International Journal on Oncology and Radiotherapy

Metastatic Gastrointestinal Stromal Tumor to the Omentum and Endometrium: A Case Report

Case Report

Volume 3 Issue 2- 2022

Author Details

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Article History

Received: August 01, 2022 Accepted: August 12, 2022 Published: August 15, 2022

Abstract

Gastrointestinal Stromal Tumor (GIST) is an uncommon stromal malignancy of Gastrointestinal (GI) tract. GISTs have been increasingly reported in sites other than GI tract. Currently, GISTs are considered metastatic when they occur outside GI tract; however, there is a possibility of a primary stromal tumor of omentum and/or gynecologic tract with similar mutation profile and histopathology but different prognosis and clinical behavior. Here, we report a case of 52-year-old female with widespread lesions in her abdomen and pelvis, which turned out to be a GIST; however, no lesions were identified in the GI tract which raises the possibility of omental or ovarian primary stromal tumor. Since GISTs are mutation derived tumors, it is highly likely that the stroma of other locations can undergo similar tumorigenesis due to mutations in c-KIT and/or PDGFRA genes and present similarly to primary GI tract GISTs. More studies are required to look for other possible primary sites and difference in clinical behavior and prognosis to appropriately stage the patient before treatment, as GISTs that occur outside GI tract tends to behave aggressively and are usually resistant to imatinib therapy.

Keywords: Gastrointestinal stromal tumor; Omentum; Endometrium; Metastasis; Epithelioid; Carcinomatosis

Abbreviations: GIST: Gastrointestinal Stromal Tumor; DOG1: Discovered on GIST-1; PLAP: Placental Like Alkaline Phosphatase; ER: Estrogen Receptor; PR: Progesterone Receptor; Melan-A: MART-1/Melanoma Antigen Recognized by T-cells; PDGFRA: Platelet Derived Growth Factor Receptor A; c-KIT: Receptor Tyrosine Kinase Protein known as Tyrosine-Protein Kinase KIT; CEA: Carcinoembryonic Antigen; CA 19-9: Cancer Antigen 19-9; CA 125: Cancer Antigen 125; STAT-6: Signal Transducer and Activator of Transcription 6; CD: Cluster of Differentiation

Introduction

Gastrointestinal stromal tumors are rare stromal neoplasms but represent the gastrointestinal tract's most common neoplasm of mesenchymal origin. GIST occurs most often, in decreasing frequency, in the stomach, small intestine, colon and esophagus [1]. In addition, these tumors are believed to represent metastatic disease when present outside the tubular gastrointestinal tract, such as retroperitoneum, peritoneal/omental or mesenteric surfaces, and liver. Here, we present a case of a widely metastatic gastrointestinal stromal tumor with unknown primary and will discuss some challenging characteristics and associated pitfalls.

Case Presentation

A 52-year-old post-menopausal female, known case of hypertension, hypothyroidism, generalized anxiety disorder and Gastroesophageal Reflux Disease (GERD), presented with increasing constipation, abdominal distention, nausea, vomiting and light-colored stools for two months (since August 2020). Her tumor markers (October 2020) were elevated including increased CA-125 of 721.0 U/mL (normal range:1.0-35.0) and CA 19-9 of 49.3 U/mL (normal range: less than 1.2-35.0), Her CEA level was normal (1.60 ng/mL; normal range: 0-5.0 ng/mL). This prompted a Computed Tomography (CT) scan of her abdomen and pelvis (October 2020), which showed diffuse heterogeneous attenuation of liver, diffuse fatty infiltration of pancreas and scattered large necrotic abdominal masses; largest was in left abdomen (13.6 x 11.3 cm), suggestive of omental metastasis. Her CT chest was clear and there was no evidence of metastatic disease within the thorax. Magnetic Resonance Imaging (MRI) of pelvis (October 2020) showed extensive heterogeneous partially cystic/necrotic omental and peritoneal implants consistent with peritoneal carcinomatosis. The site of origin was uncertain. Bilateral ovaries demonstrate cystic components and heterogenous enhancing soft tissue. There were multiple perihepatic, subcapsular and intraparenchymal T2 hyperintense liver lesions,

consistent with metastatic implants. Her endoscopy and colonoscopy were unremarkable. The patient underwent diagnostic laparoscopy with omental as well as endometrial biopsies on 10/19/2020. Grossly there were multiple tan small nodules (2.8 cm in aggregate). Hematoxylin and eosin staining showed an organoid pattern of atypical proliferative epithelioid spindle cells. There was no high-grade cytologic atypia and tumor necrosis and hemorrhage was less than 5%. The mitotic rate was approximately 18/50 high-power field (HPF) (Figure 1).

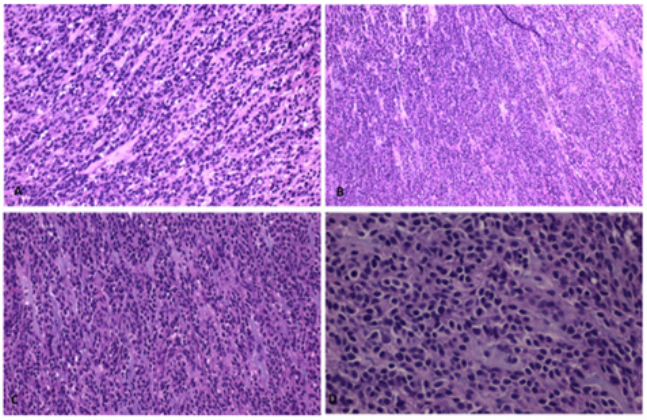

Figure 1: Hematoxylin and eosin staining shows an epithelioid proliferation of cells in an organoid pattern (A: 10x, B-C: 20x, D: 40x). No high-grade atypia was identified; hemorrhage and necrosis were minimal.

Immunohistochemical stains show diffuse and strong positive staining for DOG-1 (Figure 2A) and CD117/c-kit (Figure 2B). Several tumor cells were labeling for p53, consistent with wild-type pattern (Figure 2D). The tumor cells were negative for PLAP, Melan-A, Beta-Catenin, Chromogranin, CK7, WT-1, progesterone receptor (PR), CK20, Synaptophysin, Inhibin, TTF-1, Sox-10, CDX-2, Actin, Pan-keratin, Desmin, Calretinin, Estrogen Receptor (ER), CD10 (Figure 2C), Neuron-Specific Enolase (NSE) and PAX-8.

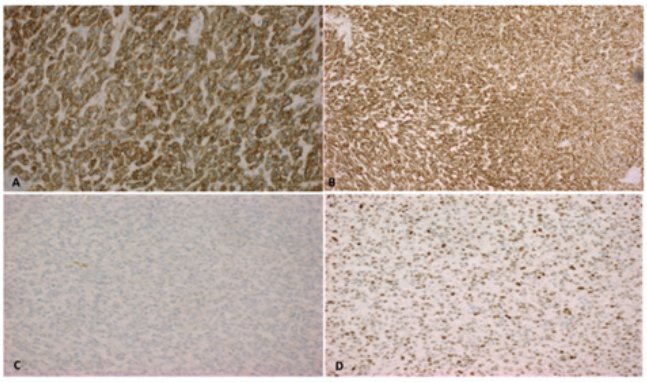

Figure 2: Immunohistochemical staining shows tumor cells to be strongly positive for DOG-1 (A) and CD117 (B), thus confirming gastrointestinal stromal tumor (GIST). CD10 is negative (C) ruling out low-grade endometrial stromal sarcoma. p53 is patchy positive (D, wildtype).

A Next Generation Sequencing (NGS) based analysis was performed and identified a mutation in exon 11 of KIT (c.1669T>A, p.W557R). No mutations were seen in KIT exons 9, and 13-17 and PDGFRA exons 8, 10, 12, 14 and 18. The overall findings supported the diagnosis of a Gastrointestinal Stromal Tumor (GIST), epithelioid type. The patient had widespread metastases in her abdomen and pelvis and was therefore a poor candidate for surgical resection. She was started (December 2020) on imatinib 400mg daily (a tyrosine kinase inhibitor, usual first choice for treatment of GIST) to which she initially responded; however, her disease progressed and she was switched (in June 2022) to sunitinib (a multi-targeted receptor tyrosine kinase inhibitor) and is currently under treatment.

Discussion

Microscopically, GIST is distinguished by short fascicles of monomorphic spindled cells; however, epithelioid morphology may be present as in our case. Most GISTs have a bland cytomorphologic appearance, with indistinct borders forming a syncytial appearance. Occasionally, clear perinuclear punched-out cytoplasmic vacuoles can be appreciated and are a hallmark of GIST [2].

The tumors presenting as omental masses are divided into two main subgroups: solitary (often shows cytomorphology like gastric tumors, median mitotic count of 2/50 HPFs, median tumor size of 14 cm and a better prognosis) and multiple (resembles GIST arising in the intestine, median mitotic count of 14/50 HPFs and the tumor median size was 16 cm and worse prognosis [3]. Often, a primary tumor is never definitively identified; an omental mass is discovered in approximately 20% of cases with no identifiable primary site and no evidence of disease in the gastrointestinal tract [3].

Most GISTs are positive for c-kit, cytoplasmic, or dot-like positivity adjacent to the nucleus. However, a small percentage of GISTs are c-kit negative, and these tumors are more often epithelioid [4]. DOG-1 (also known as discovered in GIST-1) was shown a sensitivity and specificity superior to 95% for GIST and appears to be uniformly expressed in spindle cell, epithelioid types, in a large subset of c-kit negative GISTs and does not correlate with the mutational status of kit or platelet-derived growth factor receptor-α (PDGFR-α) [4].

The majority of GISTs have activating mutations of KIT or PDGFR-α; the mutational status of these oncoproteins predicts a rapid and complete metabolic response to imatinib [5]. Conversely, PDGFR-α mutations can explain response and sensitivity to imatinib in some GISTs lacking KIT mutations [6]. The best prognostic features are tumor size and mitotic activity; however, it does not predict the risk for disease progression and malignant potential accurately because of the scarcity of primary omental GIST [7-10]. There are a few reported cases of GISTs that involved gynecologic tract and presented as pelvic or omental masses, therefore mimicking primary omental or ovarian neoplasm [8,9,11-14].

The principal differential diagnosis of GIST outside the tubular gastrointestinal tract includes desmoid fibromatosis, Solitary Fibrous Tumor (SFT), schwannoma, and leiomyosarcoma. The spindle cell fascicles of desmoid tumors are longer and more flattened than those in GIST. In schwannomas, thick-walled, hyalinized blood vessels usually accompanied the strongly and diffusely positive for S-100 protein cells. Leiomyosarcomas are composed of long fascicles of spindle cells positive for desmin and SMA and with more cytologic pleomorphism [15]. None of these tumors in the differential diagnosis will express c-kit. Other markers are less reliably positive in GISTs, including CD34, SMA, and caldesmon. Solitary Fibrous Tumor (SFT), especially those with unusual morphology can be another differential [16]; however, SFT will demonstrate features like patternless pattern, staghorn vessels, and intervening "ropey collagen", and is usually positive for STAT6 due to a specific NAB2-STAT6 fusion [16].

Other pitfalls to consider in this case with metastasis to the endometrium are low-grade and high-grade Endometrial Stromal Sarcomas (ESS). The low-grade ESS is typically positive for CD-10, Estrogen Receptor (ER) and Progesterone Receptor (PR) and will show variable positivity for cyclin D1, whereas CD117 (c-kit) is negative in most cases. Low grade ESS has a characteristic JAZF1-SUZ12 t(7;17)(p15;q21) fusion in most cases [16]. In contrast, high-grade ESS is typically negative for CD-10, ER, and PR and shows strong and diffuse positivity for cyclin D1; and has YWHAE-NUTM2A/B fusion or BCOR rearrangements/internal tandem duplications [17,18]. Other

useful immunohistochemical stains, in this case, were chromogranin and synaptophysin, to rule out neuroendocrine tumors, along with inhibin and calretinin to rule out sex cord stromal tumors.

Wherever possible, complete removal of tumor and/or imatinib therapy are the primary alternatives for the patient, although the response is slightly worse than with GIST of the tubular gastrointestinal tract [11-12, 14]. New therapies and/or clinical trials are under assessment; more studies are required to further elaborate these cases which primarily occur in the omentum and/or gynecologic tract to better understand the pathophysiology and prognosis of these "metastatic cases with unknown primaries".

Conclusion

There might be a possibility of a separate stromal tumor with similar genetic/mutation profile, with primary site to be omentum and/or gynecologic tract; however, no definite studies have been done to differentiate those tumors from primary gastrointestinal stromal tumors. We might be able to come up with a separate entity of stromal tumors primarily arising in the omentum and/or endometrium and be able to differentiate them from conventional GIST in order to properly stage those patients and treat them accordingly.

Declarations

None.

Consent

Not applicable (no identifying information is present in the case report).

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable (no identifying information is present in the case report).

Availability of Data and Materials

Not applicable.

Competing Interests

None.

Funding

None.

Authors' Contributions

All authors contributed to preparation of this manuscript with most writing done by first and second authors.

Acknowledgements

None.

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