Case Report

Synchronous gastrointestinal stromal tumor of stomach and neuroendocrine tumor - A rare case report

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ABSTRACT

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor occurring in the stomach with characteristic morphological features. Approximately 7–8% of all neuroendocrine tumors (NETs) are gastric NETs. However, simultaneous occurrence of both of them in stomach is a rare event. Here we present a rare case of synchronous GIST and NET in stomach of a 73 years old female patient. In our case, GIST showed Low risk category morphology as well as characteristic CD117 positivity proven by Immunohistochemistry. NET, our case, was well differentiated Grade I type showing positivity for synaptophysin and chromogranin A. Reporting of such rare cases is important for surgeons as well as pathologists to provide better patient management.

KEY WORDS: Synchronous; Gastrointestinal Stromal Tumor; Stomach; Neuroendocrine Tumor

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract originating from interstitial cells of Cajal, showing characteristic positivity for CD117. Prior to their recognition as distinct tumors, GISTs were most commonly classified as smooth muscle tumors or neural tumors.[1] They commonly occur in stomach, frequently in the fundal region. They occur usually in adult patients and their prognosis depend upon the size of tumor and mitotic activity.

GI neuroendocrine tumors (NETs) occur in small intestine, rectum, stomach, colon, esophagus and appendix. Gastric NETs constitute 7–8% of all NETs[2,3] and 0.1–0.6% of all gastric cancers.[4] In the stomach, most NETs are located in the corpus or fundus, arising from enterochromaffin-like (ECL) cell of gastric mucosa. Gastric NETs are usually associated with achlorhydria, antral G cell hyperplasia, hypergastrinemia, diffuse ECL cell hyperplasia. NETs are divided according to their differentiation (well or poorly differentiated) and whether they produce symptoms of excessive hormone secretion or not (functional/non-functional). They can also occur in pancreas, lung and other endocrine organs.

Though rarely, GIST can occur simultaneously with well differentiated NET of ileum or pancreas. However, synchronous occurrence of GIST and well differentiated NET in stomach is a very rare event. Thereby, we present such a case reported in our institution.

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CASE REPORT

73-year-old female was admitted for abdominal pain. During hospitalization, an episode of vomiting occurred, following which she underwent upper GI endoscopy; which revealed mass in lesser curvature of stomach with diffuse bulge in mucosa. Distal gastrectomy was performed.

On gross examination of the specimen, a large lump was palpated along lesser curvature of stomach [Figure 1].

On c/s: Soft to firm, brownish tumor was seen, size 9.5 × 5.5 × 4.3 cm [Figure 2].

One pinkish grey distinct nodular area was seen on the under surface of tumor, 1.3 × 1.1 × 0.9 cm.

Histology from large gastric mass revealed a stromal neoplasm with epithelioid and spindled morphology with abundant areas of haemorrhage and necrosis. Epithelioid cells are round, having high N: C ratio, granular chromatin, moderate clear/eosinophilic cytoplasm. The mitotic activity was <5/50 hpf [Figure 3]. The tumor cells expressed c-kit (CD117), DOG-1, CD34 and smooth muscle actin (focal) and were immunonegative for desmin and S-100 protein (IHC done at SRL Mumbai).

Section from the distinct nodule revealed a well differentiated NET, with small round to oval cells, having high N: C ratio, "salt and paper chromatin", scanty cytoplasm [Figure 4]. IHC work-up of the same showed Cytokeratin, Synaptophysin and Chromogranin A positivity.

The Mib-1 labeling index was <2%.

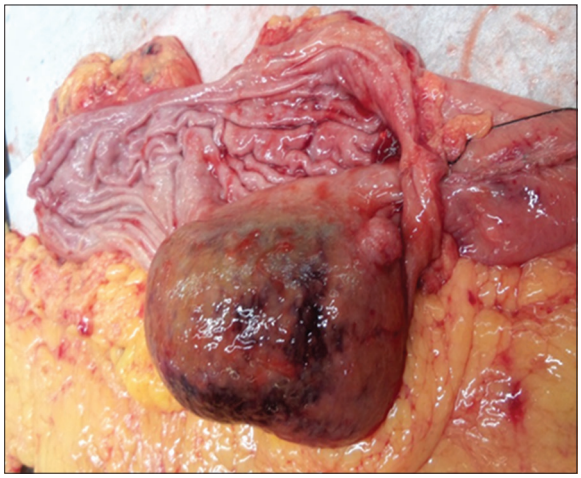

Figure 1: Gross examination of the specimen

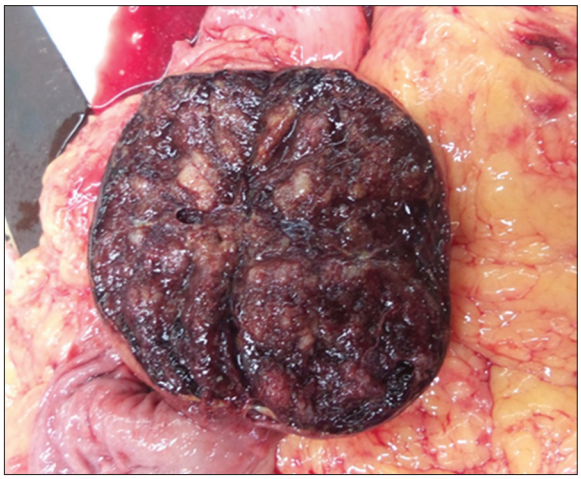

Figure 2: Cut section

One regional lymph node revealed metastasis of well differentiated NET.

DISCUSSION

GISTs are the commonest mesenchymal tumors of GI tract predominantly involving the stomach (50–62%), small intestine (20–30%), colon (11%) and the rectum (7%).[5] As discussed above, they arise from interstitial cells of Cajal and show characteristic immunoreactivity for CD117. Most GISTs are initiated by mutations in proto-oncogene c-kit or platelet derived growth factor receptor A (PDGFR-A).

Usually occurs in older adults, GISTs present with abdominal pain, gastric outlet obstruction, mass effect, melena; or they may be completely asymptomatic.

Microscopically GISTS have 4 main types based on morphology of the proliferating cells and mitotic activity: Benign cellular spindle cell tumor, spindle cell sarcoma, benign epithelioid gastric stromal tumor, malignant epithelioid gastric stromal tumor; mixed patterns can also occur. In our case, GIST showed mixed cellular patterns with

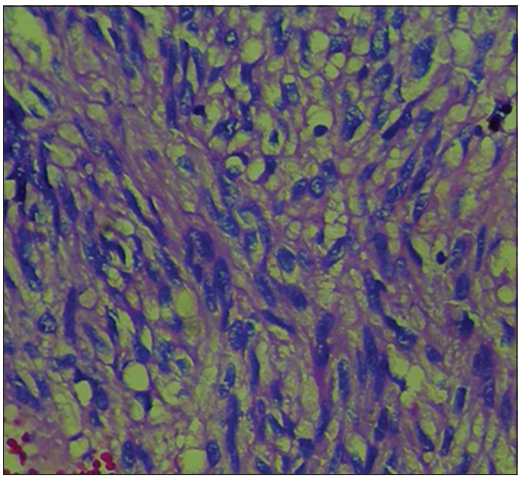

Figure 3: Histology of gastrointestinal stromal tumor

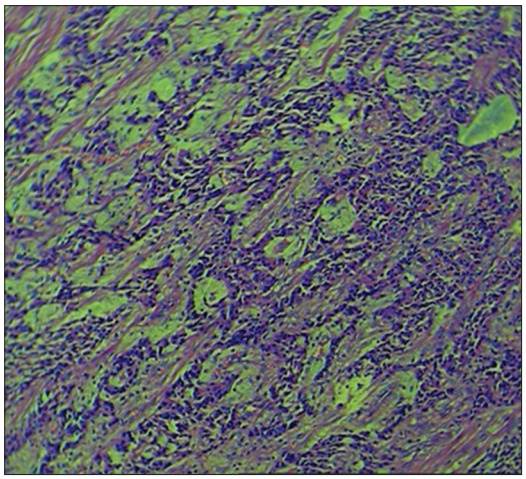

Figure 4: Histology of neuroendocrine tumor

both spindle and epithelioid cell component. Mitotic activity was <5/50 hpf.

Their clinical behaviour and risk stratification depends mostly on tumor size, mitotic activity and Location. Our case, considering the size of tumor in greatest dimension (9.5 cm) and above mentioned mitotic activity, belongs to the low risk category. However, tumor with same features, if present in jejunum/ileum carries a moderate risk.

Treatment includes, targeted therapy (imatinib mesylate) in cases with kit mutations and many with PDGFRA mutations; it inactivates the ability of kit to perform intracellular signaling. Complete surgical excision is advised for metastatic disease or high risk tumors. Tumors without kit or PDGFRA mutation will not respond to imatinib treatment. Our case was CD-117 (c-kit) positive however, surgical excision was done because of the tumor size.

Prognosis is usually better for tumors carrying a low risk according to guidelines for risk stratification.

Gastric NETs are divided into four types: (a) Type I, associated with autoimmune chronic atrophic gastritis (A-CAG), (b) Type II, linked to multiple endocrine neoplasia type 1 or to zollinger-ellison syndrome, (c) Type III, sporadic, unrelated to hypergastrinemia or A-CAG, with maximum potential to metastasize and (d) Type IV, having multiple small lesions which show hypertrophy and hyperplasia of parietal cells with vacuolated cytoplasm.[6]

Gastric NETs usually present with features of achlorhydria, antral G cell hyperplasia, hypergastrinemia, diffuse ECL cell hyperplasia and rarely present as carcinoid syndrome, symptoms of which include redness due to histamine production.

For prognostic purposes, NETs are divided into well/poorly differentiated tumors and graded into 3 grades according to mitotic activity [Table 1].

Treatment usually includes endoscopic or surgical resection of the tumor. Type I may benefit from antrectomy but subtotal or total gastrectomy is more advisable. Type III cases should be treated with total/subtotal gastrectomy.

In a study done by Liszka *et al*., the incidence of GIST occurring simultaneously with other diagnosed neoplasms is reported between 3% and 33%.[7]

Whether this synchronous occurrence of GIST with other tumors is incidental or related to similar pathophysiology is a matter of debate.[8] Some authors have suggested that they may share common carcinogenic pathways or genetic mutations with differentiation towards distinctive cell lines.[9]

Role of *Helicobacter pylori* is also suggested, though no clear evidences have been found. Thus, Lin *et al*. did not conclude any definite relationship between coexisting GIST-NET and *H. pylori*.[10]

Among the coexisting tumors, GI carcinomas are the most common secondary neoplasms. Other tumors are carcinomas of prostate, kidney, breast, female genital tract, lung, lymphoma/leukemia, soft tissue and bone sarcomas, malignant melanoma and seminomas.[11]

GIST has been shown to co-exist with well differentiated NETs of ileum or pancreas, however, gastric NET and GIST very rarely occur simultaneously. Very few cases are reported so far, to our best knowledge.[10,12]

Table 2 shows morphological features of both the tumors.

In our case, GIST was a low risk category and NET was of benign clinical behavior though with micrometastasis in one of the lymph nodes.

Prognosis in such synchronous cases of GISTs is mainly determined by the other malignancy and not by

Table 1: World health organization 2010 classification of NETs in the GI and pancreatobiliary tracts

Grade	Mitotic count/10 HPFs	Ki-67 labeling index, %
NET, Grade 1	<2	<3
NET, Grade 2	2–20	3–20
NEC, Grade 3	>20	>20

HPF: High-power field, NEC: Neuroendocrine carcinoma, NET: Neuroendocrine tumors

Table 2: Correlation of morphological features of GIST and NET

Correlation of morphological features of GIST and NET in our case									
GIST								NET	
Tumor size	Morphology	Mitotic index	Necrosis	Nuclear pleomorphism	CD117 reactivity	Malignant potential/risk category	Location	Tumor size	Morphology and grade
9.5×5.5×4.3 cm	Epithelioid and spindled morphology	<5/50 hpf	Present	mild	present/ positive	Low risk	Stomach	1.3×1.1×0.9 cm	Well differentiated NET, Grade I

NET: Neuroendocrine tumors, GIST: Gastrointestinal stromal tumor

GIST.[13] Therefore treatment approach should emphasize on the prognostically relevant malignancy-NET in our case.[13] A meticulous intra-operative examination of abdomen supplemented by awareness of GIST and their morphological characteristics is necessary for recognition of coincidental GIST and to provide appropriate treatment.[13]

Incidence of synchronous GIST with other tumors has been increased because of increased reporting of one tumor incidentally while evaluating the other tumor. Reporting of such cases is mandatory for better management and to improve prognosis of the patient.

CONCLUSION

We present this rare case of co-existing GIST and NET in stomach. In order to avoid extensive metastatic disease, surgeons and pathologists should be aware of such rare co-existence of tumors, so that appropriate initial therapeutic approach and a meticulous follow up can be planned for such patients.

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