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

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Abstract

BACKGROUND

Gastrointestinal stromal tumors (GIST) 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 showed 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 (RTR). Nevertheless, only few cases of GIST's onset among transplanted patients have been reported in the literature.

CASE SUMMARY

Here we described two cases of gastric GIST occurring during the follow up of RTR. We also review existing literature concerning GIST's occurrence in transplanted patients. In total and in association with our two cases, 16 patients have been reported. Median age was 59.5 years and 69% were male. With a median tumoral 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 rises to 29% during follow-up. Surgical treatment was systematically performed when tumor was operable (94%). The use of adjuvant therapy was uncommon (19%).

CONCLUSION

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

Key Words: Gastrointestinal stromal tumors; Imatinib mesylate; Transplantation; Kidney transplantation; Proto-oncogene proteins 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 (RTR), few cases of gastrointestinal stromal tumors (GIST) have been reported. We describe two cases of gastric GIST among RTR and offer a review of the literature. We report 16 patients with a median age of 59.5 years, 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 rises to 29%. Surgical treatment was commonly performed (94%). The use of adjuvant therapy was uncommon (19%).

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract[1]. GISTs arise from interstitial cells of Cajal (ICC), which are specialized mesenchymal cells located within the muscle of the gastrointestinal tract. ICC play a critical role in regulating smooth muscle function and gastrointestinal tract motility[2]. GISTs are mainly located in the stomach (55%) or the small bowel (30%). About 10% to 47% of patients have a 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 *PDGFRA* gene mutation[6]. Among KIT-negative GISTs, immunohistochemical expression of DOG-1 (discovered on GIST-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 (RTR), an increased risk of cancer has been reported especially for non-melanoma skin cancer, virus-associated cancer and lymphoproliferative disorders[9]. Nowadays, malignancy represents a major cause of mortality among RTR[10]. Nonetheless, only few cases of GIST have been reported among transplanted patients. Overall, 8 cases of GIST[11-17] and two case of extra

GIST (EGIST)[14,18] have previously been reported in RTR and respectively 3 cases[19-21] and 1 case[22] in liver transplant recipients.

We here report two cases of GIST occurring in RTR and offer a review of the existing literature concerning GISTs' occurrence in transplanted 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 gastrointestinal hemorrhage.

History of present illness

Case 1: A hepatic magnetic resonance imaging (MRI) was performed to explore abnormal hepatic tests. MRI revealed a 32 millimeters spherical tumor of the lesser curvature of the stomach.

Case 2: The upper gastrointestinal hemorrhage led to perform 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 *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 µmol/L, (normal range 53 µmol/L to 97 µmol/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 the transplantation, induction immunosuppressive therapy combined basiliximab, steroids, MMF, cyclosporine, and intravenous immunoglobulins. Ten days 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[24], C4d immunostaining was negative). A treatment with high dose steroids, 5 plasma exchanges and rituximab[25] was initiated allowing improvement of renal function with a nadir in serum creatinine level of 170 µmol/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: A body computerized 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 gastrointestinal endoscopy found a 3 centimeters 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 (Figure 1) confirming the diagnosis of GIST.

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.

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

FINAL DIAGNOSIS

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

Case 2: Histopathology report described a 51 millimeters GIST strongly positive for KIT harbouring a mitotic count of /10 mitosis for 5 mm^2). 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 time of diagnosis.

OUTCOME AND FOLLOW-UP

Case 1: The patient remains in remission after one year follow-up.

Case 2: Two years later, a follow-up MRI revealed hepatic vascular nodules compatible with metastatic lesions. A treatment with imatinib mesylate was initiated. In absence of tumor response, imatinib was discontinued 4 mo later and sunitinib (SUTENT©; Bayer, Germany), an anti-angiogenic multikinase inhibitor (anti VEGFR-1, -2, -3, PDGFR-α, -β, c-KIT, FLT-3 and RET) was introduced. Five months later, the onset of thrombopenia, neutropenia, and hepatic cytolysis led to replace sunitinib by regorafenib (STIVARGA ©; Bayer Pharma AG, Germany), another multikinase inhibitor. Due to sides 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 stop 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 here describe two cases of typical GIST occurring early in the course of kidney transplantation. The first patient developed an isolated gastric GIST five months after transplantation and the second four years after. Both were non metastatic at diagnosis although the second patient developed multiple hepatic metastasis two years after complete tumor resection. Of note the mutation of *PDGFRA* D842V in the second case, is associated with resistance to imatinib mesylate.

We looked for previously reported cases of GIST in literature in the course of transplantation. We searched in 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 non-transplanted patient or bone marrow transplanted patients. We also excluded article types different than case reports or case series.

The Table 1 summarizes the main features of these patients including the two cases described in the present manuscript. Table 2 and Table 3 give details on the 14 cases reported. In our review of literature, the typical patient profile was a male patient with a median age of 59.5 years-old who developed large non metastatic gastric tumors (median size 45 mm). The delay between transplantation and the diagnosis was highly variable ranging between 5 mo and 21 years. Histopathological data mostly revealed high risk of progression (42.8%) and death occurs in 29% of the cases during follow-up. Surgical treatment was systematically performed if 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 biologicals consequences, even if they are associated with different prognostics. Molecular predictors of response to imatinib have been widely studied. Underlying *KIT* or *PDGFRA* mutations are the strongest predictor 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 *PDFGRA* exon 18 D842V mutations is associated with imatinib resistance. Nevertheless, these mutations have been correlated with opposite courses of the disease, indolent for *PDFGRA* 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 in 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 CYP3A4, interaction occurrence has been documented[12]. Reduction in dosage of cyclosporin should be performed if this treatment is maintained. Mammalian target of rapamycin inhibitors (mTORi) have shown antiproliferative properties among transplanted patients. Schöffski *et al*[34] highlights 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 transplanted patient with imatinib-resistant GIST. Among patients described in Table 1 and 2, mTORi have been initiated or switched in 4. Three of them were alive and relapse free at last follow-up and the last patient died from pneumonia 2 years after GIST diagnosis.

We could notice several limitations in this study. 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 is unclear if GIST was a *de novo* feature in our first patient because of the short delay (5 mo) between transplantation and the tumor discovery. Unfortunately, the latest available CT scan was performed seven years before the transplantation. However, some previously cases report GIST onset within the first year following transplantation [14,18-22].

CONCLUSION

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

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