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Editorial

Wild Type Gastrointestinal Stromal Tumor (Wt-GIST)

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The majority are sporadic, solitary tumors that harbor mutually exclusive KIT or PDGFRA gain-of-function mutations.1 The type of mutation in addition to risk stratification corresponds to the biological behavior of GIST and response to treatment. Up to 85% of pediatric GISTs and 10-15% of adult GISTs are devoid of these (KIT/PDGFRA) mutations and are referred to as (wt-GIST)“Wild-type” gastrointestinal stromal tumors and are characterized by the lack of KIT and PDGFRA mutations, Although the pathogenesis is largely unknown, It has been shown that these wt-GISTs are a heterogeneous tumor group with regard to their clinical behavior and molecular profile. Recent advances in molecular pathology helped to further sub-classify the so-called "wt-GISTs". Based on their significant clinical and molecular heterogeneity, wt-GISTs are divided into a syndromic and a non-syndromic (sporadic) subgroup. recent studies have uncovered germline mutations ..... [to be continued]

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The majority are sporadic, solitary tumors that harbor mutually exclusive KIT or PDGFRA gain-of-function mutations [1].

Up to 85% of pediatric GISTs and 10-15% of adult GISTs are devoid of these (KIT/PDGFRA) mutations and are referred to as (wt-GIST) “Wild-type” gastrointestinal stromal tumors and are characterized by the lack of KIT and PDGFRA mutations, Although the pathogenesis is largely unknown, It has been shown that these wt-GISTs are a heterogeneous tumor group with regard to their clinical behavior and molecular profile [2].

Recent advances in molecular pathology helped to further sub-classify the so-called "wt-GISTs". Based on their significant clinical and molecular heterogeneity, wt-GISTs are divided into a syndromic and a non-syndromic (sporadic) subgroup. recent studies have uncovered germline mutations involving succinate dehydrogenase (SDH), most commonly in the subunit genes SDHB and SDHC, resulting in a complete loss or reduction in SDH protein [3]

The SDH-ubiquinone complex II is an enzyme complex found in the Krebs cycle and the electron transport chain. Loss of function of SDH is thought to play a central role in the pathogenesis of many

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WT-GISTs [4]. Deficiency of SDH complex leads to accumulation of succinate, resulting in hypoxia-inducible factor (HIF)1-α stabilisation and constitutive activation of hypoxic signalling and tumorigenesis[1, 4]. In parallel, succinate accumulation also inhibits key enzymes that regulate the epigenome leading to hypermethylation of DNA and histones [5,6]. Mutations of SDH are not solely exclusive to GIST pathogenesis and have been associated with other tumors such as malignant pheochromocytoma and renal cell carcinoma [7].

All GIST with no detectable KIT or PDGFRA mutations should be analysed by SDHB immunostaining. If a GIST is SDH-deficient by SDHB-IHC, sequencing of SDHx in the tumour and germline should be performed. If no SDH mutation is identified, then the presence or absence of SDHC promoter methylation should be determinedIf an SDHx mutation is found in the germline then genetic counselling is indicated, together with mutation screening of first-degree relatives, and regular screening for paraganglioma, pheochromocytoma, or other tumours. SDHC promoter hypermethylation is generally not germline, therefore genetic counselling for these patients is not required, but do still require screening for paragangliomas, as they are often associated with syndromic GIST [8,9] SDHB-competent cases should be analysed by next-generation sequencing assays to identify potential other targetable alterations (BRAF, NF1, NTRK, FGFR1…).

Loss of SDH protein expression is effectively demonstrated using traditional immunohistochemistry so, the use of succinate dehydrogenase B (SDHB) by immunohistochemistry has been used to stratify GIST into an SDHB-retained and an SDHB-deficient group [10,11], as WT GISTs lacking somatic mutations or deletions in SDH subunits had either complete loss of or substantial reduction in SDHB protein expression, whereas most KIT mutant GISTs had strong SDHB expression [12].

SDH-deficient GISTs are characteristically multinodular, most commonly have either exclusively epithelioid or mixed spindled/epithelioid cytomorphology, and are almost exclusively gastric [3]. Whereas other GISTs rarely present with lymphovascular invasion or lymph node metastasis, these occur frequently in SDH-deficient GISTs. Tumor cells show loss of the SDH complex because of both germline and somatic mutations in the SDH subunit genes. Mutation of any subunit, most commonly SDHA, leads to loss of the complex that can be reliably detected by immunohistochemistry for SDHB [12] SDH-deficient GISTs have increased genomic methylation, different from conventional KIT/PDGFR-α–mutant GISTs. SDH-deficient GISTs are usually restricted to the stomach, occur predominantly at a young age, and are clinically heterogeneous, with some patients having other SDH-deficient tumors, especially paragangliomas.. [13,14] Consequently, standard GIST therapies (ie, imatinib and sunitinib) are less efficacious in this clinical group

Discovered on GIST1 (DOG1) is a promising new marker which has proven in early studies to be a sensitive and specific marker for GISTs [15,16,17] . It is immunoreactive in pediatric GISTs and NF1-associated GISTs. Notably, DOG1 stains about onethird of KIT-negative GISTs.(18)Given that up to 5% of GISTs do not express KIT, this marker is especially useful for diagnosis.

Although GIST is now a well-recognized entity, the pathologist must be aware of the wide morphologic spectrum of GISTs, including the common morphologic subgroups, the unusual morphologic variants, and the morphologic changes that may be encountered after treatment. Despite these differences in morphology, however, almost all cases can be assessed for risk stratification using the 2007 and 2010 The National Comprehensive Cancer Network (NCCN) and guidelines along with those from the European Organisation for Research and Treatment of Cancer (EORTC), which include mitotic activity, tumor size, and tumor location. In light of the morphologic spectrum, immunohistochemistry for KIT and CD34 among others is exceedingly useful in distinguishing GISTs from their morphologic mimics. Promising new immunohistochemical markers, such as DOG1, will likely be diagnostically valuable, especially in GISTs lacking KIT expression. Currently, there is no standard of care requiring routine molecular testing in situations other than confirmation of the diagnosis in KIT-negative or DOG1-negative cases. However, in the future, molecular testing may become commonplace for guiding initial treatment. It is also likely that the treatment of GIST will evolve toward the simultaneous use of multiple TKIs and perhaps agents that act through other mechanisms in order to avoid the emergence of resistance [14].

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