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Transplanted kidney loss shortly after initiation of adjuvant chemotherapy for colon cancer: A Case report.

A transplanted kidney loss shortly after initiation of adjuvant chemotherapy for colon cancer. Case report and review of the literature.

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Abstract

BACKGROUND

The overall risk of de novo malignancies in kidney transplant recipients (KTRs) is higher than that in the general population. It is associated with long-lasting exposure to immunosuppressive agents and impaired oncological vigilance due to chronic kidney disease. Colorectal cancer (CRC), diagnosed frequently in an advanced stage, is one of the most common malignancies in this cohort and is associated with poor prognosis. Still, because of scarce data concerning adjuvant chemotherapy (CTH) in this group, there are no clear guidelines for the specific management of the CRCs in KTRs. In this study, we present a case of a patient who lost her transplanted kidney shortly after the initiation of adjuvant CTH for colon cancer.

CASE SUMMARY

A 36-year-old woman with a medical history of kidney transplantation (2005) because of end-stage kidney disease, secondary to chronic glomerular nephritis, and long-term immunosuppression was diagnosed with locally advanced $pT_{4A}N_{1B}M_0$ (clinical stage III) colon adenocarcinoma G2. After right hemicolectomy, the patient was qualified to adjuvant CTH containing oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-4). The deterioration of kidney graft function after two cycles caused CTH cessation and initiation of hemodialysis therapy after a few months. Shortly after that, the patient started palliative CTH because of cancer recurrence with intraperitoneal spread.

CONCLUSION

Several risk factors, including long-lasting immunosuppression, may contribute to CRC development at a younger age in kidney transplant recipients. We acknowledge the risk of rapid kidney graft loss, timely associated with the initiation of adjuvant chemotherapy for colon cancer, but may rather be a consequence of underimmunosuppression due to the worse drug absorption and/or treatment changes driven by the cancer diagnosis.

Key Words: kidney transplantation; colorectal cancer; adjuvant chemotherapy; graft loss; complications; case report

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Core Tip: The occurrence of colorectal cancer (CRC) in kidney transplant recipients (KTRs) is higher than that in the general population. Advanced stage CRC is usually associated with poor outcome. Adjuvant chemotherapy (CTH) may accelerate transplanted kidney loss.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies both in the general population (1) and in kidney transplant recipients (KTRs) (2,3). The risk of CRC development is reported to be higher in transplant patients because of long-lasting exposure to immunosuppressive agents (4). Although the patient survival rate for the KTR population with advanced CRC (stage III-IV) at the time of diagnosis is worse, mainly due to higher rates of recurrence, in early cancer, there was no significant difference in a 5-year patient survival (5). It was also noted that CRC in KTRs displayed atypical characteristics in tumor location, polyp size, and occurrence. The rate of ascending colon cancer was higher, whereas the rate of rectal cancer was lower in the transplant group (5,6). Also, the number and size of polyps observed in preoperative colonoscopy were larger than in control patients. One of the possible causes of inferior survival of KTRs with advanced cancer may be insufficient CRC treatment, i.e., tendency to less frequent use of adjuvant chemotherapy (5,6) because of concern of incompatibility with immunosuppression regimen and the risk of deterioration of

kidney graft function. The abovementioned obstacles preclude the formulation of clear guidelines for the management of CRC in KTRs.

Hereby, we present a description of a patient with advanced colon cancer diagnosed 16 years after a successful kidney transplantation with an irreversible deterioration of kidney graft function shortly after the initiation of adjuvant chemotherapy (CTH), widely discussing the possible causes of kidney graft loss.

CASE PRESENTATION

Chief complaints

A 36-year-old woman with a medical history of kidney transplantation in 2005, after recent right hemicolectomy due to locally advanced $pT_{4A}N_{1B}M_0$ (clinical stage III) colon adenocarcinoma (G2), was qualified (in March 2021) to adjuvant chemotherapy based on oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX-4) regimen. At that time, the kidney graft function was satisfactory; however, the slow increase of serum creatinine up to 1.4 mg/dL was observed during the few preceding months. The blood tests showed anemia (Hb, 8.4 g/dL), C-reactive protein 11.2 mg/L, CA125 18.7 U/mL and CEA 0.95 ng/mL. After two FOLFOX-4 cycles, the substantial deterioration of kidney graft function was observed, resulting in the discontinuation of CTH and the return to hemodialysis therapy.

History of present illness

In October 2020 (16th posttransplant year), the patient started to report recurrent mild abdominal pain without concomitant hematochezia, diarrhea, change in bowel motility, or weight loss. At the same time, a slight increase of serum creatinine from 1.0 to 1.4 mg/dL (eGFR 45 mL/min/1.73m^2), with no proteinuria, was noticed. In January 2021, the patient was admitted to the surgery department with clinical suspicion of herniation of terminal ileum into the caecum. During surgery, a large caecum tumor was found (diameters 7 × 5.5 × 5 cm), and a right hemicolectomy with terminal ileum-transverse colon graft was performed. Histologic diagnosis was adenocarcinoma G2 with invasion

into peritoneum and blood vessels, with metastases to 2 of 24 resected mesenteric lymph nodes ($pT_{4A}N_{1B}$)—corresponding to clinical stage III. A multidisciplinary team qualified the patient to adjuvant CTH (FOLFOX-4), which was suspended due to abdominal wall abscess after previous surgery. On March 17, 2021 (7 wk since hemicolectomy), the first FOLFOX-4 cycle was administered, the second was on April 1, 2021. However, the subsequent CTH cycles were cancelled due to progressive kidney graft insufficiency. There was no deterioration of blood pressure control during CTH.

Meanwhile, immunosuppression was modified by conversion from mycophenolate mofetil 250 mg BID to everolimus 0.75 mg BID (Figure 1). Notably, during the subsequent 2 mo, the blood trough levels of everolimus were low (1.0–1.4 ng/mL). Finally, the drug was discontinued because of its poor gastric tolerance. In addition, the tacrolimus level started to fluctuate (with a nadir of 2.5 ng/mL), and *de novo* proteinuria was noticed up to 4.2 g/24 h. Lately, tacrolimus once-daily was switched to twice-daily formulation to achieve adequate blood trough levels. Serum creatinine level increased up to 3.4 mg/dL.

History of past illness

The patient was diagnosed with chronic glomerular nephritis at the age of 10 years. It was confirmed by kidney biopsy and the therapy with glucocorticoids, and cyclophosphamide was started. In 2001, the hepatitis C virus infection was diagnosed, and the patient underwent a successful 12-month interferon-γ treatment. Hypertension was diagnosed at the age of 18 years in the course of chronic kidney disease. The patient developed end-stage kidney disease and started hemodialysis at the age of 19 years (2004). After 8 mo of dialysis therapy, she underwent kidney transplantation (2005) with basiliximab induction. The kidney graft function on an immunosuppressive regimen consisting of tacrolimus, mycophenolate mofetil, and steroids was excellent, with a serum creatinine of 1 mg/dL for many years. The immunosuppression schedule was modified between the 4th and 8th posttransplant year by converting mycophenolate to azathioprine due to the planned pregnancy. She passed two

pregnancies, giving birth during the 5th and 8th posttransplant years. During the whole observation, there were no episodes of acute kidney rejection or proteinuria. The blood trough levels of tacrolimus and mycophenolate mofetil were stable, approximately 6 to 7 ng/mL and 2.7 ng/mL, respectively.

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Personal and family history

Family history was unremarkable.

Physical examination

Physical examination revealed no abnormalities except surgical scars.

Laboratory examinations

Because of the increase of serum creatinine up to 3.4 mg/dL, a kidney graft biopsy was performed on June 1, 2021. Histological examination revealed overlapping features of active chronic rejection and focal segmental glomerulosclerosis (FSGS). Overall, interstitial fibrosis and tubular atrophy covered more than 50% of the interstitial area (Figure 2). Donor-specific antigens were not present, whereas a moderate Epstein-Barr viremia (7485 copies/mL) was detected. The other virologic results (HBV, HCV, CMV) were negative at that time.

Imaging examinations

The computed tomography (CT) with contrast media administration was performed twice, during the oncological work-up, in June and September 2021. The second examination visualized the intraperitoneal spread of colon adenocarcinoma, confirmed by PET-CT (Figure 3), and corresponding with recent patient complaints about abdominal pain.

FINAL DIAGNOSIS

The diagnosis of active chronic rejection of transplanted kidney with features of recurrent glomerulonephritis and further intraperitoneal spread of colon cancer was made.

TREATMENT

Hemodialysis therapy was initiated after creating an arterio-venous shunt when serum creatinine level exceeded 6 mg/dL. Before initiation of palliative CTH, *KRAS*, *NRAS* and *BRAF* genotyping has been performed. The analysis revealed mutation in the 12 codon of the second exon (35 G>T) of *KRAS*, resulting in the resistance to anti-EGR therapy. FOLFOX-4 regiment was chosen as the first line in palliative CTH due to early discontinuation of this regimen as an adjuvant, frequent intestinal toxicity of irinotecan in hemodialysis patients, and restriction in the reimbursement of bevacizumab in patients with chronic kidney disease.

OUTCOME AND FOLLOW-UP

The patient remains under the care of an oncologist and nephrologist, continuing hemodialysis and palliative CHT. The timeline of the information presented in this case report is shown in Table 1.

DISCUSSION

Cancer is the second most common cause of mortality and morbidity in kidney transplant recipients after cardiovascular disease (7). This increased cancer risk in the KTR population is driven mainly by *de novo* cancers, with CRC being the third most common cause of cancer death after non-Hodgkin lymphoma and lung cancer (8). Notably, CRC in KTRs is reported to have a worse 5-year survival rate than in the general population (9,10) and develops more often at a younger age (9-11). Even so, our patient was diagnosed with an advanced CRC at the age of 36. However, analysis of Australia and New Zealand Dialysis and Transplant Registry Data revealed that cancer rates in KTRs are similar to non-transplanted subjects 20 to 30 years older (12).

However, it is worth noticing that there were also some additional risk factors for such early development of cancer in the given patient, except for the posttransplant immunosuppression. First, the primary kidney disease was glomerulonephritis treated with steroids and cyclophosphamide, whereas the pretransplant immunosuppressive treatment was shown to increase the cancer risk (12,13). Second, the use of azathioprine could be an independent risk factor for advanced colorectal neoplasia in KTRs (14). The patient has received this medication for 5 years because of the planned conception. Third, unlike the virus-related malignancies such as Kaposi's sarcoma and cervical cancer, CRC used to develop late in the posttransplant observation (15), like in our case.

Nevertheless, when considering the undoubted tendency to the CRC development in relatively younger KTRs in comparison to the general population, modified screening strategies were suggested in this specific cohort, including increased colonoscopy frequency (9) and early initial posttransplant colonoscopy within 2 years (10). To date, KDIGO Guidelines suggested that screening for CRC should be performed as recommended for the general population (16). Moreover, a cost-benefit ratio is another issue, as it was shown that eight (6-12) colonoscopies were needed to identify one case of advanced neoplasia in KTRs cohort older than 50 years (17). Although some authors suggested that screening colonoscopy in KTRs should be expanded to include recipients younger than 50 years (11) or even at age 35 to 50 years (18), such a policy would be cost-ineffective, in contrast to screening program with fecal hemoglobin testing (18). However, the latter measure is characterized by poor sensitivity but reasonable specificity. Besides, a fecal hemoglobin concentration can be used to stratify probability for the detection of advanced colorectal neoplasia in individuals with positive fecal immunochemical test (19).

In KTRs diagnosed with cancer, treatment includes conventional approaches based on surgery, radiotherapy, and CTH (7). Such a complex treatment, often complicated by the adverse effects, was effective even in advanced CRC cases (20). Although administration of an adjuvant CTH is a current standard of care in stage III colon cancer, the assessment of complication risk of such therapy is strongly recommended,

especially among patients with preexisting kidney dysfunction (1). The data concerning adjuvant and palliative CTH and their outcomes in KTRs patients are very limited (Table 2). Some advanced stage transplant patients did not receive adequate CTH because of the concern of drug-to-drug interactions with the immunosuppressive regimen (21). Notably, despite partly elimination of oxaliplatin and 5-fluorouracil with urine, the renal toxicity potential of anti-CRC drugs is relatively low, except *de novo* proteinuria and arterial thromboembolic events observed during bevacizumab therapy (21). Nevertheless, the oxaliplatin-based CTH is neither nephrotoxic (22) nor interferes with blood levels of immunosuppressants (21). On the other hand, it has already been reported that repeated cycles of oxaliplatin administrated to the patient with prior renal impairment may cause deterioration of kidney function (23). In our case, the kidney graft function before the FOLFOX-4 initiation was already impaired (eGFR 45 mL/min/1.73m^2), but it rapidly deteriorated during the first 2 mo of therapy. However, it might be mainly caused by active chronic rejection coexisting with recurrent glomerulonephritis, which probably started earlier, as indicated by the previously slowly rising serum creatinine concentration. Moreover, both processes mentioned above might be accelerated by decreasing net immunosuppression strength caused by modification of the immunosuppressive regimen and impaired drug absorption after hemicolectomy. Nevertheless, although reducing immunosuppression treatment with or without the conversion to mTOR inhibitor is suggested in KDIGO guidelines (16) and literature (7,24), the risk of rejection and graft loss is not to be disregarded.

CONCLUSION

Several risk factors, including long-lasting immunosuppression, may contribute to CRC development in kidney transplant recipients at a younger age. We acknowledge the risk of rapid kidney graft loss, which occurred during the initiation of adjuvant chemotherapy for colon cancer, but may rather be a consequence of underimmunosuppression due to both the impaired drug absorption and treatment changes driven by the cancer diagnosis. Hence, any modification of

immunosuppressive regimen in newly diagnosed cancer patients should be carefully considered to balance the potential risks and benefits, still bearing in mind the maintenance of kidney graft function.

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