

Novel perspectives on gastrointestinal stromal tumors (GISTs)

BOGDAN STELIAN MASTALIER MANOLESCU¹⁾, CRISTIANA GABRIELA POPP²⁾, VALENTIN POPESCU¹⁾, DAN ANDRAȘ¹⁾, SABINA ANDRADA ZURAC²⁾, COSTIN BERCEANU³⁾, AIDA TÎNCUȚA PETCA⁴⁾

¹⁾Department of General Surgery, "Colentina" Clinical Hospital, Bucharest, Romania

²⁾Department of Pathology, "Colentina" Clinical Hospital, Bucharest, Romania

³⁾Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Romania

⁴⁾Department of Obstetrics and Gynecology, "Elias" Emergency University Hospital, Bucharest, Romania

Abstract

Since they were described, gastrointestinal stromal tumors (GISTs) are, for pathologists and not only for them, a subject of controversy regarding histological origin, differentiation, nomenclature, malignant potential and prognosis. Before 1998, there were no certainties that GISTs were fundamentally different from other types of abdominal cancers in the big family of mesenchymal tumors. Before the discovery of *KIT* gene mutations, GISTs were most often classified as leiomyoma, leiomyosarcoma, leiomyoblastoma, and gastrointestinal autonomic nerve tumor. When a tumor is discovered, the first data obtained are initially assessed by one or more imaging tests, such as an ultrasound, computed tomography scan or magnetic resonance imaging. The imaging results define the size of the lesion and its anatomic location, which in the case of GIST is usually within the wall of the stomach or intestine. Depending on the experience of the medical team – radiologist, gastroenterologist or surgeon – reviewing the imaging tests and correlating them with the general patient profile, the differential diagnosis is reduced and GIST may become the main suspect.

Keywords: gastrointestinal stromal tumors, mesenchymal tumors, gastrointestinal cancer.

Introduction

Since they were described, gastrointestinal stromal tumors (GISTs) are, for pathologists and not only for them, a subject of controversy regarding histological origin, differentiation, nomenclature, malignant potential and prognosis. All these controversies have two eras: one before *c-kit* and the other one after discovering *c-kit* (CD117) proto-oncogene and its role in GISTs. In 1998, Hirota *et al.* [1] sequenced *c-kit* complementary DNA and described the genes that encodes for a proto-oncogenic receptor tyrosine kinase. They initiate their study from five cases of GIST (name introduced in 1983 by Mazur & Clark) [2] that showed mutations in the region between the transmembrane and tyrosine kinase domains [1]. This study postulated also other significant data about GISTs: their demonstrated origin in interstitial cells of Cajal and their precursors (also demonstrated by Kindblom *et al.* in the same year, using immunohistochemical and ultrastructural data [3]), their large immunohistochemical positivity for CD117 and CD34 and the fact that multiple mutations of *c-kit* are possible in GISTs [1].

Later, in 2003, another set of mutations was identified in the 5% of GIST that were negative for *c-kit*: platelet-derived growth factor receptor α (*PDGFR* α) activating mutations [4, 5]. These studies established that mutations of *c-kit* and *PDGFR* α are mutually exclusive in GISTs, both oncogenic events having the same biological consequence. This discovery came in the era of imatinib, the first antineoplastic agent that was efficient in treatment of

GISTs by inhibiting tyrosine-kinase. *PDGFR* α mutation was linked by a more frequent resistance to imatinib but also with some characteristic features: *PDGFR* α -positive GISTs have more often epithelioid morphology, gastric localization and are negative for CD117 immunohistochemical assay [5].

From clinical point of view, GISTs are a rare type of tumors, yet the most common mesenchymal tumor of the digestive tract. They represent less than 1% of all gastrointestinal (GI) tumors [6]. The importance of correct identification of GIST resides in the use of the available specific, molecular-targeted therapy with tyrosine kinase inhibitors (TKIs) [7].

The annual incidence reported in the literature varies by region: 3.2–6.8 cases per million persons in the United States; 2.1–14.5 cases per million persons in Europe; and 11.3–19.7 cases per million persons in Asia [8]. However, the real incidence cannot be evaluated, because many tumors have not been tested for the characteristic *KIT* or *PDGFR* α gene mutations. In addition, small, indolent GIST, only a few millimeters in diameter, are common in the general population and are not included in cancer registries [9, 10].

Multiple studies created a profile of GIST patients: these tumors are more common in older males, blacks, and Asian/Pacific Islanders. The average age at diagnosis ranges from 62 to 75 years, with peak incidence in the 8th decade of life. It is estimated that approximately 10% to 25% of patients have metastatic disease at presentation [11].

Pathology and genetics

The typical origin is within the muscularis propria of the GI tract. Before the discovery of *KIT* mutations, GISTs were frequently classified as leiomyoma, leiomyosarcoma, leiomyoblastoma, schwannoma, and gastrointestinal autonomic nerve tumor. Some of these tumors have the origin in the smooth muscle tissue of the GI tract (leiomyoma and leiomyosarcoma), while others have neural origin (schwannoma, neuroendocrine tumor), and some such as fibromatosis or desmoid tumor are derived from connective tissue cells.

GISTs frequently associate gain-of-function mutations in the *c-KIT* gene. In normal cells, activation of the receptor only occurs after binding of the corresponding ligand (the stem cell factor), while gain-of-function mutations result in a constitutively active receptor without the ligand binding activation. This auto-activation results in stimulation of numerous downstream signal transduction pathways including the RAS/RAF/ERK (transforming oncogene found in rat sarcoma/rapidly accelerated fibrosarcoma/extracellular signal-regulated kinase), JAK/STAT (Janus kinase/signal transducer and activator of transcription), PI3K/Akt/mTOR [phosphatidylinositol 3 kinase/protein kinase B (PKB) a.k.a. Akt/mechanistic target of rapamycin], and SRC (sarcoma proto-oncogenic tyrosine) kinase pathways and ultimately results in malignancy [12].

In tumors without mutated *c-KIT*, the mutations responsible for the activation are in the *PDGFR α* gene. In total, 3–5% of all GISTs have a mutated *PDGFR α* [13], which induces activation on the same signal transduction pathways as *c-KIT*. In 5–10% of tumors, neither mutations (*c-KIT* nor *PDGFR α*) can be found, but the explanation resides in the phosphorylation of *KIT* that was observed, so it is likely that other kinases yet to be identified are involved in tumor development [12].

Less than 5% of GISTs occur in conjunction with syndromes/diseases, such as neurofibromatosis type 1 (NF1), Carney triad syndrome, and other familial diseases [10, 14, 15].

Diagnosis

Clinical diagnosis

GISTs are associated with a broad range of presentations. Many are identified clinically because they cause symptoms, but some are identified at autopsy, especially small, intestinal tumors. Small GISTs that are smaller than 2 cm usually do not produce any symptoms and are detected incidentally during abdominal exploration, endoscopy, or radiological imaging [16]. In a recent population-based study, the median tumor size of GISTs that were detected based on symptoms, incidental findings, or during an autopsy were 8.9 cm, 2.7 cm, and 3.4 cm, respectively [17].

Patients with a suspected GIST may present with various symptoms, including, but not limited to, early satiety, fatigue secondary to anemia, intraperitoneal hemorrhage, intraluminal gastrointestinal bleeding, or abdominal discomfort from pain or swelling. Some patients may present with an acute abdomen (as result of tumor rupture,

gastrointestinal obstruction, or appendicitis-like pain), which requires immediate medical attention [18]. Despite the large size of some GISTs, clinical evidence of gastrointestinal obstruction is uncommon.

Dissemination may occur through locoregional infiltration or a hematogenous route of spread, most often to the liver, omentum, and peritoneal cavity. Metastases can also be found in the soft tissues (such as the abdominal wall) and rarely in the lungs and pleura, bone, or lymph nodes.

Imaging

Imaging is performed to assess tumors (including diagnosis, initial staging, restaging), monitor response to therapy, and perform follow-up surveillance of possible recurrence. Computed tomography (CT) scan and magnetic resonance imaging (MRI) are very effective at delineating extent of disease. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) is very effective at identifying extent and activity of GIST [18].

GIST can be suspected whenever there is a rounded to oval, circumscribed mural or extramural non-mucosa-based mass of any size that involves or is closely associated with the stomach, intestinal segments, or lower esophagus. However, in some cases, such lesions prove to be other mesenchymal tumors, unusual variants of carcinomas, neuroendocrine tumors, or even lymphomas.

The radiology of GISTs, especially the gastric ones, can be highly variable including tumors with intraluminal, intramural, external components and with pedunculated extramural and cystic appearances. Any larger GIST in the intestines typically forms an externally extending mass that is often centrally cystic and may fistulate into the lumen. Some small intestinal GISTs form dumbbell-shaped masses with intramural and external components [11, 19, 20].

CT (or occasionally MRI) is the initial imaging modality when evaluating abdominal mass or nonspecific abdominal symptoms. Contrast-enhanced CT is the preferred imaging modality to characterize and evaluate the extent of an abdominal mass, and assess the presence or absence of metastasis at the initial staging workup for biopsy-proven GIST. At presentation, the mass is typically exophytic, and the origin may be difficult to identify when the mass is very large. When a small tumor is found incidentally during endoscopy, the extraluminal extent of disease should be evaluated using CT.

Baseline CT should be performed with oral contrast administration to define bowel margins. More importantly, use of intravenous contrast is essential to observe the degree and pattern of enhancement and the tumor vessels. The portal venous phase images of enhanced CT (routine CT at most radiology practices) may mask the hypervascular hepatic metastases from GIST, because the enhancement of the tumors becomes similar to that of the surrounding hepatic parenchyma. Well-performed multiphasic (*e.g.*, biphasic or triphasic) imaging techniques would be necessary to recognize these hypervascular hepatic metastases. However, if unenhanced and enhanced CT images are carefully compared, this assessment may

avoid “missing” and “pseudo new” lesions on follow-up CT. Unenhanced CT images are also useful in detecting intratumoral hemorrhage, which can mask a decrease in tumor density or enhancement in responding tumors [18].

Typically, GIST is a solid hyperdense-enhancing mass on CT. However, large GISTs (>10 cm) are often more complex because of necrotic, hemorrhagic, or degenerating components.

CT scans with intravenous contrast yield excellent results for monitoring patients during therapy and surveillance, and are the preferred routine imaging modality for patients with GIST on TKIs therapy [18]. When a GIST responds to imatinib, it generally becomes homogenous and hypodense. The tumor vessels and solid enhancing nodules disappear. These changes can be seen within one to two months in most GISTs with a good response to imatinib, and have been shown to have a prognostic value and represent a favorable effect of therapy on the disease, even in the absence of anatomic shrinkage of the tumor bulk. Recognizing the pattern of tumor response on CT is particularly important in the early stage. For patients with marginally resectable GISTs, knowledge of these early changes might be beneficial in surgical decision-making. In CT scans, peripheral thickening and enhancing of cystic metastases can be a sign of an evolving resistance and newly progressing tumor even without size increase [21, 22].

In patients who have undergone surgical resection of GISTs, CT is performed for surveillance of metastatic or recurrent disease, and abdominal/pelvic CT scans should be obtained every three to six months. For very low-risk GISTs, less-frequent follow-up is appropriate. In patients with advanced disease, CT is an excellent imaging modality to monitor disease during the course of treatment and surveillance. FDG-PET can be considered when CT findings are inconclusive or inconsistent with clinical findings.

Gross examination

GISTs are ranging from a couple of millimeters to large tumors with maximum diameter over 10 cm. Most patients have, in the moment of diagnosis tumors larger than 5 cm [23]. The most common localization is the stomach (about 60%), followed by jejunum and ileum (about 30%). They are rare in the other parts of digestive tract (4–5% duodenum, 4% rectum, 1–2% colon and appendix, <1% esophagus) [22] and extremely rare in extra-digestive sites (mesentery, omentum, abdominal wall, retroperitoneum, urinary bladder) [24, 25].

GISTs gross appearances are diverse, usually they present as nodular mass within the digestive wall, but they also can be described as endoluminal (submucosal) or exoluminal (serosal) processes [26, 27]. Also, cystic and diverticular tumors have been described [22, 27, 28]. Sometimes, large tumors can protrude to the serosal surface, having a significant extra-digestive component that can mask the real localization [28, 29]. Submucosal tumors are sometimes ulcerated [28]. Macroscopic evaluation reveals usually a soft, elastic tumor, tan-white

on the cut-surface, with areas of hemorrhagic necrosis and cystic degeneration (especially in large tumors) [28].

Microscopic features

GISTs can exhibit two cardinal microscopic patterns:

(1) Spindle cell type is the most common. The tumor is composed of densely packed short fascicles and whorls (Figure 1, a–c). Tumor cells are spindle-shaped, monotonous with large, ovoid nuclei with uniform chromatin and inconspicuous nucleoli (Figure 1d). Cytoplasm is usually abundant, pale-eosinophilic, with fibrillar aspect (Figure 1, d–f). Nuclear palisading is frequent (Figure 2, a–c). Usually, spindle-cell GISTs are exhibiting minimal cytological atypia and variable mitotic activity (Figure 1d). Clear perinuclear vacuoles are seen (Figure 1e). These are processing artifacts and are not visible on frozen section specimens. In small bowel GISTs, are frequently seen brightly eosinophilic, prominent collagen fibrils, called skenoid fibers [28, 30].

According to Miettinen & Lasota [31], spindle cell GISTs can be subdivided in four subtypes: sclerosing spindle cell, palisading-vacuolated, hypercellular and sarcomatous subtype with different morphologic features and prognosis [31].

(2) Epithelioid type exhibits, usually, mild or even marked pleomorphism. The proliferation is composed from sheets and nodules of more round cells with abundant cytoplasm and more visible cellular limits (Figures 3a; Figure 4, a–f; Figure 5, a–c) [14, 28]. This type is more frequent in the gastric antrum [31].

Also, Miettinen & Lasota identified four subtypes with variable morphology and malignant potential: sclerosing epithelioid, dyscohesive, hypercellular and sarcomatous [31].

Mitotic index is the main criterion of grading GISTs and, therefore, must be reported in all cases. Most pathologists are reporting mitotic count on 50 HPFs (high-power fields) (an area of approximately 8 mm²) from the most mitotically active area, as recommended first by Miettinen *et al.* [19]. This feature needs thorough evaluations, since within the tumor there are multiple structures than can be mistaken for mitotic figures: irregular-shaped lymphocytes, neutrophils, apoptotic bodies (Figure 1f) [32]. Newer recommendation, including *World Health Organization* (WHO) guidelines, are proposing an area of 5 mm² for analysis [33]. It is also very important to choose the accurate “hot-spot” for assessment of mitotic index, since GISTs can have a high intratumoral heterogeneity that can lead to significant errors [34].

Succinate dehydrogenase (SDH)-deficient GIST is a newly described subtype of GISTs that fail to respond to imatinib. They are gastric epithelioid GISTs, usually multiple, with indolent course, commonly diagnosed in metastatic stage (with liver and lymph nodes metastases). Although they do not respond to imatinib, they have a long evolution with a very good survival even if they are diagnosed in metastatic stage. The majority of pediatric GISTs are included in this category, some of them arising in patients with Carney–Stratakis syndrome [35–37].

Immunohistochemistry

The vast majority of GISTs is strong and diffuse positive for CD117 (c-kit) (Figures 1g, 2d, 3b and 5d) [28, 38]. Even though *KIT* receptor tyrosine kinase is a transmembranar protein, positivity is usually pan-cytoplasmic [19, 38]. This expression is considered to be constitutional and not related strictly to the mutation, since some GISTs without c-kit mutation are (strong or weak) immunohistochemical positive for CD117 [15, 19]. A minority of GISTs (about 5%) are negative for CD117, usually the ones harboring *PDGFRA* mutation [39]. Although CD117 is a highly sensitive marker for GISTs, it lacks specificity. Many tumors with some similar morphology and frequent intra-abdominal localization are positive for CD117: angiosarcoma, granulocytic sarcoma, seminoma, clear cell sarcoma, mastocytoma, angiomyolipoma, epithelioid sarcoma, gastrointestinal autonomic tumor, mesenteric fibromatosis, synovial sarcoma [40–44].

PDGFRA

Although it is probable that *PDGFRA* mutant GISTs can be stained with this marker, it is not widely used because it did not demonstrate its reliability on paraffin-embedded tissue [31, 45, 46].

DOG1 marker was discovered in GISTs (its name comes from “discovered on GIST 1”) and has the great quality of being expressed ubiquitously in these tumors, irrespective of *KIT* or *PDGFRA* mutation status [47]. DOG1 is a calcium-activated chloride channel protein expressed specifically in GISTs. Although DOG1 gene was identified, several studies failed to identify mutations of this gene in GISTs (Figures 1h, 2e, 3c and 5e) [48, 49].

CD34

This hematopoietic stem cell antigen is positive in most GISTs, but its lack of specificity (it is also positive in vascular, fibroblastic and different stromal tumors)

limits its use in diagnosis of GISTs [31]. Usually, spindle cell type tumors are more diffusely positive than epithelioid variants of GISTs (Figures 1i, 2f and 3d) [40].

Muscle cell markers

Some GISTs are positive, at least focally, for alpha-smooth muscle actin (α -SMA) (Figures 1k, 2g, 3e and 5f), desmin (more often gastric epithelioid tumors) (Figure 1j), heavy-caldesmon, but these are not specific, nor sensible markers and do not help differential diagnosis [31, 50].

Prognostic markers

Ki67 is a proliferation marker, expressed in all nuclei except those in G0 phase (Figure 2i). Multiple studies failed to identify a “cut-off” value for Ki67 expression useful in routine practice, but still, there is widely accepted that a high Ki67 index indicates a high risk of unfavorable evolution [31, 51, 52].

p53 is a transcription factor, involved in the tumor suppression. Usually, p53 prevents mitosis of genetically damaged cells, directing them to apoptosis. In many tumors, including GISTs, p53 gene is mutated. Over-expression of p53 in GISTs is a negative prognostic factor [53].

p16, a regulator of cell cycle from the cyclin-dependent kinase 4-inhibitor complex, is also a tumor suppressor. In GISTs, p16 expression is usually lost, fact considered a poor prognostic indicator [31, 54].

bcl-2, an antiapoptotic mitochondrial protein, over-expression in GISTs is associated, by some authors, with the malignant behavior. More recent studies failed to verify this hypothesis [31, 55].

Other markers

Some GISTs are expressing, usually weak and focal, different markers like: S100 protein (especially small intestine tumors) (Figure 2h), nestin, neurofilament 68, keratins 18 and 8 [50, 56]. Vimentin is uniformly positive in all GISTs [31].

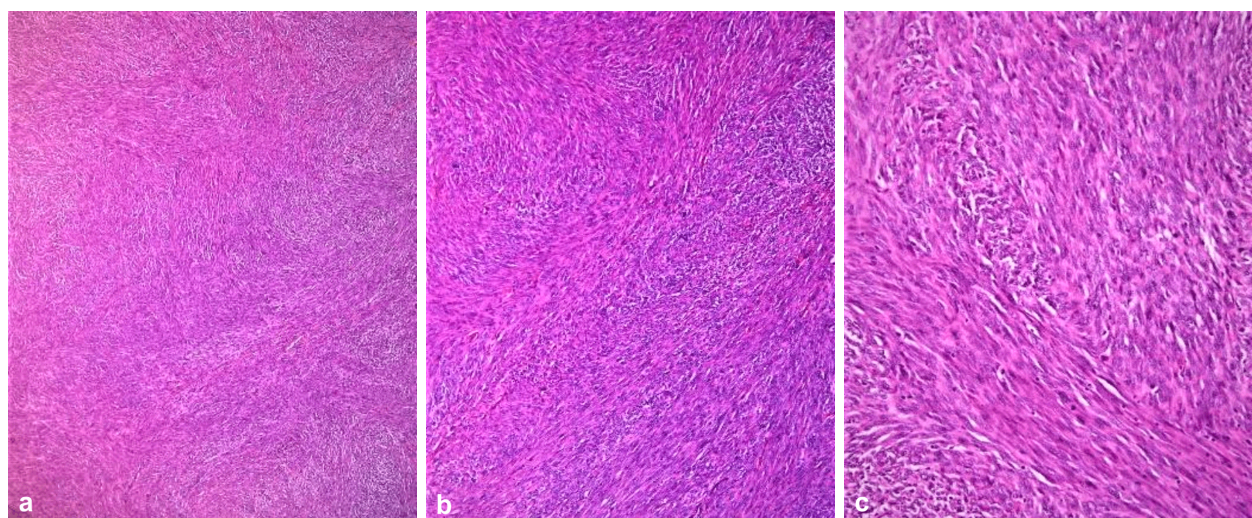


Figure 1 – Gastric GIST (male, 77 years old). Spindle cell GIST. Highly cellular proliferation (a) composed from short fascicles (b) of spindle-shaped, elongated cells with mild pleomorphism (c). Hematoxylin–Eosin (HE) staining: $\times 40$ (a); $\times 100$ (b); $\times 200$ (c).

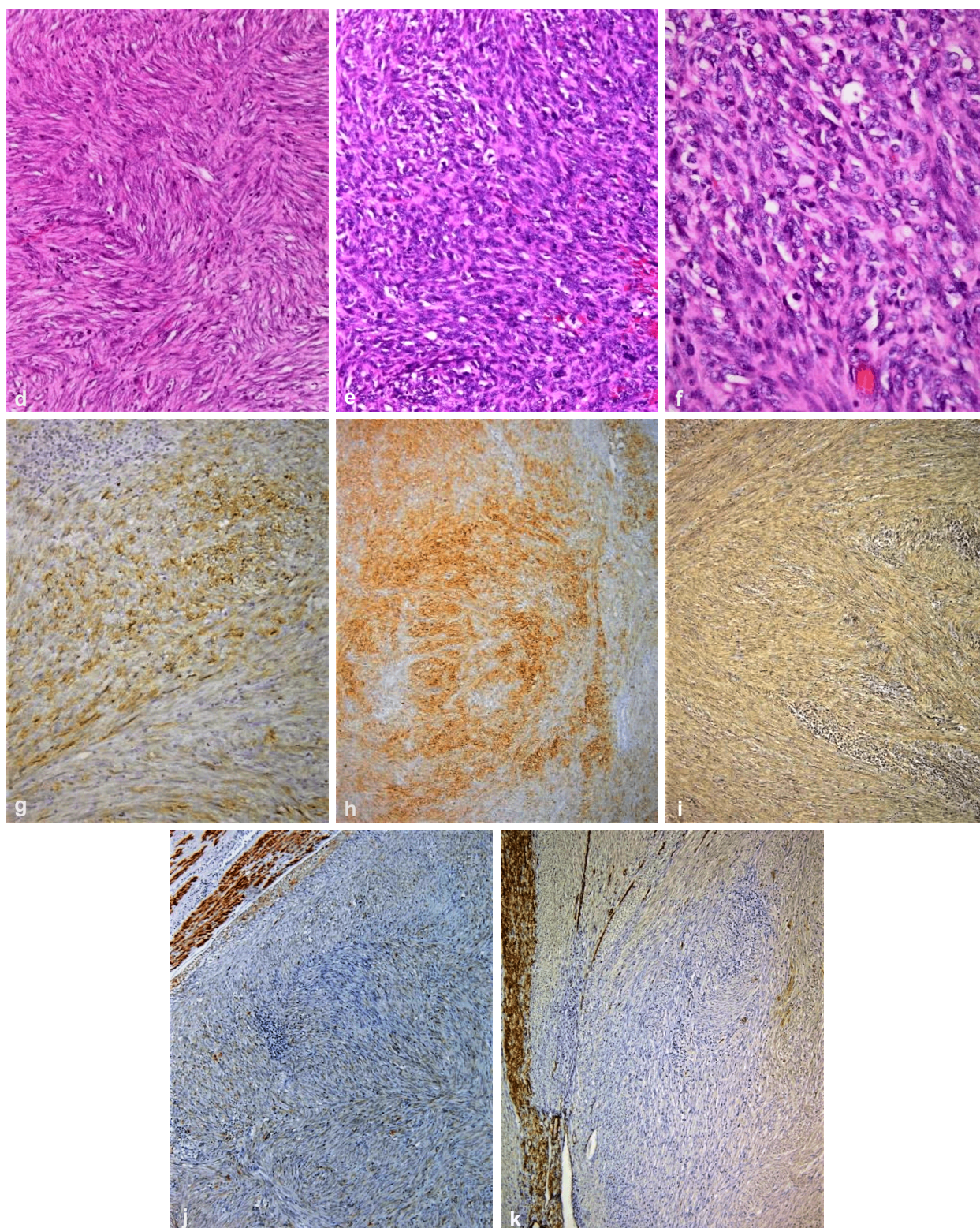


Figure 1 (continued) – Gastric GIST (male, 77 years old). Spindle cell GIST. Tumoral cells have large, ovalar nuclei, granular chromatin and inconspicuous nucleoli (d). Some clear perinuclear vacuoles are readily visible (e). Numerous lymphocytes and mast cells are visible, as small cells with dark, round nuclei and scarce cytoplasm, among tumoral cells (f). Note one asymmetrical mitosis (d). Tumoral cells are positive for CD117 (c-kit) (g), DOG1 (h) and CD34 (i). Tumoral cells are negative for desmin (j), which is positive in smooth muscle fibers from gastric muscularis propria (left superior corner), and α -SMA (k), which is also positive in smooth muscle fibers from gastric muscularis propria (left third) and in vascular walls. HE staining: $\times 200$ (d and e); $\times 400$ (f). CD117 immunostaining: $\times 200$ (g). DOG1 immunostaining: $\times 100$ (h). CD34 immunostaining: $\times 100$ (i). Desmin immunostaining: $\times 100$ (j). α -SMA immunostaining: $\times 100$ (k).

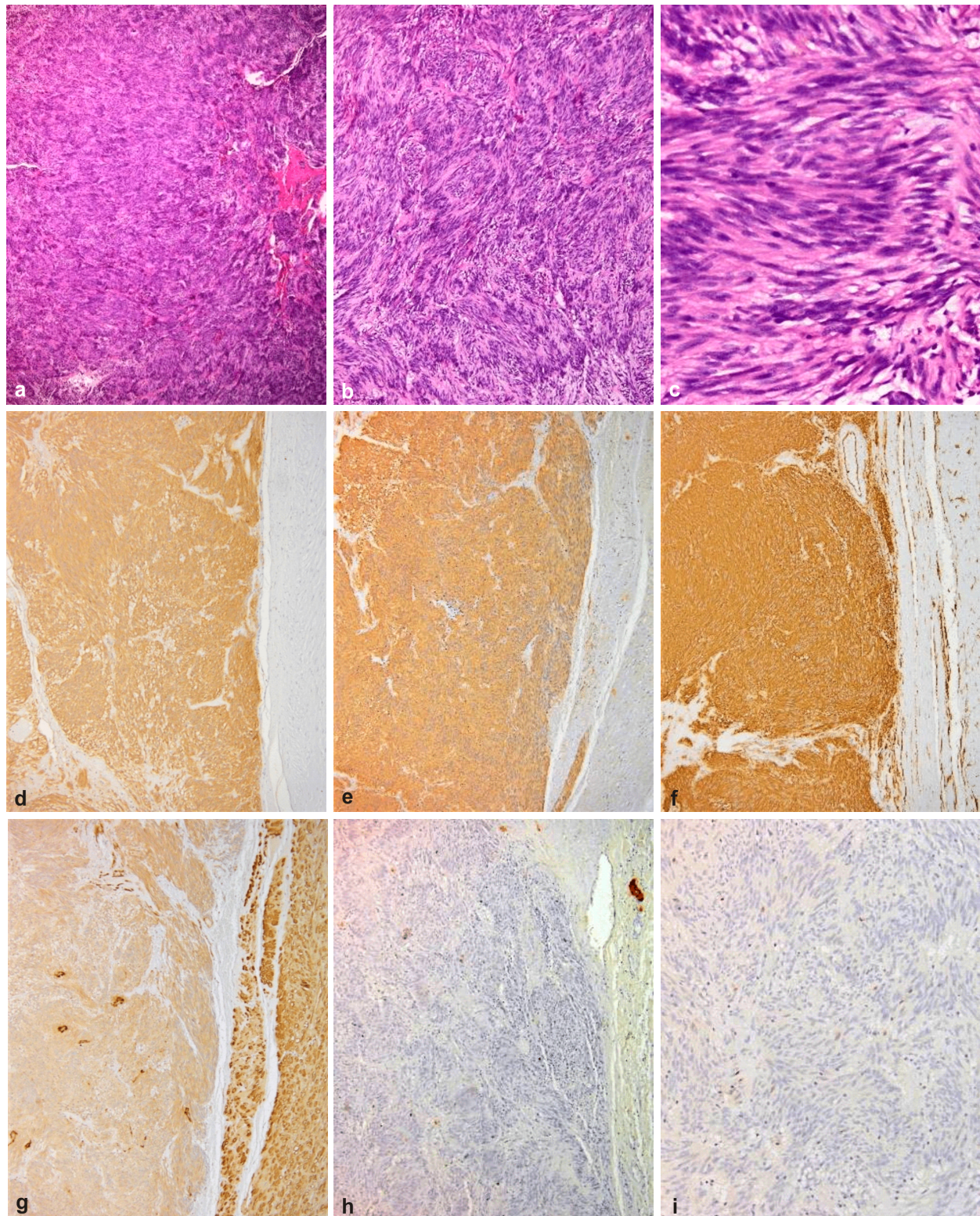


Figure 2 – Ileal GIST (male, 70 years old). Spindle cell GIST with prominent palisading of nuclei and schwannoma-like appearance (a). Note dense cellular proliferation composed from spindle-shaped large cells with elongated nuclei, arranged in small bands (b), alternating with somehow more clear areas, devoid of nuclei (c). Tumor cells are strongly positive for CD117 (d), DOG1 (e) and CD34 (f). Note, in all three images, muscularis propria (right third), which is negative for all these markers. Weak positivity of tumor cells for α -SMA (g) – note the strong positivity of vascular walls and smooth muscle fibers (right third). S100 (h) is negative in tumor cells – note in the upper right corner a small nervous fascicle, which is strongly positive. Ki67 (i) is positive in some of the tumor nuclei (global index 6–7%). HE staining: $\times 40$ (a); $\times 100$ (b); $\times 400$ (c). CD117 immunostaining: $\times 100$ (d). DOG1 immunostaining: $\times 100$ (e). CD34 immunostaining: $\times 100$ (f). α -SMA immunostaining: $\times 100$ (g). S100 immunostaining: $\times 100$ (h). Ki67 immunostaining: $\times 200$ (i).

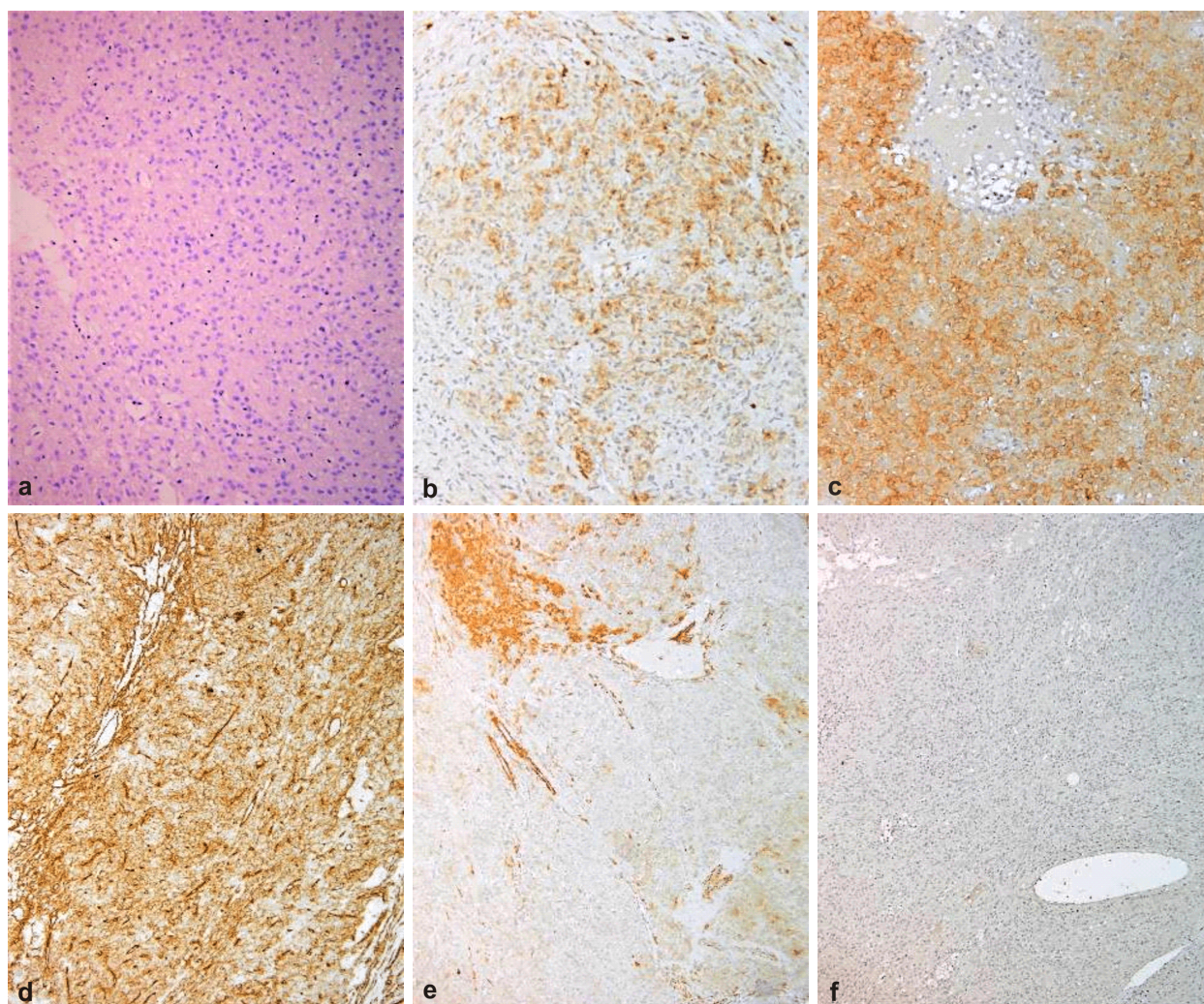


Figure 3 – Colonic GIST (female, 69 years old). Epithelioid GIST. Sheets of medium size ovalar cells, with no significant polymorphism or atypia (a). Tumor cells are positive for CD117 (c-kit) (b) and DOG1 (c). CD34 (d) diffusely and strongly positive in tumor cells. α -SMA (e) and cytokeratin (CK) 8/18 (f) are negative in tumor cells. Note, in the (e) image, that α -SMA is positive in vascular walls and in some smooth muscle fibers in the left superior corner. HE staining: $\times 200$ (a). CD117 immunostaining: $\times 100$ (b). DOG1 immunostaining: $\times 100$ (c). CD34 immunostaining: $\times 100$ (d). α -SMA immunostaining: $\times 100$ (e). CK 8/18 immunostaining: $\times 100$ (f).

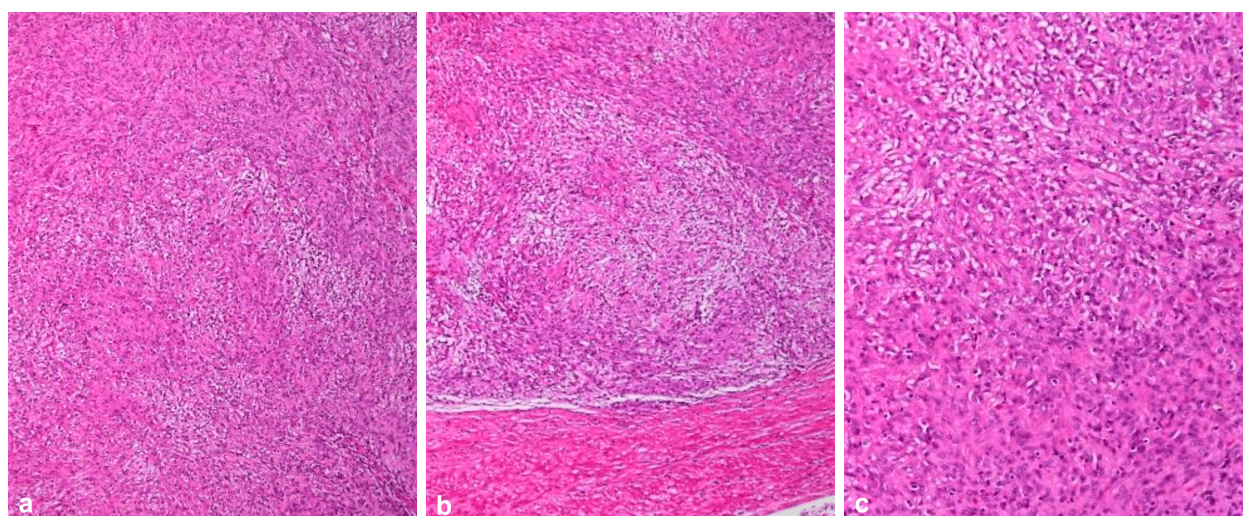


Figure 4 – Gastric GIST (male, 64 years old, hepatic metastasis in the moment of diagnostic). Epithelioid GIST. Sheets and poorly defined nodules composed of ovalar cells, intermingled with rare spindle-shaped ones (a). In the (b) image, you can see, in the inferior third, muscularis propria. Also, some perinuclear clear vacuoles are visible (c). HE staining: $\times 100$ (a and b); $\times 200$ (c).

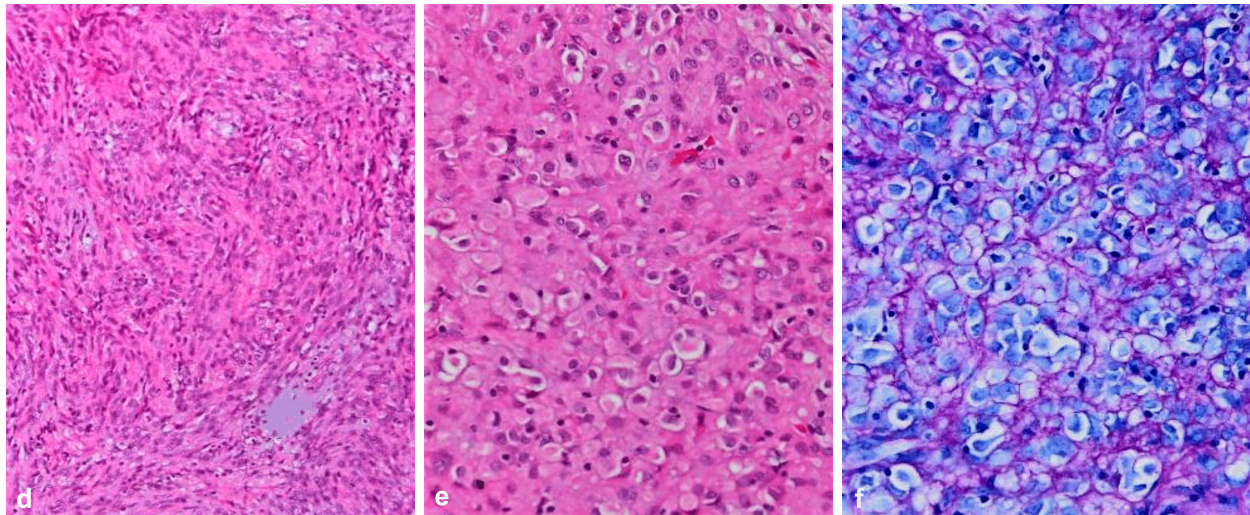


Figure 4 (continued) – Gastric GIST (male, 64 years old, hepatic metastasis in the moment of diagnostic). Epithelioid GIST. Epithelioid cells with visible cell borders, abundant cytoplasm and hyperchromatic, slightly irregular nuclei (d–f). Note, in the (d) image, an area of myxoid change of the tumor stroma. HE staining: $\times 200$ (d); $\times 400$ (e). Giemsa staining: $\times 400$ (f).

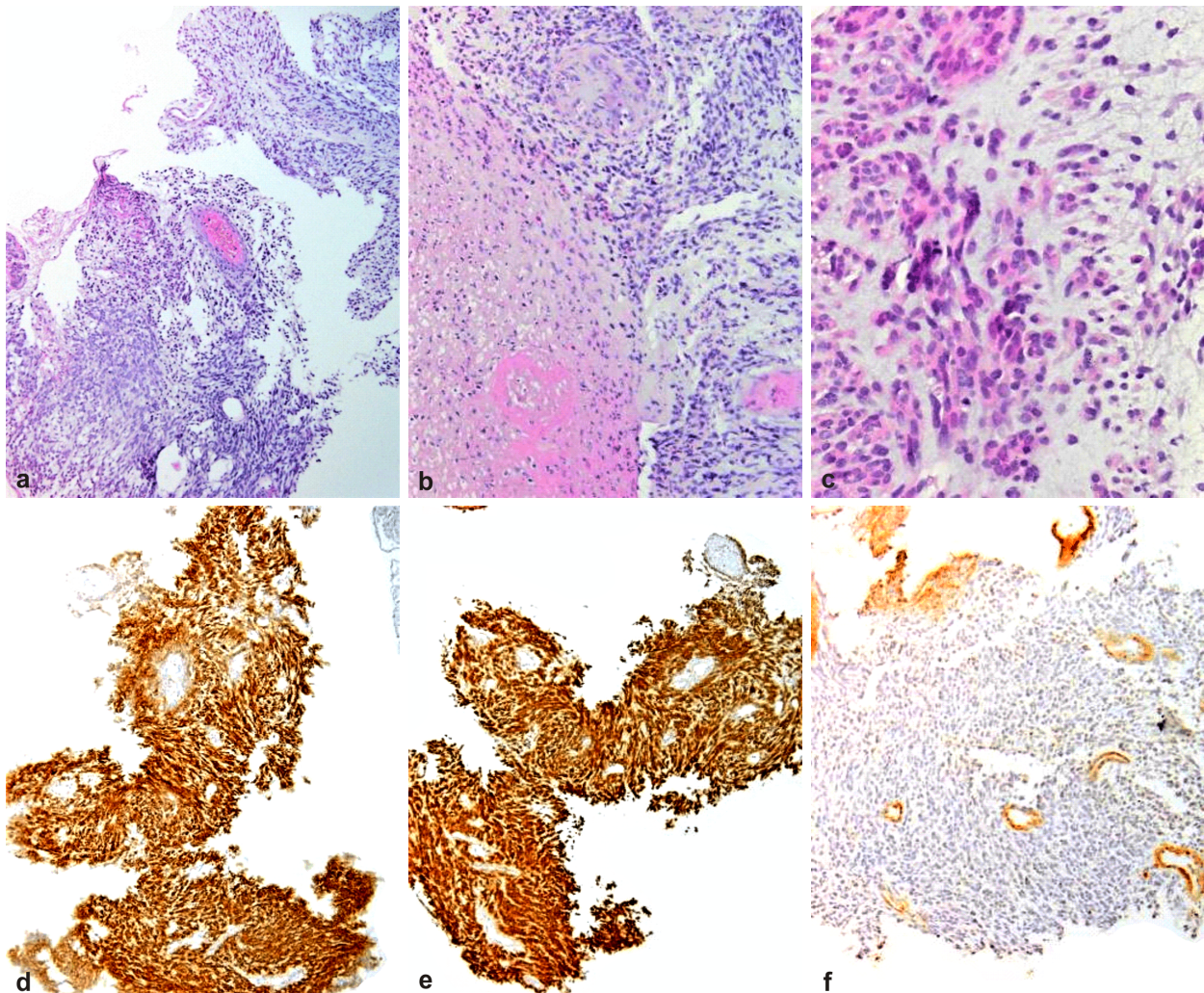


Figure 5 – Gastric GIST (female, 49 years old, large, ulcerated, hemorrhagic tumor identified and biopsied during an emergency endoscopy for an acute gastrointestinal bleeding). Dense epithelioid proliferation (a) with areas of coagulative necrosis (b). Tumor cells are small, ovalar and spindle-shaped, with minimal atypia. Note one bipolar, asymmetrical mitotic figure in the (c) image. Tumor cells are positive for CD117 (d), DOG1 (e) and negative for α -SMA (f), which is positive in vascular walls. HE staining: $\times 100$ (a); $\times 200$ (b); $\times 400$ (c). CD117 immunostaining: $\times 100$ (d). DOG1 immunostaining: $\times 100$ (e). α -SMA immunostaining: $\times 200$ (f).

Management of patients with GIST

Initial workup in patients with suspected GIST should include history and physical examination, appropriate imaging of abdomen and pelvis using CT scan with contrast and/or MRI, endoscopy with or without endoscopic ultrasound (EUS) in selected cases of primary gastric or duodenal mass, liver function tests (LFTs), complete blood cell counts, and surgical assessment to determine tumor resectability and whether metastatic disease affects this decision [18]. Patients presenting with an acute abdomen require immediate surgery and are often not evaluated for GIST until after the pathology report is received. In these patients, it is important to confirm that the disease has been completely resected, assess for metastases (liver ultrasound or abdominal/pelvic CT), and determine stage.

In general, patients should be managed by a multidisciplinary team with expertise in sarcoma or tumors of the gastrointestinal tract. However, referral of patients with early stage or straightforward, uncomplicated metastatic disease to such specialists may not always be essential. All cases should be presented at a tumor board whenever possible. Any patient with complicated or unusual features or those patients with advanced refractory disease should be appropriately referred to a center with specialty expertise and experience in the management of GIST [18].

Treatment

The optimal management of GIST requires a combined effort among multiple disciplines. Thus, patients must be managed with combined pathology, medical oncology, surgical oncology, and imaging expertise in both initial evaluation and management and in continued follow-up. Reducing recurrence, optimizing timing of surgery and organ preservation, prolonging survival, increasing the number of resectable cases through pharmacological debulking, and possibly enhancing response to imatinib through surgical cytoreduction are all potential benefits of multidisciplinary management [18].

Surgery remains the mainstay of therapy for patients with primary GIST with no evidence of metastasis, and should be initial therapy if the tumor is technically resectable and associated with acceptable risk for morbidity.

Wedge resection is the most common surgery for a small to medium-sized gastric GIST and sufficient margins can usually be obtained. Larger GISTs necessitate more extensive resections, such as distal gastrectomy for tumors involving the pyloric region or lesser curvature regions [57, 58]. Total gastrectomy may be needed for very large or multiple and recurrent GISTs that include the SDH-deficient GISTs in young patients. Localized intestinal GISTs are handled with segmental resections. At laparotomy, the abdomen should be explored thoroughly with careful inspection of the peritoneal surfaces, particularly the lesser sac in gastric GIST; the rectovaginal or rectovesical location; and the liver, to identify metastasis [18]. Lymphadenectomy is usually unnecessary because lymph node metastases are rare with GIST and sarcomas in general [59].

GISTs should be handled with care to avoid tumor rupture. If the pseudocapsule is torn, bleeding and tumor rupture may ensue. The goal is complete gross resection with an intact pseudocapsule and negative microscopic margins. Results vary about the significance of microscopically negative margins after gross resection. While in one study a microscopically positive margin was not found to be a significant adverse factor [60], another study found it an adverse factor for survival [61].

Laparoscopic surgery is increasingly used for small or medium-sized GISTs (at least up to 5 cm). Reported series have shown excellent survival results (92–96%) [62, 63], which also reflect the fact that most gastric GISTs <5 cm are clinically favorable [31]. One study also found that laparoscopic vs. open surgery offered similar 30-day morbidity and outcome but shorter hospital stay (four vs. seven days) and slightly less blood loss with the laparoscopic group. Conversion into open surgery was often the result of a tumor location in the gastroesophageal junction or lesser curvature [64]. Tumor manipulation and rupture should be avoided, as this increases the possibility of peritoneal seeding.

For recurrent or metastatic GIST, standard treatment is now imatinib, a tyrosine-kinase inhibitor. Surgery of metastases following imatinib treatment is practiced in selected instances. The indications include excision of metastases with developing imatinib resistance and emergency surgery for ruptured cystic metastases [65]. In a study of 90 patients with metastatic GIST, Bauer *et al.* showed that imatinib enabled 12 patients with mostly recurrent and advanced metastatic disease to subsequently be considered for resection of residual disease [66].

Several studies have evaluated the impact of cytoreductive surgery on survival in patients with advanced GIST after treatment with imatinib. The first large study to report survival rates in patients who underwent resection of advanced GIST after medical therapy found that outcomes of surgery and survival rates correlated with response to TKIs therapy [18].

Evolution

Since GISTs are heterogeneous tumors with very variable risk of unfavorable evolution, ranging from perfect benign tumors with practically no risk of evolution after surgical resection, to very aggressive tumors with high risk of recurrence and metastasis even after chemotherapy, scientists are looking for the best system for risk stratification.

The most used system is called Miettinen's criteria [or *Armed Forces Institute of Pathology* (AFIP) criteria] and it is the result of a large study with a long follow-up [19, 31].

This system divides GISTs in risk groups: none, very low, low, moderate and high risk, according to the rates of metastases and occurrence of tumor-related deaths after surgical resection. It includes localization, size and mitotic count (Table 1).

In 2010, *International Union against Cancer* proposed TNM staging for GISTs, including not only a staging but also a classification of this tumor (Table 2) [33, 34].

Table 1 – Rates of metastases or tumor-related deaths in GISTs [31]

Group	Tumor parameters		% of patients with progressive disease during long-term follow-up and characterization of risk of metastasis			
	Size [cm]	Mitotic rate [mitoses/50 HPFs]	Gastric GISTs	Jejunal and ileal GISTs	Duodenal GISTs	Rectal GISTs
1	≤2	≤5	0 none	0 none	0 none	0 none
2	>2≤5	≤5	1.9 very low	4.3 low	8.3 low	8.5 low
3a	>5≤10	≤5	3.6 low	24 moderate		
3b	>10	≤5	12 moderate	52 high	34 high	57 high
4	≤2	>5	0 none	50 high	No cases in this study	54 high
5	>2≤5	>5	16 moderate	73 high	50 high	52 high
6a	>5≤10	>5	55 high	85 high		
6b	10	>5	86 high	90 high	86 high	71 high

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields.

Table 2 – TNM staging and classification of GISTs

Tumor size [cm]	Mitotic rate [mitoses/50 HPFs]	T-stage gastric	T-stage non-gastric	UICC gastric	UICC non-gastric
≤2	≤5	T1	T1	IA	I
>2–5	≤5	T2	T2	IA	I
>5–10	≤5	T3	T3	IB	II
>10	≤5	T4	T4	II	IMA
≤2	>5	T1	T1	II	IMA
>2–5	>5	T2	T2	II	NIB
>5–10	>5	T3	T3	IMA	NIB
>10	>5	T4	T4	NIB	NIB

GISTs: Gastrointestinal stromal tumors; HPFs: High-power fields; UICC: Union Internationale Contre le Cancer (International Union against Cancer).

The above-mentioned UICC stages are valid for N0 M0 tumors. All tumors with lymph node or other metastasis are considered UICC stage IV [34].

Other risk factors

Other risk factors include:

- Beside the localization, dimension and mitotic activity, other risk factors for malignant behavior were identified;
- Presence of necrosis that is correlated usually with tumor size and rate of progression [67];
- High cellularity [68];
- Serosal invasion [69];
- Incomplete surgical resection of the tumor – important especially in low- and moderate-risk GISTs [70];
- Tumor rupture, considered to be a negative prognostic factor whether the rupture is produced spontaneously or during surgery or biopsy [71];
- Presence, in the moment of diagnosis, of peritoneal dissemination, distant metastases or local invasion in adjacent organs [72].

Conclusions

Despite the fact that GISTs elicit a large number of researches and publications, they remain a difficult issue for clinicians and pathologists, since they are rare tumors with peculiar and sometime surprising evolution. Multi-disciplinary teams (including surgeons, imagists, pathologists, oncologists) are best suited for GIST patient

management. Surgery is the best treatment for localized disease, but can be a solution even for advanced cases. Histopathology report must offer, besides diagnosis, prognostic factors that are essential for the outcome of the patient. In the last decade, the genetic and molecular characteristics of this tumor type are better described and opened the path for molecular treatment.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author

Cristiana Gabriela Popp, MD, PhD, Department of Pathology, “Colentina” Clinical Hospital, 19–21 Ștefan cel Mare Highroad, Sector 2, 020125 Bucharest, Romania; Phone +40721–298 871, e-mail: brigaela@yahoo.com

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