Surgical management of a giant metastatic Gastrointestinal Stromal Tumor without neoadjuvant therapy with TKI: Case Report

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Abstract

Introduction: Gastrointestinal Stromal Tumors (GISTs) are the most frequent tumors of mesenchymal origin and can be found throughout the alimentary truck, from the lower oesophagus to the anus but most commonly are located in the stomach (60%), followed by the jejunum and ileum (30%), duodenum (5%), and colorectum (<5%) [1]. These tumors are presented equally in both genders, and the peak age of onset is the 5th and 6th decade of life although they can also occur in any age group [2]. The incidence of GISTs in Greek population is estimated in 140 new cases each year, with mean age of appearance in the 6th decade of life and a somewhat male predominance (male: female 1.4:1) [3].

Introduction

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract. GISTs may vary in size and occur throughout the GI tract, from the lower oesophagus to the anus but most commonly are located in the stomach (60%), followed by the jejunum and ileum (30%), duodenum (5%), and colorectum (<5%) [1]. These tumors are presented equally in both genders, and the peak age of onset is the 5th and 6th decade of life although they can also occur in any age group [2]. The incidence of GISTs in Greek population is estimated in 140 new cases each year, with mean age of appearance in the 6th decade of life and a somewhat male predominance (male: female 1.4:1) [3].

Usually, they are asymptomatic and the diagnosis is often incidental, either during endoscopy for other diseases such as gastrooesophageal reflux and peptic ulcer disease or on computed tomography imaging, performed for the investigation of other conditions. Clinical manifestations are non specific and include early satiety, anorexia, nausea and vomiting, depending on the location. Seldom, acute gastrointestinal obstruction or bleeding may be the first symptom [4]. The most frequent site of metastasis is the liver, were liver related symptoms might be present. Giant GISTs (>15cm) are relatively rare and the differential diagnosis, especially in tumors extending extramurally, is often difficult. GIST presenting as a palpable mass is considered rather rare, according to Patil et al, and only 25 such cases have been reported since 2001, whereas 21 of them received surgical resection as primary therapy [5].

Herein, we present the case of a giant GIST originating from stomach, extending extramurally and adhering to surrounding organs, and we discuss the challenging initial diagnosis and current treatment options.

Case report

A 67 year old male patient was referred to our clinic with a palpable mass extending from the epigastrium to the left iliac fossa. He complained of early satiety, anorexia, nausea, fatigue and great weight loss, persisted for the past six months.
The patient had a free medical history and his laboratory examination had no pathological significant findings, except of a minor decrease of hematocrit (37.1%). A contrast enhanced Computed Tomography (CT) was performed and revealed a large mass extending from the left hepatic lobe and stomach to the left iliac fossa, as well as two hypodense lesions in the right hepatic lobe (fig. 1, 2, 3). Gastroscopy didn’t reveal any lesions intraluminarly. The mass seemed to significantly compress the stomach extramurally, reducing its volume. Magnetic Resonance Imaging (MRI) confirmed the findings of the CT but could not clarify the origin of the tumor (fig. 4, 5).

Figures 1,2,3. A contrast enhanced Computed Tomography (CT) revealed a large mass extending from the left hepatic lobe and stomach to the left iliac fossa as well as two hypodense lesions in the right hepatic lobe.

Figures 4, 5. Magnetic Resonance Imaging (MRI) confirmed the findings of the CT.

Sarcoma was the initial diagnosis suspected. A computed tomography guided biopsy was performed and pathology examination revealed a GIST. Neoadjuvant treatment with Tyrosine Kinase Inhibitor (TKI) was proposed due to enormous size of the tumor in combination with the two liver metastasis.

The patient refused conservative medical treatment and laparotomy was performed, considering the persisted tumor clinical manifestation and patient’s strong will. Laparotomy revealed a large mass which was seemed to originate from the lesser gastric curvature adhering to left hepatic lobe (fig. 6, 7). The tumor was resected en block with the left segments of the liver (segments II and III) and the distal stomach (fig. 8, 9) while a gastroenterostomy was performed for GI continuity. Postoperative period was uneventful and our patient was discharged on the 10th postoperative day. Pathology results described a 28 x 21 x 15 cm tumor, strong adhering to the hepatic specimen and originate from the lesser gastric curvature. Neoplastic cells were spindle shaped, positive to vimentin, CD34, antigen CD117/C-kit and S-100 protein, which confirmed the diagnosis of a high risk Gastrointestinal Stromal Tumor. Adjuvant therapy with imatinib (400 mg x 1) was administered. Six months postoperatively, patient is still under imatinib, with a stable liver disease.

Figure 6. Preoperative picture demonstrating the marked abdominal distention caused by the tumor.

Figure 7. Laparotomy revealed a large mass which seemed to originate from the lesser gastric curvature adhering to left hepatic lobe.
Discussion

Gastrointestinal Stromal Tumors are the most common mesenchymal tumors of the gastrointestinal tract and have characteristic histologic features with either spindle cell, epithelioid, or occasionally pleomorphic mesenchymal morphology. GISTs also share phenotypic characteristics with the intestinal pacemaker cells, known as interstitial cells of Cajal and are thought to arise from a common cell precursor. Immunohistochemical analysis has demonstrated that nearly all GISTs (95%) express c-kit protooncogen CD117, a transmembrane tyrosine kinase receptor for stem cell factor. Other markers, identified on immunohistochemistry, include protein kinase C theta (80%), CD34 (60%-70%), and smooth muscle actin (30%-40%). Some GISTs, although a far lower proportion, also demonstrate immunopositivity for S-100 protein (5%), desmin (1%-2%), and keratin (1%-2%). This characteristic immunohistochemical profile of GISTs differentiated them from smooth muscle tumors (ie, true leiomyomas, myoblastomas and leiomyosarcomas) and schwannomas [6, 7].

According to the 2002 U.S. National Institutes of Health (NIH) consensus criteria, the most relevant factors for risk stratification, after resection of localized GISTs, are tumor size and mitotic index. Recently, tumor size has been proposed as an independent prognostic factor, given the fact that gastric GISTs are less aggressive than intestinal GISTs of the same size. Tumor rupture is considered as an independent risk factor, as well. According to the above mentioned criteria, GISTs are categorized as very low risk, low risk, intermediate risk and high risk [1] [table 1]. Thus, surgery remains the first line treatment for localized resectable primary disease and is also considered curative in cases of very low and low risk GISTs. Laparoscopic approach may be considered in surgical management of these tumors, provided that oncologic principles of surgery are followed, that is complete R0 excision, avoidance of tumor rupture and use of a retrieval bag to avoid spillage of tumor cells in the abdominal cavity. Therefore, a laparoscopic approach is discouraged for tumors larger than 5 cm and is generally supported for wedge excision of small gastric tumors [8].

The advent of current treatment options changed the natural history of GISTs. Dramatic improvement in GIST management occurred with the recognition of mutational activation of KIT or PDGFRA stimulated growth of these cancer cells. This led to effective systemic therapies in the form of small molecule Tyrosine Kinase Inhibitors (TKI), such as imatinib mesylate (Gleevec; Novartis Pharma, Basel, Switzerland) or sunitinib malate (SU11248; Sutent, Pfizer Inc, New York, NY) [9, 10]. Adjuvant therapy with TKI improved the outcome of surgical resection, in patients with localized disease. Although the optimal duration of therapy has not yet been established, a one year therapy is recommended for intermediate and high risk GISTs, while no treatment is recommended for very low and low risk GISTs [9].

Table 1. Proposed modification of consensus classification for selecting patients with GIST for adjuvant therapy [1].

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Tumor size (cm)</th>
<th>Mitotic index (per 50 HPF)</th>
<th>Primary tumor site</th>
</tr>
</thead>
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<tr>
<td>Very low risk</td>
<td>&lt;2.0</td>
<td>75</td>
<td>Any</td>
</tr>
<tr>
<td>Low risk</td>
<td>2.1-5.0</td>
<td>75</td>
<td>Any</td>
</tr>
<tr>
<td>Intermediate</td>
<td>5.1-10.0</td>
<td>&gt;5</td>
<td>Gastric</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;10 cm</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>&gt;10</td>
<td>Any</td>
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<td>5.1-10.0</td>
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<td>Nongastric</td>
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</table>

* Adjuvant imatinib therapy, (TKI)*

On the other hand, since complete resection of advanced GIST is not always achievable, the median survival varies in range [11]. These unresectable locally advanced tumors, either recurrent or metastatic, had showed a longer progression-free survival after therapy with imatinib [12], with at least a partial tumor response to reach up to 80-90% of the cases [13]. In such cases, of locally advanced tumors where complete excision might not be feasible or in large tumors where intraoperative bleeding or tumor rupture is a perceivable risk, neoadjuvant therapy with TKI should be considered for 6 to 12 months preoperatively to reach tumor-downsizing and thus increased rates of complete tumor resection [14]. Moreover, when clones of disease that have acquired drug resistance are resected, surgical debulking may prolong survival in patients with metastatic disease, as long as the remaining disease remains drug responsive [10]. Thus, the role of surgery is now reassessed in the treatment of advanced GISTs and surgical resection following imatinib or sunitinib therapy might be helpful in some patients with advanced disease.

Although neo-adjuvant therapy with TKI is proposed for advanced and metastatic GISTs, this strategy is not a panacea. There have been reports of large tumor necrosis and rupture up to 3% under imatinib therapy [15] and according to others
it is established an increased risk of tumor bleeding as a result of neoadjuvant therapy [16,17]. These adverse effects, although rare, raise thought over, whether TKI therapy on giant tumors should be performed during hospitalization, or in cases of duodenal GISTs where chances of bleeding are greater, and it is proposed that surgery should be considered as first line treatment [16].

In addition, despite the benefits of neoadjuvant therapy there is a portion of patients that cannot stand the psychological burden of a neoplasm being left inside them. These patients do not conform to the conservative medical treatment and demand earlier surgical intervention, especially in cases of aggravated clinical manifestations. However, since such operations are demanding, trying to achieve organ or function sparing intent, and in most of the cases are carrying extremely risk, they should be tried in well selected cases. Thus, surgery in advanced GISTs without neoadjuvant TKI therapy could be justified in cases where tumor size or tumor location cause persisted symptoms, jeopardizing the patient’s well-being, depriving the luxury of a six month waiting period under TKI.

Conclusion
In localized resectable GISTs, surgery is still the primary treatment option although high and intermediate risk patients exhibit high recurrence rates and needs adjuvant therapy with TKI which increases overall and recurrence free survival rate. In patients with advanced or metastatic disease, TKI administration, as neoadjuvant therapy, is a well established management and contributes to improved outcomes, either inducing tumor shrinkage prior to surgery or prolonging survival rates. However, early surgical intervention in advanced GISTs, without neoadjuvant TKI therapy, is challenging and may be used, in well selected cases, as an alternative method when clinical manifestations force to it, or there is increased risk of tumor complications.

References
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