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Case Report Open Access

Indolent Gastrointestinal Neuroectodermal Tumor (GNET) of the Colon: A New Entity?

Gail Prado[1], Steven A Gorcey[2], Arpad Szallasi[1*] and Horacio Maluf[3]

[1]*Department of Pathology, Monmouth Medical Center, Long Branch, New Jersey, USA*

[2]*Monmouth Gastroenterology, Eatontown, New Jersey, USA*

[3]*Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA*

Corresponding author: *Arpad Szallasi, Department of Pathology, Monmouth Medical*

Center, Long Branch, New Jersey, USA, Tel: 732-229-8711; Email: aszallasi@barnabashealth.org

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Abstract

With less than 50 reported cases, Gastrointestinal Neuroectodermal Tumor (GNET) is a rare malignant neoplasm. Here we report an unusual case of GNET with indolent clinical behavior. The patient is a 59-year-old Caucasian man whose 2 cm sigmoid colon mass did not increase significantly in size during a 10-year surveillance colonoscopy. This mass was recently resected due to change in bowel habits. H&E sections revealed a polypoid, low-grade spindle cell neoplasm, arising from the submucosa and infiltrating the muscularis propria. Negative CD117 and DOG-1 stains excluded a diagnosis of Gastrointestinal Stromal Tumor (GIST). The tumor cells were positive for vimentin, S-100, synaptophysin, and CD56. Pertinent negative stains included Melan-A, HMB-45, smooth muscle actin, CD34, and cytokeratin. Electronmicroscopy showed no obvious sign of differentiation. A presumptive diagnosis of GNET was made. FISH for rearrangement of the EWSR1 gene was, however, negative. There was no evidence of metastatic disease at the time of surgery. One year after surgical removal of this tumor, the patient is asymptomatic. We propose that a subset of GNET may follow an indolent clinical course.

Keywords: Gastrointestinal neuroectodermal tumor; Indolent GNET; EWSR1 rearrangement; CD56 stain

Abbreviations:

GNET: Gastrointestinal Neuroectodermal Tumor; GIST: Gastrointestinal Stromal Tumor; CCS: Clear-Cell Sarcoma; EM: Electron Microscopic.

Introduction

Colorectal carcinoma is the third leading cause of cancer death both in men and women in the US. Approximately 5% (or 1 in 20) of Americans will be diagnosed with cancer of the colon or rectum in their life time [1]. The incidence and death rate of colorectal carcinoma increases with age: overall, 90% of the cases occur in people 50 and older. By comparison, mesenchymal tumors of the GI tract are rare, representing only 0.1% of malignant tumors in the large intestine [2]. However, these tumors may affect younger patients.

Clear-Cell Sarcoma (CCS) was first described by Enziger [3] in the deep soft tissue of the distal limbs. In 1993, a similar tumor was reported by Ekfors and colleagues [4] in the duodenum that shared some features with the "malignant neuroendocrine tumor of the jejunum with osteoclast-like giant cells" that Alpers and Beckstead described in 1985 [5]. CCS was eventually renamed as "malignant melanoma of the soft part" due to its melanocytic differentiation [6]. By contrast, CCS of the GI tract turned out to have a primitive neural phenotype [7]. Many cases also showed translocations involving the EWSR1 gene [8,9], not seen in CCS. To clearly distinguish these two morphologically similar tumors, in 2012 Stockman and coworkers [7] renamed the CCS of the GI tract as GNET.

With less than 50 cases reported in the English language literature, GNET is now recognized as a rare neoplasm that predominantly arises from the small intestine [10,11], followed by the stomach [12], esophagus [13], and the colon [14]. Patients commonly complain of abdominal pain and weight loss, and some also experience fever, anemia, and melena [7,12]. GNET is usually treated by surgical excision, followed by chemotherapy if metastatic disease is present [11]. Indeed, almost half of the patients showed lymph node involvement at the time of diagnosis, and many had metastatic liver disease [12]. For esophageal GNET, pulmonary metastasis was also reported [15]. Recently, a link between GNET and Ewing sarcoma was postulated [16]. Therefore, GNET is thought to follow malignant behavior.

Here we report a case of spindle-cell neoplasm in the distal colon of a 59 year old man that shared many histological, immunohistochemical, and ultrastructural features of GNET; yet, it followed an indolent clinical course (no increase in size during a 10-year surveillance colonoscopy and no evidence of metastatic disease at the time of surgery). One year after surgical removal of this tumor, the patient is asymptomatic. We propose the existence of indolent GNET.

Case Presentation

A 59-year-old Caucasian man with recent change in bowel habits (constipation and flatulence) was admitted for surgical removal of a 2 cm polypoid submucosal mass in the sigmoid colon which was first noted 10 years ago during screening colonoscopy performed at an outside institution. Reportedly, during the colonoscopy this mass was

believed to represent a submucosal lipoma and the decision was made not to biopsy. Until recently, this mass did not cause clinical symptoms, nor did it increase perceptibly in size. Endoscopic mucosal resection of the sigmoid colon mass was planned. However, during the procedure it was determined that this mass also involved the muscularis propria, therefore full-thickness excision was performed. The resected mass was sent for pathologic examination.

Cross examination revealed a firm, yellow to tan, well-circumscribed mass in the submucosa of the sigmoid colon, measuring 2.5 cm in greatest dimension. Frozen section was performed and interpreted as "Spindle cell neoplasm (GIST); defer to permanents." The specimen was then fixed in 4% buffered formalin and embedded in paraffin blocks.

H&E-stained sections showed a nodular proliferation of spindle and round cells with scant amounts of cytoplasm, mild cytologic atypia, and minimal mitotic activity (Figure 1).

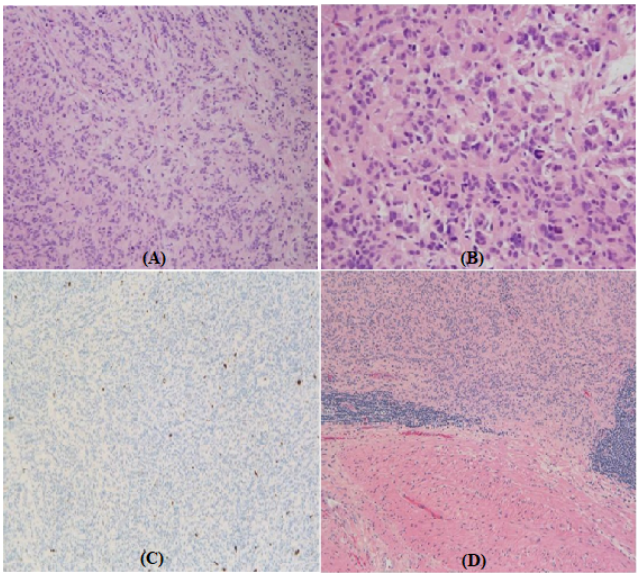

Figure 1: H&E histomorphology of the tumor **(A)** at low (10X) and **(B)** high magnification (40X). **(C)** Paraffin immunohistochemical stain for Ki67 reveals low mitotic activity. **(D)** The tumor evokes a prominent lymphocytic response and superficially invades into the muscularis propria.

Atypical mitotic figures were not seen. The tumor was predominantly located in the submucosa with infiltration into, but not through, the muscularis propria (Figure 1D). The borders of the tumor were ill-defined (no capsule was seen) and neither necrosis nor hemorrhage was appreciated.

Paraffin immunohistochemical stains revealed strong immunoreactivity in the tumor cells for vimentin (Figure 2A) and S100 (not shown), and a weaker staining for synaptophysin (not shown) and CD56 (Figure 2B). Pertinent negative stains included CD117, DOG-1, Melan-A, HMB-45, SMA, desmin, CD34, and the pan-cytokeratin AE1AE3.

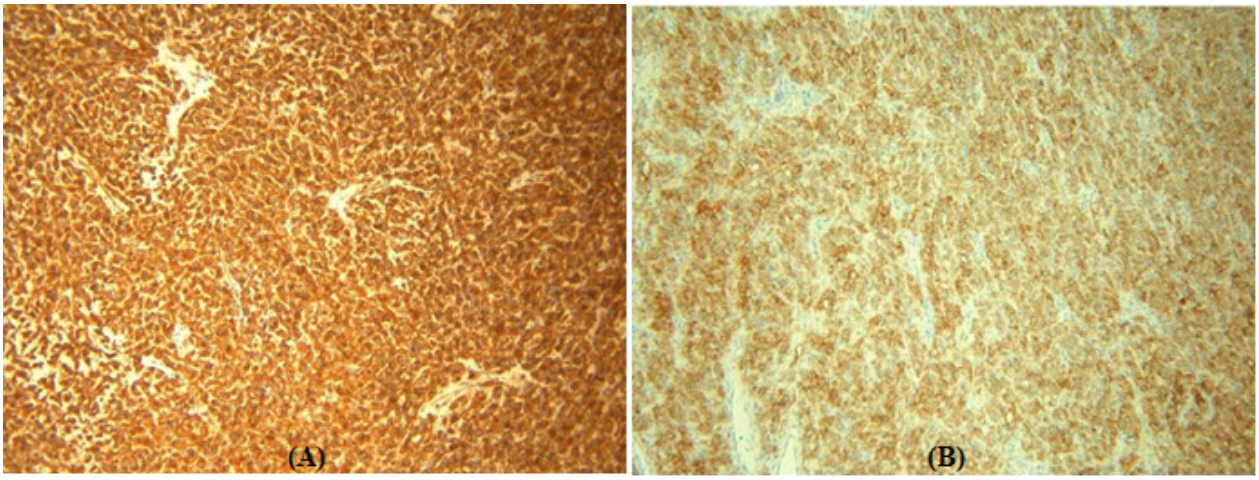

Figure 2: Most tumor cells are strongly and uniformly positive for **(A)** Vimentin and **(B)** CD56.

Fluorescent In-Situ Hybridization (FISH) was performed utilizing a commercial EWSR1 (22q12) break-apart probe set (Abbot Molecule, Des Plaines, IL; http://www.molecular.abbott/us/en/chromosome/22.html). Although 2% of the 200 interphase cells examined contained a split of Spectrum Orange and Spectrum Green signals (Figure 3), this finding was not detected in a significant number of cells to meet the diagnostic criteria for a positive result. However, a pair of EWSR1 ranging from 3 to 4 copies was seen in 14% of the cells.

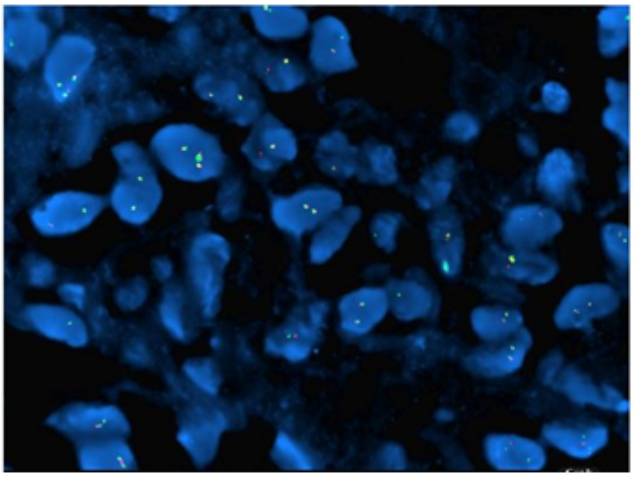

Figure 3: Fluorescent In-Situ Hybridization (FISH) using a commercial EWSR1 (22q12) breakapart probe set (Abbot Molecule, Des Plaines, IL) shows a split Spectrum Orange and Green signal in a small (~2%) of the 200 interphase cells. This does not meet the diagnostic criteria for a positive result. However, a pair of EWSR1 ranging from 3 to 4 copies was seen in 14% of the cells. Picture captured at 100X magnification.

Electron Microscopic (EM) analysis revealed small primitive appearing cells with scant cytoplasm with microfilaments and small amount of glycogen (Figure 4). A rare dense core granule was present, as well as rudimentary cell junctions (not shown).

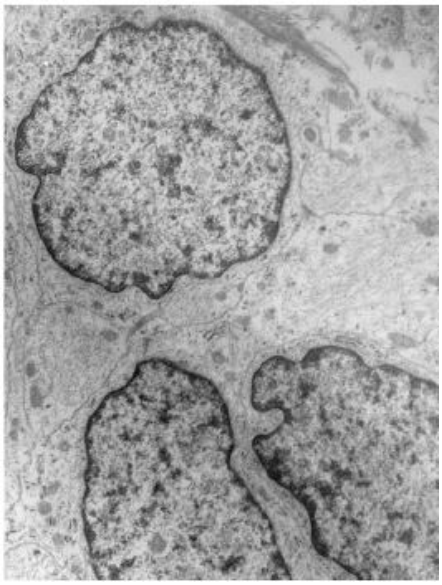

Figure 4: Electron microscopy reveals a primitive cell with microfilaments, rare dense granules, and a small amount of glycogen (HV 100 kV; direct magnification 10,000 X).

Discussion

GNET is a rare visceral spindle cell neoplasm, characterized by neural differentiation in the absence of melanocytic features [6,7,10]. The differential diagnosis for GNET is broad and ranges from GIST through smooth muscle tumors (e.g., low-grade leiomyosarcoma), perivascular epithelioid cell tumors (so-called PE Comas), monophasic synovial sarcoma and schwannoma to metastatic tumors. In our case, GIST was excluded based on the negative immunohistochemical stains for CD117 and DOG1. Melanocytic differentiation markers (Melan-A and HMB-45) were also negative, thereby ruling out PEComa and melanoma. The negativity of smooth muscle actin and desmin further

excluded smooth muscle neoplasms such as leiomyoma or low-grade leiomyosarcoma. The negative AE1AE3 stain combined with the immunoreactivity for synaptophysin and CD56 (Figure 2B) was inconsistent with a diagnosis of synovial sarcoma. Nerve sheath tumors (schwannoma and malignant peripheral nerve sheath tumor) are also negative for synaptophysin and CD56. Furthermore, schwannomas have a characteristic EM picture (e.g., intertwining terminal cytoplasmic processes) that was not present in our case. In conclusion, the combination of morphology, ultrastructure, and immunophenotype of our case was most consistent with a diagnosis of GNET.

Although many of the reported GNET cases showed rearrangement of the EWSR1 gene [8,9], the small number of cases examined so far precludes this finding as a sine qua non diagnostic criterion of GNET. Indeed, EWSR1 rearrangement is often detected in other sarcomas and non-mesenchymal tumors. Conversely, the original series of 16 cases of GNET that Stockman and colleagues described contained cases with no involvement of the EWSR1 gene [7]. In other words, the negative EWSR1 FISH does not exclude the diagnosis of GNET. In keeping with this, Stockman et al [7] defined GNET by its "distinctive ultrastructural features and absence of melanocytic differentiation." Of note, in our case the FISH study did show amplification of the EWSR1 gene in a subset of tumor cells (Figure 3). The biological significance of this observation remains to be determined.

GNET may arise within the wall of the GI tract at any site, with the small intestine being the most common location. As a general rule, GNET follows aggressive clinical behavior with death from disease in the majority of patients. Indeed, about half of the patients already have lymph node involvement, and some also metastatic disease (liver or lung), at the time of diagnosis [12]. GNET affects both young and old patients with no gender preference. In the original case series of Stockman and colleagues the youngest patient was 17-year old and the oldest patient was 77 year old [7]. Of the 16 patients, eight was male and another eight was female. The mean tumor size was 5.2 cm (range=2.4 to 15.0 cm). Some GNETs showed predominantly epithelioid morphology whereas others were mostly spindled with or without osteoclast-like giant cells [7]. Pseudopapillary [11] and oncocytic [17] variants were also described as potential diagnostic pitfalls.

As mentioned above, the most common location of GNET in the GI tract is the small intestine, closely followed by the stomach and the esophagus. To the best of our knowledge, only four GNET cases have been reported in the colon. Stockman and colleagues described two patients, a 31-year old man and a 77-year old woman, both dead of disease [7]. One case (the 77-year-old woman) showed the EWSR1-ATF1 translocation whereas the other did not. The exact location or size of the tumor in the colon was not provided in the paper. Fukuda and co-workers described a 74-year-old Japanese man whose GNET recurred 9 month post-surgery [14]. Most recently, a fourth patient (a 22-year-old man) was reported with a 7 cm mass in his proximal transverse colon that revealed EWSR1 gene rearrangement [18]. Our patient is a 59-year old man whose sigmoid colon mass was first noted 10 years ago. The size of the tumor remained fairly stable during a 10-year follow-up by colonoscopy and CT scan after the initial observation had been made. The tumor was removed when the patient developed constipation and bloating. The morphology, immunophenotype, and ultrastructure of the tumor were most consistent with a diagnosis of GNET. FISH analysis did not reveal rearrangement of the EWSR1 gene, although 14% of the cells showed EWSR1 gene amplification. At the time of surgery, there was no evidence of metastatic disease. The patient remains asymptomatic 1 year after surgery.

In conclusion, our case suggests that indolent GNET exists. An alternative explanation of our findings is that malignant GNET represents transformation in a pre-existent low-grade GNET. In our patient, the tumor was first detected in the sigmoid colon during screening colonoscopy and was removed 10 years later when the patient detected changes in bowel habits. The reported malignant GNET cases seem to represent more advanced disease. If so, akin to GIST, GNET may be thought of as a tumor of uncertain malignant potential where size (the median size of the reported malignant cases was 6 cm, this should be compared to the size of the tumor, 2.5 cm, in our patient), location (most malignant GNET cases seem to arise from the upper GI tract), and the presence of EWSR1 gene rearrangement indicate unfavorable prognosis.

Disclosures

This study was approved by the Monmouth Medical Center Institutional Research Review Board (IRB Study # 15-032). Informed consent was also obtained.

Authors' contributions: Arpad Szallasi wrote the manuscript and is the article guarantor. Gail Prado did the grossing of the specimen and carried out the paraffin immunostains. Horacio Maluf performed the EM and FISH studies. Steven A Gorcey took care of the patient and provided the clinical information.

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