

Gastrointestinal Stromal Tumors (GISTs)

Essay

*Submitted for Partial Fulfillment of Master Degree in
General Surgery*

Presented By

Mohamed Hussein Abd El-Alim Boshnaq
(M.B., B.Ch.)

Under Supervision of

Prof. Dr. Reda Abd El-Tawab Khalil
*Professor of General Surgery
Faculty of Medicine – Ain Shams University*

**Prof. Dr. Mohamed Abd El-Moneam
Ibrahim**
*Professor of General Surgery
Faculty of Medicine – Ain Shams University*

Dr. Mohamed Aly Nada
*Lecturer of General Surgery
Faculty of Medicine – Ain Shams University*

**Faculty of Medicine
Ain Shams University**

2010

List of Contents

Title	Page
• List of Abbreviation	I
• List of Figures	II
• Introduction	1
○ Incidence	3
○ Risk Factors	4
• Pathology of Gastrointestinal Stromal Tumors	6
○ Cells of Origin (Interstitial cells of Cajal)	6
○ Pathological Features	10
○ Histological Features of Gastric GISTs	12
○ Histological Features of Small Intestinal GISTs	16
○ Histological Features of GISTs of Other Sites	17
○ GIST Pathogenesis	18
○ Immunohistochemical Features of GISTs	23
○ Histologic Differential Diagnosis pf GISTs	27
• Diagnosis of Gastrointestinal Stromal Tumors	35
○ Clinical Features of GISTs	35
○ Investigations for GISTs	36
1- Blood tests	36
2- Endoscopy:	37
3- Ultrasonography	38
4- Endoscopic ultrasound (EUS)	41
5- Conventional barium studies	43

List of Contents (Cont.)

Title	Page
6- Computed Tomography (CT)of the Abdomen	46
7- Magnetic Resonance Imaging (MRI)	58
8- Positron emission tomography (PET).....	62
9- Angiography	62
10-Esophagogram, Chest radiograph, Chest computed tomography.....	64
11- Plain radiography.....	65
• Treatment of Gastrointestinal Stromal Tumors	67
○ Treatment Modalities of GISTs	67
1- Surgery.....	68
▪ Surgical Procedures for Primary GISTs	72
▪ Surgery for Metastatic GISTs	80
▪ Surgery for Drug-Resistant Tumours	81
2- Chemotherapy.....	82
▪ (A) Imatinib Mesylate (IM)	83
▪ (B) Sunitinib Malate (SUL1248)	88
3 - Hepatic Arter Embolization.....	91
4 - Radiofrequency Ablation.....	93
○ Prognosis of Gastrointestinal Stromal Tumors	95
○ Survival Rate of Gastrointestinal Stromal Tumors	97
• Summary	98
• References	102
• Arabic Summary	--

List of Figures

Fig. No	Title	Page
1.	Hematoxylin and eosin of malignant gastrointestinal stromal tumor (GIST) with epithelioid morphology.....	8
2.	Microscopic appearance of the malignant tumor with highly cellular areas consisting of predominantly epithelioid cells.....	10
3.	Endoscopic image of GIST in fundus of stomach, seen on retroflexion	11
4.	Same GIST seen on forward view of the endoscope showing overlying clot.....	15
5.	Histologic spectrum of gastric gastrointestinal stromal tumour	17
6.	Histologic spectrum of small intestinal gastrointestinal stromal tumour (GIST).....	19
7.	Schematic representation of KIT and platelet-derived growth factor receptor alpha (PDGFRA) molecules and KIT and PDGFRA mutations in gastrointestinal stromal tumour (GIST)	24
8.	Examples of KIT positivity in gastrointestinal stromal tumour	33
9.	Important differential diagnoses for gastrointestinal stromal tumor (GIST) with illustrative immunostainings.....	38
10.	Endoscopic image of polyp in small bowel detected on double-balloon enteroscopy.....	39
11.	A large exophytic gastric GIST arises from the greater curve. Transverse view of trans-abdominal sonography	40
12.	Benign GIST of gastric body	40

List of Figures (Cont.)

Fig. No	Title	Page
13.	GIST of the lesser curve stomach	40
14.	Small gastric GIST shown by EUS.....	42
15.	Left parasagittal view of Transrectal sonography shows an exophytic hypoechoic mass arising from the anterolateral wall of rectum	43
16.	Gastric GIST over the lesser curve.....	44
17.	Distal jejunal GIST. Enteroclysis reveals a small submucosal lesion (white arrows) displaces and mildly stretching the ileal loops	45
18.	Gastrointestinal stromal tumour with central bull's eye appearance, which is compatible with contrast material collection in an ulceration	45
19.	Large ileal GIST with central necrosis, cavitation and sinus tract formation.....	47
20.	Gastric GIST arises from greater curve.....	48
21.	Jejunal GIST.....	49
22.	Gastric GIST.....	50
23.	Seventy-year-old male with GIST of the stomach with liver metastases	52
24.	Fifty-six-year-old male with benign GIST of gastric body	53
25.	Seventy-seven-year-old male with a GIST of the gastric antrum and body	54
26.	Twenty-eight-year-old male with duodenal GIST.....	55
27.	Fifty-six-year-old male with GIST of gastric fundus	56
28.	Seventy-year-old male with large GIST of the small bowel mesentry	57

List of Figures (Cont.)

Fig. No	Title	Page
29.	Rectal GIST.....	59
30.	Forty-four-year-old female with GIST of the lesser curve stomach.....	61
31.	Ileal GIST presented with intermittent gastrointestinal bleeding.....	63
32.	Esophagogram shows large, irregular intramural mass.....	64
33.	Gastric GIST arises from the lesser curvature.....	65
34.	Gastric GIST arises from greater curve.....	66
35.	Segmental gastric resection (GIST of the greater curvature).....	70
36.	Laparoscopic resection of 2 cm gastric GIST.....	72
37.	1 Normal esophagus , 2 and 3 esophagectomy	73
38.	Billroth I surgery: before and after.....	75
39.	Billroth II surgery: before and after	76
40.	Roux-en-Y Total Gastrectomy: Before and after	77
41.	Pre-surgery anatomy (top panel) and pancreas-duodenectomy either sparing the pylorus (second panel) or with resection of the pylorus.....	78
42.	Chemical structure of imatinib mesylate.....	83
43.	Hepatic artery embolization of GIST	92
44.	Outlines a proposed treatment algorithm for patients who are diagnosed with GIST in the imatinib era	94

List of Abbreviations

ALK	Anaplastic Lymphoma Kinase
CB	Clinical Benefit
CML	Chronic Myeloid Leukemia
CT	Computed Tomography
DOG1	Discovered on GIST
EUS	Endoscopic Ultrasound
GANTs	Gastrointestinal Autonomic Tumor
GIPACTs	Gastrointestinal Pacemaker Cell Tumors
GISTs	Gastrointestinal Stromal Tumors
HAE	Hepatic Artery Embolization
ICCs	Interstitial Cells of Cajal
MRI	Magnetic Resonance Imaging
PD	Prognosis Disease
PDGFRA	Platelet Derived Growth Factor receptor- α
PET	Positron Emission Tomography
PR	Partial Response
RFA	Radiofrequency Ablation
SD	Stable Disease
SMA	Smooth Musclar Actin
SUVmax	Maximum Standardized Uptake Value
VEGFR	Vascular Endothelial Growth Factor Receptor

Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequent mesenchymal tumors of the gastrointestinal tract (*Hinz et al., 2006*).

Mesenchymal tumors are a family of related tumors including those named plexosarcomas, leiomyoblastomas, leiomyosarcomas, GISTs, gastrointestinal autonomic tumors (GANTs), and gastrointestinal pacemaker cell tumors (GIPACTs) (*Megan et al., 2004*).

In 1941, Golden and Stout described a set of mesenchymal tumors arising in the bowel wall. Under the mistaken assumption that these tumors originated from smooth muscle cells, they designated them as leiomyoblastoma, leiomyoma, and leiomyosarcoma, based on their morphologic appearance (*Muna et al., 2005*).

In the late 1960s and early 1970s, electron microscopy revealed that few of these tumors had evidence of smooth muscle differentiation, an observation that was corroborated later with the addition of immunohistochemistry in the late 1980s (*Rubin, 2006*).

Mazur and Clark proposed the term *stromal tumors* for these mesenchymal lesions because it did not specify a line of differentiation (*Nikolas et al., 2005*).

In 1984, Herrera et al studied a subset of these tumors showing positivity for S100 protein by immunohistochemistry and evidence of schwannian and neuroaxonal differentiation by electron microscopy and proposed the name *plexosarcomas* for them. Later, they become known as *gastrointestinal autonomic nerve tumors* (**Muna et al., 2005**).

In the late 1990s, 2 main approaches were available for dealing with these lesions. One approach classified all mesenchymal tumors of the GI tract as GISTs, regardless of the immunohistochemical profile. The second approach excluded true smooth muscle and neural tumors in an attempt to identify a subset of mesenchymal tumors with unique clinicopathologic features. Although the second approach ultimately proved to be correct, initially its reproducibility was flawed by the lack of a sensitive and relatively specific diagnostic marker (**Fletcher et al., 2008**).

This situation changed drastically in 1998, when Hirota and colleagues discovered that most GISTs harbored c-kit mutations that resulted in full-length KIT proteins with ligand-independent activation. Furthermore, the authors demonstrated that GISTs were usually positive for CD117 (c-kit) by immunohistochemistry. This single discovery changed our understanding of the pathogenesis of GISTs (**Hirota et al., 1998**).

Later, it became clear that a subset of GISTs harbored mutations in the platelet-derived growth factor receptor α

(PDGFRA). The term GIST is currently applied to “specific, generally CD117+ and KIT or PDGFRA mutation driven mesenchymal tumors of the gastrointestinal tract with a set of characteristic histologic features including spindle cells, epithelioid and rarely pleomorphic morphology” according to the definition proposed by Miettinen et al and agreed upon on the GIST workshop held at the National Institutes of Health in April 2001 (*Miettinen et al., 2006*).

Incidence:

GISTs account for 5% of all soft tissue sarcomas, predominantly occur in middle aged and older patients (fifth to seventh decades) (*Barnes et al., 2005*).

The total annual incidence of GISTs or GIST-like tumors increased from 20.8 per million inhabitants in 1995 to 25.4 per million inhabitants in 2003. Simultaneously, the annual incidence of GISTs increased from 2.1 to 12.7 per million inhabitants whereas the annual incidence of GIST-like tumors, mostly leiomyomas and leiomyosarcomas, decreased from 18.7 to 12.7 per million inhabitants. The increased incidence of GISTs may be explained by an improved understanding of the pathobiology of GISTs and the central role of activating KIT mutations in the pathogenesis of GISTs, which led to the recognition of the new and reliable phenotypic marker CD117 antigen. The true incidence of GISTs is probably even slightly higher, including asymptomatic GISTs and small and clinically

insignificant GISTs, which were not biopsied or resected at the time interval studied. The increase in the observed incidence of GISTs until 2000 reflects the increased knowledge on the diagnostic pathology criteria of GISTs but after the introduction of immunohistochemical staining against CD117, the incidence of GISTs seems to be rather stable (*Wim et al., 2005*).

Gastrointestinal stromal tumors may occur anywhere along the length of the digestive tract from the esophagus to the anus. They account for approximately 1–3% of gastric neoplasms, 20% of small bowel tumors and 0.2–1% of colorectal tumors. Approximately 60–70% of the GISTs arise in the stomach, 20–30% in the small intestine, 5% in the colon and in the rectum, less than 5% in the esophagus and Sometimes develop outside the intestinal tract, in the abdominal cavity (*Nikolaos et al., 2005*).

The distribution of GISTs in the stomach is as follows: pars media (40%); antrum (25%); pylorus (20%); submucosa (60%); subserosa (30%); and intramural (10%) (*Leah et al., 2008*).

Risk Factors:

Risk factors and aetiology are unknown, but there is said to be a rare association with neurofibromatosis type I. Some studies show no significant sex difference, whilst others show a male predominance. Most GISTs occur in older patients, typically between the ages of 50–60. Sporadic instances are rare

before the age of forty. However, GISTs can be familial, thus can be present in younger patients (*O'Sullivan et al., 2006*).

Stromal tumors of the gastrointestinal tract have rarely been reported in patients with AIDS. The few sporadic cases are from pediatric and adult patients with AIDS who were diagnosed with malignant GISTs showing smooth muscle differentiation. One study noted an association of these tumors with Epstein-Barr virus and suggested that it may contribute to the pathogenesis of these tumors in patients with AIDS (*Anthony et al., 2005*).

Pathology of Gastrointestinal Stromal Tumors

Until recently GISTs have been subsumed under the group of intra- abdominal leiomyoma, leiomyosarcoma or leiomyoblastoma. However, GISTs have been shown to share certain immunohistochemical features with interstitial cells of Cajal and therefore have been named GANTs (gastrointestinal autonomic nerve tumors) or GIPACTs (gastrointestinal pacemaker cell tumors). More importantly, most GISTs were found to harbor a gain of function mutation of the KIT or PDGFR α receptor tyrosine kinases which best defines GISTs as a separate sarcoma entity. Using modern histopathological and immunohistochemical techniques, a differentiation from other sarcomas can easily be made by an experienced pathologist. The leading immunohistochemical feature is the expression of c-KIT (CD117), besides which CD34 and S100 can often be expressed. KIT expression may not be present in 5% of patients, but the diagnosis if not based on histopathological features alone can be confirmed by mutation analysis of KIT and PDGFR α for which in these cases mutations can be found in 13% and 75% respectively (*Joerg et al., 2006*).

Cells of Origin (Interstitial cells of Cajal):

The cells of Cajal are intercalated between the autonomic nerves and the muscle layers of the gastrointestinal tract, functioning as gastrointestinal pacemaker cells that are

important for the autonomous intestinal motility (*Anthony et al., 2005*).

Interstitial cells of Cajal (ICCs) play important roles, such as the pacemaker that enables cooperative peristalsis or as the mediator of nitric oxide-mediated transmission from nerve terminals to smooth muscle cells in the gastrointestinal tract. Simultaneous expression of specific molecules such as KIT, CD34, the embryonic isoform of myosin heavy chain (SMemb), and nestin in both ICCs and GISTs leads the pathologists to consider that GISTs may develop from ICCs or their progenitor cells (*Shinji et al., 2004*).

GISTs can be classified on the basis of tumor size and mitotic count into very low risk, low risk, intermediate risk, and high risk. Alternatively, they are classified according to site, size, and mitotic activity into 3 categories: benign, malignant, and uncertain or low malignant potential. Gastrointestinal stromal tumors subclassified according to their cellular pattern into spindle, epithelioid, and mixed patterns. A final consensus on GISTs classification has not been achieved, and the biological behavior is often uncertain. Whether borderline GISTs are precursors of malignant GISTs that accumulate genetic alteration during malignant transformation or whether they represent a biologically indolent and distinct subset of GISTs is still uncertain (Figure 1) (*Muna et al., 2004*).

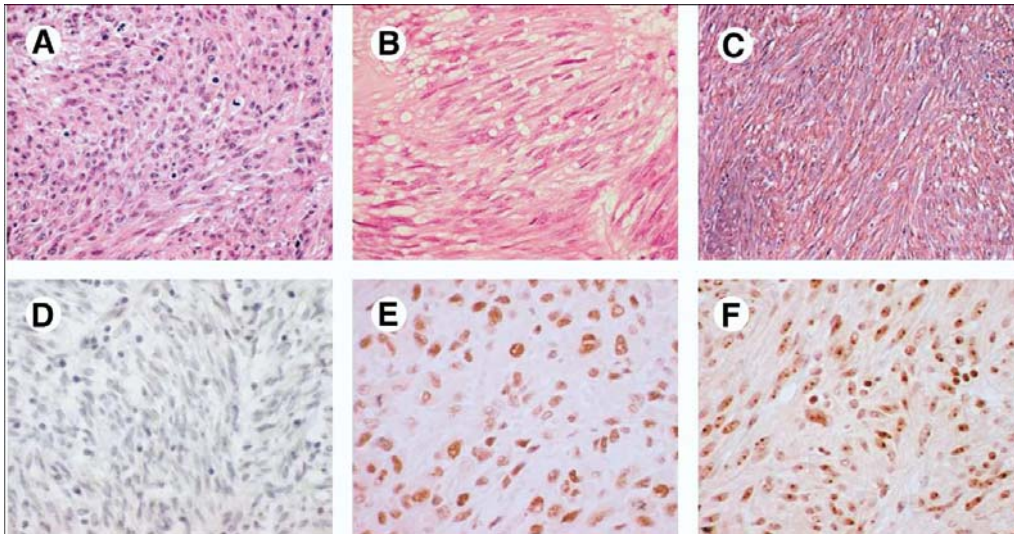


Figure (1): (A) Hematoxylin and eosin of malignant gastrointestinal stromal tumor (GIST) with epithelioid morphology. (B) Hematoxylin and eosin of low-malignant-potential GIST with spindle cell morphology. (C) Diffuse strong positive immunostaining with CD117. (D) Negative human telomerase reverse transcriptase (hTERT) immunostaining in a low-malignant-potential GIST. (E) Strong positive hTERT immunostaining in a recurrent GIST. (F) hTERT staining in a primary malignant GIST showing speckled pattern in the nucleolus. Original magnification, $\times 400$ (*Muna et al., 2004*).

From a prognostic point of view, GISTs have been divided into three prognostic groups: benign, borderline, and malignant. Low-grade GISTs with 1-5 mitoses/50 high-power fields (HPF) have a median survival of 98 months, while high-grade tumors with more than 10 mitoses / 10 HPF have a median survival of 25 months. For patients with a complete resection, histological grading is the major prognostic determinant with 18% 5-year survival rate for high-grade tumors and 72% 5-year survival rate for low-grade tumors. low-