Gastrointestinal Stromal Tumors (GISTs)

Essay

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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 PDGFRα 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 PDGFRα for which in these cases mutations can be found in 13% and 75% respectively ***(Joerg et al., 2006)***.

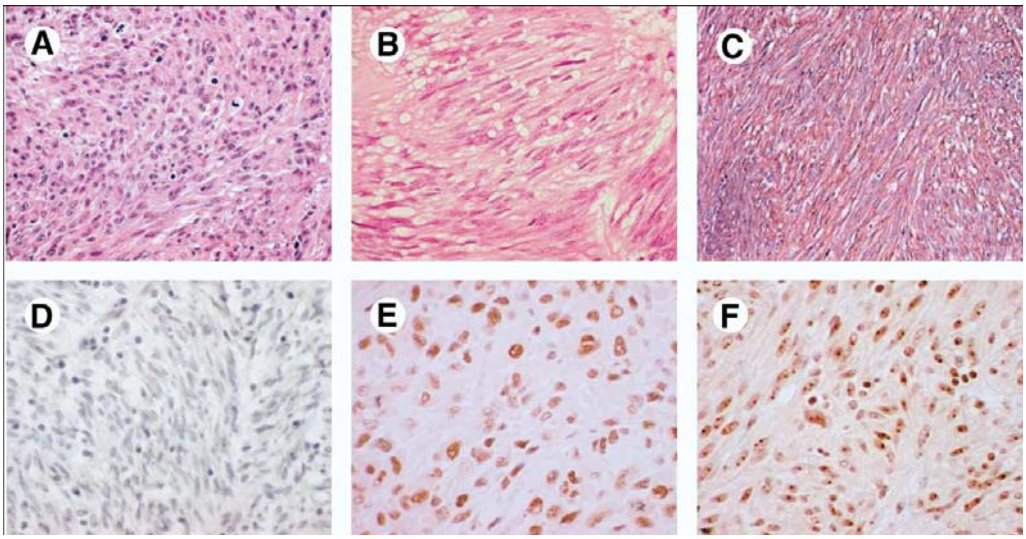
Cells of Origin (Interstitial cells of Cajal):

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)***.



Figue (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, ×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-