Gastrointestinal stromal tumors: epidemiology, clinical picture, diagnosis, prognosis and treatment

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Abstract: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. They originate from the myenteric ganglion cells, termed the interstitial Cajal cells. The majority, i.e. 95% of GIST, show expression of the membrane receptor protein CD117 with a tyrosine kinase activity c-kit. Gastrointestinal stromal tumors constitute less than 1% of all digestive tract tumors. They may be benign or malignant (30%), and occur in every part of the gastrointestinal tract, however the stomach is the most common localization. They develop with the same prevalence in men and in women, usually above the age of 50 years. The peak incidence is observed between the fifth and the sixth decade of life. Symptoms are not typical and depend on the localization and the tumor size. About 10–30% of GIST are completely asymptomatic, and are discovered accidentally during the endoscopy or X-rays evaluation as well as during surgical interventions performed for various reasons. The malignant tumors metastasize most commonly to the liver and peritoneum. The metastases are rarely found in the lungs, pleura and bones. The detection of GIST is based on imaging, endoscopy, histological and immunohistochemical examinations. A useful and promising diagnostic procedure is positron emission tomography. The final diagnosis is mostly based on the pathologic findings of the removed tumor. The prognosis of GIST depends on its size, mitotic activity in 50 high power fields and mucosal infiltration. Radical surgery is the best treatment of GIST.

Key words: diagnosis of gastrointestinal stromal tumors, epidemiology, prognosis, symptoms

INTRODUCTION

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. This group has been formed on the basis of specific immunophenotype that differs from other non-epithelial digestive tract tumors, including leiomyosarcomas, neuromas, neurofibromas. Stromal tumors represent less than 1% of all of the gastrointestinal tract tumors [1-7].

On the basis of immunohistochemic studies, it has been assumed, that GIST originate from the myenteric ganglion cells, so called the interstitial Cajal cells, or its precursors [8,9]. Cajal cells are the pacemaker cells, show properties of both smooth muscle cells and cells of the autonomous nervous system and regulate bowel movements. According to another theory, GIST develop following neoplastic transformation of the precursor pluripotential stem cells positive for CD34 antigen, which turn into pacemaker cells. The majority, i.e. about 95% of the gastrointestinal stromal tumors, are characterized by the expression of c-kit receptor tyrosine kinase – so called CD117 antigen, whereas about 60–70% of the tumors express antigen CD34 [5,10-14].

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Epidemiology

Gastrointestinal stromal tumors have been commonly diagnosed for only the recent several years. The epidemiologic data are being collectedl, therefore they are not precise. Untill now the proportion between benign and malignant tumors is unclear. The current results of the epidemiologic studies demonstrate that the prevalence of stromal tumors amounts to 20–40 per million inhabitants per year [10]. These data differ between various populations. On the basis of retrospective studies conducted in Sweden by Kindblom et al. [15] and Nilsson et al. [16] it has been estimated that GIST prevalence, including potentially malignant as well as benign tumors, is 14.5–16 per million inhabitants per year. In Iceland GIST prevalence amounts to 11 per million inhabitants per year [10]. In the United States there are about 5000 new cases annually, providing 15–20 cases per million per year, and the black race is a risk factor [17,18]. On the basis of data obtained from 14 different countries from all over the world participating in the EORTC study the incidence rate was calculated as approximately 4–5 cases per million per year [19]. The data for the Polish population mean more

than 500–600 new cases per year according to the Swedish studies or 120–195 according to the results of other studies. The prevalence of clinically significant GIST, that is inoperable, metastatic and high-risk GIST amounts to 20–30%, equivalent to approximately 3–4 cases per million. According to the Polish Clinical GIST Registry seated in the Department of Soft Tissues and Bone Sarcomas at the Cancer Center in Warsaw, in Poland the number of registered patients treated with imatinib (selective inhibitor of the tyrosine kinase) as well as and the number of new cases and the number of patients operated for GIST, are however lower, demonstrating that some of the cases are missed [19,20].

The prevalence of GIST is similar in men and women. According to Polish data, 48% of GIST patients were women and 52% men, nevertheless, among the patients with metastatic disease men outnumber women by far. Gastrointestinal stromal tumors usually appear in patients above 50 years of age, whereas the maximum incidence is observed in the 5th and the 6th decade of life. The mean age at the diagnosis is 55–63 years [18]. However, it is estimated, that about 20% of the tumors manifest themselves in patients below 40 years of age and extremely rare during the first 20 years of age. Metastatic disease is more common in younger patients [20].

In about 10% of patients with stromal tumors other malignancies such as clear-cell renal carcinoma, cervical, breast carcinoma, and carcinoma of the stomach and lung are encountered. There are few reports of familial GIST. In the case of familial GIST, the family members present with a mutation of c-kit protooncogene. These individuals are characterized by particular genotypic features including nuchal, neck, hand, perianal and perioral skin hyperpigmentation. Moreover, a number of other syndromes associated with c-kit mutation and multiple stromal tumors have been described, and they manifest as dysphagia, skin hyperpigmentation or histologically confirmed hyperplasia of Cajal cells or myenteric ganglion cells. The risk of GIST is increased in family members of patients with von Recklinghausen diseases [21]. Carney's triad is a genetic syndrome of young women, presenting with multiple stomach GIST, extra-adrenal paraganglioma and pulmonary chondroma [10,22].

Clinical presentation

More than 80% of the tumors are primary localized in the gastrointestinal tract. Significantly less frequently, i.e. in about 10% of the cases, GIST are primarily found in the retroperitoneal space and in pelvis minor. The majority of GIST (40–70% according to various studies) are found in the stomach, usually in the fundus, and they constitute 1–3% of the stomach neoplasms. About 20–50% of GIST are localized in the small intestine, usually in the jejunum; they can be very rarely found in the large intestine and the rectum – about 5%, and less than 5% of them are localized in the esophagus [23]. The primary localization in the omentum and the mesentery has been reported only in single cases. Sporadically, the ectopic GIST was found in the reproductive organs or in the pelvis minor, in the appendix, gallbladder, mesentery or omentum [24-28]. In about 6% of the cases, due to the progression of the disease and multifocal intraperitoneal dissemination it is impossible to determine the primary localization of the tumor [19]. Within the digestive tract, gastrointestinal stromal tumors may have submucosal, intramural or subserous localization. The clinical presentation is not characteristic and depends on the localization and the size of the tumor. About 10–30% of GIST are completely asymptomatic, discovered incidentally during the endoscopic, radiologic diagnostics as well as during surgical interventions performed for various reasons. If present, the clinical symptoms are non-specific and include: abdominal pain (20–50%), early satiety, flatulence, subileus or ileus (10–30%), prolonged gastrointestinal bleeding (about 50%), anemia of unknown origin, weight loss, vomiting, acute abdomen [29-31]. Gastrointestinal stromal tumors may present as an abdominal tumor on physical examination. Sometimes, women with GIST of the small intestine are operated due to suspicion of ovary cancer [24,25]. The clinical symptoms depend on localization of the tumor and manifest themselves similarly to tumors showing other histological features. Esophageal tumors are usually small and asymptomatic, larger lesions present with dysphagia, odynophagia, retrosternal pain, hematemesis and weight loss, and sometimes they may be found accidentally, as an abnormal mediastinal shadow on chest X-ray. Stomach tumors may cause epigastric pain, anorexia, nausea, vomiting, weight loss. Tumors localized in the small intestine usually present with abdominal pain, sometimes mimicing biliary colic; duodenal tumors may cause jaundice. Colonic lesions manifest themselves as abdominal pain or abnormalities of bowel habits. Independently of localization GIST may cause ileus, perforation, symptoms of "acute abdomen", as well as gastrointestinal bleeding. Rarely, the tumor may be manifested as paraneoplastic syndrome in the form of hypoglycemic episodes, due to the production of insulin-like growth factor II [7,10,19,32,33].

There are two routes of GIST metastases, hematogenous and lymphogenous and they are usually limited to the abdominal cavity. In the majority of cases (54%), metastases are found in the liver, in 22% they are isolated lesions, and in 32% they coexist with intraperitoneal dissemination. Gastrointestinal stromal tumor liver metastases are usually multiple, large in diameter, and localized in both lobes. The second most common site of metastases is the peritoneum. Intraperitoneal dissemination without liver metastases is found in about 31% of the patients [19]. Gastrointestinal stromal tumors rarely metastasize to the lungs (usually rectal tumors), pleura and bones [34]. The casuistic metastatic brain changes have been reported [35]. Usually, no metastasis is found in the regional lymph nodes, therefore during surgical resection of GIST lymphadenectomy is not necessary [19].

Diagnostics

The diagnostic evalaution of gastrointestinal stromal tumors is based on imaging techniques, with a special role of endoscopic examination, because it is commonly accessible, however the most important diagnostic tools are the histological and immunohistochemical examinations.

Small, asymptomatic lesions are usually discovered accidentally during endoscopy performed because of various indications, bigger ones during endoscopy as well as during other diagnostic investigations – ultrasonography, computer tomography, endosonography carried out in order to diagnose various non-specific clinical symptoms. Large tumors localized for example in the esophagus are usually visible not only during endoscopy, but also at the chest X-rays, manifested as mediastinal widening, and in such cases computed tomography of this region should be carried out. The macroscopic picture of gastrointestinal stromal tumors is heterogeneous. Endoscopic examination usually describes GIST as submucosal changes, in the majority of cases oval, observed through the gastrointestinal lumen as protrusion or indentation. The mucosa covering the tumor may be intact, sometimes with a navel-like depression, and as concerns larger cases often with ulceration. Computed tomography shows these lesions as a solid mass, that displays contrast enhancement after its oral or intravenous administration. The lesions showing homogenous enhancement and protruding into the gastrointestinal lumen are in the majority of cases benign [36,37]. Besides endoscopy and computer tomography, endoscopic ultrasonography (EUS) plays an important role in the diagnostic work-up of stromal tumors. As a rule the EUS shows GIST as hypoechogenic mass originating from different layers of the gastrointestinal tract wall, usually from the *muscularis propria* and *muscularis mucosa*. Endoscopic ultrasonography is a useful diagnostic method, especially in the identification of malignant tumors. This examination features associated with malignant GIST are independently: size more than 40 mm, an irregular outer margin, the presence of cysts and non-homogenous echo pattern. It should be emphasized that on the basis of EUS, it is not always possible to differentiate between stromal tumors and leiomyosarcomas or other mesenchymal tumors. Leiomyosarcomas are more common in the esophagus and in the large intestine, and rare in the stomach and in the small intestine, which may be a diagnostic indication if the ultrasonography results is questionable. However, the diagnosis may never be established only on the basis of typical or untypical localization and the endoscopic or EUS imaging [10]. The final diagnosis is established on the basis of histological examination of biopsy specimen of the change suspected to be GIST. The tumor samples obtained by endoscopic biopsy are not always representative because of the reach of the biopsy forceps. Other method is based on endoscopic submucosal-mucosal resection, which makes it possible to radically treat GIST smaller than 2 cm in diameter and limited to the submucosal layer, as well as endoscopic ultrasound guided fine-needle biopsy. This method is not always useful in the histopathologic assessment of the tumor and discrimination between benign and malignant changes, although it helps obtain the specimen for immunohistochemic studies, including CD117 expression, as a most sensitive marker for GIST, present in more than 90% of the stromal tumors, as described above. Another significant marker in the diagnosis of GIST is CD34 antigen, the expression of which is the highest in the esophagus and in the large intestine. Smooth muscle actin (α-SMA) is expressed in 20–40% of GIST localized in the stomach that are CD34 negative. Therefore CD34 and α-SMA are two markers that are helpful in the diagnosis of about 10% of CD117 (–) GIST. Standard immunohistochemic studies help not only diagnose stromal tumors, but also exclude submucosal lesions other than GIST [38]. Here the determination of the protein PS-100 as well as of desmine should be mentioned. These two antigens are typical of other then GIST mesenchymal tumors. The protein PS-100 occurs in neurogenic tumors and if it is found the diagnosis of schwannoma is confirmed, whereas the determination of desmin may help in differentiation between GIST, where it is negative, and tumors of myogenic origin, especially with leiomyosarcoma [10,39,40]. Immunohistochemic and histopathologic investigations are crucial to the diagnosis of GIST. A useful and promising diagnostic method is 18F-fluoro-deoxyglucose positron emission tomography) [10,41]. According to data derived from the Clinical GIST Registry, the majority of tumors are surgically treated without any previous histological verification and the final diagnosis is based on the pathologic examination of the resected tumor. It is usually caused by difficulties in obtaining diagnostic tissue, due to the intramural development of the tumor [10,19,42].

Prognosis

To assess the clinical malignancy of the tumor the above mentioned diagnostic procedures should be completed with chest roentgenogram (not only in the case of esophageal tumors), and the ultrasound and computed tomography of the abdomen in order to confirm or exclude dissemination of the neoplasm and assess the position of the tumor in relation to adjacent structures. About 20% of malignant GIST are diagnosed when the neoplastic process has already generalized. It refers especially to small lesions, which for a long time are asymptomatic, and are discovered accidentally. The mean time to the presentation of symptoms is approximately 4–6 months, and to the generalization of the neoplastic process – 2 years. The mean duration of the disease in patients with the metastatic form is estimated to be 41 months [19]. Among the asymptomatic tumors, the majority are localized in the stomach and in the duodenum. The longest survival time is observed in patients with gastric tumors. The clinical malignancy of the tumors increases in the more distal segments of the gastrointestinal tract [10,19].

The prognosis depends on the size of the tumor and on the number of mitosis per 50 high-power microscopic fields (assessed by a histopathologist) on the depth of the mucosal infiltration that may manifest itself macroscopically in the form of ulceration. Small tumors that not exceed 2 cm with less than 5 mitosis per 50 high-power microscopic fields are usually benign and have good prognosis. The malignant stromal tumor of the stomach has better prognosis in women than in men [9,10].

The recurrence rate and the metastatic risk of the stromal tumors depend on the staging of the neoplasm and it is presented below in detail: if the clinical malignancy has been assessed as low or medium the metastatic risk is estimated at 0%, in the high risk group at 54–73%, and in the majority of them during the first 3 years. The recurrence rate in the group of a very low risk amounts to 46%, in both low and medium risk 19%, and in high risk patients – 11–24% [10]. The evaluation of the clinical malignancy is presented in Table 1.

Table 1. Assessment of the clinical malignancy in GIST patients according to National Institutes of Health GIST Workshop [26]

Clinical malignancy	Size*	Mitotic count
Very low	<2 cm	<5/50 HPF
Low	2–5 cm	<5/50 HPF
Medium	<5 cm	6–10/50 HPF
	5–10 cm	<5/50 HPF
High	>5 cm	<5/50 HPF
	>10 cm	every
	every	>10/50 HPF

* determined by the maximum diameter of the tumor

Abbreviations: GIST – gastrointestinal stromal tumor, HPF – high power field

Treatment

The radical surgical treatment is the most effective treatment option for GIST. The 5-year survival rate after surgery amounts to 28–65% [43-46]. It is not necessary to resect the regional lymph nodes during the operation, because (as mentioned above) gastrointestinal stromal tumors do not metastasize to the regional lymphatic system. In more than 3/4 of the operated patients it is possible to perform macroscopically radical resection. However, in about 1/4–1/5 of these patients the surgical interventions are non-radical based on microscopy. About 20–40% of the surgery patients have intra-abdominal dissemination or liver metastasis. The subsequent reoperation of the relapse does not usually lead to the recovery. The mean survival time of patients with relapse of the neoplasm is estimated at 9–20 months [20]. Last years brought an enormous progress in the treatment of GIST, because endoscopic dissection (submucosal-mucosal resection) has been introduced, which allows a radical therapy of small tumors without malignancy features and limited to the submucosal layer.

Until recently patients with inoperable tumors have been qualified only for symptomatic treatment, because GIST are resistant to the conventional chemotherapy, and the role of radiotherapy has not yet been decisively established. The introduction of imatinib, an inhibitor of tyrosine kinase inhibitor (among others of KIT receptor), into clinical practice was a breakthrough in the treatment of patients with non-operative or metastatic GIST. Currently, several other drugs that could be used alternatively in patients with GIST resistant to imatinib, are being tested during clinical studies [10,19]

Gastrointestinal stromal tumors are a new and growing clinical problem. They have been commonly diagnosed for only the last several years and their diagnostics is extremely difficult. The most important diagnostic tool, besides the visualization, is histological and immunohistochemical examination. Sometimes only the surgical intervention is necessary to establish the diagnosis. Stromal tumors represent an enormous challenge, requiring close cooperation of gastrologists, surgeons, histopathologists and oncologists to make a quick, precise and correct diagnosis. The primary goal should be to balance the number of the diagnosed cases with the actual incidence because it seems that GIST have been so far underdiagnosed.

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