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Gastrointestinal Stromal Tumor (GIST)

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KEYWORDS

Gastrointestinal stroma tumor, mesenchymal tumor, malignancy, metastatic

ABSTRACT

Gastrointestinal stromal tumor (GIST) are the most common mesenchymal tumor of the gastrointestinal tract and most common malignancy of the small intestine. Although the exact prevalence of GIST is not known, GIST was recognized as tumor it's arise from interstitial cells of Cajal. Most of the GISTs driven by a KIT or platelet-derived growth factor receptor alpha (PDGFRA) mutation. Histologically, GISTs look like spindle cell tumors most of the time, but they can be epitheoid or mixed type. Clinically, patients with small GISTs remain asymptomatic. In another case, patients with larger GISTs present with various symptoms depending on the location of the GISTs. Most of GISTs are located in the stomach or small bowel. But, they can involve almost any segment of the gastrointestinal tract from distal esophagus to anus. Diagnosis is suspected on imaging and endoscopic studies, and confirmed by tissue acquisition with immunohistochemical staining. The various endoscopic modalities of resection are increasingly tried. Surgical resection is the treatment of choice. In management of larger GISTs, tyrosine kinase inhibitors are extremly useful. Treatment options for metastatic GISTs also include radiotherapy, chemotherapy, hepatic artery embolization, chemoembolization, and radiofrequency ablation.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors in the gastrointestinal tract. GIST can occur at various locations in the digestive tract, with the stomach being the most common location. Although most GISTs are sporadic with no known risk factors, some factors such as age and the presence of genetic disorder syndromes can increase the risk of GIST (Gheorghe et al., 2021). GIST diagnosis can be made through imaging and endoscopic examination, and surgery is one of the treatments of choice(Ahmed, 2020).

METHOD

Methods and Procedures This literature review is prepared using various sources of scientific journal articles related to the topics discussed. The keywords used in article search are "gastrointestinal stromal tumor", "Clinical manifestations", "Diagnosis",

"Management", "Prevention". The article search procedure is carried out carefully and pays attention to its validity.

RESULTS AND DISCUSSION

1. Gastrointestinal Stromal Tumors

1.1 Definitions

Gastrointestinal stromal tumor (GIST) is a rare sarcoma of soft tissues that can be found in all parts of the digestive tract. GIST is most commonly found in the stomach, starting from the small intestine, large intestine, and rectum. Initially, GIST was misclassified as leiomyoma, leiomyosarcoma, and schwannoma. In its development, ultrastructural, immunohistochemical, and molecular biology techniques have made it possible to recognize that GIST originates from Cajal interstitial cells (ICC) or common progenitor cells. ICC is found throughout the digestive tract acting as *pacemaker cells* to regulate peristalsis. GIST can develop through oncogenic acquisition of functional mutations of the KIT gene or platelet-derived growth factor receptor (PDGFR) which plays a role in producing constitutive activation of tyrosine kinase receptors (Mantese, 2019).

1.2 Epidemiology

Gastrointestinal stromal tumors (GIST) are known to have an incidence incidence of at least 14-20/1 million in population-based studies from Northern Europe. These estimates represent a minimum incidence, as subclinical GISTs are much more common. In the United States, about 5000-6000 new cases of GIST are diagnosed per year. Based on surveillance, epidemiology, and final result databases, the incidence of GIST increased from 0.55/100,000 population in 2001 to 0.78/100,000 population in 2011. Another study published in 2006 showed that there has been a 25-fold increase in GIST incidents in the U.S. in the last 10 years since 1992. In Europe, the incidence of GIST varies from 6.5 to 14.5 per million per year (Miettinen and Lasota, 2013).

Soreide et al reviewed 29 studies consisting of 13,550 patients from 19 different countries with GIST between January 2000 and December 2014. The median age was 65 (range, 10-100) with a male to female ratio of 1:1. The highest incidence rates (19-22 per million per year) were recorded in Hong Kong, Shanghai, Taiwan, and Norway. The lowest incidence was recorded in China's Shanxi province with 4.3 per million per year. Eighteen percent (range, 5–40%) of GISTs were discovered by chance (Parab *et al.*, 2019).

Most GISTs appear in the stomach (60–65%), followed by the small intestine (20–25%), rectum (3–5%), colon (1–2%), esophagus (1%) and other locations (8–10%). GIST occurs in young patients, children, and young adults (<30 years) appears mostly in the stomach (Blay *et al.*, 2021). GISTs are found in the stomach (56%), small intestine (32%), colon and rectum (6%), esophagus (0.7%), and other locations (5.5%). About 10% to 30% of GISTs develop into violence. GISTs that occur outside the stomach are associated with a higher potential for malignancy. Exophytic growth was recorded in 79% of GISTs, while intraluminal or mixed growth occurred less frequently (Parab *et al.*, 2019).

1.3 Etiology and Risk Factors

Gastrointestinal stromal tumors (GIST) are generally sporadic with no known risk factors or cause, only about 5% of cases are due to familial genetic factors (Gheorghe *et al.*, 2021). Factors that are thought to increase the risk of GIST, namely age factors and the presence of genetic disorder syndrome.

a. Age

One of the risk factors for GIST is age. The age at risk of GIST, namely middle age to the elderly. These tumors are most often diagnosed in individuals between the ages of 50 and 70, while in terms of gender distribution, the ratio of males to females is approximately equal (Gheorghe *et al.*, 2021).

b. Genetic disorders syndrome

Genetic disorder syndromes are caused by gene mutations. Genetic disorder syndromes that can cause GIST, namely Carney–Stratacis syndrome (CSS), Carney triad, Neurofibromatosis type 1 (NF1), and primary familial GIST syndrome (Gheorghe *et al.*, 2021).

1) Carney-Stratacis syndrome (CSS)

Carney-Stratakis syndrome or Carney-Stratakis dyadis is diagnosed in adolescents or young adults at an average age of 19-21 years. These patients typically have GIST and paraganglioma associations (Gheorghe *et al.*, 2021).

This genetic disorder includes two types of tumors, pheochromocytoma (PHEO)/paraganglioma (PGL) and gastrointestinal stromal tumor (GIST) and is inherited autosomal dominant. This syndrome affects both men and women during childhood and adolescence. CSS is caused by mutations in the SDHB, SDHC and SDHD subunits, with subunits B and D mutating at higher frequencies. A study studied patients with CSS who developed gastrointestinal stromal tumors and identified germline mutations in SDHB, SDHC and SDHD. In addition, mutations of loss of SDHA function have also been identified in patients with CSS (Pitsava *et al.*, 2021).

2) Carney Triad syndrome

Carney Triad syndrome is found in young women with GIST, pulmonary chondroma, and paraganglioma (Gheorghe *et al.*, 2021). Carney's triad is caused by SDH mutations, more specifically, SDHC (Pitsava *et al.*, 2021).

3) Neurofibromatosis type 1 (NF1)

GISTs associated with NF1 syndrome are localized in the small intestine in >70% of cases. These are usually multifocal tumors and have a low rate of mitosis. Unlike sporadic GISTs, mutations in the PDGFRA and KIT genes are rare. GIST associated with NF1 syndrome has an incidence of 1 in 4000 in the general population and is an autosomal dominant genetic disease with a wide range of clinical-pathological features and an uncertain course of the disease. Mutations in the NF1 gene, which codes for neurofibromin, cause loss of function of that gene and result in Ras activation that promotes tumor formation. (Gheorghe *et al.*, 2021).

4) Primary familial GIST syndrome

Primary familial GIST syndrome is characterized by a tendency to early development of multiple tumors, located in the stomach or small intestine. This syndrome is caused by a KIT or PDGFRA mutation. Patients with germline mutations in the KIT gene can have paraganglioma, dysphagia or hyperpigmentation of the skin associations, and patients with mutations in the PDGFRA gene can have polyp associations of inflammatory fibroids or intestinal fibromatosis (Gheorghe *et al.*, 2021).

1.4 Pathophysiology

Uncontrolled proliferation of ICC led to the growth of GIST. The C-kit protooncogene located on chromosome 4q 11-12 encodes transmembrane tyrosine kinase. Exon 11, which is the transmembrane domain, is involved in 90% of KIT gene

mutations. Mutations that activate KIT cause hyperplasia of the ICC and GIST. This KIT gene mutation activates tyrosine kinase, which is found in 75% of GIST cases.

The PDGFRA gene on chromosome 4q12 controls the production of PDGFRA which is part of the receptor tyrosine kinase (RTK) protein. The most common PDGFRA mutation found is the Asp842Val mutation in exon 18. Intragenic activation mutations in the PDGFRA gene with RTK production were found in 35% of GIST cases without KIT mutations. Therefore, the growth of GIST is based on mutations of the KIT gene, which accounts for 75% of GIST cases or PDGFRA gene mutations which account for 10% of GIST cases. The oncogenic mechanism of these two mutations is exclusive, meaning that only one of them can occur in one case of GIST (Monjur Ahmed, 2020).

In 15% of undetected GIST cases, KIT or PDGFRA mutations are called *wild-type GIST or* pediatric *GIST*. Wild-type GISTs need to be examined for mutations in the SDH gene. Clinically, this GIST cannot be distinguished from a KIT mutation GIST or PDGFRA because it has the same morphology, expresses high levels of KIT, and can appear anywhere in the GI tract. There are also other gene mutations found in *wild-type GISTs*, including BRAF, HRAS, NRAS, and PIK3CA (Monjur Ahmed, 2020).

1.5 Management

The standard treatment of a local GIST is surgery. The tumor and pseudo-capsule must be removed in order for surgery to be performed with an adequate margin because the primary goal is complete removal (R0). Given the fact that GISTs rarely metastasize to lymph nodes, resection of the lymph nodes is not required. The presence of metastases does not represent a contraindication to the operation of the main tumor (Gheorghe *et al.*, 2021).

Other treatment methods for non-metastatic GISTs are endoscopic techniques, such as enucleation, submucosal surgery, submucosal excavation, thickness resection, submucosal resection, and endoscopic cooperative surgery (Gheorghe *et al.*, 2021).
Based on endo-sonography, GISTs are grouped into four subtypes, depending on the location of the propria muscularis, including:
Type I: Tumors that enter the digestive lumen are slightly connected to muscularis propria.
Type II: Tumors that stick out into the digestive lumen are strongly connected to muscularis propria.
Type III: A tumor located in the middle of the stomach wall.
Type IV: A tumor that protrudes into the serous wall of the stomach.

Enucleation of endoscopy can be performed for type I GISTs and allows for type II GISTs. Types III and IV may be more effective than the following endoscopic treatment techniques: submucosal surgery, submucosal excavation, full resection, submucosal resection, laparoscopy, and endoscopic cooperative surgery (Gheorghe *et al.*, 2021).

In cases where the status of the KIT mutation is unknown, an alternative treatment can be chosen, namely using kinase inhibitors. The presence of mutations in PDGFRA D842V was confirmed to have significant resistance to imatinib. So, avapritinib is recommended for patients with symptoms or progressive disease and PDGFRA D842V mutations. However, in patients with asymptomatic mutations or who have indolant disease (slow-growing tumors), regular monitoring is needed to decide on avapritinib administration. Another pharmacological therapy option for patients with PDGFRA D842V mutations is ripretinib or dasatinib. In the demonstration of the INVICTUS study, there

was an increase in the life expectancy of patients with advanced GITS given ripretinib as *four-line* TKI. The study was conducted on 129 patients with advanced GIST, 10 patients showed the presence of *wild-type* mutation status KIT and PDGFRA (Gheorghe *et al.*, 2021).

1.6 Prognosis

Patient survival is related to a number of factors. The average survival of GITS patients is 60 months in those with no evidence of metastasis, and this is significantly reduced by approximately 19 and 12 months if there is continued disease at onset or subsequent recurrence occurs (Zhang and Liu, 2020). The parameters to determine the prognosis of a GIST are tumor size and mitotic ratio per 50 hpf. GIST with a tumor size of ≤ 5 cm and mitosis ≤ 5/50 HPF has a good prognosis, with a risk of metastasis of 3-5%. (George Mantese, 2019). Meanwhile, a poor prognosis has a tumor size of >5 cm and mitosis with a total area of 5 mm2 (Alessandro *et al.,* 2019). The location of the tumor also seems to affect the decreased survival of patients (Zhang and Liu, 2020). Patients with metastases and tumors that are not recessionary also have a poor prognosis (Gina *et al.,* 2021).

1.7 Complications

Complications that can occur in GIST include gastrointestinal bleeding and intestinal obstruction.

a. Gastrointestinal bleeding

Gastrointestinal bleeding is the most common and most dangerous complication, often requiring emergency surgery where this emergency surgery also has a higher risk. GIST patients with chronic bleeding show symptoms of anemia, weight loss, and melena. In case of acute bleeding, peritonitis and shock may occur. Most hemorrhagic stromal tumors are associated with intact serous tunica. Bleeding is provoked by ulceration of the mucosa due to the invasion of the tumor into the blood vessels.

The causes of GIST intraluminal hemorrhage may be related to mucosal and submucosal damage by tumor growth, vascular invasion leading to vascular rupture, tumor necrosis, and joint action of digestive juices, gastrointestinal peristalsis, and fecal transmission. GISTs are relatively fragile and have a lot of vascularity compared to other common gastrointestinal tumors resulting in frequent bleeding. In general, by the time symptoms of gastrointestinal bleeding appear, the tumor has already reached a relatively large size. The probability of stromal tumor bleeding in the small intestine is much greater than in the stomach. This is related to the difference in the size of the space in each of these digestive tracts (Liu *et al.*, 2018).

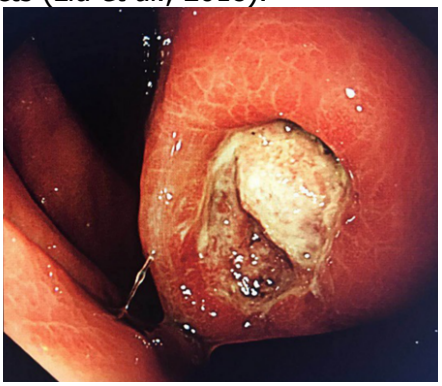

Figure 1. Endoscopic manifestations of GIST with ulceration and active bleeding

b. Intestinal obstruction

GISTs that occur in the duodenum and other parts of the intestine may show any growth pattern, but generally grow exophytically (growths that protrude from the surface of tissue). A complication often seen in GIST of the small intestine and colon is cavitation. The mass effect can result in regional complications such as hydronephrosis and intestinal obstruction. Hydronephrosis can occur due to a mass in the intestine pressing on the ureter so that urine cannot flow into the bladder (Scola *et al.*, 2017).

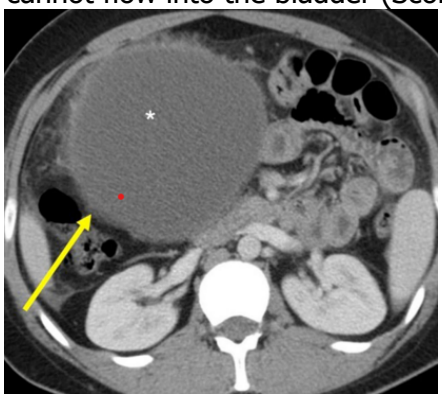

Figure 2. GIST-induced obstruction

CONCLUSION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors in the gastrointestinal tract. GIST risk factors include middle age to the elderly and the presence of genetic disorder syndromes such as Carney-Stratacis syndrome, Carney triad, Neurofibromatosis type 1 (NF1), and primary familial GIST syndrome. GIST diagnosis can be made through imaging and endoscopic examination, and surgery is one of the treatments of choice. Other treatment methods for non-metastatic GISTs are endoscopic techniques such as enucleation, submucosal surgery, submucosal excavation, thickness resection, submucosal resection, and endoscopic cooperative surgery. GIST prognosis is influenced by tumor size, mitotic rate, tumor location, presence of metastases, and total tumor removal success. Complications that can occur in GIST include gastrointestinal bleeding and intestinal obstruction.

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