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Letter to Editor

Cancer Treatment with Immune Checkpoint Inhibitors in Kidney Recipients

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To The Editor

After an organ transplant, cancer stands as one of the three primary culprits leading to mortality, alongside cardiovascular disease and infection (1,2). Notably, advancements in screening, prophylaxis, and interventional therapies have contributed to a decline in the occurrence of cardiovascular disease and infection, enhancing post-transplant outcomes. However, immunosuppressive regimens remain be most important causes for increased cancer risk in this population. Research findings reveal a notable increase in the risk of cancer, ranging from two to four times the baseline rate, following organ transplantation (3).

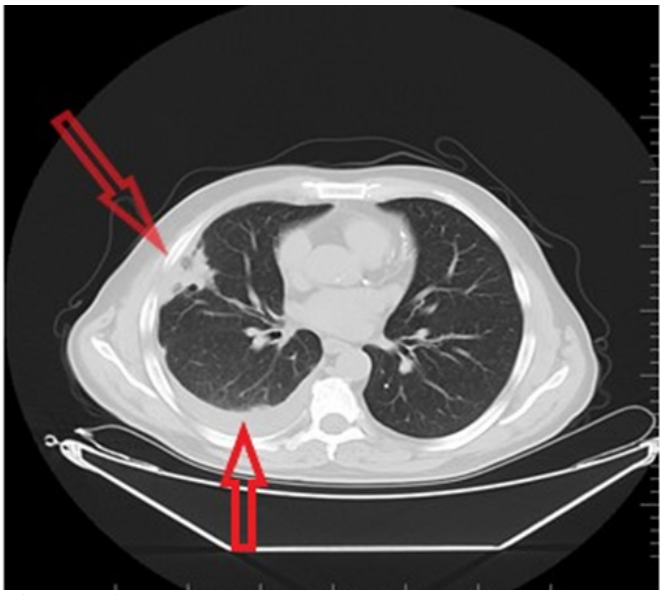
In the past decade, a transformative shift in cancer therapy has emerged through the targeted manipulation of the immune system via immunotherapy. This revolutionary approach involves the modulation of the patient's existing immune system using immune checkpoint inhibitors (ICIs), such as anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), anti-programmed cell death (PD1), and anti-programmed cell death ligand 1 (PDL1), resulting in sustained remissions across diverse tumor types (4,5). In the CheckMate-057 and CheckMate-017 trials, nivolumab demonstrated a significant enhancement in overall survival compared to docetaxel in patients with advanced non-small cell lung cancer experiencing disease progression following platinum-based chemotherapy (the median overall survival in patients who received nivolumab was 3 months longer (12.2 months vs 9.2 months) (6).

The utilization of immune checkpoint inhibitors in kidney transplant recipients is linked to markedly elevated rates of acute rejection (7). In a recent multicenter retrospective cohort study involving kidney transplant recipients (KTRs) with cancer receiving immune checkpoint inhibitors (ICIs), findings indicated that 42% of patients experienced acute graft rejection, with 65.5% of those cases progressing to end-stage kidney disease (ESKD) necessitating dialysis (8).

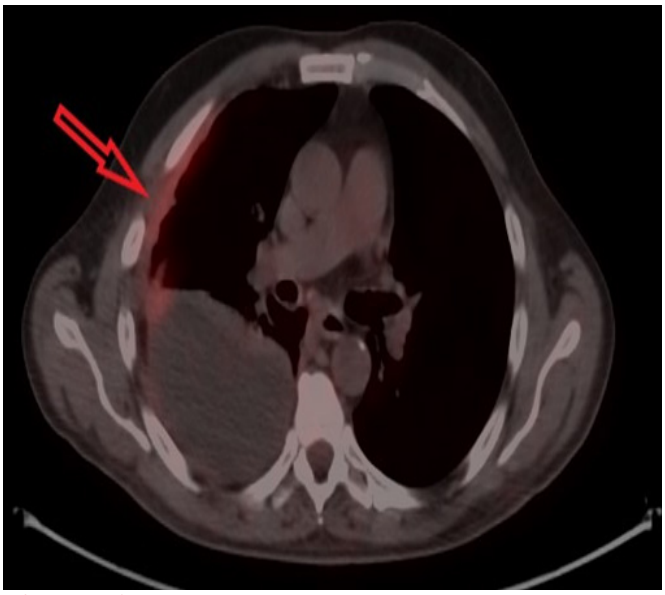
Given all, ICIs are potent to lead to posttransplant acute rejection and rejections mainly occur within the first month following initiating the treatment. Unfortunately, an acute rejection following an ICIs course will confuse all clinical outcomes, since the most potent anti-rejection treatment is not possible during an active malignancy (9). Moreover, the worsening allograft function will confuse the dosing of chemotherapy and increase unadorable hospitalization. So, considering an ICIs regimen + chemotherapy in an organ recipient under immunosuppressive treatment stands there as a crucial dilemma in modern medicine. Nevertheless, it is crucial to highlight that not all immunomodulators exhibit uniform effects regarding allograft rejection. For instance, studies indicate that nivolumab demonstrates a higher potency in inducing allograft rejection, whereas ipilimumab exerts a comparatively lesser impact on rejection outcomes (10).

In this context, here we present a briefcase to highlight the importance of the issue.

Case: A 53-year-old male patient, who lost his kidney in 2009 due to recurrent kidney stone obstruction and pyelonephritis, underwent a living donor transplant in 2016. A total of 300 mg (3 mg/kg total dose) of ATG was administered. The patient, with no history of rejection and stable renal function, presented to the organ transplantation clinic four months ago with complaints of persistent cough, fever, and right abdominal pain. Clinical, laboratory, and radiological examinations revealed findings related to lower right lung lobe infiltration and pleural effusion (**Picture 1**). The initial diagnosis was lobar pneumonia, and the second evaluation suggested lung cancer. Due to the preliminary diagnosis of malignancy, mycophenolic acid was discontinued, the tacrolimus dose was reduced by 50%,



Picture 1. Right lung-located involvement and ipsilateral pleural effusion (Arrows)



Picture 1. 18-FDG PET-CT demonstrates an increased pleaural glucose uptake (Arrow)

and the prednisolone dose was doubled. Additionally, 1.5 mg/day everolimus in divided doses was added to the treatment. The patient underwent a two-week treatment course comprising moxifloxacin, fluconazole, and oseltamivir (since the initial antibacterial treatment was ineffective, subsequent treatments were targeted to viral or fungal etiologies). A lung biopsy was scheduled for the patient who did not respond to this treatment and experienced fever, cough, chest pain, and high CRP.

Since the patient's lung biopsy was compatible with non-small cell lung cancer (squamous cell cancer), and squamous cell cancer was also detected cytologically in the pleural effusion fluid, the patient underwent lobectomy and pleurectomy + decortication surgery (PET-CT; **Picture 2**). PD-1 expression rate on malignant cells was approximately 80%. The patient was scheduled for chemotherapy, consisting of paclitaxel (175-225 mg/m2, every 3 weeks) + nivolumab (240 mg every 15 days).

At the first outpatient polyclinic control 4 weeks after the treatment of malignancy with administrating nivolumab, creatinine was found to be twice as high as the baseline value. Nivolumab treatment was discontinued, and the paclitaxel dose was halved. An allograft biopsy was performed since serum creatinine level continued to be elevated after 10 days (after excluding all possible causes of creatinine elevation). Biopsy findings were consistent with mixed-type acute rejection.

The patient was treated with 3 doses of 100 mg mini-pulse glucocorticoid and titrated to maintain the tacrolimus trough level at 5 ng/dl. Everolimus level was titrated to 5-8 ng/dl and monitored. Unfortunately, the patient's disease progression continues, and the estimated glomerular filtration rate (eGFR) at the last follow-up is 16 ml/min/1.73 m2. The clinical outcome is projected to be renal replacement therapy shortly (baseline serum creatinine was 1.3 mg/dl and current is 4.23 mg/dl).

In conclusion, the presented case underscores the intricate challenges at the intersection of organ transplantation and cancer therapy. The complex management of immunosuppression, coupled with the potential for acute rejection during cancer treatment, highlights the need for careful, individualized approaches. In renal transplant recipients, the use of ICIs should be carefully evaluated, with consideration given only to cases where these drugs can make a substantial contribution to patient survival.

DECLARATIONS

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