Fibrous Gastrointestinal Stromal Tumor

by Cesar V. Reyes, Dean Muldong, Joyce Casis, and Theresa Kristopaitis

Gastrointestinal stromal tumors are a heterogeneous group of neoplasm that by immunohistochemical and ultrastructural studies demonstrate smooth muscle, neural, or both smooth muscle and neural differentiation. In some primitive tumors, analyses fail to identify a line of differentiation. A small bowel stromal tumor exclusively composed of fibrous differentiation and initially recognized in a loop of small bowel incarcerated in an inguinal hernia is described.

INTRODUCTION

The precise lines of differentiation of the gastrointestinal stromal tumors (GISTs) remain enigmatic and controversial. Assessment by histochemical, immunohistochemical, and ultrastructural analyses reveal that the vast majority of these neoplasms are of smooth muscle, neural, or combined smooth muscle and neural differentiation, or that they are primitive and undifferentiated (1–11). The following report describes a rare small bowel stromal tumor phenotype composed exclusively of fibrous tissue and initially recognized within a segment of small bowel serosa herniated into the inguinal canal.

CASE REPORT

A 58-year-old man with a two-year history of enlarging, reducible left inguinal hernia developed left inguinal pain and was unable to self-reduce the hernia a few weeks prior to admission. The patient denied abdominal pain, nausea, vomiting, melena and weight loss. He had no other medical problems. Ultrasound of the left inguinal area showed a mass lesion within the loop of small intestine in the hernial sac, measuring 5 × 4 centimeters (Figure 1). A left inguinal hernia repair was recommended.

The operative finding was an indirect inguinal hernia with a loop of incarcerated small bowel. In addition, an intramural tumor was incidentally noted within the wall of the herniated bowel. Resected was a 10-centimeter segment of the bowel which was primarily anastomosed. The postoperative recovery was uneventful. The patient is tumor-free 5 years to date.

GROSS PATHOLOGY

The middle part of the resected small bowel was deformed by a well circumscribed, firm, unencapsulated, submucosal mass that measured 6 × 5 × 5 centimeters, effaced the muscular coat, and extended into the sub-

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serosa. The cut surfaces of the mass were pink-tan, solid, tan and fibrous (Figure 2). The rest of the intestinal segment was unremarkable.

LIGHT MICROSCOPY

The tumor epicenter appeared to be the muscularis propria. It was composed of bundles and intertwining fascicles of benign spindle cells with significant collagenous stroma. The tumor cells showed minimal or negligible variation, hyperchromatic and vesicular nuclei with pointed ends and occasional prominent nucleoli. Their cytoplasm seemed to blend with the surrounding stromal collagen (Figure 3). Mitosis appeared regular and counted less than two per 10 high power fields. There were scattered foci of hemorrhage in the periphery of the lesion, but no necrosis. Masson trichrome stain and van Gieson stain (Figure 4) highlighted the predominant fibrocollagenous nature of the tumor.

IMMUNOHISTOCHEMISTRY

With a panel of immunohistochemical stains, using a standard modified streptavidin-biotin-peroxidase immunostaining procedure, the neoplastic cells stained positive for vimentin and neuron-specific enolase, and were negative for desmin, smooth muscle actin, glial fibrillary acid protein, neurofilament, S-100, synaptophysin, chromogranin, keratin CAM5.2, and keratin AE1/AE3.

Staining with a monoclonal antibody to the proliferating cell nuclear antigen (PCNA) via a standard modified streptavidin-biotin-peroxidase for PCNA index was determined by counting 500 stromal cells in random fields at 400×. The number of cells with strong unequivocal nuclear staining (n = 340) was divided by
the total number of cells counted (n = 500) to determine the PCNA index which was 68%. With MIB<sub>1</sub>, a monoclonal antibody which recognizes the same antigen as Ki-67 in formalin-fixed and paraffin-embedded tissues and based on a 500 cell count, the Ki<sub>-67</sub> labeling index of the stromal cells was less than 1%.

**ELECTRON MICROSCOPY**

Several representative tumor tissue samples fixed in 5% glutaraldehyde demonstrated exclusively benign-appearing fibroblasts with numerous and striking rough endoplasmic reticulum and thick-banded collagen in abundance, surrounding neoplastic cells (Figure 5). Their nuclei had a large amount of heretochromatin and occasional nucleoli. The cytoplasm also showed occasional golgi apparatus. No evidence of actin, myosin, tonofilaments, basal lamina, or desmosomes was observed.

**DISCUSSION**

GISTs can be broadly defined as the most common mesenchymal neoplasms arising from the wall of a hollow viscera of the alimentary tract (11). Most GISTs are of smooth muscle origin, however, a variety of other cell types such as neurons, Schwann cells, and interstitial cells of Cajal have also been implicated as possible progenitor cells (8,10). Our unique case consisted exclusively of fibrous tissue. GISTs are a clinicopathologically distinctive, but poorly understood, group of mesenchymal tumors, with respect to their origin, cellular differentiation, and prognosis (10).

GISTs predominantly affect adults with a peak incidence during the fifth and sixth decades (10). Symptoms depend on tumor size and site of presentation (7). A significant amount of gastric and small intestinal GISTs are small and asymptomatic. The most common clinical presentation of GISTs is bleeding (86%) and anemia (80%) while the most common...
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A CASE TO REMEMBER

Figure 5. Electron microscopy of exclusively fibrocytic cells exhibiting numerous rough endoplasmic reticulum, occasional golgi and, in between cells, abundant thickband collagen. The nuclei contained large heterochromatin (×4,300).

symptoms are pain (50%–70%) and bleeding (20%–50%) (7). The small bowel GISTs usually present with bleeding, pain, and even obstruction (7). In our case, the obstruction was not caused by the tumor itself but rather an inguinal hernial incarceration of the intestinal loops.

GISTs are commonly found in the stomach (62%) or in the small intestine (10,11). They have been reported in the esophagus and rectum, rarely in the colon. In addition, some cases are found outside the gastrointestinal tract, including the omentum, peritoneum, and retroperitoneum (10).

GISTs are usually submucosal (with or without ulceration of the overlying mucosa), intramural or subserosal. Tumors can range in size from 1-2 centimeter to more than 20 centimeters in diameter. They are almost generally unencapsulated, although a pseudocapsule may be seen. Grossly, the lesions are soft to firm, fleshy, lobulated and well circumscribed with tan to heterogeneous cut surfaces. Areas of hemorrhage, necrosis, or cystic degeneration may also be present (10).

Other studies have also demonstrated that within the GIST groups there appears to be a variability in cellular differentiation at a morphological, immunohistochemical, and ultrastructural level (1–11). The stroma can be myxoid, hyalinized, or collagen. When collagen is present it appears to surround aggregates of cells, accentuating the organoid architecture of the tumor. Within the cellular clusters, the cells are juxtaposed tightly with intervening stroma (9). The histological spectrum of variants with solid sheets, fascicular or storiform arrangement, palisading nuclear pattern reminiscent of nerve sheath tumors, organoid or alveolar arrangement in cell clusters resembling neuroendocrine tumors, and examples with focal to prominent are frequently composed of both spindle and epithelioid cells. The tumor cells frequently have abundant eosinophilic cytoplasm (9). Nuclear features of GISTs are highly variable, ranging from a monotonous, oval and spindly to pleomorphic; and they may contain nucleoli of variable size. Multinucleation may be seen (10). Depending on the location GISTs display different histological profiles (1,7). Among the gastric GISTs, there may be a wide spectrum of histological features but 70%–80% of the tumors are spindle cell while 20%–30% are epithelioid in character (7). Small intestinal GISTs, on the other hand, present as spindle cell tumors that display a whorled extracellular collagen fiber appearance termed skenoid fibers (7) Most esophageal and rectal GISTs demonstrate a spindle cellularity and are clinically and histologically malignant (7).

Ultrastructural analyses have identified cytoplasmic filaments in 100% of GISTs, intercellular junctions 95%, membrane bound dense granules 43%, pinocytotic vesicles with dense bodies along with contracted nuclei 33%, basal lamina 24%, and interdigitating cytoplasmic filopodia harboring intercellular junctions and skenoid fibers 29% (3,4,6,8). In our case we observed only fibrocytic cell differentiation under electron microscopy.

Immunohistochemistry yields a more diverse array of data (10). The most commonly used antibodies to characterize GISTs are those directed against vimentin, desmin, muscle specific actin, smooth muscle actin, S100-protein, neurofilament, neurope specific enolase, PGP9.5, CD34 and CD117 (c-kit).10 The best defining feature of GISTs is CD117 expression (7). Most GISTs, whether benign or malignant, express CD117, a c-kit proto-oncogene protein and a transmembrane receptor for a mast cell growth factor (9). In addition, most GISTs are also positive for CD34, a hematopoietic progenitor cell antigen and a transmembrane protein of unknown function. However, malignant GISTs display a lower frequency of CD34 compared to benign tumors (7).

Despite these markers, GISTs still represent a challenging group of lesions that pose difficult diagnosis, classification and treatment strategies (11). For (continued on page 42)
example, clinical signs and symptoms of GISTs such as nausea, vomiting, abdominal pain, anemia, and melena are nonspecific and consequently not helpful for diagnostic purposes (10). However, the consistent expression of CD117 and CD34 along with positive staining with vimentin has enabled physicians to preoperatively diagnose GISTs via endoscopic ultrasound-guided fine-needle aspiration biopsy (FNAB). Most tumors are discovered at the time of operation in an acute setting for bleeding, obstruction, or perforation (11). This trend is changing due to the use of preoperative endoscopic ultrasound-guided FNAB and immunohistochemical evaluation of GISTs. For the most part, these tumors do not involve the mucosa but rather originate in the deeper wall of the small intestine (3). On the other hand, colonoscopy and gastroscopy have limited value when it comes to obtaining adequate biopsies for the diagnosis of GIST (9). Other forms of diagnosis include endoscopy and CT scans (11).

While determining the phenotypes of GISTs is challenging, the prediction of the malignant potential of a given tumor is just as challenging and clinically relevant. Criteria for determining the behavior of GISTs are numerous, and at times fail to correctly separate benign from malignant lesions. Tumor size of greater than 5 centimeters and mitotic rate of >2 mitoses per high power field are two features of GISTs that have most closely correlated with aggressive clinical behavior (7,8). PNAC index may also serve as a valuable prognostic tool (7,8). However, it is still not clear whether the same criteria for risk assessment can be applied to all GIST tumor types or of GISTs at different sites (7,8). For example, GISTs with autonomic differentiation may behave in a more aggressive manner than smooth muscle tumors (7,8).

The present tumor is 6-centimeter size with low mitotic rate and Ki-67 labeling index but with 68% PCNA index. Other authors have noted the absence of correlation between PCNA index with mitotic rate and Ki-67 index. The dimension of this stromal tumor with the PCNA index greater than 10% suggests that there may be a risk for aggressive clinical behavior (1,2). Thus, accurately predicting the behavior of this previously unclassified GIST with exclusively fibrous differentiation is not possible.

Currently, there is no staging system available for GISTs (11). Therefore, no specific histological criteria has yet been identified to enable an unambiguous prediction of biological behavior (10). Some believe that the benign and malignant categories of GISTs should be classified into low-or-high-risk tumors in relation to their ability for recurrence or metastasis (7).

To date, the mainstay of treatment for GISTs remains to be surgical resection. The role of adjuvant treatment is unclear. However, it is generally accepted that the most reliable features predictive of the clinical course are tumor size, invasion of adjacent structures at the time of surgery, and mitotic activity (8).

In summary, this is a case of a small bowel stromal tumor of fibrous type. Its clinical presentation as an incarcerated inguinal hernia, coupled with its distinctive cell differentiation, makes the lesion notably unique. Our report has emphasized the fact that GISTs are heterogeneous and require ancillary techniques for proper diagnosis and classification. Whether the clinical behavior of fibrous GISTs differs from the previously and more commonly recognized phenotypes is yet to be determined.

Reference