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Review Article

Gastrointestinal Stromal Tumor

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Abstract

Gastrointestinal stromal tumors (GISTs) are a rare soft tissue sarcomas arising from gut pacemaker of mesenchymal stem cell origin, interstitial cell of Cajal. It may be benign or malignant. The most common site of origin is in the stomach, followed by small intestine, colon and rectum, oesophagus, mesentery, omentum, retroperitoneum and pelvis. Biological behaviour depends on tumor size and mitotic index. Diagnosis is delayed due to vague clinical features. Most of the recent investigations are not conclusive. Conventional histopathology could not differentiate it from leiomyoma or leiomyosarcoma. Only immunohistochemical staining by CD117 is confirmatory for diagnosis. Conventional chemotherapy is not effective but imatinib mesylate, a tyrosine kinase inhibitor, and sunitinib, a multikinase inhibitor are effective for adjuvant or neoadjuvant therapy. Surgery is the definitive therapy for the patients with GISTs. Radical surgical extirpation offers the only chance for cure.

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Introduction

Gastrointestinal stromal tumours (GIST) are soft tissue sarcomas. They are the most common mesenchymal neoplasm of the gastrointestinal tract[1]. Overall, GISTs are rare and rank a distant third in prevalence behind adenocarcinomas and lymphomas among the histologic types of gastrointestinal tract tumours. They are very difficult to treat, being resistant to conventional chemotherapy.

Epidemiology

GISTs are rare. They represent 0.1-3% of all gastrointestinal cancers[2]. There are approximately 900 new cases in UK[3]. They can occur in either sex and at any age but 75% are diagnosed in > 50 years olds[4]. Approximately 10-20 persons per million population are diagnosed with GISTs each year in United States. Retrospective reviews from Western Europe, Asia and Africa have produced similar rates of disease.

Aeteology

Gain-of-fuction mutations in exon 11 of the c-kit proto-oncogene are associated with most GISTs[5]. These mutations lead to constitutive overexpression and autophosphorylation of c-kit, provoking a cascade of intracellular signaling that propel cells toward proliferation or away from apoptotic pathways.

Studies have reported a small subset of KIT-negative GISTs in which mutation of platelet-derived growth factor receptor-alpha (PDGFA), Protein kinase C, and FLJ10261 were detected.

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Pathophysiology

The actual cell of origin of GISTs is a pluripotential mesenchymal stem cell programmed to differentiate into the interstitial cell of Cajal[6]. These are GI pacemaker cells and are largely responsible for initiating and coordinating GI motility. Perhaps the most critical development that distinguishes GISTs as a unique clinical entity was the discovery of c-kit proto-oncogene mutations in these tumours by Hirota and colleagues in 1998[5].Some families have mutation in tyrosine kinase platelet derived growth factor alpha. The biological behaviour of these tumor is unpredictable but size and mitotic index are the best predictors of metastasis[7].

GISTs can occur anywhere in the gastrointestinal tract. They are submucosal lesions, which most frequently grow endophytically in parallel with the lumen of the affected structure. GISTs may also manifest as exophytic extraluminal excrescences. The size of the tumour ranging from smaller than 1 cm to as large as 40 cm in diameter. Apprpximately 50-60% of GISTs in the stomach. The small intestine is the second most common location, with20-30% of GISTs arising from the jejunum. Less frequent sites of origin include the colon and rectum (5-15%) and esophagus (5%). Primary omental or mesenteric GISTs have been reported but very rare.

Histologically, these lesions were classified as leiomyomas or leiomyosarcomas because they possessed smooth muscle features when examined under light microscopy.

GISTs typically stain intensely for the CD117 molecule, which is an epitope of KIT. In GISTs, according to Fletcher et al, CD117 appears diffusely in the cytoplasm in a punctuate or Golgilike pattern[8]. CD34 staining results are also positive in approximately 60% of GISTs.

Clinical features

The most common symptoms associated with GISTs are vague, nonspecific abdominal pain or discomfort. Patients also describe early satiety or a sensation of abdominal fullness. Rarely, an abdominal mass is palpable. GISTs may also produce symptoms secondary to obstruction or haemorrhage. In some cases, the GIST is an unexpected finding during emergency surgery for a perforated viscus.

No physical findings specifically suggest the presence of a GIST. Some patients present with a palpable abdominal mass. Others may present with nonspecific physical findings associated with GI blood loss, bowel obstruction, or bowel perforation and abscess formation.

Differential diagnosis

GISTs should be differentiated from other gastrointestinal nonepithelial neoplasms such as leomyomas, leomyosarcomas and schwannomas by immunohistochemical staining.

Investigations

Plain abdominal radiography

Plain abdominal radiography is nonspecific but may be ordered to detect possible bowel obstruction or perforation.

Double-contrast barium series

It usually detect GISTs that have grown to a size sufficient to produce symptoms.

Endoscopic ultrasonography

Endoscopic ultrasonography is a modality that allows localization of lesions and their character. Fine-needle aspiration biopsy specimens also may be obtained via the endoscope under sonographic guidance.

CT scnnning of the abdomen and pelvis

It provides comprehensive information regarding the size and location of the tumor, its relationship to adjacent structures, presence of multiple tumors and can provide evidence of metastatic spread. Ghanem and colleagues performed CT scanning on patients with histologically confirmed primary (n=20) or recurrent (n=16) GISTs[9]. These investigators described the CT characteristics of

GISTs, dividing them into small (<5 cm), intermediate (5-10 cm), and large (>10 cm) tumors. Small GISTs were sharply demarcated, homogeneous masses, mainly exhibiting intraluminal growthpattern. Intermediate GISTs were characterized by irregular shape, heterogeneous density, an intraluminal and extraluminal growth pattern, and signs of biological aggression, including adjacent organ infiltration in 9 primary and 2 recurrent lesions. Large GISTs featured irregular margins, heterogeneous densities, locally aggressive behavior, and distant and peritoneal metastasis.

MRI

Similar to CT scanning, MRI can depict the tumor or tumors and yield information about surrounding structures. It can also be used to detect the presence of multiple tumors and metastasis. In 1997, Shojaku and colleagues described a GIST as appearing hypointense on T2-weighted images[10].

Positron emission tomography scanning with 2-[F-18]-fluro-2-deoxy-D-glucose

Positron emission tomography scanning has recently been touted as an excellent study for detecting metastatic disease. It has also been used to monitor responses to adjuvant therapies such as imatinib mesylate[11].

Endoscopy

Endoscopic features of GISTs include the suggestion of a smooth submucosal mass displacing the overlying mucosa.

Histologic Findings

Histologically the lesions are classified as leiomyoma or leiomyosarcoma.

Immunohistochemistry

GISTs typically stain intensely for the CD117 molecule, which is an epitope of KIT. In contrast, desmoids, schwannomas, leiomyomas,and leiomyosarcomas do not. CD117 appears diffusely in the cytoplasm in a punctuate or Golgilike pattern[8]. CD34 staining results are also positive in approximately 60% of GISTs.

Treatment

Medical

The only effective, specific, nonsurgical therapy for GISTs is imatinib mesylate. The optimal dose for imatinib mesylate in the adjuvant or neoadjuvant setting remains to be defined. Adult dose, 400 mg PO qd with food; may increase to 800 mg/d divided bid in absence of adverse effects. Pediatric dose is not established.

Sunitinib, a multikinase inhibitor is indicated to whom, who are unable to tolerate treatment with imatinib. Standard adult dose: 50 mg PO qd on a schedule of 4 wk on treatment followed by 2 wk off treatment, then repeat cycle. Dose modification: Increase or decrease dose in 12.5 mg increment based on individual safety and tolerability. Pediatric dose is not established.

Systemic chemotherapy

Systemic chemotherapy trials have almost exclusively been associated with poor results. Overall partial response rate were approximately 10% or less. The best results have been achieved using doxorubicin-based regimens, plus decarbazine, with or without the addition of ifosfamide. Response rates greater than 10% with these regimens were reported by Antman et al in 1993 (n=60. response=15%) and Elias et al in 1989 (n=11. response=27%)[12,13].

Intraperitoneal Chemotherapy

The role of intraperitoneal chemotherapy as salvage therapy in patients in whom imatinib mesylate fails is being investigated. Agents that have been tried include cisplatin and doxorubicin by Berthet and collegues in 1999, and mitoxantrone by Eilber and coworkers in 1999 and 2000[14,15]. Some encouraging results have been achieved in patients with disease limited to the peritoneum.

Radiation Therapy

Radiation therapy is not a part of widely accepted adjuvant therapy protocol for GISTs. Case reports describe radiation treatment of lesions fixed to the abdominal wall or adjacent organs.

Surgical care

Surgery is the definitive therapy for patients with GISTs. Radical and complete surgical extirpation offers the only chance for cure. Surgery is also indicated in symptomatic patients with locally advanced or metastatic disease. Debulking large lesions is helpful when adjuvant therapy with imatinib mesylate is contemplated.

In 2003, Wu et al published their experience with 57 patients who underwent surgical treatment of GISTs from 1995-2002[15]. 28 patients (49%) underwent surgery with curative intent. The remainder were referred to the authors with metastatic disease after undergoing operative treatment at other institutions. In the curative-intent group, resections with completely negative margins were accomplished in 22 patients (79%). In 3 of the patients with resections, metastatic disease was totally resected along with the primary tumor. An additional 2 patients had subsequent complete resection after favorable clinical responses to imatinib mesylate therapy. CD117 staining was positive in 96% of the resected specimens. The authors monitored the entire cohort for a median duration of 18 months. 23 patients (40%) remained alive and free of disease. An additional 22 patients (39%) are alive with disease. Of the remainder,7 are known to have died and 5 have been lost to follow up. Treatment with imatinib effected disease stabilization or regression in 22 (85%) of the 26 treated, with a median duration of response of 19 months.

Laparoscopic surgery may be used for small tumors. A follow-up CT should be performed at three months[16].

In unresectable and metastatic disease that is KIT-positive, imatinib, a tyrosine kinase inhibitor, should be used. Patients should be closely followed up and surgical resection should be performed if the tumor becomes resectable[17].

Conclusion

Complete resection with negative margins is still the only potentially curative treatment for GISTs. Imatinib therapy for metastatic disease is associated with good clinical response rates.

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