PARTICULAR FORMS OF GASTROINTESTINAL STROMAL TUMOURS (GIST)

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Abstract: *Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract (80%). A few of GISTs (5%) are reported to occur in association with the following tumour syndromes: familial forms of GIST, neurofibromatosis type 1 (NF1) and Carney triad syndrome. The purpose of this article is to provide a brief bibliographic summary of these particular forms of GIST which, although rare, continue to show great interest.*

Cuvinte cheie: *GIST, diagnostic, neurofibromatoză tip 1, pediatric, imunohistochimie, gastric*

Rezumat: *Tumorile stromale gastrointestinale (GIST) sunt cele mai frecvente tumori mezenchimale ale tractului gastrointestinal (80%). O mică parte din GIST-uri (5%) sunt asociate cu următoarele sindroame tumorale: formele familiale de GIST, neurofibromatoza tip 1 (NF1) şi triada Carney. Scopul acestui articol este de a realiza o scurtă sinteză bibliografică despre aceste forme particulare de GIST care deşi rare continuă să prezinte un interes deosebit.*

GISTs form a distinct group of gastrointestinal tumours with origin in interstitial Cajal cells (named after the man who discovered them, namely the Spanish anatomist and the Nobel laureate Santiago Ramon y Cajal 1852-1934). These cells control the peristaltic activity of the intestinal tract (gastrointestinal motility and autonomous nervous function) and normally expressed CD117 (c-Kit), which is part of the growth factor receptor tyrosine kinases of the stem cell. c-Kit is the best feature of GIST defined in terms of immunoreactive, differentiating them from the tumours with real origin in the smooth muscle (ex. leiomyoama, leiomyosarcoma) and tumours derived from neural crest (eg. schwanoma, neurofibromas); is considered the most specific criteria for diagnosis of GIST.

The present paper aims at making a brief summary on the current bibliography of these forms of GIST, which have a particular clinical behaviour compared to the common forms, yet incompletely understood. These forms of GIST although rare continue to show great interest.

THE CLINICAL DIAGNOSIS OF GIST

The first symptoms in the patients with GIST depend on the tumour size and its location. GISTs are often large upon diagnosis. Approximately one third of tumours are discovered incidentally during surgery for other conditions or when conducting laboratory investigations (colonoscopy, diagnostic laparoscopy). Another third is found when conducting computer tomography for symptoms different of GIST. The remaining third is discovered when the tumour is bulky and is symptomatic in this situation, the possibility of metastasis is very high. The symptoms and the signs of this disease become clinically evident up to 72% of cases and vary according to location, growth and tumour diameter.

Gastrointestinal stromal tumours can be asymptomatic until the tumour volume reaches increased sizes or may manifest in a nonspecific way. The symptoms are related to the tumour mass (abdominal pain, discomfort, fullness, palpable abdominal mass, occlusive syndrome) or anaemia (gastrointestinal bleeding as a result of ulcers, occult or manifested particularly in the large tumours). Over 25% of patients are suffering from acute bleeding in the intestinal tract or peritoneal cavity by tumour rupture. The submucosal location of the tumour can cause obstruction or perforation, especially in locations such as the esophagus or the small intestine. Esophageal tumours may present with dysphagia and those that occur in the duodenum may be associated with the compression of CBP, with fever and jaundice. Rectal GIST may be associated with mass effect symptoms (dysuria) or oligoanuria because of the bladder invasion. Other symptoms include weight loss, hepatomegaly, asthenia and fatigue, especially in the patients with liver metastases or disease evolution. On physical examination, an intermittent abdominal distention may be described, pain caused by the deep palpation of the abdomen or an abdominal tumour may be palpated.

SPECIFIC TYPES OF GIST

Familial forms of GIST may occur occasionally (KIT and PDGFRA gene mutations). There are fewer than 20 reports of familial GIST in the medical literature and most of them appear in Japan and France. As the mutations already exist in all the cells of the organism, the first step in the development of GIST takes place before birth (there is a greater probability for the development of multiple occurrences of GIST than of sporadic ones). These usually occur at younger ages than in the sporadic cases. Most cases diagnosed with familial GIST are between 25-45 years old.(1) The pattern of transmission is AD.(2) Individuals affected with familial GIST present interstitial cell of Cajal hyperplasia in the myenteric plexus (prior to the multiple tumoral growth). Mutations of the genes encoding the KIT receptor have been identified in most familial forms of GIST. It is important to mention that there are different

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mutations of these genes within different families affected with GIST.

In these particular circumstances, besides the clinical manifestations of the tumour itself, cutaneous hyperpigmentation, cutaneous nevi, urticaria pigmentosa, disphagia or achalasia may occur. Mutations of the PDGFRA genes have been detected in only one case with familial transmission. There is no sign of the previously enumerated cutaneous modifications and deglutition disorders within this family.(3)

The persons affected with **neurofibromatosis type 1** present high risk factors of developing GIST, as compared to the general population. Neurofibromatosis type 1(NF1) is a disease of the suppressor gene that encodes the neurofibromin protein (member of the RAS family that regulates other proteins). The incidence of this disease is about 1/3000 new-borns. In most cases it has an autosomal dominance pattern of transmission. The clinical manifestations of the patients diagnosed with NF1 include: pygmentary abnormalities (cafe-au-lait spots), predisposition to the occurrence of different types of cancer and also multiple neurofibromatosis (benign peripheral nerve tumors). Approximately 10% of the patients develop malignant peripheral nerve tumours. GIST prevalence is about 5-25%, but in the population diagnosed with NF1, it can be greater if the asymptomatic cases found at autopsy are taken into consideration.(4,5) Symptomatic GISTs in the patients with NF1 are diagnosed at younger ages than in the sporadic GISTs cases (before 50 years old). Patients with NF1 have multiple GISTs especially with an intestinal location as compared to the sporadic forms, where the predominant location is the gastric region. In these cases, as in the ones with familial transmission, there is an interstitial cell of Cajal hyperplasia. GIST in the patients with NF1 does not involve mutations of the c-KIT or PDGFRA genes, but it presents the normal type or the „wild-type".(6)

There are only a few cases in the medical literature that do not follow this rule, and in 2005, Takazawa and his collaborators reported mutations in at least one tumour in 3 out of 9 patients with NF1 (c-KIT or PDGFRA). GIST developed from NF1 presents a high reactivity at the S 100 protein as compared to the sporadic forms (because of the existence of the myenteric nervous fibres).(7) In 2009, Yamamoto and his collaborators discovered the positivation of GIST developed in NF1 for the proteinkinasis C theta. Regarding the GIST response in NF1 to the treatment with Imatinib and Sunitinib, there are still no accurate studies on this subject, just a few published papers demonstrate the occurrence of tumoral resistance after a response initially reduced by treatment.(8)

Paediatric GIST is described as GISTs having a first occurrence in patients between the ages of 0-18 years old, and it is much more common in girls than in boys. The most frequent cases that occur are with gastric location and they generally involve multiple tumoral formations.

Clinically, it can manifest by palpating a tumoral formation in the upper part of the abdomen, hematemesis, anaemia, melena and constipation. Some authors have reported the presence of lymphatic perigastric metastasis in the case of gastric location in children in comparison to the sporadic forms where the ganglionic affectation is rare.(9) Paediatric GIST also has a higher tendency for local recidivation than the sporadic one. Paediatric GISTs develop metastasis less frequently than the sporadic ones (the most frequent metastasis are the hepatic ones). Another characteristic of the paediatric GIST is its more benign evolution even in the case of the occurrence of hepatic metastasis as compared to the sporadic form.(10)

There are some reports of congenital GIST that have manifested through intestinal obstruction immediately after birth (Wu and his collaborators, 1999; Bates and his collaborators, 2000; Geramizadeh and his collaborators, 2005), the solving of such cases being a surgical solution without subsequent recurrence. Only some cases of paediatric GIST have been tested for genetic mutations, out of 9 cases, 8 have been reported with "wild-type" (Prakash and his collaborators, 2005; Price and his collaborators, 2005; Li and his collaborators, 2002). A singular case of mutation of the exon 9 has been described in a boy with gastric GIST (Price and his collaborators, 2005). Knowledge about paediatric GIST is still sparse and it seems that the genetic mutations causing it have not been identified yet.

GIST is one of the tumours that forms the **Carney triad**, the other two are the functional extra-adrenal paraganglioma (tumours arising from neural-crest-derived chromaffin cells) and the pulmonary chondroma (benign cartilaginous tumours).(11) Gastric location of GIST in the Carney triad is predominant.(11) This is an extremely rare syndrome, with fewer than 30 cases with the complete triad reported in the medical literature and fewer than 100 cases having two tumour types present (usually GIST and chondroma). It predominantly affects females (80% of the cases) with the first tumour appearing in adolescence (gastric GIST). Because there is a latency period between the occurrence of the first tumour and the appearance of the second type of tumour, all paediatric GISTs cases should be considered as potential Carney syndromes.(11) Gastric GISTs in Carney triad are multi-focal and of an epithelioid type. Even with the occurrence of hepatic metastasis the prognosis is better than in cases of GIST that occur in adults. There are high-risk factors of local recurrence. There is no evidence of genetic mutations in the cases of GIST in the Carney triad.(12)

Conclusions:

GIST was and remains a great challenge to the surgeons all over the world because of their unpredictable clinical behaviour. Future studies on these particular forms of GIST that will try to elucidate the mechanisms that distinguish them from the common forms of GIST will have a role in completing the multimodal treatment of this condition.

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