the jejunum was extending towards the para-cololic gutter and displacing the splenic flexure (Figures 2, 3, 4, 5, 6, 7). Endoscopic ultrasound guided biopsy is reserved for cases in which diagnosis cannot be confirmed with CT, due to the added risk of bleeding (Kays et al., 2018).

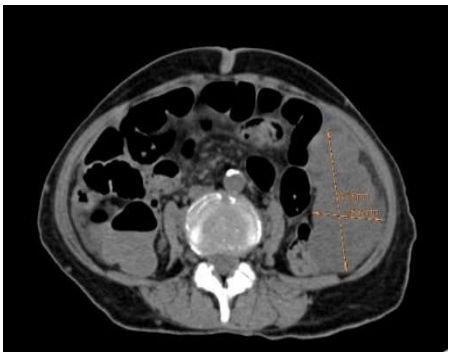

Figure 2 Non-contrast CT scan showing the mass in the jejunum measuring 8x4.6 cm–axial view

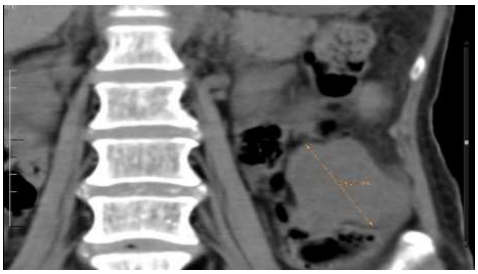

Figure 3 Non-contrast CT scan showing the mass in the jejunum–coronal view

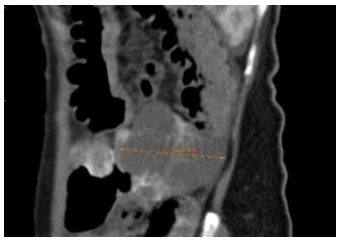

Figure 4 CT with contrast arterial phase-sagittal view showing an enhancing mass

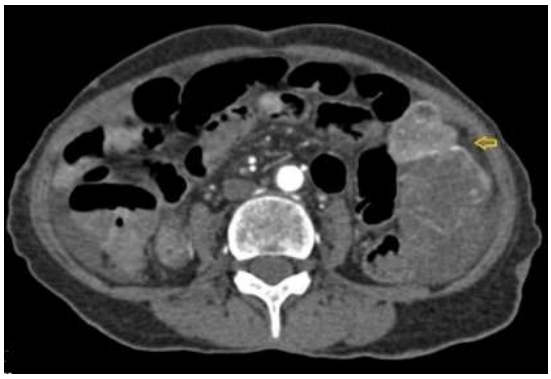

Figure 5 CT with contrast arterial phace-axial view showing an enhancing mass

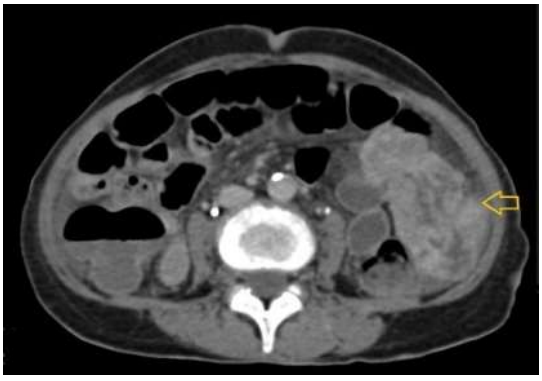

Figure 6 CT with contrast delayed arterial phase–axial view showing a peripherally enhancing mass with central necrosis

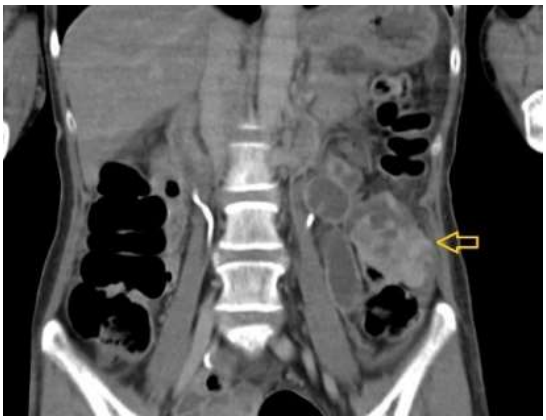

Figure 7 CT with contrast delayed arterial phase–coronal view showing a peripherally enhancing mass with central necrosis

Following excision or biopsy, confirming the diagnosis of GIST is done by means of Immunohistochemistry using several antibodies staining e.g., CD117, DOG1, protein kinase C (PKC)-theta, nestin, CD34, smooth muscle actin (SMA), desmin, S100 and CD171. Amongst those, DOG1 and CD117 were the most sensitive and specific, while CD34 staining was less sensitive (Novelli et al., 2010). All GISTs in this case are of spindle type and were positive for both DOG1 and CD117 (Figure 8, 9).

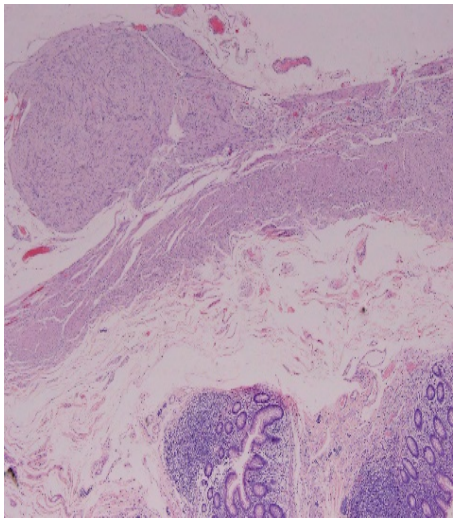

Figure 8 A

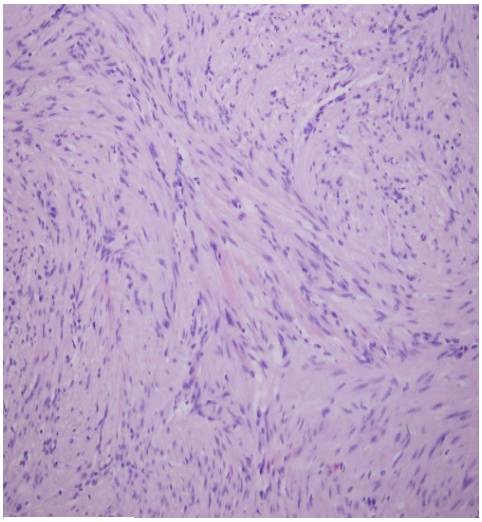

Figure 8 B

Figure 8 Microscopic histopathology showing interlacing fascicles of spindle cells with elongated nuclei and eosinophilic cytoplasm–hematoxylin-eosin, original magnification x40 (A) x200 (B)

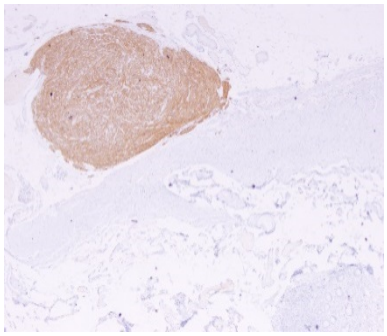

Figure 9 A

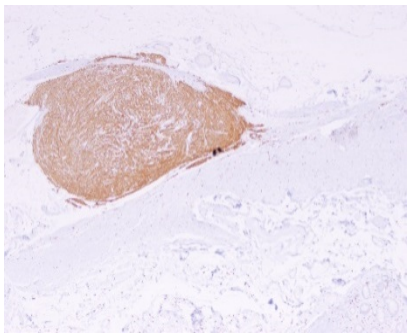

Figure 9 B

Figure 9 The tumor cells show strong and diffuse staining for cKIT, DOG1 (A) and CD117 (B) Immunohistochemistry, original magnification x40

Histopathologic analysis is essential for tumor risk stratification. Historically, cut off value of 5 was used to determine tumor risk status (size >5cm vs <5cm) and (mitotic count >5/50HPF vs <5/50HPF). This was replaced by different stratification systems like national institute of health (NIH) or fletcher's criteria, which classify GIST into 4 different risk groups, assuming they all carry some malignant potential. The armed force institute of pathology (AFIP) criteria or the Miettinen's criteria, which along with size and mitotic count, takes the anatomical location into account, stratified these tumors into 8 prognostic subgroup in regards to their malignant potential (Kays et al., 2018). In our case, AFIP was used. The tumor in the jejunum was about 5cm with mitotic rate of 15/50 HPF making it a high-risk tumor another GIST was found in the jejunum about 3cm with a mitotic count of 1-2/50HPF. The GIST in the terminal ilium was 1.4cm with a mitotic rate 1-2/50 HPF. The last one found in the appendix was 0.3cm in size with <1/10HPF. Apart from the largest GIST, all remaining tumors were classified as low risk. Testing for the presence of c-KIT and PDGFRA mutations is a standard part of the initial analysis for any GIST to determine their susceptibility to TK inhibitors. Unfortunately, this analysis was not available in our institution.

Surgery remains a cornerstone in treatment for GIST tumors. It can offer complete cure in 60% of cases (Sorour et al., 2014). In the past, unresectable, metastatic or recurrent GIST carried a dire prognosis, as these tumors don't respond to traditional chemothrpy. TK inhibitors such as imatinib have improved the prognosis dramatically. Unfortunately, wild-type GIST such as those occurring in NF1 do not respond to imatinib and surgery is the only resort for these patients. While sufficient for localized

tumors, surgical excision is not ideal either. No improvement in outcome was noted following multiple or extensive surgeries (Kays et al., 2018) and recurrence rate is not low even after radical resection. It's recommended that surgery is attempted initially but further resection is reserved for symptomatic (Sorour et al., 2014), bleeding or obstructing tumors. So it is advised that tumor risk stratification is to be considered and follow-up plans are tailored for patients accordingly (Agaimy, 2010).

4. CONCLUSION

This case represents a unique opportunity to examine how GIST tumors may present differently in NF1 patients and how they require different management. Our understanding of GIST tumors has improved significantly in the past few years. The recent knowledge about tumor molecular biology and the introduction of tyrosine kinase inhibitors has changed the prognosis and treatment for such tumors. NF1 associated GISTs however, are considered a special entity within this group. They present differently and lack sensitivity to TK inhibitors. Thus, they pose their own challenges in the diagnosis and treatment. More research is needed to improve our understanding of the on cogenesis in NF1 associated GIST, so treatment and follow-up plans can be updated and integrated within the management of NF1 patients.

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Author Contributions

Sawsan Yaseen Abdulla Ali Isa: Both authors were involved in the following stages of this case report, Acquisition of data, Analysis and interpretation of findings, Drafting the manuscript, Revising the manuscript for intellectual content and Approval of the version of the manuscript for publication; Yaser Ebrahim Alderazi: Acquisition of data, Analysis and interpretation of findings, Drafting the manuscript, Revising the manuscript for intellectual content and Approval of the version of the manuscript for publication; Aalaa S Shubbar: Provided histopathology data, Assisted in drafting the manuscript and Revising the manuscript for intellectual content.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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