Urothelial Carcinoma in an Allograft kidney

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Abstract
Patients who have been kidney transplanted have an increased risk of developing cancer. This case report presents a rarely described case in which a patient, who had received a kidney transplant from a deceased donor, was diagnosed with disseminated urothelial carcinoma originating from the allograft. After the removal of the allograft and the immunosuppressive treatment, there was regression in the cancer. Unfortunately, it was not a complete regression of the urothelial cancer and the patient died. This case indicates that there is a risk of getting cancer from the transplanted kidney from a deceased donor, but also that the immunosuppressive treatment can contribute to the development of this cancer.

Introduction

There is an increased risk of developing cancer in kidney transplanted, especially due to the immunosuppressive treatment [1, 2], but there is also a risk of getting cancer transmitted from the donor via the allograft, especially if the transplant is from a deceased donor. We present a patient with a kidney transplant, who was diagnosed with disseminated urothelial carcinoma originating from the allograft.
Case

A 40-year-old man had received three kidney transplants due to chronic interstitial nephritis. The first kidney graft he received was at the age of 15 years and was located in the left side of the abdomen. Unfortunately, it was rejected after 2 months and was later removed. The second graft he received was at an age of 20 years. It was located in the right iliac fossa and was rejected 10 years after. Both kidney grafts were rejected due to chronic interstitial nephritis. The third kidney transplant was implanted 8 years prior to his death and came from a deceased donor. This graft was located in the left iliac fossa (see Fig. 1). The patient still has his native kidneys and two of the grafts.

The patient had been receiving immunosuppressive treatment (tacrolimus, mycophenolate mofetil, prednisolone, and periodic steroid regimens) for 25 years as he started getting this treatment at the time of the first kidney transplant. The target on tacrolimus was 3–5 μg/L.

At a routine follow-up, creatinine levels had increased and an ultrasound-guided biopsy of the kidney allograft was made focusing the kidney and the urinary tract. The biopsy showed normal histology and no signs of rejection.

Two months later, he was hospitalized with abdominal pain and the blood samples showed a further increase in creatinine. During hospitalization, a CT scan was performed, suggesting edematous allograft suspicious of a rejection reaction and sub ileus. This resulted in a rebiopsy of the allograft kidney (see below) and medical treatment for the sub ileus.

During admission, abdominal pain worsened, interpreted as complete ileus, which prompted an immediate surgery. The surgeon found a stenotic tumor in the colon sigmoideum, with adhesion to the 3rd and latest implanted kidney allograft, which led to appendectomy, sigmoideum resection, and an ileostomy. The cause of the obstructive ileus was the stenotic tumor in colon. Pathological evaluation of the stenotic tumor revealed an urothelial carcinoma.

Fig. 1. PET-CT scan showing metastatic cancer. The arrow shows one of the malignant changes on the allograft kidney (the whole allograft kidney lights up and is inhomogeneously suggesting malignant changes).
The kidney biopsy performed prior to surgery consisting of 15–20 glomeruli, showed that there was sclerosis in 7–11 glomeruli and signs of borderline rejection. Additional staining revealed the presence of urothelial carcinoma cells stage T3. A PET-CT scan was performed, showing disseminated malignant disease with heavy glucose uptake in the kidney allograft and in the liver, bone, retroperitoneum, and the abdominal wall suggesting metastatic cancer (shown in Fig. 1). In conclusion, the scan indicated disseminated urothelial carcinoma originating from the kidney allograft. The allograft kidney was removed and the pathological examination revealed urothelial carcinoma originating from the renal pelvis and normal renal tissue without sign of rejection. After the removal, the immunosuppressive treatment was withdrawn and hemodialysis was started.

Due to his disseminated disease, the oncologists could only provide palliative care, and because of his poor condition, he was admitted to a hospice. Surprisingly, during the first month in hospice, the clinical condition improved spontaneously and the patient was discharged. He gradually began to work and got a normal everyday life.

The patient’s cancer was monitored by the oncologists with CT scans. The first 2 years after the allograft removal CT scans showed regression of malignant manifestations, which was attributed to the withdrawal of the immunosuppressive treatment. During this period, the patient did not receive any treatment of the cancer as he was not a candidate for chemotherapy. Unfortunately after 2 years, a CT scan, and later a PET scan, showed enlarged lymph nodes in the mediastinum, which was confirmed by a biopsy to be urothelial carcinoma.

The patient then received experimental oncological treatment with pembrolizumab. Despite the treatment, the cancer rapidly progressed, and this led to his death 6 months after.

**Discussion**

The cause of death in this case is disseminated urothelial carcinoma, which most likely originated from the allograft. In general, patients with kidney transplants have greater risk of cancer compared to people in dialysis and the general population [1–3], but the risk of getting urothelial carcinoma in the allograft, as in this case, is rare [4]. In this case development of the cancer could have occurred in two ways: either transmitted from the donor at the time of transplantation or de novo development in the patient after transplantation.

With the current screening for deceased donors, small cancers, which are not macroscopically visible, can be transmitted to the recipient via the allograft. CT scans with contrast are routinely performed in living donors to detect tumors but not in deceased donors, most likely due to the limited time to run tests for ethical reasons [5]. Routine CT scans of donors may detect small not macroscopically visible cancers. In this case, the cancer was diagnosed 8 years after receiving the allograft kidney. The timeframe suggests that the cancer developed in the recipient after transplantation and thus would not have been found with a CT scan of the donor at the time of transplantation. One possible cause of the patient’s cancer could be vesicoureteral reflux prompted by either the patient’s underlying disease or by the transplanted kidney.

The immunosuppressive treatment is known to increase the risk of certain cancers such as Kaposi sarcoma and non-Hodgkin lymphoma in kidney transplant recipients [1]. It is unclear if this is also the case for urothelial carcinoma [6]. However, discontinuation of the immunosuppressive treatment in allograft patients with cancer also constitutes a risk, as it can lead to complications such as the development of donor-specific antibodies and rejection of the allograft. In this case, there was regression of the cancer after the
withdrawal of immunosuppressive treatment, indicating that this treatment indeed played a major role in the development of urothelial cancer. However, the regression was not complete.

The cancer was only diagnosed when the patient had disseminated disease, and perhaps the cancer could have been detected at an earlier stage if there had been a screening for urothelial cancer in kidney-transplanted recipients. But the clinical guidelines disagree on whether screening for urothelial cancer should be offered, due to the lack of evidence [3, 7, 8]. As urothelial cancer in the allograft kidney is rare [4], some guidelines recommend against screening due to the risk of finding too many false positives, thereby causing potential harm for the patients [7]. The guidelines that recommend annual screening for urothelial cancer base it on the increased risk of morbidity and mortality [8].

It is concluded that with the current screening for deceased donors, the risk of getting cancer from the transplanted kidney cannot be completely avoided. This case indicates that the immunosuppressive treatment could promote development of urothelial cancer. However, the risk of developing this type of cancer is low, and due to lack of evidence, the clinical guidelines disagree on whether the screening for urothelial cancer should be offered.

Statement of Ethics

No ethics approval or exemption for ethics approval is required in publication of a case report form according to Danish Legislation. Written informed consent was obtained from the patient for publication of the details of his medical case and the accompanying image. Before the patient’s death, he gave consent himself in written form. Written informed consent was also obtained from the patient’s next of kin for publication of the details of his medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Maria Baand Hejlesen has written the entire script. Frank Holden Mose and Jesper Noergaard Bech have read the manuscript and made corrections. Mohammad Hassan Youssef made the pictures for the case report.

Data Availability Statement

The case report includes all relevant data relevant for the sufficient presentation of the case. Additional data are not publically available due to patient discretion.
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