CASE REPORT

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Severe upper gastrointestinal bleeding from gastrointestinal stromal tumor of the stomach

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Abstract

Gastrointestinal stromal tumor (GIST) is a mesenchymal tumor originating from the Cajal interstitial cells, immunologically characterized by the c-kit gene. The evolution may be asymptomatic, discovered by chance during a necropsy, upper gastrointestinal endoscopy or due to complications of type-algic, occlusive or hemorrhage. We present the case of a voluminous gastric GIST complicated with serious upper gastrointestinal bleeding in a patient with multiple hard associated diseases, undergoing an emergency surgery in hemorrhagic shock. The surgery consisted in the resection of the upper polar esogastric, the pathological and immunohistochemistry tests confirming the diagnosis of GIST. The evolution was unfavorable at discharge after 45 days after surgery by an anastomotic fistula.

Keywords: gastrointestinal stromal tumor, upper gastrointestinal bleeding, immunohistochemistry, Ki67.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract tumors [1–4]. Most of them are located in the stomach (60–70%), but can be located in other segments of the digestive tract from the esophagus to the rectum and outside the digestive tract (mesenteries, omentum) [5–8]. In 1983, Mazur & Clark published the first report about the heterogeneous origins of the non-epithelial gastric wall tumors, and introduced the term "gastrointestinal stromal tumor (GIST)" [9]. This tumor has interstitial Cajal cells as a starting point, with the immunological characteristic of c-kit [1, 10]. Histologically, about 95% of GISTs express the CD117 transmembrane receptor, but in the situation lacking the kit mutation, 35% of them have a mutation on platelet-derived growth factor receptor alpha (PDGFRA) [2]. The incidence is estimated between 0.1–3% of the whole malignant digestive tumor [11–13] and they affect male and female in an equal proportion, predominantly in the 6th and 7th decades of life [14, 15]. The most frequent GIST's related emergency is gastrointestinal bleeding [16], that could vary from asymptomatic occult bleeding to massive bleeding, life-threatening hematemesis requiring emergency surgery [17, 18]. Surgery based on oncological principles (resection with free tumor margins histological confirmed, minimum 2 cm) is the main therapeutic option. The adjuvant therapy consists in Imatinib and Sunitinib (thyrosine kinase inhibitors), the prognostic factors described in the literature are: tumor size more than 10 cm, tumor location, involvement of the serosa, mitotic index (>5 mitoses/50 HPFs – high-power fields), nuclear atypia positive resection margins, tumor rupture, c-kit mutation, that may interfere with molecular target therapy, efficacy and Ki67 [19, 20].

In this article, we present the case of a patient with a hemorrhagic shock by bulky ulcerated gastrointestinal stromal tumor in stomach, which required emergency laparotomy and tumor resection and the specific features of acute presentation of GISTs in the emergency unit.

Case presentation

A 69-year-old male, admitted in Department of Surgery, within the Emergency County Hospital, Craiova, Romania, from the Emergency Unit for severe upper gastrointestinal bleeding, presented with hematemesis and melena. From personal history, we found significant: ethanol cirrhosis, portal hypertension, cholecystectomy, incisional hernia. The current disease onset was sudden after 24 hours by hematemesis and melena, leading fast to severe post-hemorrhagic anemia, crash pressure (blood pressure 70/40 mmHg, resting heart 130 beats/min, oxygen saturation 95%). At present admission, the physical examination revealed at palpation an epigastric tumor of 12/6 cm. Rectal examination highlights melena. The serum parameters revealed severe anemia (hemoglobin 5.8 g/dL, hematocrit 19%), hyperleukocytosis, urea 50 mg/dL, the other serum parameters being at normal limits. The emergency upper endoscopy showed esophageal varices of first degree, uncomplicated, not bleeding, and at the upper gastric pole, a submucosal proliferative process that ulcerates the mucous on a length of 0.5 cm with active bleeding.

Therapeutic management

The endoscopic injection therapy with adrenalin did

not stop the bleeding. Therefore, we decided to perform an emergency surgery. We performed an exploratory median xyphoumbilical laparotomy. Intraoperatively, we found: a tumor located in the upper gastric region, 12/6 cm in size, the stomach distended by the hematic content, blood-filled small bowel. The local condition required upper polar esogastrectomy with esogastric anastomosis.

The unfavorable postoperatory evolution encumbered by an appearance of anastomotic fistula on the 6th post-operatory day. The general condition got worse rapidly and, despite life support treatment and local care for anastomotic fistula, death occurred on the 45th post-operative day.

Macroscopic and histological features of the surgical specimen

The resection piece highlighted a tumor of 12/6 cm, with gastric edge of resection not invaded. The gastric wall thickness present in the muscle layer of a mesenchymal cell proliferation with fusiform and epithelioid aspect, arranged in a solid pattern, which ulcerates mucosa, with over 30 atypical mitoses. The pathological aspect suggested a malignant gastrostromal tumor.

For the histological study, there was used the classical staining with Hematoxylin–Eosin (HE). The selected tissue samples were fixed in 10% neutral formalin solution for 24 hours, subsequently being included in paraffin using the standard histopathological protocol.

The immunohistochemical (IHC) analysis was done using sections displayed on slides treated first with poly-L-lysine. IHC was performed on 3 μm thick sections from formalin fixed-paraffin embedded specimens.

The method used was an indirect tristadial Avidin–Biotin complex technique, with a NovoLink Polymer Leica detection system using a novel control polymerization technology to prepare polymeric HRP (horseradish peroxidase)-Linker antibody conjugates according to the manufacturer's specifications.

Briefly, the procedure comprised: deparaffinization in toluene and rehydration in alcohol series, washing in phosphate-buffered saline (PBS), blocking with normal serum, for 5 minutes, incubation with primary antibody for 60 minutes, incubation with post-primary block 30 minutes, then with NovoLink Polymer 30 minutes. Cross-sections were further incubated with 3.3'-diaminobenzidine (DAB) substrate/chromogene and counterstained with Mayers' Hematoxylin.

The antibodies used for IHC were CD117, CD34, Ki67, S100 protein, alpha-smooth muscle actin (α-SMA) (Table 1).

Table 1 – ***Primary antibodies used in the immuno-histochemical study***

Antibody	Specificity	Antigen retrieval	Dilution	Clone	Source
α-SMA	Myofibroblast	3 cycles citrate	1:50	1A4	Dako
CD34	Vascular endothelium	5 cycles citrate	1:100	QBEnd-10	Dako
Ki67	Cellular proliferation	7 cycles citrate	1:100	MIB-1	Dako
S100 protein	Neural cells	7 cycles citrate	1:500	Z0311	Dako
CD117	Interstitial Cajal cells	7 cycles citrate	1:40	NCL-L	Leica Biosystems

Antigen retrieval techniques for some of the above-mentioned antibodies were done according to the manufacturer's specifications. Both positive and negative controls were used.

The negative control was performed by using a primary irrelevant antibody or by replacing the secondary antibody with PBS. The positive control was made comparatively with the expression of antibody investigated in the peri-tumoral normal tissue structures (positive internal control on slides). To ensure the reliability of the experimental study, internal quality control of histopathological and IHC techniques were performed as a part of implemented and certified quality assurance system. All slides were examined and photographed on a Leica ICC50 HD microscope.

The immunohistochemistry test revealed CD117-positive and diffuse into fusiform tumor cells with fascicular pattern (Figure 1), α-SMA positive in vessels and smooth muscle, negative in tumor cells (Figure 2), CD34-negative in tumor cells, positive in vessels (Figure 3), S100 protein positive in threads nerve and rare mesenchymal cells, negative in tumor cells (Figure 4), Ki67 positive in more than 25–30% of the nucleus of tumor cells (Figure 5). Based on the clinicopathological and immunohistochemical data, the final diagnosis was GIST with malignant potential (pT4NxMx) with high degree of malignancy (G2) and the risk of disease progression by 86%.

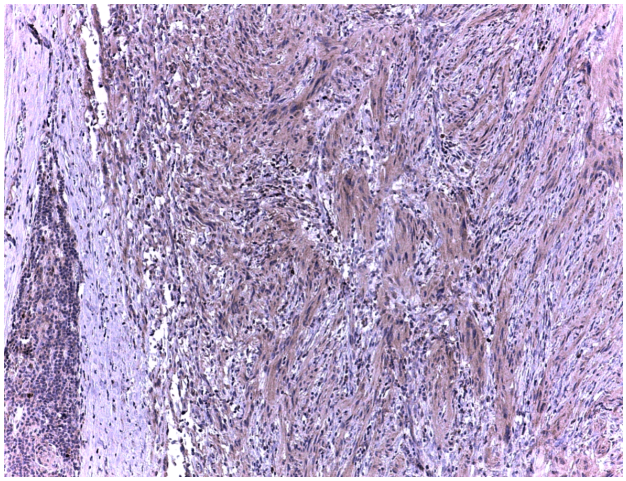

Figure 1 – ***CD117-positive and diffuse fusiform tumor cells, ×100.***

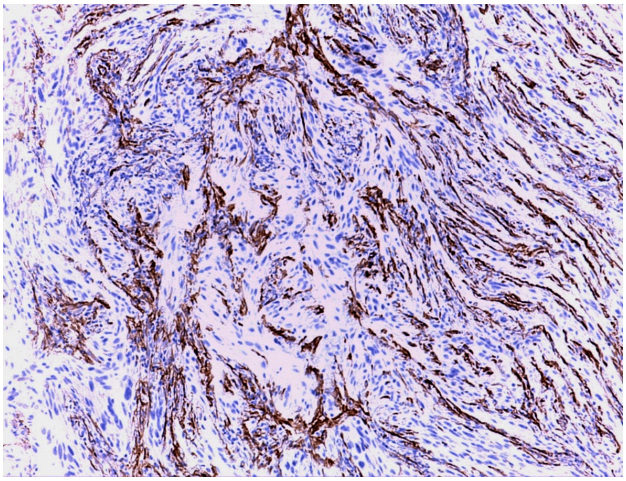

Figure 2 – ***α-SMA positive in vessels and smooth muscle, negative in tumor cells, ×100.***

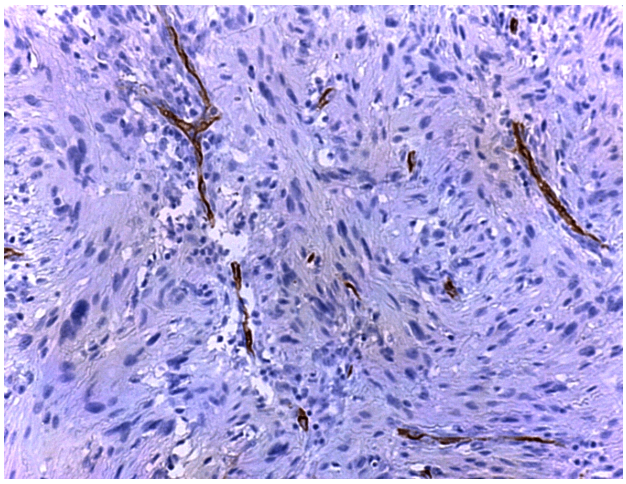

Figure 3 – ***CD34 negative in tumor cells and positive in vessels, ×200.***

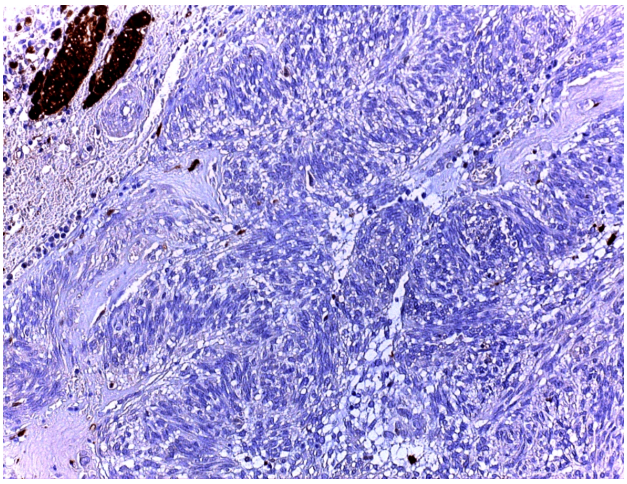

Figure 4 – ***S100 protein positive in threads nerve and rare mesenchymal cells and negative in tumor cells, ×200.***

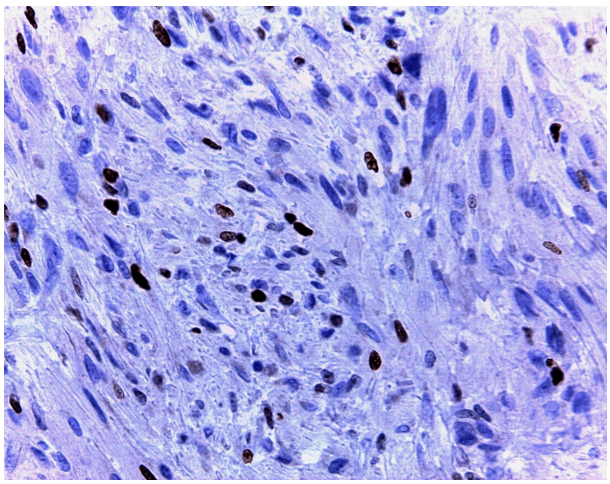

Figure 5 – ***Ki67 cell proliferation index positive in more than 25–30% of tumor cells nuclei, ×400.***

Discussion

Gastrointestinal stromal tumors are mesenchymal tumors originating from the Cajal interstitial cells and immunological expression KIT (CD117) or CD34, or both [1]. The most frequent location is the stomach [5–7]. One of the most prominent characteristics of gastrointestinal stromal tumors is their unpredictable and variable behavior [21]. The range of clinical feature of GISTs ranges from symptomatic bleeding to incidental detection during a routine endoscopy [5]. The most important clinical presentations of GISTs are bleeding and pain, depending on the tumor size and location [22, 23]. In the above-presented case, we describe a massive hematemesis from a GIST followed by hemorrhagic shock. Bleeding came through mucosal ulceration of the tumor, also highlighted by upper gastrointestinal endoscopy.

Endoscopic hemostasis has improved over the past decade by introducing hemoclips on bleeding vessels of ulcer gastrointestinal stromal tumors [24]. The first report of the upper gastrointestinal bleeding by "Dieulafoy like" lesion was made in 2006 by Vats *et al.*, but we do not have a description regarding the relationship between the pattern of growth and incidence of bleeding, the data not being fully understood yet [25].

From the beginning, the preoperative diagnosis raised the suspicion of GIST with massive upper gastrointestinal hemorrhage, once established severity of bleeding and lack of response to endoscopic therapy was required exploratory laparotomy. The goal was the removal of the tumor with negative edge of resection with a hemostatic and healing purpose. We conducted upper polar esogastrectomy and the resection edges were histopathologically and immunohistochemically negative.

Fletcher's classification regarding gastric GISTs highlights four groups: very low risk (<2 cm in diameter and <5 mitoses/50 HPFs), low risk (2–5 cm in diameter and <5 mitoses/50 HPFs), intermediate risk (<5 cm in diameter and <6–10 mitoses/50 HPFs or 5–10 cm in diameter and with <5 mitoses/50 HPFs), and high risk (>5 cm in diameter and >5 mitoses/50 HPFs or >10 cm in diameter and any number of mitoses or any diameter with >10 mitoses/50 HPFs) [6]. The Ki67 index shows no difference between acute and chronic onset of GISTs [16]. Also, Ki67 mitotic index indicated a poor prognostic when its value was more than 10% [26], and in our case, Ki67 index was positive in more than 25–30% of the nuclei of tumor cells. Bleeding is the most common acute complication of GISTs with gastric location, probably because the stomach is a highly vascular organ [27].

From this point of view, our patient was part of the high-risk group, not submitted intratumoral necrosis or hemorrhage, and although the index Fletcher looks high risk, we would expect a satisfactory outcome, but anastomotic fistula and associated comorbidities (ethanolic cirrhosis, portal hypertension) led to death.

The endoscopic hemostasis of tumor lesions remained a challenge, because none of endoscopic therapies did not prove superiority, the choice of therapy depending on tumor characteristics and personal experience of the endoscopy technician. Literature data showed that the application of hemoclips to obtain hemostasis was followed by success, with some situations of failure [28–31].

In our case, the application of hemoclips could lead to the tearing of mucosa with consecutive bleeding, the application of endoloop for this lesion would not have been possible. We defined acute presentations as those cases that required an emergency surgical procedure within 24 hours from admission [16]. The primary goal of surgery is

complete removal of the tumor with free resection margins. Avoiding the pseudocapsule rupture is very important because intra-abdominal dissemination negatively influenced the prognosis [32]. It is not necessary to perform lymphadenectomy because nodal metastases are exceptional [33]. The gastric wedge resection is the most frequently performed procedure for GISTs, and it is recommended as the treatment of choice; however, in some cases, tumor size and location may indicate extensive surgery, including a partial or total gastrectomy [34, 35].

Regarding the laparoscopic treatment in our case, there would not have been imposed due to tumor size, but in case the tumor size was up to 5 cm, current protocols recommended laparoscopic treatment [32]. The peculiarity of this case is the upper gastrointestinal bleeding present with hematemesis and melena, at a cirrhotic patient with portal hypertension, and parenchymal decompensation, susceptible to bleeding complications in the upper digestive tract determined by a hemorrhagic GISTs. Gastrointestinal stromal tumor localized in the upper gastric pole was confirmed by upper gastrointestinal endoscopy, histopathology and immunohistochemistry.

In the case with acute bleeding, the most frequent immunohistochemical aspect of GIST is the spindle type [16], and we found a similar aspect in our case.

Conclusions

Gastrointestinal stromal tumors are mesenchymal tumors originating in Cajal interstitial cells and immunological expression KIT (CD117) or CD34, or both, with the most frequent localization in the stomach and with unpredictable and variable behavior. The massive upper gastrointestinal hemorrhage raised the suspicion of gastrointestinal stromal tumors. Gastric wedge resection is the most frequently performed procedure for gastrointestinal stromal tumors, and it is recommended as the treatment of choice; but tumor size and location may indicate extensive surgery. The peculiarity of this case is the upper gastrointestinal bleeding, present with hematemesis and melena, at a cirrhotic patient with portal hypertension, and parenchymal decompensation, susceptible to bleeding complications in the upper digestive tract determined by hemorrhagic gastrointestinal stromal tumors.

Conflict of interests

The authors declare that there is no conflict of interests.

Author contribution

Laurenţiu Augustus Barbu and Ştefan Mugurel Ghelase equally contributed to the manuscript.

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