Abstract

Gastrointestinal stromal tumors (GISTs) are the most common neoplasms arising from connective tissue in the gastrointestinal tract, representing less than 1% of all neoplasms of the gut. GISTs may be found along the digestive tract, from the esophagus to the internal anal sphincter. The most common gastrointestinal location is the stomach (60% GASTs - gastric stromal tumors). Patients with GIST have symptoms according to the size and location of the tumor. Patients diagnosed with GISTs may have pain, symptoms of pressure, dysphagia, early satiety and obstruction. More rarely, the patients may present with anemia due to a chronic bleeding the source being a smaller tumor with overlying mucosal ulceration or even acute hemorrhage from a large sub mucosal tumor. We discuss the case of a 75 years old male patient presented with upper digestive bleeding as primary manifestation of a sub mucosal gastric GIST situated under the cardia on the greater curvature. The diagnosis is based on the pathological examination using Immunohistochemical staining. CD 117 is found in more than 95% of GIST cases being widely accepted as a criterion for the positive diagnosis of these tumors. The imaging findings using computed tomography, upper gastrointestinal endoscopy, and endoscopic ultrasound are helpful for the initial diagnosis and may permit the preoperative biopsy. The biopsy is important for the final diagnosis but also is offering information’s about the malignant potential of the GIST. The preoperative evaluation according with the site of tumor is allowing an accurate surgical management to obtain a complete resection with maximal organ preservation. The malignant potential is important in choosing the appropriate surgical approach, the size of the surgical resection and the type, dosage, period of time of the targeted therapy with biologic agents. The mainstay of therapy remains the surgical resection. The tyrosine kinase receptor inhibitors are used as neoadjuvant as well as adjuvant therapy increasing the recurrence-free survival and overall survival rates, stabilizing the disease and offering patients a significant improvement of quality of life.
**Keywords:** gastric GIST, bleeding, diagnosis, treatment

**Introduction**

Gastrointestinal stromal tumors (GISTs) are the most common neoplasms arising from connective tissue in the gastrointestinal tract, representing less than 1% of all neoplasms of the gut. The general incidence of GISTs is around 15 cases /million /year [1]. The annual incidence of GIST in the United States is around 2000 cases [2]. GISTs may be found along the digestive tract, from the esophagus to the internal anal sphincter. The most common location is the stomach (60% GASTs -gastric stromal tumors), followed by the small intestine, rectum and esophagus [2,3]. GISTs discovered outside of the alimentary tract are defined as extra-gastrointestinal stromal tumors (EGISTs) and may be found in less common locations including the omentum, mesentery, mesocolon, retro peritoneum [4,5]. Also GISTs were identified in rare sites such the genitourinary tract (vaginal septum), portal vein, gallbladder, liver, pancreas, pleura [6,7,8,9,10,11]. The omental GISTs represent the largest proportion of EGISTs.

Patients with GIST have symptoms according to the size and location of the tumor. In case of small GISTs, the tumors are asymptomatic being discovered during investigations for other diseases, during surgery for another reason or accidentally at necropsy. The GIST symptomatology is non-specific. The gastric GISTs have a variegated clinical onset. Most frequently, anorexia, weight loss and abdominal pain are the clinical signs that bring the patient to seek medical attention. The gastric location of the tumor is playing a very important role in the symptom pattern. The proximal tumors manifest with nausea and vomiting with or without signs of upper digestive bleeding. The distal location is producing obstructive symptoms. The GISTs unlike adenocarcinoma do not present often with chronic anemia due to a hemorrhage from an ulcerated lesion. The bleeding is uncommon. Also GISTs in advanced phases of the disease do not send metastases like adenocarcinoma to the pelvis, Blumer shelf, in periumbilical region, Sister Mary Joseph node, or in the supraclavicular area, Virchow node. The metastases in GISTs appear at the level of liver, omentum, and peritoneum. Patients with a gastric GIST forming a bulge into the lumen of the organ or with a big sub mucosal ulcerated mass may present with blood loss, anemia and fatigue. Patients with large gastric GISTs which developed outside the organ may have palpable tumors with symptoms of pressure and pain. This kind of large GIST may cause gastrointestinal bleeding or hemoperitoneum due to a tumor rupture representing a surgical emergency.

The mainstay of therapy remains the surgical resection according with the investigations findings. The tyrosine kinase receptor inhibitors are used as neoadjuvant as well as adjuvant therapy representing the targeted therapy with biologic agents. We describe a case of gastric GIST with upper digestive bleeding as primary manifestation.

**Case Report**

A 77-year-old male patient presented with hematemesis, melena, weight loss, epigastric pain, vomiting and quick sensation of fullness after meals. The first symptom was melena appearing two months ago. The upper GI bleeding was the reason why the patient finally presented himself to the gastroenterologist. Laboratory tests reveal: alanine transaminase (ALT) 15U/L, aspartate transaminase (AST) 13 U/L, amylase 133 U/L, glycemia 116 mg/dl, International Normalized Ratio 1,22 (INR), white blood cells (WBC) 8.71, hematocrit 28% (HCT), hemoglobin 7.7g/dl, red blood cells (RBC) 2,58X1012/L. The patient's medical history includes arterial hypertension, benign prostatic hyperplasia. After the correction of secondary anemia with two units of homologous O-negative blood, the imagistic investigations were performed.

The esophago-gastro-duodenoscopy (OGD) discovered a 4-5 cm diameter tumor under the cardia on the posterior gastric wall near the greater curvature. The findings include a sub mucosal mass forming a bulge into the lumen of the stomach. The overlying mucosal ulceration was the source of bleeding and anemia (iron deficiency due to chronic blood loss) (Figure 1). Also two bioptic tumoral fragments were sampled.

The abdominal ultrasonography shows a tumor with a maximum diameter of 5 cm, on the posterior

![Figure 1. Gastric GIST endoscopic image](image-url)
wall of the gastric fundus, under the cardia near the greater curvature and an infundibular gallstone image in the cholecyst.

The computed tomography shows a tumor size 3/5 cm on the posterior gastric wall near the cardia and greater curvature and cholelithiasis. The formation appears like a sub mucosal mass with smooth borders and rounded shape (Figure 2). No other pathological modifications were found.

The pathological exam of the biopsies revealed tumoral tissue composed mostly by spindle cells. The cells are elongated, arranged in short fascicles, with ovoid or elongated nuclei and mildly fibrillar cytoplasm suggesting a GIST tumor requiring further Immunohistochemical tests after the tumoral resection.

The patient was transferred to a Department of General Surgery. A superior polar gastrectomy with gastro-esophageal-anastomosis E-E and cholecystectomy were performed. The postoperative evolution of the patient was uneventful the patient being discharged in the 13th day of hospitalization.

The macroscopic aspect of the tumor showed a sub mucosal mass with diameter of 5 cm forming a bulge into the lumen of the stomach but also incorporating the entire gastric wall passing into the serosa (Figure 3).

The microscopic study on the classical staining with Hematoxylin-Eosin (HE) showed a tumor made up of fusiform cells with abundant cytoplasm, mildly basophilic, oval normochromic large nuclei. The tumor cells are arranged in fascicles in a myxoid stroma, with strongly congested vessels and marked lymphocytic infiltrate. The preliminary diagnosis was GIST. For the positive and differential diagnosis we used immunohistochemical markers: anti CD117 antibody (c-kit), known as a specific marker for GIST, which appeared moderately positive at the membrane level of tumoral cells; CD34 strongly positive in all tumoral cells and Vimentin intensely positive in all the tumoral cells.

The Ki-67 marker was positive in less than 5% of tumoral cells, showing a low mitotic activity. In order to differentiate it from muscular tumors we also evaluated the reaction to alpha-smooth muscle actin (α-SMA) which was decreased. The final diagnosis was a gastric GIST with fusiform cells with intermediate risk of aggressive behavior (5cm diameter, <5/50HPF mitotic rate). The patient started an Imatinib adjuvant therapy at three weeks after the surgical intervention.

Discussion

In this case report, the origin of the tumor is the posterior wall of the gastric fundus, under the cardia near the greater curvature. The correct diagnosis of GIST is very important for the surgical therapy and the medical therapy as well. Most of this GISTs tend to regress or do not progress to clinical GISTs. Patients diagnosed with GISTs may have pain, symptoms of pressure, dysphagia, early satiety and obstruction. More rarely, like in our case, the patients may present with anemia due to a chronic bleeding. The source of bleeding is being a smaller tumor with overlying mucosal ulceration, or even acute hemorrhage from a large sub mucosal tumor. The preoperative evaluation according with the site of tumor is allowing an accurate surgical management to obtain a complete resection with maximal organ preservation. The imaging findings using computed tomography, upper gastrointestinal endoscopy, and endoscopic ultrasound are helpful for the initial diagnosis and may permit the preoperative biopsy.

The pathologist has the key role in the determination of positive and differential diagnosis as well as for the estimation of tumoral cell proliferative ability, using several tumoral markers. The positive diagnosis is always the pathological examination using immunohistochemical staining. CD 117 is found in more than 95% of GIST cases being widely accepted as a criterion for the positive diagnosis of these tumors.
CD 117 (CD nomenclature) is a protein representing a tyrosine kinase receptor type III also known as stem cell growth factor receptor (SCFR) or proto-oncogene c-Kit or tyrosine-protein kinase KIT [12]. Overexpression of Kit in the tumor cells results from constitutive activation of the Kit tyrosine receptor. The activation leads to intracellular signaling that causes increased cellular proliferation and cell survival leading to tumor formation.

The biopsy is important for the final diagnosis but also is offering information about the malignant potential of the GIST. The malignant potential is directly proportional with the tumor size and mitotic count. The group with high risk of aggressive behavior is represented by the GISTs over 5 cm in size and over 5/50 HPF mitotic count, GISTs over 10 cm in size with any mitotic rate, GISTs with any size and over 10/50/HPF [13].

GISTs represent a rare and unique type of mesenchymal tumor. These tumors for a very long time were categorized as leiomyomas or leiomyosarcomas and thus remained unrecognized as a separate diagnostic entity. Microscopically GISTs are composed mostly of spindle cells like smooth muscle cells or epithelioid cells [14]. That is why these tumors were previously considered to originate from the muscular layers or nerve cells of the alimentary tract. The development of histopathological techniques, improved immunohistochemical staining and electron microscopy studies have allowed to discover specific molecular features of GIST. The immunohistochemical staining demonstrated decreased staining for desmin and smooth muscle antigen, decreased presence of neural crest markers. All these findings point to a new, distinct type of tumor. The GIST was introduced as a diagnostic term in 1983 [15].

CD 34 extracellular membrane protein was found in GIST (70% of cases); protein that is rarely identified in leiomyomas. The presence of CD 34 supported the distinct classification. CD34 is a cluster of differentiation and is a cell surface glycoprotein and functions as a cell-cell adhesion factor, mediating the attachment of stem cells to bone marrow extracellular matrix or directly to stromals [16].

Further research identified the presence of protein CD117 on the extracellular membrane of GISTs cell. CD 117 (CD nomenclature) is a protein representing a tyrosine kinase receptor type III also known as stem cell growth factor receptor (SCFR) or proto-oncogene c-Kit or tyrosine-protein kinase KIT [12]. KIT was first described by the German biochemist Axel Ullrich in 1987 as the cellular homolog of the feline sarcoma viral oncogene v-kit [17]. KIT belongs to the type III receptor tyrosine kinase (RTK class III) subfamily, whose members include Platelet-derived growth factor receptors (PDGF-R) alpha and beta each encoded by a different gene [18]. Platelet-derived growth factor receptors are important factors regulating cell proliferation, cellular differentiation, cell growth [19]. CD 117 is found in more than 95% of GIST cases being widely accepted as a criterion for the positive diagnosis of these tumors [2]. The development of CD117 immunohistochemical staining in tumor tissue allowed us to differentiate it from leiomyomas, leiomyosarcomas and retroperitoneal sarcomas using also in addition to CD34 other immunohistochemical markers like alpha smooth muscle actin, desmin, and protein S100. The frequency of expression of these markers varies according to the origin site of the GIST at the level of alimentary tract. Leiomyomas are negative for CD117 and CD 34 but positive for α-SMA and desmin. Desmin is rarely positive in GIST. Gastrointestinal schwannomas are positive for S100 and negative for CD 117. S100 is rarely positive in small intestine GISTs. Also several other tumors such as melanoma and extra skeletal Ewing sarcoma can express CD117. Focal CD117 staining can be discovered in retroperitoneal leiomyosarcomas and liposarcomas [20]. Vimentin belongs to the proteins present in intermediary filaments of mesenchymal cells helping in the positive and differential diagnosis. Ki67 marker allows an accurate evaluation of tumoral cell proliferation, as a sign of malignant potential.

The development of immunohistochemical techniques, the discovery and use of more and more specific tumoral markers allowed the identification of this distinct pathology, the identification of the originating cell, the interstitial cell of Cajal (ICC), the understanding of the molecular mechanism of carcinogenesis in GISTs, the discovery and use of specific targeted therapy with biologic agents. GIST evolved from isolated cases to a very rich subject for research in multiple fields. The interstitial cells of Cajal (ICCs), the pacemaker cells of the gastrointestinal tract are considered the originating cells of these tumors, given the similar expression of CD34 and CD117. The ICCs were identified in 1893 by the Spanish pathologist, histologist, neuroscientist, and Nobel laureate (1906) Santiago Ramón y Cajal, who named them interstitial cells for their interposition between nerve endings and smooth muscle cells in the gut wall [21]. GIST can occur wherever there are Cajal cells, the gastric localization being the most frequent.

The malignant potential is important in choosing the appropriate surgical approach, the size of the surgical resection and the type, dosage and period of time of the targeted therapy with biologic agents. That is the reason...
why we perform in our case a limited resection, a superior polar gastrectomy with gastro-esophago-anastomosis E-E for a gastric GIST with spindle cells with intermediate risk of aggressive behavior having a 90% probability of 5 year recurrence-free survival according with the prognostic normogram developed by Gold et al in 2009 recognized by the National Comprehensive Cancer Network (NCCN) in 2010, used into clinical practice since then [22]. The mainstay of therapy remains the surgical resection. Gastric tumors, the most common location for GIST typically do not require a total gastrectomy. A subtotal gastrectomy or gastric wedge resection is most often adequate to achieve an oncologic intervention especially when the tumor does not have a high risk of aggressive behavior according with size and the mitotic count. Great care is needed intra-operatively, to avoid the violation of the tumor causing subsequent tumor seeding into the peritoneum. Lymphatic dissection is not required for GIST which hematogenous spread, the liver and peritoneum being as the most common sites of metastases.

The discovery in 2001 of the spectacular effect of imatinib, a tyrosine kinase receptor inhibitor in the treatment of a metastatic GIST, achieving a significant tumoral reduction represents an important landmark in the treatment of this pathology [23]. In the pre-imatinib era the survival of metastatic GIST patients was 1-2 years. On the other hand now under the treatment with tyrosine kinase receptor inhibitors the survival rose to at least 5 years [24]. The tyrosine kinase receptor inhibitors are used as neoadjuvant as well as adjuvant therapy increasing the recurrence-free survival and overall survival rates, stabilizing the disease, offering patients a significant improvement of quality of life. Our patient started an Imatinib adjuvant therapy at three weeks after the surgical intervention.

**Conclusions**

We describe a case of gastric GIST with upper digestive bleeding as primary manifestation. Anemia caused by the chronic bleeding or hemorrhage due to direct erosion of the gastrointestinal mucosa covering a sub mucosal GIST is rare. The final diagnosis is achieved using the immunohistochemical staining, the tumor being positive for CD117 and CD34. The preoperative evaluation is very important in planning the adequate resection with maximal organ preservation according to the malignant potential. Complete surgical resection remains the mainstay of treatment. The neoadjuvant as well as the adjuvant therapy is based on targeted therapy with biologic agents called tyrosine kinase receptor inhibitors like imatinib, increasing the recurrence-free survival and survival rates.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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