

Immunohistochemistry Division

8267 Elmbrook, Suite 100, Dallas, Texas 75247-4009

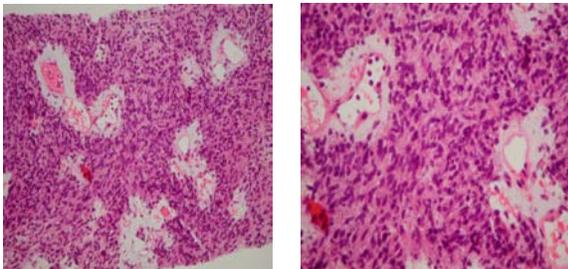
Lab (214) 638-2000, ext 2037, Fax (214) 237-1730

<http://www.propathlab.com/> E-mail: rmiller@propathlab.com

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GASTROINTESTINAL STROMAL TUMORS (GIST)

Gastrointestinal stromal tumor (GIST), broadly defined, is the most frequently occurring non-epithelial tumor of the stomach and small bowel. Despite that, there remains a certain aura of mystery about these tumors which fosters confusion among pathologists and clinicians alike. Much of this has to do with their confusing nosology and the confusing terminology that has grown out of that such as GANS, GANT, and plexosarcoma. The inability to accurately predict tumor behavior based on its histomorphology adds further mystery. Another source of confusion relates to the observation that these tumors may be located outside the GI tract and present as soft tissue masses in the omentum, mesentery and retroperitoneum. Thus, GIST should be considered in the differential when the pathologist is presented with a soft tissue mass with spindle cell morphology arising in these sites. Pictured below is a typical GIST. This tumor presented as a primary retroperitoneal mass, and was not considered in an otherwise exhaustive differential presented by the submitting pathologist because of its location.



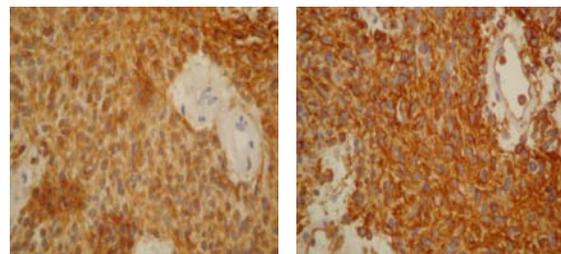
Note the monotonous spindle cell morphology with a tendency for nuclear palisading.

For some time this neoplasm has been known to arise from an undefined cell population located within the muscular wall of these organs. This origin within the muscular wall was felt to account for the curious “dumbbell” shape the tumor was often noted to have on gross and microscopic examination. The cell of origin was considered to be pluripotential, giving rise to mesenchymal tumors that varied considerably in their differentiation. Naturally, this resulted in considerable nosologic confusion.

In the past GIST's were considered to be of smooth muscle origin, and were classified as leiomyomas, leiomyoblastomas and epithelioid leiomyomas or leiomyosarcomas or as neural depending upon the

dominant morphologic features as studied by light and electron microscopy (EM). With the advent of immunohistochemical (IHC) methods the immunomorphologic features of these tumors have revealed an even more complex nosology than was heretofore appreciated.

Four basic broad subgroups of gastrointestinal stromal tumor have been defined based upon morphology and immunophenotype and have constituted the working paradigm of this lesion for most pathologists until recently. The first and most common group shows smooth muscle differentiation as evidenced by EM and immunostaining for desmin and muscle-specific actin (HHF-35). The second most common group is said to show gastrointestinal autonomic neural differentiation (GANS or GANT) as defined primarily by EM features. Most of these tumors have been negative for S-100 protein, neurofilament protein, chromogranin, and synaptophysin. Tumors which express both smooth muscle and neural differentiation comprise the third group, defined by IHC & EM criteria. Finally there remains a relatively small, “uncommitted” group which expresses no definite smooth muscle or neural differentiation. It is this subgroup which has come to be called GIST by most investigators recently. A high proportion of this group of neoplasms has been found to express the CD34 stem cell ligand.



CD117 (c-kit)

CD34

High power view showing prominent cytoplasmic staining for CD117 (c-kit) and surface membrane expression of CD34 ligand.

Study of this group of tumors and understanding of their nosology has been revolutionized recently by the observation that the true GIST, as narrowly defined, is characterized by uniform (100%) expression of the c-kit

proto-oncogene (CD117) receptor while only slightly more than 75% of the tumors are CD34 positive.

CD34 is the ligand of the tyrosine kinase encoded for by c-kit during embryogenesis, and this interaction is essential for the development of hematopoietic stem cells, melanocytes, mast cells and the interstitial cells of Cajal (ICC), among other cell types, during embryogenesis. Recent investigations have shown that the gastrointestinal stromal tumor differentiates toward an ICC phenotype. This and other work has led to a rethinking of the broad concept of GIST described above, resulting in revision of the old concept of the four groups of gastrointestinal stromal tumor.

The ICC have been known for over 100 years since their discovery by histochemical studies where they were found intercalated between the Auerbach myenteric neural plexus and the smooth muscle of the GI tract wall. They have been known to have a pacemaker function since the early 1980's. In the normal ICC the cells are always CD117 positive, but only a small fraction stain with anti-CD34. In the tumor itself and in the hyperplastic (or pre-neoplastic) ICC nodules near the tumors, the CD34 ligand is strikingly upregulated, suggesting that this has something to do with the neoplastic transformation of these cells. The ICC are felt to be derived from smooth muscle cells, much like the cardiac conduction system represents modified cardiac myofibers. As such they show immunohistochemical and ultrastructural evidence of both myoid and neuroid differentiation. In the paper by Kindblom, et al the 78 GI stromal tumors which they studied showed a spectrum of ultrastructural and immunohistochemical features which are identical to those observed in different subsets of ICC. That is, some of the tumors showed primitive myoid differentiation (10/78 cases), and some showed GANT-like differentiation (synapse-like structures by EM in 6/78 cases) while others showed a mixed phenotype. Neither the type of differentiation or the presence or absence of the CD34 ligand in these tumors correlated with their clinical behavior (benign vs. malignant). The expression of CD34 also did not correlate with the histomorphology, ultrastructural or other IHC features of these tumors. These observations suggested to the authors that GI stromal tumors represent a single entity with a wide morphologic spectrum and varying degrees of differentiation toward an ICC phenotype. They proposed the term GIPACT (GI Pacemaker Cell Tumor) as a unifying concept for the tumor as it has been narrowly defined, i.e., c-kit positive and showing no obvious neural (including schwannian), smooth muscle (other than the SMA positivity & EM evidence of actin-like filaments), or other differentiating features.

Unfortunately, these new markers serve only to help in the diagnosis of this tumor, and are not predictive in any way of the biologic behavior of an individual tumor. For that we must rely on the usual morphologic features of size, location, mitotic activity, hypercellularity, nuclear atypia and necrosis. Currently, those stromal tumors showing only neural differentiation (GANS or GANT) have been considered to be malignant, although only 58% of the tumors in the series reported by Lauwers, et al from Memorial Hospital in New York exhibited malignant behavior. They found that aggressive clinical behavior of the tumors they termed GAN's correlated with tumor size

of > 10 cm, and a mitotic rate of $\geq 5/10$ HPF. Kindblom, et al. considered their 6 cases that were classified as GANT to probably represent a more differentiated variant of GI stromal tumor, also originating from the ICC. They classified their GIPACT tumors as benign, intermediate or malignant based upon mitotic activity ($\geq 5/50$ HPF), necrosis and hemorrhage, nuclear atypia and degree of mucosal infiltration, features which have long been used to predict biologic behavior in tumors of all types.

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- Marc Hapke, MD
Dermatopathologist and Immunopathologist
214 237-1620
E-mail: mhapke@propathlab.com