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Case Report

Laparoscopy-assisted resection of CD117 and CD34 negative gastrointestinal tumor of stomach following tyrosine kinase inhibitor therapy

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rare case of giant CD117/CD34 negative GIST of proximal stomach, whose large size, loss of interface with adjacent vital organs, and poor general condition of the patient precluded safe upfront surgery but dramatic response to neoadjuvant TKI rendered subsequent laparoscopy-assisted resection possible.

Case report

A 60-year-old female patient presented with epigastric pain, anorexia, early satiety, and significant loss of weight of 3 months duration. Examination revealed pallor, no generalized lymphadenopathy, Zubrod performance stage 2, and a vague lump in epigastrium. Laboratory investigations revealed low hemoglobin – 8.4 gm% and low serum albumin – 2.7 gm%. Computerized tomography (CT) demonstrated a large heterogeneous mass (25 cm × 20 cm × 15 cm) involving proximal stomach, closely abutting the left dome of diaphragm, left lobe of liver, abdominal aorta, and pushing down the splenic vessels and pancreas (Fig. 1). There was loss of interface between the tumor and its surrounding structures. The patient underwent trucut biopsy, following unsuccessful endoscopic biopsies, which showed spindle cell tumor consistent with GIST; however, CD117 was negative. Patient underwent neoadjuvant Imatinib therapy for 4 months, which reduced tumor to less than half its original dimensions (Fig. 2a). Laparoscopy-assisted resection

Introduction

Gastrointestinal stromal tumors (GISTs) constitute a small proportion (3%) of gastrointestinal malignancies, stomach being the commonest site.¹ GIST characteristically stains positive for CD117 and CD34. Tumors staining negative for these markers constitute less than 5% of GISTs and are, hence, rare.¹ Rarer still is the response of such tumors to tyrosine kinase inhibitor (TKI) therapy. We present a

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Fig. 1 – (a) Coronal and (b) sagittal reconstructed computerized tomography images showing gastrointestinal stromal tumors of stomach before Imatinib therapy.

Fig. 2 – (a) Coronal reconstructed computerized tomography image showing gastrointestinal stromal tumors of stomach after Imatinib therapy. (b) Intraoperative photo showing the tumor.

Fig. 3 – Histopathology picture of gastrointestinal stromal tumor. Tumor is seen in the submucosa, while the overlying mucosa is normal. Inset shows the tumor in high-power view.

of proximal stomach and esophagogastric junction was done with esophagogastric anastomosis (Fig. 2b). Tumor was exophytic and 10 cm × 10 cm × 6 cm in size. Histopathology confirmed GIST with mitotic count of 5/50 HPF

(Fig. 3). The tumor was CD117, CD34, smooth muscle actin, and desmin negative but vimentin positive (Fig. 4). Patient had an uneventful recovery and is well on a year's follow-up on Imatinib therapy.

Fig. 4 – Immunohistochemistry panel of the tumor showing positive staining for vimentin and negative staining for SMA, CD34, CD117, S100, and desmin.

Discussion

GIST originates from the interstitial pacemaker cells of Cajal and accounts for <3% of all gastrointestinal malignancies.¹ GIST occurs most commonly in stomach (70%), small gut (20%), and esophagus/large gut (10%). They are also seen, occasionally, in other intra-abdominal sites, such as, omentum, mesentery, uterus, and retroperitoneum. In stomach, the commonest site is body, followed by fundus and antrum. Most GISTs occur sporadically (95%); however, a minority (5%) occurs associated with familial GIST, Carney's triad, Carney–Stratakis triad, and neurofibromatosis-1.² c-kit, a transmembrane tyrosine kinase receptor for steel factor/stem cell factor, which is responsible for proliferation and decreased apoptosis, is mutated in most GISTs (85–95%).^{2,3} Mutations are most common in exons 11 (70%), 9 (30%), 13 (10%), and 17 (<1%). Gastric GISTs have most commonly exon 11 mutation – either in-frame codon deletion or missense point mutation. PDGFRA is mutated in 5–7% of GISTs, in its exons 12, 14, and 18. These GISTs behave more aggressively. 5–15% of GISTs do not have either of the above two mutations and are labeled as wild GISTs.^{1–3} They are known to be less responsive or unresponsive to Imatinib therapy.

A third of the GISTs are asymptomatic (30%), but most present with abdominal discomfort/pain, palpable lump, and bleeding.¹ Bleeding, due to erosion into lumen, is mostly slow, hence, present as anemia. However, melena and hematemesis due to severe bleeding is well known. Depending on the location and adjacent organ being compressed/invaded, other manifestations, such as, satiety, anorexia, nausea/vomiting, dysphagia, jaundice, and obstruction, are also well known.^{2,4} Metastases are mostly intra-abdominal and occur in peritoneum, omentum, mesentery, liver, and pancreas. Lymph node metastasis is exceptional.¹

CT forms the backbone of diagnosis.^{5,6} GISTs can have exophytic, intramural, endoluminal, or combined dumbbell-shaped growth pattern. Being subepithelial, most GISTs originate from muscularis propria. Endoluminal tumors are covered with smooth overlying mucosa and have well-defined margins, which make obtuse/right angles with the bowel wall. Larger tumors (>2 cm) may have central ulceration, consequent to necrosis, seen as bull's eye sign on imaging. Greater degeneration/necrosis may form large cavities in the tumor communicating with the lumen. Areas of hemorrhage and necrotic degeneration are seen as high and low attenuation areas. CT is also used to assess response to TKI therapy, by Choi criteria, where decrease in tumor size by 10% and tumor density by 15% denote response.³ Positron-emission tomogram coupled with CT (PET CT) is sensitive in detection of metastasis and in objective assessment of tumor response to TKI therapy by fall in Standard Uptake Value (SUV) value by 15–25% after 1 cycle.³

Imaging forms sufficient basis to proceed with surgery. However, unresectable cases, cases needing neoadjuvant TKI therapy, and cases where diagnosis is in doubt are the ones that need preoperative biopsy.¹ Endoscopy has poor yield for biopsy, as seen in our case, tumor being beneath the mucosa.² Endoscopic ultrasonography-guided biopsy may prove better. We opted for trucut biopsy, as we had a bowel-free window,

and had a need to downstage tumor in view of its large size, loss adjacent organ interface, and poor performance status.

GISTs are of 3 histologic types: spindle cells (70%), epithelioid cells (20%), and mixed spindle–epithelioid cells (10%).³ The crucial diagnostic test for GISTs is immunohistochemistry (IHC).^{1–3} In addition to the important CD117 (95%), which is the epitope on the extracellular domain of kit, GIST stains positive for less specific CD34 (60–70%), vimentin/smooth muscle actin (15%), caldesmon, calponin, and embryonic smooth muscle myosin. Discovered on GIST-1 (DOG-1) and Protein Kinase C Theta (PKC θ) are novel markers, which are seen in 97% of GISTs, including those which are wild type; hence, it may prove of benefit in identifying them.^{1,2}

Staging of GISTs take into account the size, Mitotic index (< or >5/50 HPF), and the site of tumor.¹ Our case fell into the moderate-risk category.

Surgical excision without lymphadenectomy is the recommended treatment.¹ However, unresectable disease, very large tumors, and tumors needing radical/multivisceral resection are best treated by initial neoadjuvant TKI therapy followed by resection when adequate response is seen.^{1–3} This option was adopted in our case, as the tumor was very large and had no clear interface with surrounding aorta, diaphragm, left lobe of liver, and renal vessels. Free resection margin is desirable; however, R1 resection does not mandate re-resection, but adjuvant therapy.^{1,2} The optimal period of neoadjuvant therapy is not clear. However, it is better to wait for maximal response, which is no further improvement between 2 successive CT scans.³ Small submucosal tumors can be addressed by endoscopic submucosal dissection or endoscope-guided laparoscopic resection.^{2,3}

TKI therapy is recommended for tumors >5 cm and tumors with mitotic count >5/50 HPF for at least 2 years following resection.^{1–3} Imatinib mesylate is the model TKI that has maximal response in tumors, which are CD117 positive. However, tumors not expressing c-kit, such as ours, may also respond to Imatinib.² Resistant cases may respond to higher doses of Imatinib or to Sunitinib.^{1,2} Newer generation TKIs, such as Regorafenib, Nilotinib, Sorafenib, Dastinib, Dovitinib, Pazopanib, and Crenolanib, may need to be exhibited in resistant cases.^{2,3}

Newer drugs on trial are Heat-Shock Protein-90 inhibitors, such as, Tanespimycin and Ganetespib, which show promise for resistant and metastatic GISTs.²

Summing up, CD117 and CD34 negative GISTs are rare. Response to TKI therapy renders the tumor amenable to minimal access surgery.

Conflicts of interest

The authors have none to declare.

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