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GIST Mimicking Ovarian Tumor in a Tertiary Care Hospital

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Abstract: To report the various presentations of patients who presented with abdominal or pelvic mass and were later diagnosed to be gastrointestinal stromal tumor. Gastrointestinal stromal tumors (GIST) should always be considered as a differential diagnosis in patients presenting with abdominal mass or pelvic mass. In such circumstances, the complete resection and appropriate adjuvant treatment will result in remission.
Keywords: Adnexal mass, ovarian tumor, gastrointestinal stromal tumor, incidental finding.

INTRODUCTION

GIST is mesenchymal neoplasms of gastrointestinal tract, whose counterpart is interstitial cells of Cajal which are pacemakers for gastrointestinal motility. The incidence of GIST is estimated as 10-20 patients in 1 million population [8]and can occur at any age but has a median occurrence at 60-65 years.It is more common in males than females [1].Site of occurrence is stomach(>50%),small bowel(25-30%),large bowel(10%),esophagus(5%) or elsewhere in the abdominal cavity(-omentum and mesentry(5%)[9].Rarely, GIST may occur in areas outside the GI tract such as uterus, rectovaginal septum, vagina, mesentery and retro peritoneum [10].

Clinical presentation of GISTs may vary and symptoms are related to their location. The patients usually seek medical help for bleeding due to mucosal ulceration. Abdominal mass, nausea, vomiting, weight loss, abdominal discomfort and pain are among other symptoms [2]. Intraperitoneal GISTs may be detected as palpated abdominal mass, but occasionally they may be confused with ovarian mass [1]. It typically expresses the receptor tyrosine kinase c-kit, also known as CD117). Tyrosine kinase, CD34 and CD 117 receptor positivity can be used in differentiating GISTs from other mesenchymal masses [10].The prognosis of patients is based on tumor size, mitotic rate and site of origin. These are mostly asymptomatic and found incidentally during laparoscopy, surgical procedures or radiological studies. Diagnosis is based on histology and immunohistochemistry, while the role of imaging studies is not specific. Ultrasound and MRI are not able to differentiate a GIST from ovarian cancer. Surgical resection of the local disease is the mainstay therapy. Fletcher *et al*.[3], classified these tumors in to very low, low, intermediate and high risk, categories according to tumor size and mitotic count. Tumors <2 cm and mitotic count <5/50 high power field (HPF) were categorized as very low risk; tumor size 2–5 cm and mitotic count <5/50 HPF as low risk; tumor size <5 cm and mitotic count 6–10/50 HPF or tumor size 5–10 cm and mitotic count <5/50 HPF as intermediate risk; tumor size >5 cm and mitotic count >5/50 HPF or tumor size >10 cm and any mitotic rate or tumor any size and mitotic rate >10/50 HPF as high risk. The published literature on this is limited to isolated case reports and single case series.

The goal of this retrospective study was to report on patients who presented with presumptive diagnosis of ovarian malignancy in gynaecology department and was finally diagnosed to have GIST. We have described the clinical presentation, surgical management and overall outcome of the patients. We have also discussed the published literature on GIST presenting as ovarian cancer.

Pre-operative diagnosis is difficult with clinical picture and particularly in female patients; GISTs may get confused with gynaecological malignancies due to their location and symptoms. In this case report, with the guidance of literature we aim to discuss in details a patient whose suspected diagnosis was postmenopausal ovarian malignancy and operated accordingly but later found to be a case of small intestine GIST during the operation.

Objectives

- GIST does not have any unique clinical signs and symptoms or unique appearance in USG. If a pelvic

mass is detected, the possibility of a non-gynaecological tumor like GIST has to be considered.

- A timely referral to get better surgical treatment and post-operative chemotherapy or radiotherapy in a tertiary care centre.

CASE REPORT 1

A 50years old female, P5+0, post-menopausal, came with pain abdomen and lump lower abdomen for 4 months to our GOPD. Swelling was over the left side initially and later attained huge size up to the umbilicus within a short span of time. Patient lost about 5kgs in 4 months. Mass was about 15x15 cm^2 size, firm and mobile.

Apart from routine investigations of blood and urine, she underwent USG whole abdomen which showed a predominantly solid ovarian tumor 12.5x8x11.3cm^3 in size, without ascites. MRI Pelvis revealed a well-defined encapsulated heterogeneously enhancing mass lesion abutting the anterolateral wall of uterus and distal ileal loop with internal haemorrhage and necrotic areas. Laparotomy revealed 15x12x10cm3 mass arising from ileum about 40cm proximal to ileocaecal junction. Resection of the mass and end-end anastomosis was done. Histopathological report- high grade GIST. Immunohistochemistry was CD117/C-KIT positive.

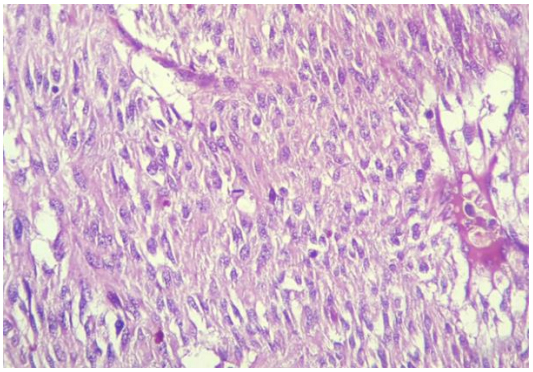

Fig-1: Histopathological examination of case 1-GIST is composed of uniform eosinophilic cells with ovoid nuclei arranged in fascicles

CASE REPORT 2

A 58 years old postmenopausal, para 2 ,live 1 presented to our GOPD on 27-07-17 with chief compliant of abdominal distention for 2 months along with pain abdomen and loss of appetite for past 2 years. She had history of gradual enlargement of abdomen for past 2 months, gradual in onset and insidious in nature. She had associated loss of appetite and generalized weakness for 2 years but more pronounced for past 2 months. Due to her loss of appetite she had lost weight and her day to day activities were affected. She had gone to Jorhat Medical College for the above compliants and she was referred to GMCH for the same. She had history of cholecystitis in 2013 for which she had cholecystectomy done. There was no other significant past history of any medical or surgical illness.

All routine investigations were done including ultrasonography of abdomen and MRI .Her Ca125 was 103.05 U/ml and Ca19-9 was 2.50 U/ml.

The reports were the following

USG Abdomen- mildy hypoplastic kidneys with normal parenchymal echopattern. Poorly marginated cystic mass with solid components and thick internal septae measuring 16.8*7*9.4 cm extending from the right side of the pelvic cavity to the umbilicus level. No lymphadenopathy or free fluid in the peritoneal cavity

MRI Pelvis 27/07/17

Large heterogenous abdomino- pelvic mass with irregular enhancement of the rim with lobulations blood fluid level possibility like GIST or malignant ovarian neoplasm. There is a heterogenous expansile lesion in the second sacral region possibly hemangioma.

Explorative laparotomy was done and the intraoperative finding was a cystic mass arising from the posterior wall of stomach adhering to the transverse colon. Uterus and ovaries were found to be normal.

Resection of en-mass with distal subtotal gastrectomy with Bill roth Type 1 Anastomosis with transverse colectomy with side to side anastomosis and the specimen was sent for histopathological analysis.Postoperative period was uneventful.

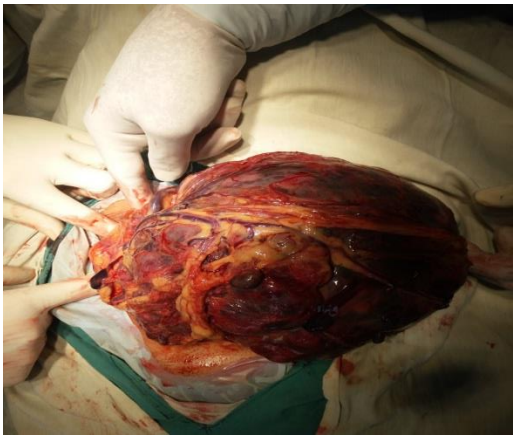

Fig-2: Intraoperative findings of case report 2

HPE findings

22*14*12 cm in size blackish brown mass with nodular outer surface. On cut section , cystic with solid areas were noted which were whitish in colour. Multiple locules containing hemorrhagic and necrotic material was noted.Cyst wall was thick at places and greyish white in colour on cut section.Two tubular segments measuring 8 and 9 cm in length were adherent to the mass. On microscopic examination, spindle cell tumor with high pleomorphism, stromal myxoid change, haemorrhage and necrosis was seen. Mitotic count was >5/50 HPF , part of the tumor showed clear cell change. Possibility of GIST undergoing malignant change was suggested.Multiple sections taken from omental fat were free from Tumor cells.

Immunohistochemistry done was immunoreactive for CD117 with score 3+ in lesion and immunoreactive for CD34 with score 3+ in lesional cells (immunoreactive in 51-75% cells).

Review of Literature

A case report by Kadam *et al.* [4] reported a 55-year-old multiparous postmenopausal female presenting with history of lower abdominal pain, decrease in appetite, constipation and weight loss since 2 months. On clinical examination her vitals were normal and a soft large mobile mass was felt arising from the pelvis. Her CA-125 (20 U/ml) and CA 19-9 (0.6 U/ml) were normal but CEA was raised (12.99 ng/ml). MRI pelvis revealed altered signal intensity mass of size 15 × 11 cm in axial plane and 16 × 10 cm in sagittal plane extending up to mid abdomen arising from pelvis, suggesting possibility of ovarian mass . She was taken for exploratory laparotomy with provisional diagnosis of malignant ovarian tumor. On exploration uterus and both ovaries were found to be normal but a large retroperitoneal mass of size 28 cm × 22 cm which was adherent to small bowel was seen. Resection of retroperitoneal mass was done which was followed by total abdominal hysterectomy with bilateral salphingo-oophorectomy and infracolic omentectomy. While respecting the retroperitoneal mass, a small rent was present over the small intestine which was repaired. Histopathology report showed the retroperitoneal mass to be a malignant epithelioid gastrointestinal tumor. Her cytology report was negative. Histologically the tumor showed the mass to be a malignant epithelioid gastrointestinal stromal tumor with mitoses in 8 - 9 of 10 high-power fields. Immunohistochemical study showed positivity for c-kit (CD117) and S-100 with neural and muscle differentiation present.

A 54-year-old woman reported by Chen *et al.* [5],who was gravida 4, para 2, with type I neurofibromatosis presented with abdominal distension that deteriorated progressively in the months before her visit. Ultrasonography showed a solid right adnexal mass and minimal ascites. Computed tomography (CT) confirmed a 14-cm pelvic mass containing cystic and solid components, dilated bowel loops, and left hydronephrosis. Laboratory data showed a low level of serum hemoglobin (7 g/dL) and elevated level of serum CA 125 (363.6 U/mL). Preoperative colonoscopy and gastroscopy did not show any intraluminal mass and other tumor markers; in particular, carcinoembryonic antigen and cancer antigen 19-9 were within normal limits. Preoperatively it was suspected to be an ovarian malignancy. Exploratory laparotomy was performed and a 14-cm necrotic and semisolid tumor was found. It was densely adhered to the uterine fundus and ileum. Frozen section pathological examination revealed that the mass was a sarcoma. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection, and partial omentectomy were then performed with segmental resection and anastomosis of the ileum because of tumor-related segmental stenosis. No residual tumor remained after surgery. The final histopathological examination showed that the tumor was a malignant GIST. The mitotic index of the tumor was 5-10 per 50 high power fields. The tumor cells stained positive for CD117 (diffuse), S-100 (focal), and vimentin, and stained negative for actin and desmin. The patient received imatinib (400 mg daily) during a 3.5-year follow-up period, and her postoperative course was uneventful. The CA125 levels declined after surgery (51.12 U/mL at 1 month postsurgery, 11.88 U/mL at 2 years postsurgery, and 10.37 U/mL at 3 years

postsurgery). At the 3.5-year follow up, there was no evidence of recurrent GIST.

In the case reported by Nilay Karaca *et al*. [6] , a 52 years old postmenopausal female patient was referred for routine gynaecological exam. She was hypertensive for 5 years and had diabetes mellitus for 18 years. Gravida 3, para 2, abortus 1 patient had total vaginal hysterectomy operation 3 years ago because of abnormal uterine bleeding. Otherwise, she had no peculiarity in her medical history. In her gynaecological exam vulva, vagina and vaginal cuff were normal in appearance; in bimanual exam a mobile mass app. 30-40 mm in size concordant with left adnexal area was detected. Uterus couldn't be observed in transvaginal ultrasound due to previous operation. Right ovary was 22x17 mm in size and normal in appearance. A semisolid appearing cystic mass 47x44 mm in size was observed in the area concordant with left ovarian lodge. Left ovarian border couldn't be clearly detected. Among tumor markers cancer antigen 125 (Ca125)- 21 IU/ml, Ca19-9: 12 IU/ml, carcinoembryonic antigen (CEA)- 2 IU/ml, alpha feto protein (AFP)- 0.8 IU/ml were in normal range. Enhanced computerized tomography revealed solid lesion with prominent enhanced material fixation and a necrotic component in the central in left ovarian lodge; the lesion had bilobular appearance and was 66x45 mm in size. In light of this information the patient was operated. General evaluation after obtaining abdominal lavage fluid indicated that omentum was adherent towards left inguinal region. Uterus couldn't be seen due to previous operation. Right ovary was in normal location but atrophic and in the left ovary , lodged a mobile semisolid cystic mass with partially regular borders app. 40x40 mm in size was observed. The mass was attached to ovarian tissue. Ovary was atrophic and in normal appearance. The existing mass started from serosa of distal ileum and a general surgeon was invited for surgery. Mass was removed along with 15 cm intestinal segment and frozen section was done. Macroscopic examination of the mass revealed that it was adjacent to intestinal segment and nodular with regular outer surface and 7*5*4 cm in size. Section surface was relatively soft in consistency and included occasional yellow coloured regions concordant with necrosis. The result of frozen section was reported as gastrointestinal stromal tumor. Exploration showed that there was no metastasis in abdominal cavity. After end-to-end anastomosis, bilateral salphingo-oophorectomy and partial omentectomy the operation was terminated. Microscopic examination of the excised tissue revealed that it's considered generally from proliferating spindle cells showing tumoral features. Prominent increase in cellularity and increase in mitosis activity of cells (grade 2) with accompanying wide necrosis and bleeding areas were observed. In some regions tumoral tissue was attached to intestinal mucosa and partial mucosal ulceration areas were recognized (Figure 4). CD117 (C-KIT) staining by immunohistochemically method performed in an external lab for differential diagnosis revealed diffuse and strong positivity, Ki 67 positivity was 40% and Pan Cytokeratin was negative. Pathologic stage was stage IIIb, there was no complication in the post-op follow up and the patient was referred to medical oncology clinic.

As reported by Goyal *et al*.[7] A 54-year-old multiparous postmenopausal female presented to the gynaecology outpatient department with gradual onset pain in the right lower abdomen for last 1 month. There was no history of anorexia, bone pains, bowel and bladder complaints, postmenopausal bleeding, or symptoms of hyperestrogenism/androgenism. General physical examination was unremarkable. Per abdomen examination revealed a mobile, nontender, firm lump of approximately 8 × 8 cm in the right iliac region extending into the pelvis. Per speculum examination showed chronic cervicitis with a healthy vagina. On pervaginal examination, a firm irregular nontender mass with restricted mobility was felt in the right fornix, which could not be made out separately from the uterus. Clinically, a possibility of right ovarian mass was considered.

Ultrasound abdomen showed a well-defined, heterogeneous mass measuring 13 × 9 × 7.9 cm with internal vascularity and echogenic foci in right pelvic and right iliac fossa, suggestive of right ovarian mass. CECT abdomen revealed a heterogeneously enhancing mass lesion in the region of right adnexa. Lesion was displacing and abutting the adjacent small bowel loops and sigmoid colon. Multiple well-defined nodular lesions were seen in omentum, mesentery, and bilateral round ligaments. Because the right ovary was not visualized separately, possibility of carcinoma ovary was suggested. Serum CA-125, CA 19.9, β-hCG, and CEA levels were found to be within normal limits.

Cell block showed predominantly interlacing spindle cells with few round-to-oval cells. On immunocytochemistry, the tumor cells were negative for cytokeratin, inhibin and calretinin, desmin, and S-100, and showed strong positivity for vimentin, smooth muscle actin (SMA), and CD117. Based on high cellularity, presence of loose fragments with single cells, focal areas of necrosis, and immunocytochemistry, diagnosis of GIST - inconclusive for malignancy was offered.

The patient underwent an exploratory laparotomy that revealed a large peritoneal mass which was attached with the serosa of small bowel, 5 cm distal to the duodeno-jejunal junction. Bilateral adnexa and uterus were normal. Excision of the tumor with resection anastomosis of an ileal segment (7.5 cm) was done.

On the basis of morphology and immunohistochemistry, brisk mitoses >5/50 hpf,

necrosis, tumor size of 18 cm, and presence of multiple implants all over the mesentery and peritoneum, a diagnosis of malignant intestinal GIST was offered on histopathology.

Giorgio Calmagno et al reported a case of a 42-year-old woman presented with pelvic pain, palpable pelvic mass extended to the epigastric region, and elevated CA-125 (61.8 U/ml). Computed tomography (CT) imaging showed a left 6 × 5 cm cystic ovarian lesion and a 12 × 9.5 cm solid mass in the epigastric region. A preoperative diagnosis of metastatic ovarian malignancy or FIGO stage III ovarian malignancy was made. At laparotomy, a left ovarian cyst was seen along with a solid mass attached to the greater curvature of stomach which was easily dissected from it. Histologically, the lesion was composed of a proliferation of spindle cells embedded in an abundant myxoid stroma, without evidence of frank atypia or anaplasia. Histochemical stains showed strong positive staining with muscle actin, positive staining with CD34 and weak positive staining with CD117, while it was negative for S-100. The histological work up was conclusive for a low malignancy GIST – myxoid variant, being the mass volume the only risk factor, the ovarian mass on the other hand was a follicular cyst. Due to the lack of clear risk factors for recurrence, and due to complete surgical tumor resection, the patient was advised follow up only.

Kermiglow *et al*. reported a patient, 45- year-old woman who presented with a palpable mass filling the pelvis. The CA 125 value was 42.7 U/ml. A mass of approximately 15x16 cm in size, filling the whole abdomen, originating from the caecum was observed intraoperatively. The uterus was normal in size, and the bilateral fallopian tubes and ovaries were atrophic. The general surgery team participated the operation. Right hemicolectomy was performed along with removal of the mass. Furthermore, a 10 cm portion of the intestinal loop in which a mass was detected was excised and an end-to-end anastomosis was performed. The patient was then handed over to the gynaecology team after having performed an ileocolic anastomosis. The mass was sent for frozen section examination. Tumoral tissue showed diffuse cytoplasmic membraneous staining immunohistochemically with CD117, showed strong focal strong cytoplasmic staining with SMA. It was stained negative with desmin, S-100 and CD3 .On histopathological examination, a 16x12x8 cm portion of smooth, broad-based tumoral mass was observed in the serosal surface of the excised colon segment. Tumor cells comprising fusiform cells histologically showed moderate cellular pleomorphism. The number of mitosis was higher than 15/10 HPF; the Ki 67 score was higher than 10%.The histopathological diagnosis was reported as malignant gastrointestinal tumor. Molecular analysis of KIT gene with DNA sequencing was performed to identify mutations of exon 9 and 11 after polymerase chain reaction and amplification of genomic DNA. The patient had no mutations within KIT exon 9 or 11. The patient completed the postoperative recovery period was handed over to the medical oncology department for adjuvant chemotherapy.

DISCUSSION

GIST is the most frequent non-epithelial tumor occurring in the stomach and small bowel. The confusion surrounding this tumor is its enigmatic origin, difficulty in differentiating from others and difficulty in identifying reliable prognostic criteria. In the past, GISTs was classified as submucosal tumors as they were thought to originate from muscular or neuronal tissue. But now it has become clearer that they cannot be placed in any of these groups.

Table-1: showing classification of mesenchymal tumors

Benign submucosal tumors	Malignant submucosal tumors
Leiomyomas	Leiomyosarcomas
Schwannomas	Gastrointestinal stromal tumors
Granular cell tumors	
Heterotopic pancreatic tissue	
Lipomas	
Neurofibromatosis	
Vascular tumors	

The preoperative diagnosis of GIST is uncommon due to their rarity and different modes of presentation and lack of distinguishing characteristics on imaging studies.

On ultrasonography, GIST exhibit a variety of features lacking a typical pattern.These are hyperechoic central areas,due to myxoid degeneration or formation of microcysts within the mass,large hypoechoic mass ,surrounded by a peripheral rim of residual echogenic parenchyma.

Here we discuss the different features and clinical presentations of GIST in comparison to other cases reported in literature.

Name of the study	Age(yrs)	Clinical presentation	Radiologic findings	Ca125(IU/mL)
Case 1	50	Abdominal mass and pain	USG- solid ovarian tumor 12.5x8x11.3cm^3 in size, without ascites MRI-well defi ned encapsulated heterogeneously enhancing mass abutting uterus.	22
Case 2	58	Abdominal distention and pain abdomen	USG-Poorly marginated cystic mass with solid component and internal septae.	103.05
Kadam *et al.*	55	Pain abdomen	MRI-altered signal intensity mass 15*11 cm in axial plane.	20
Chen *et al.*	54	Abdominal distention	USG-solid right adnexal mass with minimal ascites CT-14 cm pelvic mass with solid and cystic components	363.6
Karaca *et al.*	52	No complaints	CT-solid lesion with prominent enhanced material and necrotic components.	216
Goyal *et al.*	54	Pain abdomen	USG-well defined heterogenous 13*9*7.9 cm mass with echogenic foci	NA
Carlmagno *et al.*	42	Pelvic pain and lump	CT-6*5 cm cystic ovarian lesion and 12*9.5 cm solid mass in epigastric region.	61.8
Kermiglow *et al.*	45	Lump abdomen	NA	42.7

As shown in the above table 2, GIST tumors in these patients had a wide variety of presentations ranging from pain abdomen to lump abdomen.

As shown in the above table 3, all the cases of GIST consistently showed positivity for CD117 immuohistochemical marker.

Table-3: GIST and its correlation with immunohistochemically markers and site of tumor

Name of the study	CD117	Other IHC markers	Site of GIST intraoperatively
Case 1	+		Ileum
Case 2	+	CD34+	Posterior wall of stomach
Kadam *et al.*	+	s-100+	Retroperitoneal mass adherent to small intestine
Chen *et al.*	+	s-100+ vimentin+ Actin- Desmin-	Ileum
Karaca *et al.*	+	Pancytokeratin-	Distal ileum
Goyal *et al.*	+	Vimentin + SMA+ s-100- Cytokeratin- Desmin- Calretinin- Inhibin-	Distal to duodenojejunal junction
Carlmagno *et al.*	Weakly+	Actin++ CD34+ s-100-	Greater curvature of stomach
Kermiglow *et al.*	+	SMA++ Desmin- s-100-	Caecum

CONCLUSION

GIST may mimic gynaecological tumors, mostly ovarian malignancies and uterine leiomyoma. GISTs do not have a unique appearance on ultrasound examination for definitive diagnosis. If a pelvic mass is detected on ultrasonography, especially if related to unusual clinical signs, the possibility of a non-gynaecological tumor has to be considered and efforts made to identify the origin. Searching for 'sliding organ sign' may be useful to sort out the clinical situation, distinguishing a possible mass adherent to the uterus or separate from it. Misdiagnosis may have significant therapeutic and prognostic implications because of the targeted imatinib –based therapy now available.

Hence, gastrointestinal stromal tumors should be considered in the differential diagnosis of patients presenting with an abdominal or pelvic mass or pelvic pain in gynaecology department.

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