Editorial: Gastrointestinal Stromal Tumors

John C. Deutsch, MD

EssentiaHealth
Duluth, MN

This issue of VHJOE includes a capsule endoscopy presentation by Dr. David Hass. He illustrates the findings in a patient who presented with anemia and was ultimately found to have metastatic gastrointestinal stromal tumor (GIST). The definitive diagnosis was made by liver biopsy, in which neoplastic cells were found that stained for c-KIT (CD 117).

The past 15 years have been quite remarkable in the understanding of this tumor. Prior to the late 1990’s, GIST’s were usually felt to be leiomyomas or leiomyosarcomas. They were quite refractory to standard chemotherapy. The discovery of gain-of-function mutations in c-Kit receptor in 1998,1,2 and the simultaneous development of directed therapies3,4 have changed both the diagnostic and therapeutic abilities of the medical community. The KIT protein is a cell membrane-spanning signaling receptor tyrosine kinase that normally functions to trigger cell growth when it is activated by its specific ligand. Mutated KIT are constitutively activated without needing a ligand, and this leads to unregulated growth. It is currently felt that 70-80% of GISTs have mutation in KIT. Another 10% have a mutation in a closely related protein, PDGFRa (platelet derived growth factor receptor alpha) which activates the same downstream cellular elements as KIT5. There are a remaining group of tumors that are histologically similar to KIT-mutated GIST, and who express protein kinase theta (Like the usual GIST) in which KIT and PDGFa receptor mutations are not identified. These are referred to as wild-type GISTs6. Neither KIT/ PDGFRa or wild type GISTs mark with neural or smooth muscle stains.

There are some demographic data in the literature that can be a bit confusing when one is trying to decide if a GIST is dangerous, particularly in the stomach. Reports suggest that GIST occur in 10-20 patients per million7,8, yet endoscopists often find GISTs in the stomach either due to bleeding or as an incidental subepithelial lesion. It appears that malignant GISTs are uncommon, but there are related micro GISTs of the stomach that are much less of a problem. Depending on the report, these small GISTs may be found in as many of 35% of selected population8. These tumors often have KIT mutations, but rather than progress, they seem to involute. It appears that several other factors are required for a GIST to develop malignant behavior, including loss of heterozygosity. Perhaps only 1/10,000 small gastric GIST lesions develops into a malignancy.

This does not appear to be true for non-gastric sites, where the rate of malignant transformation seems to be higher. It appears that gastric GIST have a better survival of small bowel GISTs of similar size and mitotic activity as reflected in the IUCC staging system for GIST, where similar lesions are assigned a more advanced stage if found in small bowel rather than stomach9.

The serious nature of small bowel GISTs is suggested by Dr. Hass’s case in this edition of VHJOE. By capsule endoscopy, a rather small lesion is identified, whereas CT shows rather extensive metastatic disease. Physicians should be familiar with the appearance of GIST during capsule endoscopy, to hopefully allow earlier management of this interesting but potentially lethal disease process.
References:


