Received: 25 December 2022 | Revised: 3 May 2023 | Accepted: 23 May 2023

DOI: 10.1002/ccr3.7463

CASE REPORT

Clinical Case Reports Open Access WILEY

Pathologic complete response to neoadjuvant imatinib of a gastric stromal tumor with concomitant mutations in *KIT*: A case report and literature review

Mariem Ben Rekaya[1,2] | **Feryel Ksontini**[3] | **Linda Bel Haj Kacem**[1,2] | **Farah Sassi**[2] | **Emna Harigua-Souiai**[4] | **Ryma Boujneh**[3] | **Ahmed H'mayada**[1] | **Yosra Zaimi**[5] | **Mouna Ayadi**[3] | **Mediha Trabelsi**[6] | **Ridha Mrad**[6] | **Soumaya Rammeh**[1,2]

[1]Theranostic Biomarkers, UR17ES15, Faculty of Medicine of Tunis, Université Tunis El Manar, Tunis, Tunisia

[2]Pathology Department, Charles Nicolle Hospital, Tunis, Tunisia

[3]Medical Oncology Department, Salah Azaiez Institute, Tunis, Tunisia

[4]Laboratory of Molecular Epidemiology and Experimental Pathology – LR16IPT04, Institut Pasteur de Tunis, Université de Tunis El Manar, Tunis, Tunisia

[5]Gastroenterology Department, Charles Nicolle Hospital, Tunis, Tunisia

[6]Department of Hereditary and Congenital Disorders, Charles Nicolle Hospital, Tunis, Tunisia

Correspondence
Farah Sassi, Pathology Department, Charles Nicolle Hospital, Tunis, Tunisia
Email: sassi.farah@outlook.fr

Key clinical message

We report the first case of pathologic complete response (pCR) to neoadjuvant imatinib in a gastric stromal tumor harboring *KIT* mutations in both exons 11 and 9. The significance of this co-occurrence is unknown and might increase the responsiveness of gastrointestinal stromal tumors (GISTs) to imatinib.

Abstract

pCR of GIST to neoadjuvant imatinib is rare. We report a case of pCR to neoadjuvant imatinib in a gastric stromal tumor that harbored co-occurrence of multiple *KIT* mutations in exons 11 and 9. This co-occurrence in exons 9 and 11 is the first to be reported in the English literature.

KEYWORDS

imatinib, KIT, mutation, pathologic complete response, PDGFRA

1 | INTRODUCTION

The gastrointestinal stromal tumors "GISTs" are driven in 90% of cases by somatic mutations in the proto-oncogene receptor tyrosine kinase *KIT* also known as (C-*KIT*, CD117) or the platelet-derived growth factor receptor alpha *PDGFRA* also known as (CD140A, PDGFR2). These two genes are located in the same chromosomal region 4q2, and code for the same sub-family of proteins within the family of receptor tyrosine kinases.[1] Most primary *KIT* mutations in GISTs occur in exon 11 or exon 9, and rarely in the exons 13, 14, or 17. However, *PDGFRA* mutations are most often in exon 18 (mainly the p.D842V substitution) and rarely exon 12. *KIT* and *PDGFR* inhibition is the primary therapeutic modality for unresectable and metastatic GISTs.[2] Imatinib mesylate competes with ATP for the ATP-binding site of several receptor tyrosine kinases. It selectively blocks the activation of *KIT* and *PDGFR*

receptors.[3] GIST's pathologic complete response (pCR) after neoadjuvant imatinib therapy is rare and its molecular mechanisms are not well defined. Molecular findings of reported cases with pCR after neoadjuvant imatinib showed recurrent deletions that affect specific amino acid positions in *KIT* exon 11.[4] A recent study suggested that the mutation type and affected codon locations of *KIT* predict progression-free survival to first-line imatinib in GISTs.[5] In this study, we report a case of pCR of a locally advanced gastric stromal tumor treated by neoadjuvant imatinib and harboring concomitant mutations in exons 11 and 9 of the *KIT* gene. This co-occurrence has not been reported in the English literature.

2 | CASE REPORT

A 41-year-old woman with a family history of breast cancer in her mother at the age of 60, consulted for abdominal pain and recurrent diarrhea for 1 month. On clinical examination, there was nothing significant. Ultrasound and computed tomography (CT) scan revealed a solid mass of 9×10 cm with circumscribed contours and heterogeneous enhancement with central necrotic areas close to the small-gastric curvature filling the back cavity of the epiploons. The enhancement was moderate after injection of contrast with loss of the fatty safety border (Figure 1). These radiological features were suggestive of a gastric stromal tumor. Fibroscopy showed a submucosal process of the small subcardial curvature. Colonoscopy did not show any abnormality. The biopsy showed a spindle cell tumor related to a GIST with CD117 and DOG1 strong immuno-expression. There were no mitoses in the specimen that totalized 30 fields at high power magnification (Figure 2).

For molecular analysis, four FFPE sections of 10 µm thickness from the biopsy specimen were processed for DNA extraction using QIAmp DNA Mini *KIT* (Qiagen) according to the manufacturer's instructions. Specific primers were designed using the Primer3 software v. 0.4.0. The details of the primer sequences, their annealing temperatures and product sizes are shown in Table 1. Five targeted sequences were amplified by polymerase chain reaction (PCR) using the Qiagen hot start PCR *KIT*. PCR conditions were as follows: 94°C for 15 min, 40 cycles of 94°C for 1 min, 55°C for 35 s, 72°C for 45 s and finally 30 min at 72°C. PCR products were purified using the innuPREP PCR pure *KIT*. PCR sequencing was performed using the Big Dye V.3.1 Terminator *KIT* (Applied Biosystems). Sequencing reactions were purified using the reaction Wizard™ MagneSil™ Sequencing Reaction Clean-Up System and sequencing was performed in an ABI Prism 3500 sequencer (Applied Biosystems). The five hot spot regions, including the exons 9, 11, and 17 of *KIT* and 12 and 18 of *PDGFRA* and their flanking regions were analyzed.

Sequence analysis showed the co-occurrence of six coding and one intronic variation in the exons 9 and 11 of *KIT* gene. Exon 9 contained two variations: one was a missense variant, p.Ala502Asp not previously described and the other was an intronic variant predicted by mutation taster as a splice donor variant (c.1540+8T>A). For exon 11, there were five coding variants. Two are known, the

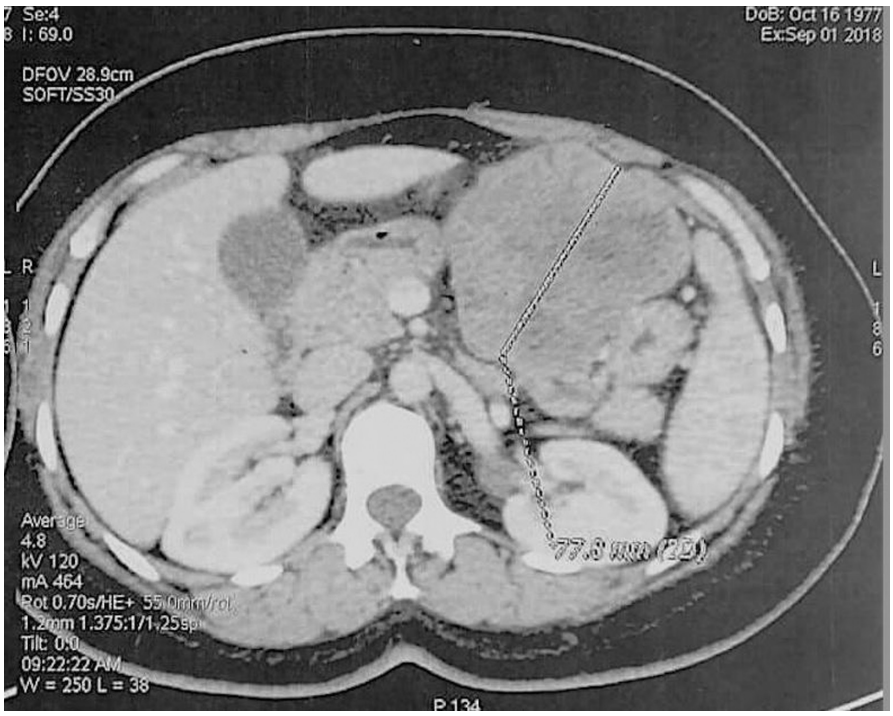

FIGURE 1 Abdominal CT scan injected at portal time showing a rounded mass with circumscribed contours and heterogeneous enhancement with central necrotic areas. The enhancement is moderate after injection of contrast. It is mainly exophytic at the expense of the small curvature of the stomach close to the body of the pancreas and the first jejunal intestines with loss of the fatty safety border.

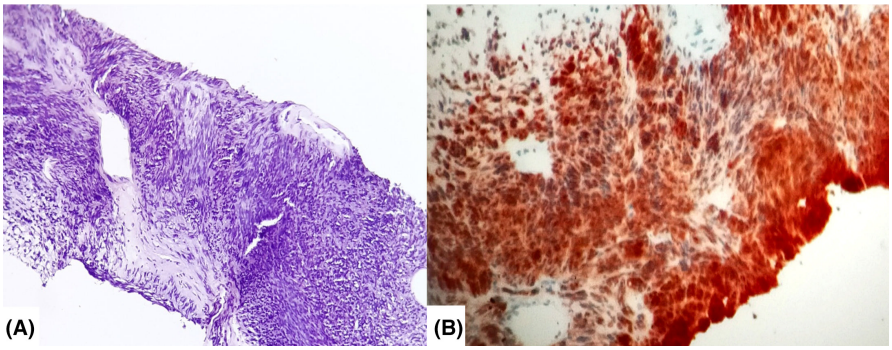

FIGURE 2 (A) Dense spindle cell proliferation (HE ×200). (B) Strong expression for c-KIT (IHC ×200).

TABLE 1 List of PCR primers for amplifying and Sanger sequencing of *KIT* exons 9, 11, 17, and *PDGFRA* exons 12 and 18.

Gene	Exon	Primer	Sequence 5′→3′	Ta	Product size
KIT	Exon 9	*KIT*9F	TCCTAGAGTAAGCCAGGGCTT	55	284 bp
		*KIT*9R	TGGTAGACAGAGCCTAAACATCC		
	Exon 11	*KIT*11F	GATCTATTTTTCCCTTTCTCC	55	174 bp
		*KIT*11R	AGCCCCTGTTTCATACTGAC		
	Exon 17	*KIT*17F	TACAAGTTAAAATGAATTTAAATGGT	55	228 bp
		*KIT*17R	AAGTTGAAACTAAAAATCCTTTGC		
PDGFRA	Exon 12	*PDGFRA*12F	TCCAGTCACTGTGCTGCTTC	55	260 bp
		*PDGFRA*12R	GCAAGGGAAAAGGGAGTCTT		
	Exon 18	*PDGFRA*18F	ACCATGGATCAGCCAGTCTT	57	247 bp
		*PDGFRA*18R	GGAGGATGAGCCTGACCAG		

Abbreviations: Ta, annealing temperature; bp, base pair.

Leu576Pro (rs121913513 or COSM1290) and the Pro577Ser (HGMDCI050498). Three have not been described: two were missense variants (Gln575Pro and Thr574Pro) and one was a silencing variant (c.1731T>C; Pro577Pro). All variations identified in *KIT* exon 17 and *PDGFRA* exon 12 were polymorphisms with neutral effects (Table 2).

Comparative modeling of the mutated KIT protein structure was performed using the Modeller software. The 1T46 PDB entry of the *KIT* structure co-crystallized with the STI-571 inhibitor (imatinib) was considered a template. The latter structure contains multiple truncated regions. It starts at residue Gly565 and ends at residue ASN933. Only mutations on the juxta-membranous (JM) domain were included (Thr574Pro, Gln575Pro, Leu576Pro, and Pro577Ser). The best scored model was further refined using the Galaxy Refine 2 tool. Then, structural alignment of the refined model and the reference structure 1T46 using PyMOL (Schrodinger, LLC. 2010) was performed. The mutated KIT model showed no conformational changes at the binding site of STI-571. Molecular docking of imatinib into its binding site on the 1T46 structure, then on the mutated KIT model using AutoDock 4.2 was performed. Input files of the receptors and ligand were prepared using AutoDock Tools. The crystal pose was re-obtained with estimated binding energy of −14.15 kcal/mol. The best docking pose on the mutated KIT model was −12.89 kcal/mol. Since the standard deviation of this scoring function was +/−2 kcal/mol, both docking scores were considered equivalent. This confirms that the mutations on the JM domain had little to no effect on the binding mode of imatinib on the KIT protein (Figure 3).

Surgical resection was not deemed feasible due to the tumor's large size and the potential for incomplete removal. The patient had a neoadjuvant treatment with imatinib (400 mg/day). Four months after the treatment, a 40% decrease in the volume of the mass and a decrease in its density higher than 15% on the CT scan were observed, which implied a good tumor response according to the CHOI criteria.[8] Seven months after the beginning of the treatment, there was a 10% additional decrease in the tumor size without change in its density (Figure 4). The patient underwent a subtotal gastrectomy with Finsterer gastro-jejunal anastomosis. The histopathological examination revealed total hyaline fibrous transformation of the GIST without viable residual tumoral cells. The surgical margins were free. Three weeks after surgery, imatinib treatment was continued in an adjuvant setting for a total of 3 years. The postoperative course was uneventful without any complications. After 48 months of follow-up, the patient was under treatment with good tolerance and with no recurrence.

TABLE 2 The HGVS annotation of identified somatic variants and in silico-predicted function.

Genes	Target regions	Genomic descriptions	Transcript descriptions	Protein descriptions	Types	Mutation taster prediction	Rs numbers/ Cosmic	Clin Var (references previously described the variant)
KIT	Exon 9	NC_000004.11:g.55592181C>A	NM_000222.2(*KIT*_ v001):c.1505C>A	NM_000222.2(*KIT*_ i001):p.(Ala502Asp)	Non synonyme	Disease causing	Unknown	Unknown
		NC_000004.11:g.55592224T>A	NM_000222.2:c.1540+8T>A	Protein features might be affected	Splice site changes Donor increased	Disease causing	Unknown	Unknown
	Exon 11	**1**-NC_000004.11:g.55593654A>C	NM_000222.2(*KIT*):c.1720A>C	NM_000222.2(*KIT*_i001):p .(Thr574Pro)	Non-synonymous	Disease causing	Unknown	Unknown
		2-NC_000004.11:g.55593658A>C	NM_000222.2:c.1724A>C	NM_000222.2(*KIT*_ i001):p.(Gln575Pro)	Non-synonymous	Disease causing	Unknown	Unknown
		3-NC_000004.11:g.55593661T>C	NM_000222.2(*KIT*_ v001):c.1727T>C	NM_000222.3(*KIT*_ i001):p.(Leu576Pro)	Non-synonymous	Disease causing	rs121913513 COSM1290	Likely pathogenic described at germinal and somatic levels[6–39]
		4-NC_000004.11:g.55593663C>T	NM_000222.2(*KIT*_ v001):c.1729C>T	NM_000222.3(*KIT*_ i001):p.(Pro577Ser)	Non-synonymous	Disease causing	COSM1293HGMD CI050498	Previously described in leukemia patients[7]
	C TJS EX11	**5**-NC_000004.11:g.55593665T>C	NM_000222.2(*KIT*_ v001):c.1731T>C	NM_000222.2(*KIT*_ i001):p.(=)	Synonymous	Disease causing with splice site effect	Unknown	No
	Exon 17	NC_000004.12:g.54733224C>A	NM_000222.2(*KIT*_ v001):c.2484+32C>A		Intronic	Polymorphism	Unknown	Unknown
			NC_000004.12:g.54733236A>T		Intronic	Polymorphism	Unknown	Unknown
			NC_000004.12:g.54733241C>A		Intronic	Polymorphism	rs201112416	Unknown
PDGFRA	Exon 12		NC_000004.11:g.55152143T>A	NG_009250.1(*PDGFRA*_ v001):c.2562+13T>A	Intronic	Polymorphism	Unknown	Unknown
			NC_000004.11:g.55152144T>A	NG_009250.1(*PDGFRA*_ v001):c.2562+14T>A	Intronic	Polymorphism	Unknown	Unknown
			NC_000004.11:g.55152148T>A	NG_009250.1(*PDGFRA*_ v001):c.2562+18T>A	Intronic	Polymorphism	Unknown	Unknown
			NC_000004.11:g.55152153G>C	NG_009250.1(*PDGFRA*_ v001):c.2562+23G>C	Intronic	Polymorphism	Unknown	Unknown
			NC_000004.11:g.55152154G>A	NG_009250.1(*PDGFRA*_ v001):c.2562+24G>A	Intronic	Polymorphism	Unknown	Unknown

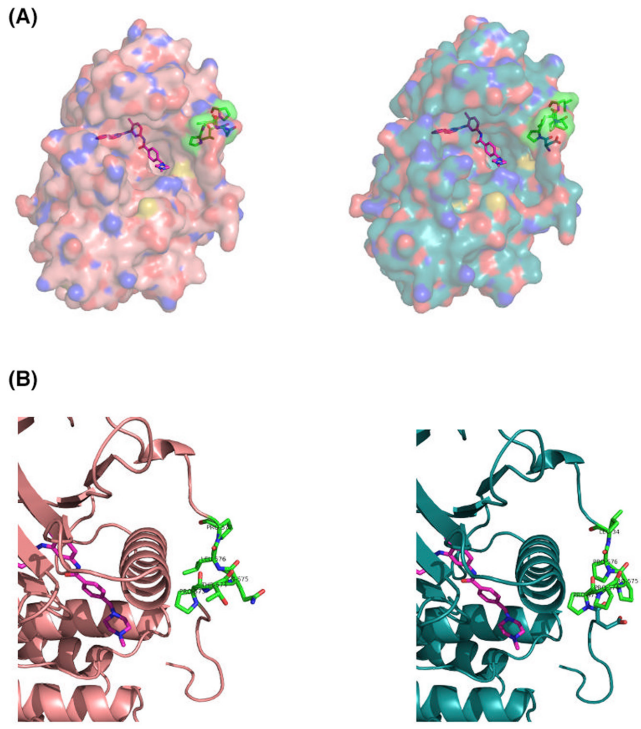

FIGURE 3 The structure of KIT protein. Panel (A) is a representation of the protein surface. On the left, the 1T46 structure and on the right the mutated KIT protein model. Panel (B) is a cartoon representation of the 1T46 (on the left) and the mutated KIT model (on the right) with a zoom on the mutated residues shown in green carbon licorice representation. The STI-571 molecule is shown in pink carbon licorice on all sub-figures.

3 | DISCUSSION

We report a case of a pCR to neoadjuvant imatinib of a gastric stromal tumor. Our literature review showed that there were only 33 reported GISTs with pCR after neoadjuvant imatinib.[4,9–25] Mutation analyses were reported in 16 of these cases. All reported cases had deletion mutations that affected residues between 550 and 559 positions (Table 3). Only one case had co-existence of two mutations in exon 11: deletion of residues 558 to 559 and missense mutation W557C.[18] Our case displayed substitution mutations that affected codons 574, 575, 576, and 577 in exon 11 and one mutation that affected codon 502 in exon 9. Both mutations in exon 11, that encode for the JM, and mutations in exon 9, that encode for the extracellular domain of *KIT*, allow receptor dimerization in the absence of a ligand, thus resulting in a conformational change that relieves the suppression of the activation loop of the kinase domain.[26] In our case, the co-occurrence of sensitive mutations might increase imatinib sensitivity and explain the pCR. But we cannot determine if mutations were cis (in the same allele) or trans (in different alleles) in distinct clones within the same tumor or in the same tumor cell.

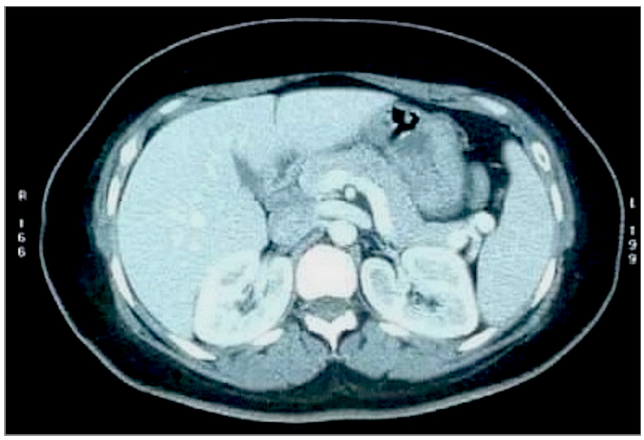

FIGURE 4 The postoperative CT scan at portal time shows 50% regression of the mass syndrome with only minimal fat infiltration remaining.

Two mutations (Leu576Pro, rs121913513, COSM1290) and (Pro577Ser, COSM1293, HGMD CI050498), determined in our case, have been previously described. The Leu576Pro mutation has been found in many cancers, mainly in GISTs,[27] leukemia cells,[7] melanomas[27] and thymic carcinomas.[28] Pro577Ser mutation has been found in melanomas and at germinal level in leukemic patients, but not in GISTs.[7]

All variations found in the present case in *PDGFRA* were polymorphisms without any functional effect. It is currently admitted that mutations of *KIT* and *PDGFRA* are mutually exclusive in primary untreated GISTs.[29] Mutations in *KIT* exon 11 lead to destabilization of the JM domain, which tends toward a more extensive conformation and can no longer exercise its regulatory activity. The kinase is then activated constitutively independently of its ligand; although a small proportion of kinase remains in self-inhibiting conformation because the mutations are in the heterozygous state.[30]

Molecular modeling of the four concomitant mutations in this study suggests that the effect of the mutations of the JM domain on STI-571 efficacy is indirect. These mutations would infer a series of four consecutive prolines at the sequence level: a Pro573 (non-mutated) followed by three Proline residues at positions 574, 575, 756 (mutated). Prolines are underrepresented in proteins, but are frequent mutations that increase protein stability.[31] Multiple (3 or more) prolines incur a specific rearrangement on the protein surface. In the case of KIT, this may lead to stabilizing the JM domain in a conformation favorable for STI-571 binding. Such Proline-induced molecular mechanisms have been described in other systems.[32]

The therapeutic response of GISTs harboring multiple driver concomitant mutations in the same gene is not well known. A recent study found that a cell line of non-small-cell lung cancer with two copies of EGFR mutations was

TABLE 3 Literature review of gastrointestinal stromal tumors with imatinib pathologic complete response.

Reference	Number of patients	NAD (m)*	Resected (*n*)	pCR(*n*)	Site	Molecular findings
7	126	10	17	2	6 colon, 4 stomach, 6 small bowel, 1 unknown	NR**
8	90	12,2	12	1	42 stomach, 42 small bowel, 8 large bowel, 8 retroperitoneum	NR
9	1	6	1	1	Stomach	W557_V559delins *KIT* exon 11
10	1	13	1	1	Small bowel	NR
11	180	12	22	2	Rectum	NR
43	141	14	32	3	NR	NR
13	1		1	1	Stomach	NR
14	1	12	1	1	Rectum	6 pb deletion in *KIT* exon11
15	46	12.9	11	1	NR	NR
16	2	2	2	1	Rectum	*KIT* exon 11 deletion of residues 558 to 559 and W557C
17	1	2,5	1	1	Rectum	NR
18	1	18	1	1	Rectum	NR
19	9	1–6	6	1	Rectum	NR
20	1	18	1	1	Stomach	NR
21	1	10	1	1	Extra intestinal location	NR
22	1	NR	1	1	Extra-gastrointestinal stromal tumor (rectum and bladder)	NR
4	171	12.5/4.4–62.4	26	12	9 stomach, 11 small bowel, 5 colon-rectum, 1 other	*KIT* deletion mutation at codons 550–558 in exon 11 in all 12 patients
23	1	6	1	1 Near pCR (viable cells <5%)	Large gastric (cardia, distal pancreas, and splenic hilum)	K558 deletion of *KIT* exon 11
This study	1	7	1	1	Stomach	Exon 9:Ala502Asp; Exon 11:Thr574Pro, Gln575Pro, Leu576Pro, Pro577Ser

Abbreviation: pCR, pathologic complete response.

*NAD (m), median duration of neoadjuvant imatinib in months.; **NR, Not reported.

markedly more sensitive to EGFR-TKIs compared with parent cells with KRAS mutation alone and suggests that the presence of concomitant EGFR mutations affects the TKI response.[33] Studies, using high-throughput sequencing and deep sequencing, reclassified considered wild-type GISTs as *KIT* or *PDGFRA* mutated[34] and identified concomitant mutations in two downstream effectors: BRAF and FGFR3 in *KIT* mutated tumors and PIK3CA and KRAS in *KIT*/*PDGFRA* wild-type GISTs.[35] Braggio and al.[36] identified complex mutations with five concomitant in-frame deletions and insertions and one in-frame deletion plus missense mutation in exon 11 of *KIT* that mainly affected codons 577 and 578 and suggested that GISTs with complex deletion and insertion *KIT* mutations have poor prognosis.[36] A recent study showed the aggressive biology of mutation of codons 557/558 deletions/delins of exon 11 than downstream or upstream mutations of these codons in the metastatic setting and allow for prediction at the baseline, which GIST patients would develop resistance to first line imatinib treatment earlier. Additionally, patients with deletions or disinsertion regardless of codon regions, had a significantly better complete response rate

(557/558: 40%; other codons: 37.5%) compared to patients with other pathogen variants.[5] Complete clinical response and pCR in GISTs are rare and more evidence is needed to indicate watch and wait strategy. Surgery remains the standard of care in resectable forms. Nevertheless, watch and wait could be an option in particular cases such as elderly with co-morbidities, strong wishes for "wait-and-see", or in long surgery waiting lists.[37]

Imatinib-sensitive biomarkers of GISTs: KIT expression (CD117), *KIT* mutations in exons 9 and 11, *PDGFRA* mutations in exons 12 and 18. However, resistance biomarkers are *BRAF* mutation,[38] secondary mutation in the ATP binding domain or the activation-loop domain of *KIT* (exon 13 and 14 and rarely 17),[39] or codon 842 in exon 18 of *PDGFRA*, over expression of KIT in Neurofibromatosis Type 1 associated GIST cells and loss of KIT expression[6] accompanied by activation of alternative pathways. To improve patient's management, a thorough assessment of all potential causes and mechanisms influencing the imatinib response is crucial.

4 | CONCLUSION

We report a case of pCR to neoadjuvant imatinib in a gastric stromal tumor that harbored co-occurrence of multiple *KIT* mutations in exons 11 and 9. This co-occurrence has not previously been described. Its significance is unknown. It might increase the responsiveness of GISTs to imatinib.

AUTHOR CONTRIBUTIONS

Mariem Ben Rekaya: Conceptualization; formal analysis; investigation; methodology; writing – original draft. **feryel ksontini:** Conceptualization; investigation; supervision. **Linda Belhadj kacem:** Investigation. **Farah Sassi:** Methodology; writing – original draft; writing – review and editing. **Emna Harigua-Souiai:** Investigation; supervision; writing – original draft. **Ryma Boujneh:** Resources; supervision. **Ahmed H'mayada:** Conceptualization; investigation; methodology; resources. **Yosra Zaimi:** Resources. **mouna ayadi:** Investigation; supervision. **Mediha Trabelsi:** Formal analysis; investigation. **Ridha Mrad:** Conceptualization; investigation; methodology. **Soumaya Rammeh:** Supervision; validation; writing – original draft; writing – review and editing.

FUNDING STATEMENT

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

Not applicable.

CLINICAL TRIAL REGISTRATION

Not applicable.

ORCID

Farah Sassi https://orcid.org/0000-0003-2078-6795

REFERENCES

1. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. *Histopathology*. 2008;53(3):245-266.
2. Desai J. Response assessment in gastrointestinal stromal tumor. *Int J Cancer*. 2011;128(6):1251-1258.
3. Kee D, Zalcberg JR. Current and emerging strategies for the management of imatinib-refractory advanced gastrointestinal stromal tumors. *Ther Adv Med Oncol*. 2012;4(5):255-270.
4. Cheng C, Tsai C, Yeh C. Clinical significance of pathological complete response in patients with metastatic gastrointestinal stromal tumors after imatinib mesylate treatment—lessons learned. *Anticancer Res*. 2014;34:6617-6625.
5. Incorvaia L, Fanale D, Vincenzi B, et al. Type and gene location of KIT mutations predict progression-free survival to first-line imatinib in gastrointestinal stromal tumors: a look into the exon. *Cancers (Basel)*. 2021;13(5):933.
6. Mearadji A, den Bakker MA, van Geel AN, et al. Decrease of CD117 expression as possible prognostic marker for recurrence in the resected specimen after imatinib treatment in patients with initially unresectable gastrointestinal stromal tumors: a clinicopathological analysis. *Anticancer Drugs*. 2008;19(6):607-612.
7. Hussain SR, Babu SG, Naqvi H, Singh P, Mahdi F. The frequency of mutations in exon 11 of the c-kit gene in patients with leukemia. *Turk J Haematol*. 2012;29(1):10-16.
8. Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol*. 2007;25(13):1753-1759.
9. Scaife CL, Hunt KK, Patel SR, et al. Is there a role for surgery in patients with "unresectable" cKIT+ gastrointestinal stromal tumors treated with imatinib mesylate? *Am J Surg*. 2003;186(6):665-669.

10. Bauer S, Hartmann JT, de Wit M, et al. Resection of residual disease in patients with metastatic gastrointestinal stromal tumors responding to treatment with imatinib. *Int J Cancer*. 2005;117(2):316-325.
11. Melichar B, Voboril Z, Nozicka J. Pathological complete response in advanced gastrointestinal stromal tumor after imatinib therapy. *Intern Med*. 2005;44:1163-1168.
12. Chacón M, Roca E, Huertas E, Loria FS, Domenechini E. Dramatic responses to therapy in rare tumors. *J Clin Oncol*. 2005;23(7):1580-1582.
13. Bonvalot S, Eldweny H, Péchoux CL, et al. Impact of surgery on advanced gastrointestinal stromal tumors (GIST) in the imatinib era. *Ann Surg Oncol*. 2006;13(12):1596-1603.
14. Rutkowski P, Gronchi A, Hohenberger P, et al. Neoadjuvant imatinib in locally advanced gastrointestinal stromal tumors (GIST): the EORTC STBSG experience. *Ann Surg Oncol*. 2013;20(9):2937-2943.
15. Suzuki S, Sasajima K, Miyamoto M, et al. Pathologic complete response confirmed by surgical resection for liver metastases of gastrointestinal stromal tumor after treatment with imatinib mesylate. *World J Gastroenterol*. 2008;14(23):3763-3767.
16. Salazar M, Barata A, André S, et al. First report of a complete pathological response of a pelvic GIST treated with imatinib as neoadjuvant therapy. *Gut*. 2006;55(4):585-586.
17. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with imatinib. *Ann Surg Oncol*. 2007;14(1):14-24.
18. Mandalà M, Pezzica E, Tamborini E, et al. Neoadjuvant imatinib in a locally advanced gastrointestinal stromal tumour (GIST) of the rectum: a rare case of two GISTs within a family without a familial GIST syndrome. *Eur J Gastroenterol Hepatol*. 2007;19(8):711-713.
19. Hou YY, Zhou Y, Lu SH, et al. Imatinib mesylate neoadjuvant treatment for rectal malignant gastrointestinal stromal tumor. *World J Gastroenterol*. 2009;15(15):1910-1913.
20. de Azevedo C, Paiva T, Rossi B. Pathologic complete response with neoadjuvant imatinib for locally advanced pelvic GIST. *Int J Clin Oncol*. 2011;16:279-283.
21. Machlenkin S, Pinsk I, Tulchinsky H, et al. The effect of neoadjuvant imatinib therapy on outcome and survival after rectal gastrointestinal stromal tumour. *Colorectal Dis*. 2011;13(10):1110-1115.
22. El Mesbahi O, Brahmi SA, Akasbi Y, et al. Pathological complete response in advanced gastric stromal tumor after imatinib mesylate therapy: a case report. *J Med Case Reports*. 2011;5:197.
23. Quezada N, Acevedo F, Marambio A, et al. Complete pathological response to imatinib mesylate in an extraintestinal gastrointestinal stromal tumor. *Int J Surg Case Rep*. 2014;5(10):681-685.
24. Rediti M, Pellegrini E, Molinara E, et al. Complete pathological response in advanced extra-gastrointestinal stromal tumor after imatinib mesylate therapy: a case report. *Anticancer Res*. 2014;34(2):905-907.
25. Brown JB, Pai RK, Burgess MA, Chennat J, Zureikat AH. Pathologic complete response in a large gastric GIST: using molecular markers to achieve maximal response to neoadjuvant imatinib. *J Natl Compr Canc Netw*. 2018;16(12):1424-1428.
26. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. *Nat Rev Cancer*. 2011;11(12):865-878.
27. Lasota J, Kowalik A, Felisiak-Golabek A, et al. Primary malignant melanoma of esophagus: clinicopathologic characterization of 20 cases including molecular genetic profiling of 15 tumors. *Mod Pathol*. 2019;32(7):957-966.
28. Yoh K, Nishiwaki Y, Ishii G, et al. Mutational status of EGFR and KIT in thymoma and thymic carcinoma. *Lung Cancer*. 2008;62(3):316-320.
29. Mei L, Smith SC, Faber AC, et al. Gastrointestinal stromal tumors: the GIST of precision medicine. *Trends Cancer*. 2018;4(1):74-91.
30. Chan PM, Ilangumaran S, La Rose J, Chakrabartty A, Rottapel R. Autoinhibition of the kit receptor tyrosine kinase by the cytosolic juxtamembrane region. *Mol Cell Biol*. 2003;23(9):3067-3078.
31. Trevino SR, Schaefer S, Scholtz JM, Pace CN. Increasing protein conformational stability by optimizing beta-turn sequence. *J Mol Biol*. 2007;373(1):211-218.
32. Gaddie KJ, Kirley TL. Proline residues link the active site to transmembrane domain movements in human nucleoside triphosphate diphosphohydrolase 3 (NTPDase3). *Purinergic Signal*. 2010;6(3):327-337.
33. Tsukumo Y, Naito M, Suzuki T. Influence of EGFR-activating mutations on sensitivity to tyrosine kinase inhibitors in a KRAS mutant non-small cell lung cancer cell line. *PLoS One*. 2020;15(3):e0229712.
34. Astolfi A, Indio V, Nannini M, et al. Targeted deep sequencing uncovers cryptic KIT mutations in KIT/PDGFRA/SDH/RAS-P wild-type GIST. *Front Oncol*. 2020;10:504.
35. Mavroeidis L, Metaxa-Mariatou V, Papoudou-Bai A, et al. Comprehensive molecular screening by next generation sequencing reveals a distinctive mutational profile of KIT/PDGFRA genes and novel genomic alterations: results from a 20-year cohort of patients with GIST from North-Western Greece. *ESMO Open*. 2018;3(3):e000335.
36. Braggio E, Braggio Dde A, Small IA, et al. Prognostic relevance of KIT and PDGFRA mutations in gastrointestinal stromal tumors. *Anticancer Res*. 2010;30(6):2407-2414.
37. Li Y, Chen X, Ma X, Lu X. Computed tomography in the size measurement of gastric gastrointestinal stromal tumors: implication to risk stratification and "wait-and-see" tactics. *Eur J Surg Oncol*. 2022;48(8):1739-1745.
38. Agaram NP, Wong GC, Guo T, et al. Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. *Genes Chromosomes Cancer*. 2008;47(10):853-859.
39. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res*. 2005;11(11):4182-4190.

How to cite this article: Rekaya MB, Ksontini F, Kacem LBH, et al. Pathologic complete response to neoadjuvant imatinib of a gastric stromal tumor with concomitant mutations in *KIT*: A case report and literature review. *Clin Case Rep*. 2023;11:e7463. doi:10.1002/ccr3.7463