

A RARE GIANT EXTRA-GASTROINTESTINAL STROMAL TUMOR (GIST) IN A YOUNG MALE PATIENT

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Gastrointestinal stromal tumors (GIST-s) are the most common mesenchymal tumors. They occur usually in older age, through the whole digestive tube, but predominantly in the stomach (60%), and most rarely in oesophagus (<1%). Symptoms and signs of GISTs depend on the size and localization of the tumor. Diagnosis is based on pathohistological analyses that include immuno-histochemical staining. Prognosis of these tumors depend of mitotic index, size of tumor, localization, presence of necrosis, bleeding in tumor, infiltration of mucosa and serosa, presence of lymphogenic and liver metastasis. Regarding these parameters, GISTs are classified as high, intermediate, low or very low risk tumors. Standard therapy for GISTs is surgical treatment, and adjuvant treatment with inhibitors of tyrosine kinase depends on risk stratification. In this paper, the case of 37-year old male with giant GIST of extraintestinal localization is described. Tumors of this localization are extremely rare, and data about this issue in literature are scarce. *Acta Medica Medianae* 2014;53(4):37-41.

Key words: giant GIST, CD117, CD34, surgical treatment, Imatinib

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Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. The estimated incidence is 1/150000(1), but this covers only the clinically significant cases, while the number of microscopical GISTs is much higher. These tumors appear to arise from the interstitial Cajal cells or their precursors in myenteric plexus of gastrointestinal tract. Most commonly, they occur at the age over 50 in the stomach (60%), jejunum and ileum (30%), duodenum (4-5%), rectum (4%), colon and appendix (1-2%), and esophagus (<1%), and rarely as apparent primary extraintestinal tumors in the vicinity of stomach or intestines (2). However, GIST is extremely rare in patients younger than 30 years of age and in pediatric population (3). GISTs can be associated with diverse clinical presentations, depending on tumor localization and size. Symptoms of GISTs include early satiety, symptoms of anemia, intraperitoneal or gastro-

intestinal haemorrhage, abdominal pain or swelling. Some patients present with acute abdomen because of tumor rupture or intestinal obstruction (4). Size of GISTs in the majority of cases is approximately 5 cm at presentations, but they can be larger than 30 cm (5). Macroscopically, GISTs usually present as single nodules which on cross section can show cystic degeneration, necrosis or haemorrhage. Endoscopic biopsies are often insufficient for the diagnosis, and laparoscopic or laparotomic excisions are required for adequate histological diagnosis. The diagnosis of GIST is based on the morphology and the immunohistochemistry (CD117 and/or DOG1) (6). About 5% of GIST are CD117-negative. The number of mitosis has prognostic value and should be expressed as the mitosis count on a total area of 5mm², which refers to 50 high-power fields (HPFs). If the diagnosis is doubtful, mutational analysis for known mutations involving c-KIT and platelet-derived growth factor receptor alpha(PDGFRα) genes can establish the diagnosis of GIST (1).

The most important prognostic factors of GIST behavior are their size, mitotic index, and lately localization of tumors (1,4). Regarding disease behavior and metastatic potentials, GISTs are divided into very low, low, intermediate and high risk tumors. High risk GISTs have significantly worse prognosis than the others (1). Recently, several studies has shown that Ki67 index of proliferativity could be an independent prognostic factor for patients with GIST (7,8).

Standard treatment of localized GIST is surgical excision. The risk of relapse depends on

risk classifications. Adjuvant therapy with tyrosine kinase inhibitor, imatinib, over the three years after surgery is superior, regarding the overall survival, to one-year treatment (9). Therefore, adjuvant three-year treatment with imatinib is a standard treatment for high risk patients. Adjuvant therapy is not an option when the risk is low. For intermediate risk GISTs, it comes to a shared decision (10).

If it comes to the tumor rupture during surgery, adjuvant therapy is recommended, because of the risk of tumor dissemination. If surgery is not an option, imatinib pretreatment is recommended. This is also a case if the surgeon estimates that the surgery is safer after citoreduction (1,11).

Case report

Male patient, 37 years old, was admitted to emergency room because of abdominal swelling and weight loss, which started 6 weeks before admission. His general condition was good, and except for a palpable abdominal mass, other physical examinations were unremarkable. After the initial ultrasound and CT examinations, the patient underwent magnetic resonance, which described an intraperitoneal cystic tumor 310x260 mm compressing the liver ventrally and expanding to the pelvic region, with ascites in pelvis. The chest X ray showed mild pleural effusion on the right side. Laboratory findings showed high sedimentation rate - 80, and increased CRP -167mg/L, with mild leukocytosis and thrombocytosis and mild microcytic anemia. Complete biochemistry, except for mildly elevated lactat dehydrogenase, as well as coagulation parameters, were normal. During preoperative preparations, esophagogastroduodenoscopy and colonoscopy were performed, and the results were normal. After completion of diagnostic procedures, the patient was operated. Medial laparotomy was performed, and giant, partially cystic and partially solid tumor was observed. (Figure 1.)

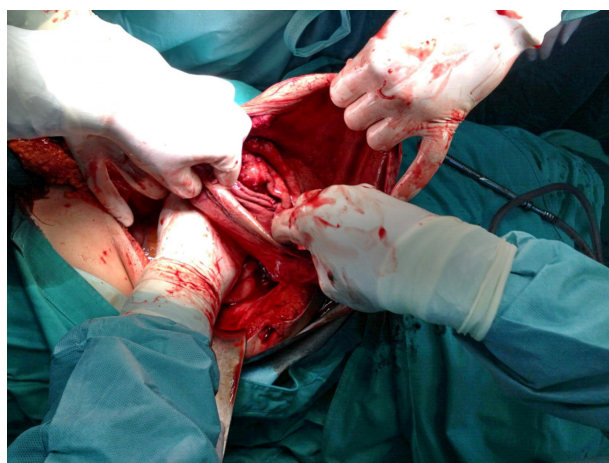


Figure 1. Intraoperative finding - tumor after fenestration of its cystic part and evacuation of liquid

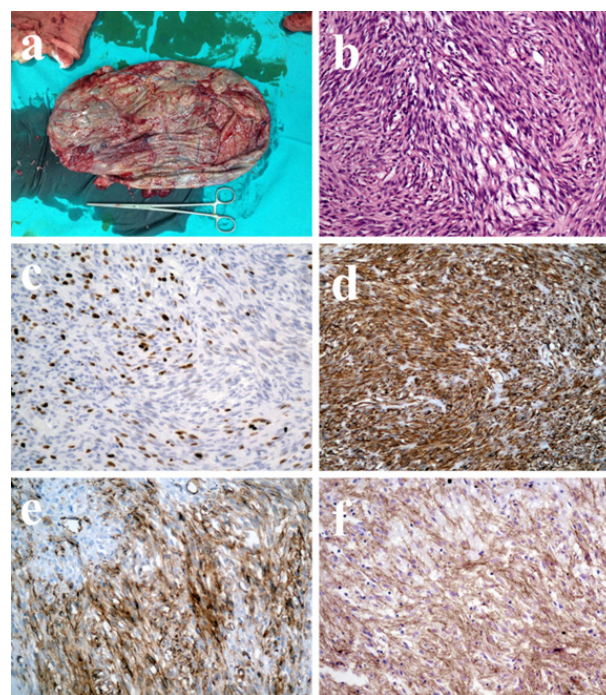


Figure 2. Extraintestinal GIST: a) Macroscopic aspect with haemorrhagic fields and focal necrosis; b) Spindle tumor cells with focal presence of nuclear pleomorphism (HEEx200); c) moderate expression of Ki67 in tumor tissue (LSABx200); d) diffuse strong expression of vimentin (LSABx200); e) diffuse moderate expression of CD34 (LSAB x 200); f) diffuse weak to moderate expression of CD117 (LSABx 200)

Tumor infiltrated the urinary bladder, parietal peritoneum and part of the jejunum. Fenestration of cystic part of tumor was performed, and 10 liters of "chocolate" liquid was aspirated. Extirpation of tumor *in toto*, with the resection of 15 cm of jejunum, part of greater omentum and urinary bladder roof was performed. Excision of infiltrated part of peritoneal peritoneum was also done. Jejunum-jejunal L-L anastomosis with linear stapler and closing of bladder roof was done, and the material was sent to pathohistological examination.

Pathohistological examination (Figure 2.) revealed tumor tissue built of bundles of spindle cells with focally present nuclear pleomorphism and necrosis in 10% of tumor tissue. Angioinvasion and prineural infiltration were absent. Margins of tumor were expansive and ruptures of tumor tissue were present. Mitosis count was 51/50 HPF. Tumor immunophenotyping showed positive CD 117, CD 34 and Vimentin; S-100 was positive in a small number of tumor cells, while Actin, Desmin and epithelial membrane antigen (EMA) were negative and Ki67 was 20%. There was no tumor tissue in resected part of jejunum, greater omentum, parietal peritoneum and urinary bladder roof.

Patient started to take Imatinib 400mg daily immediately after surgery, and one year after he was asymptomatic, without signs of tumor recurrence on control CT exams.

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common neoplasms of the gastrointestinal tract, making 0.1%-3% of gastrointestinal malignant tumors (12,13). In the past, these tumors were classified as leiomiomas, leiomyosarcomas, leiomyoblastomas or schwannomas. Mazur et Clark in 1983 had first described the concept of non-epitheloid tumors, and after that, these tumors were detached into separate histopathological category (14).

When it comes to GIST histogenesis, it is accepted that these tumors originate from interstitial Cajal cells, which come up from autonomous nervous system and are in charge of regulation of the gastrointestinal tract motility. These cells transfer the signals from ganglia to the muscular part of the gastrointestinal wall, enabling peristalsis; that is why they are called "pacemaker" cells (15,16). However, there are some opinions that GISTs rise from primitive cells of the gastrointestinal tract, which can differentiate into Cajal cells, and that could explain the appearance of these tumors in the omentum, mesenterium, retroperitoneum or gallbladder, meaning outside of the wall of digestive tube, where Cajal cells normally are not present (17).

The precise incidence of GISTs is not completely established, but it is observed that frequency of these tumors rise with age (18). The patient that we described was male, 37 years old at the time of surgery. It was pointed out in literature that GISTs more commonly occur in the 5th and 6th decades of life, however, there are reports about these tumors occurring in patients younger than 40 years, even in children (19,20). Numerous studies have shown the higher incidence of these tumors in men (21,22), but Lv et al. (18) demonstrated, based on extended research, that there is no significant difference in GIST distribution regarding gender. Same authors have observed that these tumors in men are more often associated with worse outcome compared to women.

GIST diagnosis, in spite of modern diagnostic procedures, represents a substantial surgical problem, regarding the fact that the final diagnosis is usually established intra- or postoperatively. In these circumstances, the extent of resection is determined according to morphological characteristics of tumor in operative field according to preoperative symptoms; the most reliable preoperative diagnostic procedures are CT and MRI (23,24). GISTs are asymptomatic in 10-30% of cases, detected incidentally or on autopsy. Symptoms generally depends on the localization in the gastrointestinal tract, but it was pointed out that GISTs can reach enormous size before the onset of symptoms and signs, like bleeding and anemia (24,25). Our patient was generally in a good condition, and except for weight loss and abdominal swelling, other symptoms were absent. Traditionally, it is considered that the tumor size is the

most important risk factor for the development of metastasis or local recurrence of tumor. Tumors greater than 10 cm belongs to high risk group of GISTs (26).

For the final diagnose of GIST, histopathology is the gold standard. These tumors are usually composed of spindle cells, rarer epitheloid, but mixed histological variants are also seen (2,2-4). There are some observations that GISTs, consisting of epitheloid cells, are more often localized in the stomach, while spindle cell GISTs are more often present in the jejunum and ileum (2,26).

Regarding that 95% of GISTs show expression of CD117, and 70% express CD34, these two markers are most important link in the histopathological diagnosis. In 20-30% of GISTs, expression of smooth muscle actin (SMA) is present, and 10% of these tumors show expression of S-100 protein. Taking into account that GISTs are of mesenchymal histogenesis, they all show expression to vimentin. Proliferative activity of tumor is determined regarding the expression of nuclear proliferative antigen Ki67 (26,27). We should have in mind that CD117 is not specific GIST marker, because of presence of his expression in rhabdomyosarcoma, angiosarcoma, glioma, germinoma and fibromatosis (26). The most important parameters of the tumor biological behavior are tumor size, mitotic index, localization, presence of necrosis and bleeding in tumor, infiltration of mucosa and serosa, and presence of lymphogenic and liver metastasis. One of the negative prognostic factors is tumor rupture as well (1,23,28,29).

It is accepted that GISTs, regarding the biologic behavior, are classified into several categories: very low risk (refers to benign type of tumor), low, intermediate and high risk GISTs that refer to aggressive biologic behavior (1,2,30). Tumors smaller than 2cm in diameter with mitotic activity < 5/50HPFs belongs to very low risk group (1,2). However, low mitotic index does not exclude malignant potential of tumors (22,24). GISTs usually give metastasis in the liver, rarely lungs and bones (31). It is observed that GISTs of small intestine have significantly worse prognosis compared to those in the stomach and oesophagus (1).

The final diagnosis in case of our patient was established according to the macroscopic appearance of tumor, localization, histologic type of growth and immunohistochemical analysis. The size of tumor (310x260mm) that fulfills the whole abdominal cavity infiltration of urinary bladder, parietal peritoneum, part of jejunum and tumor rupture, morphologic growth pattern (bundles of spindle cells with focally present nuclear pleomorphism), necrosis of 10% of tumor tissue, mitosis count of 51/50HPFs, positive expression of CD117, CD34 and vimentin point out to the high risk GIST.

It is established that in patients with locally advanced or metastatic GIST, Imatinib in the dose of 400mg daily, is a standard lifelong treatment

(1). In case of tumor progression, the dose of Imatinib increases to 800mg daily. If patient does not tolerate Imatinib, other tyrosine kinase inhibitor, Sunitinib, is introduced (1).

Conclusion

In this case report, we have presented the case of a rare giant GIST of extraintestinal localization in a younger male patient. Tumor, although

practically asymptomatic, infiltrated the urinary bladder, parietal peritoneum, and part of the jejunum. It can be concluded that the whole diagnostic algorithm was adequately performed. Both in the choice of surgical treatment and degree of surgical radicality we were guided by the tumor size, infiltration of local structures and presence of tumor necrosis. Postoperative micromorphologic and immunohistochemical analyses have confirmed the presumption for high risk GIST.

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RIJEDAK GIGANTSKI EKSTRA-GASTROINTESTINALNI STROMALNI TUMOR (GIST) KOD MLADOG BOLESNIKA

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Gastrointestinalni stromalni tumori (GIST) najčešći su mezenhimalni tumori. Pojavljuju se najčešće kod starijih osoba, duž cijele digestivne cijevi, ali dominantno u želucu (60%), a najređe u jednjaku (<1%). Simptomi i znaci GIST-a zavise od veličine i lokalizacije tumora. Dijagnoza se postavlja patohistološkim pregledom koji podrazumijeva i imunohistohemijske analize. Prognoza GIST-a zavisi od mitotskog indeksa, veličine tumora, lokalizacije, prisustva nekroze i krvarenjenja u tumoru, infiltracije mukoze i seroze, prisustva limfogenih metastaza i metastaza u jetri. U zavisnosti od ovih parametara, GIST mogu biti visokog, intermedijarnog, niskog i veoma niskog rizika. Osnovu terapije predstavlja hirurški tretman tumora, a dalji tretman sa inhibitorima tirozin kinaze zavisi od procjene stepena rizika. U ovom prikazu je predstavljen slučaj 37-godišnjeg muškarca sa gigantskim GIST-om ekstra-intestinalne lokalizacije. Tumori ove lokalizacije su ekstremno rijetki, a podaci o njima u literaturi oskudni. *Acta Medica Medianae* 2014;53(4):37-41.

ključne reči: gigantski GIST, CD117, CD34, hirurški tretman, Imatinib