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Case Report

Spindled signet ring cell-like gastrointestinal stromal tumor

Amanda B. Moyer[1], Jae Y. Ro[1], Luan D. Truong[1], Diana Liang[2], Wade Rosenberg[2], Mojgan Amrikachi[1]

[1]Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, Texas, Weill Medical College of Cornell University, New York, New York, [2]Department of Surgery, Houston Methodist Hospital, Houston, Texas, Weill Medical College of Cornell University, New York, New York

Address for correspondence:
Mojgan Amrikachi, Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Medical College of Cornell University, 6565 Fannin St. Suite M227, Houston 77030, Texas.
Tel.: 713-441-6477,
Fax: 713-793-1603.
E-mail: mamrikachi@houstonmethodist.org

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ABSTRACT

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the GI tract. It is usually well-demarcated and comprised of sheets or fascicles of uniform spindled or epithelioid cells. Although focal cytoplasmic vacuolization has been described in epithelioid GISTs, generally, it is a minor component of the tumor. GIST is usually positive for c-kit, CD34, and DOG1, negative for desmin, and variably stains for smooth muscle actin (SMA), S-100 protein, and cytokeratin. Completely resected GISTs usually have a good prognosis. We report a rare case of a GIST composed exclusively of spindled signet ring cells (SRC), an entity previously reported only once in the stomach. The 74-year-old female patient presented with an incidental 6.8 cm gastric mass. The submucosal lesion, completely excised with a rim of gastric mucosal tissue, was round, tan-white, hemorrhagic, and focally cystic. Histologically, the tumor consisted of spindle cells with prominent SRC morphology, mitotic count <2 mitoses/50 high-power fields, and no pleomorphism or necrosis. The tumor was positive for c-kit and CD34, and negative for cytokeratin, S-100 protein, and SMA. The immunohistochemistry helped distinguish the GIST from other SRC neoplasms that can be found in the same location, such as adenocarcinomas, metastatic melanomas, and schwannomas. Extensive signet ring changes can occur in GIST but are rare. Signet ring changes can lead to misdiagnosis of GIST as a more aggressive tumor, particularly in biopsies with limited tissue sampling. Therefore, it is important to be aware of and recognize the SRC morphology in GIST.

KEY WORDS: Gastrointestinal stromal tumor, signet ring cell, electron microscopy

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common GI mesenchymal tumor. In general, GIST is a well-demarcated lesion comprised of sheets or fascicles of uniform spindled or epithelioid cells [1]. Its location within the muscular wall of the GI tract, particularly in the stomach, is also observed in other tumors such as gastric adenocarcinomas and gastric schwannomas [2-4]. Most GISTs are categorized as low risk, indolent lesions with rare metastatic potential. Immunohistochemical testing is positive for c-kit, CD34, and DOG1, and staining results are variable for smooth muscle actin (SMA), S-100 protein, and cytokeratin [1]. The gold standard of treatment is surgical resection.

Recently, we encountered a rare case of a GIST of the stomach with a prominent signet ring cell (SRC) appearance. Recognition of the variant is important because of the potential to misinterpret it for a SRC variant of gastric adenocarcinoma or gastric schwannoma.

CASE REPORT

A 74-year-old woman presented with an asymptomatic abdominal mass found on computed tomography scan. On physical examination, abdomen was soft without tenderness or distention. There were no laboratory abnormalities. Endoscopic evaluation revealed a well-circumscribed mass in the fundus, 3 cm from the gastroesophageal junction. Laparotomy was performed in the standard fashion for a working clinical diagnosis of gastric cancer versus GIST. Abdominal exploration revealed a large pedunculated mass a few centimeters away from the lesser curvature of the stomach, pushing on the body of the

pancreas. The stomach was transected adjacent to the mass to resect the tumor.

Gross examination showed a 6.8 cm well-circumscribed mass with a smooth pink-red serosal surface and a small piece of attached gastric tissue [Figure 1a]. The cut surface revealed a round, well circumscribed, tan-white, hemorrhagic, solid and focally cystic lesion [Figure 1b]. Histologically, the tumor showed fascicles of uniform spindled cells with variably sized, prominent cytoplasmic vacuolization and eccentrically located nuclei, creating a signet ring appearance [Figure 2]. Less than two mitotic figures were identified in 50 high power fields (HPF). The resection margin was negative for tumor. Immunohistochemical studies, consistent with GIST, showed diffuse positivity for c-kit and CD34, and negative staining for SMA, cytokeratin (not pictured), and S-100 protein [Figure 3]. Electron microscopy shows large, unilocular, unlined intracytoplasmic vacuoles and smaller microvesicles with a single layer lining [Figure 4]. Some of the nuclei show nuclear molding around the cytoplasmic vacuoles.

DISCUSSION

GISTs are tumors arising in the muscular wall of the GI tract. There are two main types: spindle cell and epithelioid. The spindle cell variant is more common, and is characterized by spindled cells in sheets or fascicles. The epithelioid GIST is composed of uniform rounded cells in sheets, nests or clusters with eosinophilic to clear cytoplasm. Prominent cytoplasmic vacuolization resembling SRC has been described in epithelioid stromal tumors [5], though generally as a minor tumor component and only rarely as the predominant morphology [6]. Electron microscopy has been used to evaluate the intracellular vacuoles [5] with the conclusion that these perinuclear inclusions are either true lumina or structures resembling lumina, such as lipid [7]. The cytoplasmic microvesicles in our case were empty, often pushing the nuclei toward the periphery, and were either unlined (larger vacuoles) or lined (smaller microvesicles). The lack of a lining in some empty spaces could be due to artifact from paraffin block preparation.

Here, we report a spindled SRC GIST in which the fascicles of vacuolated spindle cells were not merely a focal feature of interest within an otherwise typical GIST; rather, they composed the entire tumor. Gastric adenocarcinoma, melanoma, and gastric schwannoma were also considered in the differential diagnosis because all these entities have been reported to show SRC morphology [3,6,8]. The similarity between SRC GIST, adenocarcinoma, melanoma, and schwannoma of the stomach raises the concern for misdiagnosis, particularly in biopsy specimens with limited and/or superficial tissue sampling.

SRC adenocarcinomas are usually diffuse and ill-defined but can mimic the radiographic appearance and location of a GIST [4]. Adenocarcinomas have a higher malignant and metastatic

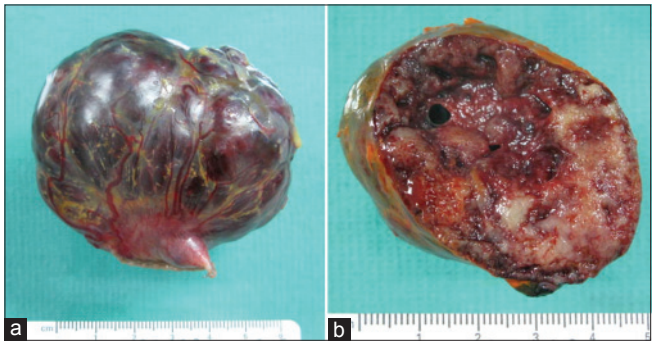

Figure 1: Gross photographs of tumor. (a) A well circumscribed, serosal covered mass with rim of stomach at the base, (b) tan-white, hemorrhagic, solid and focally cystic cross section of the mass

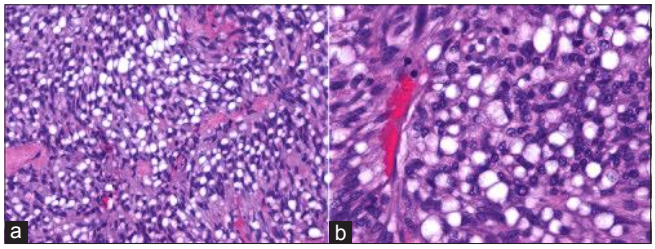

Figure 2: H&E signet ring cell gastrointestinal stromal tumor: (a) Uniform spindled cells with prominent cytoplasmic vacuoles (×10 magnification), (b) signet ring cell morphology (×20 magnification)

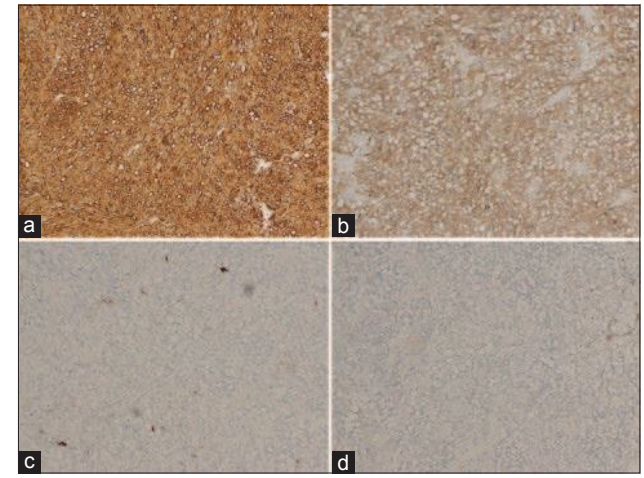

Figure 3: Immunohistochemistry of signet ring cell gastrointestinal stromal tumor (×10 magnifi cation): (a) CD34, (b) c-kit, (c) S-100 protein, (d) smooth muscle actin. Cytokeratin was also negative (photograph not shown)

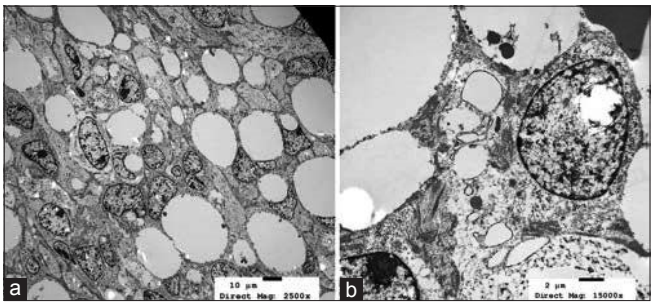

Figure 4: Electron micrographs of spindled cells with ovoid nuclei displaced by empty intracytoplasmic vacuoles and microvesicles: (a) ×2500 magnification, (b) ×15000 magnification

potential than GIST, thus it is important to distinguish between the two [9]. We rely on histologic examination, via biopsy or excision, to differentiate. SRC adenocarcinoma stains diffusely positive for cytokeratin and negative for S-100 protein, c-kit, and SMA. Adenocarcinoma can arise simultaneously with GIST in the stomach [2,10-12] or as GIST-adenocarcinoma collision tumors [12], further complicating diagnosis.

Schwannoma, another rare spindle cell tumor of the GI tract, is also found in the stomach. Similar to a GIST, it presents as a well circumscribed, submucosal nodule. Histologically, the SRC gastric schwannoma is composed of sheets of large epithelioid cells with mucinous cytoplasm and hyperchromatic, peripherally displaced nuclei in a myxoid stroma. It stains diffusely positive for S-100 protein and negative for c-kit, cytokeratin, and SMA [3].

Malignant melanoma with SRC features has rarely been reported. Malignant melanoma is commonly known as the great histologic mimicker of other tumors and can present with diverse morphologic variants, including SRC melanoma [8]. It stains diffusely positive for S-100 protein and HMB45, and is usually negative for c-kit, cytokeratin, and SMA.

Since these tumors can demonstrate foci of SRC morphology, it is important not only to sample extensively but also to look for variability in immunohistochemical staining patterns. Homogeneous positivity/negativity makes it less likely that a tumor is a collision tumor. The tumor we examined showed diffuse, strong, positive, homogeneous staining pattern for c-kit and CD34, and negative for SMA, cytokeratin and S-100 protein [Figure 3], as well as histological features that were consistent with GIST.

Molecular genetics have revealed that most GISTs harbor oncogenic activating mutations: 75% of GISTs have a kit gene mutation, most commonly in exon 11, and 10% have a platelet-derived growth factor receptor-α mutation [1]. The gold standard treatment for GIST is surgical excision. However, targeted therapy with the tyrosine kinase inhibitor imatinib, a drug that inhibits the kit signaling pathway, is recommended in cases of advanced, metastatic or unresectable GIST.

In summary, this is a case report of a rarely-documented entity, a spindled GIST with signet ring cell features. This rare presentation of GIST highlights the difficulty in distinguishing signet ring cell entities in the stomach. It also reflects the importance of recognizing GIST variants to avoid over-diagnosing a malignancy with more aggressive behavior. The unusual appearance of a nonepithelioid SRC GIST should thus be considered in the differential diagnosis of vacuolated spindle cell lesions of the GI tract.

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