Overview on gastrointestinal stromal tumor

Abstract:

GISTs (gastrointestinal stromal tumours) are benign tumours that most usually affect the gastrointestinal (GI) system. GISTs can strike at any age, however, they are most typically diagnosed in later life, with a median diagnostic age in the 60s. Abdominal ultrasound, CT scan, magnetic resonance imaging (MRI), and positron emission transverse tomography (PET) can all be used to detect GISTs (PET).CT enterography is the most effective method for determining the location of these tumors. Histopathology and immunochemistry are used to diagnose GISTs. Surgical excision remains the therapy of choice for gastrointestinal stromal tumours more than 2 cm that are readily resectable. Due to the possibility of resistance to standard treatment, mutational analysis should be undertaken when considering adjuvant and neoadjuvant therapy. In this review, we'll be looking at the disease etiology, epidemiology, diagnosis, and management.

Introduction:

GISTs (gastrointestinal stromal tumours) are benign tumours that most usually affect the gastrointestinal (GI) system. These tumours are the most prevalent mesenchymal tumours of the GI tract, accounting for just 0.1 percent to 3% of all GI malignancies. [1] Approximately 80%-90 percent of GISTs have a mutation in the c-KIT or PDGFRA genes, and most GISTs (> 95 percent) are positive for the KIT protein (CD117) by IHC staining. Due to the possibility of resistance to standard treatment, mutational analysis should be undertaken when considering adjuvant and neoadjuvant therapy. The development of tyrosine kinase inhibitors has resulted in a revolution in the treatment of GISTs, which can be used as adjuvant, neoadjuvant, or recurrent disease therapy. That is why this condition need a comprehensive approach. [2] GISTs are malignant in around 30% of cases. GISTs can appear anywhere in the GI tract, although they're most prevalent in the stomach (60 percent) or small intestine (40 percent) (20 percent to 30 percent). GISTs are seldom seen outside of the gastrointestinal tract, most typically in the omentum, mesentery, or retroperitoneum. GISTs were assumed to be smooth

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muscle tumours when they were first identified in the 1980s; however, during the last 20 years, advances in immunohistochemistry and the detection of gain-of-function mutations have led to the acknowledgment of GISTs as a distinct entity. [1,3-8]

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Although GISTs are considered uncommon tumours, the real prevalence is unclear because most GISTs are identified by chance. Because traditional chemotherapy and radiation are ineffective against GISTs, surgical excision has historically been the treatment of choice. The therapy of malignant cancers has evolved substantially since the identification of mutations linked to them. Imatinib mesylate, a selective tyrosine kinase receptor inhibitor (TKI), is used as an adjuvant or neoadjuvant treatment for GISTs to reduce morbidity and mortality. Sunitinib and regorafenib are effective second-line TKIs due to rising resistance. [9-16]. Most "GI smooth muscle tumours" varied from conventional smooth muscle tumours by their absence of smooth muscle-specific ultrastructure, according to electron microscopic examinations conducted in the late 1960s and early 1970s. Smooth muscle antigens, particularly desmin, were missing immunohistochemically. GGI stromal tumour was offered as a histogenetically non-committal label for these tumours because they lacked Schwann cell characteristics as well. The present notion of GIST – a usually KIT positive and KIT mutation-driven mesenchymal neoplasm exclusive to the gastrointestinal tract – was founded on the finding of KIT expression and gain-of-function KIT mutations in GIST in 1998. [17-21]

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Etiology and pathogenesis:

Huizinga and coworkers revealed in 1995 that a knockout mouse model of KIT failed to express in Cajal cells' interstitial cells. This discovery led to the notion that KIT was required for the growth of Cajal cells' interstitial cells. Hirota and colleagues discovered KIT mutations in GISTs in 1998, and 95 percent of GISTs are immunohistochemically positive for the receptor tyrosine kinase KIT (aka CD117). KIT mutations, which allow the kinase to be activated all of the time, are now known to be present in 70-80% of GISTs. CD117 has emerged as a critical diagnostic marker for GIST, while mutant KIT has emerged as a therapeutically essential therapeutic target in GIST therapy. [22-25] While it is known that gastrointestinal stromal tumours are related to Cajal's interstitial cells, it is

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unclear whether they originate from these cells or their predecessors. Mutations in the KIT (CD 117) or platelet-derived growth factor receptor alpha (PDGFRA) have been demonstrated to cause constitutional activation of their encoded tyrosine kinase receptors in roughly 85 percent of sporadic instances of GISTs. This stimulation causes hyperplasia, which leads to neoplasia. KIT and PDGFRA mutations can be inherited, leading to the much rarer familial GISTs, in addition to being responsible for the bulk of the more common sporadic occurrences of GISTs. This stimulation causes hyperplasia, which leads to neoplasia. KIT and PDGFRA mutations can be inherited, leading to the much rarer familial GISTs, in addition to being responsible for the bulk of the more common sporadic occurrences of GISTs. [1]

In GIST, oncogenetic activation of the KIT gene is the most common pathogenetic pathway. Although germline mutations have been observed in familial GIST, the bulk of KIT mutations in GIST are somatic. The juxtamembrane domain, which is encoded by the 5' end of exon 11 of the KIT receptor, is where the greatest mutations in KIT are detected. Exon 11 mutations induce the active conformation of the normal kinase activation loop by altering the usual juxtamembrane secondary structure. In-frame deletions of various sizes, point mutations, and deletions followed by substitutions are among the mutations. [22]

Epidemiology:

GISTs can strike at any age, however, they are most typically diagnosed in later life, with a median diagnostic age in the 60s. According to population-based research in Europe and SEER (surveillance, epidemiology, and end outcomes) statistics from the United States, the yearly incidence rate ranges from 6.5 to 14.5 per 10,000, with an age-adjusted incidence rate of 0.68 to 0.8 per 10,000. Unfortunately, because to the relative homogeneity of prior population-based investigations, the global prevalence of GISTs is unknown. GISTs affect both men and women in about similar numbers. [1] GISTs are more common in elderly people, with a median patient age of 60–65 years in the main series. GISTs are uncommon in people under the age of 40, with only 1% occurring before the age of 21. A little male preponderance has been seen in several datasets. GISTs are found in the stomach in more than half of cases. GISTs are found in the jejunum or ileum in around 30% of cases, the duodenum in 5% of cases, the rectum in 5%

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of cases, and the esophagus in 1% of cases. According to our analysis of Armed Forces Institute of Pathology (AFIP) cases, up to 10% of all GISTs are diagnosed as advanced, diffused abdominal tumours with unclear origins. [17]

Diagnosis and Pathology:

Although GISTs are the most prevalent mesenchymal tumour of the GI tract, the differential diagnosis should include a number of other malignancies. GIST must be correctly identified since therapy varies depending on the kind of tumour. Smooth muscle tumours, schwannoma, desmoid fibromatosis, inflammatory myofibroblastic tumour, inflammatory fibroid polyp, solitary fibrous tumour, synovial sarcoma, follicular dendritic cell sarcoma, glomus tumour, and melanoma are the most common differential diagnoses. Kirsch and colleagues offered an in-depth look at the diagnostic problems and practical approaches to GIST differential diagnosis. [22] Abdominal ultrasound, CT scan, magnetic resonance imaging (MRI), and positron emission transverse tomography (PET) can all be used to detect GISTs (PET). CT enterography is the most effective method for determining the location of these tumours, any perforation, tumour invasion into surrounding tissues, and metastasis. The final diagnosis of GISTs can also be aided by CT-guided biopsy. Some cancers are identified by chance or in an emergency where a preoperative biopsy is not possible. [9]

GIST range in size from a few millimeters to more than 30 centimeters, with a typical size of 5 to 8 centimeters. GIST has an exophytic development pattern, and the most typical intra-operative appearance is a mass connected to the stomach, protruding into the abdominal cavity, and displacing other organs. In 50% of instances, mucosal ulceration can be seen near the apex of the lesion. On the surface, they seem to be smooth grey and white tumours that are well-circumscribed and often have a pseudo-capsule. It's possible to see a tiny region of bleeding, cystic degeneration, and necrosis. Gastric GISTs can be solid or nested, and they frequently contain a hyalinized stroma with a myxoid alteration. Spindled GISTs in the small intestine are more common than epithelioid GISTs, and they may have a paragangliomatous pattern. Another distinguishing feature is the collagen-based eosinophilic structures, which are prominently stained with periodic acid-Schiff (PAS) stain. [26-29]

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Although magnetic resonance imaging (MRI) offers diagnostic performance equivalent to CT and the advantage of avoiding ionising radiation, CT is still the chosen first imaging technique for disease screening and staging. There are certain exceptions to this rule; for example, some individuals are unable to receive intravenous contrast due to a variety of factors (allergies, IR). Furthermore, MRI is sometimes the best option for GISTs detected in specific sites (such as the rectum) and is particularly beneficial for assessing the anatomical degree of surgery or the suspicion of liver metastases. [2] Differential diagnosis may be aided by anatomic location. Intramural leiomyomas are most typically seen in the esophagus, with stomach and small intestine leiomyomas being uncommon. GISTs frequently have syncytial cell shape, whereas leiomyomas have highly eosinophilic cytoplasm with clear cell boundaries. GISTs and leiomyomas share similar immunohistochemical markers, such as SMA and h-caldesmon, however, spindle cell GISTs seldom express desmin, which is more characteristic for leiomyomas. Desmin staining is positive in epithelioid GISTs that lack KIT expression. CD117 is absent in leiomyomas. [22]

Histopathology and immunochemistry are used to diagnose GISTs. Spindle (70 percent), epithelioid (20 percent), and mixed type GISTs (10 percent) all have variable histologic findings. Before immunohistochemical examination, they are frequently misdiagnosed as leiomyoma or leiomyosarcoma. Microabscesses can also be visible on microscopy if tumours perforate. CD117 and DOG-1 positivity is seen in about 88 percent of GISTs. CD117 and DOG-1 were shown to be positive in 95.71 percent and 88.57 percent of GIST patients, respectively, in a recent study of 70 cases. [9] The immunohistochemical examination, in addition to the relevant morphologic findings, provides the foundation for the diagnosis of GIST. KIT and anoctamin are the most prevalent markers. KIT positivity is seen in around 95% of GISTs. For the remaining 5%, anoctamin 1, also known as diagnosed on GIST 1 (DOG1), is deemed diagnostic when combined with CD34 and the proper morphologic characteristics. Exon 11 mutations are the most prevalent of the four identified KIT mutations. Because of their lower sensitivity and resistance to tyrosine kinase inhibitors, exon 9 and 17 mutations are the most clinically significant. [1]

Simple endoscopy is unable to discriminate between intramural and extramural malignancies properly. Endoscopic Ultrasonography (EUS) has shown to be a

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beneficial technology in this regard, allowing for the identification of the layer of origin and the acquisition of tissue via a guided puncture for anatomopathological diagnostic research that is appropriate for immunohistochemistry assays. Endoscopic biopsies don't always get enough tissue for a conclusive diagnosis, and loop biopsies can induce a perforation, so they're best avoided. [2]

DOG-1 appears to be more sensitive and specific than CD117, according to the literature. Sensitivities in GISTs with a PDGFRA mutation, on the other hand, drop to 9% and 79 percent, respectively. Small tumours have homogenous densities, but bigger tumours show irregular lobulated borders, mucosal ulcers, central and coagulative necrosis, bleeding cavitation, and heterogeneous enhancement on imaging. GISTs can develop necrosis, which can be observed on histology images, and calcifications, which can be seen using CT or MRI imaging. [9]

Management:

Surgical excision remains the therapy of choice for gastrointestinal stromal tumours more than 2 cm that are readily resectable. The surgical objective is to achieve full resection (R0) with grossly negative margins and no rupture of the tumour pseudocapsule. Laparoscopic surgery is a safe and successful surgical method for tumour excision in individuals with GISTs smaller than 5 cm. Open surgery is advised for bigger GISTs to reduce the danger of pseudocapsule perforation and subsequent seeding of the abdomen, which increases the chance of recurrence. Because lymph node metastases is uncommon, lymphadenectomy is not necessary in addition to tumour excision. [1]

In individuals whose illness is managed with imatinib, the role of metastasectomy is debatable. PFS with imatinib was found to be influenced by the size of the tumour. This suggests that debulking metastatic disease after an initial stabilisation or response to imatinib might aid in disease management by limiting the formation of resistant clones. Although prospective randomised trials examining the benefits of debulking surgery were unable to recruit enough patients, the findings of one small randomised trial show that resection of residual disease while on imatinib therapy increases OS. A retrospective study found that patients who had debulking surgery that resulted in R0 or R1 sections had a longer OS than those who had surgery that left a gross tumour behind. The

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usage of imatinib may be extended if a focused advancing lesion is resected, but not if the lesion is diffusely progressing. [30-34]

Although surgery is the preferred treatment option, it does not always cure GIST. In around 85% of patients, total resection is achievable, although 50% of patients will have recurrence or metastasis after complete resection. The 5-year survival rate is around 50%, and the median time to recurrence following primary high-risk GIST resection is 2 years. In postsurgical patients, adjuvant imatinib has been demonstrated to enhance PFS and OS. Imatinib has been proven to be advantageous if maintained for 36 months in patients who have not received preoperative imatinib and have undergone total resection, especially in individuals with an intermediate or high risk of recurrence. [26]

In situations of locally advanced primary or recurrent illness, unresectable or perhaps resectable metastasic tumours, and potentially resectable disease in difficult anatomic sites, neoadjuvant Imatinib-Mesylate should be explored to shrink the tumour and reduce associated morbidity. There is no unanimity on the length of Imatinib-Mesylate treatment; nevertheless, 3-12 months of treatment with many imaging control studies would be an appropriate management strategy. The maximum tumour response usually occurs after 4 to 12 months of therapy. [2]

Conclusion:

GISTs are benign tumours that can strike at any age but more common in later stages of life, Although GISTs are considered uncommon tumours, the real prevalence is unclear because most GISTs are identified by chance. Because traditional chemotherapy and radiation are ineffective against GISTs, surgical excision has historically been the treatment of choice. Surgical procedure depends on size and location of tumour The surgical objective is to achieve full resection (R0) with grossly negative margins and no rupture of the tumour pseudocapsule. Laparoscopic surgery is a safe and successful surgical method for tumour excision in individuals with GISTs smaller than 5 cm.

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