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Case Report
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Metastatic Gastric GIST: How far Can We Go?

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Abstract

Gastrointestinal stromal tumors or GISTs have benefited from undeniable progress in both diagnosis and therapy.

Thanks to immunohistochemistry and molecular biology, these tumors are increasingly well characterized. And their histoprognostic profile is more accurately assessed.

Targeted therapy has changed the therapeutic approach and has allowed surgeons to be increasingly bold in the curative resection of locally advanced and metastatic forms.

The aim of this case report is to propose a multidisciplinary vision of the therapeutic management of GISTs, in the light of the experiences acquired within the multidisciplinary committees, and to push the limits of resections even in metastatic forms, which are the only guarantee of a better survival.

Keywords: GISTs; Diagnostic criteria; Targeted therapy; Multidisciplinary concertation meeting in oncology

Introduction

GISTs (Gastro Intestinal Stromal Tumor) are mesenchymal tumors that develop at the expense of the connective tissues of the wall of the organs of the Digestive Tract (DT). They are thought to originate from Cajal's cells or "pace maker cells", which form a network of spindle-shaped cells interposed between muscular fibers and nerve plexuses, activating peristalsis of the DT. They are often discovered by chance, but can lead to complications such as digestive hemorrhage. The presumptive endoscopic diagnosis is most often confirmed by the typical echo-endoscopic appearance. Diagnosis of certainty is based on anatomopathological examination (proliferation of spindle or epithelioid cells) and, above all, immunohistochemical examination with positivity for CD34 discovered in 1994 by Van de Rijn [1] and for the KIT or CD117 protein discovered in 1998 by Sarlomo-Rikala [2]. Targeted therapy has revolutionized the therapeutic approach and enabled surgeons to be increasingly daring in the curative resection of locally advanced and metastatic forms of the disease.

Case Presentation

Patient S.N. aged 53, blood group O+, WHO 1, obese (BMI 36) consulted for digestive hemorrhage (melena) associated with epigastralgia. On examination, there was intense mucocutaneous pallor with hemodynamic stability (blood pressure 10/07 cmHg; pulse 84/min). Abdominal palpation revealed a 10 cm deep epigastric mass extending into the right hypochondrium.

A blood count revealed severe anemia with a hemoglobin level of 06 g/dl, requiring the patient to be hospitalized and transfused with two iso-group iso-rhesus red blood cells.

An upper endoscopy revealed a mucous lake in the stomach containing digested blood. There was a voluminous submucosal mass with surface ulceration at the level of the lesser curvature, oblong in shape and apparently extending from the subcardial region to the antero-fundal region. The angulus was healthy, and the antrum was normokinetic and healthy. The pylorus was patent and centric. Multiple biopsies were taken.

Microscopic examination of the various fragments showed normal antral gastric mucosa

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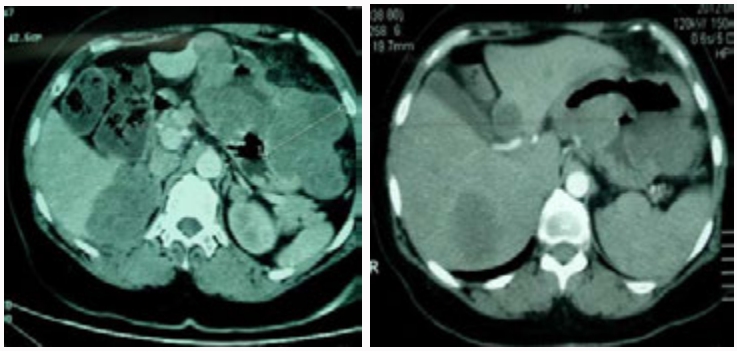

Figure 1: Gastric GIST metastatic to the liver.

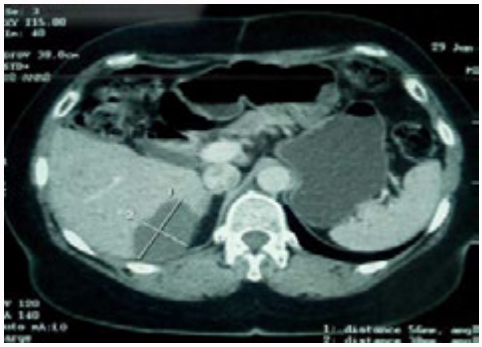

Figure 2: CT after R2 resection of gastric GIST and two years of Imatinib.

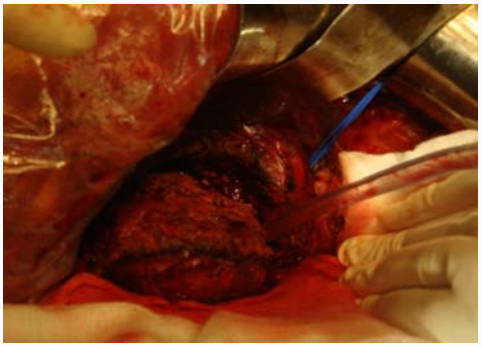

Figure 3: Intraoperative view of segment VI metastasectomy.

with chronic inflammatory changes. Overlying a mesenchymal neoplastic proliferation of spindle cells with elongated basophilic nuclei, immunostaining was positive for CD117 and negative for chromogranin. No genotypic studies were performed.

A thoracic-abdominal-pelvic CT revealed a significant tumor thickening of exoluminal and circumferential development of the gastric wall, exceeding 07 cm in places, which was moderately enhanced after injection of iodinated contrast, delimiting large areas of necrosis within it, with the following relationships:

- It infiltrates the 2nd and 3rd portions of the duodenum below;
- It comes into contact with the left hepatic tongue;
- It came into contact with the left colonic angle with disorganization of the fatty cleavage line.

There were several satellite adenopathy's. The liver was heterogeneous, with the presence of several metastatic nodules with similar radiological features, the largest of which was located in segment VI, measuring 80 mm × 67.4 mm (Figure 1).

The patient was 53 years of age and presented with metastatic gastric GIST (TNM Stage IV). She was started on Imatinib 400 mg/d on the advice of our digestive Multidisciplinary Oncologic Team (MOT).

A CT performed after one year of Imatinib treatment did not reveal any secondary locations in the thorax. In the abdominal region, there was still a gastric tumor mass measuring 74 mm × 58 mm that had developed at the edges of the small curvature, with heterogeneous enhancement (hypodense areas of necrosis), blurred boundaries and irregular contours, with clear densification of the perilesional fat and a lymph node of 08 mm near it. This mass invaded the left hepatic flap and came into contact with the pylorus, without duodenal involvement.

The liver was normal in size, with two hepatic nodules in segments IV and VI measuring 17 mm × 18 mm and 41 mm × 59 mm respectively.

The patient underwent an atypical gastrectomy at the level of the small gastric curvature extended to the left hepatic tongue, with Heineke-Mikulicz Pyloroplasty. The segment VI metastasis was not resected.

Histological study confirmed the stromal nature of the gastric tumor measuring 10 cm long, with a mitotic index estimated at less than 05 mitoses per 50 fields at high magnification (Grade 1), infiltrating the hepatic parenchyma and completely removed.

The patient continued treatment with Imatinib at a dose of 400 mg/d for two years, on the advice of the MOT, and was monitored regularly. A follow-up CT showed persistent segment VI liver metastasis measuring 49 mm long with a necrotic component of over 70%. The rest of the liver parenchyma was without abnormalities (Figure 2).

The patient underwent resection of the metastasis in segment VI with concomitant treatment with Imatinib (Figure 3). After 10 years of follow-up, since her first consultation, no local or general recurrence has been found.

Discussion

Fifteen to twenty percent of GIST liver metastases are synchronous and 20% to 25% are metachronous. They are often multiple (89%) and bilobar (74%). Their resectability rate is only 17% [3]. In 60% of cases, they are associated with peritoneal sarcomatosis or local

recurrence. Following diagnosis of a locally advanced and metastatic form of GIST, neoadjuvant therapy by Imatinib at a dose of 400 mg/d is given with a high level of evidence (Grade A), despite the genotype not being known. If a KIT or PDGFRA exon mutation is proven, the dose is increased to 800 mg/d. During treatment, compliance must be ensured, and side-effects (asthenia, oedema and digestive disorders), the risk of perforation, hemorrhage (02.7%) and above all tumor rupture must be monitored.

Early reassessment by CT is carried out between 04 and 08 weeks of treatment. If there are sonographic signs of a good response (a reduction of more than 10% in size and a decrease of more than 15% in density), treatment is continued for 06 to 12 months, followed by a late reassessment. PET-CT is very sensitive in the early detection of a response to imatinib treatment: A fall of more than 25% in metabolic activity or a reduction of more than 10% in tumor size, as well as a reduction of more than 15% in density (HU) at two months of treatment are considered criteria for a good response to targeted therapy [4]. However, an increase in parietal thickness or the appearance of nodules is indicators of resistance to Imatinib or targeted therapies [5]. Surgery in locally advanced and/or metastatic forms is scheduled when the response to Imatinib is maximal, after a minimum of 06 or 12 months of treatment [6]. The intraoperative discovery of limited metastatic disease during resection of the primary tumor poses a delicate problem. No benefit has been shown from initial tumor reduction of metastases (for fear of spreading the disease and ending up with sarcomatosis). In these cases, resection of the primary tumor alone if it is symptomatic (bleeding, compressive signs) as in your case, combined with treatment with Tyrosine Kinase inhibitors is more suitable.

After resection of a GIST metastasis, Joensuu recommends continuing Imatinib for at least 03 years instead of one. This is the only way to achieve 92% overall survival and 65.6% recurrence-free survival at 05 years [7]. Imatinib is stopped a few days before surgery and restarted as soon as possible.

The median survival after R0 resection of hepatic metastatic GIST is 39 months with a 05-year survival of 30%. Recently, Seesing et al. obtained a median survival of 90 months and a 05-year survival of 76% [8]. The overall survival of GISTs ranges from 13.6 years for primary GIST at diagnosis, to only 6.4 years for metastatic GIST. The occurrence of GIST in female subjects confers a better survival, as in our observation [9].

Follow-up of patients at high risk of recurrence is based on clinical examination, spiral CT or abdominal MRI. Follow-up is performed every 03 months for the first 03 years, then every 06 months for up to 05 years, then annually [6]. Any uncharacterized radiological abnormality should be further investigated by PET scan.

Conclusion

Locally advanced and metastatic forms of GIST must undergo neoadjuvant targeted therapy with early reassessment to detect resistance to IMATINIB and adapt the therapeutic strategy. In the event of a good response, surgery is proposed. The surgical strategy should aim for R0 surgery, even if it cannot be performed all at once: in other words, a 2-stage strategy to achieve R0 resection. Any therapeutic decision should only be taken within a MOT.

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