



An Unusual presentation of Gastric Gastro intestinal Stromal Tumour: A Case Report

Authors

Waqar Ahmed Ansari¹, Priyanka Saha², Rohan Khairatkar³, Madhukar Gupta⁴, Dnyaneshwar Raut⁵, Metsivi Iralu⁶

¹Associate Professor & Head of Unit, Department of General Surgery, Grant Government Medical College and Sir JJ group of Hospitals, Mumbai-400001

²Resident, Department of General Surgery, Grant Government Medical College and Sir JJ group of Hospitals, Mumbai-400001

³Assistant Professor, Department of General Surgery, Grant Government Medical College and Sir JJ group of Hospitals, Mumbai-400001

^{4,5,6}Resident, Department of General Surgery, Grant Government Medical College and Sir JJ group of Hospitals, Mumbai-400001

Corresponding Author

Priyanka Saha

Email: dr.saha.priyanka@gmail.com

Abstract

Gastro-intestinal stromal tumours (GIST) are uncommon malignancies of the gastro-intestinal tract and can occur in any part of the alimentary canal, from esophagus to anus. The most common sites of presentation are stomach, small bowel and rectum. 95% of GIST are positive for KIT (CD117) and Platelet Derived Growth factor Receptor Alpha (PDGFRA). Treatment of choice is complete surgical excision with negative margins (R0 resection).

A 68 years old male presented with slowly progressive abdominal lump in the right iliac fossa. CECT abdomen suggestive of hypervascular heterogenous mass arising from pelvis with low central attenuation with no distant metastasis. Patient was taken up for exploratory laparotomy and intra operatively it was found to be a huge exophytic, well circumscribed tumour arising from the lesser curvature of stomach, complete surgical resection was done. Microscopically diagnosis of gastric GIST of spindle cell morphology was found which was strongly positive for DOG1/CD34 and immunonegative for CD117. Medical oncology reference was taken on follow up and patient was started on imatinib therapy.

This case report sites a rare presentation of gastric GIST in right iliac fossa with inconclusive CT reports. So a high index of suspicion must be kept in mind for diagnosing such rare tumours.

Keywords: *Gastro intestinal stromal tumours, GIST, abdominal lump, CD117, DOG 1, imatinib,*

and immunohistochemical features these are believed to arise from interstitial cells of Cajal. GIST cells express hematopoietic progenitor cell marker CD 34 and growth factor receptor c-Kit. CD 117 expression has emerged as important defining feature of GISTs. Approximately 80% of GISTs

Introduction

Gastro intestinal stromal tumours (GIST) are rare neoplasms representing about 0.1-3% of gastro intestinal malignancies^[1]. They account for 80% of visceral soft tissue sarcoma. Due to their histologic

have mutation of gene encoding KIT receptor tyrosine kinase and 5-10 % have mutation in gene encoding PDGFRA receptor tyrosine kinase^[2].

The most common site of GISTs are stomach (60%), small intestine (30%), but can arise from anywhere along the gastro intestinal tract. Median age of presentation is 60 years with equal incidence in male and female with no racial/ ethnic predilection. Majority of GIST is sporadic but hereditary GIST can occur in Von Recklinghausen's neurofibromatosis, Carney's triad and Carney – Stratakis syndrome^[3].

GIST are generally symptomatic in about 69% individuals presenting as early satiety, abdominal pain or gastro intestinal bleeding and very rarely as abdominal lump, intestinal obstruction , perforation. The initial study for a suspected GIST is contrast enhanced computed tomography of the abdomen and pelvis. Surgery is the treatment of choice with R0 resection as goal. The primary goal of treatment for localized gastric GISTs is surgical resection with negative margins. A 1- to 2-cm margin was necessary for adequate resection^[4]. The surgical goal for GIST is complete resection with a negative margin.^[5] As lymphatic spread is rare, hence routine lymphadenectomy is not routinely advocated.. Laparoscopic wedge resection for gastric GISTs is practiced frequently because of the advantage of small incision, less pain and ease of oncological safety^[6].

The European GIST consensus conference in 2004 stated that laparoscopic approach should be done for small gists (<2cm) and whereas the Japanese guidelines suggested laparoscopic approach for lesions smaller than 5 cm and only when performed by skilled surgeons. However, no absolute indication for laparoscopic surgery for GISTs has yet been established.

Case Presentation

A 68 years old male presented with abdominal lump in right iliac fossa, insidious in onset and gradually progressed to attain the present size of 4.5 cm x 8 cm .Patient had history of tobacco addiction for last 30 years. Ultrasonography done suggestive of a

large mass arising from right iliac fossa measuring 11 x 9 cms , irregular with variegated consistency mostly arising from small bowel loops. Contrast enhanced computed tomography of abdomen showed a large heterogeneously enhancing soft tissue density mass lesion arising from right iliac fossa extending upto supra umbilical location. Lesion showing areas of necrosis, calcification and internal vascularity producing mass effect over adjacent abdominal viscera suggestive of mitotic pathology /? GIST with origin most probably from small bowel loops.

Patient was operated for exploratory laparotomy with midline incision. Intra operatively an exophytic growth attached to posterior border of stomach projecting into abdominal cavity and displacing other organs measuring 13 x 12 x 5.5 cm. On gross appearance it was a smooth gray well circumscribed, encapsulated tumour with areas of haemorrhage and cystic degeneration. Wedge resection was done keeping 1 cm margin. Histopathological study of the resected specimen revealed Gastro intestinal stromal tumour, spindle and epitheloid cells.3 MF/50 HPF. No necrosis identified. Tumour is strongly immunoreactive for DOG1/CD 34 and immunonegative for CD 117 (c-kit) /SMA/MSA/ S100 protein. The Ki67 proliferative index is less than 1 %. Tumour was classified under group 3B (Size > 10 cm , mitotic rate < 5 MF / HPF) under the classification proposed by Miettinen and Lasota, J Semin Diagn pathol 2006;23:70-83^[7]

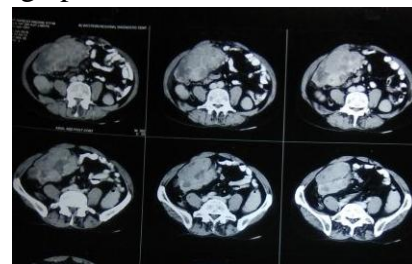


Fig. 1 . Axial view of the Gastric GIST

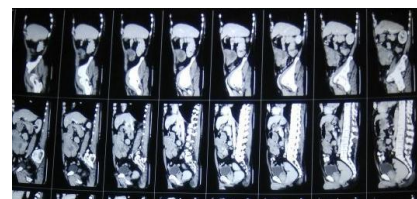


Fig. 2 . Sagittal view of gastric GIST



Fig 3 Intraoperative the growth from anterior surface of stomach



Fig 4 On gross appearance

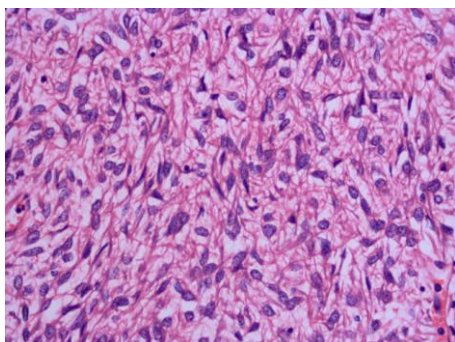


Fig 5 Epithelioid and spindle tumor cells

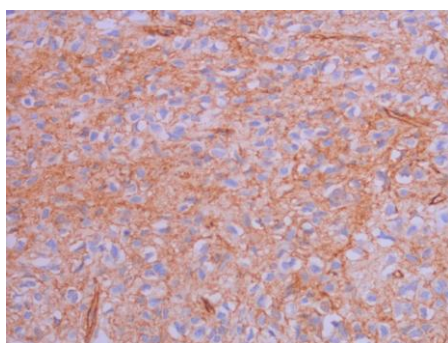


Fig 6 IHC 400x CD34 positive

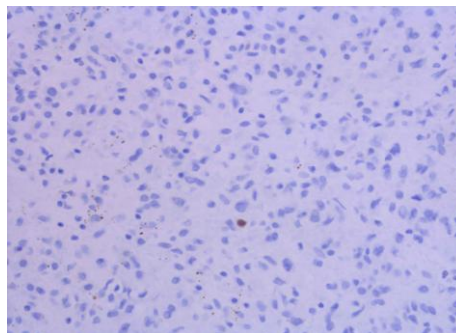


Fig 7 IHC 400x CKi67 less than 1%

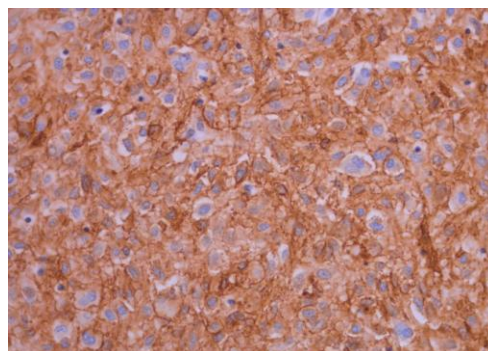


Fig 8 IHC 400x DOG 1 positive

Discussion

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. It has a median age of diagnosis of 65 years. Adults between the 6th and 8th decade are primarily affected. GIST accounts for 2.2% of malignant gastric tumours in SEER data. There is no gender preference (M:F, 1.1:1). There is no such predisposing factors. They derive from the interstitial cells of Cajal, which serve as a gut pacemaker as they create the basal electrical rhythm leading to peristalsis and segmentation of the smooth muscle^[8]. GIST most commonly occur in the stomach (60%–70%), followed by the small intestine (20%–30%); They are also rarely found elsewhere in the abdominal cavity, such as in the mesentery, the omentum, or the retro peritoneum. GIST are most commonly caused by gain-of-function mutations in the proto-oncogene KIT (cKIT)^[9]. In 75% of the cases, the primary mutation is found in exon 11, which encodes for the juxtamembrane domain of the protein, thus activating the receptor regardless of the presence of its ligand (stem cell factor). In 15% of cases, mutations are found in exon 9 of the cKIT gene encoding the extracellular domain. Exons 13 and

17, encoding the kinase domain of the protein, are mutated in approximately 5% of GIST^[10]. In 5% of cases, mutations are found in the homologous gene PDGFRA (platelet-derived growth factor receptor alpha)^[11]. Most of these mutations (85%) are found in exon 18, encoding for the second kinase domain, and more rarely in exons 12 (juxtamembrane domain) and 14 (first kinase domain). The remaining GIST (12%) are wild type for both cKIT and PDGFRA genes. Mutational status of cKIT is a major prognostic and predictive factor in patients with GIST.

For localized primary GIST, surgical resection with curative intent is the mainstay of therapy. The clinical presentation of GIST varies from incidental to symptomatic with various symptoms, such as abdominal pain or discomfort, early satiety, bloating, obstructive jaundice, dysphagia, fever and anaemia-related symptoms such as fatigue and palpitations or they may present an abdominal tumour with no symptoms. Between 10% and 25% of patients present with metastatic disease^[12]. GISTs frequently give rise to metastasis in peritoneal, omental, mesenteric surfaces and liver. Extra-abdominal metastases are rare. Lymph node metastases are also rare. Because of their submucosal location endoscopy is often non diagnostic. Pre operative staging done by contrast enhanced CT scan of chest, abdomen and pelvis^[13]. Two main classification systems, the Fletcher and Miettinen, consisting of prognostic factors such as primary site, size, and mitotic index, facilitate the stratification of patients into low-, intermediate-, and high-risk groups of recurrence^[14]. Small gastric GISTs appear as serosal, submucosal or intramural nodules that are usually incidental findings during abdominal surgery or endoscopy^[15]. Some tumours may ulcerate, especially the epithelioid stromal tumours. The larger tumours protrude intraluminally or to the serosal side, and may have a massive extragastric component that masks the gastric origin. Intraluminal tumours are often lined by intact mucosa, but ulceration occurs in 20-30% of cases^[16]. Infiltration by direct extension to the pancreas or liver occurs. On sectioning GISTs vary

from slightly firm to soft, tan, often with foci of haemorrhage. Larger tumours may undergo massive haemorrhagic necrosis and cyst formation leaving only a narrow rim of peripheral viable tissue; malignant tumours may form complex cystic masses. Multinodular peritoneal seeding is typical of malignant GISTs. GISTs may stain positively for smooth muscle actin (SMA, 30–40%), but they are usually negative (95%) in immunostaining for S-100 (a neural cell marker) and for desmin (98%, an intermediate filament protein typical of muscle)^[18]. Most GISTs are positive for KIT (CD117), which may show membrane, diffuse cytoplasmic or a perinuclear accentuation pattern.^[19] Approximately 70-80% of GISTs are positive for CD34 (typically membrane pattern). 30-40% are focally or diffusely positive for α -smooth muscle actin, very few show reactivity for desmin (< 5%), and very few for S100-protein (< 5%, usually weak reactivity).^[20]

AJCC stage	Stage grouping	Stage description*
IA	T1 or T2 N0 M0	The cancer is: 2 cm (4/5 of an inch) or less (T1) OR Larger than 2 cm but not more than 5 cm (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
	T3 N0 M0	The cancer is larger than 5 cm (2 inches) but not more than 10 cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
II	T1 N0 M0	The cancer is 2 cm or smaller (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
	T2 N0 M0	The cancer is larger than 2 cm but not more than 5 cm (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
	T4 N0 M0	The cancer is larger than 10 cm (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is low.
IIIA	T3 N0 M0	The cancer is larger than 5 cm (2 inches) but not more than 10 cm (T3). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
IIIB	T4 N0 M0	The cancer is larger than 10 cm (T4). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). The mitotic rate is high.
IV	Any T N1 M0	The cancer is any size (Any T) AND it has spread to nearby lymph nodes (N1). It has not spread to distant sites (M0). The cancer can have any mitotic rate.
	Any T Any N M1	The cancer is any size (Any T) AND it might or might not have spread to nearby lymph nodes (Any N). It has spread to distant sites such as the liver (M1). The cancer can have any mitotic rate.

*The following additional categories are not listed in the table above:

- **TX:** Main tumor cannot be assessed due to lack of information.
 - **T0:** No evidence of a primary tumor.
- NX:** Regional lymph nodes cannot be assessed due to lack of information.

Table 1 AJCC staging of GIST ^[21]

Risk category	Tumour size (cms)	Mitosis/50 HPF
Very low risk	<2	<5
Low risk	2-5	<5
Intermediate risk	<5	6- 10
	5- 10	<5
High risk	>5	>5
	>10	Any
	Any size	>10

Table 1 National institute of Health consensus criteria for GIST estimated risk of recurrence ^[22]

Tumor size (cm)	Mitoses/ 50HPFs	T-stage gastric	T-stage non-gastric
≤2 cm	≤5	T1	T1
>2-5 cm	≤5	T2	T2
>5-10 cm	≤5	T3	T3
> 10 cm	≤5	T4	T4
≤2cm	>5	T1	T1
>2-5 cm	>5	T2	T2
>5-10 cm	>5	T3	T3
> 10 cm	>5	T4	T4

The above UICC stages are valid for NO MO tumors. All tumors with lymph node or other metastasis are considered UICC stage IV ^[23]

Imatinib is an oral, selective, small-molecule tyrosine kinase inhibitor, which targets the Kit protein and the PDGFRA ^[24]. It has been demonstrated that imatinib significantly improves survival in patients with advanced GIST, and it has become the standard of care in this setting ^[25]. ACOSOG Z9001, a double blinded trial Adjuvant imatinib administered in high-risk patients for 12 months after surgical removal of GIST with Kit protein expression has been showed to prolong recurrence-free survival (RFS) compared to placebo ^[26]. Based on these results, imatinib was approved at a daily dose of 400 mg by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) in 2008 and 2009, respectively, as adjuvant therapy for high-risk patients following complete surgical resection of GIST. ^[27]

So there is still a diagnostic dilemma with GIST, to

overcome we have to do a thorough clinical examination with history and collaborate with radiological investigation with a strong clinical suspicion.

Conclusion

Gastrointestinal stromal tumors (GISTs) are a group of biologically distinct tumour which is different from other smooth muscle and neural tumours of the gastro intestinal tract (GIT). The incidence of detection of GIST has risen significantly in the past two decades owing to development in better diagnostic modalities like immunohistochemistry in detecting expression of proto-oncogene. The identification of these mutations has resulted in a better understanding of their oncogenic mechanisms. We conclude that GIST should be considered as a possible differential in rare cases where more common causes have been ruled out. It also highlights the importance of considering differential diagnoses in patients who represent with ongoing symptoms despite a presumed preceding diagnosis.

References

1. H.H.F., L. (2007). Gastro-intestinal stromal tumours: A review of current management options. *Hong Kong Medical Journal*, 13(1), 61–65.
2. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumours, *Science*, 2003, vol. 299 (pg. 708-710)
3. Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H, et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. *Nat Genet*. 1998;19:323–4.
4. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. *J Clin Oncol*. 2004;22(18):3813–3825. [PubMed]
5. M.N. Wente, M.W. Buchler, J. Weitz Gastrointestinal stromal tumors (GIST).

- Surgical therapy *Chirurg*, 79 (2008), pp. 638-643
6. J.A. Sexton, R.A. Pierce, V.J. Halpin, et al. Laparoscopic gastric resection for gastrointestinal stromal tumors *Surg Endosc*, 22 (2008), pp. 2583-2587
 7. <http://www.ncbi.nlm.nih.gov/pubmed/17193820>
 8. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal stromal tumours show phenotypic characteristics of the interstitial cells of Cajal. *Am J Pathol*. 1998;152:1259–1269
 9. Duensing, A. et al. Mechanisms of oncogenic KIT signal transduction in primary gastrointestinal stromal tumors (GISTs). *Oncogene*23, 3999–4006, 10.1038/sj.onc.1207525 1207525 (2004).
 10. Hirota, S. et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. *Science* 279, 577–580 (1998)
 11. Wozniak, A. et al. Prognostic value of KIT/PDGFR mutations in gastrointestinal stromal tumours (GIST): Polish Clinical GIST Registry experience. *Ann Oncol*23, 353–360, 10.1093/annonc/mdr127 mdr127 (2012).
 12. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 2007;25:1753–9. [PubMed]
 13. Bamboat ZM, DeMatteo RP. Updates on the management of gastrointestinal stromal tumors (GIST). *Surg Oncol Clin N Am* 2012;21:301–16. [PMC free article] [PubMed]
 14. Joensuu H, Fletcher C, Dimitrijevic S, Silberman S, Roberts P, Demetri G. Management of malignant gastrointestinal stromal tumours. *Lancet Oncol*. 2002;3 (11):655–664. [PubMed]
 15. Miettinen M, Virolainen M, Maarit Sarlomo R. Gastrointestinal stromal tumour of the stomach: a clinicopathologic, immunohistochemical and molecular genetic study of 1765 cases with long-term follow-up. *Am J Surg Pathol*. 2005;29:52–68. doi: 10.1097/01.pas.0000146010.92933.de. [PubMed] [Cross Ref]
 16. Cegarra-Navarro MF, de la Calle MA, Girela-Baena E, García-Santos JM, Lloret-Estañ F, de Andrés EP. Ruptured gastrointestinal stromal tumors: radiologic findings in six cases. *Abdom Imaging*. 2005;30:535–542. doi: 10.1007/s00261-005-0308-6. [PubMed] [Cross Ref]
 17. Ma, Y. Y. et al. Involvement of c-KIT mutation in the development of gastrointestinal stromal tumors through proliferation promotion and apoptosis inhibition. *Onco Targets Ther*7, 637–643, 10.2147/OTT.S60458 ott-7-637 (2014)
 18. De Silva MVC, Reid R. Gastrointestinal Stromal Tumours (GIST): C-kit Mutations, CD 117 Expression, Differential Diagnosis and Targeted Cancer Therapy with Imatinib. *Pathol Oncol Res*. 2003;9:13–19. [PubMed]
 19. Chabot, B., Stephenson, D. A., Chapman, V. M., Besmer, P. & Bernstein, A. The proto-oncogene c-kit encoding a transmembrane tyrosine kinase receptor maps to the mouse W locus. *Nature* 335, 88–89, 10.1038/335088a0 (1988).
 20. Emile, J. F. et al. Clinicopathologic, phenotypic, and genotypic characteristics of gastrointestinal mesenchymal tumors. *Clin Gastroenterol Hepatol*2, 597–605, S1542356504002435 (2004).
 21. International union against cancer (UICC) Sobin LH, Wittekind Ch, editors. 7th ed. New York: Wiley; 2010. TNM classification of malignant tumours.
 22. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, Miettinen M, O'Leary TJ, Remotti H, Rubin BP, Shmookler B, Sobin LH, Weiss SW.

Diagnosis of gastrointestinal stromal tumors:

A consensus approach. *Hum Pathol.* 2002;33:459–465. [PubMed]

23. International union against cancer (UICC) Sobin LH, Wittekind Ch, editors. 7th ed. New York: Wiley; 2010. TNM classification of malignant tumours.
24. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.* 2002;347(7):472–480. [PubMed]
25. Dematteo RP, Ballman KV, Antonescu CR, et al. American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo controlled trial. *Lancet.* 2009;373(9669):1097–1104. [PMC free article] [PubMed]
26. Nilsson B, Sjölund K, Kindblom LG, et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST) *Br J Cancer.* 2007;96(11):1656–1658. [PMC free article] [PubMed]
27. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. *N Engl J Med.*