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Gastrointestinal stromal tumors: A review and considerations on histogenesis and differential diagnosis

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Gastrointestinal stromal tumors (GISTs) represent the most common mesenchymal tumors of gastrointestinal tract (up to 85%), most frequent non-epithelial tumors of digestive tract (42%) and the most important group of all intra-abdominal spindle cell tumoral lesions (10% of all GISTs). Initially, these gut tumors were presumed to be of "true" smooth muscle origin with histologically similar extra-gastrointestinal counterparts. Contrary, the term GIST was later used only for gut tumors with no clear morphological and/or immunohistochemical features of smooth muscle or neural differentiation. Two distinctive subsets of these tumors were previously excluded on the basis of ultrastructural and immunohistochemical analyses as leiomyoblastoma, mostly and inconsistently expressing features of myogenic differentiation, and as plexosarcoma or gastrointestinal autonomic nerve tumors GANT showing autonomic nerve - like morphologic features on electron microscopy. However, further investigations showed strong and diffuse CD34 (hematopoietic progenitor cell antigen) immunopositivity in majority of GISTs and confirmed GIST as a new entity regarding clinicopathologically similar group of tumors with morphological variants. Since expression of CD117 (transmembrane receptor encoded by the *c-kit* gene) was being consistently found in GISTs by Kindblom et al. in 1998, a new era of understanding of GISTs` biology entered modern oncology. Tumorigenic gain-of-function mutations in the juxtamembranous domain of the *c-kit* gene provoke activation of the CD117 receptor and a significant correlation was found between *c-kit* mutations and the malignant potential of CD117 expressing GISTs.

In keeping with this, GISTs are currently defined as *c-kit*/CD117 expressing and c-kit signaling driven mesenchymal tumors, often with *c-kit* activating mutations. This designation includes both c-kit (immuno)expression and *c-kit* mutations. The former concerns differentiation toward interstitial cells of Cajal, and the later concerns *c-kit* protein (tyrosine kinase receptor) as a single target molecule, to which a specific chemotherapeutic is directed (signal transduction inhibitor, STI-571). *c-kit* signaling pathways are known to regulate many aspects of cellular behavior, including proliferation, apoptosis, adhesion and differentiation. Mutations of *c-kit* gene activate kit protein (tyrosine kinase receptor) that stimulates proliferation of GIST tumor cells and may inhibit apoptotic cell death. The advent of new adjuvant therapeutic agent, STI-571 (imatinib (Gleevec®); Novartis, Basel, Switzerland) reduce *c-kit* tyrosine kinase activity and seems to be very promising treatment of metastatic GISTs. This put attention to histogenesis and molecular pathology of GISTs and in pragmatic way determine the proper selection of patients for this therapy and even the possibility to use it in nonmetastatic GISTs with malignant potential. Thus, GISTs could be considered as a prototype of modern oncopathology and single molecule targeted chemotherapy.

Clinical and epidemiological studies revealed slight male preponderance, mostly found in fifth and sixth decades with estimated incidence of GISTs as 10-20/million with 20%-30% malignant biological behavior. They are most commonly found in the stomach (60%-70%) followed by small intestine (20%-30%), colon and rectum (5%) and esophagus (less then 5%). In addition, about 10% of GISTs seem to appear in some extra-GI sites, mostly in the omentum, mesentery and retroperitonenum. They are often found incidentally, but can provoke dysphagia, GI bleeding, pain, obstruction or vague symptoms. Gross pathology is presented as well circumscribed, but not encapsulated polypoid, nodular (often ulcerated on mucosal side) or (semi)cystic transmural or submucosal/subserosal mass. Combination of simultaneous exophytic and endophytic growth sometimes produces so-called dumbbell form with intact serosal but not mucosal protuberant surface. Histomorphology reveals wide spectrum of architectural (fascicular, whorled, storiform, palisading, nested or compact and patternless) and cellular appearances with two principal patterns: a spindle cell in about 60%-70% of cases and an epitheloid in about 30% of GISTs, including combination of both types. Not so rarely solid, myxoid, nest-like, even round cell or giant-cell types could be seen. Some GISTs, many of which in small bowel show characteristic skeinoid fibers of unclear histogenesis, often believed to represent extracellular collagen globules. Furthermore, perinuclear vacuolization, clear abundant or amphophilic, even oncocytic cytoplasm could be present more often with epithelioid cellular type. Nuclear pleomorphism is not prominent feature, but could be seen as well as multinucleation. Stromal edema, hemorrhage, necrosis, and pseudocystic degeneration are more often seen with growing size of GISTs.

Prognosis and biological behavior remain problematic both to pathologist and clinician, as no single parameter or group of criteria can reliably predict malignancy. Contrary, it appears that all GISTs are potentially malignant. Small or mitotically inactive GISTs showed "benign" metastases, but quite large tumors showed more indolent clinical course. Only large, highly pleomorphic and obviously high-graded sarcomatous appearances could be found as predictive for rapid peritoneal seeding or hepatic metastases (rarely in lungs and bones). Moreover, GISTs seem to be site dependent with distal localization as prognostically worse. In keeping with it, current prognostication respects proximal (gastric) and distal (intestinal) site as a basis for estimation of probable benign, probable malignant or uncertain (intermediate, borderline, low-risk) malignant potential. Mitotic activity up to 5 or more than 5 mitoses on 50 HPF (400x) found to be discriminatory in a combination with tumor size up to 2 cm, 2 cm to 5 cm, and more than 10 cm. In recently proposed approach, in a category of less 5 mitoses / 50 HPF two subgroups were recognized: very low risk (size less than 2 cm) and low risk (2-5 cm). Intermediate risk GISTs should be categorized if only one parameter has a value "more than 5" (size in centimeters or mitotic count per 50 HPF) and high-risk GISTs if both have value "more than 5" or anyone has value "more than 10". In addition, several studies showed Ki-67 labeling index very helpful and *c-kit* mutations are associated with aggressive features. Also, immunohistochemical phenotype towards some "committed or specialized" cellular type, i.e. smooth muscle or neuroglial/schwannian differentiation could favor slightly better prognosis than those without or showing "uncommitted or precursor" type such as CD117, CD34 or "null" phenotype, irrelevant to simultaneous coexpression of "spe-

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cialized" immunoprofiles. For instance many GISTs bearing CD34 positivity are highly malignant and associated with colorectal and esophageal site of GISTs and epithelioid cell morphology.

Immunohistochemical and ultrastrucural similarities of GISTs and interstitial cells of Cajal proposed histogenetic origin of these tumors. Interstitial cells of Cajal are known as autonomic nerve related GI pacemaker cells that regulate gut motility and shows features of between or both smooth muscle and nerve cells. Hence, GISTs were designated as "pace maker cell tumors" (GIPACT) to separate from term GIST which originally relates to non-myogenic non-neurogenic GI mesenchymal tumor. In the same manner histological distinction was made previously for GANT cases with autonomic nerve-like differentiation. The origin of GISTs was suggested from CD34 positive subset of Cajal cells and/or immature mesenchymal cells or from a common precursor (multipotential) cell. Furthermore, interstitial cell of Cajal itself can differentiate into smooth muscle cell and can serve as a precursor cell. Immunophenotypic characterization of GISTs made recently great progress to both practical (oncological) and possible histogenetic classification. The former includes only GISTs with known c-kit driven pathogenetic pathway i.e. with strong diffuse expression of *c-kit*/CD117 (stem cell factor receptor), separating them from not so small subgroup of *c-kit*/CD117 negative GISTs with possible other (unknown) or additional pathogenetic pathways, such as involvement of PDGFRA (Platelet derived growth factor receptor- alpha) activating mutations. In fact, many of "true" GISTs have focal/mosaic or cytoplasmic "dot-like" positivity in "majority" of cells and show (co)expression of CD34, smooth musce actin (SMA), nestin, h-caldesmon (but not calponin) and/or embryonic myosin, rarely and/or focally desmin and S-100 protein. Still, "true" GISTs comprise a separate oncological entity concerning activating *c-kit* protein inhibition by imatinib mesylate (Gleevec). Partially successful and time limited responses in many (not all) kit-driven GISTs generate further questions on molecular and histomorphological pathogenesis and diversity of GISTs. Is tumor morphology related to differentiated grade of some precursor cell (histogenetic model) and does it make sense after the advantage of c-kit protein activation inhibition?

Considerations on differential diagnosis (clinical, histological and immunohistochemical simulation) of GISTs are also associated to *c-kit*/CD117 immunoexpression. At first, there are several well recognized groups of tumors which does not express CD117 and/or CD34 positivity and most often have distinctive morphology, such as true leiomyo(sarco)ma, schwannoma, dedifferentiated liposarcoma, inflammatory myofibroblastic tumor (inflammatory pseudotumor) or its hypercellular variant (inflammatory fibrosarcoma), spindle cell carcinoids, spindle cell carcinomas and mesenteric fibromatosis (intraabdominal desmoid), or expressing only CD34 immunopositivity (inflammatory fibroid polyp of Vanek). On the other side are tumors expressing *c-kit*/CD117 immunopositivity such as (spindle cell) metastatic melanoma, angiosarcoma, clear cell sarcoma, Ewing sarcoma, germinoma, some carcinomas (endometrial, pulmonary small cell anaplastic carcinoma), and lymphomas (anaplastic large cell, acute myeloid leukemia, mastocytosis).

CONCLUDING REMARKS

In conclusion, the term/diagnosis GIST should not mean only CD117-positive stromal tumor of gastrointestinal tract. In our opinion GISTs should include all cases of abdominal tumors showing: histologic features resembling GISTs with spindle and/or epithelioid cellular morphology, strong diffuse *c-kit*/CD117 and/or CD34 immunoexpression or a lack of both (only vimentin-positive, so-called "null" immunophenotype) in any non-inflammatory GIST-like tumor, i.e. other than those which show significant specific cell-lineage expression. In addition, we stand for this immunophenotypic (histogenetic) classification as it probably better correlate prognosis and metastatic potential in respect to well-established prognostic importance of mitotic rate, tumor size, site and Ki-67 labeling index. Moreover, genetic identification of *c-kit* activating mutations found in most but not all *c-kit*/CD117 positive GISTs are far from routine in vast majority of diagnostic laboratories. Strictly speaking, GISTs are understood only as *c-kit* signaling driven tumors, but this does not always follow *c-kit*/CD117 immunoexpression in GISTs and other possible *c-kit* driven tumors. It seems also that some tumors could be treated successfully with imatinib in inconsistent *c-kit*/CD117 expression, since expression without mutation and vice versa is quite possible. Furthermore, suboptimal *c-kit*/CD117 immunostaining as well as false results could misinterpret or rule out "true" GISTs diagnosed by a single criterion.

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