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Review

Small bowel sarcoma: Tumor biology and advances in therapeutics

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ABSTRACT

Spindle cell neoplasms are rare mesenchymal tumors of the gastrointestinal tract. GIST (Gastrointestinal stromal tumor) and leiomyosarcoma share similar clinical presentations, gross and microscopic characteristics making distinction difficult in the absence of immunohistochemical (IHC) studies. A multidisciplinary approach is required for treatment planning and ensuring best outcomes. Surgery remains the mainstay of curative treatment for both tumors. Significant advances in targeted molecular therapies have occurred in the past decade in the treatment of GIST with improvement in morbidity and mortality. Similar newer discoveries for treatment of leiomyosarcoma have failed to show any significant survival benefits as yet. Early diagnosis and R0 surgical resection offers the best long term outcome for leiomyosarcoma. Here in we review and discuss the concepts of genetic alterations, newer markers, possible cancer pathways and advances in treatment strategies for these sarcomas.

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1. Introduction

Mesenchymal tumors of the gastrointestinal tract are rare and constitute approximately 8–15 % of primary small bowel malignancy [1]. Prior to discovery of KIT immunohistochemistry; the majority of gastrointestinal mesenchymal tumors were classified as leiomyoma, leiomyoblastoma and leiomyosarcoma on histologic criteria. GIST (Gastrointestinal stromal tumors) is the most common and comprises 85% of all sarcomas arising within the GI tract followed by leiomyosarcoma. In the small intestine their frequency seems to be 1 for every 30 GISTs [2]. Other non-GIST sarcomas albeit rare include liposarcoma, fibrosarcoma, Kaposi's sarcoma and angiosarcoma. Given the rarity of leiomyosarcoma and different treatment options for GIST it is of utmost importance for surgeons to understand the biology and natural history differentiating the two. This review summarizes the current treatment strategies for the two most common visceral sarcomas, leiomyosarcomas, and

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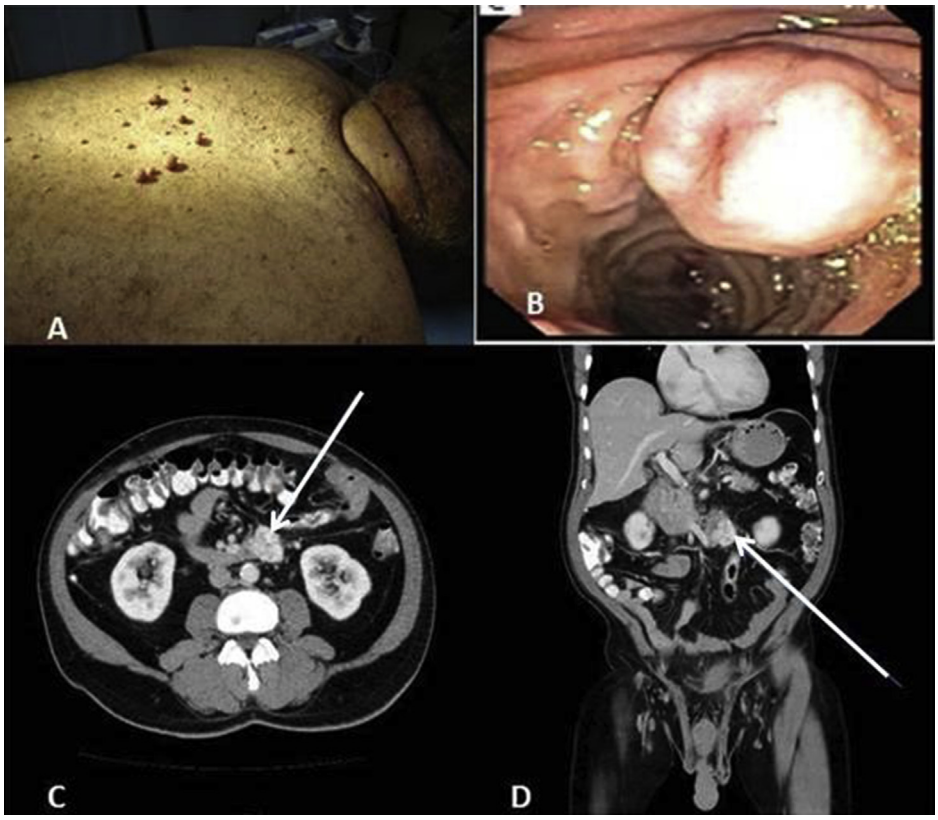

Fig. 1. 68 year old male with neurofibromatosis (A), diagnosed with large GIST of the duodenum on endoscopy (B), CT scan showing locally advanced GIST (arrows) with extramural extension (C, D).

gastrointestinal stromal tumors.

2. Tumor biology, markers and signaling pathways

2.1. GIST

GIST and leiomyosarcoma share similar clinical and pathological characteristics making distinction difficult in the absence of IHC and mutation studies. GIST arises from interstitial cells of Cajal, while leiomyosarcoma arises from denovo mutations in the smooth muscles of the gastrointestinal tract [3].

These tumors may present as asymptomatic incidental finding, as intraluminal or extraluminal mass, or reach giant sizes with symptoms of bleeding, obstruction, hemoperitoneum. Most sarcomas are diagnosed on CT scans and may present as a mass that can be smooth, irregular or lobulated in appearance (Fig. 1) with regions of low attenuation, central necrosis and cystic degeneration, ulceration, calcification or direct extension into adjacent organs and vascular encasement [4,5]. The pattern of metastases differs between GIST and leiomyosarcoma. While GIST may attain large size, they usually are localized tumors and peritoneal cavity and liver are typical sites of metastases. Leiomyosarcomas (Fig. 2) have a predilection for hematogenous spread and metastases are frequently noted to the liver, lungs. Both tumors infrequently involve the local lymph node basin [3,4, and 5]. GISTs typically occur in older adults and with a slight male predominance and a higher incidence among Asian-Pacific islanders [6,7]. They may arise anywhere in the gastrointestinal tract but is commonest in the stomach and small bowel. It is a tumor driven by KIT or PDGFRA mutation.

Hirota et al. first described the presence of an activating mutation of KIT, a tyrosine kinase receptor proto-oncogene and resulting expression of KIT protein in most GISTS [8]. Approximately 85–90% of tumors have KIT (cd117) or PDGFRA mutation. Molecular studies of adult GISTS have confirmed activating mutations in the KIT gene (exons 9, 11, 13, 17) in 90%, most frequently in exon 11. These distinctive KIT mutations have clinical and treatment implications [9]. Three to five percent of all GISTs have been shown to have a mutation in the PDGFRA gene. Lack of KIT expression is associated with mutations in the PDGFRA gene (exons 12, 14, 18). KIT and PDGFRA are mutually exclusive of each other. Another marker DOG1 (Discovered on GIST), also known anoctamin 1 is a mouse monoclonal antibody and a marker reported to have increased sensitivity and specificity. Immunoreactivity is present in 94% of GIST and equivalent to the KIT immunopositivity. DOG 1 stains exclusively the GIST cells and native cells of Cajal. In humans it is localized in chromosome 11q13 and is identified as calcium dependent, receptor activated chloride channel protein [10]. Together KIT and DOG1 confirm nearly 100% of sporadic GIST and is the standard IHC tests used to diagnose GIST [3,10].

Binding of the KIT ligand induces dimerization and auto phosphorylation of KIT, which initiates a cascade of intracellular signaling (Fig. 3) involved in tumor genesis, proliferation, adhesion and differentiation through the constitutive activation of RAS, MAPK, and P13K pathways [11]. Both KIT and PDGFRA mutations activate the same above mentioned activating pathways.

Approximately ten percent of GIST patients do not have a detectable mutation in either KIT or PDGFRA [11]. This group of heterogeneous wild type GISTs may harbor other rare mutations in the BRAF, NF-1, succinate dehydrogenase and RAS family of genes