c-KIT positive malignant gastrointestinal stromal tumor in a male child: A rare case

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, representing 1–3% of gastrointestinal malignancies. The majority of GISTs present at age 50–70 years. Pediatric GISTs are considered to be biologically distinct from adult GISTs. The incidence of malignant GISTs is less in children than in adults. Significant clinical and genetic differences are also noted between the two. A pediatric case typically affects females; is multifocal; is sited more commonly in the stomach and follows an indolent course. Histologically, epithelioid morphology is common and genetically most tumors lack mutations in the KIT or PDGFRA genes. We report a 12 year old male child presenting with a highly vascular stomach GIST for whom we did a pylorus-preserving wide local excision. On histopathology it was a malignant variety of GIST of epithelioid type; positive for c-KIT & CD34. The boy is now on Imatinib Mesylate chemotherapy and is asymptomatic.

1. Case report

A 12-year old boy presented to us with complaints of dull-aching continuous epigastric pain, nausea and generalized weakness for six months. He had significant weight loss (4 kg in one month) and also had a single episode of melena 3 months before. He had significant pallor and a soft abdomen with no palpable lump. Per rectal examination was normal. Ultrasound of the abdomen showed a 6 cm × 6.5 cm heterogenous mass in the lesser sac continuous with the stomach but free from surrounding structures. Contrast enhanced computerized tomography (CECT) showed extensive breakdown within the mass which was continuous with stomach but free from surrounding structures, without lymphadenopathy or liver metastases (Fig. 1). An ultrasound guided biopsy showed only fibrocollagenous tissue with inflammatory cells. Blood transfusion was given to correct anemia and the child was explored through a vertical midline incision. We found a large 8 × 8 cm vascular and friable mass arising from the lesser curvature of the stomach with well defined margins. As the mass was very vascular and friable, and USG guided biopsy was inconclusive for malignancy, only an incisional biopsy was taken. Histopathology showed epithelioid cells highly suggestive of GIST with rare

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possibility of epithelioid hemangioendothelioma. The child was re-explored after 8 days, once the definitive diagnosis of GIST was made, and wedge resection of the tumor was done along the lesser curvature with 2 cm normal margin, saving the pylorus (Figs. 2–4).

Postoperative course was uneventful. Final histopathology report of the mass proved it to be GIST of high malignant potential. On immunohistochemistry, the tumor was positive for CD34 & c-KIT but negative for DOG-1, EMA and CK. He was started on Imatinib Mesylate chemotherapy (200 mg twice daily) and is continuing the same without any side effects. Follow up after 1.5 year shows no evidence of recurrence on computed tomography scan (Fig. 5) (not mandatory). Child is growing well, has continued his education.

2. Discussion

GISTs are rare tumors arising from interstitial cells of Cajal, which are normally part of the autonomic nervous system of the intestine. They serve a pacemaker function in controlling motility. The diagnosis of GISTs might have often been missed in the past. A more stringent definition of the disease and the introduction of a specific molecular targeted therapy drew attention to it and its differential diagnosis. Thus, the annual incidence which earlier was thought to be 0.5/100,000, is now almost 1.5/100,000 new cases per year [4]. These tumors were initially thought to belong to the smooth muscle cell family [5]. Later on, cases with nerve sheath differentiation were described (gastrointestinal autonomic nerve tumors, or GANT, now considered a variant of GISTs), along with cases lacking characteristics of either [6,7]. A relationship to the interstitial cells of Cajal has now been established on the basis of some common phenotypical features of GISTs [4]. The differential diagnosis is conventional leiomyosarcomas; however both have different natural history and drug sensitivity [8,9]. Physiologically, the system of interstitial cells of Cajal is involved in the control of gut motility. In fact, interstitial cells of Cajal are known as the gastrointestinal pacemaker cells, hence the alternative term GIPACT (gastrointestinal pacemaker cell tumors) has been proposed for GISTs.

There are important differences between pediatric GISTs and adult GISTs (Table 1). Pediatric GISTs can be further divided into subgroups. The most familiar and commonest type is simply called “Pediatric GISTs.” It most commonly affects girls aged 6–18 years and almost always starts in the stomach. However, it can occur after the age of 18 years [10–12]. The second well-known type of GISTs in children is called “Carney’s Triad” named after Dr. J. Aidan Carney who first described it in 1977. Patients with Carney’s triad must

Table 1

<table>
<thead>
<tr>
<th>Adults</th>
<th>Pediatrics</th>
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<tbody>
<tr>
<td>Males &gt; female</td>
<td>Females &gt; males</td>
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<tr>
<td>Can start anywhere in the GI tract</td>
<td>Usually starts in the stomach</td>
</tr>
<tr>
<td>Starts at a single tumor site</td>
<td>May present with multiple stomach tumors (“multifocal” or “multinodular”)</td>
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<tr>
<td>Rarely metastasizes to the lymph nodes</td>
<td>Lymph node metastases are more common</td>
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<tr>
<td>Faster growing</td>
<td>Slower growing</td>
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<tr>
<td>Tumor cells usually have a spindle shape</td>
<td>Tumor cells usually have an epitheloid shape</td>
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<tr>
<td>Has a high response rate to the current first-line drug treatment, Imatinib</td>
<td>Has an undefined; but generally lower response rate to Imatinib</td>
</tr>
<tr>
<td>Mesylate</td>
<td>Mesylate</td>
</tr>
<tr>
<td>Typically has mutations in either KIT or PDGFRA genes</td>
<td>Typically does not have KIT or PDGFRA mutations</td>
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Fig. 1. Picture of preoperative computerized tomography scan.

Fig. 2. Intraoperative picture with tumor.

Fig. 3. Intraoperative picture post excision of tumor.
follow-up of these patients in the pre-Imatinib era showed a prolonged survival with slow growth and tumor progression even in the absence of targeted kinase inhibition. These findings suggest distinct tumor biology of GISTs affecting children, with possibly alternative molecular mechanisms and signaling pathways downstream of the KIT receptor.

The clinical findings vary depending on the location and size of the tumor at presentation. If the tumor is small, it may be only an incidental finding during radiological imaging or surgery for some other cause, whereas a large exophytic lesion may present as an abdominal mass due to its large size. Lesions in the stomach, small bowel, or colon may present with gastrointestinal bleed in the form of hematemesis, melena, or occult blood in stools; alternatively, there may be abdominal pain, nausea, and vomiting. An esophageal GIST most commonly presents with dysphagia [15].

As is evident from the case being reported, a pediatric gastric GIST can pose a diagnostic dilemma even after an USG guided biopsy and should be considered a differential diagnosis in lesser sac tumors despite atypical presentation and in cases of inconclusive biopsies.

GISTs can occur anywhere along the GI tract, but most often are found in the stomach or small intestine. The American Joint Committee on Cancer (AJCC) Staging Manual lists the distributions in this order: stomach (60%), small intestine (30%), rectum (3%), colon (1–2%), esophagus (<1%), omentum/mesentery (rare) [16]. A single case has been reported of GISTs occurring in appendix [17].

Because most of these tumors in pediatric as well as adult patients are submucosal in location, they usually attain a large size without causing bowel obstruction by the time of diagnosis [18]. Many of these tumors have an exophytic component as they arise from the muscularis propria (Marla et al. [19]). Lee et al. [20,21] found GIST to be well-defined tumors with homogenous enhancement, while Levy et al. found large heterogeneously enhancing masses due to areas of necrosis or cystic degeneration. They described ulceration as a common feature of GISTs.

Metastases from GISTs in pediatric as well as adult patients commonly occur to the liver and peritoneal cavity and occasionally soft tissues, lungs, and pleura. Marla et al. also found that tumors that enhanced homogeneously (nine out of 53 cases in their series) showed no metastases when they were followed for a mean period of 2.6 years as compared with those that enhanced heterogeneously. According to Nilsson et al. [22], at least 50% of these tumors have metastasis at presentation.

Surgery is the definitive therapy for patients with GISTs. Radical and complete surgical extirpation offers the only chance for cure. For localized primary GISTs, surgical resection is the mainstay of therapy with the 5-year survival rate after complete resection averaging approximately 50–65%. Surgery is also indicated in symptomatic patients with locally advanced or metastatic disease. Debulting large lesions is helpful when adjuvant therapy with Imatinib Mesylate is contemplated.

Preoperative Imatinib should be considered if surgical morbidity would be improved by cytopreducing the size of the tumor.

Postoperative Imatinib has been shown to increase recurrence-free survival after complete resection of localized GISTs. In 2012, Joensuu et al. showed that 36 months of Imatinib improved recurrence free survival and overall survival of GISTs patients with a high risk of GIST recurrence, compared with 12 months of adjuvant Imatinib.

The optimal follow-up schedules are not known. High-risk patients undergo a routine follow-up with CT scan or MRI every 3–6 months for 3 years during adjuvant therapy (with tighter clinical follow-up due to the need to manage the side effects of adjuvant therapy), unless contraindicated, then on cessation of adjuvant therapy every 3 months for 2 years, then every 6 months until 5

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**Fig. 4.** Picture of specimen.

**Fig. 5.** Picture of computerized tomography scan at 1 year follow up.
years from stopping adjuvant therapy and annually for an additional 5 years. For low-risk tumors, the usefulness of a routine follow-up is not known; if selected, this is carried out with a CT scan or MRI every 6–12 months for 5 years. Very low-risk GISTs probably do not deserve routine follow-up, although one must be aware that the risk is not nil. X-ray exposure is a factor to take into account, with abdominal MRI being an option as an alternative option to a CT scan [23].

Factors such as tumor size, mitotic rate, tumor location, kinase mutational status and occurrence of tumor rupture have been proposed as predictors of outcome. Adjuvant Imatinib is proposed as an option for those patients with a substantial risk of relapse. Unresectable metastatic or recurrent GISTs can be treated with Imatinib, with a remarkable response rate (50–70%) and prolonged survival (median progression-free survival: 18–20 months; median overall survival: 51–57 months). Sunitinib is licensed as a second-line therapy following progression on Imatinib. Other promising systemic therapies include Regorafenib and agents targeting the PI3K/mTOR pathway [24].

3. Conclusion

Gastrointestinal stromal tumors are very rare in pediatric age group more so in males, when they are usually c-KIT negative and have doubtful response to Imatinib. However as is evident in the indexed case, boys may be c-KIT positive and have a better prognosis and good response to Imatinib.

References