ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2019 December 26; 7(24): 4172-4425

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Semimonthly

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https://www.wjgnet.com/2307-8960/editorialboard.htm

EDITORIAL OFFICE
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PUBLICATION DATE
December 26, 2019

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World J Clin Cases 2019 December 26; 7(24): 4398-4406

DOI: 10.12998/wjcc.v7.i24.4398

ISSN 2307-8960 (online)

CASE REPORT

KIT and platelet-derived growth factor receptor α wild-type gastrointestinal stromal tumor associated with neurofibromatosis type 1: Two case reports

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Author contributions: Wang Z and Kou YW conceived the study concept, conducted the analyses, and drafted the manuscript; Wang Z and Fu YP collected clinical samples and analyzed clinical data; Zhang Y performed and analyzed DNA sequencing experiments; Fu YP assisted with figures and experimental design; Wang Z and Kou YW developed the theoretical frameworks, interpreted data, and critically reviewed the manuscript; All authors read and approved the final manuscript.

Supported by National Natural Science Foundation of China, No. 81601692; Program of Liaoning Province Department of Education, No. LK2016002.

Informed consent statement: Consent was obtained from the patients.

Conflict-of-interest statement: The authors declare no conflict of interest.

CARE Checklist (2016) statement: The manuscript was revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

Gastrointestinal stromal tumors (GISTs) associated with neurofibromatosis are uncommon compared to their gastrointestinal counterparts. Patients with neurofibromatosis type 1 (NF-1) have an increased risk of developing gastrointestinal tumors, including rare types such as GIST.

CASE SUMMARY

A 60-year-old male Chinese patient was diagnosed with NF-1 10 years ago and presented with upper abdominal discomfort and black stools. Endoscopic ultrasonography and an enhanced abdominal computed tomography scan revealed a mass located 4 cm from the muscular layer of the descending duodenum. A 59-year-old Chinese woman who was diagnosed with NF-1 25 years ago presented with sudden unconsciousness and black stools. Multiple masses in the duodenum were noted by echogastroscopy and an enhanced abdominal computed tomography scan. Both patients presented with cutaneous neurofibromas. The histologic examination of tumors from both patients revealed spindle cells and low mitotic activity. Immunohistochemically, the tumor cells showed strong positivity for KIT (CD117), DOG-1, CD34, and Dehydrogenase Complex Subunit B, and negativity for SMA, desmin, S-100, and β-catenin. None of the six tumors from two patients had *KIT* exon 9, 11, 13, or 17 or *platelet-derived growth factor receptor a* exon 12 or 18 mutation, which is a typical finding for sporadic GISTs. None of the six tumors from the two patients had a *BRAFV600E* mutation. The patients were alive and well during the follow-up period (range: 0.6-5 yr).

Manuscript source: Unsolicited manuscript

Received: September 27, 2019
Peer-review started: September 27, 2019
First decision: November 19, 2019
Revised: November 22, 2019
Accepted: November 26, 2019
Published online: December 26, 2019

P-Reviewer: Bystrom P, Jaggi M
S-Editor: Wang JL
L-Editor: Filipodia
E-Editor: Liu JH

CONCLUSION
There have been only a few previous reports of GISTs associated with NF-1. Although GISTs associated with NF-1 have morphologic and immunohistochemical similarities with GISTs, the pathogenesis, incidence, genetic background, and prognosis are not completely known. A medical history of NF-1 in a patient who has gastrointestinal bleeding or anemia and an intra-abdominal mass with nonspecific computed tomography features may help in diagnosing GIST by virtue of the well-known association of these two entities. Molecular genetic studies of cases indicated that GISTs in NF-1 patients have a different pathogenesis than sporadic GISTs.

Key words: Neurofibromatosis; Gastrointestinal stromal; *KIT* and platelet-derived growth factor receptor α wild type; Molecular genetic studies; Neurofibromatosis type 1; Case report

Core tip: Gastrointestinal stromal tumors (GISTs) associated with neurofibromatosis are uncommon compared to their gastrointestinal counterparts. Here we reported two cases of *KIT* and platelet-derived growth factor receptor α wild-type GISTs with neurofibromatosis type 1. Although GISTs with neurofibromatosis type 1 have morphologic and immunohistochemical similarities with common GISTs, the pathogenesis, incidence, genetic background, and prognosis are not completely known. A medical history of neurofibromatosis type 1 in a patient who has gastrointestinal bleeding or anemia and an intra-abdominal mass with nonspecific computed tomography features may help in diagnosing GIST by virtue of the well-known association of these two entities.

Citation: Kou YW, Zhang Y, Fu YP, Wang Z. *KIT* and platelet-derived growth factor receptor α wild-type gastrointestinal stromal tumor associated with neurofibromatosis type 1: Two case reports. *World J Clin Cases* 2019; 7(24): 4398-4406
URL: https://www.wjgnet.com/2307-8960/full/v7/i24/4398.htm
DOI: https://dx.doi.org/10.12998/wjcc.v7.i24.4398

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms characterized by activating mutations in the related receptor tyrosine kinases [*KIT* and platelet-derived growth factor receptor α (*PDGFRA*)][1,2].

GISTs occur throughout the gastrointestinal tract. GISTs are twice as common in the stomach as the jejunum and ileum. GISTs are relatively rare in the duodenum, rectum, and elsewhere. GISTs usually occur in older adults (median age: 55–65 yr) and most cases are sporadic[2]. *KIT*-positive GISTs have been documented in connection with the neurofibromatosis type 1 (NF-1) tumor syndrome, and most gastrointestinal tract mesenchymal tumors in patients with NF-1 tumors previously interpreted as other tumor types were likely GISTs. The pathogenesis of GISTs with NF-1 is unclear. Data derived from a clinicopathologic and molecular genetics study of NF-1 patients with GISTs are scant[3,4].

In this study, we analyzed two cases of GISTs in NF-1 patients and reviewed the literature to develop a more complete understanding of the clinicopathologic profile, prognosis, and *KIT*, *PDGFRA*, *dehydrogenase complex subunit B* (*SDHB*), and *BRAF* mutation status.

CASE PRESENTATION

Chief complaints

Case 1: A 60-year-old man was admitted to our hospital due to upper abdominal discomfort and black stools for 10 d.

Case 2: A 59-year-old woman was admitted to our hospital due to gastrointestinal bleeding for 1 wk.

History of present illness

Case 1: Ten days prior to admission, the patient presented with upper abdominal discomfort and black stool.

Case 2: One week prior to admission, the patient presented with sudden unconsciousness when she ascended a flight of stairs. The patient subsequently had black stool. She was evaluated at a local hospital and underwent gastroscopy, which showed superficial gastritis and multiple duodenal protuberant lesions. Therefore, she was transferred to our hospital for further treatment.

History of past illness

Case 1: He had a 6-mo history of hypertension. The blood pressure was well-controlled with nifedipine sustained-release tablets. Resection of a cervical fibroma was performed 5 years ago.

Case 2: The patient did not have any history of hypertension, type 2 diabetes mellitus, or chronic gastric ulcer. The patient had no history of hepatitis or tuberculosis.

Personal and family history

Case 1: The patient was diagnosed with NF-1 10 years ago. All of his children (two males and one female) had neurofibromatosis, but no GISTs were demonstrated. The patient had no other significant past history or family history.

Case 2: The patient had neurofibromatosis and was diagnosed 25 years ago. Her brother and two children (one male and one female) had neurofibromatosis, but no GISTs were reported in her family. The patient had no other significant past history or family history.

Physical examination upon admission

Case 1: The patient's blood pressure and blood glucose were normal. His body temperature was normal 6 d before the operation. The physical examination did not reveal any abdominal masses, and the abdomen was non-tender with no rebound tenderness. There were numerous café-au-lait patches and multiple cutaneous neurofibromas involving the upper limbs and abdomen (Figure 1A). There were no abnormalities in the electrocardiogram, chest x-ray, or preoperative echocardiogram.

Case 2: The patient's blood pressure and blood glucose were normal. Her body temperature was normal 6 d before the operation. The physical examination did not reveal any abdominal masses, and the abdomen was non-tender with no rebound tenderness. There were numerous café-au-lait patches and multiple cutaneous neurofibromas on the upper limbs and abdomen (Figure 2A and B). There were no abnormalities in the electrocardiogram, chest x-ray, or preoperative echocardiogram.

Laboratory examinations

Case 1: Except for average hemoglobin and red blood cell level under normal value, other laboratory examinations were normal.

Case 2: Except for average hemoglobin and red blood cell level under normal value, other laboratory examinations were normal.

Imaging examination and operation

Case 1: Endoscopic ultrasonography revealed hypoechoic protuberant lesions of the proper muscular layer of the descending duodenum. An enhanced abdominal computed tomography (CT) scan showed a mass at the junction of the descending and horizontal duodenum that was highly suggestive of a stromal tumor (Figure 1B). The enhanced CT scan also showed subcutaneous nodules of the abdominal wall that were slightly hypodense and had no apparent enhancement.

Intra-operatively, a large (4.0 cm × 3.0 cm × 3.0 cm) basal mass, hard and growing outside the intestinal wall, was noted at the junction of the descending and horizontal duodenum. After completely dissociating the mass, a local duodenectomy, distal subtotal gastrectomy, and anterior gastrointestinal anastomosis were performed. Two subcutaneous tumors were removed at the same time. The operation was successful and the recovery was uneventful.

Case 2: A contrast-enhanced CT scan was performed and revealed multiple tumors in the initial segment of the duodenum and jejunum, suggesting a diagnosis of GISTs (Figure 2C). On the basis of the radiologic findings, the tumors were surgically

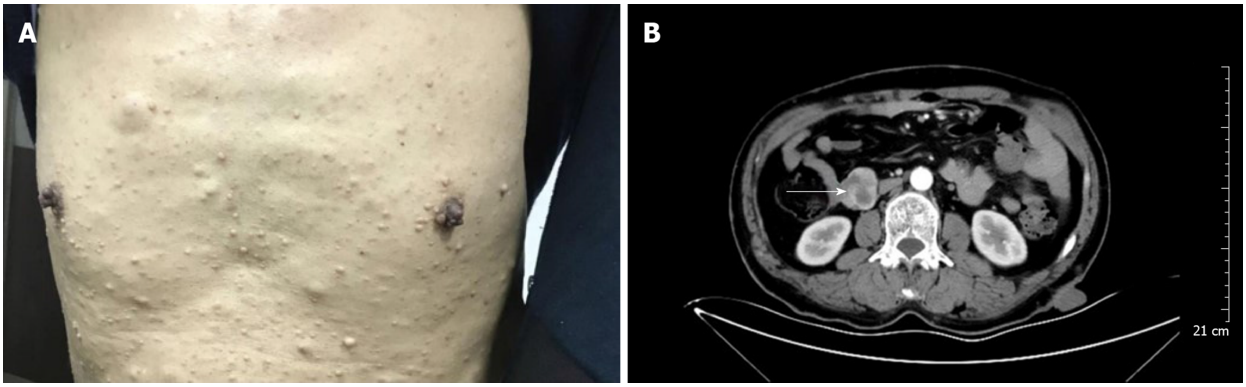

Figure 1 Multiple nodules from the skin and abdomen. A: Multiple nodules of varying sizes with brown spots are visible on the skin; B: Enhanced computed tomography of the abdomen showed a mass at the junction of the descending and horizontal duodenum (arrow), suggesting a diagnosis of a gastrointestinal stromal tumor.

excised during the operation (Figure 2D). One mass in the duodenum was located in the anterior wall of the bulbar junction with the following characteristics: 2 cm × 2 cm in size; exogenous type; and completely encapsulated. A larger mass in the small intestine was located approximately 40 cm away from the Treitz ligament (4 cm × 4 cm × 4 cm in size), accounted for 80% of the intestinal lumen, and was brown-tan in color with a hemorrhagic appearance. The cut section had the appearance of fish flesh. The other two masses (1.5 cm × 1 cm in size) were located approximately 15 cm away from the Treitz ligament. The duodenal neoplasms were resected, the duodenum was repaired, and a distal gastrectomy, Roux-Y anastomosis before the gastrointestinal-jejunal colon, partial intestinal resection, and excision of the intestinal wall tumors were performed. The operation was performed without complication. The postoperative recovery was uneventful.

Pathology diagnosis and molecular analysis

Case 1: Pathology diagnosis and molecular analysis were performed after the operation. Histologically, multiple nodules from skin were typically composed of relatively uniform long spindle cells. Immunohistochemical staining revealed the following: CD34 (+); VIM (+); S-100 (+); CK (-); EMA (-); SMA (-); desmin (-) and Ki67 (2%) (Figure 3).

Histologically, multiple tumors from the duodenum were typically composed of relatively uniform spindle-shaped cells. Immunohistochemical staining of the nodule from duodenum revealed: CD117 (+), DOG-1 (+), CD34 (+), SDHB (+), SMA (-), S-100 (-), desmin (-), β-catenin (-), and Ki67 (2%) (Figure 4).

No significant mitotic cells were found in the above tissues. *KIT*, *PDFGRA*, and *BRAFV600E* mutation status were analyzed in GIST tissues. None of the tumors had a *KIT* exon 9, 11, 13, or 17, *PDGFRA* exon 12 or 18, or *BRAFV600E* mutation (Figure 5).

Case 2: Pathology diagnosis and molecular analysis were performed after the operation. Histologically, the multiple tumors from the duodenum were typically composed of relatively uniform spindle cells. Immunohistochemical staining of the tumors revealed the following: CD117 (+), DOG-1 (+), CD34 (+), SDHB (+), SMA (-), S-100 (-), desmin (-), β-catenin (-), and Ki67 (2%) (Figure 6). Scant mitotic cells were noted in all of the above tissues. The mutation status of *KIT*, *PDFGRA*, and *BRAFV600E* were analyzed in tumors. None of the four tumors had a *KIT* exon 9, 11, 13, or 17, *PDGFRA* exon 12 or 18, or *BRAFV600E* mutation (Figure 5).

TREATMENT

Case 1

Imatinib treatment was not recommended post-operatively.

Case 2

Because the tumors were shown by molecular analysis to be wide-type GIST, the patient was not recommended for imatinib treatment post-operatively.

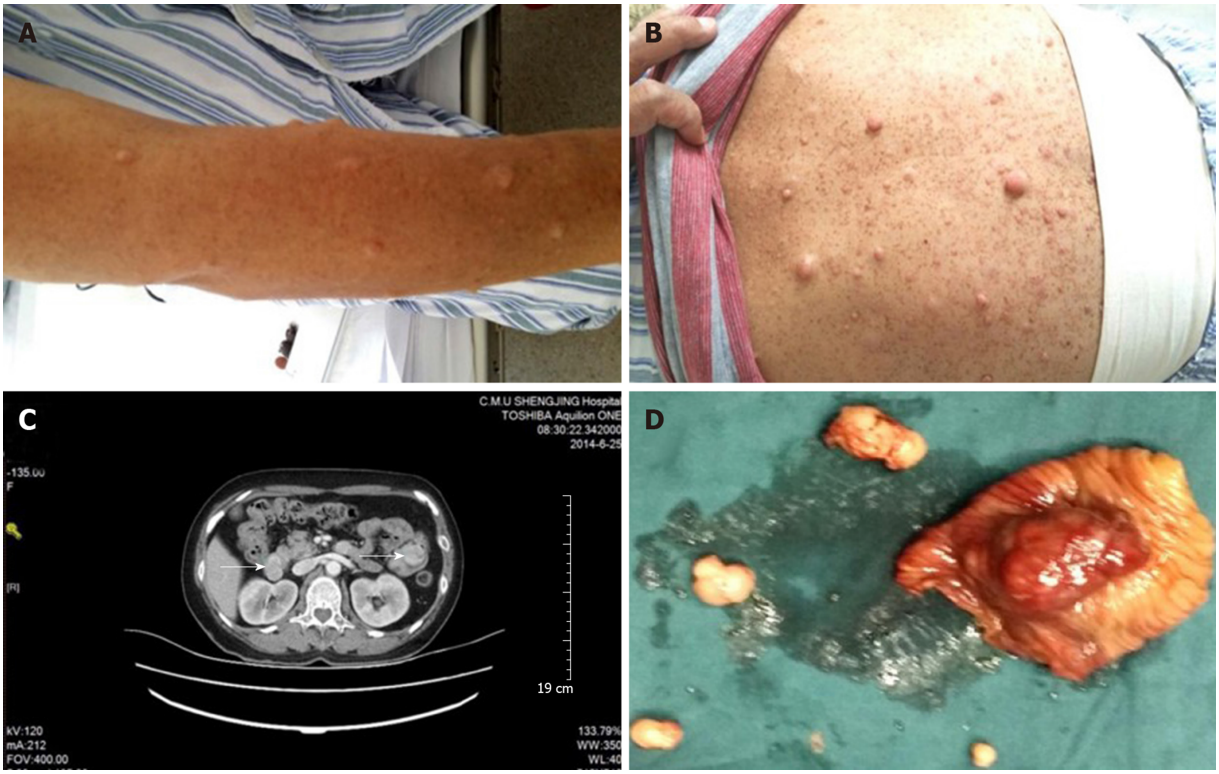

Figure 2 Multiple nodules from the skin and abdomen. A, B: Multiple nodules of varying sizes with brown spots are visible on the skin; C: Enhanced computed tomography of the abdomen showed multiple tumors in the initial segment of the duodenum and jejunum (arrows), suggesting a diagnosis of gastrointestinal stromal tumors; D: Gastrointestinal stromal tumor specimen.

OUTCOME AND FOLLOW-UP

Case 1

No tumor recurrence and metastasis were found on regular CT scan review after 0.6 years of follow-up.

Case 2

No tumor recurrence or metastasis was demonstrated on regular CT scan review after 5 years of follow-up.

DISCUSSION

NF-1 is the most common inheritable disease. The birth incidence is estimated to be 1:3000 *via* autosomal dominant transmission[5]. The underlying pathogenesis is thought to be based on biallelic loss of the NF-1 tumor suppressor gene that leads to loss of neurofibromin, a negative regulator of RAS signaling[6].

In addition to cutaneous, soft tissue, and visceral (plexiform) neurofibromas, this syndrome is associated with several types of gastrointestinal and abdominal tumors, including neuronal hyperplasia (neuromas), ampullary carcinoids, pheochromocytomas, and GISTs. Indeed, GISTs have been suggested to be the most common NF-1-associated gastrointestinal tumor.

Neurofibromatosis with GISTs is rare. The pathogenesis of NF-1-associated GISTs has not been established. Several studies have confirmed that NF-1-associated GISTs are different from sporadic GISTs with respect to clinicopathologic characteristics, and *KIT* and *PDGFRA* gene mutations[1,5]. Moreover, the age and location of onset differ. Specifically, the median age of 45 patients with NF-1-associated GISTs reported by Miettinen *et al*[3] was 49 years, which is younger than patients with sporadic GIST (median age: 56 years). Women are more likely to have tumors in the small intestine, especially the jejunum, which differs from sporadic GISTs (most likely in the stomach). Most of these tumors occur in the small bowel with multifocal tumors, which is rare in sporadic GISTs.

The six tumors from our two cases were located in the duodenum and jejunum. The immunophenotypes also differed. Approximately 90% of NF-1-associated GISTs are

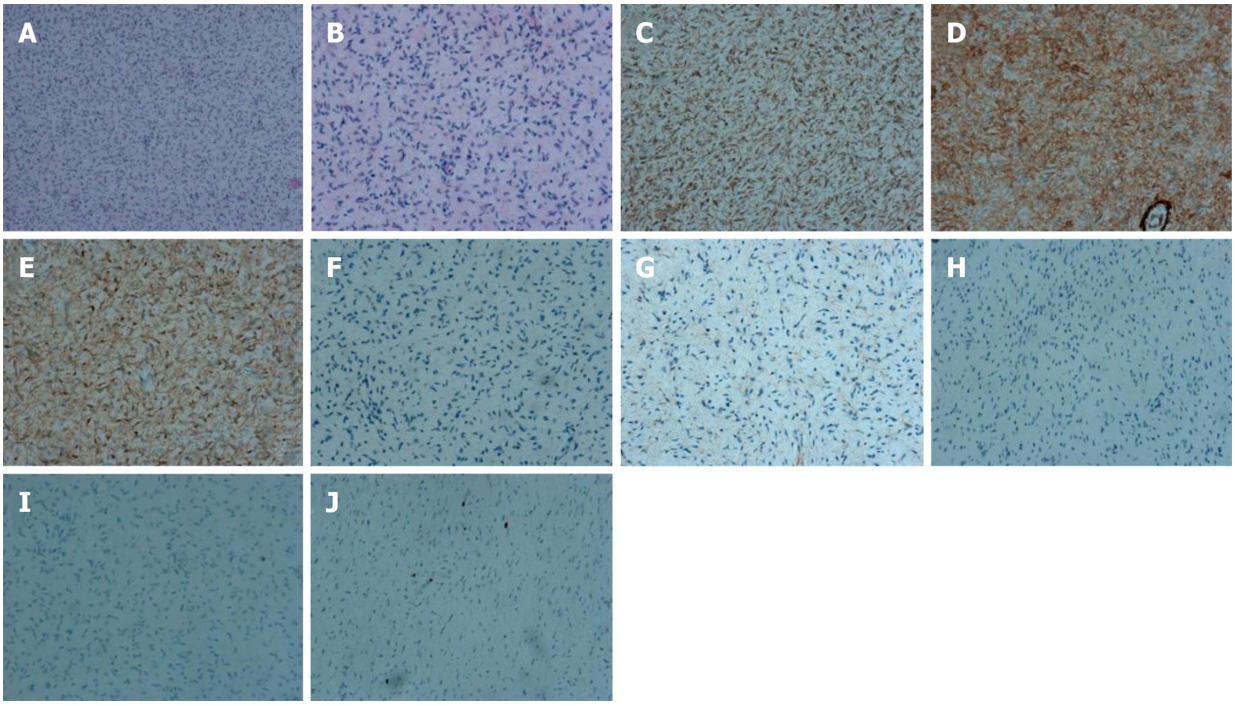

Figure 3 Microscopic and immunohistochemical features of multiple nodules from the skin. A, B: Tumor composed of spindle cells with eosinophilic cytoplasm (A: × 100; B: × 200, hematoxylin-eosin staining); C: Positive for CD34 [3,3'-Diaminobenzidine (DAB) staining]; D: Positive for S-100 (DAB staining); E: Positive for VIM (DAB staining); F: Negative for CK (DAB staining); G: Negative for EMA (DAB staining); H: Negative for SMA (DAB staining); I: Negative for desmin (DAB staining); J: The percentage of Ki67 positive cells was approximately 2% (DAB staining).

CD34-positive, which is higher than sporadic GISTs. The S-100 protein-positive rate was higher than sporadic small intestinal GISTs. Moreover, the genotypes are different. Approximately 90% of sporadic GISTs have *KIT* gene mutations and 5% have *PDGFRA* gene mutations, while most NF-1-related GISTs have no *KIT* and *PDGFRA* mutations, suggesting that the pathogenesis of the two kinds of GISTs is different. It has been reported that < 5% of sporadic GISTs have *SDHB* or *BRAFV600E* gene mutations. The tumor cells from our two cases had strong positivity for KIT (CD117), DOG-1, CD34, and SDHB, and were negative for SMA, desmin, β-catenin and S-100.

The two patients signed an informed consent form before molecular analysis. The data revealed that none of the six tumors from the two patients had a *KIT* exon 9, 11, 13, or 17, *PDGFRA* exon 12 or 18, or *BRAFV600E* mutation, which typically occurs in sporadic GISTs. It is reported most of the GISTs associated with NF-1 are well differentiated histologically, small in size, exhibit low proliferative activity, are often benign, and have a good prognosis[1,4]. Surgical resection of GIST is still the preferred method. So far, the prognosis in these two cases is similar to that reported in the literature. No recurrences or metastases were found after long-term follow-up, but there are a few exceptions. Momani *et al*[6] reported a recurrent GIST in a patient with neurofibromatosis. The tumor cells from our two cases were well differentiated and low proliferative activity, and tumors were small in size. The GISTs in both patients did not recur or metastasize after surgery during the follow-up period.

GISTs are considered pathologic oddities and are somewhat neglected by oncologists as chemoresistant sarcomas. However, GISTs have now emerged as distinct pathogenetic entities that reinforce the concept of molecular targeted therapy. Imatinib therapy has produced dramatic results in the management of metastatic and unresectable GISTs. However, the response to imatinib is usually confined to GISTs harboring detectable *KIT* or *PDGFRA* gene mutations. Interestingly, nearly all GISTs associated with NF-1 lack a detectable *KIT* gene mutation[7]. Despite these observations, there have been only a limited number of studies on NF-1-associated GISTs, and a few studies have reported on the GIST response to imatinib in such patients[8,9]. Although all of the reported cases in two large series expressed CD117, the patients with metastatic tumors had a poor response to imatinib. NF-1-associated GISTs are usually *KIT*/*PDGFRA* wild-type, although sporadic *KIT*/*PDGFRA* mutations have been reported in some cases[4,10,11].

NF-1-associated GISTs exhibit increased signaling through the mitogen-activated protein kinase signaling cascade, raising the possibility that treatment with *MEK*

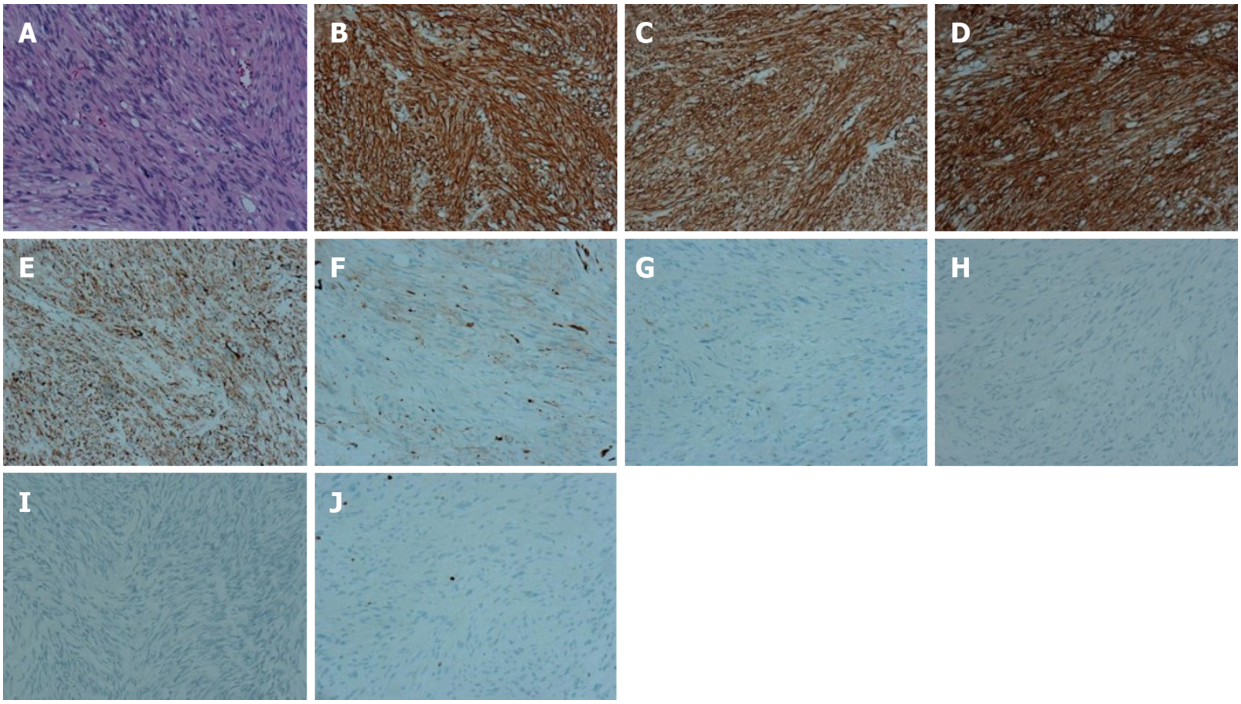

Figure 4 Microscopic and immunohistochemical features (× 200). A: Tumor composed of spindle or polygonal cells with eosinophilic cytoplasm (Hematoxylin-eosin staining); B: Positive for CD117 [3,3'-Diaminobenzidine (DAB) staining]; C: Positive for DOG-1 (DAB staining); D: Positive for CD34 (DAB staining); E: Positive for SDHB (DAB staining); F: Negative for SMA (DAB staining); G: Negative for S-100 (DAB staining); H: Negative for desmin (DAB staining); I: Negative for β-catenin (DAB staining); J: The percentage of Ki67 positive cells was approximately 2% (DAB staining).

inhibitors could be promising. Comprehensive genomic profiling studies have identified a number of gene fusions in *KIT*/*PDGFRA* wild-type GISTs that involve neurotrophic tyrosine kinase receptor type 3 and fibroblast growth factor receptor 1, some of which might represent actionable alterations[12]. A study reported two cases of metastatic GISTs in NF-1 patients who responded favorably to imatinib despite the absence of mutations in the *KIT* and *PDGFRA* genes.

Tyrosine kinase inhibitors, such as imatinib or sunitinib, were not recommended in our two cases. The GISTs in both patients did not recur or metastasize after surgery. Furthermore, patients with NF-1 are at high risk of developing neurogenic, neuroendocrine, and mesenchymal intra-abdominal tumors. Patients with NF-1 and abdominal symptoms should be treated with a high index of clinical suspicion and thoroughly evaluated to rule out multiple tumors[13-15]. Ultrasonography is an effective and safe method for the diagnosis of abdominal diseases[16-18]. If the symptoms of gastrointestinal bleeding occur in patients with NF-1, then endoscopic ultrasonography should be performed first[19-22].

The limitations of this study are the small number of patients enrolled and the relatively short period of follow-up. The follow-up is still in progress, and a further study with a larger number of cases is needed.

CONCLUSION

Our cases illustrate the increased prevalence and association of GISTs in patients with NF-1. GISTs typically occur in the small intestine, are multiple, do not have *SDHB*, *BRAFV600E*, *KIT*, or *PDGFRA* mutations, and exhibit favorable clinical behavior. A medical history of NF-1 in a patient who has gastrointestinal bleeding or anemia and an intra-abdominal mass with nonspecific CT features may help in diagnosing GISTs by virtue of the well-known association of the two entities.

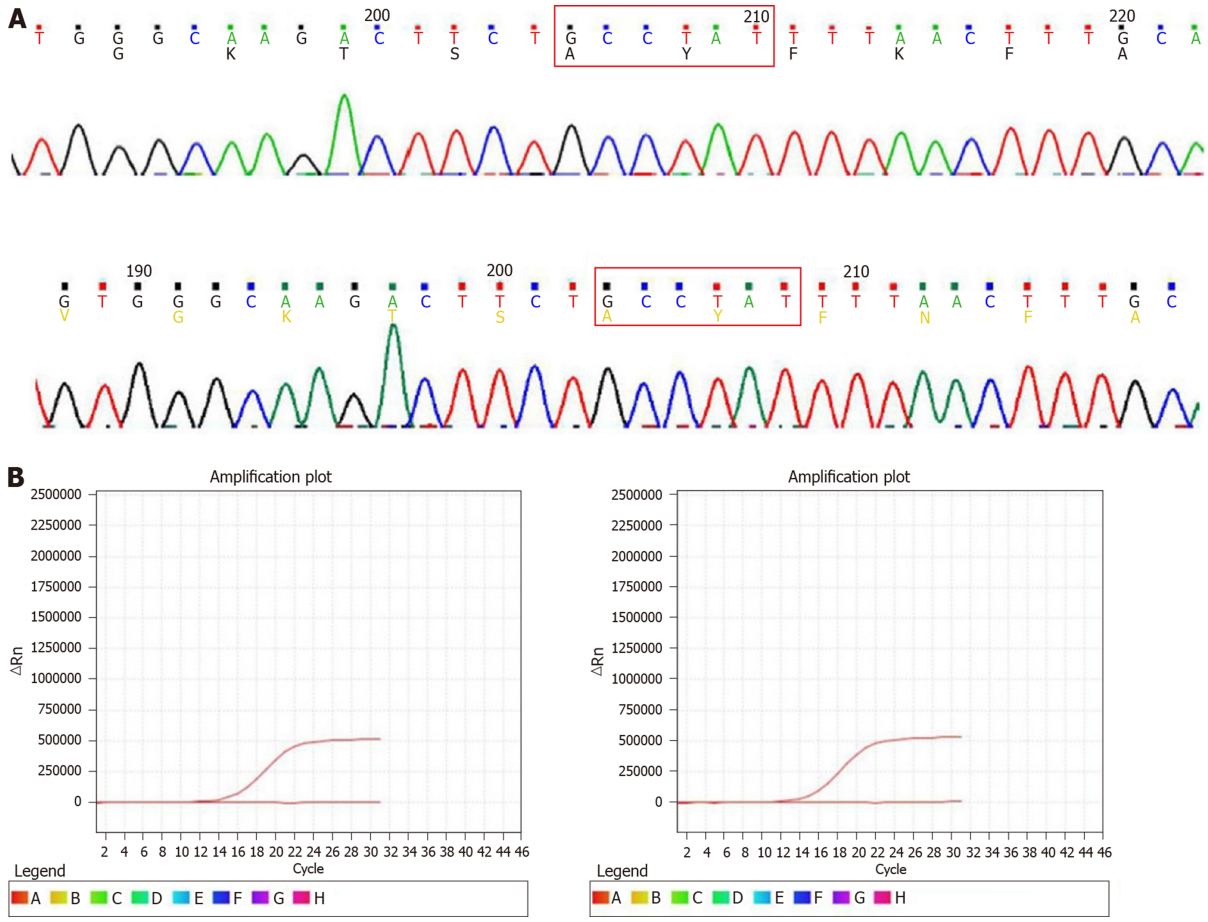

Figure 5 Molecular analysis of gastrointestinal stromal tumor. A: Detection of *KIT*/platelet-derived growth factor receptor α (*PDGFRA*) mutations by Sanger sequencing. None of the six tumors from two patients had a *KIT*/*PDGFRA* mutation; B: Detection of *BRAFV600E* mutation by real-time polymerase chain reaction. None of the six tumors from two patients had a *BRAFV600E* mutation.

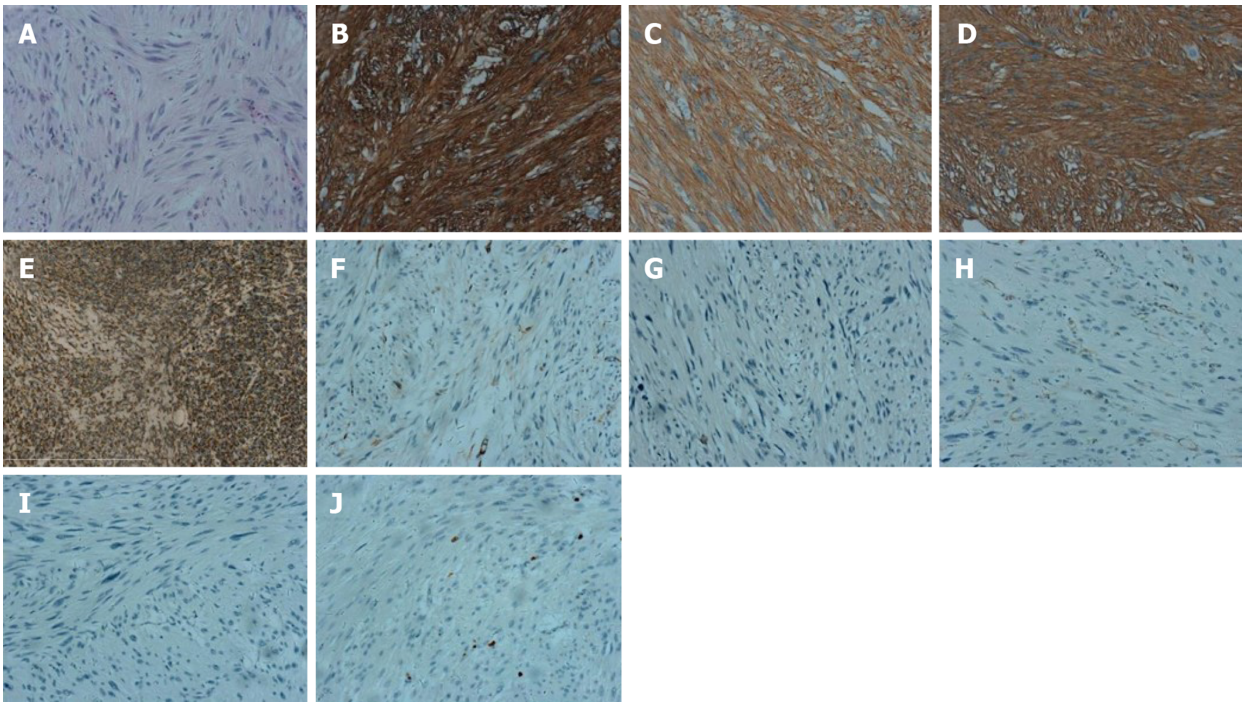

Figure 6 Microscopic and immunohistochemical features (× 200) of a mass located approximately 40 cm away from the Treitz ligament. A: Tumor composed of spindle cells with eosinophilic cytoplasm (Hematoxylin-eosin staining); B: Positive for CD117 [3,3'-Diaminobenzidine (DAB) staining]; C: Positive for DOG-1 (DAB staining); D: Positive for CD34 (DAB staining); E: Positive for SDHB (DAB staining); F: Negative for SMA (DAB staining); G: Negative for S-100P (DAB staining); H: Negative for desmin (DAB staining); I: Negative for β-catenin (DAB staining); J: The percentage of Ki67 positive cells was approximately 2% (DAB staining).

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