Abstract  Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. They are defined here as KIT (CD117, stem cell factor receptor)-positive mesenchymal spindle cell or epithelioid neoplasms primary in the GI tract, omentum, and mesentery. GISTs typically present in older individuals and are most common in the stomach (60–70%), followed by small intestine (20–25%), colon and rectum (5%), and esophagus (<5%). Benign tumors outnumber the malignant ones by a wide margin. Approximately 70% of GISTs are positive for CD34, 20–30% are positive for smooth muscle actin (SMA), 10% are positive for S100 protein and <5% are positive for desmin. The expression of CD34 and SMA is often reciprocal. GISTs commonly have activating mutations in exon 11 (or rarely exon 9 and exon 13) of the KIT gene that encodes a tyrosine kinase receptor for the growth factor named stem cell factor or mast cell growth factor. Ligand-independent activation of KIT appears to be a strong candidate for molecular pathogenesis of GISTs, and it may be a target for future treatment for such tumors. Other genetic changes in GISTs discovered using comparative genomic hybridization include losses in 14q and 22q in both benign and malignant GISTs and occurrence in various gains predominantly in malignant GISTs. GISTs have phenotypic similarities with the interstitial cells of Cajal and, therefore, a histogenetic origin from these cells has been suggested. An alternative possibility, origin of pluripotential stem cells, is also possible; this is supported by the same origin of Cajal cells and smooth muscle and by the common SMA expression in GISTs. GISTs differ clinically and pathogenetically from true leiomyosarcomas (very rare in the GI tract) and leiomyomas. The latter occur in the GI tract, predominantly in the esophagus (intramural tumors) and the colon and rectum (muscularis mucosae tumors). They also differ from schwannomas that are benign S100-positive spindle cell tumors usually presenting in the stomach. GI autonomic nerve tumors (GANTs) are probably a subset of GIST. Other mesenchymal tumors that have to be separated from GISTs include inflammatory myofibroblastic tumors in children, desmoid, and dedifferentiated liposarcoma. Angiosarcomas and metastatic melanomas, both of which are often KIT-positive, should not be confused with GISTs.

Keywords  Gastrointestinal stromal tumors · Smooth muscle actin · GI tract · GI autonomic nerve tumors

Introduction

Gastrointestinal stromal tumors (GISTs) are specific mesenchymal tumors of the GI tract that may occur in the entire length of the GI tract, from the esophagus to the anus and, sometimes, even in the omentum and mesentery adjacent to but separate from the stomach and intestines. These tumors have a wide clinical spectrum from benign, small, incidentally detected nodules to frankly malignant tumors. The recent understanding on their molecular pathogenesis, namely common presence of activating mutations in the gene encoding KIT, may have significant clinical importance, making it necessary to accurately define and clinically diagnose these tumors and separate them from other mesenchymal tumors of the abdomen.

In the earlier literature, GISTs were designated as smooth muscle tumors: leiomyomas, cellular leiomyomas, leiomyoblastomas, and leiomyosarcomas [2]. However, electron microscopic studies in the 1960s demonstrated a lack of typical smooth muscle differentiation in...
gastric leiomyoma [78]. Mazur and Clark [35] found that the GI mesenchymal tumors of the stomach, formerly defined as leiomyomas, lacked immunohistochemical features of Schwann cells (S100 protein negative) and did not have ultrastructural characteristics of smooth muscle cells. Therefore, these authors used the histogenetically neutral designation “gastric stromal tumors”, which subsequently has become applied to other, similar tumors in the intestines, and GIST has become the widely applied term now used on the specific mesenchymal tumors of the GI tract.

Because the majority of all mesenchymal tumors of the GI tract (except esophagus) are GISTs, older data on gastric and intestinal smooth muscle tumors [1, 17, 53, 67] largely reflect GISTs. This review will discuss the definition, clinical behavior and prognostic factors, and histological and immunohistochemical spectrum of GIST, pathogenesis and genetics, and the relationship between GISTs and smooth muscle tumors and GISTs and GANTs. The differential diagnosis of GISTs from other mesenchymal tumors of the GI tract will also be discussed.

**Definition of gastrointestinal stromal tumors**

Gastrointestinal stromal tumors (GISTs) are defined here as cellular spindle cell, epithelioid, or occasionally pleomorphic mesenchymal tumors of the gastrointestinal (GI) tract that express the KIT (CD117, stem cell factor receptor) protein, as detected using immunohistochemistry. The majority of GI mesenchymal tumors are GISTs and are strongly and nearly uniformly KIT positive. Relative few other tumors may also be KIT positive, but these tumors, metastatic melanoma, angiosarcoma, pulmonary small cell carcinoma, Ewing sarcoma, some other carcinosmas, mastocytoma, and seminoma, only rarely enter in the differential diagnosis of GISTs [3, 42, 44, 48, 72].

This definition specifically excludes gastrointestinal true smooth muscle tumors (leiomyomas and leiomyosarcomas) and schwannomas and neurofibromas. There is a small, somewhat problematic group of tumors that are in the histological range but do not express KIT. These undifferentiated mesenchymal tumors typically lack all other cell-type markers employed in the differential diagnosis of GIST [CD34, smooth muscle actin (SMA), desmin and S100-protein]. The classification of such tumors with a “null-phenotype” is open. Some investigators may include them among GISTs (when applied in a broad sense), whereas others may exclude them. Correlated morphologic and molecular genetic studies are necessary to determine whether or not these tumors biologically belong to the GIST group.

**Epidemiology**

According to a population-based sample, we estimate the incidence of GISTs as 10–20/million. Of these, 20–30%