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Clinical and Morphological Characteristics of Gastrointestinal Stromal Tumor

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Rezumat

Aspecte clinice și morfologice ale tumorilor stromale gastrointestinale

Introducere: Tumorile stromale gastrointestinale (GIST) sunt o formă rară de cancer localizată în tractul gastrointestinal (GI), definite ca tumori cu celule fusiforme, epitelioide sau ocazional mixt. Ele îşi au originea în celulele interstiţiale ale lui Cajal, ce au funcţia de „pacemaker" al motilităţii gastrointestinale. Comportamentul lor este dictat de modificări ale genei c-kit/PDGFRA, care este adesea evidenţiată prin imunomarcare.
Metode: Raportăm caracteristicile clinice, macroscopice, microscopice şi imunohistochimice ale pacienţilor diagnosticaţi cu tumori gastrointestinale care au fost rezecate chirurgical în centrul nostru în perioada 2008-2022.
Rezultate: Am inclus 20 de pacienţi consecutivi. La majoritatea subiecţilor, prezentarea a fost considerată o urgenţă chirurgicală care a necesitat intervenţie chirurgicală imediată. Cea mai frecventă localizare a fost intestinul subţire (n=9, 45%), urmat de stomac (n=7, 35%), colon (n=3, 15%) şi peritoneu (n=1, 5%). Histologic, tumorile au fost predominant mixte (n=10, 50%) urmate de tip fusiform (n=8, 40%) şi epitelioide - 2 cazuri (10%).
Concluzii: Prezentarea clinică a GIST rămâne eterogenă, iar diagnosticul este preponderent postchirurgical, utilizând analize imunohistochimice complexe. Dimensiunea tumorii şi numărul de mitoze sunt puternic asociate cu prognosticul pe termen lung.

Cuvinte cheie: tumoră stromală, gastointestinal, celule Cajal

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Abstract

Introduction: Gastrointestinal stromal tumors (GIST) are a rare form of cancer located within the gastrointestinal (GI) tract, defined as tumors with spindle, epithelioid, or occasionally pleomorphic cells. They originate in the interstitial cells of Cajal, with the function of "pacemaker" of gastrointestinal motility. Their behavior is dictated by changes in the c-kit/PDGFRA gene, which is often highlighted by immunolabeling.

Methods: We report the clinical, macroscopic, microscopic, and immunohistochemical characteristics of consecutive patients diagnosed with GIST who underwent surgical removal of the tumor in our department between 2008-2022.

Results: We included 20 consecutive patients. The presentation was considered a surgical emergency requiring immediate surgical intervention in most subjects. The most common localization is the small intestine (n=9, 45%), followed by the stomach (n=7, 35%), colon (n=3, 15%), and peritoneum (n=1, n=5%). Histologically, the tumors were predominantly mixed (n=10, 50%) followed by spindle type (n=8, 40%) and epithelioid - 2 cases (10%).

Conclusion: The clinical presentation of GISTs remains heterogeneous, and the diagnosis is predominantly postsurgical, using complex immunohistochemistry analysis. The tumor size and number of mitoses are strongly associated with the long-term prognosis.

Key words: stromal tumor, gastrointestinal, Cajal cell

Introduction

Gastrointestinal stromal tumors (GISTs) account for about 20% of soft tissue sarcomas (1) and are defined as immunohistochemically KIT-positive (CD117) and KIT signaling-driven primary mesenchymal tumors of the gastrointestinal tract (2).

The tumor originates from the spindle cells of Cajal (ICC) and therefore can be identified in the entire length of the gastrointestinal tract (3). The preferred site of occurrence is the stomach (60–65%), followed by the small intestine (30–35%) (4). Other rare sites such as the esophagus, the colon, the rectum, and the peritoneum (5-10%) were reported in small case series (2,5). GISTs that develop outside the digestive tract are called extra-GISTs (EGISTs).

Macroscopically, they are well-defined, spherical tumors. They can be isolated or multiple and the sizes vary from microscopic intramural lesions to giant tumor masses. They arise from the muscle layer and can protrude from the outside as exophytic subserous lesions. In the case of large tumors, cystic transformation, hemorrhage, and necrosis can be found (6,7).

Histologically, gastrointestinal stromal tumors are characterized by spindle, epithelioid, or mixed cells. GISTs with spindle cells are characterized by short bundles, cut by uniform cells with fibrillar eosinophilic cytoplasm with perinuclear vacuoles and palisade ovoid nuclei. Epithelioid GIST can present a solid or myxoid growth pattern, with large cells with vacuolated or clear cytoplasm and perinuclear cytoplasmic condensation and round or oval nuclei with finely dispersed chromatin and small nucleoli.

The clinical presentation is variable ranging from asymptomatic incidental findings to life-threatening conditions such as perforation or occlusion, which require immediate surgical intervention. According to studies, one in five GISTs are accidentally diagnosed (8).

This study presents the clinical, macroscopic, and histologic characteristics of consecutive GIST admitted to and managed in our hospital.

Methods

We included consecutive patients who were admitted between 2008-2022 and were diagnosed with GIST. Demographic and clinical data were collected on the date of admission.

All the tumoral samples were obtained during the surgical procedure, and the histopathological examination was performed according to the protocols of our hospital. The surgical fragments were fixed in formalin, embedded in paraffin, sectioned at 5 microns, and then stained standard with hematoxylin and eosin. Immunolabeling was also performed with antibodies against CD117 (c-kit), CD34, S100 and Ki67.

Statistical Analysis

Clinical and demographic characteristics are provided as mean ± standard deviation for continuous variables, or as absolute number or percentage for categorical variables. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL). Significance was set at a two-tailed probability level of < 0.05.

Results

We included 20 patients (male=14, 70%) aged between 45 and 82 years (mean= 63.2 ± 11 years). Most patients presented as a surgical emergency (n=18, 80%). The presentation was either obstruction (n=9, 45%) or gastrointestinal hemorrhage (n=6, 30%), hemoperitoneum (n=2, 10%), and in one case (5%) generalized peritonitis.

The remaining two patients presented with non-specific symptomatology and the diagnosis of GIST was established post-surgery by the histopathological examination.

All tumors were well-defined and located mainly in the small bowel (n=9, 45%) followed by the stomach (n=7, 35%), colon (n=3, 15%), and the peritoneum (n=1, n=5%) (*Fig. 1*).

The size of the tumors varied between 1.5 cm and 18 cm, with an average of 9.5±2.1 cm. Overall, the majority of the tumors had a diameter between 5 and 10 cm (n=12, 60%). The remaining were either under 2 cm (n=1, 5%), between 2 and 5 cm (n=3, 15%) and over 4 cm (n=4, 20%).

The number of mitoses varied between 0 and 10 (average=4.3), with 11 patients having > 5 mitoses per 50 HPFs. In the vast majority of patients with mitoses > 5, the localization was in the small intestine (n=9)

Most of the tumors were of intermediate grade (5 cases - 50%) and low malignancy (3 cases - 30%), and only 2 cases (20%) belonged to the group of tumors with a high degree of malignancy.

Depending on the histological appearance, tumors were divided into spindle cell variants, epithelioid and mixed subtypes as follows: predominantly mixed (n=10, 50%) followed by spindle cells (n=8, 40%), and epithelioid - 2 cases (10%).

Immunohistochemically, all cases except 1 (localization in the peritoneum) were CD117 (c-kit) positive (95%). Fourteen cases were CD34 positive (70%), 12 cases S100 positive (60%), and Ki 67 showed positivity in percentages varying between 5% and 50%.

All subjects underwent uneventful tumor resection procedures. A complete surgical resection with clear margins was possible in all cases through laparotomy. There were no perioperative complications, and all subjects were discharged from the hospital after a mean of 8±2 days.

Discussion

Gastrointestinal stromal tumors are a group of tumors that range from small benign tumors to sarcomas at all sites of occurrence. They are extremely rare, accounting for less than 1% of all gastrointestinal (GI) malignancies (7).

The tumors are referred to as potentially malignant and despite recent advances in imagining, they require surgical resection because differentiating GISTs from benign non-GISTs is considered to be difficult. Overall, up to 30% of all GISTs turn out to be malignant (9). Computed tomography, magnetic

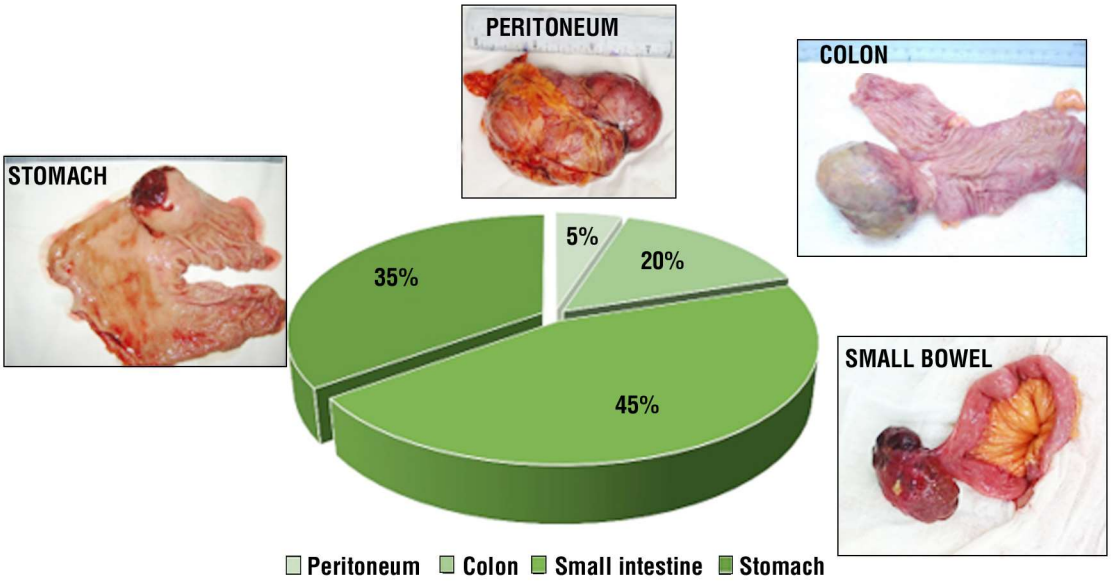

Figure 1. Topographic distribution of the GIST in the study population

resonance imaging (MRI), and 18F-fluoro-deoxyglucose positron emission tomography (PET) have shown variable potential in differentiating GISTs from non-GISTs and high-risk GISTs from low-risk GISTs (10).

GISTs are usually diagnosed in the decades 50-70 of age (11) with ranges extending from 16 to 94 (2,12,13). The findings of our study are in accordance with the reported data in the literature.

The gender predisposition and the influence of gender on the tumor prognosis remain controversial. While some studies report a similar prevalence between the genders (8), others report a higher incidence in men (14). In our study group, the male gender was prevalent.

The localization of GISTs appears to favor the stomach. We report a slightly higher incidence in the small intestine compared to the stomach. Given the small study group, the significance of our findings could be incidental. According to previous studies, small intestine tumors seem to show a poorer long-term prognosis than gastric tumors of similar size and mitotic activity (15).

The localization in the colon is relatively uncommon, representing 0.1% of all colorectal cancers (16). The clinical presentation is usually an emergency, with either bleeding or obstruction (17,18). In our 3 reported cases, the subjects presented obstruction.

GISTs that develop in sites outside the digestive tract, such as in the omentum, retro-peritoneum (19), liver (20), and mediastinum (21) are extremely rare. We identified a single patient with peritoneal localization of the GIST. The tumor was large, approximately 14 cm, with spindle cells and 4 mitoses per 50 HPFs.

Among the 20 patients, the dimensions of the tumors varied from very small (1.5 cm) to large (18 cm) tumors. Another important aspect is the number of mitoses, which suggests how quickly the cancer cells divide. Both the tumor size (>5 cm) and the number of mitoses (>5) per 50 HPFs have been shown to correlate significantly with a higher risk of recurrence and malignancy (2).

In our study group, the small intestine localization was associated with the highest level of mitoses per 50 HPFs.

The histological descriptions of GISTs demonstrate three typical morphologies:

spindle cell, epithelioid, or mixed. In our study group, the mixed type was the most common followed by the spindle cell variant. In previous studies, however, the spindle cell variant was more commonly reported, accounting for 70% of tumors from the entire GI tract (22). The small study group may impact the difference in our results.

The protein CD117 (c-kit) remains the primary marker for identifying GISTs and the positive staining for CD117 establishes the diagnosis. As expected, the vast majority of the tumors (95%) were positive for CD117. A smaller proportion, 70%, were positive for CD34, an alternative marker for diagnosis of GIST.

The presence of kit mutations has both a diagnostic and therapeutic role. Targeted therapies with drugs like imatinib, sunitinib, and regorafenib are currently used to inhibit the activity of the mutated proteins driving the growth of GISTs and seem to reduce tumor recurrence and improve prognosis (23,24).

Last, we also obtained the Ki-67 index, which is associated with cell proliferation and is often used to provide insights into the aggressiveness of the tumor (25).

Conclusions

The GIST diagnosis is difficult because the tumors are asymptomatic for a long time. The combination of immunohistochemical markers, along with other factors such as tumor size, mitotic rate, and mutation status, is used to provide a comprehensive diagnosis and assess the prognosis of GISTs. Surgery is the main curative treatment combined with adjuvant therapy.

Study Limitations

First, this is a single-center study and our findings may reflect characteristics related to specific demographic factors. Secondly, we did not have access to preprocedural imaging data that could be correlated with the intra-operative findings.

Last, the patients were not followed-up, so we could not provide data regarding survival or tumor reoccurrence.

Author's Contributions

Conceptualization, A.M. and S.P.; methodology, S.B.; software, S.B. and S.L.; validation, A.M., V.S.; formal analysis, S.P.; investigation, A.M.; data curation, S.L., P.R.; writing—original draft preparation, S.P. and S.L.; writing—review and editing, V.S. and P.R.; supervision, V.S. and P.R; project administration, P.R. All authors agreed to the final version of this manuscript.

Conflict of Interests

The authors declare no conflict of interest.

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Availability of Data

The data used or analyzed in this study can be obtained from the corresponding authors on reasonable request.

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