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Case Report

# GIST associated with von recklinghausen disease: Report of two cases and review of literature

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ABSTRACT

*Introduction and importance:* Neurofibromatosis type 1 (NF1), or Von Recklinghausen's disease, is an autosomal dominant condition that affects the central nervous system. Gastrointestinal stromal tumor (GIST) refers to non-epithelial tumors of the gastrointestinal tract lacking smooth muscle structural features and schwann cell immunohistochemical characteristics. The risk of patients with NF1 to develop a GIST is 7%.

*Case presentation:* GIST is a soft tissue sarcoma that probably arises from the interstitial Cajal cells of the intestine. GIST associated with NF1 syndrome appears to have a distinct phenotype, occurring in younger patients compared to sporadic GIST.

*Clinical discussion:* The clinical presentation can be highly variable, the association of gastrointestinal tumors associated with Von Recklinghausen's disease is up to 7%, postoperative treatment with imatinib is reserved for patients with a high risk of recurrence.

*Conclusion:* The treatment of primary GIST is complete surgical resection with free microscopic margins and an intact pseudocapsule.

## 1. Introduction

Neurofibromatosis type 1 (NF1) or Von Recklinghausen's disease, is an autosomal dominant condition that affects the central nervous system. The characteristic skin tumors of NF1 present as discrete, small, benign neurofibromas in the dermis in over 95% of patients, and as plexiform neurofibromas that affect portions of the peripheral nerves and infiltrate surrounding tissues and have the potential to develop malignant tumors of the peripheral nerve sheath in 2%–16% of cases [1].

The term gastrointestinal stromal tumor (GIST) was introduced by Mazur and Clark to designate non-epithelial tumors of the gastrointestinal tract lacking smooth muscle structural features and immunohistochemical Schwann cell characteristics [2]. They represent the most common neoplasm of mesenchymal origin of the gastrointestinal tract and up to 1% of all gastrointestinal tract neoplasms [3].

## 2. Presentation of cases

### 2.1. Clinical case 1

54-year-old female patient with a history of neurofibromatosis diagnosed at 35 years of age. She presented three bleeding episodes, of three, two and one year of evolution, respectively. In the last one, she required blood transfusion. She was diagnosed a year earlier with a duodenal polyp located in the second portion of the duodenum, just in front of the ampulla of Vater (photo 1).

The histopathological study of the biopsy taken by endoscopy reported the presence of a gastrointestinal stromal tumor, the computerized axial tomography scan also reported a tumor in the second portion of the duodenum measuring 42 × 36 mm and the immunohistochemical study was positive for CD117, CD34 and DOG1.

These studies were carried out as a protocol, during the year 2016, and at the end, laparotomy was chosen as the surgical approach, during

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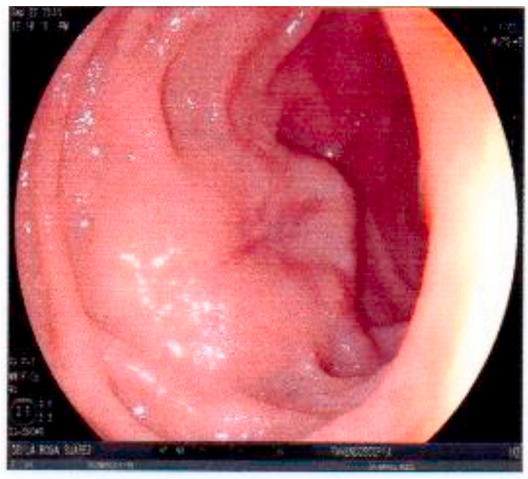

**Fig. 1.** Endoscopic view of the tumor in the second portion of the duodenum in front of the ampulla.

which a 3-cm tumor was identified in the lateral wall of the duodenum. A wedge resection was performed, giving a macroscopic margin of 1 cm to the lesion by performing a primary closure in two planes. Post-operative course was remarkable with medical management and surveillance.

The patient evolved without complications and was discharged on the eighth day. The pathology study reported a duodenal tumor compatible with a gastrointestinal stromal tumor of low risk of malignancy with a size of 4 × 3x3cm, with tumor-free surgical margins at 1mm (photo 2) and an assessment was requested from the medical oncology service. Those who start using imatinib 400mg every 24 hours for 36 months, started in January 2017.

Currently, the patient attends medical follow-up in the services of general surgery, surgical oncology and medical oncology with the latest control reports on February 12, 2018 of PET/CT with 18F-FDG without evidence of tumor activity.

### 2.2. Clinical case 2

We present a 59-year-old female patient from Oaxaca, México, with a history of congenital neurofibromatosis, a history of cholecystectomy at age 40. She presented in the adult emergency department with clinical picture of pain of severe epigastric pain, with frank evidence of peritoneal irritation, accompanied by asthenia and adynamia, this being the third time with a similar abdominal pain picture.

The computerized axial tomography reported free air in the cavity,

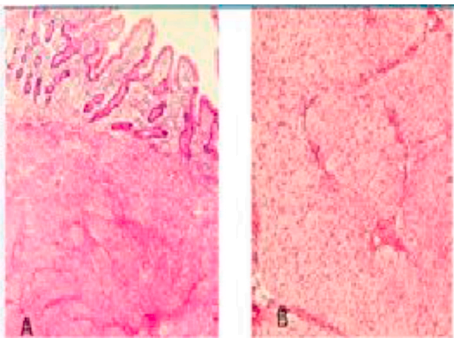


**Fig. 2.** (HE 10X) Y B (40). A) A mesenchymatose neoplasic proliferation, intramural, well delimited, not encapsulated, formed by elongated cells (fusocellular pattern), with scarce pleomorphism, is observed. B) The cells are elongated, arranged in a swirl form, with nuclei of vesicular aspect, fewer pleomorphism and less than 2 mitoses/50 chap.

thickening of the mucosa from the ascending colon to the sigmoid, with a possible perforated hollow viscus. Perforated gastric ulcer may be a first possibility (photos 3 and 4).

These studies were carried out as an emergency surgical protocol, which at the end, laparotomy was opted for as the surgical approach, with the findings of generalized peritonitis and abscesses in the pelvic cavity and right iliac fossa. In the pelvic cavity, a perforated ileal tumor was identified at 100 cm of the ligament of Treitz, approximately 5 cm in diameter. Intestinal resection was performed with end-to-end intestinal anastomosis, and for postoperative management, a double scheme of antibiotics and analgesic management were administered.

The patient evolved without complications, a diet was started on the fifth day and she was discharged on the seventh day with follow-up by the general surgery and surgical oncology outpatient clinic. During the follow-up by the outpatient clinic, the result of an ileal tumor was received, compatible with a gastrointestinal stromal tumor with a size of 6 × 4 cm, 4 cm from the nearest surgical border (photograph 5).

At present, the patient is attending follow-up in general surgery, surgical oncology and medical oncology services, with the following immunohistochemistry report: CD 117 (++) in 100% of neoplastic cells, DOG1 (++) positive in 100% of neoplastic cells; CD 34 (+++) positive in 100% of neoplastic cells.

The medical oncology service determined that there is no benefit with the adjuvant management since there is no evidence of systemic disease.

## 3. Discussion

GISTs associated with NF1 syndrome appear to have a different phenotype, occurring in younger patients compared to sporadic GISTs, which are often multiple and appear in the small intestine. However, in both clinical cases that we present, they occurred in the sixth decade of life, coinciding with the second most frequent presentation in the small intestine, duodenum and jejunum, respectively [4].

A worldwide incidence of 10–20 cases per million inhabitants is reported each year; however, it has increased since 1990 as a result of greater awareness in this type of tumors, due to more appropriate diagnoses with the help and advancement of immunohistochemistry [1].

The genetic basis of this disease is a mutation in the NF1 gene. Located on chromosome 17q11.2, NF1 encodes neurofibromin, a tumor suppressor protein. Neurofibromin predisposes to the development of both benign and malignant tumors. Neurofibromin regulates cell proliferation through the inactivation of Ras, a protein that stimulates signal transduction through MAP kinase [5–7].

GIST is a soft tissue sarcoma that probably arises from interstitial cells of Cajal (ICC), gastrointestinal pacemaker cells with a role in motility. Most GISTs express the tyrosine kinase receptor KIT (CD 117) [8]. About 85% of GISTs are characterized by a sporadic activation of the mutation in the KIT gene. KIT mutations most commonly occur in exon 11 (60%) but can also occur in exons 9 (15%), 13, or 17 (5%). Less commonly, GISTs harbor a mutation in the platelet-derived growth

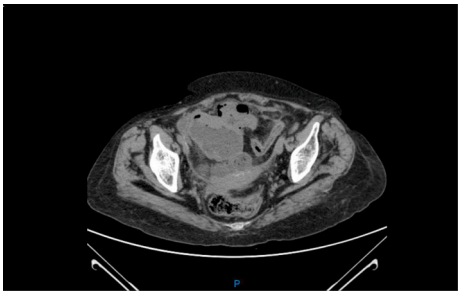

**Fig. 3.** Abdominal CT scan shows little free fluid, with a thickened wall of the small intestine with striated fat, adjacent to the bladder.

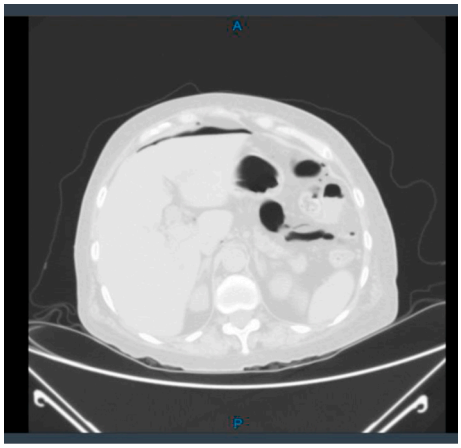

**Fig. 4.** Abdominal CT showing free air in the cavity, seen with pulmonary window.

factor receptor alpha (PDGFRA), which also encodes a receptor tyrosine kinase, these mutations can occur in exons 12 or 18, both tyrosine Kinases play a key role in GIST tumorigenesis through signal transduction via PI3K-AKT, MAP kinase, and JAK-STAT3 pathways [9,10].

GISTs may be associated with the Carney's triad (epithelioid leiomyosarcoma, paraganglioma, and pulmonary chondroma). Its most frequent location is in the stomach (50–70%); this represents only 2–3% of all gastric tumors. Second in frequency is occupied by the small intestine (20–30%) and other locations include the colon, anorectum or esophagus [7].

Biologically, GISTs are considered potentially malignant, in different degrees (very low, low, medium, and high) depending on their size and the number of mitoses; therefore, all of them require surgical treatment [8]. Surgery is the main treatment for primary resectable diseases, but for unresectable and metastatic diseases, a targeted therapy with imatinib mesylate, a tyrosine kinase inhibitor with activity in both KIT and PDGFR, is indicated [4].

In both clinical cases, the age of presentation is in the sixth decade of life, they are not related to gender, geographic residence or ethnic group. Based on a Swedish study of 70 patients with type I neurofibromatosis, the incidence of GIST in this population is approximately 7%. Why the tumors arise in a minority of these patients remains a mystery [8]. In the cases presented, the average age does not correlate with that reported in the literature, although there is no relationship with gender, both cases that we present occurred in female gender, and of Mexican origin.

GISTs associated with patients with NF1 have been described as clinically indolent and often asymptomatic; the most frequent clinical manifestation of symptomatic GIST in these locations is gastrointestinal bleeding due to ulceration of the mucosa (45%), as occurred in clinical case 1, followed by abdominal pain that can be chronic or acute although in a high percentage it is asymptomatic and is diagnosed incidentally by imaging studies, surgery or histology [11]. The second case that we present manifested as an acute abdominal pain.

Ultrasound is usually the initial diagnostic technique in many patients with GIST tumors, usually showing low ecogenicity tumors. The 18F-FDG PET provides information on metabolic activity and allows the degree of malignancy to be determined since the greater the uptake of glucose by the tumor, the greater the metabolic activity and therefore the greater the aggressiveness. The computerized axial tomography (CAT) with oral and intravenous contrast is the method of choice for all patients with suspected abdominal tumors. The CAT reveals exophytic growth, heterogeneous and vascularized tumors with the associated presence of hemorrhage, necrosis or cystic transformation [12].

Adjuvant treatment should be carried out with imatinib mesylate for the suppression of CD117 receptors, and for the prevention of recurrence or metastasis of the tumor [13]. In the same way that case 1 was treated, it is of paramount importance that these patients require multidisciplinary management in order to determine the best decision in their management.

## 4. Conclusion

The association of gastrointestinal stromal tumors and Von Recklinghausen's disease is up to 7%. We report two clinical cases of the association of GIST with NF1, its clinical picture, the diagnostic process and its management.

Clinically, it presents in a very variable way, as described above, it can be asymptomatic and diagnosed as findings, or present with an emergency clinical condition, such as acute abdominal symptoms. The support of imaging and endoscopic studies are a guide, but they do not set a clear guideline for its accurate diagnosis at first contact.

The final diagnosis must be based on immunohistochemistry, as in the cases we present. Treatment of primary GIST is complete surgical resection of free microscopic margins and an intact pseudocapsule. Reported overall survival after complete surgical resection of localized primary GIST is 40%–55% at 5 years.

Postoperative treatment with imatinib is reserved for patients at high risk of recurrence, but there is not a sufficient level of evidence about the optimal duration of such treatment. Although there is controversy in the use of imatinib since adjuvant treatment could help to eradicate the microscopic disease, but it could also reduce the effectiveness of the drug in the treatment of recurrent GIST and facilitate the appearance of resistant clones to treatment, however, the drug can be used by multidisciplinary teams with experience in this type of tumors. This case report has been arranged in line with SCARE guidelines [14].

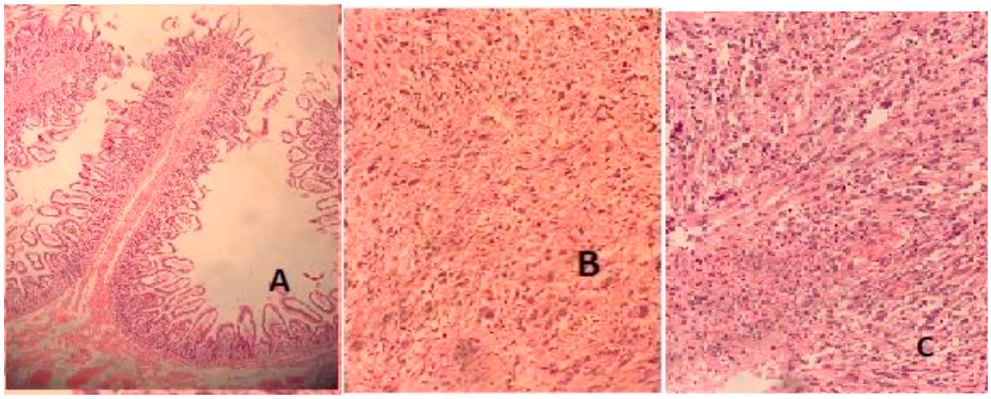


**Fig. 5.** A. (HE 10X) and B (40). A) It is observed, mucosa of the small intestine, constituted by vellosities coated by a simple cylindrical epithelium, with basal nuclei, in the lamina itself, a moderate chalphous inflammatory infiltrate and chalphous lymphostic infiltrate of expenses. B and C) A malignant neoplastic lesion is observed, constituting cells of fusiform aspect, of eosinophyl cytoplasm and basophyl nucleus, heterogeneous, forming a verticilate and plastic inflastic infiltrated pattern of crylamasphous infiltrated inflasmos.

## Ethical approval

This case report is exempt from ethnical approval in our country.

## Author contribution

Amador Jimenez: Responsible for literature review, Teresa de Jesus Galicia writing and manuscript preparation. Arcenio Luis Vargas Operator of surgery. Julian Vargas & Israel de Alba: Responsible for manuscript preparation. Victor Gibran Reyes & Fernando Narvaez: Responsible for manuscript review.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Registration of research studies

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## Declaration of competing interest

The authors report no declarations of interést.

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