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Editorial

Advances in the Diagnosis and Management of GIST and GANT Tumors

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Gastrointestinal stromal tumors (GISTs) account for 0,1 to 3% of all gastrointestinal tumors. Most authors agree that are the most common mesenchymal tumors of the GI tract arising probably from the intestinal cells of Cajal. The vast majority of the cases develops in stomach and small intestine (55% and 30% respectively) and rarely in rectum (5%) and in other locations as the rest of the colon, in the omentum, mesentery, retroperitoneum and finally in pelvis.

Although most of the GISTs represent sporadic cases, can also be part of familiar syndromes, such as the Carney triad, the Carney-Stratakis syndrome and neurofibromatosis type 1, or coexist with other tumors of the GI tract, such as adenocarcinoma of the colon, or paraneoplastic syndromes [1].

The Modified GIST Classification presented from National Institute of Health (NIH), describes the factors that associate with the aggressiveness and prognosis of the disease. The current classification includes all the independent risk factors as the tumor size, tumor site, mitosis count, occurrence of curative resection and post-operative imatinib therapy, but also includes the occurrence of tumor rupture, spontaneously or during surgical or invasive procedures factor that related with the therapy and alter the risk of recurrence [1,2]. Macroscopically GISTs may vary from grey to white, or to red and brown color. They are usually solid or partially cystic and may contain necrotic areas. Microscopically may characterized by spindle cell, epithelioid, or a compilation of both patterns (mixed type) [3].

For surgeons and clinicians the treating options and alternatives is the most important. All the existing data and evidence indicates that surgical treatment remains the cornerstone in the management for localized GIST. The curative results of the appropriate surgical treatment range over 50%. More problematic is the treatment of locally advanced, complicated or metastatic GISTs, which are refractory to conventional radio- and chemo- therapy. Recent studies reported the discovery of gain mutations regarding the KIT and PDGFRA genes which contributed to establish an adjuvant therapy with imatinib. In cases of imatinib resistance, second line treatment with sunitinib and regorafenib has been approved. After this evolution in adjuvant treatment life expectancy of patients with advanced GIST tumors has been increased. Although in most of the GISTs cases modern and advance medicine offers treating alternatives there are some cases with resistance to tyrosine-kinase inhibitors treatment. Immunohistochemistry has evidenced the presence of GIST, without KIT/PDGFRA mutations, called Wild-type GIST (WT-GIST). These WT-GIST case are imatinib resistant, mainly due to alternative pathways of mutations or due to acquisition of secondary mutations in KIT/PDGFRA. All these unidentified mutations and pathways complicate the treatment and the clear cut-off point of the adjuvant therapy in high-risk WT-GIST or the best systemic treatment remains unknown [1,4].

The various classifications of the GIST tumors and the extended reference in biological and genetic characteristics, genes and mutations may be confusing for the mean clinical doctor or surgeon. Simplifying the existing knowledge and research in genes and mutations, we can classify the GIST tumors into three main types.

Type 1: (C-KIT mutated GIST): This is the first type which accounts for almost 75% of all GISTs present gain-function mutations in KIT gene. This results in downstream pathways activation (RAS/RAF/MAPK, JAK/STAT3, PI3K/AKT/mTOR) that increase proliferation or evade apoptosis. The c-KIT mutation is a clinically important therapeutic target as it has been proved that adjuvant therapy with imatinib may be helpful. Differential diagnosis of GIST type it has been difficult, mainly due to the fact that clinical signs and symptoms are not specific (nausea, vomit, abdominal pain, ane-

mia, melaena), and thus not very helpful. Such tumors tend to be of spindle cell histology and can be present in the entire GI tract. They tend not to metastasize to lymph nodes and there is no difference when compared to sporadic GISTs, in terms of medical or surgical treatment [4].

Type 2: (PDGFRA mutated GIST): In this second type, mutations in this gene are less frequent (15%). They are also gain-of-function mutations, which may activate the same transduction pathways as the c-kit. This type of GIST presents a more benign clinical course and is almost exclusively (95%) of prognostically better gastric origin. KIT or PDGFRA detection by immunohistochemistry does not mean that there is also a molecular mutation [5].

Type 3: (Wild Type (WT)-GIST): The last type which accounts approximately for 10% of GISTs includes the cases without any mutations in the above mentioned two genes (KIT or PDGFRA). These tumors are called Wild Type GISTs (WT-GIST), and they are less sensitive to tyrosine-kinase inhibitors. The molecular biology of these GIST tumors has become more complex, due to the discovery of different subgroups, which harbor mutations in succinate dehydrogenase (SDH complex), NF-1 gene (neurofibromatosis), BRAF or KRAS genes. With reference to KITwt/PDGFRAwt GISTs, they can be divided in two groups, based on the immunohistochemical status of succinate dehydrogenase subunit B (SDH-B). The tumors in the first subgroup present normal expression of SDH-B protein (SDH-B+), which include NF-1 mutated GIST and cases of sporadic GIST. Such sporadic GIST may be RAS/BRAF mutated GIST or Quadruplewt GIST, a term that indicates the absence of mutation in all known genes (KITwt/PDGFRAwt/SDHwt/RAS-Pwt). Tumors in the second subgroup are characterized by the lack of expression of SDH-B protein (SDH-B-). This group is divided further by the inactivation or not of the SDH-A. The lack of expression of the SDH-A protein (SDH-A-) is considered responsible for pediatric or young-adults SDH-A mutated GISTs. On the other hand, the normal expression of SDH-A (SDH-A+) associated with SDH-B- is encountered in Carney-Stratakis syndrome, in Carney triad or in sporadic GISTs having mutations in all SDHx complex [4-6].

Gastrointestinal autonomic nerve tumors (GANTs), are rare stromal tumors that considered a rare subtype of GIST and accounting for 1% of all malignant GI tumors. GANTs are slow-growing tumors, potentially malignant, with an aggressive clinical course that is associated with poor prognosis. Their aggressiveness correlates to their size, proliferative activity, site, mitotic count, degree of necrosis and surgical resectability. Liver is the most common reported site of metastasis, followed by lungs, adrenal glands, bones and musculoskeletal system. Their histological features are similar to GIST although their ultrastructural characteristics suggest that they originate from the myenteric plexus of Auerbach. The definite diagnosis of GANT can be achieved by electron microscopy or/and immunohistochemical analysis. Most frequently they develop in small intestine and in stomach. They do not present sex predilection, and can occur at any age, although there is a slight prevalence between the 6^{th} - 7^{th} decades of life, without any. Clinical signs and symptoms, as it has already previously been reported in GISTs, are not specific, making thus the differential diagnosis difficult. Histologically, spindle and large epithelioid cells arranged in sheets, fascicles or nests, can be found but this is not a specific characteristic as they can also be found in GISTs tumors. The cells show intense staining for vimentin, S-100 protein, neuron-specific enolase, chromogranin and synaptophysin. Immunohistochemically, GANT is diffusely positive to vimentin, neuron-specific enolase or S-100 protein. Ultrastructural, GISTs present rich villous cytoplasmic processes and dispersed intermediate filaments, while GANTs present neurosecretory granules and skeinoid fibers. Ultrastructural examination and analysis which reveals dendritic processes with dense neuroendocrine granules is the crucial exam to set the correct diagnosis and to identify a tumor as GANT and not GIST [7-9].

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