CASE REPORT

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Stage IV duodenal GIST requiring emergency pancreaticoduodenectomy – diagnosis difficulties and therapeutic options

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Abstract

This paper presents a very rarely encountered case of a 45-year-old female, admitted in our Surgical Clinic for upper digestive bleeding (repeated hematochezia). The upper endoscopy was negative, but the barium meal discovered an apparently extrinsic duodenal (D_3) stenosis; abdominal ultrasound diagnosed a left liver mass suggesting a metastatic tumor. The hematochezia relapse, with hemodynamic instability imposed emergency surgery; on laparotomy, a bleeding tumor located on the duodenopancreatic region was discovered, and a pylorus-preserving pancreaticoduodenectomy (Traverso–Longmire) was performed. The histology and immunohistochemistry established the diagnosis of duodenal stromal tumor, CD34 and CD117 positive, with an estimated progression risk of 34%. The postoperative evolution was favorable, the patient being alive, four years after the surgery.

Keywords: duodenal GIST, progression risk, CD34, CD117, pancreaticoduodenectomy.

Introduction

Gastrointestinal stromal tumors (GISTs) represent a more and more often encountered entity, small bowel GISTs representing 20–30% of all GISTs, duodenum being the rarest origin, with 5–11.4% of all GISTs [1, 2]. With the advent of the tyrosine kinase inhibitors (Imatinib, Sunitinib), the prognosis of the resected GISTs has been considerably improved, even for advanced, metastatic disease [3, 4].

The positive diagnosis is established by histology and immunohistochemistry, but non-specific symptoms and the large size of the tumor create, in many cases, confusion with a pancreatic head carcinoma [5, 6]. The surgical option, in many cases is pancreaticoduodenectomy; the preoperative knowledge of the GIST histological diagnosis may influence the surgical option toward a more limited resection, with the same long-distance results, but with lower postoperative morbidity [7, 8]. However, an emergency performed pancreaticoduodenectomy, as in our case, is seldom reported, excluding the possibility of a preoperative diagnosis of the duodenal GIST. The final diagnosis, adjuvant treatment and prognosis is based on histology and immunohistochemistry, which demonstrate the positivity for CD34, CD117, and also other important histological markers.

This paper's aim is to bring in discussion the main problems raised by this case, emphasizing the preoperative diagnostic difficulty of a duodenal stromal tumor; also, the pancreaticoduodenectomy indication in an emergency setting, on a patient with liver metastasis, represents another important reason of debate.

Case presentation

Patient L.M., female, 45-year-old, was admitted in February 22, 2012, into Department of Surgery, Caracal Municipal Hospital, Romania, for hematochezia and subsequent severe anemia. At admission, the patient was in very poor condition, pale, with signs of acute anemia, shortness of breath and tachypnea, accompanied by hematochezia, which had repeated several times during hospital in stay. The physical examination does not highlight any useful data excepting the anemia. At that time, the hemoglobin levels were 7 mg/dL and still after 3 blood units administered, the levels kept their initial values. Meanwhile, the patient had three more hematochezia stools, so the patient was transferred to a superior rank hospital in the same day, in the II[nd] Surgical Clinic, Emergency County Hospital, Craiova, Romania, for urgent surgical treatment. History revealed a similar upper digestive hemorrhage 7–8 months before the admission, with an upper digestive endoscopy failing to detect an obvious cause of the bleeding.

The written consent of the patient was obtained and also the approval from the Hospital Ethics Committee.

The upper digestive endoscopy was repeated, but fails again to identify an underlying cause of the bleeding until the D_2; still, blood was discovered in the distal duodenum. A barium meal was administered and a D_3 apparently extrinsic stenosis was discovered (Figure 1).

The abdominal ultrasound revealed a 10/8 cm inhomogeneous mass, located laterally from the pancreatic

head; on the left hepatic lobe, a 42/30 mm nodular mass was identified (metastasis) (Figure 2).

The patient repeats the hematochezia stool, requiring massive blood transfusions (3 blood units), and was transferred to our Clinic; on admission, the digestive bleeding recur, with tachycardia (100 beats/min) and a blood pressure of 100/70 mmHg. A nasogastric catheter was inserted, allowing a small quantity (<100 mL) of clear gastric juice to be evacuated; the hemoglobin level was 8.3 g%, after 3 blood units transfused, all other usual investigations being normal. An emergency abdominal computed tomography (CT) was intended, but the patient presented two more hematochezia stools, the nasogastric tube drainage becomes red (active severe bleeding) and the blood pressure drops to 80/60 mmHg. The emergency midline laparotomy was performed two hours after the admission in our Clinic, without the possibility of a preoperative abdominal CT scan.

During laparotomy, a 10 cm tumor was discovered on the pancreatic head region, with irregular surface, and inhomogeneous structure, with harden areas alternating with soft ones, elastic areas, with pseudo-cystic appearance; the morphology of the tumor was highly consistent, with the GIST diagnosis, and the intraoperative biopsy was not indicated. On the left hepatic lobe, an area of inhomogeneous, increased consistency was palpated, with no expression over the hepatic surface (no intraoperative ultrasound available); no enlarged lymph nodes are discovered. The small bowel and colon are filled with blood, but no other suspected lesions are discovered.

Considering the importance of the bleeding and the absence of another bleeding source on the upper digestive segment, a pylorus-preserving pancreaticoduodenectomy was performed (Figure 3); the normal caliber of the hepatic duct (5–6 mm) have imposed the stenting of the hepatico-jejunal anastomosis, with a tube exteriorized through the anterior wall of the anastomotic bowel loop. Intraoperatively, other 3 blood units were administered.

Starting from the 5th postoperative day, the patient's evolution was complicated by an external pancreatic fistula, with an output of 100–150 mL/day at the onset, fistular debit that diminished quickly in the following days, the patient being discharged on the 15th postoperative day with a fistula output less than 50 mL/day. The biliary stent was removed after two months, and the pancreatic fistula was completely healed on the 68th postoperative day.

Pathological examination was performed after 24-hour fixation in 10% formalin solution of the resected specimen. Gross examination revealed a 9/10/7 cm specimen, with a 13.5 cm small intestine fragment; on the longitudinal section, it was identified 8.5 cm tumor, grayish colored and containing hemorrhagic areas. Microscopic examination on serial sections through the tumor of the intestinal wall pointed out an infiltrate in the muscular layer of a neoplastic proliferation with fusiform and medium size epithelioid cells (Figure 4), without the invasion of duodenal mucosa and pancreatic parenchyma, containing areas of necrosis and hemorrhage (Figure 5). According to the microscopic aspect, the tumor was considered a duodenal GIST. The mitotic index was less than five mitoses/50 high-power field (HPF).

For the positive and differential diagnosis, we used the following immunohistochemical (IHC) markers (Table 1).

The IHC study of tumoral cells was positive intense and diffusely cytoplasmatic and membranous for CD117 (Figure 6), positive intense and diffusely cytoplasmatic for CD34 (Figure 7). The proliferative activity of tumor cells was investigated by using Ki-67. In our case, the Ki-67 proliferation index was 5% (Figure 8). S100 protein was negative in tumoral cells and positive in nerve threads (Figure 9). α-SMA was negative in tumoral cells and positive in blood vessels (Figure 10).

The pathological and IHC diagnosis was well-differentiated duodenal stromal tumor (G1) with low malignant potential.

One month postoperatively, an abdominal CT confirms the liver metastasis on the left lobe, and also a small nodular mass was identified on the right liver lobe (Figure 11).

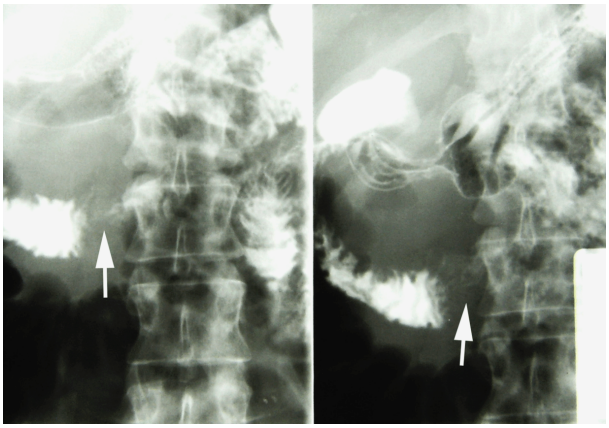

Figure 1 – ***The barium exam showing a D_3 extrinsic stenosis.***

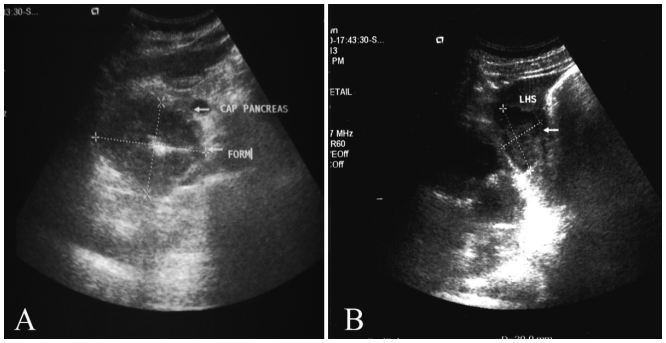

Figure 2 – ***Preoperative abdominal ultrasound: (A) A mass on the pancreatic head region; (B) A metastasis on the left lobe of the liver.***

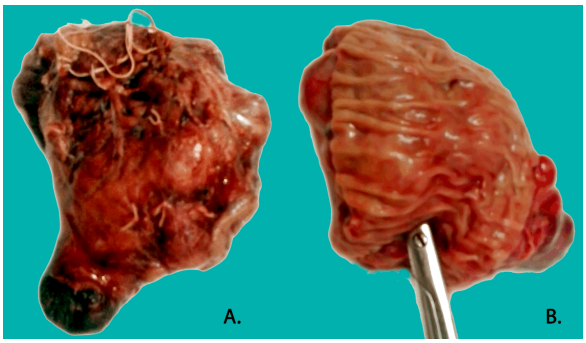

Figure 3 – ***(A) Fresh resection specimen – posterior aspect; (B) Fresh resection specimen with duodenum sectioned and papilla major catheterized, with no obvious mucosal lesion.***

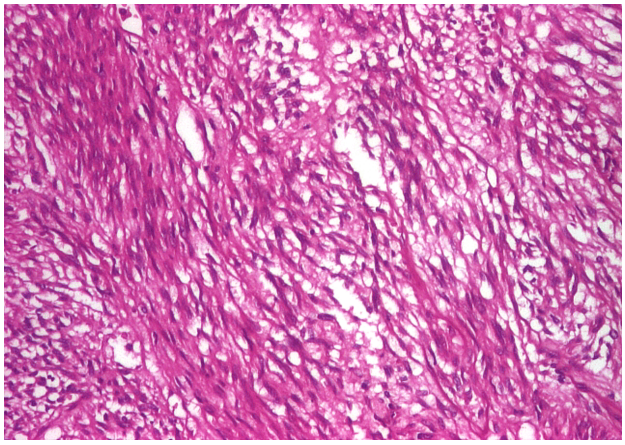

Figure 4 – ***Fusiform and medium size epithelioid cells [Hematoxylin–Eosin (HE) staining, ×200].***

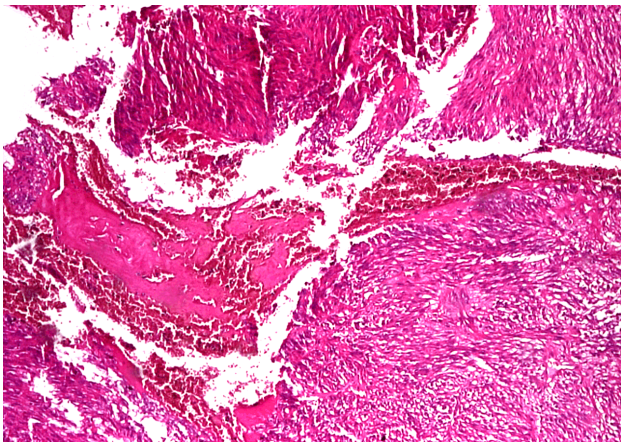

Figure 5 – ***Fusiform and medium size epithelioid cells; areas of necrosis and hemorrhage (HE staining, ×100).***

Table 1 – ***Characteristics of the antibodies used in this study***

Antibody	Marker	Source	Clone	Dilution	Pretreatment microwave oven
CD117 (*c-kit*)	Cytoplasmatic and membranous, Cajal cells, germinals, melanocytes	LEICA	T595	1:40	Seven cycles citrate buffer
CD34	Membranous, endothelials, blood cells	DAKO	QBEnd/10	1:100	Five cycles citrate buffer
Ki-67	Nuclear	DAKO	MIB-1	1:20	Seven cycles citrate buffer
S100	Cytoplasmatic, Schwann cells, myoepithelial, mesenchymal	DAKO	Polyclonal	1:500	–
α-SMA	Cytoplasmatic, smooth muscle cells	DAKO	1A4	1:50	Three cycles citrate buffer

CD: Cluster of differentiation; *α*-SMA: Alpha-smooth muscle actin.

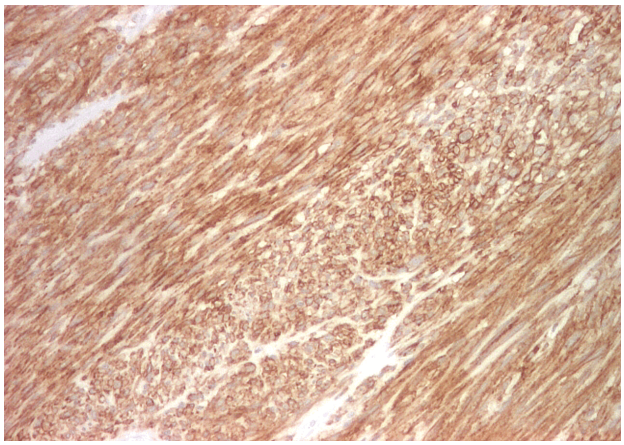

Figure 6 – ***IHC image of the specimen, with CD117 intense and diffusely cytoplasmatic and membranous positivity in tumoral cells (Anti-CD117 antibody immunostaining, ×200).***

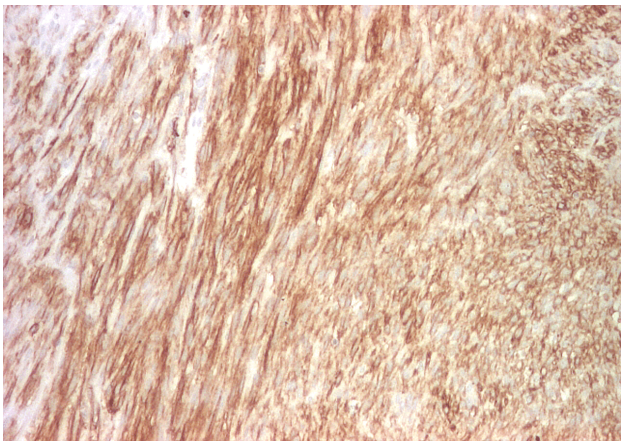

Figure 7 – ***IHC image of the specimen, with CD34 intense and diffusely cytoplasmatic positivity in tumoral cells (Anti-CD34 antibody immunostaining, ×200).***

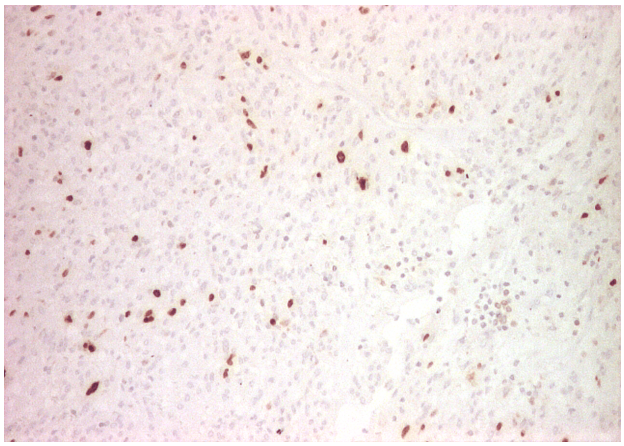

Figure 8 – ***IHC image of the specimen, with Ki-67 positivity in 5% of tumoral cells (Anti-Ki-67 antibody immunostaining, ×100).***

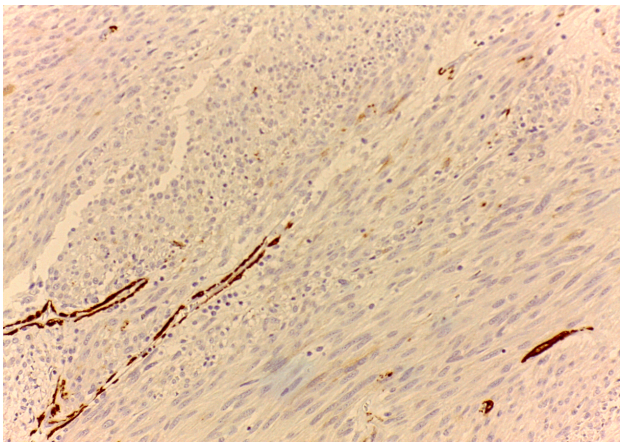

Figure 9 – ***IHC image of the specimen, with S100 protein negative in tumoral cells and positive in nerve threads (Anti-S100 antibody immunostaining, ×100).***

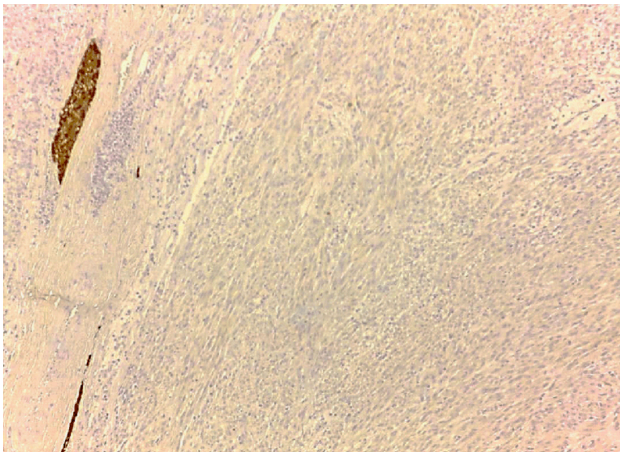

Figure 10 – ***IHC image of the specimen, with α-SMA negative in tumoral cells and positive in blood vessels (Anti-α-SMA antibody immunostaining, ×100).***

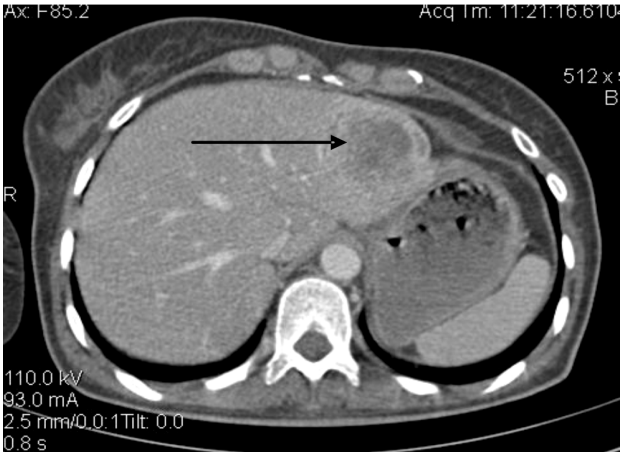

Figure 11 – ***Postoperative abdominal CT scan with liver metastasis on the left lobe.***

The patient was considered a candidate for Imatinib therapy, which was started three months later (in June 2014). However, after two years of Imatinib, the liver metastases manifest a growing tendency and the Imatinib dose was raised to 800 mg daily. In the third postoperative year, the liver metastases appear relatively stabilized, with cystic transformation, but the patient developed severe adverse effects on Imatinib: necrotizing, flictenular dermatitis, ecchymosis, generalized edema, loss of appetite, severe anxiety; the surgical resection of the liver metastases was contraindicated, due to their extent, and possible insufficient remnant liver parenchyma. The patient was proposed for second line Sunitinib therapy, with important improvement of the general condition; at the present time (four years after the diagnosis), the patient is alive, with no subjective accuses, with an apparently regression of the liver's metastases on abdominal CT.

Discussions

The presented case was a rarely encountered circumstance, in which an upper digestive bleeding produced by a very rare duodenal tumor requires an emergency pancreaticoduodenectomy. Due to its rarity, but also due to the difficulty of the surgical intervention, this case raises difficult diagnosis and therapeutic problems, preoperatively but also intraoperatively and postoperative follow-up.

The preoperative diagnosis of a duodenal GIST is mainly empiric, since the endoscopic biopsy is often unsuccessful, due to the submucosal development of the tumor, and not rarely, due to inaccessibility of the tumor to usual endoscopic examination [9–11], as in our case. Bleeding (melena, chronic anemia) is present in up to 22–83% of the duodenal GIST [1, 7, 12, 13] and the endoscopy has the advantage of excluding other major sources of bleeding [10, 14]. If possible, a barium meal may detect the tumor in the duodenum [10, 13], as in our case. However, major bleeding from a GIST requiring emergency surgical intervention is very rare [14, 15].

Aside of the uncertain preoperative diagnosis, the main preoperative problem was related to the operative timing, in order to offer the best condition and minimizing the risk for the patient. Practically, the operative indication was established following the upper digestive bleeding criteria: a severe, repeated hematochezia, and the tendency toward hemodynamic instability in spite of the repeated blood transfusions (more than 4 blood units used for compensation in less than five hours since the bleeding had started), similar with the case presented by Shaw *et al.* [14].

The intraoperative exploration has the role to establish the etiology and the topography of the bleeding, a midline laparotomy offering adequate exposure. Since the intraoperative exploration did not identify other suspected lesion, excepting for the tumor located on the pancreatic head region, the digestive hemorrhage was considered to have the origin in an area of the duodenal wall invasion and ulceration.

A delicate intraoperative problem in a big tumor of the duodenal and pancreatic head region is to establish the real site of origin of the tumor and its histological structure, in order to adopt the best surgical procedure [5, 6, 12]. If a preoperative or an intraoperative diagnosis of duodenal GIST is available, there are two main surgical options, in the presence of the resectability, with the mandatory condition of clear surgical margins: a more demanding pancreaticoduodenectomy [16, 17] or more limited procedures (wedge resection or segmental duodenectomy) [1, 9, 10, 14]; several studies have reported similar long distance results between these procedures [7, 8, 10, 11, 16, 17].

Limited resections may be conditioned by the topography on the pancreatic side of the duodenum [8] or on the D_2, due to the proximity with the Vater's papilla, pancreatic duct and/or bile duct [7], the large size of the tumor (>5 cm is more likely to be resected through a pancreaticoduodenectomy than a limited resection) [7, 12] and/or the presence of a small implantation pedicle that may allow a wedge resection, even if the tumor is larger [9]. Obviously, the unknown pre or perioperative structure of the duodenal tumor (GIST or other histological type) represents a formal indication for pancreaticoduodenectomy [12]. A combined laparoendoscopic local resection was also reported [18].

Although in operable GISTs the tumoral biopsy is prohibited due to the risk of recurrence, if the tumor is unresectable, tumoral biopsies must be taken into account, considering the good response of the GISTs on Imatinib [19–21].

Limited resections have lower postoperative morbidity [7, 8], but not always with statistical significance [12]. However, the risk of the postoperative anastomotic leakage exists in both types of the procedures, but usually they are solved through conservative measures [13].

In our case, it was impossible to take into consideration the possibility of a limited resection, due to the fact that histology was unavailable in emergency, and also the duodenal origin of the tumor was almost impossible to be predicted intraoperatively, due to the big size of the tumor and the development predominantly toward the pancreatic head, the duodenum appearing mainly compressed by the tumor. Consequently, the only type of intervention that could ensure the hemostasis was the pancreaticoduodenectomy [16].

The indication of a pancreaticoduodenectomy in the presence of the liver metastases is largely debatable, but the massive bleeding has made this procedure mandatory. On the other hand, the postoperative diagnosis of the duodenal GIST confirmed the value of this surgical procedure, even in the presence of the liver metastases, considering the good response on the Imatinib therapy, and unexpected long distance survival in some reported cases, even with repeated cytoreductive surgeries for metachronous metastases [3, 4, 19, 22].

Establishing the resectability in the presence of a big tumor, involving the duodenum and almost entire pancreatic head represents a delicate moment; a large Kocher maneuver, until the aorta, and primary identification and isolation of the superior mesenteric artery [23] represents important objectives in these cases, along with the delicate dissection between the portal vein and the pancreas.

Interestingly, the examination of the resected specimen failed to identify a lesion of the duodenal mucosa (confirmed also by the histology, which showed no invasion into the mucosal layer of the duodenum), thus the bleeding was exteriorized into the digestive tract through the Vater's papilla (*hemosuccus pancreaticus* or Wirsungorrhage) [24], representing another peculiarity of this case.

Histological and molecular diagnosis

Although the GIST pathological diagnosis is based on the histological tumor profile, IHC staining is mandatory to establish a proper diagnosis [25].

GISTs are masses with some macroscopically features: well-circumscribed fleshy, pink or tan white. Complications, such as bleeding, necrosis or cystic degeneration, are frequently encountered in large tumors [26]. There are three different histological subgroups of GIST: spindle-cell GIST, which is the most frequent (70%) and is represented by cells with pale eosinophilic fibrillary cytoplasm, with ovoid and uniform nuclei and ill-defined cell borders; epithelioid GIST (20%) is represented by rounded cells with clear eosinophilic cytoplasm disposed in nests and sheets; mixed type (10%), which contains spindle and epithelioid cells [26].

According to the risk assessment criteria (size of the tumor, low mitotic index and location) in accordance with *Armed Force Institute of Pathology* (Miettinen's Criteria) [27] and endorsed by *European Society of Medical Oncology* [28], the histopathological and IHC diagnosis was well-differentiated duodenal stromal tumor (G1) with low malignant potential.

The correct diagnosis is obtained by IHC staining of the tissue samples for KIT, CD34, α-SMA, desmin, Ki-67 and S100 [25, 29].

Approximately 95% of GISTs are positive for the KIT, which is not frequently expressed in other abdominal tumors. Furthermore, 60–80% of all GISTs have positive CD34. The histological diagnosis is possible even if the tumor is negative for KIT but positive for CD34. When the tumor is negative for KIT, CD34, α-SMA and S100, a correct diagnosis is very difficult to establish. The recent discovered antibody against DOG1 (calcium-activated chlorine channel protein expressed especially in GISTs) was found in approximately 90% of KIT-positive GISTs and in approximately 35% of KIT-negative GISTs. Due to the sensitivity and specificity of DOG1, which is higher than in KIT staining, the diagnosis can be correctly established even if the tumors are negative for KIT but positive for DOG1 [30, 31].

Problems related to postoperative strategy

Postoperative strategy, after resecting a GIST includes the Imatinib therapy, which has clear indication in the presence of metastasis, even if the estimated progression risk of the tumor itself is low [4, 32]. The postoperative problems in our case were related mainly to an important delay in Imatinib therapy start (almost five months, delay after the histological confirmation of the disease) and the attitude toward liver metastases. Although the resistance to Imatinib was demonstrated, there are some reports of 6–10 years with usage, without significant adverse effects, and long distance survival for these advanced cases [3, 22]. A second line Sunitinib represents another option in case of resistance to Imatinib.

At the initial time of surgery, the left hepatectomy for left lobe metastasis, although reported as a feasible procedure in synchronous metastatic GISTs [33], was not a reasonable option, due to the high risk of the pancreaticoduodenectomy in the presence of an acute severe hemorrhage. Therefore, we choose to follow-up the evolution under the Imatinib and a reasonable re-evaluation after one year of treatment, surgical removal of the metastases remaining a viable option, depending on their response on treatment, and if other metastases will occur or not [17, 19, 20, 32].

In spite of the good prognosis of the GISTs, the prognosis of our case remains reserved, considering that stage IV represents a significantly negatively influencing factor of survival [7].

Conclusions

Duodenal GIST, although very rare, presents delicate problems of diagnosis and treatment, often requiring complex procedures (pancreaticoduodenectomies). Still, an urgent indication for the procedure remains a rarity. In our case, the surgical procedure represented the only chance in order to achieve hemostasis. The exteriorization of the bleeding through duodenal papilla was another particularity of the case. The histopathological and IHC exams remain the standard for the diagnosis of certainty of this pathology and also for establishing the prognosis and an appropriate oncological therapy. The best treatment of the liver metastases remains an open discussion, especially considering the young age of the patient.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Cecil Sorin Mirea and Emil Moraru contributed equally to preparing the manuscript.

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