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Microscopic features and immunohistologic characterization of gastrointestinal stromal tumors

KEYWORDS: Gastrointestinal Neoplasms; Stromal Cells; Muscle, Smooth; Immunohoistochemistry; Microscopy; Proto-Oncogene Protein c-kit

ABSTRACT

Gastrointestinal stromal tumor (GIST) is a neoplasm that exhibits differentiation to a specific type of cells in the gastrointestinal tract. The cell lineage of GI mesenchymal tumors has been debated for a long time. Many recent studies found these tumors be neither muscle cell or schwannian in nature of the basis of immunohistochemical investigations. Now, is known that GIST originates from ICC, located between the circular and longitudinal layers of the muscularis propria, intimately associated with or enclosing Auerbach's ganglia, performing a pacemaker function. GIST also are known for their variability in clinical behavior and for the difficulty in determining their malignant condition. Gastrointestinal autonomic nerve tumor (GANT) represents GIST type with neutral differentiation. Its identification as a subgroup of stromal tumors rests mainly on ultrastructural identification of tumor cells. A panel of antibodies are used to characterize the histogenesis and differentiation of the GI tract GISTs. By using selected lineage-directed monoclonal antibodies for smooth muscle cells (pan-muscle actins, HHF-35, SMA and desmin), SCHwann cells (S-100 protein), enteric glial (glial fibrillary acidic protein-GAFP), and nerve cells (neurofilaments) in order to characterize immunohistologically this preplexing group of tumors. All GISTs reveal strong homogenous immunoreactivity for the c-Kit receptor, as does ICC of adjacent and control GI walls. CD34 antigen, a myeloid cell progenitor cell antigen, identified the majority of stromal tumors and aids in their distribution from GI leiomas and shcwannomas, which are CD34 negative. It has been concluded that GI stromal tumors show striking morphological and immunophenotypic similarities with ICC and that they may originate from stem cells that differentiate toward pacemaker cell phenotype.

DEFINITION

Gastrointestinal stromal tumor (GIST) is the most frequent nonepithelial neoplasm in the stomach and intestine. In the past, GIST was simply believed to be smooth muscle in origin based on histological features (1). Subsequent immunohistochemical and ultrastructural studies have shown that the tumors consist of mesenchymal cells with or without differentiation to smooth muscle cell, neuronal cell, or both, thus casting doubt on the uniformity of GIST. However, the possibility has recently been raised that GIST is a neoplasm that exhibits differentiation to a specific type of cells in the gastrointestinal (GI) tract (2,3).

HISTOGENESIS

Despite numerous studies, GISTs remain problematic with regard to origin, differentiation, nomenclature and prediction of prognosis. Their morphological spectrum is wide, ranging from bland to frankly malignant tumors with spindled and/or epitheloid appearances. Hence, a variety of names such as epitheloid or bizarre leiomyomas, epitheloid leiomyosarcomas or leiomyoblastomas, and gastrointestinal autonomic nerve tumors (GANT) have been used for these tumors reflecting the various views regarding their differentiation, classification, and prognosis. The cell lineage of GI mesenchymal tumors has been debated for a long time. Many recent studies found these tumors be neither muscle cell of schwannian in nature on the basis of immunohistochemical investigations (2).

INTERSTITIAL CELLS OF CAJAL

The existence of a complex system of interstitial cells of Cajal (ICC), which are intercalated between the autonomic nerves and the muscle walls of the GI tract, has been known for over 100 years. Now, is known that ICC have a pacemaker function (3,4,). Most ICC are located between the circular and longitudinal layers of the muscularis propria, intimately associated with or enclosing Auerbach's ganglia, and sprouting out into the smooth muscle walls. Typically these cells are spindled or stellate and somewhat enlarged compared with corresponding cells in the nontumor controls, having more abundant cytoplasm and hyperchromatic, large nuclei with prominent nucleoli (5,6). GIST also are known for their wide variability in clinical behavior and for the difficulty in determining their malignant condition. A large number of cases with complete follow-up are needed to establish reliable criteria of malignancy in the GIST. The current study is designed to elucidate the histogenesis of these tumors, by using various immunohistochemical markers, and to identify parameters that will help in establishing the criteria of malignancy in the GIST.

CATEGORIZATION OF THE TUMORS

The GI mesenchymal tumors form a heterogeneous group that consists of several different entities with distinctive clinicopathological profiles. The main entities include benign leiomyomas and schwannomas, and the group of less differentiated tumors is often referred to as GISTs (1,2,5,7,8); a noncommittal term that reflects the incomplete understanding of their cell lineage and uncertain relationship with the differentiated smooth muscle and Schwann cell tumors. On the basis of previously published experience, the tumors are assigned to categories of histological malignancy on the basis of mitotic counts as follows: benign 2, borderline 2-5, and malignant 5 mitoses/10 high-power field (HPF, single field area of 0,20 mm2) (5,9); as an exception, one mitotically inactive epitheliod tumor is considered malignant because of its large size 6 cm in diameter. The tumors were histologically categorized into spindle cell and epitheloid groups on the basis of the predominant morphological pattern (9).

GIST with Spindle Cell Pattern: Histologically Benign (<2 Mitoses/10 HPF). Very often they are small incidental nodules on the gastric serosa, to 1,5 cm in diameter. The others are located in the muscular wall or protruding in the lumen, often presenting with gastrointestinal hemorrhage, and measured 3-15 cm in diameter. The majority of these tumors are located in the stomach, then

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in the small intestine, but rarely in the other parts of the GI tract (8). None of the studied cases that had follow-up showed metastases (2,8). Histologically, these tumors showed high cellularity and were composed of elongated spindle cells showing nuclei with tapered ends. Sometimes the nuclei were arranged in a palisading fashion, and some cases showed a semi-organoid clustering of the tumor cells. There was variable collagenous-appearing matrix and calcifications in some cases. The cases of GIST were typically more cellular than ordinary leiomyomas and did not show cytoplasmic eosinophilia. Histologically Borderline (3-5 Mitoses/10 HPF). Mostly of them measured more than 5 cm in diameter. Sometimes, they give multiple intra-abdominal metastases. Malignant GIST, Spindle Cell Pattern (>5 Mitoses/10 HPF). These tumors are highly cellular showing spindle cell morphology with pleomorphic features; mitoses 10/10 HPF with metastases in the omentum, liver or both (8,9). GIST, Epitheloid Pattern: Histologically, the epitheloid tumors show clusters and sheets of polygonal, epitheloid-appearing cells with ample cytoplasm, often with a markedly vacuolated cytoplasm. They correspond to the previous designation leiomyomblastoma. Malignant GIST, Epitheloid Pattern (>5 Mitoses/10 HPF or Size 6 cm in Diameter). They give metastases in omentum or liver (9).

MICROSCOPIC FEATURES OF MALIGNANT POTENTIAL OF GISTs

(1) mitotic rate: which was determined by counting mitotic cells seen in 50 consecutive high-power fields (HPF) (x 400) of active areas of a tumor; (2) nuclear atypia, which was classified as none, slight, or marked; and (degree of cellularity, which was estimated to be mild, moderate, or marked. Each tumor further evaluated for the presence or absence of hemorrhage, necrosis, degeneration, including hyalinization and liquefaction. Tumors are routinely classified as sarcomas when the mitotic rate is 5 or more per 50 HPF. In these tumors, nuclear atypia is more or less marked and the degree of cellularity is moderate marked. Based on mitotic rate, sarcomas are further divided into two groups: low grade (5 to 15 per 50 HPF) and high grade (16 or more per 50 HPF) (9). GANT, Gastrointestinal Autonomic Nerve Tumors, represents GIST type with neural differentiation (7). Its identification as a subgroup of stromal tumors rests mainly on ultrastructural identification of tumor cells with prominent axon-like cytoplasmic processes, loosely organized intermediate filaments, scattered microtubules and occasional dense core granules and tumor cells associated with bulbous-synapse-like structures. However, the ultrastructural features described as being diagnostic as GANT are, in fact, characteristics of GI pacemaker cells. It is therefore possible that tumors previously described as GANT are part of neoplastic spectrum with GANT displaying a higher degree of ICC differentiation, including neuronal contact, that is seen in most stromal tumors (2,3,7).

ULTRASTRUCTURAL APPEARANCE-GIST RESEMBLE INTERSTITIAL CELLS OF CAJAL

A striking feature seen, at least focally, in both the spindled and epitheloid tumor cells of GISTs is the presence of prominent delicate filopodia-like cytoplasmic projections that interdigitated in a complex fashion and sometimes invaginated deeply into neighboring cells. The most striking cytoplasmic features include an abundance of large mitochondria, prominent tubular cisternae of smooth endoplasmic reticulum and large Golgi zones, networks of intermediate filaments, and microtubules (7). There are scattered or grouped dense core granules within cytoplasmic processes or more commonly associated with the Golgi zones. There are also aggregates of so-cold skenoid fibers in the matrix of some tumors.

IMMUNOHISTOCHEMICAL STAINING

The development of immunohistochemistry and commercial availability of monoclonal antibodies created a rise in the number of studies aimed at defining the immunophenotype of GIST (9-12). Not surprisingly, the results have varied from study to study. Much of this variation can be attributed to technical and interpretative differences between investigators. A panel of antibodies IS used to characterize the histogenesis and differentiation of the GI tract GISTs. By using selected lineage-directed monoclonal antibodies for smooth muscle cells (pan-muscle actins: HHF-35, alpha-smooth muscle actin-SMA, and desmin), Schwann cells (S-100 protein), enteric glial (glial fibrillary acidic protein-GFAP) and nerve cells (neurofilaments) antibodies, in order to characterize immunohistologically this perplexing group of tumors. Recently it was realized that ICC express proto-oncogene c-kit, resulting in great studies of the morphology and function of ICC (12). Immunohistochemistry for c-Kit receptor (c-kit gene product) clarified distribution of ICC and demonstrated their three-dimensional network. The c-kit proto-oncogene encodes a type III receptor tyrosine kinase, the ligand of which is stem cell factor (SCF) (12). SCF-KIT interaction is essential for development of melanocytes, erytrocytes, germ cells, mast cells and ICCs. All GISTs reveal strong, homogeneous immunoreactivity for the kit receptor as does ICC of adjacent and control GI walls. Immunohistochemical analysis for the kit tyrosine-kinase receptor (CD117) shows strong expression the kit proto-oncogene, which encodes for a transmembrane tyrosine-kinase receptor (CD117) and has the stem cell factor as its ligand. CD34 antigen, a myeloid cell progenitor cell antigen, identifies the majority of stromal tumors and aids in their distinction from GI leiomyomas and schwannomas, which are CD34 negative (1,11).

CONCLUSION

It has been concluded that GI stromal tumors show striking morphological and immunophenotypic similarities with ICC and that they may originate from stem cells that differentiate toward a pacemaker cell phenotype. Because that, the authors have proposed that the noncommittal name "gastrointestinal stromal tumor" (GIST) be replaced by "gastrointestinal pacemaker cell tumor" (GIPACT) (3).

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