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MORPHOLOGICAL AND IMMUNOCYTOCHEMICAL CHARACTERISTICS OF STROMAL GASTROINTESTINAL TUMORS

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Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors of gastrointestinal system and they are characterised by extreme variability in clinical, hystopathological and genetic features. It is considered that all GISToms have a malignant potential. Ethiological factors which cause GISToms have not been clarified yet, and genetic basis is not easy to be determined since GISToms are mostly sporadic. However, certain genetic and cytogenetic aberations which have been determined can be considered to have an impact on the onset of GISToms. Macroscopic picture is polymorphic, but they can most frequently be seen as large, mushroom-like, intraluminal, clearly limited pseudo-incapsulated submucosal masses. Hystomorphology of these tumors shows a high spectar of structural and cellular variations. They are most frequently built out of spindle cells (60-70% of cases), rarely of epitheloid (about 30% of cases) and very rarely of mixed and transitional type (intermedial). Stroma is predominantly loose or poorly colagenized with neoangiogenesis, which is markedly in GISToms with a higher malignant potential. Most of GISToms (95%) express transmembrane receptors KIT (CD 117), CD 34, vimentine, specific neurogenic and smooth muscle cells markers. The most successful therapies are: surgical ressection, imatinib and sunitinib (in case of imatinib resistence) therapy (tyrosine kinase receptor blockers). Research are being conducted all over the world with the aim of finding new and more efficient drug therapies that would not manifest resistency. *Acta Medica Medianae 2010;49(3):58-64.*

Key words: *gastrointestinal stromal tumors, GIST, c-kit protein, imatinib, morphology*

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchimal tumors of gastrointestinal system. Their apperance is characteristic of the male population. Even if they can be found in patients of all ages, it is often diagnosed in patients between the age of 40 and 80. GISTs used to be poorly defined tumors, resistant to therapy, but with the help of science progress they have become well-defined tumors that are possible to treat. They are characterised by extreme diversity in clinical, hystopathological and genetic characteristics. They gained in their importance since they became a real model for successful molecular therapy of tumors (1). They are very rare (their frequency of occurence is 10 to 20 cases per million residents in western countries); however, GISTs account for 1-3% of all the gastrointestinal neoplasms and about 5% of sarcomas of all soft tissues (2-4). It is believed that all GISTs have malignant potential, although small GISTs (diameter up to 1cm) have benign biological potential and micromorphology in high percent of cases (5,6). About 60-70% of GISTs occus in the stomach, 20-30% in the small intestine and 5% in colon and rectum and even esophagus. Rarely GISTs can develop in omentum, mesentery or even retroperitoeally (1,7).

Ethiology of GISTs

Ethiological factors that cause GISTs are not clearly defined, and their genetic basis is difficult to be determined since they are mostly sporadic. There are only a few cases in which GISTs have occured in more than one member in a family. About 85% of stromal tumors express mutation in exon 9, 11, 13, 17 in KIT proto-oncogen which codes c-Kit (CD117), a tirosin kinase receptor, while 3-18% express a mutation in exons 12, 14 and 18 on the platelet derived growth factor receptor alpha (PDGFRA) gene which codes PDGFRA. It is believed that interstitial

Cahal cells (ICC) extremely express KIT and that the loss of KIT receptor has a consequence of losing ICC function. No mutations were have been found in 5% of cases and it has been sugested that mutations are not always responsible for histogenesis of GISTs (2,3,8).

It is pointed out that cytogenetical aberations that involve the loss of 1p, 13q, 14q or 15q, loss of heteosigosity of 22q, numerical chromosomal aberations (monosomy of chromosome 14, monosomy of chromosome 22) and instability of nuclear and mitochondrial microsatelites are responsible for occurence of GISTs. Molecular genetic aberations include loss of p16 (INK4A) and p14 (ARF) heterozygocity, p15 metilation (INK4B), homozygous loss of Hox 11L1 gene and amplification of CMYC, MDM2, EGFR1 and CCND1 (9,10,11).

According to latest research, type of mutation is a key point for the occurrence, development and progression of disease, and specific mutations on KIT gene contribute to a worse prognosis of GIST (12,13). Mutations in c-kit gene can lead to a familial GIST syndrome, when GISTs occur in a much earlier age than usual. Difference between this syndrome and sporadic GISTs is that we can find the inherited mutation in every cell of organism and not only in cancer cells. We can very rarely find a mutation of PDGFRA gene in the etiology of this syndrome. Skin stains that are similar to those characteristic for neurofibromatosis (*caffee-au-lait*) can be found on the skin of the patients with familial GIST syndrome, so these patients used to be mistreated until tumor markers were developed. An increased risk for development of GIST has been noticed in patients that suffer from neurofibromatosis which is a consequence of NF-1 gene mutation. Occurrence of this tumor was also noticed as a part of Carneys triad (gastric GIST, paraganglioma and lung chondrom) (1). GISTs develop from ICC that are scattered around myenteric plexus, between circular and longitudinal muscle layer. They function as intestinal pacemaker cells that regulate motility of intestines. They have spindle or radial shape, and if the tumor exists they are larger with abundant cytoplasm and hyperchromatic large nucleus with prominent nucleolus (14,15).

Macroscopic appearance of GISTs

Macroscopic appearance of GISTs is polymorphic: most frequently they appear as large, mushroom-like, intraluminal, clearly limited pseudoincapsulated submucosal masses. Mucose is intact or with numerous erosions or ulcerations (Figure 1a). Solid nodular sarcomatoid structure is evident on the intersection field, with spots of hemorrhage, necrosis or with pseudocysts of different size that are giving them specific and at the same time distinctive appearance (Figure 1b). They rarely appear as large tumor masses that fill in the whole stomach lumen, thereby gaining its shape and turning its wall into the cystic diverticuloid structure, without infiltration except in the part where it emerges from depth when they are massive, necrotic-haemorrhagic and sarcomatoid (Figure 2a). Large dimensions and large lumen of stomach let them gain a relief and sculptural appearance of white marble when numerous spherical and band-like structures interlace (Figure 2b). Sometimes they imitate leiomyomas because of intramural localization, nodular appearance and extreme strength, especially if they are small (Figure 2c). And those of subserosal localization turn to abdomen and thereby gain a size that is sometimes even larger than 20cm, but they are very rare. The smallest (<1cm in diameter), asymptomatic, intramural or subserosal can be discovered only by chance during surgical interventions of different kind, ultrasound endoscopy or autopsy. When they are found in small intestine they are macroscopically hard to differ from stomach GISTs, except for frequent local wall widening, reminding us of diverticules. In colon they appear as sparsely, polypoid, submucosal and of harder consistence, with rare field of necrosa and hemorrhage.

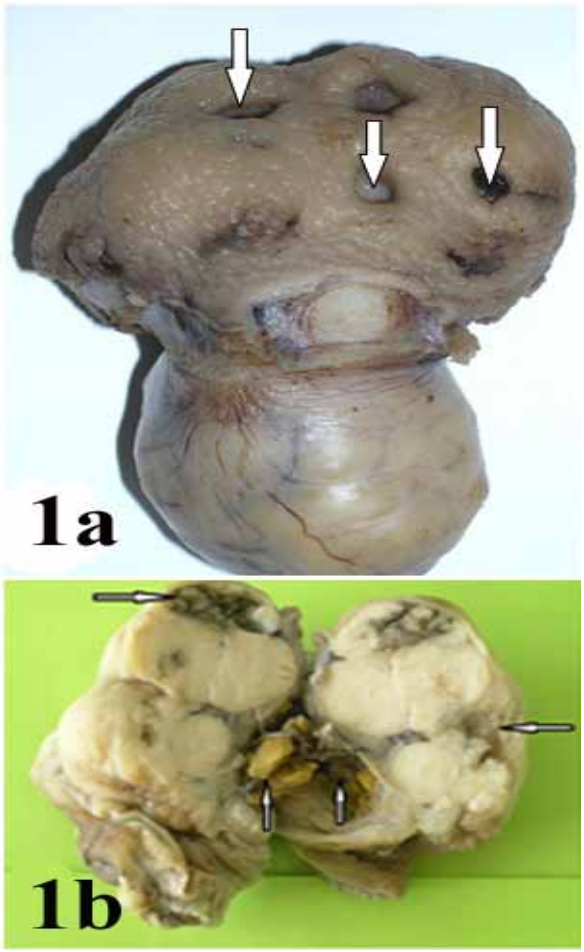

Figure 1. a) Mushroom-like appearance with pseudocapsule in the lower half and multiple ulcerations of mucosa (arrows) b) Characteristics of GISTs on section. Nodular compact structure with fields of haemorrhage (arrow pointing to the right), necrosis (arrow pointing to the left) and with cysts generation (arrow pointing up).

Figure 2 a) Compressive atrophy of the whole gastric wall with semissesile GIST. b) Irregular relief appearance of GIST, colored white. 2c) Intraoperative finding. Intramural localization of GIST with field of hemorrhage on section places.

Microscopic characteristics

Histomorphology of these tumors shows a high range of structural and cellular variations. They are most frequently built out of spindle cells (60-70% of cases, rarely of epitheloid (about 30% of cases), mixed and intermedial. Disposition of cells can be palisad, fascicular, meandering, nest-like, roseta-like or even compact and without any scheme and rule of disposition. Patohistologically spherical or giant cells can be seen and significant infiltration with mononuclears is rarely present (16). In the so called „classical presentation" with spindle cells, GIST is characterised with relatively monomorphic and homogenous distribution of cells whose borders are unclear and whose cytoplasm is pale eosinophilic. Nuclei are spindle or ovoid, with clear boundaries and unequally distribued chromatine. Sometimes, notched or lobular nuclei can be seen. Pleomorphism, polynuclearism and perripheral position of nuclei are rare, but it is possible to notice vacuolisation, nucleolysis or hyper-chromasia. Sometimes nuclei are palisad and sometimes semiorganoid layout of tumor cells is present. Colagenous matrix and fields of calci-fications are very rare (6,17-20). In the case of malignant presentation a high grade of cellularity is dominant with pleomorphic cythological and nulear characteristics (19,21). Epitheloid type of GIST is characterised by irregular nest-like organisation of cells, with frequent changes in stroma and variable celularity (Figure 3a). Cells show a less frequent equability, that is, it is possible to see a range of transitional forms – small round, poligonal, irregular, elongated and large pleomorphic forms. Cytoplasm is eosinophilic to dark eosinophilic and granular. Light cell epitheloid type is usually a consequence of vacuolisation in cytoplasm, so cells often gain a shape of a sinet ring which makes problems in diagnostics. Since this change cannot be seen on frozen preparations, it is assumed that it is an artefact that occured as a consequence of formalin fixation (19,22,23). Rare cytomorphologic types are determined by shape and size of cells, so that is how they get their names. Even thought these types occur very rarely, they represent the greatest diagnostic dillemas because of a high spectar of histopathological presentations (19).

Stroma is mostly built out of loosely or poorly colagenized connective tissue with angiogenesis, prominent in GISTs with higher malingnant potential. During tumor progression it often comes to acumulation of interstitial fluid, oedema and pseudocystic degeneration. If pseudocystic degeneration is dominant in tumor (more than 50% of tumor mass) it conditions macroscopic cystic appearance. Fibrous hyaline changes, mixoid stromal changes, haemorrhagia, necrosis and pseudocystic degeneration can be seen with the growth of GIST. One type of fibrous-hyaline changes defines a special type of „GIST with skenoid fibers", which is a prominent feature of interstitial GISTs. The so-called skenoid fibers are extracellular, thick, amorphic, dark-eosinophilic, irregular fibers, that remind us of yarn rolls or tree branches (19,21).

Immunohistochemistry

KIT protein (Figure 3b) and rarely CD34 protein are expressed on the ICC cells

membrane, so immunohistochemical detection of these receptors is a key point in GIST diagnostics. CD34 is at the same time a reliable marker for stromal neoangiogenesis of GISTs, which is an important link in malignant tumor progression (Figure 3c). KIT is expressed on differentiated ICC, mast cells and melanocytes as well on haematopoietic stem cells, pro-B and pro-T lymphocytes during development and on dendritic progenitor cells, erythroid cells, megakariocytes and myeloid line (5, 15, 24). In favor of GIST malignancy goes Intensive nuclear expression of ki-67 antigen, which detects all mithotic phases except of inactive phase (Figure 3d) (25). The most frequent used method in immunohisto-chemistry is ABC method (A-avidin, B-biotine, C-complex), which is based on a high affinity of avidin to biotine, as well as on the possibility of biotin binding to a secondary antibody which makes visualisation of wanted enzymes possible (Figure 3b, 3c, 3d). Research in the area of gene alterations is conducted with the aim to find adequate markers that would make early detection of GISTs possible as well as to warn of a relapse on time.So far, now it is known that most GISTs (95%) express transmembranous KIT receptors (CD117), CD34, vimentine, specific neurogenic and smooth muscle cell markers. A recent research showed that CD26 has a vital role as a tumor marker besides C-kit and CD34 markers that are already in the use in every day practise (26).

Diagnostics and therapy

Diagnosis of GISTs is usually made after laparotomy and formal pathological examinations, and the safest diagnostic methods represent CT and MRI because of the possibility of simultaneous examination of liver and peritoneum. The presence of GIST is rarely suspected before the operation, so diagnosis setting requires a high vigilance as well as knowledge of its visualization on radiograph. A study that included a high number of patients showed that the largest number had symptoms (GISTs in this group had an average size of 6cm), 20% did not have symptoms (the average size of tumors was 2cm) and 10% of GIST (average size of 1.5cm) are found only on autopsy.

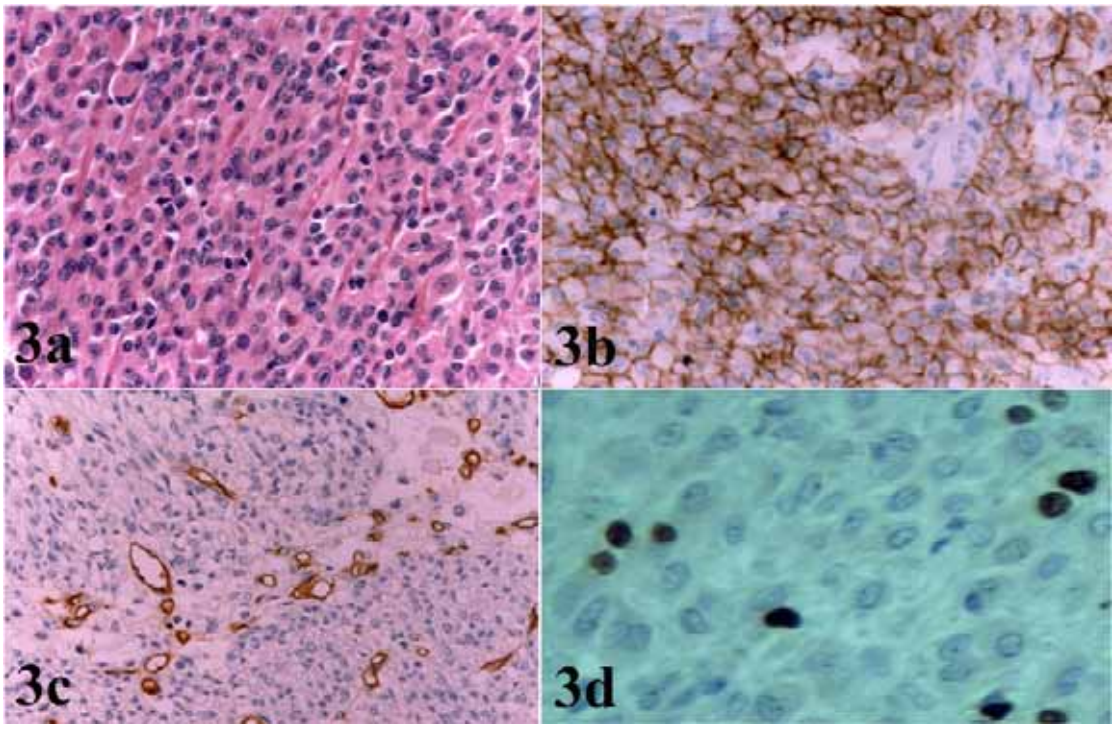

Figure 3a) Epitheloid-cell type: micromorphological characteristics. HEx250 3b) Epitheloid-cell type of GIST with intensive membrane activity. ABC: CD117x250. 3c) Striking angiogenessis in stroma. ABC: CD34x200. 3d) Intensive nuclear expression of ki-67 in rare cells. ABC: ki-67x300..

Table 1. Classification of GISTs according to the size of tumor and mithotic index (Ma CK et al, 2000)

Risk group	Size	Mithosis/50hpf
1. A group of very low risk	<2 cm	<5
2. A group of low risk	2 – 5 cm	<5
3. A group of intermediate risk	<5 cm	6 – 10 cm
or	5 – 10 cm	<5
4. A group of high risk	>5 cm	>5
or	>10 cm	Any activity
5. A group of certain malignancy: patients with proven metastases at the time of diagnosis.		

GISTs can reach extreme sizes before symptoms like hemorrhage and anemia occur. Symptoms mostly depend of the place of appearance and development and may include: dysphagia (esophagus), billiary obstruction (Vater's ampulla), intususception of small intestine, deathly hemorrhage if they rupture into peritoneum, and etc. Percutaneous biopsy of GISTs should be avoided whenever possible, because it can cause tumor rupture that results in hemorrhage and dissemination (1,4) GISTs can be classified according to tumor size and number of mitosis: group with very low risk, low risk, intermediate risk, high-risk group and certain malignant group (Table 1) (19).

Most frequently used therapy in the case of GISTs is resection and most of these tumors can be treated in that way, but recurrences occur in a high percent (20-40%). The most common complication that follows operation is distal methastasis in the liver (3,27,28). After the discovery of certain gene mutations that are a part of GIST etiology, imatinib was introduced into therapy of recurrent and unresectable GISTs. Imatinib selectively inhibits a group of tyrosinkiase receptors, including KIT and PDGFRA. Adjuvant and neo-adjuvant imatinib therapy is the most accepted in practice and it improves the prognosis of this disease, and it can be used in the case of advanced, recurrent and/or methastatic GIST. Despite great efficiency of this therapy and high security of its application, gastrointestinal and intraabdominal hemorrhage occurred in a few cases. Also, efficiency of this medication depends on a genotype that lies in the etiology of GIST as well as consequent changes of receptor functions (29). Sunitinib has the effect on imatinib resistant GISTs (15% of cases), but it also showed resistance to certain genotypes of GISTs (12,30). Studies on the impact of sunitinb on the initial stages of the disease are currently being conducted (12). Scientists hope that it will soon come to the discovery of new medications that would not show resistance (31). While pharmaceutical industry tries to find new target molecules for a safer method of treatment, the tendency of starting genetic therapy also exists (3,4,28,32,33). Imatinib and sunitinib are gaining in importance especially due to the fact that microscopic stages of tumors are discovered as well as inoperative stages of tumors in which therapy with medications is the only choice for now (24).

Conclusion

GISTs are heterogeneous group of mesenchimal tumors with moody clinical course. Because of heterogeneous cellularity, histological structure, mitotic activity and polymorphic angiogenesis, it is important to analyze numerous cutt-outs from the tumor as well as from the resection edges. Histological method is a "golden standard" of GIST diagnosis. For definite diagnosis, immunohistochemical tests are crucial: CD117 and/or CD34, smooth muscle cell actins, desmins, S-100 protein, vimentine and ki-67.

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MORFOLOŠKE I IMUNOCITOHEMIJSKE KARAKTERISTIKE GASTROINTESTINALNIH STROMALNIH TUMORA

Vuka Katić, Boris Đinđić, Vesna Živković, Danica Marković, Bojana Marković- Živković, Ivan Ilić i Dušan Mihajlović

Gastrointestinalni stromalni tumori (GISTomi) su najčešći mezenhimni tumori gastrointestinalnog trakta i karakterišu se izuzetnim šarenilom u kliničkim, histopatološkim i genetskim osobinama. Smatra se da svi GISTomi imaju maligni potencijal. Etiološki faktori koji izazivaju GISTome nisu jasno izdvojeni, a genetsku osnovu je teško odrediti jer su uglavnom sporadični. Međutim, otkrivene su izvesne genetske i citogenetske aberacije koje se mogu smatrati odgovornim za nastanak GISToma. Makroskopska slika je polimorfna, ali se najčešće javljaju u vidu velike, pečurkaste intraluminalne, jasno ograničene pseudoinkapsulisane submukozne mase. Histomorfologija ovih tumora pokazuje širok spektar strukturnih i celularnih varijacija. Najčešće su građeni od vretenastih ćelija (60-70% slučajeva), ređe od epiteloidnih (oko 30% slučajeva), i veoma retko od mešovitih i prelaznih (intermedijarnih). Stroma je pretežno sastavljena od rastresitog ili slabo kolagenizovanog veziva sa neoaniogenezom, upadljivom kod GISToma sa većim malignim potencijalom. Većina GISToma (95%) eksprimira transmembranske receptore KIT (CD 117), CD34, vimentin, specifične neurogene i glatko-mišićne markere. Najuspešnije terapije GISToma su: hirurška resekcija, terapija imatinibom i sunitinibom (blokatori tirozin kinaznih receptora). Širom sveta se sprovode istraživanja koja bi omogućila pronalaženje novih i efikasnijih lekova koji bi sprečavali rezistentnost. *Acta Medica Medianae 2010;49(3):58-64.*

Ključne reči: *gastrointestinalni stromalni tumor, GIST, c-kit protein, imatinib, morfologija*