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CASE REPORT

Extra Gastrointestinal Stromal Tumors In Ovary, Rare Case

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Abstract

Objective: This article objective is to describe a woman with extra gastrointestinal stromal tumor (extra GIST) in ovary;

Method: A case report and literature review; The author reports a woman 54 years old with complaints of swelling in the abdomen. Tumors suspected originate from ovary with an extension to abdominal wall. The patient had history of previous ovarian tumor surgery with pathological anatomy diagnosis was thecoma. Working diagnosis of the patient was residif ovarian malignancy and then suboptimal debulking was performed. Microscopically, ovarian tumors appear cellular and diffuse, partially arranged fascicles. Cells with rounded-spindle nuclei, mitosis ≥ 4 per 10 HPF. The conclusion was malignant thecoma which metastasizes to peritoneum and omentum. Differential diagnosis were GIST and leiomyosarcoma. Immunohistochemistry examination was performed with Calretinin and CD117 to rule out the differential diagnosis. Calretinin were negative and CD117 were strongly positively smeared. Based on the morphology and positive CD117 results, diagnosis was extra GIST of ovary.;

Conclusion: Extra GIST in the ovary is an unusual location so that it can be misdiagnosed as a gynecological disorder. The differential diagnosis at this location is quite limited including thecoma, fibrothecoma and leiomyosarcoma.

Keywords: extra gastrointestinal stromal tumor, ovary, thecoma

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is a mesenchymal neoplasm with variable behaviour characterized by differentiation towards the Interstitial Cell of Cajal (ICC). Interstitial Cell of Cajal is a pacemaker cell that controls the peristals of the gastrointestinal tract. Gastrointestinal stromal tumors express C-KIT / CD117 protein or have C-KIT or platelet derived growth factor receptor α (PDGFRA) mutations and show spindle cells or epithelioid cells morphology. 2

Gastrointestinal stromal tumors are the most mesenchymal neoplasms found in the gastrointestinal tract. Gastrointestinal stromal tumors comprise 5% -10% of all gastrointestinal sarcomas and represent about 1% of all gastrointestinal malignancies. The incidence is 11-14 people in 1 million population per year. Approximately 4500 to 6000 GISTs are diagnosed annually in the United States. Population-based study in Scandinavia indicate

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an incidence of 1.1-1.5 cases per 100,000 person-years. Micro GIST, which is clinically silent lesions and less than 1cm in size, is potentially available in more than 35% of the general population. The median age at diagnosis is 60-65 years. There is usually no predilection for either gender but some series suggest a slight male predominance.^{1,3,4}

Gastrointestinal stromal tumors can occur anywhere in gastrointestinal tract. The most common location is stomach and small intestine approximately 54% and 30%, respectively. About 10% of cases are primarily disseminated and the site of origin cannot be determined with certainty. Gastrointestinal stromal tumors can occur as primary tumor outside the gastrointestinal tract referred to as extra gastrointestinal stromal tumors (extra GIST). Extra GIST is a rare case that is less than 5% of all GIST. The most dominant locations of the extra GIST are omentum and mesentery (80%), the rest developing in the retroperitoneal. Extra GIST in the ovary is an unusual location so that it can be misdiagnosed as a gynecological disorder. The differential diagnosis at this location is quite limited including leiomyosarcoma and fibrothecoma.

Extra GIST usually appears in adulthood as an intraabdominal mass. The presenting manifestations depend on the site of involvement and the size of the tumor. A significant number of tumors are asymptomatic and are found incidentally on laparatomy (33%). Extra GIST lesions tend to be large (more than 10 cm) compared to GIST. Although the histological and immunophenotype characteristics of extra GIST are not different from GIST, but the degree of malignancy is higher.⁵

The most important GIST prognostic parameters are anatomical site, tumour size and mitotic index. Anatomical site consists of the gastric and small bowel (duodenum, jejunum / ileum). Extra GIST is classified according to small bowel criteria. Small bowel GIST have a higher rate of abdominal dissemination and metastasis compared gastric GIST. Metastases generally develop within 2 years after diagnosis or 10 years after surgical resection, so long-term follow-up is required.

CASE REPORT

We reported a female patient, 54 years old, with complaints of stomach enlargement since 6 months ago. Swelling initially approximately 6 cm and enlarge quickly. Complaints bleeding from the genital, drastic weight loss, and complaints of urination and bowel movements were absent. The patient underwent ovarian tumor surgery in 2016, with anatomic pathology diagnosis was thecoma (figure 1). Patient had never been control in this 3-years.

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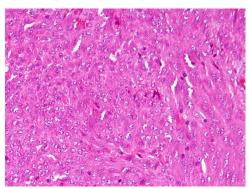


Figure 1. The coma microscopic, cellular appearance with ovoid-spindle, vesicular nuclei, abundant eosinophilic cytoplasm (x400 magnification).

Abdominal examination revealed a mass, tenderness consistency and pain was absent. Ultrasound examination showed hypoechoic mass and ascites, suspected as a residual ovarian tumor. CT scan showed suggestive impression of an ovarian tumor extruded into the abdominal wall and outside the abdominal wall with bilateral hydronephrosis (figure 2.A). Chest X-ray showed no pulmonary metastase.

Working diagnosis was a residual ovarian carcinoma and sub-optimal debulking surgery was performed. Ovarian tumor, uterine, peritoneum and omentum was removed then examined to anatomic pathology laboratory. Macroscopically, ovarian tumor was solid mass with cyst component, size 12cm x 12 cm x 7 cm (figure 2.B). The cut surface showed tan color, fragile area, and section cyst wall with papillary growths.

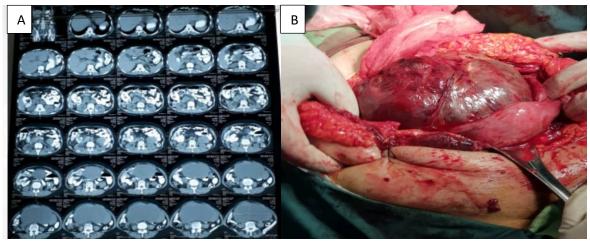


Figure 2. A. CT scan of the abdomen suggestive of an ovarian tumor, extruded into the abdominal wall B. Macroscopic ovarian tumor measuring 12cm x 12 cm x 7 cm, tan color.

Microscopically, ovarian tumors appeared cellular and diffuse, partially arranged to fasciculus pattern. Cells with rounded-spindle nuclei, prominent nucleoli, eosinophilic cytoplasm, mitosis \geq 4 per 10 HPF. There also appeared necrotic area (figure 3). Tumor cells

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were found in the peritoneum and omentum, whereas there was no tumor cell in uterus. Histopathological morphology above showed a malignant tumor that may originate from the ovarian stromal and can be diagnosed differentially with other mesenchymal tumors. The conclusion of this case was a malignant thecoma that metastasized to peritoneum and omentum. The differential diagnosis was GIST and leiomyosarcoma.

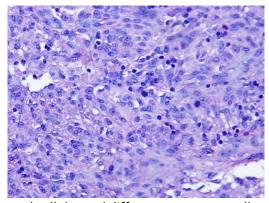


Figure 3. Microscopic showed cellular and diffuse appearance, cells with round-spindle nuclei, prominent nucleoli, mitosis easily found (magnification x400)

The differential diagnosis can be ruled out by immunohistochemical examination. Patients were immunohistochemical examination of Calretinin and CD117. Calretinin examination results showed that the nucleus and cytoplasm of the tumor cells were negative. Immunohistochemical profile was not suitable for malignant thecoma. Furthermore, the CD117 examination results showed that the tumor cells were strongly positive on the entire membrane of the tumor cells (figure 4). Based on the morphology and the positive CD117 results, a diagnosis of extragastrointestinal stromal ovarian tumor was made.

Patients were initially given chemotherapy with bleomycin, etopuside, carboplatin regimens. After the results of the immunohistochemical examination, the patient was planned to administer adjuvant imatinib. However, patient condition worsen and died before receiving adjuvant imatinib therapy.

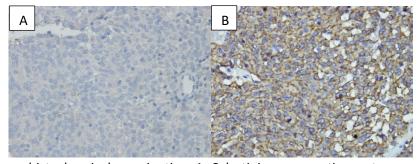


Figure 4. Immunohistochemical examination, A. Calretinin was negative on tumor cells, B. CD117 was positive on cell membranes (x400 magnification).

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DISCUSSION

Gastrointestinal stromal tumors are mesenchymal neoplasms with variable behaviour that characterized by differentiation towards the Interstitial Cell of Cajal (ICC). Interstitial Cell of Cajal are present throughout the walls of the gastrointestinal tract, the largest density occurs around the circumference of the myenteric plexus with extension between the inner and outer layers of the muscularis propria. They function to coordinate peristalsis by generating and propagating electrical slow waves of depolarization.¹

The earlier literature classified this tumor as smooth muscle or nerve sheath tumors. The term GIST was first used in 1983 by Mazur and Clark to encompass gastrointestinal non-epithelial neoplasms that lacked the immunohistochemical features of schwann cells and did not have the ultrastructural characteristics of smooth muscle cells.² Then in 1998, Hirota et.al reported that gain-of-function mutations in the KIT (c-kit) proto-oncogene are present in most GISTs.⁷

Gastrointestinal stromal tumors found along the entire length of the gastrointestinal tract, most common in the gastric (60%), jejunum and ileum (30%), duodenum (5%) and colon and rectum (less than 5%). A small number of GIST can occur outside the gastrointestinal tract, this GIST is called extra gastrointestinal stromal tumors (Extra GIST). Extra GIST accounts 5% -7% of all GIST cases, the most common locations are omentum, mesentery and retroperitoneum. ^{4,5} Other locations that have been reported are in the pelvic cavity, uterus, bladder, rectovaginal septum and ovary. ^{6,8} Extra GIST predominantly extramural and expanded to subserosa, attached to the serosa of the tubal gut. This expansion only a thin stalk of tissue so lost their connection to it into the abdominalpelvic cavity and possibly contributes to extra GIST. ^{5,9}

About 80% of GISTs mutate from proto-oncogenic KIT and 10% due to platelet-derived growth factor receptor- α (PDGFRA) mutations located on chromosome 4 (4Q12). Activation of KIT tyrosine kinase activity affects intercellular signal transduction. Membrane receptor tyrosine kinase cellular signaling pathways regulate key cell functions, including proliferation, differentiation and anti-apoptotic signaling. Auto-phosphorylation of c-KIT causes ligand-independent tyrosine kinase activity, leading to an uncontrolled cell proliferation due stimulation of downstream signaling pathways. Activating mutations of KIT most often in exon 11 or exon 9 and GIST harbour PDGFRA activating mutations usually in exon 18. Patients with PDGFRA-mutants tumors have a lower risk of metastasis than patients with KIT-mutant tumors.

This case occurred in a 54 years old woman. This is in accordance with the literature that sporadic GIST can occur at any age with a peak incidence in the sixth decade (median age 60-65 years). Gastrointestinal stromal tumors rarely occur in young adults and children.⁴ Gaballa et.al reported extra GIST located in the ovary in a 49-years-old woman with a painful

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mass in the right iliac fossa. CT-Scan examination showed right ovarian mass mainly cystic with solid component measuring 10x12x14 cm.⁸ In this case the patient complains of swelling in the abdomen without pain. The CT scan was concluded as suggestive of an ovarian tumor extruded into the abdominal wall. Extra GIST is oftem greater than 10 cm, because of the peritoneal cavity give enough space to grow. It is often asymptomatic until advanced stage.⁶

The most common presentations include abdominal mass, acute and chronic bleeding with anemia, abdominal pain, nausea, vomiting and weight loss. Based on location, Gastric GISTs show higher local recurrence rare than intestinal GISTs have more frequent abdominal dissemination and metastatis. Metastases usually develop within 2 years of diagnosis or 10 years after surgical resection, so long-term follow-up is needed. The expected pattern of metastatic spread are to the liver, peritoneal cavity and retroperitoneal space. Rare cases of metastatic disease in bone, skin and soft tissue. Very rarely metastases are the lungs and brain. Metastases in lymph nodes are very rare at less than 1%.

In this case a mass was found in the ovary that has expanded into the omentum and peritoneum. The Gaballa et.a report the same thing, when the exploratory action appeared a large ovarian mass spread to omentum and peritoneum suggesting right ovarian malignancy or pseudomyxoma peritonii.⁸ This is consistent with the literature that extra GISTs spread along the peritoneal cavity as metastatic nodules. GISTs have a characteristic pattern of metastasis that they do not metastasize to the lymph nodes, except syndromic GIST more often metastases to the lymph nodes.⁵

Extra GIST can be located in the ovary, an unusual location that is often considered a gynecological disorder. Histopathologically the differential diagnosis of extra GIST in the ovary are relatively limited including leiomyosarcoma, fibrothecoma and thecoma.⁶ Fibrothecoma is rare, often found in elderly age and post menopause. Thecomas are uncommon accounting for no more than 1% of ovarian tumours. Thecoma typically occur in postmenopausal women (mean 59 years), no more than 10% arise in women younger than 30 years.¹⁰ In this case the patient was 54 years old and had been menopausal since 5 years ago, so it can be thought of as a thecoma and fibrothecoma that has experienced malignancy.

The histomorphology GISTs varies greatly and includes pure spindle cell, pure epithelioid cell, and mixed spindle and epithelioid cell types. Spindle cell GISTs are composed of uniform, elongated cells that are consistent in size and shape. The cells have nuclei with evenly dispersed chromatin, inconspicuous nucleoli, and moderate amounts of pale to eosinophilic fibrillary cytoplasm. The architecture are that of intersecting short fascicles, sheets, whorl, storiform or palisading patterns. The vasculature can range from inconspicuous to hemangiopericytoma-like, whereas the stromal component may be inconspicuous or may exhibit prominent myxoid change, hyalinization, or dystrophic calcification.¹

Epithelioid GISTs are composed predominantly of cells with either abundant

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eosinophilic or clear cytoplasm, typically arranged in nests and sheets. The nuclei are round with vesicular chromatin and variable nucleoli. Occasionally scattered multinucleated giant cells, binucleated cells, or cells with bizarre nuclei. Epithelioid GIST can show sclerosing, discohesive, hypersellular or sarcomatous morphology with substantial atypia and mitotic activity. The stromal alterations may include hyalinization or myxoid change. 4

Anatomical location of the gastric and small bowel influences the histological appearance. Gastric GIST is dominantly composed of spindle cells. Epithelioid morphology seen in appoximately 20-25% of cases. Some cases feature a combination of spindle cells and epithelioid hystology. Nuclear pleomorphism is uncommon. Small bowel and colonic GIST are usually spindle cell tumors with diffuse sheets or stroriform pattern. Extra GIST histological features refer to the small bowel GIST.⁴

Thecomas are stromal tumours containing a significant number of cells with appreciable cytoplasm resembling to varying degrees theca cells. Thecomas are composed of sheets of uniform cells with oval to round nuclei and pale greyish-pink cytoplasm with ill-defined borders. The cytoplasm is only rarely conspicuously lipid rich. The tumours usually exhibit little or no nuclear atypia and mitoses are infrequent. Some thecomas have zones that resemble fibroma. These tumours can be classified as fibrothecomas. Suspicion of malignant thecoma can be thought of in large tumors, hypersellular cells tumor, moderate to marked nuclear atypia, mitosis per4 per 10 HPF. 12

Based on the description above, GIST and malignant thecoma have cytological similarities. Clinically patient had a history of thecoma, radiological examination suggested tumor located in the ovary and microscopically showed malignant cells with mesenchymal differentiation. The main diagnosis was malignant mesenchymal ovarian tumor, malignant thecoma and a differential diagnosis was GIST. Another possibility differential diagnosis was leiomyosarcoma because tumor cells arranged with fascicles pattern, had pleomorphic nuclei and atypical mitosis.

The key diagnosis of GIST is an immunohistochemical examination that is positive with KIT (CD117). Immunophenotypes of 95% GIST show strong and diffuse expression of KIT (CD117), which appears as cytoplasmic, membrane-associated or sometimes perinuclear dot-like staining. However, about 5% of cases, especially GIST with PDGFRA mutations, may lack KIT expression or show very limited staining. The KIT-negative tumors are often located within the stomach and have epithelioid morphology.^{1,4}

Gene expression profiling studies of GISTs have identified additional immunostains that appear diagnostically useful. Discovered on GIST 1 (DOG1), also known as anoctamin 1 (ANO1) appears to be immunoreactive with GISTs and has a sensitivity similar to that of KIT (approximately 95%). The corresponding ANO1/DOG1 antibody appears to be immunoreactive with GISTs regardless of their KIT/PDGFRA mutational status and may recue

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diagnostically as many as 50% of KIT-negative GISTs. KIT and DOG1 are both expressed in the ICC. Other antibodidy is CD34 expressed in roughly 70%, especially spindle cells GIST located in the stomach. Some GISTs express h-caldesmon, a minority express SMA, and rare examples show positivity for desmin, keratin (CK18) or S100 protein.^{1,4}

Malignant thecoma immunoreactive with sex-cord differentiation markers. The best markers are inhibin, calretinin, CD99, steroidogenic factors (SF-1), and WT1. Inhibin and calretinin are traditional immunohistochemical markers of sex-cord stromal ovarian tumors. Inhibin is an ovarian glycoprotein hormone consisting of α and β subunits measured in the form of inhibin-A and inhibin-B in serum. Calretinin is a calcium-binding protein found in nerve tissue, mesothelial cells and ovaries. Afterwards, leiomyosarcoma immunoreactive strong and diffuse with desmin and smooth muscle actin (SMA) and negative with KIT.

This patient examined with calretinin and CD117 antibodies. Calretinin examination results were negative both nucleus and cytoplasm of tumor cells. Therefore, the diagnosis of malignant thecoma was not appropriate because malignant thecoma was at least 33% positive. CD117 examination showed strong positive results on all tumor cell membranes, so the immunohistochemical profile of this case was suitable for GIST. The differential diagnosis of leiomyosarcoma can be ruled out, because leiomyosarcoma was negative with CD117.¹

The behavior of GIST varies from very low to high risk. GIST risk factors are determined by anatomic location, size and numb mitosis activity. Anatomic location consists of gastric and small bowel. Extra GIST is classified according to small bowel criteria. The mitotic rate is divided into ≤ 5 per mm² / 50 HPF and > 5 mitosis per 5 mm² / 50 HPF. The size is divided into less than 2 cm, 2 cm to 5 cm and more than 5 cm to 10 cm and more than 10 cm. Tumor rupture is also an important risk factor as a poor prognosis. Multilevel risks apply to uninodular lesions and primary GIST that have not been treated. Cases that have metastasized, not classified as formal gradual risk because it is classified as high risk. In this case there had been spread to the peritoneum and omentum so patient was classified as high risk GIST.

These multilevel risk criteria are useful for determining who will get adjuvant imatinib therapy after resection.⁵ Adjuvant imatinib therapy is given in tumor rupture. Tumor rupture is associated with an increased risk of implantation into the peritoneum.⁷ In addition, imatinib therapy is standard therapy for recurrent disease and metastasis. In this case the patient was initially given chemotherapy with bleomycin, etopuside and carboplatin regimens. After the results of the immunohistochemical examination, the patient was planned to administer imatinib therapy, but the patient's condition deteriorated and died before receiving adjuvant imatinib therapy.

Extra GISTs have a worse prognosis than gastric GIST and malignant thecoma.^{7,14} According to SEER data the 5-year survival rate of extra GIST ranges from 50% -65% after

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complete resection of localized primary tumors. However, 40-90% of patients experience recurrence or postoperative metastases. The average survival time for GIST patients with local recurrence or metastasis without obtaining imatinib is 10-20 months.⁷

CONCLUSION

Extra GIST in the ovary is an unusual location so that it can be misdiagnosed as a gynecological disorder. The differential diagnosis at this location are quite limited including mesenchymal abnormalities in the ovary such as leiomyosarcoma, thecoma and fibrothecoma. Immunohistochemical examination CD117 can confirm the diagnosis of GIST. The right diagnosis will provide appropriate therapy.

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