Annals of Case Reports
Alharthi S, et al. Ann Case Rep: 8: 1386
www.doi.org/10.29011/2574-7754.101386
www.gavinpublishers.com

Case Report

Giant Gastric Gastrointestinal Stromal Tumour GIST Resistant to Systemic Therapy Imatinib Mesylate with a Rare Sarcomatous Differentiation Subtype: A Case Report and Literature Review

Saad Alharthi[1], Wadha Almohamdi[2*], Abdulrahman Alzahrani[3], Saga Ali[2], Jameel Miro[2]

[1]Department of General Surgery, Prince Mansour Military Hospital, Armed Forces Hospital, Taif, Kingdom of Saudi Arabia

[2]Department of General Surgery, King Faisal Specialist Hospital and Research Centre, Jeddah, Kingdom of Saudi Arabia

[3]Department of General Surgery, King Fahad Armed Forces Hospital, Jeddah, Kingdom of Saudi Arabia

***Corresponding author**: Wadha Almohamdi, Department of General Surgery, King Faisal Specialist Hospital and Research Centre, Jeddah, Kingdom of Saudi Arabia

Citation: Alharthi S, Almohamdi W, Alzahrani A, Ali S, Miro J (2023) Giant Gastric Gastrointestinal Stromal Tumour GIST Resistant to Systemic Therapy Imatinib Mesylate with a Rare Sarcomatous Differentiation Subtype: A Case Report and Literature Review. Ann Case Report. 8: 1386. DOI:10.29011/2574-7754.101386

Received: 26 July 2023, **Accepted:** 31 July 2023, **Published:** 02 August 2023

Abstract

Gastrointestinal stromal tumors (GISTs) are rare neoplasms originating from the gastrointestinal tract. We presented a rare case of a young patient with a huge malignant gastric GIST not responding to systemic therapy Imatinib, successfully treated surgically. After complete resection of the malignant GIST, adjuvant therapy with imatinib was initiated. Follow-up CT and endoscopy performed 1 year later confirmed no recurrence of the disease.

Keywords: Gastric Gastrointestinal Stromal Tumours GIST; Giant GIST; Systemic Therapy; Imatinib Mesylate; Case Report

Case presentation

A 62 years old male patient, not known to have any medical illness, heavy smoker, presented to the surgical clinic complaining of upper abdominal pain. The patient was doing well till 1 month prior to his presentation when he started to have vague abdominal pain, mainly upper abdomen. He was tolerating orally well with normal bowel habit. Associated with history of unintentional weight loss of 8 kg in the last month. Performance status ECOG [1]. Upon examination abdomen is slightly distended, soft, there is a mass measures 10*8 cm extending from the left upper quadrant towards the umbilicus, smooth surface, firm in consistency, non-tender, non-pulsating, no skin changes, non-fluctuant, no other palpable masses, no cervical or inguinal lymph nodes. Laboratory tests within normal range. Computated tomography (CT) abdomen was done showed large heterogeneous mass lesion 10.3*19*22.3 cm in diameter (Figure 1). Also, upper endoscopy done as part of the investigations which revealed a large well-demarcated, heterogenous, highly vascular mass lesion noted at the area of body of stomach, fine needle biopsy was taken, biopsy revealed a spindle cell neoplasm, consistent with gastrointestinal stromal tumor (GIST) associated with mild to moderate atypia and rare mitosis (up to 1 mitotic figure), with a background of myxoid changes and necrosis. The tumor cells were positive for DOG-1, CD117(KIT), CD34, and CAM5.2. Negative for S-100 and Desmin. MMR protein test intact protein expression. IHC normal expression of MLH1, MSH2, MSH6 and PMS [2]. The case was discussed in the Gastrointestinal tumor board as patient was presented with large

mass with borderline respectable and the decision was to start him on Neoadjuvant Imatinib mesylate with frequent reassessment with imaging to assess the potential of respectability. The main aim of systemic Imatinib is to shrink the tumor for future resection if feasible. Patient was seen by medical oncologist and he started Imatinib for 3 months. Follow up CT showed interval increase in size of previously noted large abdominal mass, currently measuring 16.7*29.6*33.5 in diameter. The lesion became almost cystic with multifocal eccentric enhancing soft tissue density. The lesion displaces the bowel loops anterio-laterally and inseparable from the hepatic lobe, gallbladder and the pancreatic body and tail (Figures 2 and 3). The patient started to have more frequent abdominal pain, developed obstructive symptoms in terms of solid food intolerance with nausea and vomiting, loss of appetite, therefore the decision was made to go for surgical resection. Imatinib was stopped 1 week prior to surgery as per NCCN guidelines. He underwent open partial gastrectomy; intraoperative finding was a huge tumor occupying the whole abdomen. The cystic part was aspirated in order to gain access to the abdomen and around 3 L of blackish fluid was aspirated (Figures 4 and 5). Histopathology revealed GIST, mixed subtype spindle and epithelioid with sarcomatous differentiation. Tumor was unifocal, high grade and 32*17*5 cm in size. Mitotic rate 37/5 mm^2. Immunohistochemistry (IHC) Results for MLH1, MSH2, MSH6 and PMS2 were intact nuclear expression. (MMR) Interpretation: No loss of nuclear expression of MMR proteins: No evidence of deficient mismatch repair (low probability of MSI-H). The case was re-discussed in Gastrointestinal tumor board and the decision was to start adjuvant Imatinib. Patient was followed for 1-year post resection. He was doing well, tolerating regular diet, gaining weight with good appetite. Also, follow up CT showed no intra-abdominal or chest metastases.

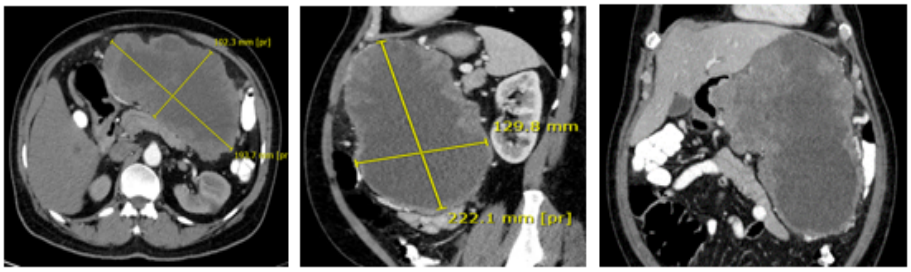

Figure 1: CT abdomen showed the mass size pre-treatment.

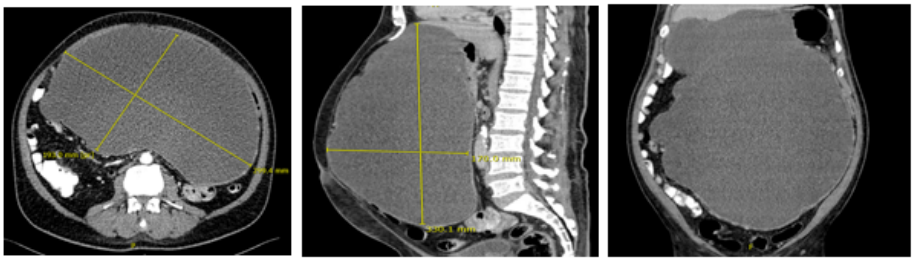

Figure 2: CT abdomen post treatment.

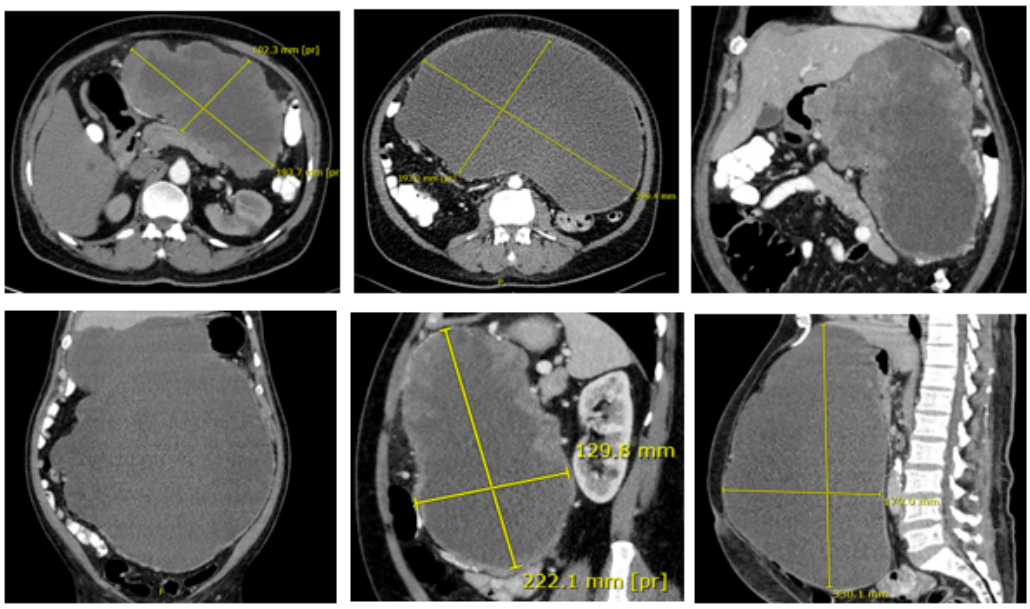

Figure 3: CT compareaion between pre and post Imatinib treatment 3 months interval.

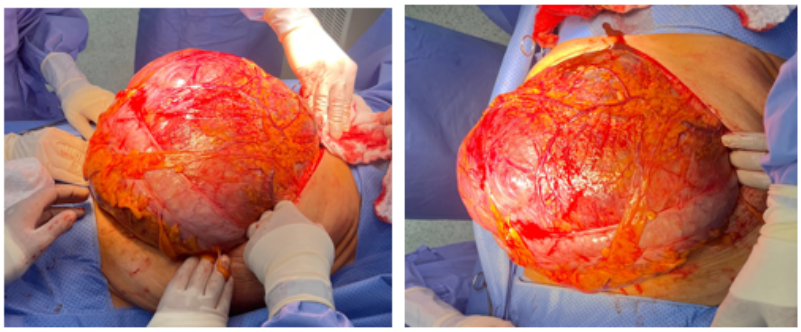

Figure 4: Mass prior to resection.

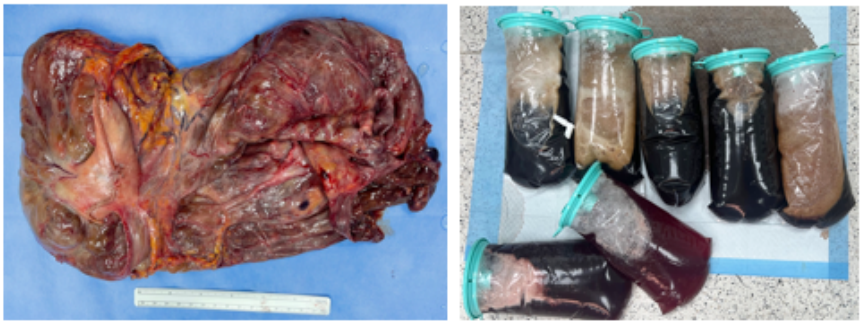

Figure 5: Specimen after resection and aspiration (A) aspirated fluids around 3L (B).

Discussion

Most of the malignant mesenchymal tumors of the gastrointestinal (GI) tract are gastrointestinal stromal tumors (GISTs). GISTs are generally rare, making up only about 1% of all gastrointestinal tumors. They can occur at any age, but are more commonly found in middle-aged and older adults. In addition, pediatric incidence is extremely rare [1]. GISTs are believed to occur in the United States on a yearly basis at an average rate of 0.68 to 0.78 per individuals, with the stomach representing the most common origin (representing 60% of cases) and the small intestine coming in second (20%–30%) [2]. Basically, there is a lack of information about incidence and prevalence for GIST really are. This is because in the past, there hasn't been diagnostic criteria for diagnosing GIST and different terms have been used to describe them. Additionally, many GISTs are considered benign or have uncertain potential for malignancy around 60% of all GIST, so they are not always reported to national cancer registries [3]. In the newest 2020 version of the World Health Organization (WHO) Classification of STS and bone sarcoma, all GISTs are now considered to be malignant, regardless of their size, origin location, or mitotic index [4]. Individuals suspected to have GISTs may experience various signs and symptoms, such as early satiety, postprandial pain, abdominal distension, bleeding to the abdominal cavity with acute abdomen, digestive tract bleeding, or exhaustion due to anemia [5]. The majority of GISTs are caused by activating mutations in KIT or PDGFRA genes, which encode the receptor tyrosine kinases that regulate the ICCs [3]. Although risk factors for the development of GISTs have been studied, no environmental factors were identified. While there is a familial predisposition associated with germline mutations of KIT or PDGFRA, these are rare occurrences [6]. Also, there is some syndromes linked to be associated with GIST as Carney triad syndrome, Carney-Stratakis syndrome and Type 1 neurofibromatosis (NF1) [7,8]. Early diagnosis and treatment of GISTs are essential for a good prognosis, as they can be aggressive and have the potential to metastasize to other organs. Diagnosis for GISTs in the stomach are typically detected through endoscopic or radiologic imaging studies, such as CT or MRI scans. The gold standard for diagnosis is Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) specificity rate around 84% as its valuable tool to visualize the tumor and to confirm the diagnosis by histopathology, determine the molecular status of the tumor and to avoid surgical resection for diseases for which it is not recommended like lymphomas [9]. Histopathological diagnosis depends on morphology and IHC. IHC around 95% being positive for CD117(KIT), DOG-1 and 5% of all GIST are CD117-negative. Regarding morphology majority of gastric GIST can be histologically classified to three main types up to 50% will represent a spindle cell type which sub classified into four types which is sclerosing, palisaded-vacuolated, hyper cellular, and sarcomatous. Epithelioid type, which ranges from 20% to 40% also sub classified into four types, which is sclerosing, hyper cellular, heterogeneous and sarcomatous. Last type, which represents 10%, only will be mixed type. Sarcomatous spindle cell tumors have marked mitotic activity (generally >20 per high-power field [HPF]; >4 per 10 HPFs) and diffuse atypia manifested by nuclear enlargement and hyperchromasia which represent a worse prognosis. Mutational analysis inclusion in the diagnostic work-up of all GISTs should be considered standard practice [10]. The referral of GIST cases to specialized tertiary centres is recommended to optimize outcomes, given the multifaceted nature of these tumors and the requisite need for expertise across a range of disciplines. Such centres frequently engage in ongoing clinical trials, thus frequently enrolling GIST patients as part of standard practice. The primary management for GISTs located in the stomach often involves surgical resection aiming to eliminate the tumor with negative margins, and R0 excision is the desired outcome [11]. Rarely there is lymph node involvement in GIST, therefore lymphadenectomy is not required with GIST resection [5]. If a complete surgical excision of the tumor is not feasible, or if there exists a significant likelihood of the recurrence, the use of tyrosine kinase inhibitors as an adjuvant therapy is advised. Additionally, adjuvant therapy is warranted in cases of unrespectable or metastatic diseases, where a considerable improvement in survival rates has been observed [2]. Adjuvant treatment with imatinib for 3 years was associated with a relapse-free survival and overall survival advantage in comparison with 1 year of therapy in high-risk patients in a randomized trial [12]. The efficacy of adjuvant imatinib may display heterogeneity according to the specific type of KIT/PDGFRA mutation, with a superior effectiveness observed in individuals harbouring KIT exon 11 deletion mutations [13,14]. Miettinen et al have proposed guidelines for assessing the malignant potential of tumors based on important prognostic factors such as mitotic rate and tumor size. These factors play a crucial role in determining the risk of metastases and recurrence. The highest risk was 86% metastatic rate in tumor size more than 10 cm and mitotic rate more than 5 mitoses/50 HPFs as presented in our case [15]. The prognosis of GISTs located in the stomach is influenced by various factors such as tumor size, location, molecular markers' presence, and the extent of the surgical resection. Generally, the survival rate for individuals with GISTs is projected to be approximately 60-70% over a five-year period. Nevertheless, this outcome can fluctuate significantly in accordance with the patient's high-risk stratification score, as previously stated. So, the recommendation for surveillance after complete resection to perform abdominal CT every 3 to 6 months for 3 and 5 years, then annually [2]. In our presented case, tumor size was 32*17*5 cm, and mitotic rate was 37mitoses/5 HPFs, giving a metastatic risk of 86%. Pathological staging was IIIB T4N0M0 with high mitotic rate as per AJCC. Histopathological wise he was positive CD117 (KIT), DOG-1. Morphological

evaluation primarily reveals a rare mixed type (spindle and epithelioid) GISTs with areas of sarcomatous differentiation (rhabdomyoblastic features) along with multinucleated tumor giant cells. As the prognostic significance of such finding is not well documented and is not part of the contemporary GIST risk assessment criteria. Up to our knowledge and literature review, there is only one case reported in 2015, Gustaw lech et al, reported a case of gastric GIST with sarcomatous feature [16,17].

Conclusion

The presented case exhibited a high metastatic risk of 86% and pathological staging categorised as IIIB T4N0M0 with a high mitotic rate as per the American Joint Committee on Cancer (AJCC) guidelines. Despite 3 months of neoadjuvant Imatinib therapy, the patient exhibited resistance and subsequently presented with obstructive symptoms. Morphological analysis revealed a rare phenotype GIST displaying mixed spindle and epithelioid features, with sarcomatous differentiation. In addition to presenting this unique case, we also conducted a literature review to draw attention to the sarcomatous features with resistance to neoadjuvant Imatinib therapy. Currently, there is a lack of reported studies exploring the correlation between tumor size, sarcomatous subtype, and the response to neoadjuvant Imatinib therapy. Our findings indicate the importance of including mutational analysis in the diagnostic work-up of GISTs. This recommendation will have a significant impact on the pathway of treatment with neoadjuvant therapies in the future.

Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Miettinen M., Lasota J (2001) Gastrointestinal stromal tumors—Definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 438: 3-12.
2. Von Mehren M, Kane JM, Armstrong SA, Riedel RF, Sicklick JK, et al (2023) NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors, Version 1.2023. National Comprehensive Cancer Network, 2023.
3. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, et al (2005) Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era – a population-based study in western Sweden. Cancer. 103: 821-829.
4. WHO Classification of Tumours Editorial Board, Soft Tissue and Bone Tumours. 5th ed. IARC, Lyon, France 2020.
5. Florin CM, Bogdan F, Cristian L, Maria TA, Mihai D, et al (2020) Surgical treatment of gastric GIST: feasibility of laparoscopic resection and postoperative outcome. J Coll Physicians Surg Pak. 30: 519-522.
6. Blay JY, Kang YK, Nishida T, von Mehren M (2021) Gastrointestinal stromal tumours. Nat Rev Dis Primers. 7: 22.
7. Gaal J, Stratakis CA, Carney JA, Ball ER, Korpershoek E, et al (2011) SDHB immunohistochemistry: a useful tool in the diagnosis of Carney-Stratakis and Carney triad gastrointestinal stromal tumors. Mod Pathol. 24: 147-151.
8. Miettinen M, Fetsch JF, Sobin LH, Lasota J (2006) Gastrointestinal stromal tumors in patients with neurofibromatosis 1: a clinicopathologic and molecular genetic study of 45 cases. Am J Surg Pathol. 2006; 30: 90-96.
9. Mantese G (2019) Gastrointestinal stromal tumor: Epidemiology, diagnosis, and treatment. Curr. Opin. Gastroenterol. 35: 555–559.
10. Miettinen, M, L. H.Sobin, and Lasota J (2005) Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic studies of 1765 cases with long-term follow-up.Am J Surg Pathol 29: 52–68.
11. Casali PG, Blay JY, Abecassis N, Bajpai J, Bauer S, et al (2022) Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 33: 20–33.
12. Joensuu H, Eriksson M, Sundby Hall K, et al (2016) Adjuvant imatinib for high risk GI stromal tumor: analysis of a randomized trial. J Clin Oncol. 34: 244-250.
13. Joensuu H, Wardelmann E, Sihto H, Erikkson M, Hall KS, et al (2017) Effect of KIT and PDGFRA mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: an exploratory analysis of a randomized clinical trial. JAMA Oncol. 3: 602-609.
14. Corless CL, Ballman KV, Antonescu CR, Kolesnikova V, Maki RG, et al (2014) Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol. 32: 1563-1570.
15. Miettinen M, Lasota J (2006) Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 23: 70-83.
16. American Joint Committee on Cancer (AJCC) Staging System for Gastrointestinal Stromal Tumor (8th ed, 2017).
17. Gustaw L, Wojciech K, Emilia K, Guzel T, Radoch M, et al (2015) Giant gastrointestinal stromal tumour of rare sarcomatoid epithelioid subtype: Case study and literature review. World J Gastroenterol. 21: 3388-3393.