Gastrointestinal stromal tumor surgery in pediatrics

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ABSTRACT

Introduction. Gastrointestinal stromal tumors (GIST) are infrequent in pediatric patients. The management of metastatic and irresectable tumors is usually non-surgical, with tyrosine-kinase inhibitors being the treatment of choice.

Clinical case. We present the case of a 14-year-old female patient with a metastatic and irresectable GIST treated with sunitinib that required surgery as a result of severe hemoperitoneum episodes with anemia and hemodynamic instability. A cytoreductive surgery with R2 resection margins was carried out. After a 10-year follow-up period, the patient remains under oncological treatment.

Discussion. The treatment of metastatic and irresectable GIST consists of tyrosine-kinase inhibitors. Evidence regarding the role of surgery remains limited, which means extreme caution should be exerted when indicating surgical treatment. However, surgery is still a useful tool within the array of therapeutic options.

KEY WORDS: Gastrointestinal stromal tumors; Pediatrics; Surgical oncology.

CIRUGÍA DE TUMORES GIST EN PEDIATRÍA

RESUMEN

Introducción. Los tumores del estroma gastrointestinal (GIST) son tumores infrecuentes en la edad pediátrica. El manejo de los tumores metastásicos e irresecables no suele ser quirúrgico, siendo de elección el uso de inhibidores de tirosin-kinasas.

Caso clínico. Se presenta el caso de una paciente de 14 años con un tumor GIST metastásico e irresecable en tratamiento con sunitinib que precisó una intervención quirúrgica por episodios de hemoperitoneo grave con anemización e inestabilidad hemodinámica. Se realizó una cirugía de citorreducción con márgenes de resección R2 previstos. Tras 10 años de seguimiento la paciente continúa en tratamiento oncológico.

Comentarios. El tratamiento de los tumores GIST metastásicos e inoperables lo constituyen el uso de inhibidores de tirosin-kinasa. El papel de la cirugía sigue siendo un área con evidencia limitada, por lo que esta debe indicarse con extrema precaución; sin embargo, esta sigue siendo una herramienta valiosa dentro del arsenal terapéutico.

PALABRAS CLAVE: Tumores del estroma gastrointestinal; Pediatría; Oncología quirúrgica.

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common type of gastrointestinal soft tissue sarcoma. It is primarily caused by activating mutations in KIT and PDGFRA genes, with a 90% mutation rate in adult patients[1]. In pediatric patients, less than 15% of GISTs have these mutations, which explains why it is known as Wild Type GIST (WT-GIST)[2].

Since this tumor is different from its equivalent in adults, management should also be considered separately. In fact, in children, despite multiple recurrences or lack of tyrosine-kinase inhibitor treatment response, survival is long. WT-GIST survival rates range from 74% to 88% in adults, whereas in children, mean survival could exceed 15 years[3]. Some authors even consider making the disease chronic as the main therapeutic goal[4].

The objective of this paper was to report our experience with a metastatic GIST, with special focus on the most relevant surgical aspects of the case, considering that surgery is usually not the treatment of choice.

CLINICAL CASE

We present the case of a 13-year-old female patient with a history of chronic abdominal pain associated with anxiety episodes since she started high-school. In 2016, the patient had an episode of syncope and was diagnosed with

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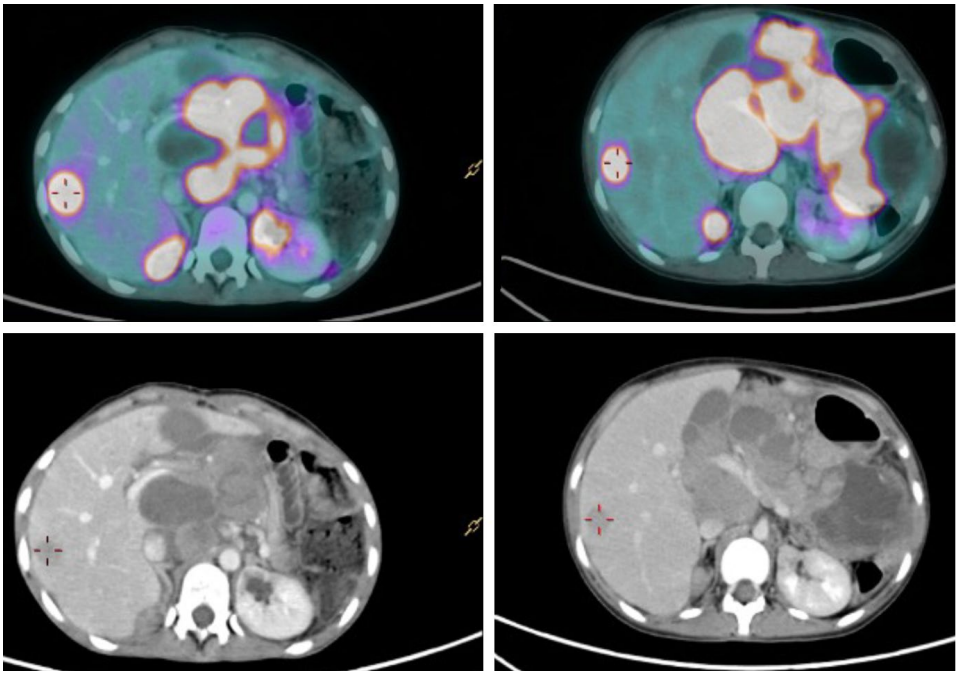

Figure 1. PET/CT-scan prior to surgery.

iron-deficiency anemia. Therefore, oral iron treatment was initiated, but hemoglobin levels did not return to normal.

In June 2017, she presented at the emergency department with an abdominal mass. Abdominal ultrasonography revealed the presence of multiple abdominal masses, without a clear organ dependency. Consequently, decision was made to perform a CT-scan and a nuclear MRI, which showed an extensive tumor with various intra-abdominal masses, the most important of which were a 13x8x12 cm conglomerate infiltrating the stomach and the first and second duodenal portion, a 6x5x6 cm conglomerate adjacent to the liver compressing the inferior vena cava, and a 6x4x5 cm pelvic mass. Various hepatic and perihepatic injuries suggestive of metastasis were also identified. PET-CT-scan confirmed the presence of neoplastic activity signs at the primary tumor located at the gastrosplenic ligament, as well as in multiple peritoneal implants and peritoneal, mesenteric, and hepatic masses (Fig. 1).

A thick needle biopsy was carried out. It was completed with a laparoscopic incisional biopsy as the initial sample was insufficient. The pathological study revealed the presence of an epithelioid, multinodular, wild-type (CKIT and PDGFRA negative) gastrointestinal stromal tumor (GIST). Succinate dehydrogenase (SDH) deficiency was also demonstrated.

Imatinib treatment was initiated in July 2017. After 5 months of treatment, and given the lack of response, the imatinib dose was increased. In February 2018, decision was made to switch to sunitinib treatment. In this period, the patient's condition had become severely worse, with three episodes of hemoperitoneum and significant anemia and hemodynamic instability. This led to Pediatric Intensive Care Unit (PICU) stays in March, April, and July 2018. Following these episodes, treatment was reconsidered, and surgery was decided upon.

In May, tumor debulking (cytoreduction) was carried out. Under general anesthesia, a supra- and infraumbilical mid laparotomy was carried out while identifying the masses previously revealed in the imaging tests. A great pelvic mass and peritoneal and abdominal wall implants were removed. Subtotal gastrectomy was conducted with removal of a transverse mesocolon implant closely related to the mesenteric vessels. Suprahepatic implants were also removed, and other implants in the gastrohepatic ligament were partially resected. As part of the scheduled resection with R2 margins, hepatic hilum, retrohepatic, and some smaller splenic hilum masses were not removed. Overall, resection covered 75% of the tumor, but this led to intense bleeding during surgery. Fibrinogen and thrombin matrixes were used for hemostatic control purposes. A Roux-en-Y gastrojejunal anastomosis was carried out, and drainages were placed in the tumor bed and the pelvis. Surgery was concluded by performing a layered closure of the abdominal wall.

In the immediate postoperative period, during PICU stay, the patient had a motor and sensory axonal neuropathy, which was assessed by the Neuropediatrics Department. It was diagnosed as a Guillain-Barré syndrome related to a Campylobacter diarrhea occurred some days before the surgical procedure.

No further episodes of anemia and bleeding were recorded following surgery. After a 10-year follow-up period, the patient remains under oncological treatment –fifth line with regorafenib after progression with pazopanib and renal failure with higher doses of regorafenib.

DISCUSSION

Complete surgical resection is the only healing treatment available. It is regarded as the primary treatment in the case of localized tumors. The management of pediatric GIST remains a clinical challenge, particularly in the presence of metastatic or recurrent disease. In most scenarios, these tumors are clinically insignificant and remain asymptomatic for decades, but approximately 45% can cause lymph node or metastatic invasion, which explains why monitoring based on imaging tests is also accepted in asymptomatic tumors[5]. However, in patients with a metastatic or irresectable disease, as it was the case here, the treatment of choice consists of tyrosine-kinase inhibitors, such as imatinib or sunitinib[5-7]. The most common approach is to avoid surgery, except in very specific cases. This is due to the fact pediatric GISTs are significantly prone to recurrence, even following complete resection[8]. According to Weldon et al.[9], these tumors have a recurrence rate of approximately 75% after surgery, and such recurrence is particularly associated with the presence of metastasis and a high mitotic index –not so much with other factors such as resection margins, age, sex, or tumor location and size. In addition, it is worth considering that the long-term sequelae of surgery in pediatric patients can impact quality of life for a longer time.

In spite of this, surgery could be indicated in certain scenarios, such as severe bleeding and intestinal perforation or obstruction[6,10]. Even though these indications typically involve urgent surgery, in our case, the surgical indication was determined by recurrent bleeding episodes. When surgery is considered in the presence of these tumors, many questions arise in significant aspects such as indication, technique, or resection prognosis, since there are no standardized guidelines for professionals[8]. Indeed, most of the evidence available is based on case reports and limited clinical series[6].

Regarding the surgical technique, Weldon et al. reported no significant differences between anatomical and atypical gastrectomy in terms of event-free survival ($p= 0.67$). However, repeated resection following baseline resection was significantly associated with a reduction in this parameter ($p< 0.01$)[9]. Similarly, as it has already been mentioned, recurrence is seemingly not related to negative resection margins, which means incomplete resection could be a good alternative in situations where morbidity-mortality and the risk of sequelae associated with surgery are considered excessive. On the other hand, WT-GIST is more prone to regional lymphatic infiltration (30%) than GIST in adults. Therefore, if complete resection is decided upon, lymph node biopsies are recommended, but standardized lymphadenectomies are not[11].

In conclusion, the treatment of metastatic and irresectable GIST consists of tyrosine-kinase inhibitors, also in children. Evidence regarding the role of surgery remains limited, which means extreme caution should be exerted when indicating surgical treatment. Due to factors such as the high recurrence rate, surgery is not the treatment of choice in most cases. However, in those situations where patients have severe complications in spite of medical treatment, surgery remains a useful tool within the array of therapeutic options. In these cases, it is particularly important to assess the risk-benefit ratio, not to rule out incomplete resection, consider lymph node biopsies, and avoid repeated resections.

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