

Point-by-point reply to the reviewer comments

Reviewer 1

This paper is a well-written case report in which a young woman with a medical history of kidney transplantation had the deterioration of kidney graft function after adjuvant chemotherapy for colorectal cancer (CRC). Careful consideration for application and selection of systemic chemotherapy is generally required in case of patients with renal dysfunction. In this paper, authors suggested that FOLFOX chemotherapy might induced rapid kidney graft loss. Moreover, they pointed out that immunosuppressive therapy in kidney transplant recipients might affect cancer progression in CRC patients. These hypotheses are very interesting and highly suggestive because the balance between the risk and the benefit of adjuvant chemotherapy is thought to be difference in kidney transplant recipients compared with general population. From this standpoint, this case report may be useful for deciding therapeutic strategy of CRC patients with a medical history of kidney transplantation. However, there are several points that remain unclear and to be revised.

Major Comments;

1. The change of immunosuppressive therapy may induce the deterioration of kidney graft function, so the shift of immunosuppressive therapy is very important to assess the cause of kidney graft loss. However, the medical history about immunosuppressive therapy is not easy to understand accurately. The authors should be better off figuring the time series of immunosuppressive therapy.

Ad 1. As suggested, we added a figure, illustrating the immunosuppression changes from the cancer diagnosis.

2. In this case, intraperitoneal metastasis was occurred in early phase of postoperative following-up. This process may suggest that the presence of synchronous intraperitoneal spread of CRC. Was intraoperative cytology for ascites fluid performed?

Ad 2. There were no intraperitoneal metastases and ascites noted during surgery. No intraperitoneal cytology has been performed. Tumor growth into the surface of the visceral peritoneum makes synchronous intraperitoneal spread highly probable.

3. What types of regimens were selected for palliative chemotherapy in this case?

Ad 3. We added this information in the text. 'FOLFOX-4 regimen 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.'

Reviewer 2

The main concerns are:

1) Uncertainty of significant additions to the literature from presentation of this single case of colorectal cancer after kidney transplantation. Loss of a transplanted kidney (after 16 years) as a sequel of chemotherapy is an expected outcome rather than its preservation, because the transplanted kidney is a fragile organ having many dangers and chronic insults such as ischemia during surgery, drug toxicity, and immunological reactions.

Ad 1. We agree with the reviewer that a long-lasting kidney graft is prone to be injured in many ways, but we tried to underline the rapid and irreversible graft function loss, which has occurred in our case, and its possible link with cancer treatment (hemicolectomy, chemotherapy) and the multifactorial burden in the immunosuppressive regimen.

2) Presentation of the case is not prepared according to CARE guidelines starting from the title. It needs to be revised and re-written. Provide a sequential-events story in the section of Case presentation. Start with the history of CKD and kidney transplantation passing through the post-transplant history. Then the new history of colonic cancer and its management. I suggest re-arranging the section of the Case presentation completely.

Ad 2. When writing our case, we were directed by the particular guidelines issued by the Journal. In fact, in the case of any discrepancies in the Journal and CARE guidelines, we obeyed the Journal ones.

3) Writing errors including spelling of words (consider the headings, text, and table) and consequence of events should be considered.

Ad 3. As suggested, we carefully checked the whole manuscript and fixed many misspelled words.

4) Intraoperative photos are deficient. They may help better understanding among readers.

Ad 4. This patient was operated on in a General Hospital. No photos are available.

Reviewer 3

The authors present a case report of transplanted kidney loss shortly after initiation of adjuvant chemotherapy for colon cancer. You did a great job. The authors addressed that 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. However, some of important issues need to be verified to improve your work as following.

1. Please provide summary data of possible drug interaction with immunosuppressive agents, the metabolism and excretion pathways of immunosuppressant and anticancer use in this case. Additionally, please provide data of the level of blood immunosuppressant, kidney function, and BP during illness and the treatment.

Ad 1. As suggested, we expand the paragraph in the Discussion section, which covers the topic of potential interactions between anti-cancer therapy and immunosuppressive regimen. Additionally, we added data concerning BP control of our reported patient.

2. Systematic reviews and meta-analyses are considered to be the highest quality evidence on a research topic because their study design reduces bias and produces more reliable findings. Please summarized the results and provide evidence from recent systematic review and meta-analysis if available. Additionally, please provide summary data of previous case reports or case series of outcomes of patients with CRC after renal transplantation.

Ad 2. Unfortunately, there is no systematic review or meta-analysis on this particular topic. There are only descriptions of CTH in 12 kidney transplanted patients (The table description of 24 cases, as outcome data presented by Kim et al. were provided for the patients with and without adjuvant CTH). We have summarized the published cases in an additional table and added references.

Liu HY, Liang XB, Li YP, Feng Y, Liu DB, Wang WD. Treatment of advanced rectal cancer after renal transplantation. *World J Gastroenterol.* 2011;17(15):2058-2060.

Xia Z, Chen W, Yao R, Lin G, Qiu H. Laparoscopic assisted low anterior resection for advanced rectal cancer in a kidney transplant recipient: A case report. *Medicine (Baltimore).* 2016;95(44):e5198.

Müsri FY, Mutlu H, Eryılmaz MK, Salim DK, Coşkun HŞ. Experience of bevacizumab in a patient with colorectal cancer after renal transplantation. *J Cancer Res Ther.* 2015;11(4):1018-1020.

3. Finally, since I am not a native English user, I did not check for typo errors and grammatical errors thoroughly. This should be done by an appropriate language reviewer.

Ad 3. The paper was edited by the professional editing service.

Reviewer 4

The authors compiled a case report with Transplant kidney loss after Chemotherapy, this is somewhat expected outcome and nothing unusual or surprising. It would have been better if the

authors would combine the case report with review of literature. Did the authors follow the recommended colonic CA screening guidelines for this patient?

Ad. Yes, it is true that kidney graft function loss may happen during cancer treatment. However, it is not a rule, as many patients preserve an excellent graft function despite the intensive cancer treatment. See Table 2 and other references.

Kaźmierczak O, Kozaczka A, Kolonko A, Kajor M, Pajak J, Chudek J. Advanced Leiomyosarcoma of the Retroperitoneal Space in a Kidney Transplant Recipient with a History of Peritoneal Dialysis: A Case Report. Am J Case Rep. 2021;22:e933267.

Bilek O, Holanek M, Jurica J, Stepankova S, Vasina J, Selingerova I, Poprach A, Borilova S, Kazda T, Kiss I, Zdrzilova-Dubská L. Drug interaction profile of TKI alectinib allows effective and safe treatment of ALK+ lung cancer in the kidney transplant recipient. Int Immunopharmacol. 2021;99:108012. doi: 10.1016/j.intimp.2021.108012.

There is no specific screening for CRC recommended to kidney transplant patients.