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The Complexity of Surgical Treatment Strategy for The Rare Variety of Gastric Pediatric-Like GISTs

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Keywords: Pediatric-like GIST; Lymphadenectomy; Laparoscopic Assisted Surgery

Abbreviations: GIST: Gastrointestinal Stromal Tumors; Ped GIST: Pediatric-Type Gastrointestinal Stromal Tumor; HPF: High-Power Fields; SDH: Succinate Dehydrogenase Complex; CSS: Carney-Stratakis Syndrome; CT: Carney Triad; TKI: Tyrosine Kinase Receptor Inhibitors; IHC: Immunohistochemistry

Abstract

Background: The standard treatment for gastrointestinal stromal tumors localized in the fundus or greater curvature of the stomach is laparoscopic wedge resection without need for lymphadenectomy. However, when tumors are located in the antrum and show histological features compatible with the pediatric type, this strategy needs to be changed.

Methods and Results: We present the case of a 49-years old woman diagnosed with two multinodular GIST tumors located into the antrum of the stomach. A laparoscopic-assisted distal gastrectomy without lymphadenectomy was performed initially. The pathological report revealed a rare variety of gastric GISTs, the nodular, pediatric-like type which actually carries a high risk of lymph node metastases. Consequently, the patient was re-operated and a loco-regional lymphadenectomy with preservation of the previously constructed gastroduodenal anastomosis was performed for accurate staging. None of the 12 lymph nodes examined by the pathologist was metastatic. The patient underwent adjuvant treatment with Imatinib for 24 months and is disease-free now, after 41 months follow-up. A review of the data in the literature regarding the characteristics and management in pediatric-like GISTs was conducted to provide the basis for treatment strategy decisions.

Conclusion: Minimally resection of gastric GIST is feasible for tumors located in the antrum although the complexity of the operation increases. Presence of multinodular disease in the antrum of a young adult female should raise the suspicion of paediatric-type GISTs and loco-regional lymphadenectomy should be added for accurate staging and indication for adjuvant treatment. Further research in this field is necessary but is hampered by the rarity of the disease.

Background

With the development of minimally invasive surgery, laparoscopic wedge resection of small (<5cm) Gastrointestinal Stromal Tumors (GIST) localized in the fundus or greater curvature of the stomach has become the standard of surgical care. However, for a pediatric-type GIST located in the antrum of an adult patient the optimal surgical management is still controversial. There are no standard guidelines regarding the best practice for treating this rare disease. Pediatric-type GISTs have a risk of lymph node metastasis reaching as high as 50%, therefore the need for lymphadenectomy in such cases should not be neglected. Moreover, wedge resection of multiple antral lesions inevitably leads to significant stenosis and is not recommended. For tumors in this location a former antrectomy is thus required, a technique which is more difficult to be performed using a minimally invasive approach. We report the case of a patient with two synchronous GIST tumors of the gastric antrum which was initially treated with a laparoscopic-assisted distal gastrectomy but

in which the final pathological report revealed the pediatric-type GIST and the surgical strategy was changed accordingly. A review of the literature focused on this rare variety of GISTs is also presented and its pathological and clinical significance are discussed. This report aims to increase the awareness of the medical and surgical teams which should ideally recognize these particular tumors preoperatively and offer them the proper treatment strategy.

Clinical Immersion

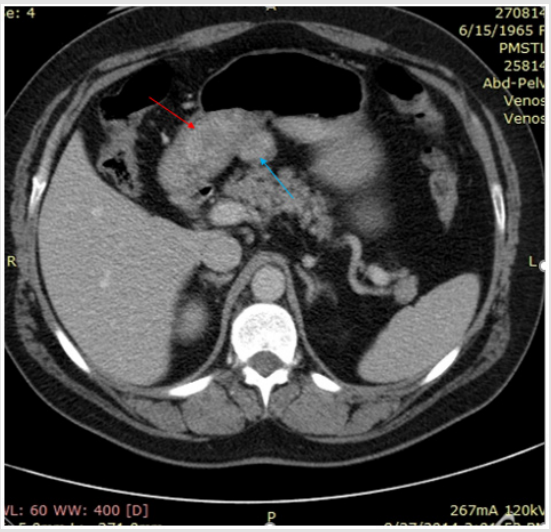

Figure 1: Axial abdominal CT, venous phase, showing 2 nodular tumors located on the posterior wall of the gastric antrum GIST with no enlarged lymph node (arrows).

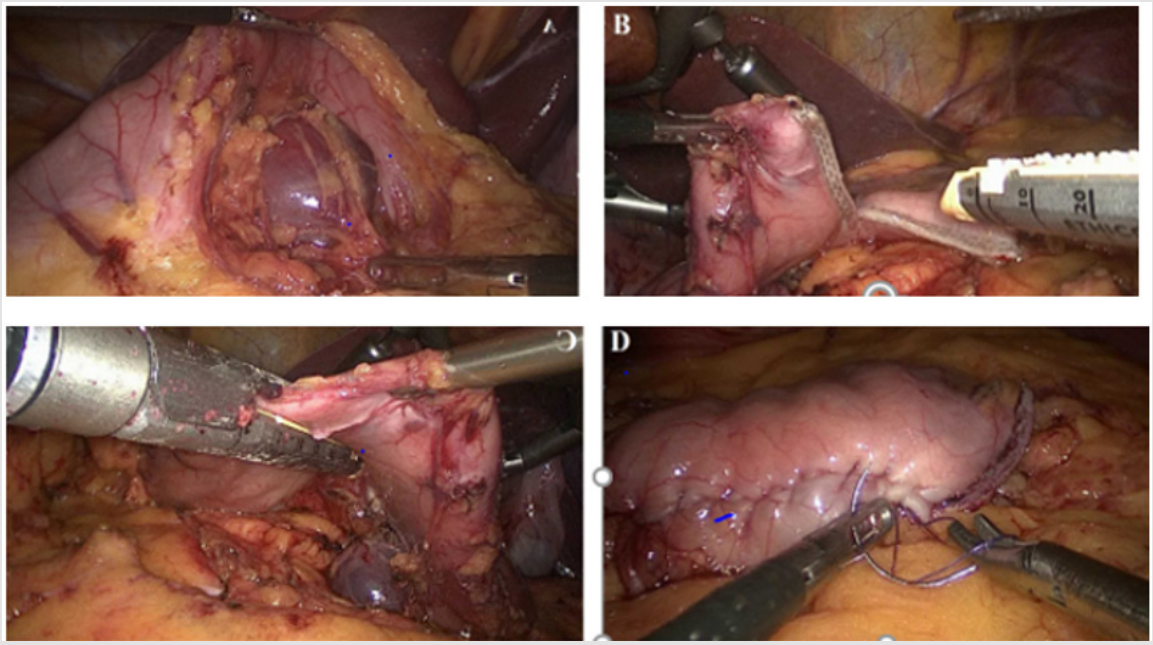

Figure 2: Intraoperative images: (A) The 2cm subserosal tumor on the posterior wall of the antrum; (B,C). Resection of the gastric antrum with endoscopic staplers; (D) Suture reinforcement of the staple line.

A 49 years-old woman with one-year history of abdominal pain, nausea, and vomiting was referred to our clinic for surgical treatment of an antral bifocal gastric tumor that showed characteristics of Gastrointestinal Stromal Tumor (GIST) on endoscopic biopsy. The upper GI examination showed a 5-cm submucosal tumor localized within the posterior wall of antrum which produced a partial stenosis of the antrum. The contrast-enhanced computer tomography scan revealed a second 2cm antral subserosal tumor in the vicinity of the submucosal GIST diagnosed endoscopically. The lymph nodes in peri gastric and loco-regional stations number 1 to14 were not enlarged (Figure 1). Given the preoperative established diagnosis of gastric antral GIST, a distal gastric resection followed by gastroduodenal anastomosis was performed using a laparoscopic-assisted approach. Four ports were used in total. The 10mm optic port was inserted near the umbilicus, another 10 mm port was placed in the right mid-clavicular line,

5cm above the umbilical line and two additional 5 mm ports were inserted, one in the left anterior-axillary line and the other one in the left mid-clavicular line. The exploration of the abdominal cavity revealed no enlarged lymph node or other abnormalities. After entering the bursa omentalis by dividing the gastrocolic and hepatogastric ligament, the smooth surfaced subserous 2cm gastric tumor was identified on the posterior wall of the antrum and the larger 5cm tumor was palpated into the gastric wall (Figure 2a). The stomach was divided proximally 3cm above the tumor using two 60mm and a 45mm gold Echelon stapler (Ethicon®) (Figure 2b & 2c). The staple line was reinforced with a hand-sewn intracorporeal running suture (Figure 2d). The duodenum was mobilized by an extensive Kocher maneuvre. The specimen and the gastric stump were extracted through a 10cm right subcostal minilaparotomy, sealed by a wound protector. The duodenum was transected 2cm distal to the pylorus and an extracorporeal hand-sewn gastroduodenal Bilroth I type anastomosis was performed using inverted Lambert sutures in one layer.

Results

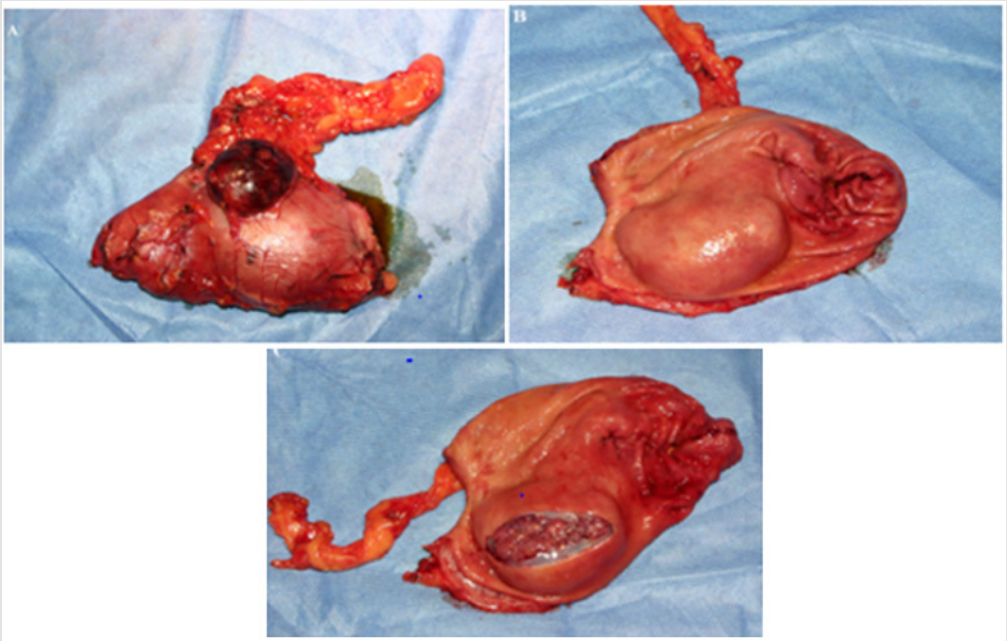

Figure 3: Surgical specimen containing the subserosal (A) and submucosal tumors (B, C).

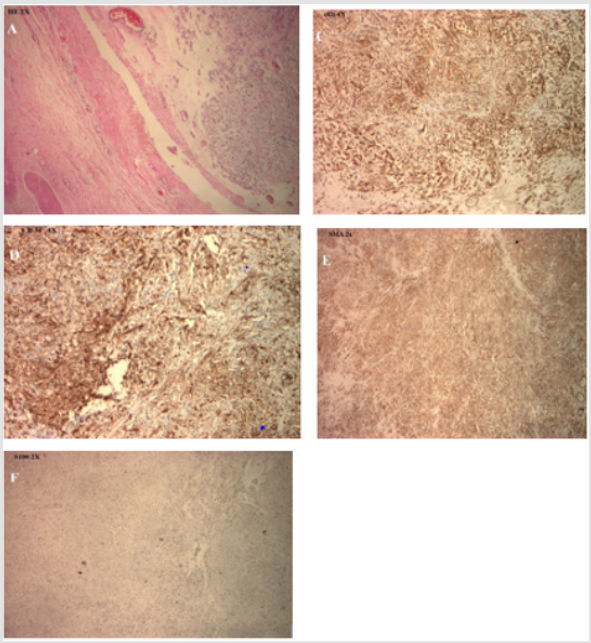

Figure 4: Histopathologic features of the tumors with hematoxylin and eosin (A, B) showing mixed epithelioid and spindled cytology in the mucosa and submucosa with a "plexiform" pattern. Immunohistochemical expression of cKIT (C), CD 34 (D), SMA (E) and S100 (F).

The postoperative course was uneventful, and the patient was discharged on the 5th postoperative day. The final pathological report revealed two nodular tumors of 5/3.5/2.3cm and 3/2/1cm respectively, the larger one in the sub-mucosal layer and the second one developed mostly into the subserous layer (Figure 3). Microscopically, these tumors were composed of spindled and epithelioid cells with multinodular architecture (Figure 4a & 4b). Less than 5 cellular mitoses per 50 High-Power Fields (HPF) were seen. Immunohistochemical examination showed intensive positive staining for the c-kit, CD34 and Smooth Muscle Actin (SMA) while S-100 protein was negative (Figure 4c & 4f). Two lymph nodes with histiocytosis were found attached to the specimen. The clinical, histological and immunohistochemical features were suggestive for a pediatric-type gastrointestinal tumor G1, pT2N0. The proximal and distal resection margins were 4cm, respectively 3cm and were free of tumor. This particular histological type of the resected tumor carries a high risk of lymph node metastases of up to 30-50% of cases. The decision of the multidisciplinary tumor board was to re-operate the patient with the aim to sample the loco-regional lymph-nodes for accurate staging. This operation was performed through an open approach by enlarging the right subcostal mini-laparotomy used during the previous laparoscopic-assisted operation.

Lymphadenectomy consisted more of a sampling of lymph nodes instead of a proper extensive dissection of the vessels feeding the gastric and duodenal stumps, since the intention was to preserve the previously constructed gastroduodenal anastomosis. Therefore, lymph nodes along the lesser curvature (station 3a), left gastric artery (station 7), common hepatic artery (station 8p), left side of hepatic pedicle (station 12a), celiac trunk (station 9) and proximal splenic artery (station 11p) were removed but with care to maintain the vascularization of the gastric stump. Lymph nodes stations 3b, 4d, 5 and 6 were already included in the specimen at the time of the first operation. The outcome after the second operation was uneventful and the patient was discharged on the 5th postoperative day. The final pathological report revealed 10 lymph nodes with histiocytosis and no metastases. The tumor board decided to add 24 months of adjuvant therapy with imatinib. At 41 months follow-up the patient is disease-free, without evidence of recurrence or any additional tumors that are reported to be associated with pediatric-like GISTs such as paraganglioma, or pulmonary chondroma.

Discussion

Laparoscopic wedge resection represents the standard of surgical treatment for gastric GISTs located in the fundus and on the greater curvature of the stomach, which can rather easily be removed laparoscopically with the help of endoscopic staplers. Due to the mesenchymal origin of these tumors and the reported low rate of lymph-node metastases associated with standard GISTs, in these patients a formal lymphadenectomy is not required.

Pathogenesis of Ped-GISTs

The Pediatric-Type Gastrointestinal Stromal Tumor (ped-GIST) is a different type of GIST defined as stromal tumor that express the protein "KIT" on surface but does not have mutations in the KIT or PDGFR genes (termed KIT/PDGFR wild-type GIST) as regular GISTs do [1]. This form of GIST was initially considered to be characteristic to children but in the last two decades it was increasingly reported in adult patients as well and therefore the name has been changed from "pediatric GIST" to "pediatric-like GIST" [2-4]. Roughly 15% of all pediatric-like GISTs are now being reported in adult patients and occur typically in the gastric antrum of women younger than 40 years, usually as multifocal tumors with a multinodular growth pattern, epithelioid morphology and lymphovascular invasion [4-6]. Clinical manifestations are gastrointestinal bleeding with symptoms of anemia, melena or hematemesis, epigastric complaints or symptoms related to systemic metastasis [6].

Unlike mutant GIST, wild-type pediatric-type GISTs are characterized by strong predilection for lymphovascular invasion, lymph node metastases being present in as much as 30-50% of cases, and a high rate of recurrence despite an apparently complete surgical resection [5-8]. They have a slow progression, an indolent clinical course and are associated with long survival even in patients with metastatic disease. Survival up to 25 years after diagnosis of liver metastases has been reported [5-10]. The natural history of ped-GISTs is very unpredictable and the GIST's conventional risk stratification system based by tumor size and mitotic index is not applicable to these tumors [3]. Th oncogenic pathogenesis of pediatric-like GISTs is still investigational. A potential mechanism highlighted by several molecular studies is related to the loss of function of succinate Dehydrogenase complex (SDH) by germline or somatic mutations of SDH subunits [6,9,10]. The SDH complex is a tetrameric enzyme complex composed of 4 subunits (SDHA, SDHB, SDHC and SDHD) involved in the Krebs cycle and mitochondrial oxidative phosphorylation which is responsible for controlling the metabolism and oxygen levels in the cells [11]. Some authors consider that the tumor`s slow progression could be related to the metabolic deficit provided by the SDH inactivity [5]. Ped-GISTs can occur sporadically or as part of several genetic syndromes: Carney triad, Carney–Stratakis syndrome and neurofibromatosis type 1. The Carney-Stratakis Syndrome (CSS) is a rare hereditary syndrome produced by autosomal dominant germline inactivating mutations of SDHB, SDHC or SDHD subunits which cause development of ped-GIST and paragangliomas [4,6,12].

The Carney Triad (CT) includes the combination of ped-GIST, paragangliomas and pulmonary chondroma to which other tumors may be added such as esophageal leiomyoma, adrenal cortical adenoma or renal tumors [6,12]. Patients with von-Rechlinghausen neurofibromatosis can also develop ped-GISTs but these tumors are SDHB positive, occur more often in the small intestine, are less

invasive than SDH deficient ped-GIST and show different hystologic features [6]. Patients with diagnosed ped-GIST may develop paragangliomas within a span of 25 years or more as part of CT or CSS syndromes [6]. Therefore, it is recommended that all SDH-deficient KIT/PDGFRA ped-GISTs be genetically tested for SDH-inactivating mutations and strictly monitored over time for development of paragangliomas or pulmonary chondroma [6,10]. Apart from the mechanisms described above, epigenetic modifications have been also reported as other possible mechanism involved in development of ped-GIST when no inactivating-SDH mutations had been found [6]. Furthermore, other several mutations have been described in ped-GISTs whose pathogenic significance is still uncertain: the BRAF exon 15 V600E substitution and over-expression of insulin-like growth factor 1 receptor [6,9].

The Current Clinical Practice

The diagnosis of SDH-deficient GIST is established by negative staining of the SDH subunit on Immunohistochemistry (IHC) but this analysis is not widely performed. In the clinical practice, suggestive for ped-GISTs is the presence of multifocal antral gastric stromal tumors with several histologic characteristics: epithelial hypercellularity with plexiform growth pattern in the muscularis propria, over-expression of CD117, positivity of CD34, DOG1 and SMA and negativity of S-100 [4,10]. In our case IHC for SDH subunit could not be performed and the diagnose of pediatric-type GIST was based on clinical and histological features. The optimal therapeutic management of the ped-GIST is not yet standardized. Data available in the literature is based mainly on case reports and retrospective small cohort studies which focus mostly on the molecular and clinical features. Therefore, the level of evidence is low while a consensus regarding the optimal therapeutic management of ped-GISTs is not available. Clinical practice guidelines published by the National Comprehensive Cancer Network [13] and the European Society of Medical Oncology [14] acknowledge the higher risk of SDH deficient GISTs for systemic and lymph-nodes metastases and recommend resection of enlarged lymph node but there is no recommendation regarding the extent of surgical margins, need and type of adjuvant therapy or the optimal follow-up protocol. Although it is widely accepted that surgery is the first-line treatment and complete surgical resection with negative microscopic margins should be performed for localized ped-GIST, there is no agreement about the extent of resection or whether lymphadenectomy should be done routinely in localized ped-GISTs [5,14]. In the absence of specific guidelines, management of these patients vary widely from one institution to another.

Review of the Literature

The data present in the literature regarding the pediatric-type GISTs is scarce. Range et al. report on 16 adult patients diagnosed with gastric ped-GIST at a median age of 31.5 years [3]. The mean tumor size was 5.4cm (range 1.8 to 11cm). Nine of the 16 patients (56% of cases) had lymph nodes metastases and 3 patients (18.66%) had liver metastases. Seven patients with lymph nodes or liver metastases at primary resection were classified as either as low risk, very low risk and no risk for metastases, according to the Armed Forced Institute of Pathology risk stratification score. There is no information available about the type of surgical excision or presence and extent of lymphadenectomy. After a median follow-up of 5 years after surgical resection, 2 patients (12.5%) have developed local recurrence and 11 patients (68.75%) developed metastases in the liver (n=3), peritoneum (n=3) and lymph node (n=5). One patient died with liver and peritoneum metastases 63 months after surgery. Adjuvant therapy with imatinib was administered to 11 patients [3]. A retrospective study of 66 patients with ped-GISTs from different institutions of which 41 were adults and 25 children was published by Miettien et al. [10]. Tumor size ranged from 1.5cm to 12cm. At diagnosis one patient had synchronous liver and lymph node metastases, three patients had liver metastases and other 2 patients had peritoneal metastases. Regional lymphovascular invasion was reported in 17 of 31 cases (54.83%) but this histological feature or presence of lymph nodes metastases were not examined in all patients. There are no details about the surgical technique used. After a median follow-up of 14.7 years (range 1.8 to 44 years), 11 cases developed local recurrence or a second primary tumor, liver metastases occurred in 10 cases and peritoneal metastases in other 3 cases.

The longest interval from the first diagnosis to development of liver metastases was 42 years. Three patients have survived with liver metastases for 10 to 18 years and 3 other patients survived 10 to 17 years after diagnosis of peritoneal metastases. Seven patients died due to progression of the disease despite a low mitotic rate of less than 5/50 HPFs in two of them. In patients with local recurrence, salvage total or subtotal gastrectomy was performed. Four patients were treated with imatinib for 6 months to 7 years and one patient underwent excision of abdominal metastases subsequent to imatinib response [10]. In 2008 the National Institutes of Health Pediatrics established a Wild-type GIST Clinic and started an observational study which enrolled both children (patients younger than 19 years) diagnosed with GIST (n=36 patients) and adult patients diagnosed with ped-GISTs (n=40 patients) [8]. In 2016 they have released the results of a retrospective study conducted on 76 patients with ages ranging from 12 to 32 years who underwent surgery for ped-GIST in different surgical centers. Median tumor size was 7cm (range 4.7-9cm). At initial diagnosis 62% of patients had local disease, 12% had loco-regional (7 patients with lymph node metastases and 2 patients with T4 tumors invading the surrounding organs) and 26% had metastatic disease. R0 resection (microscopic negative resection margins) was achieved in 93% of cases with local disease, 78% of cases with locoregional disease and 47% of cases with metastatic disease, the rest being R1 or R2 resections. The type of surgical technique used was reported for 28 patients: 1 total gastrectomy, 4 subtotal gastrectomy, 7 distal gastrectomy and 16 wedge resections. Median follow-up was 4.1 years (range 1.5-8.2 years).

Tyrosine kinase inhibitor therapy was administered before surgery in 11% of cases and as adjuvant therapy in 78% of cases. The average Event-Free Survival (EFS) was 2.5 years after surgery. 71% of patients had either recurrence or progression of the disease, 41% of them after R0 resections. Mitotic rate and elevated recurrence risks score based on tumor size, mitotic size and presence of metastasis were significantly associated with recurrence or progression of the disease. No correlation was found between extent of resection (wedge vs. anatomic resection) and EFS. Reoperation was necessary in 47% of cases and it was significantly associated with decreased EFS. The authors concluded that disease recurrence is affected mostly by the mitotic rate and presence of metastatic disease. Although tumors tend to recur despite a R0 resection, surgery remain crucial for local control of the disease and wedge resection with negative gross margin remains the most appropriate option. In the settings of recurrent or metastatic disease, surgery was recommended only for palliation of symptoms such as bleeding, pain, obstruction or perforation.

Better insight concerning optimal therapeutic management of patients with ped-GISTs was highlighted by a review published in 2016 by a group of pediatric surgeons, recommendations available for children with ped-GIST being extrapolated to the adult population [1,7]. In patients with localized ped-GIST the surgical technique recommend includes complete resection of the primary tumor with 1cm macroscopic margin and validation of R0 resection by frozen section analysis of resection margins, complete peritoneal and retroperitoneal assessment with resection or sampling of suspected lesions, sampling of peritumoral draining lymph nodes and evaluation of liver both by palpation and intraoperative ultrasound [7].

Wedge resections are advised when possible. Extensive resections such as complete gastrectomy, subtotal gastrectomy or ″en-bloc″ resection are not recommended because "these are morbid operation that significantly impact one's quality of life and it is well known that even R0 or complete resection still have a high rate of recurrence" [7]. In case of positive resection margin on frozen section analysis, re-excised is recommended if it does not present a technical challenge or increase the morbidity significantly. Extensive lymphadenectomy such as that performed for gastric adenocarcinoma is not considered necessary but lymph node sampling of all draining basins of the tumor is recommended to determine the presence of occult disease, provided that it does not significantly increase the morbidity. Enlarged lymph nodes should definitely be resected [1,7]. The role of extensive surgery for metastatic, recurrent and progressive ped-GISTs is not clearly defined. These patients may live for years with metastases while estensive surgery with multivisceral resection does not prevent recurrence but decrease quality of life; therefore, it is recommended that surgery along with adjuvant therapy should be reserved for management of symptoms and maintenance of the quality of life. Adjuvant ablative techniques such as RFA or cryosurgery are mentioned as better alternatives in these situations [7].

The laparoscopic approach for surgical resection is the preferred option for localized ped-GISTs if complete macroscopic resection without rupture of the tumor, lymph node sampling and biopsy of suspected lesion can be accomplished [13]. It has been already demonstrated that in the hands of surgeons with appropriate experience in minimally-invasive surgery, laparoscopic GIST resection significantly reduces postoperative pain, shortens hospital stay and has best cosmetic outcomes without compromising oncologic safety [15]. Laparoscopic wedge resection is therefore the standard treatment for gastric GISTs <5cm. Gastric GISTs larger than 5cm or located in the antrum can also be resected by a laparoscopic-assisted approach, providing superior outcome comparing with open approach [15] if there is appropriate experience and the principles of resection are applied just as in open surgery [14]. In the clinical case presented above a wedge resection would have been inappropriate due to the location into the antrum and multicentricity of tumors. Therefore, an antrectomy was considered adequate and was performed using a minimally-invasive technique. Lymphadenectomy was not performed during the initial operation because the preoperative diagnosis revealed a common gastric GIST, no enlarged suspect lymph nodes were seen on CT scan or during the intraoperative abdominal assessment and the medical team was not aware of the pediatric wild-type GISTs and their propensity for lymph node metastases. The multicentricity of the tumor and its presence in a young female should have risen a question mark towards ped-GIST but these features remained unremarked preoperatively.

When the definitive pathological report was available, we became aware of the high rate of lymph node metastases and the unpredictable prognosis score based on mitotic rate and tumor size associated with these tumors. For this reason, the decision was to reoperate the patient to obtain a pathological evaluation of the loco-regional lymph-node status. The extent of lymphadenectomy was also outside the standards. The previously performed gastroduodenal anastomosis had to be preserved and therefore the blood supply to the smaller and greater curvatures of the stomach maintained. In this situation, most of the lymph nodes in stations 3, 4 along the branches of the left gastric and gastroepiploic vessels have been sampled with preservation of the vessels. A proper lymphadenectomy was performed in stations 7, 8 11p and 12a. This approach was in line with the present recommendations that lymph node sampling should not alter the prognosis of the patient or increase the risk of postoperative complications. All lymph nodes analyzed by the pathologist were free of tumor but, due to the histological prognostic factors, the tumor board decided to continue therapy for 2 years with Tyrosine Kinase Receptor Inhibitors (TKI). There is limited data regarding the role of TKI in ped-GIST patients and the lack of mutations in KIT or PDGFR genes actually decrease the efficacy of TKI treatment [16].

Imatinib has some activity in adults with SDHA deficient ped-GIST though it is substantially less than is seen in the most common forms of KIT and PDGFRA mutant GIST [17,18]. Sunitinib

and regorafenib has recently been reported to offer some clinical benefits to patients resistant to imatinib [18,19,20]. Molecular studies are still ongoing in an effort to develop effective novel treatment regimens. For localized disease with complete resection without tumor spillage most authors do not recommend adjuvant therapy. They consider that tyrosine kinase inhibitors should be reserved to patients that show disease progression and should not be routinely used after complete surgery [7,8]. However, the experience is limited given the low number of cases reported worldwide and the unpredictable and variables natural history of ped-GISTs and therefore, due to the recognized invasiveness of the disease, some physicians administer adjuvant imatinib even in primary completely resected GIST. A predictive risk score could be useful for identifying those patients with higher risk for recurrence who should benefit from adjuvant therapy and a strict postoperative surveillance.

Conclusion

Pediatric-like GIST is a rare group of diseases still under investigation, different from the ordinary mutant GISTs in molecular, histologic and clinical behavior, with an unpredictable indolent progression. It should be suspicioned when gastric multifocal mesenchymal tumors are diagnosed in a young female. Surgery is the first-line treatment in patients with localized disease and should include at least loco-regional lymph node sampling for accurate staging and guidance of adjuvant therapy. The laparoscopic approach is a feasible and safe alternative to open surgery for treatment of GISTs located in the antrum. Lifelong follow-up is necessary given the unpredictable and indolent development of local and systemic metastases and the possible association with other tumors such as paraganglioma or pulmonary chondroma. The main effort of research in this area should be directed toward the collection of a large series of KIT/PDGFRA SDH-negative GIST cases worldwide to better characterize their natural history and determine the best clinical practice in these rare tumors.

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