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ABOUT COVER

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Gastrointestinal tumors in transplantation: Two case reports and review of literature

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Abstract

BACKGROUND

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. As most of them harbor a *KIT* mutation (75%), selective kinase inhibitors are the therapeutic option and show a sustained objective response among patients with metastatic or unresectable GISTs. A well-known higher risk of neoplasm has been described among renal transplant recipients (RTRs). Nevertheless, only few cases of GIST onset among transplant patients have been reported in the literature.

CASE SUMMARY

Here, we describe 2 cases of gastric GIST occurring during the follow-up of RTRs. We also review the existing literature concerning GIST occurrence in transplant patients. In total and in association with our 2 cases, 16 patients have been reported. The median age was 59.5 years and 69% were male. With a median tumor size of 45 mm, no patient displayed metastatic dissemination at diagnosis.

Time from transplantation to diagnosis was highly variable between 5 mo and 21 years. Histopathological data mostly revealed high risk of progression (43%). Death increased to 29% during follow-up. Surgical treatment was systematically performed when the tumor was operable (94%). The use of adjuvant therapy was uncommon (19%).

CONCLUSION

GISTs represent rare but potentially severe malignant complication among transplant patients.

Key Words: Gastrointestinal stromal tumors; Imatinib mesylate; Transplantation; Kidney transplantation; Proto-oncogene protein c-KIT; Case report

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Core Tip: Although a well-known higher risk of neoplasm has been described among renal transplant recipients (RTRs), few cases of gastrointestinal stromal tumors (GISTs) have been reported. We describe 2 cases of gastric GIST among RTRs and provide a review of the literature. We report 16 patients with a median age of 59.5 years, and 69% were male. No patient displayed metastasis at diagnosis. Time from transplantation to diagnosis varied between 5 mo and 21 years. Histopathology revealed high risk of progression (43%). Death increased to 29%. Surgical treatment was commonly performed (94%). The use of adjuvant therapy was uncommon (19%).

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal (GI) tract[1]. GISTs arise from interstitial cells of Cajal (ICC), which are specialized mesenchymal cells located within the muscle of the GI tract. ICC play a critical role in regulating smooth muscle function and GI tract motility[2]. GISTs are mainly located in the stomach (55%) or the small bowel (30%). About 10% to 47% of patients have metastatic disease at diagnosis[3-5]. About 95% of GISTs display positive staining for the receptor tyrosine kinase KIT (or CD117), 75% of these tumors harbor a *KIT* gene mutation and 10% a platelet-derived growth factor receptor A (*PDGFRA*) gene mutation[6]. Among KIT-negative GISTs, immunohistochemical expression of discovered on GIST-1 (DOG-1) was found in 76% of the cases[7]. Consequently, selective tyrosine kinase inhibitors targeting KIT receptor have been used. The first one, imatinib mesylate (Gleevec®; Novartis, Basel, Switzerland), has shown a sustained objective response in a phase III trial among patients with metastatic or unresectable GISTs in immunocompetent patients[8].

In renal transplant recipients (RTRs), an increased risk of cancer has been reported especially for non-melanoma skin cancer, virus-associated cancer and lymphoproliferative disorders[9]. Currently, malignancy represents a major cause of mortality among RTRs[10]. Nonetheless, only few cases of GIST have been reported among transplant patients. Overall, 8 cases of GIST[11-17] and 2 cases of extra GIST (EGIST)[14,18] have previously been reported in RTRs and respectively 3 cases[19-21] and 1 case[22] in liver transplant recipients.

We report 2 cases of GIST occurring in RTRs and provide a review of the existing literature concerning GIST occurrence in transplant patients.

CASE PRESENTATION

Chief complaints

Case 1: A 60-year-old Caucasian man without any symptoms.

Case 2: A 56-year-old Caucasian man presented with upper GI hemorrhage.

History of present illness

Case 1: Hepatic magnetic resonance imaging (MRI) was performed to explore abnormal hepatic tests.

MRI revealed a 32 mm spherical tumor of the lesser curvature of the stomach.

Case 2: The upper GI hemorrhage led to gastric endoscopy, which revealed a spherical gastric tumor in the fundus.

History of past illness

Case 1: He had end-stage renal disease with a kidney biopsy compatible with nephronophthisis despite negative screening for mutation in hepatocyte nuclear factor 1 beta (*HNF1B*) gene. Hemodialysis was initiated in 2016. In October 2019, he received a kidney transplant from a deceased donor. The initial immunosuppressive therapy combined basiliximab, steroids, tacrolimus, and everolimus. Renal function at hospital discharge was 94 $\mu\text{mol/L}$, (normal range 53 $\mu\text{mol/L}$ to 97 $\mu\text{mol/L}$). Initial maintenance immunosuppressive therapy associated steroids, tacrolimus, and everolimus. Due to relapsing lymphocele, everolimus was switched to mycophenolate mofetil (MMF). Moreover, a pre-existing mild cytolysis and cholestasis worsened after transplantation leading to the discontinuation of cotrimoxazole and MMF, which were replaced by atovaquone and belatacept (NULOJIX®; Bristol-Myers Squibb, New York, NY, United States), respectively.

Case 2: The patient developed end-stage renal disease of unknown origin. He received a kidney transplantation from a deceased donor. Due to preformed donor specific antibodies (anti-Cw15, mean fluorescence intensity of 6130) on the day of transplantation, induction immunosuppressive therapy combined basiliximab, steroids, MMF, cyclosporine, and intravenous immunoglobulins. At 10 d after surgery, a kidney biopsy was performed due to delayed graft function. It revealed acute tubular necrosis associated with possible acute humoral rejection (g1 cpt0 v0 i0 t0 according to Banff's classification[23,24], C4d immunostaining was negative). A treatment with high dose steroids, five plasma exchanges and rituximab[25] was initiated allowing improvement of renal function with a nadir in serum creatinine level of 170 $\mu\text{mol/L}$. Maintenance immunosuppressive therapy included steroids, cyclosporine, and MMF.

Personal and family history

Case 1: His other past medical history consisted in nonalcoholic steatohepatitis, Hashimoto's thyroiditis, and hypertension.

Case 2: The patient had no significant personal or family history.

Physical examination

Case 1: On admission, physical examination was unremarkable.

Case 2: Physical examination was unremarkable except for hematemesis.

Laboratory examinations

Case 1: The patient had mild cytolysis and cholestasis without any other biological abnormality.

Case 2: No abnormal blood test was noticed on admission.

Imaging examinations

Case 1: Body computed tomography (CT) scan confirmed the absence of metastatic dissemination.

Case 2: Body CT scan was consistent with local tumor without metastatic localizations.

Initial diagnosis

Case 1: Upper GI endoscopy found a 3 cm submucosal tumor of the lesser curvature of the stomach. Tumor biopsies were performed using endoscopic ultrasound guidance. Cytological examination revealed spindle-shaped cells that showed positive staining for c-KIT and DOG-1 in immunohistochemistry, confirming the diagnosis of GIST (Figure 1).

Case 2: The gastric endoscopy revealed a spherical gastric tumor in the fundus with a typical macroscopic aspect of GIST.

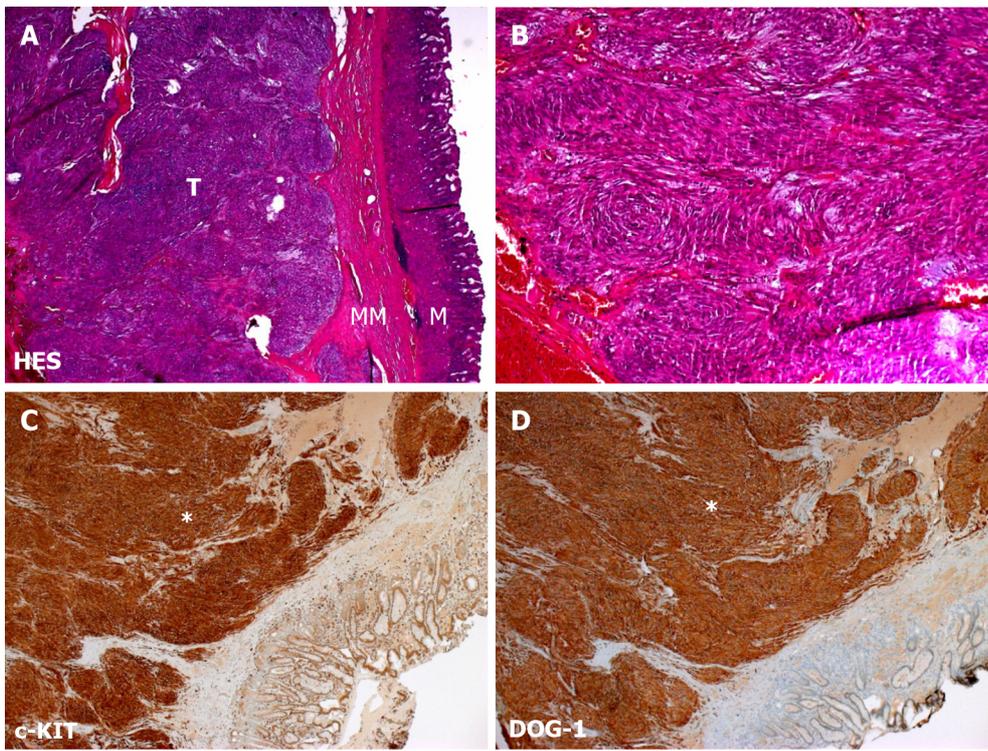
Initial treatment

Case 1: Partial gastrectomy was performed without complication.

Case 2: Partial gastrectomy was performed.

Course of illness in the hospital

Case 1: No complication associated with the GIST of its treatment was noticed.



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Figure 1 Histopathological features of case 1 gastrointestinal stromal tumor. A: Hematoxylin and eosin staining showing exophytic development of a tumor from the mucosa muscularis (magnification, 2.5 ×); B: Hematoxylin and eosin staining showing spindle cell morphology composed of relatively uniform cells arranged in short fascicles (magnification, 20 ×); C: Immunohistochemistry showing strong positive staining for the protooncogene c-KIT (white asterisk; magnification, 5 ×); D: Immunohistochemistry showing strong positive staining for discovered on gastrointestinal stromal tumor protein 1 (white asterisk; magnification, 5 ×). M: Mucosa; MM: Mucosa muscularis; T: Tumor.

Case 2: The patient was rapidly discharged after partial gastrectomy without complication.

FINAL DIAGNOSIS

Case 1

Histopathology revealed a 27 mm stromal tumor strongly positive for KIT and moderately positive for DOG-1 with a mitotic count of 2 mitosis for 5 mm². The tumor harbored an exon 11 (p. Val559Ala c.1676T>C) *KIT* mutation[23].

Case 2

Histopathology report described a 51 mm GIST strongly positive for KIT harboring a mitotic count of 10 mitosis for 5 mm². Of note, an exon 18 D842V *PDGFRA* mutation was identified.

TREATMENT

Case 1

Regarding the very low risk of progression, no adjuvant therapy was initiated.

Case 2

No adjuvant treatment was initiated at the time of diagnosis.

Table 1 Characteristics of 16 transplanted patients with gastrointestinal stromal tumors

	Overall number	
Male sex, <i>n</i> (%)	16	11 (69)
Age (yr), median (min; max)	16	59.5 (23; 74)
Type of organ transplantation, <i>n</i> (%)	16	
Kidney		12 (75)
Liver		4 (25)
Location of primitive tumor, <i>n</i> (%)	16	
Stomach		9 (56)
Small bowel		3 (19)
Colon		1 (6)
Other: pelvis, perineum, mesentery		3 (19)
Time from transplantation to diagnosis (mo), median (min; max)	16	32 (5; 252)
Metastatic dissemination at diagnosis, <i>n</i> (%)	16	0 (0)
Tumor size (mm), median (min; max)	15	45 (10; 230)
Risk of progression according to Joensuu's criteria, <i>n</i> (%)	14	
Very low		2 (14)
Low		4 (29)
Intermediate		2 (14)
High		6 (43)
Surgical treatment, <i>n</i> (%)	16	15 (94)
Adjuvant treatment, <i>n</i> (%)	16	3 (19)
Modification of immunosuppression, <i>n</i> (%)	11	9 (82)
Death during follow-up, <i>n</i> (%)	14	4 (29)

OUTCOME AND FOLLOW-UP

Case 1

The patient remains in remission at the 1-year follow-up.

Case 2

Two years later, a follow-up MRI revealed hepatic vascular nodules compatible with metastatic lesions. Treatment with imatinib mesylate was initiated. In the absence of a tumor response, imatinib was discontinued 4 mo later and sunitinib (SUTENT[®]; Bayer, Germany), an anti-angiogenic multikinase inhibitor (anti vascular endothelial growth factor-1, -2, -3, PDGFR- α , - β , c-KIT, fms-like tyrosine kinase 3, and RET) was introduced. Five months later, the onset of thrombopenia, neutropenia, and hepatic cytolysis led to replacement of sunitinib with regorafenib (STIVARGA[®]; Bayer Pharma AG, Germany), another multikinase inhibitor. Due to side effects and tumor progression, regorafenib was discontinued and dasatinib (SPRYCEL[®]; Bristol-Myers Squibb, New York, NY, United States) was introduced. Disease progression finally led to stopping all therapies in April 2019. Selective transarterial embolization was performed complicated with artery dissection of the kidney transplant requiring stent implantation. The patient was finally admitted with a clinical presentation of hydrops concomitant with acute renal injury and peritoneal carcinosis. The patient eventually died due to disease progression.

DISCUSSION

GISTs represent an uncommon malignant complication of immunosuppression state in solid organ transplantation. We describe 2 cases of typical GIST occurring early in the course of kidney transplantation. The first patient developed an isolated gastric GIST 5 mo after transplantation and the second 4 years after. Both were nonmetastatic at diagnosis although the second patient developed

Table 2 Clinical features and immunosuppression regimen of 16 transplant patients with gastrointestinal stromal tumor

Ref.	Age (yr)/sex	Transplanted organ	Time from transplantation to diagnosis	Location of primitive GIST	Metastasis at diagnosis	Evolution/delay	Immunosuppression before diagnosis	Immunosuppression after diagnosis
Agaimy and Wünsch [11]	59/F	Kidney	40 mo	Stomach	No	Relapse 68 mo	Not described	Not described
Agaimy and Wünsch [11]	58/F	Kidney	96 mo	Small bowel	No	Not described	Not described	Not described
Saidi <i>et al</i> [19]	54/M	Liver	11 mo	Colon	No	Not described	Tac, Aza	Not described
Camargo <i>et al</i> [22]	64/M	Liver	7 mo	Perineum	No	Not described	Tac, mycophenolate sodium	Not described
Tu <i>et al</i> [18]	57/F	Kidney	6 mo	Pelvis	No	Not described	Steroids, CsA, MMF	CsA and MMF at half dosage; rapamycin-containing regimens-steroids withdrawn
Mulder <i>et al</i> [12]	72/M	Kidney	21 yr	Stomach	No	Peritoneal metastasis/24 mo	Steroids, CsA	Steroids, CsA (60% reduction in dosage)
Mrzljak <i>et al</i> [20]	53/M	Liver	12 mo	Jejunum	No	No	Tac, MMF	Same
Cimen <i>et al</i> [13]	46/F	Kidney	18 yr	Stomach	No	Not described	Steroids, CsA, Aza	Same with reduced dosage of CsA
Cheung <i>et al</i> [14]	64/M	Kidney	2 yr	Stomach	No	Yes/2 yr	Steroids, Tac, MMF	Steroids, Tac (reduced dosage), everolimus
Cheung <i>et al</i> [14]	48/M	Kidney	1 yr	Mesentery	Multiple tumors	No	CsA, MMF	CsA withdrawal, sirolimus introduction
Patiño <i>et al</i> [15]	23/F	Kidney	13 yr	Stomach	No	Local relapse/3 yr	Steroids, Tac, MMF	Not described
Xie <i>et al</i> [21]	60/M	Liver	11 mo	Stomach	No	No	Tac, sirolimus, MMF	Same
Elkabets <i>et al</i> [17]	74/M	Kidney	7 yr	Stomach	No	No	Steroids, CsA, MMF	Switch CsA to mTOR inhibitor
Takahashi <i>et al</i> [16]	64/M	Kidney	72 mo	Small bowel	No	No	Steroids, CsA, MMF	Stop CsA
Stammler <i>et al</i>	60/M	Kidney	5 mo	Stomach	No	No	Steroids, Tac, MMF	Switch MMF to belatacept
Stammler <i>et al</i>	64/M	Kidney	51 mo	Stomach	No	Yes/23 mo	Steroids, CsA, MMF	Switch CsA to Tac

Aza: Azathioprine; CsA: Cyclosporine; F: Female; GIST: Gastrointestinal stromal tumor; M: Male; MMF: Mycophenolate mofetil; mTOR: Mammalian target of rapamycin; Tac: Tacrolimus.

multiple hepatic metastasis 2 years after complete tumor resection. Of note, the mutation of *PDGFRA* D842V in the second case was associated with resistance to imatinib mesylate.

We looked for previously reported cases of GIST in the literature during the course of transplantation. We searched PubMed and Web of Science databases using the following Medical Subject Headings words: “Gastrointestinal stromal tumors” AND “Kidney transplantation” or “Gastrointestinal stromal tumors” AND “Transplantation.” Using these terms, we found 8 and 31 articles, respectively. Only 12 articles were analyzed. From 2007 to 2020, 14 cases of GIST have been reported in transplant recipients [11-22]. We excluded reports of GIST occurring among nontransplant or bone marrow transplant patients. We also excluded article types different than case reports or case series.

Table 1 summarizes the main features of these patients including the 2 cases described in the present manuscript. Tables 2 and 3 give details on the 14 cases reported. In our literature review, the typical patient profile was a male patient with a median age of 59.5-years-old, who developed large nonmetastatic gastric tumors (median size, 45 mm). The delay between transplantation and diagnosis was highly

Table 3 Histopathological features, treatments, and outcome of 16 transplant patients with gastrointestinal stromal tumor

Ref.	Size (mm)	Mitotic count	Fletcher's criteria	Joensuu's criteria	Mutation identified	Resection	Initial adjuvant treatment	Second line treatment	Outcome
Agaimy and Wünsch[11]	35	< 5/50	Low	Low	Not described	Yes	No	Not described	Alive and relapse free at 68 mo
Agaimy and Wünsch[11]	230	14/50	High	High	Not described	Yes	No	Not described	Not described
Saidi <i>et al</i> [19]	25	1/50	Low	High	Not described	Yes	No	Not described	Alive and relapse free at 18 mo
Camargo <i>et al</i> [22]	50	5/50	Intermediate	High	Not described	Yes	No	Not described	Alive and relapse free at 20 mo
Tu <i>et al</i> [18]	45	2-3/50	Low	Low	<i>PDGFRA</i> exon 18 V824V	Yes	No	Not described	Alive and relapse free 24 mo
Mulder <i>et al</i> [12]	50	> 10/50	High	High	Not described	Yes	No	Imatinib 400 mg/d then 200 mg/d	Died 44 mo
Mrzljak <i>et al</i> [20]	10	1/50	Very low	Very low	Not described	Yes	No	No	Died 3 yr after from acute leukemia
Cimen <i>et al</i> [13]	150	14/50	High	High	<i>KIT</i> T574del	Yes	Imatinib 400 mg/d	Not described	Alive and relapse free at 12 mo
Cheung <i>et al</i> [14]	30	9/50	Intermediate	Intermediate	Not described	Yes	No	No	Died from pneumonia at 2 yr
Cheung <i>et al</i> [14]	Not described	Not described	Not described	Not described	Not described	No	Imatinib 400 mg/d for 1 yr	Switch CsA to sirolimus	Alive and relapse free at 10 yr
Patiño <i>et al</i> [15]	58	Not described	Intermediate or high	Intermediate of high	Not described	Yes	No	Imatinib 400 mg/d	Alive and relapse free/5 yr after imatinib initiation
Xie <i>et al</i> [21]	10	< 5/50	Very low	Very low	<i>KIT</i> exon 11	Yes	No	No	Not described
Elkabets <i>et al</i> [17]	31	Not described	Not described	Not described	Not described	Yes	No	No	Alive and relapse free at 40 mo
Takahashi <i>et al</i> [16]	110	20/50	High	High	<i>KIT</i> exon 11	Yes	Imatinib 400 mg/d reduced to 3000 mg/d	No	Alive and relapse free at 18 mo
Stammler <i>et al</i>	27	2/5	Low	Low	<i>KIT</i> exon 11	Yes	No	No	Alive and relapse free at 2 mo
Stammler <i>et al</i>	51	10/50	High	High	<i>PDGFRA</i> exon 18	Yes	No	Sunitinib then regorafenib then dasatinib	Died 56 mo later

CsA: Cyclosporine.

variable, ranging between 5 mo and 21 years. Histopathological data mostly revealed high risk of progression (42.8%) and death occurred in 29% of the cases during follow-up. Surgical treatment was systematically performed if the tumor features were suitable (94%). The use of adjuvant therapy was uncommon (19%).

Several prognostic classifications have been used to evaluate the risk of recurrence of GIST after surgery. In 2002, Fletcher *et al*[26] claimed size of the tumor and mitotic count, Miettinen and Lasota[27] in 2006 added tumor location and Joensuu *et al*[28] in 2012 adjoined rupture of the tumoral capsule and male gender. Heinrich *et al*[29] demonstrated that *PDGFRA* and *c-KIT* were mutually exclusive proto-oncogenic mutations with similar biological consequences, even if associated with different prognostics. Molecular predictors of response to imatinib have been widely studied. Underlying *KIT* or *PDGFRA* mutations are the strongest predictors of imatinib sensitivity[30]. Mutations directly located in the *PDGFRA* binding site of imatinib or inducing variations in tridimensional conformation of the tyrosine kinase receptor and subsequently hiding the binding site, may explain inefficacy of therapy. For instance, *KIT* exon 9 mutation is less sensitive to imatinib and *PDGFRA* exon 18 D842V mutations is associated with imatinib resistance. Nevertheless, these mutations have been correlated with opposite

courses of the disease, indolent for *PDGFRA* exon 18 D842V mutation but aggressive for *KIT* exon 9 mutation[31]. These data should highlight the importance of molecular biomarkers to evaluate prognosis of GIST or EGIST at diagnosis.

Guidelines for the diagnosis, treatment, and follow-up of GIST have recently been published[32]. Management of local or locoregional disease should always aim for complete resection whenever possible. Otherwise, neoadjuvant treatment with imatinib for 6 to 12 mo should be used in case of sensitive mutation with an overall response rate of 50%[30]. Moreover, high-risk patients, as previously described, should receive adjuvant imatinib for a duration of 3 years[33]. Imatinib remains the first-line therapy for metastatic GIST. Several other targeted therapies such as sunitinib or regorafenib have emerged as second- or third-line treatment, and more recently avapritinib and ripretinib. Several biomarkers, such as *KIT* or *PDGFRA* mutations, are used as predictive factors for tumoral response to refine therapeutic strategies[32]. Data are missing concerning the level of tyrosine kinase inhibitors' efficacy in transplanted patients.

Data about the management of immunosuppressive therapy after the diagnosis of GIST are scarce. As both imatinib mesylate and cyclosporin are extensively metabolized by cytochrome P450 3A4, interaction occurrence has been documented[12]. Reduction in the dosage of cyclosporin should be performed if this treatment is maintained. Mammalian target of rapamycin inhibitors (mTORis) have shown antiproliferative properties among transplant patients. Schöffski *et al*[34] highlighted the potential efficacy of association of everolimus and imatinib in imatinib-resistant GIST in a phase II trial. Cheung *et al*[14] reported a case of complete tumoral response with sirolimus in a transplant patient with imatinib-resistant GIST. Among the patients described in Tables 1 and 2, mTORis have been initiated or switched in 4 of them. Three of them were alive and relapse-free at last follow-up and the last patient died from pneumonia 2 years after GIST diagnosis.

This study had several limitations. First, the retrospective analysis of GIST cases impairs the reliability of the data. Very few cases of GIST occurring after solid organ transplantation have been described in the last 15 years reducing the significance of this literature review. Moreover, it was unclear if GIST was a *de novo* feature in our first patient because of the short delay (5 mo) between transplantation and tumor discovery. Unfortunately, the latest available CT scan was performed 7 years before the transplantation. However, some previous cases reported GIST onset within the 1st year following transplantation[14,18-22].

CONCLUSION

To conclude, GISTs represent rare but potentially severe malignant complication among transplant patients. Further analysis of prognosis value of new biomarkers should improve therapeutic strategies.

FOOTNOTES

Author contributions: Stammler R and Lazareth H designed the study; Stammler R, Lazareth H, Anglicheau D, Meatchi T, Ragot E, and Thervet E investigated the patients and collected the data; Stammler R, Lazareth H, and Landi B interpreted the data and wrote the manuscript; all authors revised the manuscript and approved the final version.

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