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CASE REPORTS

Gastrointestinal stromal tumor (GIST) with hepatic metastases

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ABSTRACT

We discuss the case of a female patient, hospitalized in our clinic for pain in the right hypochondrium and in the lower part of the right hemithorax, following a thoracic trauma. Conventional and Sonovue contrast abdominal ultrasound revealed numerous hepatic tumours, while upper digestive endoscopy confirmed the existence of exulcerated gastric tumours. Endoscopy and CT scan helped in staging the tumour, while histopathological examination and immunophenotyping established the final diagnosis: GIST. After 3-months of daily treatment with Glivec 400 mg, we observed the regression of the tumoural diameter. This case is relevant for the diagnosis of a particular type of gastric tumour using modern imaging techniques and highlights the progress made in the GIST treatment.

Key words: hepatic metastases, upper digestive endoscopy, endoscopic ultrasound, immunohistochemistry, chemotherapy

INTRODUCTION

Gastrointestinal stromal tumours (GIST) belong to mesenchymal gastrointestinal tumours, that can be accurately diagnosed in the last decade by using immunohistochemical examination (1, 2). Presently, both the mechanism triggering tumoral proliferation, the antigenic structure, the origin, the nature of tumour and the therapeutic possibilities are well known. Cellular proliferation is triggered by a mutation in the c-Kit gene, followed by activation of the KIT enzyme (tyrosine-kinase) and the uncontrolled effect of the KIT responsible for the intracellular signal transmission of cellular growth and cell survival (3). GIST are nonepithelial tumours originating in the interstitial Cajal's cells (ICC). These cells express antigens for CD 117 and/or CD 34, similar to GIST (2, 3). They can be either benign or malignant, while their clinical manifestations are polymorphic depending on tumour location. Complete surgical excision of the primary tumour offers the best chance of cure and for metastatic forms, tyrosine-kinase inhibitors

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such as Imatinib (Glivec, Gleevec) are indicated. Radiotherapy and chemotherapy have irregular treatment effects (4,5). ❑

CASE PRESENTATION

A 58-year-old female patient suffered a right thoracic trauma, followed by pain in the lower right thorax and in the right hypochondrium. After the initial assessment, the diagnostic was intercostal neuralgia and antiinflammatory drug treatment was initiated. The pain in the right hypochondrium persisted and the patient was admitted to our clinic, 3 months later.

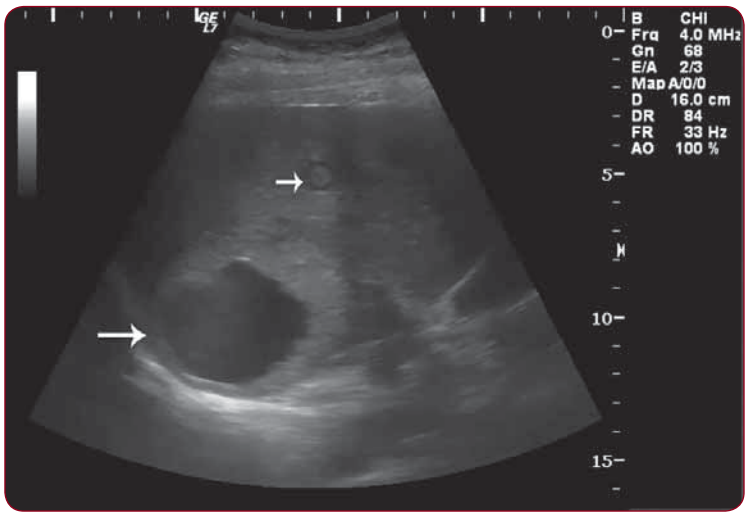

FIGURE 1. Abdominal ultrasonography which shows many liver tumours; big arrow points to cystic tumour, small arrow points to a solid tumour

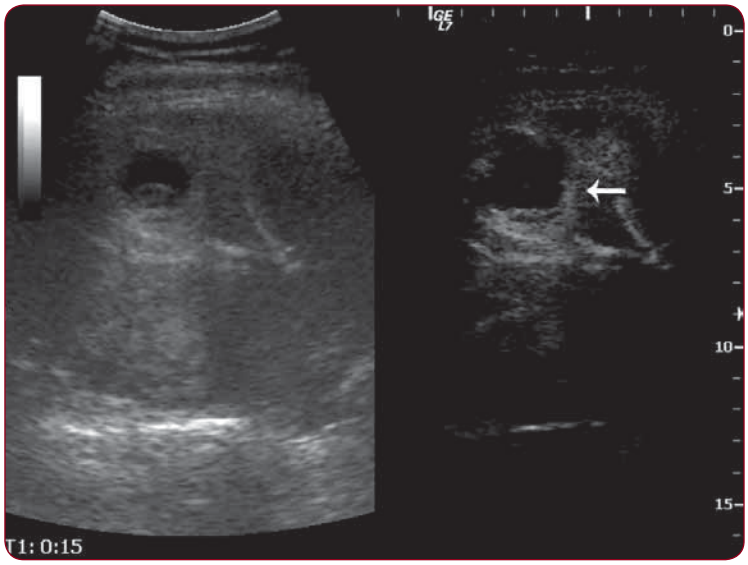

FIGURE 2. Contrast ultrasonography shows increased uptake of Sonovue in arterial phase (white arrow)

At the clinical examination we observed grade II obesity (BMI=35), enlarged abdomen due to adipose tissue, hepatomegaly hard in consistency and slight sensitivity at liver palpation. Laboratory tests showed a mild inflammatory syndrome (ESR: 40 mm at 1 hour), mild hepatocytolisis (ALT=50 U/l) and cholestasis (ALP=367 U/l, γGT=74 U/l). The rest of the lab tests were within the normal range.

We performed abdominal ultrasound and we observed numerous well-delineated hepatic tumours, with transonic centre and thick echogenic wall, as well as vascular signal at Doppler examination and round parenchimatous masses (FIGURE 1).

The next examination was the contrast ultrasonography (with Sonovue) that showed a high uptake of the medium contrast in the arterial phase and its wash-out in the tissular phase; this is usually found both in hepatic abscesses and metastases (FIGURE 2). Taking into account the lack of fever and leucocitosis, the predictive diagnostic was hepatic metastases, that was to be confirmed by biopsy.

The histopathological examination showed a tumoral mass, non-encapsulated, with dense tumoral cellular proliferation, medium size tumoral cells, irregular nuclei, pale eosinophilic cytoplasm, spindle-like shape (FIGURE 3) and frequent mitoses (14/19 HPF). Intratumoral blood vessels were noticed. Gomori staining showed a rich reticulinic network suggesting a sarcomatous appearance, while PAS staining was negative.

The immunophenotyping and the immunohistochemical profile showed positivity for C kit (CD 117) (FIGURE 4), vimentine (FIGURE 5) and partially for CD 99, as well as negativity for desmine, S 100 and keratine, suggesting GIST.

Given the frequent onset at the gastric level, upper digestive endoscopy was performed, that revealed an approximately 4 cm submucosal tumour with central ulceration and mucosal bridging (Schindler sign). The tumour was located below cardia, in the gastric body (FIGURE 6).

In order to assess the regional extension and invasion, the next procedure used was endoscopic ultrasound, that established the existence of a polylobate submucous mass of 35/35 mm, originating in the muscular layer, penetrating the serosa, but without perigastric lymph nodes (FIGURE 7).

The final diagnosis was gastric GIST with hepatic metastases, stage IV according with American Joint Committee on Cancer.

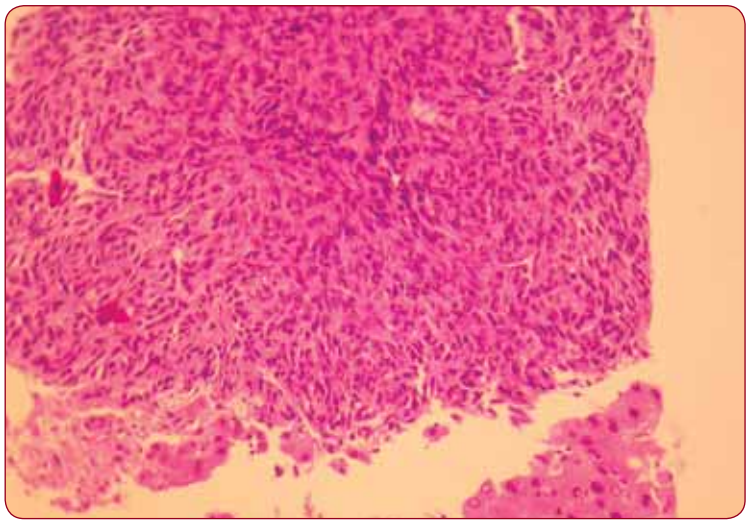

FIGURE 3. Histopathological examination – H&E stain, shows a tumoral mass with dense tumoral cellular proliferation, spindle-like shape cells

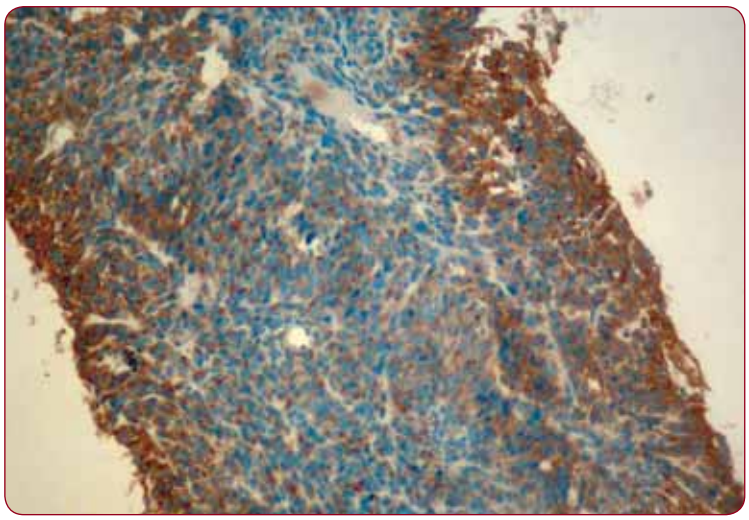

FIGURE 4. Immunohistochemical detection for c-Kit

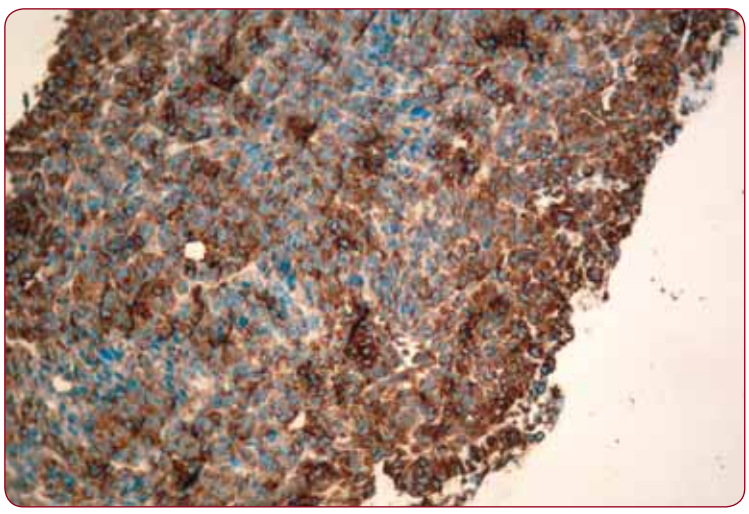

FIGURE 5. Immunohistochemical detection for vimentin

The patient was transferred to the oncology department where CT scan was done prior to initiating the treatment. The CT scan showed multiple hepatic cysts with thick wall and weak iodocaptation of maximum 70 mm in diameter. It also revealed a weak iodophile mass of 46/40 mm at the fornix level, extended both inside and outside the stomach (FIGURE 8). The patient was treated with Glivec 400 mg/day. Adverse effects signalled by the patient involved nausea, vomiting and oedema, which stopped after several weeks.

Three months after initiation of the therapy, was performed abdominal CT scan. In contrast with the previous examination, hepatic tumours appeared mostly cystic and the former mentioned gastric tumour was significantly reduced in size (34/22 mm) (FIGURE 9). ❑

DISCUSSIONS

Prior to the introduction of the immunohistochemistry, the majority of the spindle-like cell sarcomas in the digestive tract were classified as leiomyoma or leiomyosarcoma (due to the histological similarity with the smooth muscle) and occasionally as neurogenic tumors.

GISTs represent a distinctive group of mesenchymal gastrointestinal tumors, with origins in the interstitial Cajal's cells, that have pacemaker activity and regulate the intestinal peristaltic. Both Cajal's cells and GISTs express the KIT protein and have similar ultrastructural appearance (2, 6, 7). KIT is a membrane glycoprotein of 145 KD which is the final product of a C-kit proto-oncogene (CD117) and represents the receptor of tyrosin-kinase. The KIT receptor can be detected by performing immunohistochemistry for CD117, the surface antigen of the extracellular segment of this receptor. The stem cell factor, known as Steel Factor (SLF) is the ligand for KIT. The binding of SLF to KIT activates the tyrosin-kinase, its dimerization, autophosphorylation and activation, the recruitment of other signal effectors proteins and the formation of a complex that initiates a cascade signal, resulting in intranuclear changes. The activation of tyrosin-kinase leads to cellular growth and proliferation and it is dependent on the intracellular segment of the KIT receptor, the spot where Imatinib acts and binds c-Kit. The trigger factor for cellular proliferation is a mutation in the c-Kit gene (3, 5), gene that codes the membrane receptor for

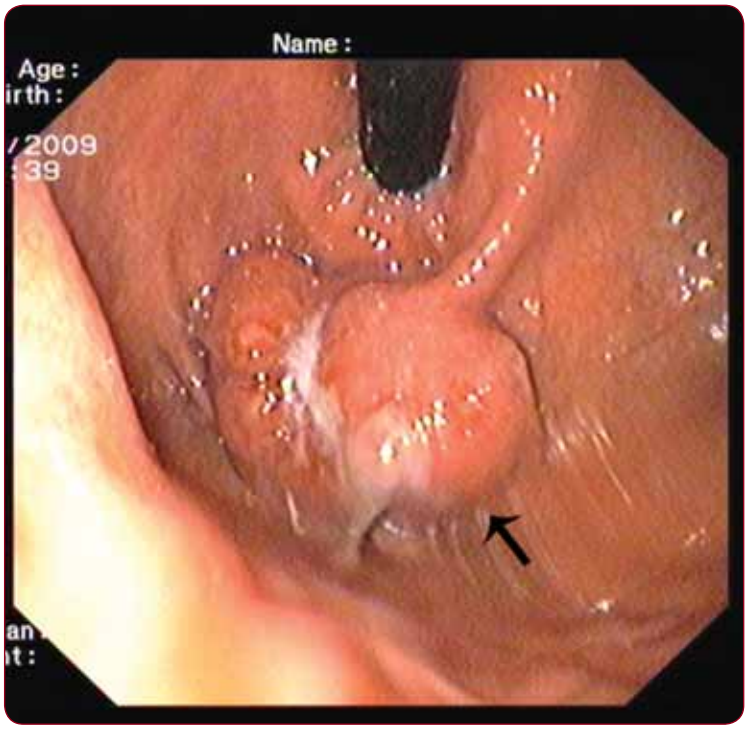

FIGURE 6. Endoscopic view of subcardial exulcerated tumour (black arrow)

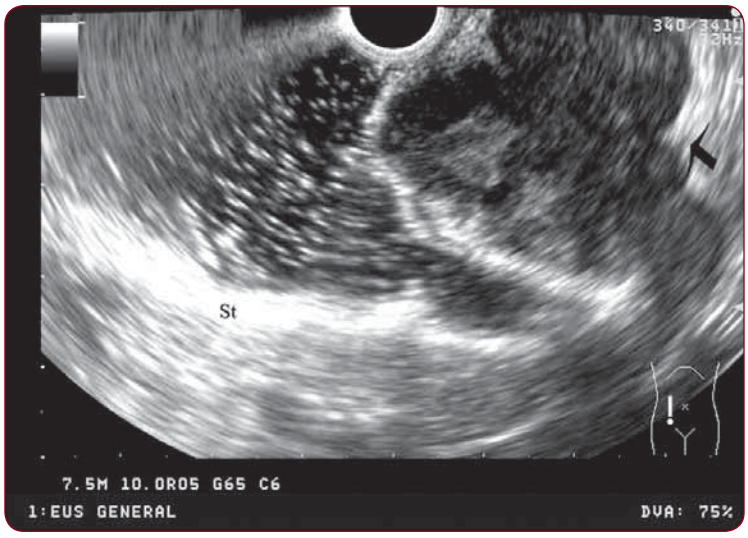

FIGURE 7. Endoscopic ultrasound image of submucosal, polilobated tumour (black arrow)

the growth factor labeled as SCF (stem cell factor). The mutation favours the c-Kit activity independent of its activation by the growth factor, respectively the uncontrolled activity of the KIT enzyme responsible for the intracellular signal transmission of cell growth and survival (3, 8).

Current data on GIST incidence varies in different parts of the world, from the lowest incidence rate of 6.8/million in the USA, up to 11/million in Island, 12.7/million in the Netherlands, 13/million in Italy, 12.8-16.4/million in Sweden, 13.7/million in Taiwan (9). Incidence increases with age especially after 50, and it is higher in males than in females cases (8.3 vs. 5.7%). It also has a higher incidence rate in black people than in Caucasian population 9.7% vs. 6% (8, 10). Five percent of GIST occur in patients with neurofibromatosis type 1 syndrome (multiple small intestinal tumors) and in Carney triad (gastric epithelioid GIST in young females) (11). Familial GISTs occur in patients with inheritable germline Kit or platelet-derived growth factor receptor alpha (PDGFRA) mutations (2).

Clinically, up to twenty percents of GISTs are asymptomatic and are accidentally diagnosed, while seventy percents are symptomatic. The most common clinical presentations are gastrointestinal bleeding (30%), abdominal pain (20%), intestinal occlusion and symptoms cased by regional invasion. When diagnose, 30% of GIST tumors are already metastasized or present regional invasion (12).

GISTs locations in the digestive tract are ordered by frequency: stomach 60-70%, small bowel 25-30%, duodenum, rectum 5%, esophagus 3%, colon 1%, other locations (omentum, mesenter) 5% (2).

GISTs diagnosis is based on imaging, which plays a major role in detecting the tumor, as well as in establishing the extension in the gastrointestinal wall, in staging, in malignant risk assessment and treatment monitoring. These medical investigations entail endoscopy, endoscopic ultrasound, contrast ultrasonography, computed tomography (CT).

Upper endoscopy accidentally detects asymptomatic submucosal tumors. By growing in size, GIST may exulcerate and bleed, consequently endoscopy becoming mandatory. Endoscopic manifestations are either submucosal mass with bridging mucosal folds (Schindler's sign), or protrusive exulcerated tumors, or polipoid

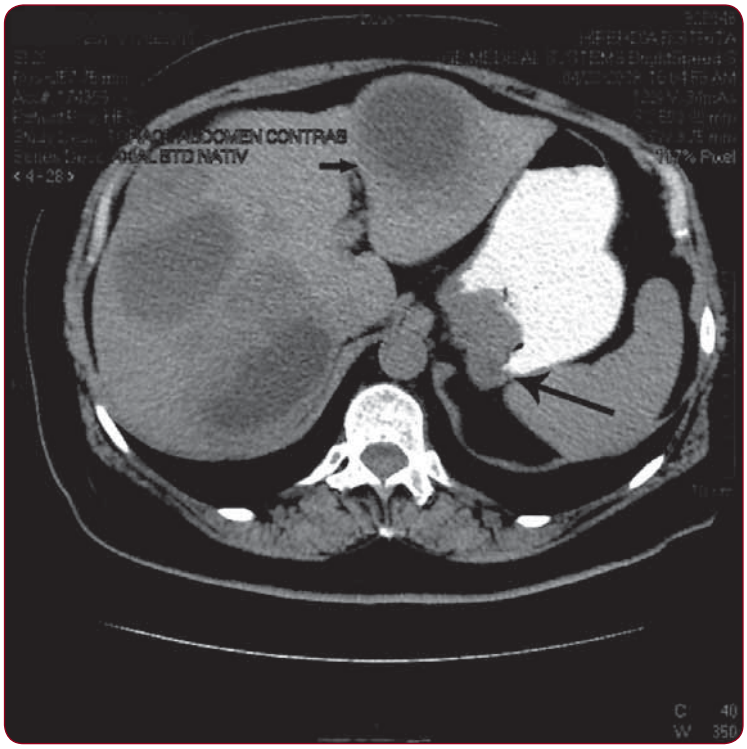

FIGURE 8. Computed tomography before starting the treatment. Multiple hepatic cysts with thick wall (small arrow) and a large gastric subcardial tumour (big arrow)

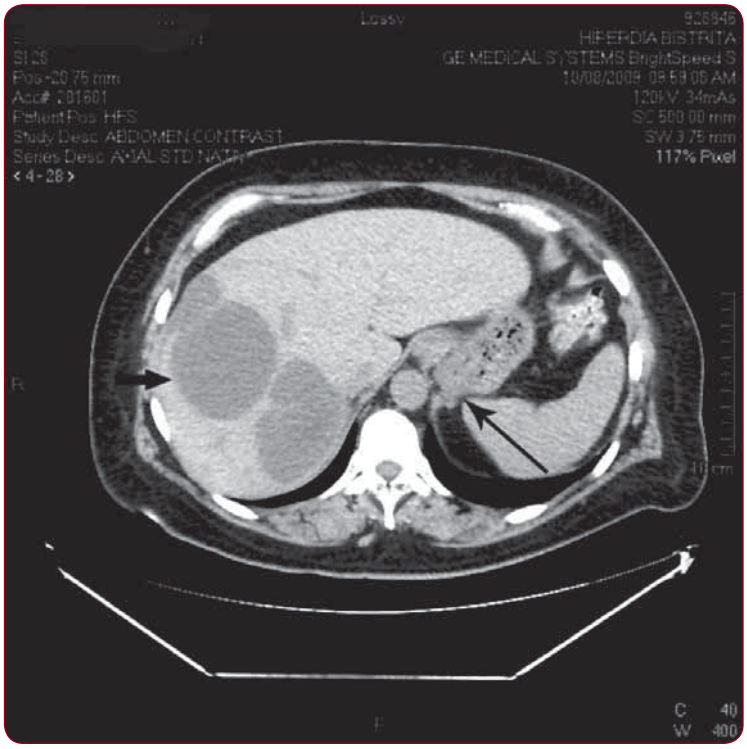

FIGURE 9. Computed tomography after treatment. Compared with previous CT, the wall of the hepatic tumour became thinner (small arrow) and the size of gastric tumour is reduced (big arrow)

tumors. Biopsy of submucosal tumors is difficult regardless of the applied technique, the percentage of positive results ranging between 35-65% (13).

Endoscopic ultrasound (EUS) is an imaging method which offers valuable information for positive and differential diagnosis and is useful in GIST patients follow-up. Endoscopic mucosal forceps biopsy, brush cytology and endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) under direct visualization, are the standard procedures for establishing preoperative diagnoses in patients with gastrointestinal malignancies. On the one hand the examination ensures the possibility to locate the tumor, to evaluate the size, the shape, the contour, as well as to establish the origin of submucosal forms. On the other hand, FNA provides the tissue necessary for immunochemistry which helps to differentiate between gastrointestinal stromal tumors (14, 15).

Patients with tumors larger than 30 mm in diameter, heterogeneous echo pattern, cystic spaces or irregular extra-luminal margin, present malignant risk (16). Endoscopic ultrasound has a sensitivity and specificity of 89% and 88% respectively, in gastrointestinal tumor diagnosis, as reported Vander Noot et al. Regarding cytology, sensitivity rate reached 96% and specificity was of 81%, while the diagnostic accuracy improved to 92% (15).

Therewith, this examination ensures the monitoring of small tumors without malignant risk (16), and the post-treatment evolution of these patients (11).

Abdominal ultrasound (US) is the first line examination usually performed for detecting focal hepatic lesions, but has the disadvantage of a lower sensitivity as compared to contrast CT scan or MRI, due to the relatively similar ultrasound pattern of malignant and benign tumors. Small tumors cannot be detected by ultrasound. Micro bubble contrast agents for ultrasonography were introduced in the 1990s and have steadily gained popularity for the investigation of liver masses (17). The use of contrast agents in ultrasonography increased the accuracy of this method in positive and differential diagnosis of benign and malignant liver tumors (18). The sensitivity and specificity of contrast ultrasound is: 92% and 86.7% in hepatocarcinoma, 96.3% and 97.5% in hemangiomas, 80% and 100% in hepatic abscesses and 99% in hepatic metastases (19).

Computed tomography is essential in GISTs staging by providing information regarding the dimensions of the tumor, the existence of liver, peritoneal, pulmonary or lymph nodes metastases. The diagnosis of malignant GIST can be suggested on CT scans with the presence of a large well-circumscribed tumour arising from the stomach or small bowel that is usually predominantly extraluminal and has a heterogeneously enhancing soft-tissue rim surrounding a necrotic centre. Usually, hepatic metastases are numerous and have cystic appearance with liquid content, hypervascularized; associated pulmonary and lymph nodes metastases are rare.

The differentiation from other primary gastrointestinal malignancies can often be made on the basis of these specific findings, since lymphomas tend to cause circumferential mural thickening with homogeneous enhancement and/or lymph node enlargement. Carcinoids are mainly found in the terminal ileum and excite a desmoplastic reaction, while carcinomas are likely to demonstrate local infiltration and visceral obstruction, especially if large (20-22).

The histopathological exam remains the gold standard in positive and differential diagnosis of this type of tumors. Macroscopically, they are well delineated tumoral masses, with exofitic growth, mostly extraluminal, and tumoral dimensions are variable, from a few millimetres, up to 400 mm. Microscopic types encounteredarespindle-cell-77%,epitheloid-15%, mixt-8% (23, 24).

Immunohistochemistry is essential for positive diagnosis and for differentiating the mesenchymal tumors of the digestive tract. C-Kit represents the best-defined immunoreactive feature of GIST, differentiating them from tumors with true origin in the smooth muscle (leiomyomas, leiomyosarcomas) and from neural crest derived tumors (schwanomas, neurofibroma) and it is considered as being the most specific criterion for diagnosis (see TABLE 1) (3, 7, 25, 26).

GIST are positive for c-KIT in 95% of cases, for CD34 in 60-70% of cases, and in 5% of cases mutations of another extracellular tyrosine-kinase receptor might occur, PDGF-R which is correlated with incomplete response at systemic target medication (3, 25). Other positive markers potentially present in GIST are: alpha smooth muscle actin (SMA) (15%-60%), S-100 Protein (10%), Desmin) (3, 7, 25, 26).

From an evolutive point of view, the majority of GIST are benign tumors, but roughly one third of them become malignant. The higher rate of malignant behaviour is found in esophageal and colonic tumors, followed by those located on the small bowel (50%), duodenum (30-40%), stomach (25%). Predictive factors for a malignant behaviour are: size of tumor (>5 cm), increased cellularity, extensive necrosis, frequent mitosis (> 5 to 50 HPF), frequent c-KIT mutations, invasion in contiguous adjacent tissues, rupture of tumor. Other factors such as: male gender, location of tumor, deletion of 11 exon or chromosomal aberrations are inconstant factors for predicting malignant behaviour (10, 26-28). Survival at 5 years is 90% (Stage I), 81% (Stage II), 56% (Stage III) and a small percent for IV Stage (28). The most important predictive factors of mortality are hepatic metastases, invasion beyond intestinal wall, mitotic index and size of tumor (29).

The treatment of GIST depends on the size and location of the tumour, if it is cancerous, whether the cancer has spread, and the person's overall health.

Treatment options involve: surgical resection, tyrosin-kinase inhibitors administration, radiotherapy and chemotherapy.

The surgical treatment is the only curative and such indication is in GIST without metastasis. The whole of the tumour must be removed, avoiding rupture of tumor. The removal of lymph nodes is not generally needed in the treatment of a GIST because it does not often spread to the lymph nodes. The curative surgical resection is followed in 50 % of cases by local reoccurrence or distant metastasis. Studies indicate a survival rate at 5 years of 32 – 78 %, depending on tumoral size, mitotic rate and location of kit mutations (4, 24, 27).

Tumor	KIT	CD34	SMA	Desmina	S100
GIST	Difuse, > 95%	60-70%	30-40%	rare	5%
Soft tissue tumors	Focal, < 5%	10-15%	+	+	rare
Schwanom	Focal, < 5%	+	–	–	+

TABLE 1. The role of immunohistochemistry in differential diagnosis of GIST

Radiotherapy is rarely used, as GIST is radioresistant. Chemotherapy requires associations of many cytostatics and only 10-15% of the patients respond to it (24).

For patients with metastasis, the elective therapy entails tyrosin-kinase inhibitors.

The first study regarding the role of Imatinib in GIST treatment was published in 2001 by Joensuu et al. Many studies (30) confirmed the usefulness of Imatinib in metastatic or unresectable GIST (28). Imatinib (Glivec) is an inhibitor of the tyrosin-kinase protein, with the role of blocking the tyrosin-kinases located on receptors on the surface of malignant cells, and by blocking these receptors, it controls the cellular division. The usual dose of Imatinib is 400 milligrams (mg) daily, in some patients the dose can be raised to 800 mg daily and the medication will be taken by patients for a prolonged period of time. Since this drug has become available, the prognosis for patients with GIST has improved considerably (24). A recent approach of Imatinib therapy analyzes tumoral regression with the later possibility to surgically remove the tumor (24, 31). Most of the patients (85%) have mutations of exon 11 and respond to treatment with Imatinib, while the rest of them have a mutation of exon 9 which blocks the response to Imatinib. In these patients indication is to administrate Sutent (or SU11248). Sunitinib (Sutent), like Imatinib, is a tyrosine-kinase inhibitor with anti-angiogenic properties, and it was approved in 2006 by the FDA for treating GIST when the tumor continues to grow even after treatment with Imatinib, or in cases where Imatinib cannot be given (32).

Response to treatment is defined by absence of tumoral growing, decrease of tumor size (assessed by performing CT scan), mixoid degeneration and decrease of vascularisation. Patient monitoring is crucial because the majority of GIST cases rebound and the follow-up is done by clinical examination, endoscopy, EUS, CT, MRI, PET, every 3-6 month in the first 2 years, and every year in the next 2 years (33).

In our case, 3 months after the beginning of the treatment with Imatinib we noted the decrease in the gastric tumour and important modifications in hepatic metastases. ❑

CONCLUSION

1. GISTs are rare tumors, often presenting as digestive haemorrhage or abdominal pain. In the presented case the tumour was asymptomatic, detected by chance, in a late stage with hepatic metastases.
2. Positive diagnosis was favoured by new imaging methods such as: ultrasonography with contrast agents, endoscopic ultrasound, and immunohistochemistry.
3. Treatment with Imatinib showed positive results after three month of therapy. ❑

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