GASTRO-INTESTINAL STROMAL TUMORS

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GISTs, the most common mesenchymal tumours of the gastrointestinal tract, hypothetically evolve from a progenitor related to the interstitial cells of Cajal.

The histopathological classification,diagnosis and subsequent treatment of GISTs was revolutionized in 1998 by the discovery that many GISTs harbour a mutation in the KIT receptor tyrosine kinase gene and the demonstration that most GISTs overexpress KIT protein (CD117),which can be demonstrated by immunohistochemistry. And its immunostaining has since become central to the diagnosis of GIST and at one point was considered to have a 'defining role' in GIST diagnosis, it was subsequently demonstrated that up to 20% of GISTs lack a mutation in KIT and that approximately 30% of these cases (approximately 6% of all GISTs) harbour a mutation in a related receptor tyrosine kinase gene called PDGFRA.

Nestin , (PKC-theta) ,SMA,CD171 are sensitive but not specific markers of GIST, currently, DOG1 is the most specific and sensitive immunohistochemical marker of GISTs, with a low false positive rate of (<1%)in spindle cell tumours.

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AES	Adverse effects
ATRA	All-trans retonic acid
CD117	Cluster designation 117
CD34	Cluster designation 34
CML	Chronic Myeloid Leukemia
CT	Computed Tomography
DOG1	Discovered on GIST
EGISTs	Extra gastrointestinal stromal tumors
ESMO	European society for medical oncology
EUS	Endoscopic Ultrasound
EUS-FNAC	Endoscopic ultrasound assisted fine needle Aspiration cytology
FDA	Food and drug administration
FDG–PET	Fluoro-deoxy Glucose positron emission tomography
GANTs	Gastrointestinal Autonomic Tumor
GIPACTs	Gastrointestinal Pacemaker Cell Tumors
GISTs	Gastrointestinal stromal tumours
GIT	Gastrointestinal tract
HK1	Human tissue kallikrein 1
ICCs	Interstitial Cells of Cajal
IGF1R	Insulin-like growth factor 1 receptor
IHC	immuno-histochemistry

KIT	Tyrosine kinase receptor
LOH	Loss of heterozygosity
Maspin	mammary serine protease inhibitor
MRI	Magnetic Resonance Imaging
NCCN	National comprehensive cancer network
NF1	Neurofibromatosis type 1
OS	Overall survival
PDGFRA	Platelet Derived Growth Factor receptor-α
PET	Positron Emission Tomography
PFS	Progression free survival
PKC-theta	Proteine kinase C theta
SMA	Smooth Musclar Actin
STUMP	smooth muscle tumour of uncertain malignant potential
TKIs	Tyrosine kinase inhibitors
VEGFR	Vascular Endothelial Growth Factor Receptor

INTRODUCTION

Gastrointestinal stromal tumours (GISTs), the most common mesenchymal tumours of the gastrointestinal tract, hypothetically evolve from a progenitor related to the interstitial cells of Cajal. ***(Joensuu 2006).***

Golden and Stout(1941) 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)***.

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 GIT 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)***.

In 1996, Rosai divided GISTs into four major types: smooth muscles, neural, combined smooth muscle-neural, and uncommitted. Recent studies have reported GISTs cells demonstrating characteristics similar to those of interstitial cells of cajal (ICC),or pacemaker cells which play a neuromotor role in normal gut motility ***(Ken-ichi M et al.,2006).***

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)***.

Gastrointestinal stromal tumours typically show expression of cluster designation 117 known as (CD117) in (95%) and frequently cluster designation 34 known as (CD34) in (70%) and these antigens can be demonstrated by immunostaining, yet a small fraction of GISTs lack both diagnostic markers ***(Hornick & Fletcher 2007).***

Identification of KIT-activating mutations as a key factor in the pathogenesis of GIST has substantially altered the diagnosis and treatment of GIST. ***(Miettinen & Lasota, 2006)***

Approximately 5 – 7 percent of GIST patients have mutations in another protein receptor called PDGFR, or platelet-derived growth factor receptor ***(Heinrich et al., 2008)***

Approximately 10–15% of GISTs that arise in adults lack detectable mutations of Tyrposine kinase receptor (KIT) or PDGFRA (referred to as wild-type GISTs). Notably, wild-type genotype is a characteristic feature of the vast majority of GISTs, which are diagnosed in children and adolescents and GISTs associated with familial syndromes such as

neurofibromatosis, Carney–Stratakis syndrome or the Carney Triad ***(Miettinen & Lasota, 2006).***

Recently, mutations of genes that encode for enzymes of the mitochondrial succinyl dehydrogenase complex, have also been found to be mutated in patients with pediatric GIST and Carney-Stratakis syndrome ***(Pasini B et al., 2008).***

KIT negative GISTs have a predilection for the stomach and omentum and are most commonly epithelioid or mixed cell in type. Most KIT-negative GISTs harbour PDGFRA mutations (80%) ***;*** the others contain KIT mutations***.(Corless et al., 2005)***

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

Historically, GISTs were misdiagnosed or went undiagnosed, but GISTs is now recognised as having a much higher incidence than previously thought. Under the current, widely accepted definition of Gastrointestinal stromal tumors as a distinct molecular and pathologic entity. Population-based studies reported GIST annual incidence rates ranging from 6.5 to 14.5 per million ***(Joensuu 2006).***

The most common sites of origin for GISTs are stomach (39–70%) and small intestine (31–45%), but GISTs may arise anywhere along the gastrointestinal tract or within the abdomen as extragastrointestinal tumours ***(Demetri et al., 2007).***

Due to the fact that these tumors are commonly fast-growing, they gradually outgrow their blood supply, create central necrosis and, subsequently, develop a fistulous connection into the GIT ***(Miettinen M et al., 2006)***

GISTs are a heterogeneous group of tumors, showing wide diversity with respect to activating mutations in KIT or PDGFRA and ranging across a wide spectrum from small indolent tumors to aggressive cancers ***(Din, O.S.; Woll, P.J. 2008).***

The manifestations of GISTs vary widely. In a population based study, 70% of patients were symptomatic, 20% were asymptomatic, and 10% were detected at autopsy ***(Gold J et al., 2006)***.

Complete surgical resections, achieving negative margins whenever possible (R0 resection), remain the standard approach for the initial management of primary localized GIST. In patients with locally advanced and/or metastatic GIST, the introduction of targeted tyrosine kinase inhibitor (TKI) therapy revolutionized the management of this previously untreatable neoplasm ***(Blanke CD et al., 2008).***