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Neurofibromatosis type 1 associated multiple and cystic gastrointestinal tumors: 02 case reports

Fatima Zahra Rahou^{a,*}, Achraf Miry (Dr)^b, Amal Bennani (Pr)^b, Mohammed Bouziane (Pr)^a^a General Surgery Department, Mohamed VI University Hospital Oujda, Morocco^b Anatomopathology Department, Mohamed VI University Hospital Oujda, Morocco

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ABSTRACT

INTRODUCTION: GIST's are the most common mesenchymal tumor of the gastrointestinal tract, clinically and radiologically heterogeneous, only a histological study can confirm the diagnosis. The link between NF1 and GISTs have been established but not fully elucidated.

CASE PRESENTATION: we report 02 cases of NF1 associated GIST, a 60 years old woman with multiples GISTs in the duodenum, proximal jejunum and in the colon presenting an iron deficiency anemia due to chronic bleeding, operated with R0 resection and a low risk of recurrences and a 41 year old male patient with acute abdominal pain with a giant abdominal mass mimicking a hydatid cyst with no relevant medical history, diagnosed at the same time for typical clinical NF1, CT scan showed the cystic mass but did not confirmed its origin, a complete resection of the mass with no capsule fraction was tricky but successful and the histopathology found a high risk of recurrences. The 2 patients received adjuvant imatinib therapy with recurrence free survival at 12 months follow up. Our cases represents a rare entity (multiples GISTs and cystic GIST) within a rarest population (NF1 associated GIST).

DISCUSSION: the diagnosis of NF1 is based on typical clinical criterias but the GISTs are known to be the variable, symptomatic or silent, small size or giant. Imaging is based on CT scan with intravenous contrast studying the vascular pattern, the extra intestinal and metastasis localizations. MRI is no superior, but useful in the study of pelvic GISTs and liver metastasis. Histopathology is the only way to confirm the diagnosis with marker staining with CD117 and DOG-1. The emerging imatinib, sunitinib and regorafenib are used as neoadjuvant or adjuvant therapies in GISTs with high or moderate risk of recurrences. No consensual guidelines are yet established for the follow up as the recurrences are more frequent.

CONCLUSION: GIST's association to NF1 is established, but the different aspects of the physiopathological, clinical and the treatment haven't been established yet with no larger population to study. We believe that the understanding of the development of this type of tumors within the NF type 1 group would allow a better treatment and follow up and may be can lead to screening.

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1. Introduction

Gastro-intestinal stromal tumor (GIST) is a mesenchymal tumor of the gastrointestinal tract that can occur in any part of it from the esophagus to the anus; arising from the interstitial cells of Cajal of the sub epithelial then the epithelial layer of the gastrointestinal tract, pathobiologically GISTs are originated from mutations of proto-oncogenes. Although More than 80 % of these mutations are sporadic, familial cases were reported and inherited germ line

mutations of the KIT gene were briefly studied. They occur in 5 % responsible for familial GISTs including primary familial GIST syndrome, carney-Startakis syndrome and neurofibromatosis (NF) type 1 [1].

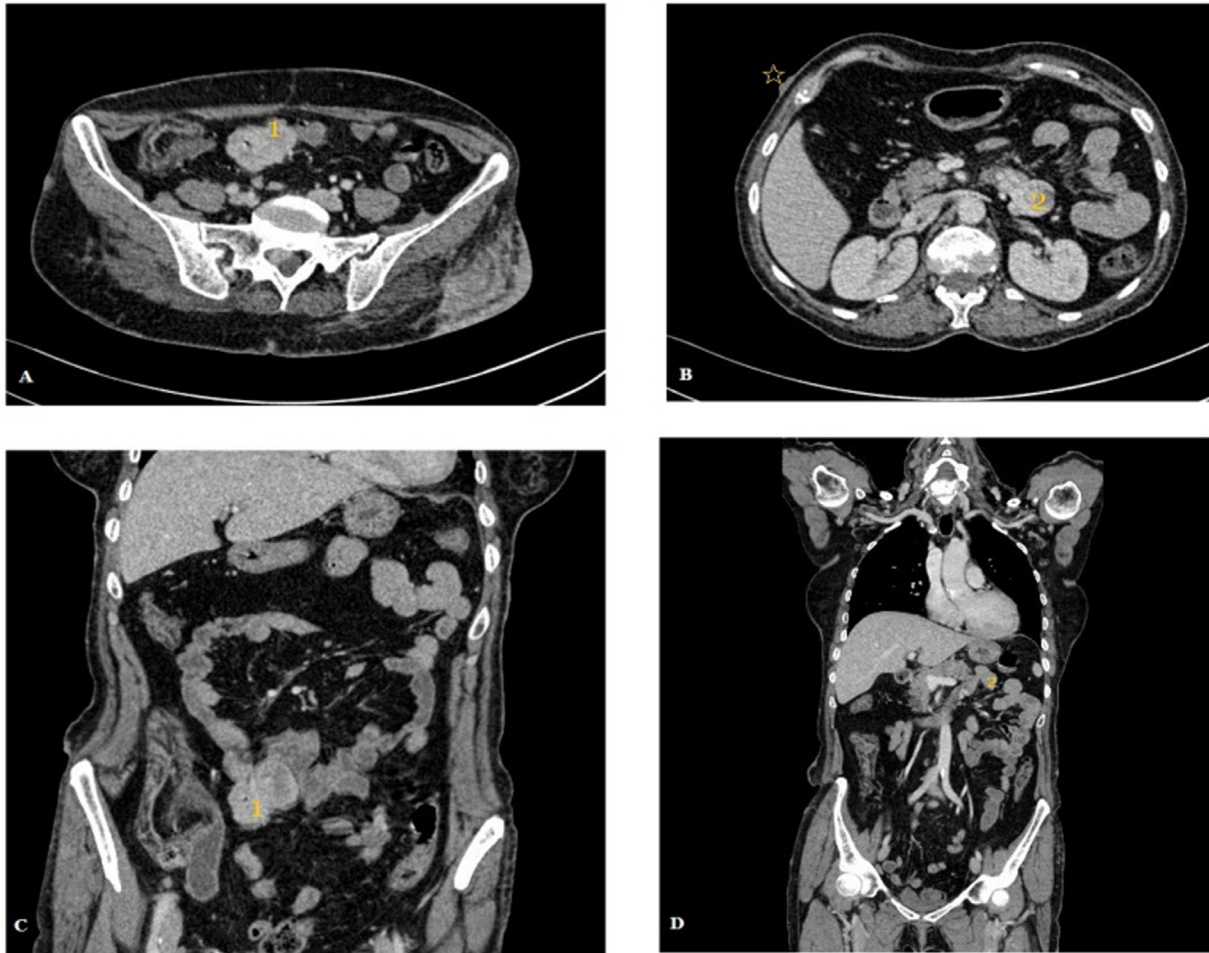
2. Patient's presentations

2.1. Case N° 1

A 60 years old female patient, consulting for paroxysmic abdominal pain and vomiting ; mistook for adhesional bowel obstruction ; already diagnosed with NF type 1, with a history of sigmoid surgery for a colon GIST with a moderate risk of recurrences and no adjuvant therapies due to financial issues. Clinical examination finds café au lait spots with spread skin lumps, the biological testing showed an

* Corresponding author.

E-mail addresses: fatimazrahou@gmail.com (F.Z. Rahou), achrafmiry@outlook.com (A. Miry), bennaniamal@gmail.com (A. Bennani), bouzianemohammed@hotmail.com (M. Bouziane).



computed tomography scan showing the radiological imagin of multiples GISTs associatd to neurofibromatosis

A;B: axial cut, C;D: sagittal cut
 1: duodenal GIST 2: ileum GIST * : skin nodules

Fig. 1. Computed tomography images of the stromal tumors.

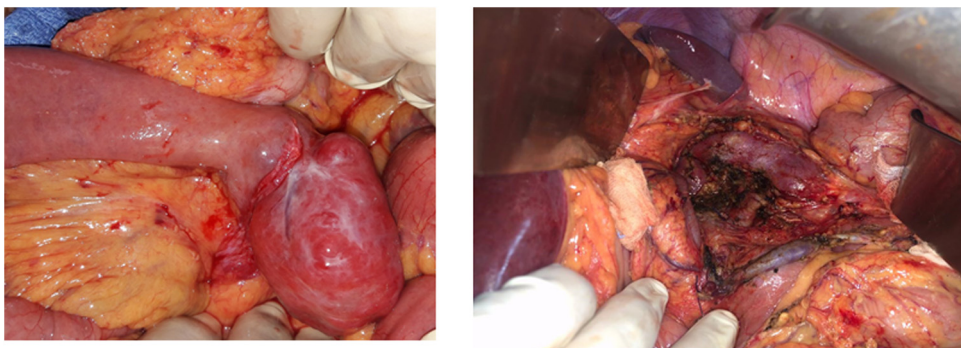


Fig. 2. Preoperative photograph showing the duodenal stromal tumor before and after resection.

iron deficiency anemia. Upper endoscopy and colonoscopy showing no origin of bleeding, a Video-capsule was carried out: multiple polypoid lesions of the small intestine. An abdominal CT scan showing multiple tumors of the duodenum, proximal jejunum and the terminal ileum (Fig. 1). An iterative midline Laparotomy exposed an Exophytic mass of the distal jejunum with another Exophytic mass of the duodenum and a mass of the gastric lesser curvature along with NF lumps of the gastric wall and Small nodes of the omentum (Figs. 2 and 3).

Lateral resection of the duodenum tumor and complete resection of distal ileum using a linear cutter with 3D staples (NTLC © Ethicon) with biopsy of the gastric nodes. Histopathology proved the diagnosis with overexpression of the CD117 receptor with low risk of recurrence according to the classification of Miettinen and Lasota (Figs. 4 and 5). The patient was candidate for adjuvant therapy with Imatinib due to her primary history colon GIST with moderate risk and the upcoming multiples GISTs considered as recurrences with no recurrences at one year follow up.

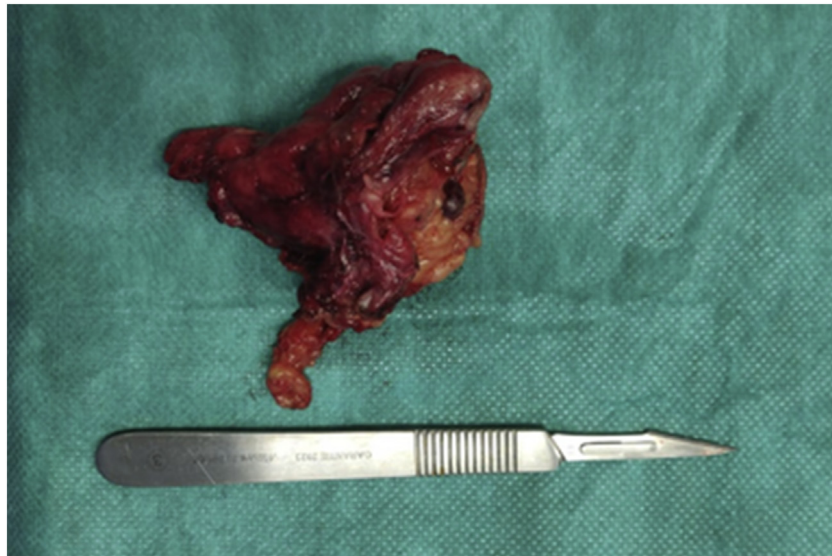
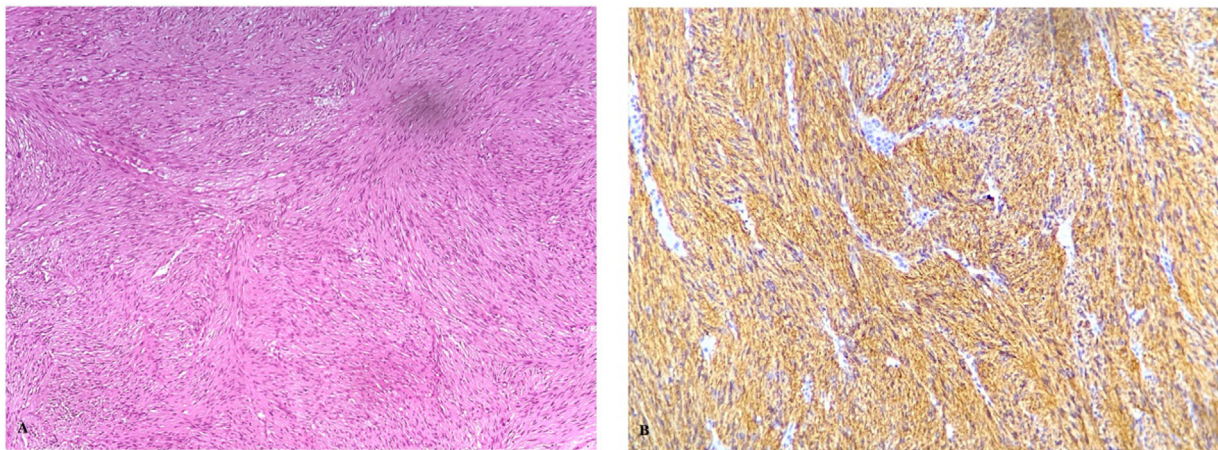
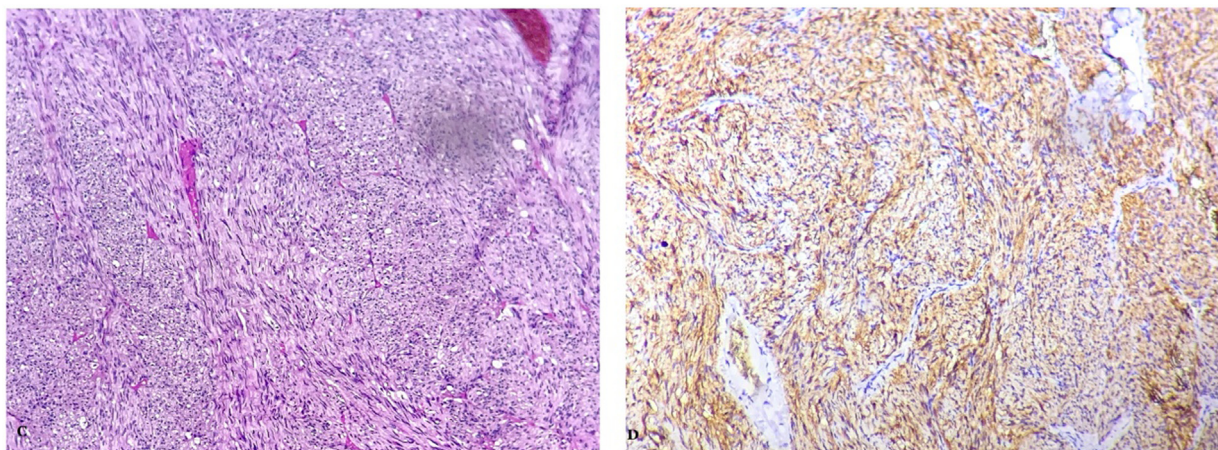


Fig. 3. Specimen of the duodenal stromal tumor.



Microscopic photography showing the histological and immunochemistry study of the duodenum stroma tumor
 A: fasciculated proliferation made of spindle cells devoid of cytonuclear atypia. (H&E; 200X).
 B: Tumor cells strongly express CD117



Micrograph of the histological aspect of the proximal jejunum GIST
 C: spindle-shaped mesenchymal proliferation organized in 90 degree crisscrossed beams. cells have discrete atypia. (HE, 200X)
 D: The tumor cells were positive for anti-CD117 antibodies.

Figs. 4–5. Histological study before and after marker staining showing the typical image of the stromal tumor.

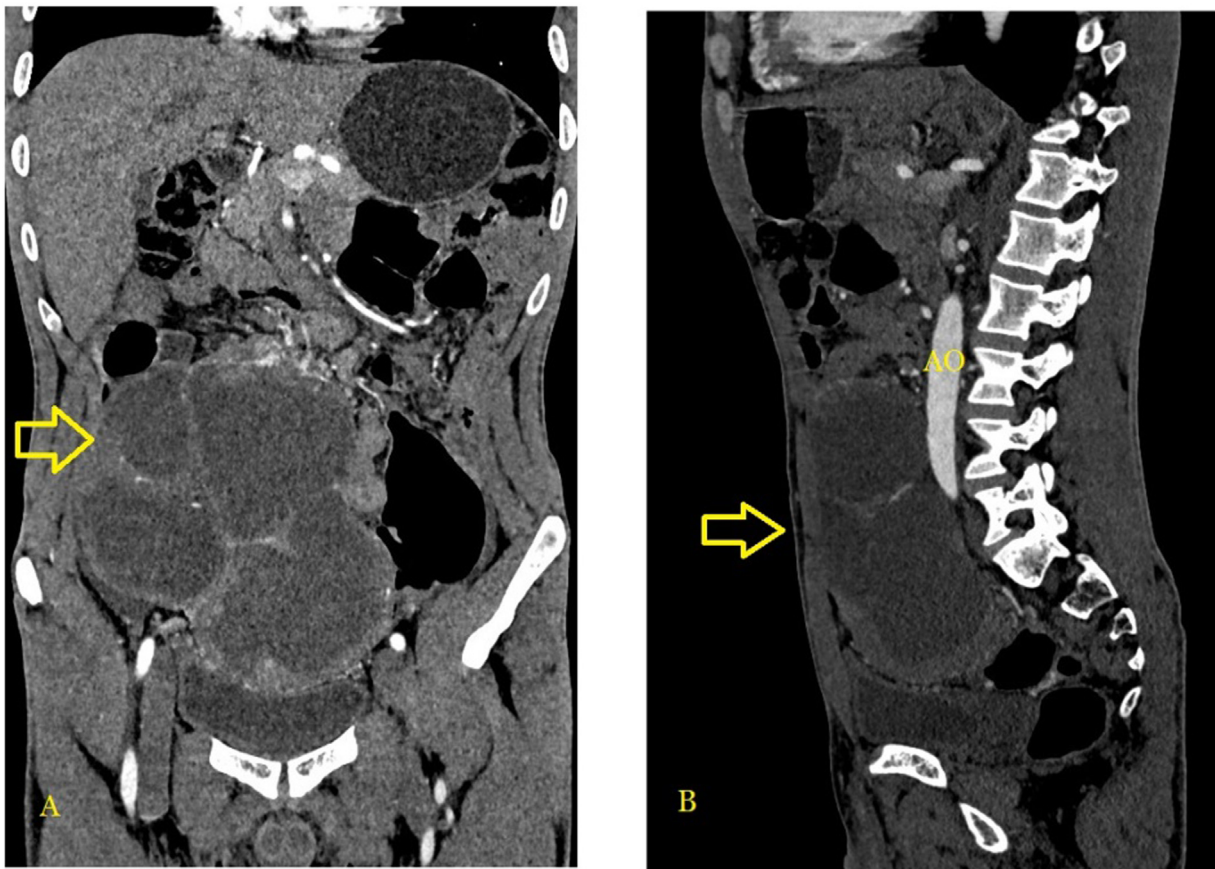


Fig. 6. Computed tomography images (coronal and sagittal cut) showing the abdominal cystic mass mimicking a hydatid cyst of the abdomen.

2.2. Case N° 2

A 41 years old male patient, with no significant pathological history consulting the emergencies for Acute abdominal pain with a giant abdominal mass evolving for 04 months on clinical examination: dehydrated patient, with skin nodes: NF I, and ophthalmoscopic fundus examination confirmed typical lisch nodules; the biological check-up was completely normal the computed tomography objectified a cystic mass 13.9 * 16.5 cm, sticking nose into the aorta with no encroachment likely A hydatid peritoneal cyst (Fig. 6). At that stage no vital emergency was detected and the patient was scheduled for a midline laparotomy 2 days after being prepped and hydrated with isotonic saline solution. The open laparotomy discovered a giant cystic mass adherent to the small intestine and to the bladder with medium abundance ascites with no peritoneal nodules (Fig. 7 and 8). The complete Resection of the mass with the intestinal bowl invaded using a linear cutter with 3D staples (NTLC © Ethicon) was done but tricky when we had to dissect it from the bladder and the Aorta with no iatrogenic lesions. The histopathology study finds a GIST of 18 cm with high metastatic risk according to the classification of Miettinen (Fig. 9). The patient undergoing an adjuvant imatinib therapy, at 08 months follow up with no signs of recurrence.

3. Discussion

A germline mutation of the tumor suppressor gene NF1 on chromosome 17 in one allele causes NF1, making it autosomal dominant however for tumor genesis, and function somatic loss in the second allele is necessary. These patients bear a higher predisposition for malignancies including GISTs, breast cancer, neuroendocrine

tumors etc [2]. A French study (Cales & al 2017) evaluating the prevalence of malignancies amongst 300 patients with NF1 concluding to only 1 stromal intestinal tumor [3] and in a review of literature, neurofibromatosis and GISTs are only discussed as case reports.

In 2005, Yantiss & al studied molecular features of 03 patients with multiples GISTs and NF1 trying to identify distinctive morphologic characteristics of these tumors within NF1 population; this study has shown that morphology and immunochemistry are identical both in sporadic and NF1 GIST patients but most GISTs don't have the same molecular abnormalities compared in both categories theorizing active KIT mutations in some patients with NF1, that is not yet confirmed [4].

From a clinical perspective, GISTs are very heterogenic, they can be symptomatic causing chronic or acute abdominal pain, gastrointestinal bleeding, rarely and bowel obstruction or asymptomatic and incidentally discovered [1]. Furthermore, it's variant radiological features make the diagnosis challenging as for small and bigger GISTs, CT scan and magnetic resonance imaging (MRI) are specifically useful in case of small intestine tumors and extra-GISTs (EGIST) where the endoscopy is not accessible. Contrast enhancing is moderate to heterogeneous depending on the tumor size, with central necrosis in large tumors. MRI is used for pelvic tumors, liver metastasis or incapacity for intravenous contrast product [5,1].

According to the European society, National Thesaurus of Digestive Cancerology (TNCD), CT scan is recommended for studying tumors characteristics and extensions, endoscopic ultrasonography (EUS), MRI and positron emission tomography (PET-scan) are optional [6].

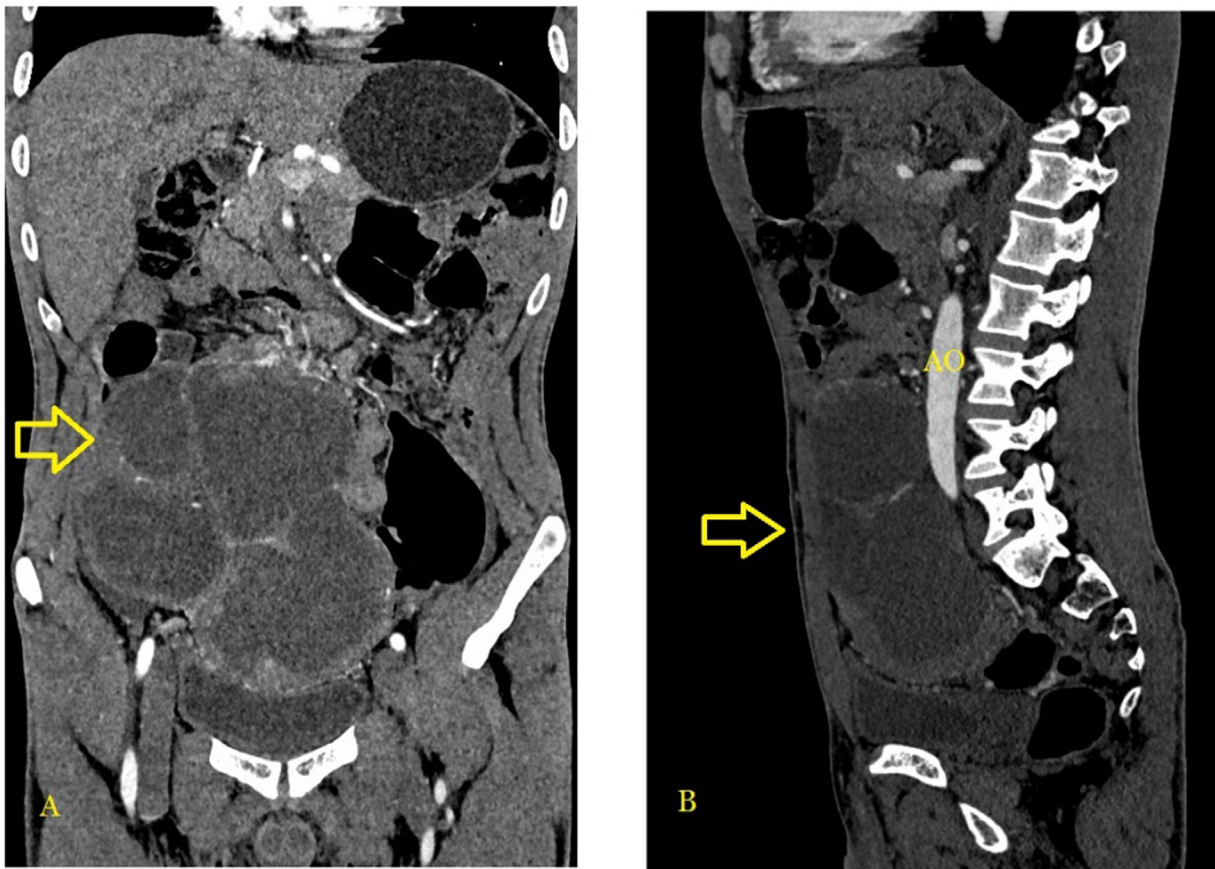


Fig. 7. Preoperative image showing the first look at the cystic tumor after the open abdomen.

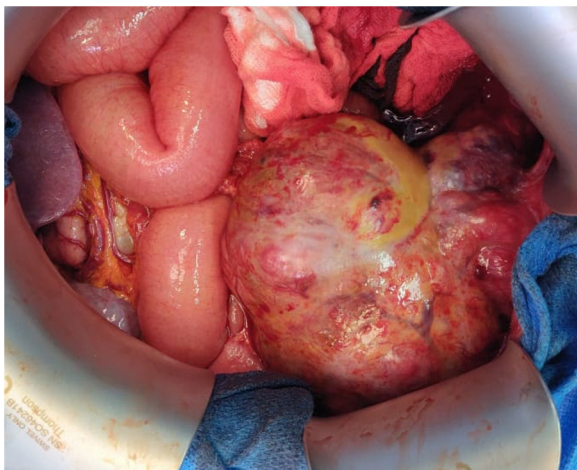


Fig. 8. Specimen after complete resection of the cystic mass.



Fig. 9. Microscopic images of the histological and immunohistochemistry study of the cystic mass showing its real origin: A stromal tumor of the small intestine.

Preoperative histological diagnosis is not mandatory when the tumor is resectable. Conversely, if the tumor is unresectable or inoperable patient; a fine needle aspiration (FNA) or a percutaneous CT-guided biopsy would be needed especially for administering neoadjuvant therapies [7].

Immunohistochemical markers distinguish GISTs from other gastrointestinal tumors (leiomyoma leiomyosarcoma, schwannoma, malignant melanoma, malignant peripheral nerve sheath tumor, myofibroblastic tumor, carcinoid tumor), with overexpression of CD117; a receptor of tyrosine kinase KIT ; found to be positive in nearly 90 % of GISTs, however an amount of tumors

Table 1

Follow up recommendations according to the French Intergroup Clinical Practice Guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO).

Risk / follow up	Recommendation options	
High	On adjuvant imatinib	3–6 months (3 years)
	After adjuvant imatinib	3 months (2 years)
		6 months (3 years)
		12 months (05 years)
Moderate	Without adjuvant imatinib	3–6 months (3 years)
		Every 06 months (2 years)
		12 months (05 years)
Low	6–12 months (05 years)	
Very low	No systematic follow up	

are CD117 negative, making it a non-definitive diagnostic marker; hopefully GISTs are found to express DOG-1 and PFC-theta [1].

National institutes of health (NIH) modified classification for risk stratification and AFIP: Armed Forces Institute of Pathology classification according to Miettinen and Lasota are the most used nowadays for localized GISTs defined by size, mitotic index, and tumor site Evaluated as low, moderate or high risk of recurrences [8,9].

Surgery is the main treatment for non-metastatic tumors performing a complete R0 resection of the tumor; however a retrospective study (Pantuso & al 2019) highlighted that positive microscopic margins R1 has no influence on the overall survival and the recurrence free survival, hence a R1 surgery can be fulfilling when R0 resection implies major functional consequences [10]. Since the arrival of tyrosine-kinase inhibitor with imatinib on the head of the list as adjuvant after surgery for moderate and high risk of recurrence or in neoadjuvant for non resectable or metastatic tumors has proven their efficiency with a gain of 13 months of median survival (Otani & al 2006) [11] and also the emerging of second line (Sunitinib) and third line (Regorafenib) therapies for resistant or intolerant GISTs validated in III phase studies [12,13], in 2014 coreless et al. studied 645 patients ; 328 patients assigned to the placebo arm and 317 to the imatinib arm for 74 months concluding that genotype don't interfere with recurrence free survival (RFS) but the size and site of the tumor along with mitotic rate influenced the RFS ; especially patients with KIT exon 11 deletion had a longer RFS after 1 year of imatinib [14].

Recurrences after primal surgery can occur at any site but mainly in the liver or the peritoneum; and they are most likely to appear in the range of 3 years to 5 after surgery or adjuvant therapy been completed. Unfortunately; due to lacking data or consensus; follow up and monitoring protocol are not standardized, but the French guidelines proposes at least an annual clinical examination and abdominal CT imaging and an optional close follow up for high risk patients or undergoing adjuvant therapies (Table 1) [6].

4. Conclusion

Curative surgery is the gold standard treatment for GISTs with R0 resection, microscopic margin R1 are an alternative to borderline GISTs. But in multiple GISTs with NF1, multiples surgeries for multiples recurrences or multiples localization might be needed, which imposes a furthermore study of this subpopulation of GISTs and a precise molecular identification that could lead to a new era of adjuvant or neoadjuvant therapies.

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Ethical approval

It's a one case report needing no ethnical approval.

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.

Author's contribution

F. Rahou: fatima zahra rahou: fatimazrahou@gmail.com (corresponding author), general surgery resident.

Have written the article, Have consulted the patient, prescribed all of the tests and prepared the patient for surgery and participated in the surgery.

A. Miry: Achraf Miry: achrafmiry@outlook.com (anatomopathology resident): have helped writing the article, confirm the histological diagnosis.

A. Bennani: Amal bennani: (anatomopathology professor): confirm the histological diagnosis.

M. Bouziane: Mohammed bouziane: bouzianemohammed@hotmail.com (oncology surgery professor): have supervised the writing of the paper, and has been the leader surgeon of the case).

Guarantor

M. Bouziane: Mohammed bouziane: bouzianemohammed@hotmail.com (oncology surgery professor).

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Declaration of Competing Interest

No conflict of interest.

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