GIST in second portion of duodenum, surgical approach, case report and literature review

GIST en segunda porción de duodeno, abordaje quirúrgico, reporte de caso y revisión de literatura

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms, although annual reported incidence rates worldwide are less than 20 per million. These tumors can arise anywhere in the digestive tract in adults. Duodenal lesions represent approximately 3 to 5%. Although duodenal GISTs are relatively rare, they account for almost 30% of all primary tumors of the duodenum, they originate most frequently in the second portion, followed in order of frequency by the third, fourth and first portions. We present the case of a 54-year-old patient with a history of neurofibromatosis, with episodes of bleeding of three years of evolution, with the diagnosis of a duodenal polyp. The histopathological study reported a GIST with an immunohistochemical study positive for CD117, CD34 and DOGL, and a count of less than 2 mitosis/50 high power fields (HPFs). At surgery, a 3-cm tumor was identified on the lateral face of the second portion of the duodenum. Wedge resection and primary closure were performed with two suture lines. Local resection is appropriate when feasible and pancreatoduodenectomy should be reserved for lesions that are not amenable to it.

RESUMEN

Los tumores del estroma gastrointestinal (GIST) son las neoplasias mesenquimales más comunes, aunque las tasas anuales de incidencia reportadas en todo el mundo son inferiores a 20 por millón. Estos tumores constituyen una enfermedad gastrointestinal primaria que puede surgir en cualquier parte del tracto digestivo en adultos. Las lesiones duodenales representan alrededor de 3 a 5%. Aunque los tumores del estroma gastrointestinal duodenales son relativamente raros, representan casi 30% de todos los tumores primarios del duodeno, se originan con mayor frecuencia en la segunda porción del duodeno, seguida en orden por la tercera, cuarta y primera porción. Se presenta el caso de una paciente de 54 años de edad con antecedente de neurofibromatosis, la cual presentó episodios de sangrado de tres años de evolución, con diagnóstico de pólipo duodenal; el estudio histopatológico reportó tumor del estroma gastrointestinal con un estudio inmunohistoquímico que fue positivo para CD117, CD34 y DOGL, con una cuenta de menos de dos mitosis/50 campos de alto poder (CAP). Se decidió el manejo quirúrgico, se identificó un tumor de 3 cm en la pared lateral del duodeno en la segunda porción, se realizó resección en cuña y cierre primario en dos líneas de sutura. La resección local es apropiada cuando es factible y la pancreatoduodenectomía debe reservarse para lesiones que no son susceptibles de resección local.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms, accounting for 80%, and are part of non-epithelial neoplasms of the third and fourth layers (submucosal and muscular). They can be mesenchymal, like a stromal tumor of various origins, GIST for example, or leiomyoma, lipoma, nerve sheath tumor (schwannomas), and even lymphomas.[1] Annual incidence rates reported worldwide are less than 10-20 per

million, with no differences in gender or race. It is a disease that can arise anywhere in the digestive tract in adults.[2]

GISTs should be considered rare tumors: accepted standards consider a disease to be rare when the prevalence is less than one case per 2,000 people. For tumors, it refers to a neoplasm occurring in less than three per 100,000 individuals.[3]

CLINICAL PICTURE

GISTs are usually diagnosed in the fifth and sixth decades of life with a higher frequency in male patients.[4] The stomach (60%) and jejunum-ileum (30%) are the most common primary sites, and only a small number of cases (< 5%), has been reported in the colon and rectum, esophagus, and appendix (< 1%).[5] GISTs have also been described in the pancreas, gallbladder, mesentery, major or minor omentum, and retroperitoneum (1.5 to 5%).[5,6] Duodenal lesions represent approximately 3 to 5% of cases.[6,7]

The most common secondary sign is intestinal bleeding, macroscopic or occult. A second symptom is abdominal pain, and a tumor may also present as compression of neighboring organs, particularly in cases where it reaches a significant size.[8]

DIAGNOSTIC ANCILLARY STUDIES

GI Endoscopy

GI Endoscopy is the first test in patients with gastrointestinal bleeding. GISTs are easily identified in the first and second duodenal portions as a smooth, broad-based well-defined protrusion with normal, sometimes ulcerated, mucosa. Submucosal tumors with clots are suggestive of malignancy.[9]

Endoscopic ultrasound

Ultrasound defines with great precision the different layers of the digestive tract and allows to visualize the neighboring organs, which makes it the best diagnostic method for submucosal lesions of the digestive tract. However, endosonography cannot discern between a GIST and any other tumor of the intestinal wall, such as a leiomyoma, so fine needle aspiration biopsy is recommended for histological diagnosis.[9]

Tru-cut needle-biopsy has been used in association with endosonography, and has been successful in diagnosing GIST in 79% of cases by histology and up to 97% when immunohistochemistry is used, but this method cannot be used for GISTs smaller than 3 cm unless a cell block is prepared for immunohistochemistry testing.[10] Some endosonographic criteria have been established to allow suspicion of a malignant GIST with a specificity of 80% and a sensitivity of 77% *(Table 1)*.[11]

CT Scan

CT scan is the most widely available radiological study to identify and diagnose GISTs. Virtually all duodenal GISTs are detected by CT.[12] It is the technique of choice for detecting local invasion and metastatic disease. GISTs are hypervascular tumors that show intense contrast in the arterial phase. Most show homogeneous contrast and appear as well-defined endo- or exophytic masses.[13]

Magnetic resonance

It is considered useful in large and exophitic GISTs to establish their location and relations

Table 1: Endosonographic criteria for suspected malignant GIST.[31]
Tumor size >3 cm
Heterogeneous appearance
Hyper-ecogenic areas
Hypo-ecogenic areas
Irregular tumor margin
Lobulated tumor margin
Calcifications of the wall or intratumoral calcifications
Cystic aspect

Taken from: Beltrán MA, Valenzuela C, Diaz R, Haito Y, Larrai C. Tumores del estroma gastrointestinal del duodeno: revisión de literatura científica actual con énfasis en el tratamiento. Rev Colomb Cir. 2014; 29: 140-154.

Table 2: Fletcher's prognostic classification.		
Risk	**Size**	**Proliferation index**
Very low	< 2 cm	< 5/50 HPFs
Low	Between 2-5 cm	< 5/50 HPFs
Medium	< 5 cm	6-10/50 HPFs
High	5-10 cm	< 5/50 HPFs
	> 10 cm	Any
	Any	> 10/50 HPFs

* HPFs = High power fields.
(Own elaboration).

to neighboring organs. It is especially indicated in anorectal GISTs.[14]

PET Scan

GISTs are very avid for the 18F-fluoro-2-deoxy-D-glucose (FDG) tracer used in PET scans. Currently, the PET/CT association has been shown to improve the diagnostic accuracy of metastases and the monitoring of clinical response to drug therapy. PET is capable of detecting tumor lesions up to 1 cm and epiploic metastases undetected by CT.[15]

Biopsy

Biopsy is not necessary when there is a high suspicion of GIST and it is resectable. However, in cases where the submucosal lesion is indeterminate or metastatic disease is present and palliative treatment is considered, histological diagnosis should always be obtained by endoscopic ultrasound-guided fine-needle puncture-aspiration, which has proven to be a safe and non-invasive technique with 100% sensitivity and 80% specificity. The diagnostic accuracy of endoscopic ultrasound-guided fine needle puncture-aspiration increases with the tumor diameter from 71% (tumors < 2 cm) to 100% (tumors > 4 cm). Percutaneous biopsy is not recommended, since GISTs are hypervascular lesions and have a risk of rupture and peritoneal dissemination.[16]

Histopathology and molecular biology

From a histological and molecular point of view, GISTs are characterized by:

a) Fusiform (70%), epithelioid morphology (20%) or mixed.
b) GISTs express a transmembrane protein receptor of the tyrosine kinase family (KIT), encoded by the c-kit proto-oncogene in chromosome 4 (4q11-q12), believed to control cell proliferation and apoptosis.[17]

Endoscopic ultrasound-guided fine-needle biopsies can evidence Ki-67 or CD 117 for GIST by immunohistochemistry.

Hirota and colleagues, in 1998, demonstrated the role of this proto-oncogene mutation in the disease process,[17] in which the KIT protein is present in 90% of GISTs. This is considered a specific marker for these tumors, it is a membrane receptor with a tyrosine kinase portion, whose activation is key to cell proliferation and survival, hyperactivated in GISTs.[18,19]

At least two proactive mutations of KIT's tyrosinase activity and another KIT-related receptor called PDGFR-α have been discovered. This finding classifies GIST into three molecular subtypes: KIT-positive (90%), PDGFR-positive (5%), and KIT/PDGFR-negative (5%), and this differentiation may have prognostic and therapeutic implications.[19]

All GISTs harbor some malignant potential, although only 10 to 30% are clinically malignant and represent 1% of all malignant tumors of the gastrointestinal tract. Primary GISTs are not classified as benign or malignant but are stratified by the probability of recurrence after complete resection into very low, low, intermediate, and high risk based on their size and mitotic rate by Fletcher's criteria *(Table 2)*.[20]

The Fletcher criteria relate tumor size and number of mitoses to the risk of aggressive behavior. PET-18F-FGD provides information on metabolic activity and allows the degree of malignancy to be calibrated, as the greater the uptake of glucose by the tumor, the greater the metabolic activity and therefore the greater the aggressiveness.[21]

DUODENAL GIST IN PATIENTS WITH NEUROFIBROMATOSIS TYPE 1

In patients with neurofibromatosis type 1 GISTs are occasionally observed. In 5% of the cases they appear associated with a familial syndrome, besides, they are described in the Carney triad and Carney-Stratakis syndrome.[22]

The anatomical origin may be another independent factor for risk stratification. Although duodenal GISTs are relatively rare, they account for 30% of all primary tumors of the duodenum and the vast majority of patients have gastrointestinal bleeding.[23] In terms of treatment, duodenal GISTs are surgically challenging because of the complicated anatomical relationship around the duodenum, unlike the stomach or other intestinal segments where complete resection with wide margins is easier. Wide resection of duodenal GISTs will usually involve a pancreatoduodenectomy (PD), highly invasive and surgically challenging.[24]

In recent years there has been an increasing trend towards limited resection (LR), which has demonstrated an effect comparable to PD in selected cases. However, the optimal surgical approach (LR or PD) for duodenal GIST is not yet standardized, as all available evidence has been derived from small retrospective series. Because of their anatomical relationships, these tumors have been classified separately from other small bowel GISTs in a separate category.[24]

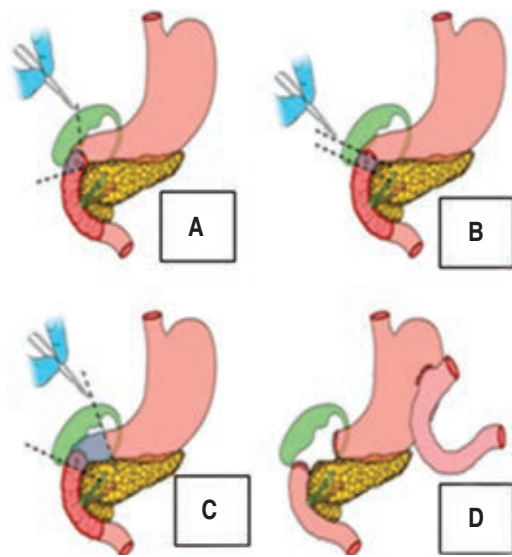| Table 3: Surgical procedures according to the location of the GIST in the duodenum.[30]				
Portion	**First**	**Second**	**Third**	**Fourth**
Lateral face GIST < 3 cm	• Wedge Resection • Segmental resection plus Billroth I/ gastro-jejunostomy Roux-en-Y	• Wedge resection plus primary closure/ duodenojejunostomy, Roux-en-Y	• Wedge resection plus Roux-en-Y primary closure/duodeno-jejunostomy	• Wedge resection • Segmental resection plus primary duodenum-jejunostomy
GIST >3 cm	• Segmental resection/ antrectomy plus Roux-en-Y gastrojejunostomy • Whipple	• Whipple	• Whipple • Segmental resection plus duodeno-duodenostomy • Resection of the third and fourth portions plus duodenojejunostomy	• Segmental resection plus primary duodenum-jejunostomy
Medial face GIST < 3 cm	• Wedge resection • Segmental resection plus Billroth I/ gastro-jejunostomy Roux-en-Y	• Whipple	• Whipple • Resection of the third and fourth portions plus duodenojejunostomy • Segmental resection plus duodeno-duodenostomy	• Segmental resection plus primary jejunostomy
GIST > 3 cm	• Whipple	• Whipple	• Whipple	• Whipple • Segmental resection plus primary jejunostomy

Figure 1: *Surgical procedures for GIST of the first duodenal portion. (A) Wedge resection with primary suture. (B) Segmental resection with primary anastomosis. (C) GIST requiring extensive segmental resection. (D) Reconstruction with Roux-en-Y gastro-jejunal anastomosis after segmental resection extended to the gastric antrum.*
(Own elaboration).

Neo-adjuvant treatment

The first successful small-molecule inhibitor imatinib mesylate, was initially developed as a specific inhibitor of PDGFRα. GIST with exon 11 mutations have the best clinical response to imatinib; patients without KIT or PDGFRα mutations do not improve with imatinib.[25] The United States Food and Drug Administration approved imatinib for the treatment of GIST in 2002.[25,26]

Indications for neo-adjuvant treatment with imatinib are preoperative tumor reduction and advanced metastatic tumors. In selected cases of locally advanced or marginally resectable GIST, cytoreductive strategy with neoadjuvant imatinib is a plausible strategy. The use of neoadjuvant imatinib in routine practice associated with surgery has good long-term results.[25,26]

Candidates for preoperative imatinib are those patients who would benefit from preoperative tumor volume reduction or in tumors with complex locations such as second and third-stage duodenal GISTs.[26]

In some series of duodenal GIST, imatinib has been used preoperatively with good results in patients with large tumors who are candidates for pancreatoduodenectomy. In these cases, the fragility of the tumor is reduced, decreasing the risk of bleeding and the possibility of capsule rupture.[26]

Dosage and management of neo-adjuvant treatment with imatinib

The recommended dose of imatinib is 400 mg daily until the maximum reaction is reached, which is confirmed with two consecutive CT scans that show no further regression of the tumor. Pre-operative treatment of four to 12 months is required to achieve maximum effect.[26]

Surgical approach

Complete surgical resection is the only curative treatment. Optimal surgical treatment includes resection of the tumor with free margins that may include adjacent organs. GISTs do not spread via the lymphatic route and do not present submucosal growth. They are also well-encapsulated tumors that rarely invade neighboring organs, so local resection or segmental duodenectomy is considered sufficient and is associated with prolonged disease-free survival. In patients with primary GIST, surgical resection offers a five-year survival rate of 48-70%.[27]

Unlike GISTs located elsewhere in the gastrointestinal tract, the optimal surgical treatment of those in the duodenum is not well characterized and is poorly established in the surgical literature.[28]

Surgical resection can be performed using several options. The approach should be dictated by the location of the tumor in the duodenum and the ability to achieve R0 resection. Local or conservative surgery consists of either wedge resection or resection of a segment, taking into account the duodenal anatomy and its proximity to adjacent structures such as the ampulla of Vater, the pancreas, mesenteric vessels, common bile duct, and pancreatic duct.[29]

Local resection is often difficult, especially in the second portion. In clinical practice, up to 86% of duodenal GISTs have been treated by pancreatoduodenectomy. The surgical options reported for these tumors depend on their location and size30 *(Table 3)*.

First portion of the duodenum

Tumors located towards the medial wall that are in intimate contact with the head of the pancreas should be treated by pancreatoduodenectomy. Those located in the lateral wall, when less than 3 cm, may be treated by wedge resection and primary suture or segmental resection[31] *(Figure 1)*.

Second portion of the duodenum

Those located in the medial wall of the duodenum in contact with the head of the pancreas or with the ampulla of Vater should undergo pancreatoduodenectomy.[31]

Tumors located in the lateral wall can be treated by local wedge resection with primary closure or distal duodenectomy and reconstruction by anastomosis between the jejunum and the remaining duodenum or by Roux-en-Y jejunum anastomosis[31] *(Figure 2)*.

Third portion of the duodenum

Small or medium-sized tumors located in the medial or lateral wall can be treated by
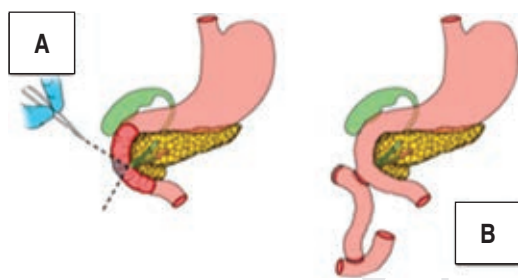

Figure 2: Surgical procedures for GIST of the second duodenal portion. (A) Wedge resection. (B) Reconstruction of a wide wedge resection of the second portion of the duodenum by duodeno-jejunal anastomosis.
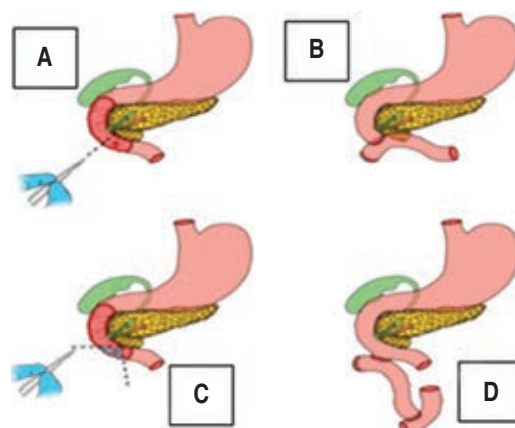*(Own elaboration).*

Figure 3: Surgical procedures for GIST of the third duodenal portion. (A) Distal duodenectomy involving the third and fourth duodenal portions. (B) Reconstruction of the distal duodenectomy by means of an end-to-end duodeno-jejunostomy. (C) Wedge resection of the third portion of the duodenum. (D) Reconstruction of the resection by a Roux-en-Y duodeno-jejunostomy.
(Own elaboration).

resection of the third and fourth duodenal portions, and primary end-to-end or latero-terminal anastomosis with the jejunum *(Figure 3 A and B)*. When wedge resection leaves a very large defect and primary closure is not possible, the defect can be solved by Roux-en-Y jejunostomy *(Figure 3 C and D)*. When the tumor is very large with infiltration into the pancreas, pancreatoduodenectomy is the option.[31]

Fourth portion of the duodenum

GISTs located in the fourth portion can be resected locally and the intestinal transit can be restored by primary end-to-end or termino-lateral anastomosis between the third duodenal portion and the jejunum *(Figure 4)*. Small tumors can be treated by wedge resection.[31]

LAPAROSCOPIC SURGERY

Laparoscopic surgery has shown advantages over traditional open surgeries showing a reduction in postoperative pain, lower incidence of infections, lower risk of hernia or dehiscence associated with incisions, as well

as faster postoperative recovery and as a result a short hospital stay. Laparoscopy provides equivalent results to open surgery as long as negative margins are achieved; however, there are still very few reports in the literature on the use of laparoscopic resection for non-gastric GIST.[32]

The use of the laparoscopic technique in large, hard-to-reach GISTs is limited. The Comprehensive National Cancer Network restricts the use of laparoscopy for tumors less than 2 cm. In GIST with difficult access, the mobility of the surgical instrument is affected, and suturing becomes difficult to perform; it may also result in inadequate resection margins and consequently, disease progression, recurrence, and short survival. The Da Vinci Surgical System offers superior ergonomics, improved vision, precision, dexterity, and control for surgeons. Recent studies also found that minimally invasive robotic resection was oncologically safe and resulted in favorable outcomes such as the earlier return of bowel function, earlier resumption of diet, shorter duration of the use of analgesia, and shorter postoperative hospitalization. However, only a few studies on the use of the Da Vinci System in oncology have been published.[33]

Other minimally invasive techniques such as endoscopic submucosal tunneling resection, full-thickness endoscopic resection, and laparoscopic endoscopic cooperative surgery have shown good clinical results, although there are not yet
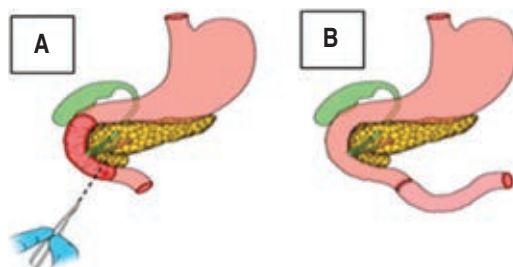

Figure 4: Surgical procedures for GIST of the fourth duodenal portion. (A) Distal duodenectomy involving the fourth portion of the duodenum. (B) Reconstruction by primary duodeno-jejunostomy. (Own elaboration)
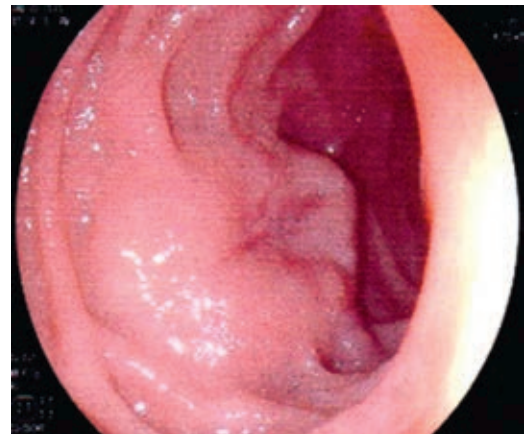

Figure 5: Tumor in the second portion of the duodenum just in front of the ampulla.

enough studies on their long-term safety or are still in course.[34]

ADJUVANT THERAPY

Imatinib mesylate is the first line of treatment in patients with advanced GIST, which improves disease-free survival and overall survival. This drug has been approved for use after resection of GIST with a high risk of recurrence, at a dose of 400 mg daily. Sunitinib maleate is the second line of treatment for imatinib-resistant GIST.[35]

PROGNOSIS

Duodenal GIST segmental or wedge resection has been shown to be sufficient and curative with satisfactory disease-free survival in series reporting only tumors of the duodenum. The table for GIST, developed in 2001 by the consensus workshop sponsored by The National Institutes of Health and The National Cancer Institute and recently modified by Joensuu, is used to establish the prognosis of these patients. The five-year survival for tumors larger than 10 cm is 20% and for tumors smaller than 5 cm it reaches 65%. In patients operated for localized duodenal GIST, the overall survival time at three years is 98% and the disease-free time is 67%. At five years the overall survival is 89% and the disease-free survival is 64%.[35]

All GISTs are associated with risk of recurrence; 40 to 50% of all patients with potentially curative resections develop metastases or recurrences. Despite current knowledge of their biology, these tumors behave erratically; even in low-risk GISTs, recurrences have been reported 20 or more years after surgical resection. Recurrences have been described in 39% of patients with duodenal GIST. In high-risk tumors, recurrence is inevitable. In series at two-year follow-up, recurrences have been found in 19%, with distant metastases in 13 to 23%, local recurrence in 2 to 15%, and local and distant synchronous recurrence in 4%. The most common site for the development of metastasis is the liver. However, it is interesting that after more than a decade of intensive research the conclusions are the same, the most important determinants of survival being mitosis count and tumor size.[35]

CASE PRESENTATION

A 54-year-old female patient with a history of neurofibromatosis diagnosed at age 35. She had three bleeding episodes three, two, and one year before, the last of which required a blood transfusion. A year earlier she was diagnosed with a duodenal polyp located in the second portion in front of the ampulla of Vater.

The histopathological study reported a gastrointestinal stromal tumor, the CAT scan similarly reported a tumor in the second portion of the duodenum of 42 × 36 mm, and the immunohistochemical study of the fine needle biopsy guided by endoscopic ultrasound was positive for CD117, CD34, and DOGL. The endoscopic ultrasound showed a lesion on the lateral wall of the second portion of the duodenum.

These studies were conducted as a study protocol in 2016. After the protocol, a 3 cm tumor was identified in the lateral wall of the duodenum. A surgical approach was chosen through a mid-supraumbilical incision. A wedge resection was performed with a macroscopic margin of 1 cm of the tumor lesion. Primary closure was made in two planes, with 2/0 chromic catgut for the first one and 2/0 silk, for the seromuscular plane. As post-surgical management, ceftriaxone was administered, 1 g IV every 12 hours for eight days, and tramadol, 200 mg in infusion for 24 hours plus ketorolac, 30 mg IV every eight hours as analgesic management *(Figures 5 and 6)*.

The patient evolved without complications and was discharged on the eighth day with follow-up by the general surgery and surgical oncology outpatient clinic. During the follow-up the pathology study revealed a duodenal tumor compatible with a GIST of 4 × 3 × 3 cm in size, of low malignancy, with tumor-free surgical edges of 1 mm *(Figure 7)*. A follow-up protocol was established, with imatinib 400 mg every 24 hours for 36 months, authorized on January 24, 2017.

Currently, the patient is attending medical follow-up in the general surgery, surgical

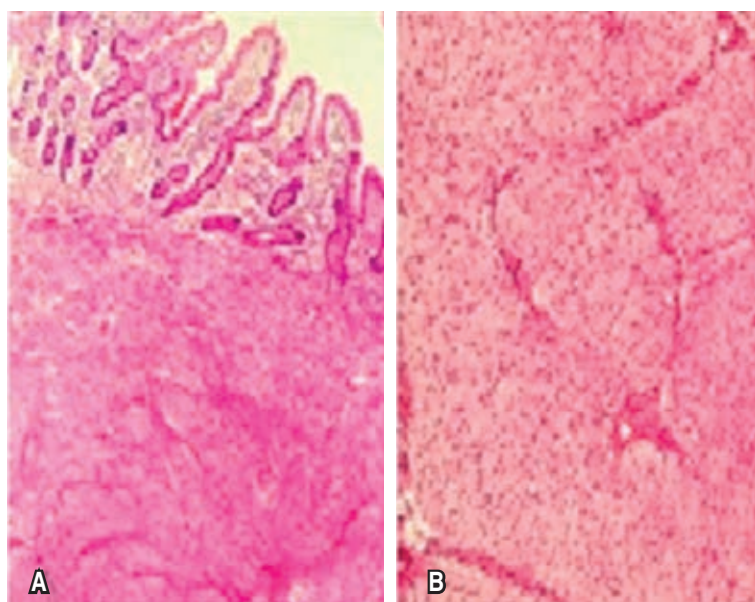*Figure 6:*

Resected duodenal GIST.

Figure 7: A (HE 10X) and B (40). In (A) there is a well-defined, non-encapsulated, intramural, mesenchymal neoplastic proliferation formed by elongated cells (fusocellular pattern), with little pleomorphism. (B) The cells are elongated, arranged in a swirl, with vesicle-like nuclei, little pleomorphism and less than two mitosis/50 HPFs.

oncology, and medical oncology services with the last monitoring, as of February 12, 2018, with 18F-FDG PET/CT reporting no evidence of increased metabolic activity.

DISCUSSION

The primary treatment of duodenal GISTs is the surgical approach, with complete tumor resection and adequate margins; in some cases, conservative surgery can be planned as in our patient's case.

We describe the most frequent surgical treatment of duodenal GIST. Local resection is appropriate when feasible and pancreatoduodenectomy should be reserved for lesions that are not susceptible to local resection, for example, those affecting the ampulla of Vater or those with Fletcher's irresectability criteria. Our patient is at low risk because of her tumor size (3 cm), and a count of fewer than two mitosis/50 HPFs. Complete surgical resection with free margins was considered curative.

GISTs do not spread via lymphatic route and do not have submucosal growth, they are well-encapsulated tumors that rarely invade neighboring organs, so local resection or segmental duodenectomy is considered sufficient and associated with prolonged disease-free survival. For this reason, tumors located in the lateral wall of the second portion can be treated by local wedge resection with primary closure or distal duodenectomy and reconstruction by anastomosis between the jejunum and the remaining duodenum by Roux-en-Y anastomosis. In the specific case of our patient, the surgical option was wedge resection with primary closure in two planes as recommended in this literature review.

Our patient received adjuvant therapy with imatinib 400 mg/day. Imatinib mesylate is the first line of treatment in patients with advanced GISTs, it improves disease-free and overall survival. Based on the prognostic table of primary GIST modified by Joensuu, tumors smaller than 5 cm have a survival rate of 65% at 5 years.

CONCLUSION

The management of these patients is multidisciplinary, consisting of radiologists, oncologists, gastroenterologists, surgeons, gastrointestinal endoscopists, and endosonographers. Almost half of the cases are diagnosed incidentally. GISTs should be considered in the differential diagnosis of digestive tumors in the presence of anemia or GI bleeding of uncertain origin.

The treatment of choice is surgical, achieving complete resection of the tumor in 70 to 80% of the cases. Chemotherapy and radiotherapy have limited utility, so there are treatments such as tyrosine kinase inhibitors that decrease the activity of the tumor in unresectable cases.

In comparison to the literature, the protocol our patient followed was adequate. With the characteristics mentioned, the best choice was the wedge resection. This approach has been gaining acceptance due to its lower morbimortality, as compared to duodenopancreatectomy.

Most reports on duodenal GISTs mention that optimal surgical treatment has not been determined. No randomized clinical studies have been done and the published reports

are the experience of a few reference centers. A careful review of these publications shows that surgical approaches for duodenal GISTs are fairly standardized, taking into account the location of the tumor in the duodenum and its anatomical relationships to decide the type of surgical approach.

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