Gastrointestinal Stromal Tumors

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Gastrointestinal stromal tumors (GISTS) are most common mesenchymal tumors of gastrointestinal tract (GIT). Recently there is progress in understanding molecular pathogenesis of these tumors, increased ability to diagnose and prognosticate increased ability to diagnose and prognosticate, introduction of them in soft tissue tumors and addition of a new group of them "SDH deficient GISTS" in 2013 by WHO.

Historically Mazur and Clark (1983) gave the name GIST and Hirota et al (1998) discovered KIT mutations in them. Interstitial cell of Cajal (ICC) is the cell of origin. These are slender spindle or stellate cells present in muscle of GIT around myenteric plexus. ICCs participate in GI motility by pacemaker activity.

GISTS form 5-20% of all sarcomas and 1% of all GI malignancies. 60% of them occur in stomach, 30% in small intestine (SI) and 10% in esophagus, appendix, colon, rectum and anus together. Extra gastrointestinal GISTS (6.7%) occur predominantly in omentum, mesentery, retroperitoneum and pelvis.

They usually occur at 50-60 years with no sex predilection and are sporadic or familial. They are incidentally detected or symptomatic. Their location in wall of GIT may be intramuscular, submucosal or subserosal and vary in size from 1-35cms. They are firm, circumscribed, solid or cystic and microscopically 70% are spindled, 20% epithelioid and 10% are mixed. Spindle cells are arranged in interlacing, interdigitating fascicles, whorls or palisades. Epithelioid GISTS have polygonal or round cells arranged in sheets or nests. Formalin fixation gives retraction of cytoplasm so it appears clear.

Differential diagnosis of these tumors is broad due to this varied microscopic appearance and immunohistochemistry is a must in all cases.

GISTS are positive for CD 117 (KIT) by IHC in 95% cases. New markers DOG1 and PKC-theta are expressed in KIT-ve cases. They are more sensitive and specific markers. There is loss of staining in GIST for succinate dehydrogenase B (SDHB) in SDH deficient group.

CT and MRI identify GIST. Endoscopic ultrasound localizes them within the wall of GIT. PET scan reveals small metastasis, gives baseline metabolic activity and helps in assessment of effectiveness of therapy. Endoscopic FNA is used increasingly for diagnosis of GISTS. With IHC markers on smears it becomes more reliable. Frozen section is done to rule out lymphoma and carcinoma and for comments on resected margins of SI and colonic GISTS.

Cytogenetically mutation of KIT or PDGFRA occurs early in micro GISTS (1-10mm). They are mitotically inactive and partially calcified suggesting tumor arrest. So these mutations alone are insufficient for tumorigenesis. Other genetic events with progression to overt GIST are loss of chromosome 14 and 22, loss of short arm of Chromosome[1] and less often from chromosome 9 and 11 which is an aggressive disease.

DNA sequencing is done for diagnosis of KIT negative cases, also if imagine therapy needs to be initiated and in high risk tumors.

For predicting the behavior of GISTS many conflicting attempts are done. Fletcher et al in 2002 considered size (<2cm upto>10cm) and mitotic count (<5/50 HPF or >5/50 HPF) and divided GISTS into very low, low, intermediate and high risk groups. However behavior of tumors was different depending also on their location in GIT.

AFIP and Miettinen in 2006 added site as the 3rd parameter and divided them into 4 sites as stomach, duodenum, jejunum and ileum, colon and rectum. GISTS were divided into 8 groups as 1, 2, 3a, 3b, 4, 5,6a and 6b but this became very complex.

WHO in 2013 followed AFIP but reduced sites into stomach and small intestine (Colon and rectum merged in SI) and classified.

GIST into Benign (grade 1, 2, 3a), GIST with uncertain malignant potential (UMP) (grade 4) and malignant GIST (grade 3b, 5, 6a, 6b).

Oncogenic mutations play a central role in GISTs while in other sarcomas chromosomal rearrangements are important. Majority of GISTS shows either C-KIT (75%) or PDGFRA (10%) mutation on chromosome 4. C-KIT proto-oncogene encodes KIT receptor whose ligand is stem cell factor (SCF). Receptor has EC, TM, JM, TKI and TK II domains. Mutation leads to ligand independent tyrosine kinase (TK) activation by oligomerisation, auto phosphorylation, activation of signaling pathways and cell proliferation. Tumors with PDGFRA mutation have cell proliferation independent of ligand PDGF-AA in a similar manner. 'Wild type' is the label given to remaining GISTs when KIT and PDGFRA mutations are absent. It includes rare mutations as SDH, BRAF, NF1 and cases where mutation is unknown.

In more than 50% wild type GISTS mutation and loss of succinate dehydrogenase (SDH) is seen and are called as "SDH deficient GISTS". These tumors always occur in stomach, and mostly in pediatric age group.

They may be multifocal, spread to lymph nodes, show multinodular growth pattern, are Epithelioid and mixed. All show negative staining for SDH by IHC. Standard risk stratification criteria do not apply for them and their behavior is indolent even in presence of metastasis. Diagnosis of this group is important because of prognostic and predictive information and their syndromic association.

Familial GISTS have KIT or PDGFRA mutations in every cell of their body. Only few families are detected. They are autosomal dominant and mutations at exon 11 are common. Multiple GISTS develop at early age. Pigmented macules, skin mastocytosis and preexisting ICC hyperplasia are present. Behaviour is indolent.

GISTS are part of several syndromes such as Familial, Carneys-Stratakis, carneys triad, NF1, sporadic SDHB pediatric, sporadic multiple.

Molecular classification is important for treatment and prognosis. KIT mutations are seen in exon 9, 11, 13, 17. Common are in 11 and 9 and respond to imagine. In SI GISTS, exon 9 mutation has unfavorable prognosis. For PDGFRA exon 12, 14, 18 mutations are seen. Commonest are at 18, show gastric omental locations, epithelioid morphology and indolent behavior. They respond less to imatinib due to absence of tyrosine kinase domain.

Treatment of GIST consists of surgical resection and targeted therapy. Imatinib was used in Finland in 2000 for the first time in solid tumors which was a recurrent metastatic GIST. With Imatinib, tumors shrink, stop growing for a time or don't respond. It is used as adjuvant, neo-adjuvant therapy and is drug of choice in metastatic GISTS where surgery is not possible. Side effects are few. Second and third generation drugs are available. Survival of advanced GIST increased from 18 months to more than 60 months with targeted therapy.

Future challenges remain such as how GISTS develop which do not show mutation? Resistance to drugs and inclusion of mutations in prognostication schemes are other challenges.

References

1. Pignatelli M, Fisher Cyril: Gastrointestinal stromal tumors. Underwood JCE Eds. In recent advances in histopathology 21. UK; The royal society of medicine press Ltd; 2005,71-88.
2. Isozaki K, Hirota S, Gain of function mutations of receptor tyrosine kinases in gastrointestinal stromal tumors, Curr. Genomics 2006;7(8):469-475.
3. Sternberg S S, Antonioli D A, Carter D, Eggleston J C, Mills S E, Oberman H A. Alimentary canal and associated organs, Eds. In Sternberg's surgical pathology Vol. II 5th ed. USA. Lippincott Williams & Wilkins, 2010;1249-1431.
4. Weidqer N, Cote R J, Suster S, Weiss L M, Gastrointestinal tract, eds. In Modern surgical pathology, In USA Saunders Elsevier, Vol. I, 2nd ed. 2009;637-866.
5. Folpe A.L, Alava E. D. Adjuvant techniques- 'IHC, cytogenetics, molecular genetics, In words CY eds.in Bone & soft tissue pathology. USA Saunders, Elsevier, Inc 2010;7:18-42.
6. Rubin B.P, Heinrich M.C., Corless C. L: Gastrointestinal stromal tumor. Lancet 2007;369:1731-1741.
7. Enzinger F M, Weiss SW : Extra gastrointestinal stromal tumors, Weiss SW, Goldblum J R eds in soft tissue tumors 4th ed USA; Mosby Inc 2001;749-768.
8. WHO pathology & genetics of tumors of digestive system, 2003.
9. WHO classification of Tumors of soft tissue & bone 2013.
10. Gastrointestinal stromal tumors: what do we know now? Christopher L Corless Modern Pathology, 2014; 27:S1–S16; doi:10.1038/modpathol.2013.17.