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Donor Origin Neuroendocrine Cancer: A Case Report and Literature Review

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Solid organ transplantation has been instrumental in improving the quality of life of patients with end-organ damage, but this does not come risk-free.[1] Because of immunosuppression, recipients of solid organ transplants are at an elevated risk of developing certain types of cancer, with some reports documenting as high as 4 times compared with their nontransplant counterparts.[2] The decreased efficacy of the immune system results in the body's inability to remove abnormal and cancerous cells before they propagate and form a tumor or mount an immune response to known carcinogenic viruses.[2] Solid organ transplantation also carries the risk of developing donor-origin cancers (DOCs). These malignancies are rare occurrences that can either be transmitted to the recipient at the time of transplantation or develop from donor tissue over time after solid organ transplantation.[1,3,4] We present a case of a patient with both high-grade DOC and low-grade DOC and review the management of this patient's complex malignancy care.

CASE DESCRIPTION

Our patient was a 69-y-old man with a medical history of end-stage renal disease on peritoneal dialysis secondary to long-standing type 1 diabetes and resultant nephrosclerosis. The patient was undergoing evaluation for renal transplant when he started to develop brittle diabetes and had numerous episodes of hypoglycemia. In February of 2017 at the age of 64 y, he underwent a simultaneous pancreas and kidney transplant from a 38-y-old deceased donor with a history of uncontrolled hypertension who passed from catastrophic intracranial hemorrhage (ICH). Before donation, the donor had a grossly normal noncontrast computed tomography (CT) scan of the abdomen and pelvis. Induction was with rabbit antithymocyte globulin, and the pancreas was transplanted into the right pelvis with venous anastomosis to the right common iliac vein and arterial anastomosis to the right external iliac artery. The donor pancreas had immediate graft function, and the patient no longer had a need for insulin. The patient had higher than expected creatinine after transplantation, resulting in a biopsy of the kidney 2 mo after transplantation, showing evidence of interstitial fibrosis without evidence of acute allograft rejection. Despite the elevated creatinine, the patient did not require renal replacement therapy after transplantation and creatinine improved. The immunosuppression plan was initially tacrolimus, mycophenolate, and prednisone, but the patient transitioned from mycophenolate to azathioprine because of diarrhea in 2020, which resolved symptoms.

The patient continued to do well in terms of graft function until early 2022, when he was noted to have an increase in lipase. The patient underwent a CT scan of his abdomen and pelvis that revealed a tumor replacing most of the donor pancreas with a biopsy diagnosing a poorly differentiated neuroendocrine small cell carcinoma with high (85%–90%) Ki-67 proliferation index (Figure 1). Short tandem repeat analysis of the biopsy revealed that the tumor was 82% donor tissue. The whole body CT scan showed innumerable lesions in the liver as well as lesions in the lungs and bones. Whole body Gallium 68 DOTA-TATE positron emission tomography CT scanning showed DOTA-TATE avid lesions in the bone (Figure 2). The pancreatic mass showed homogenous low-level DOTA-TATE activity, suggesting a moderate differentiation (Figure 2). The lung and liver masses were not DOTA-TATE avid, suggesting a poorly differentiated tumor. Given both the high and low DOTA-TATE avidity, there were concerns that there may have been a smoldering malignancy in the pancreas allograft that was of subclinical importance until conversion to a more aggressive, poorly differentiated malignancy. Following staging, the recommendation to the patient was to explant the pancreas, but the patient would not consent to the surgery. Immunosuppression was decreased, and the patient was started on chemotherapy with carboplatin and etoposide in April 2022. Patient's initial chromogranin A tumor marker was elevated at 700 ng/mL. Around the time of starting chemotherapy, the patient's pancreatic function had declined to the point at which he needed to restart

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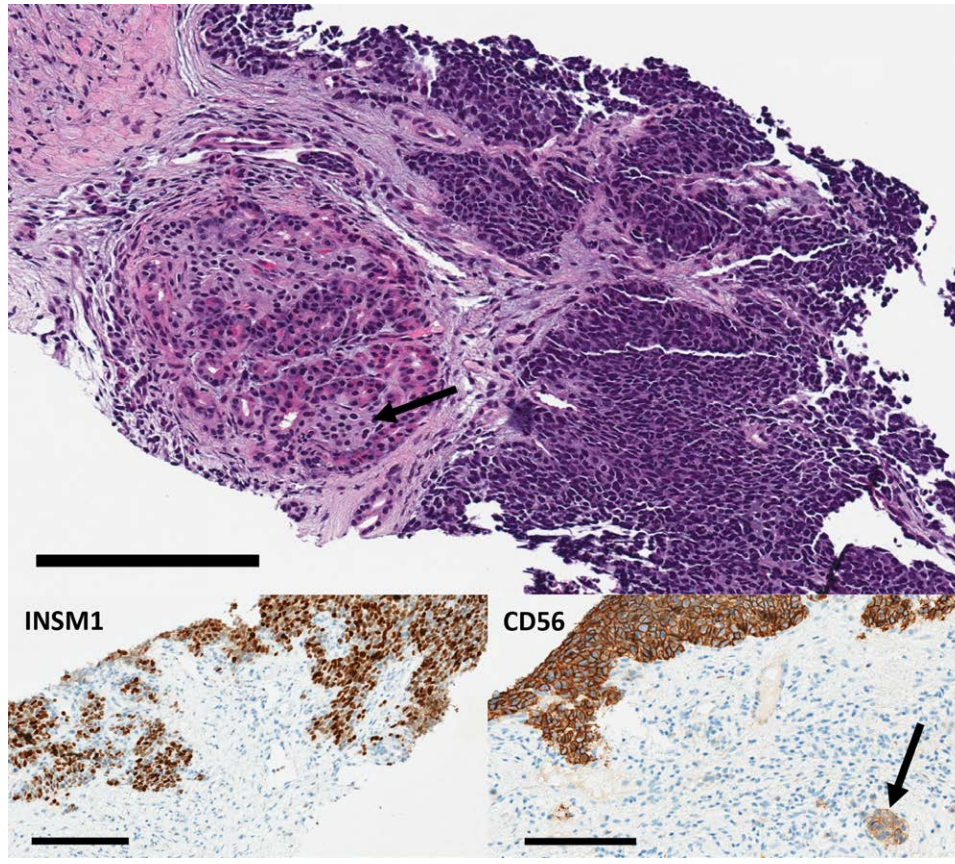

FIGURE 1. Hematoxylin and Eosin stain of the needle core biopsy with exocrine pancreatic lobule showing partial atrophy. An endocrine islet is noted (arrow). The aggregates of small "blue cells" represents an infiltrative neuroendocrine tumor. Tumor cells stain strongly positive for the neuroendocrine markers INSM1 and CD56. Weaker staining in the lower right image, noted by arrow, demonstrates endocrine islet. Bar: 200 μm.

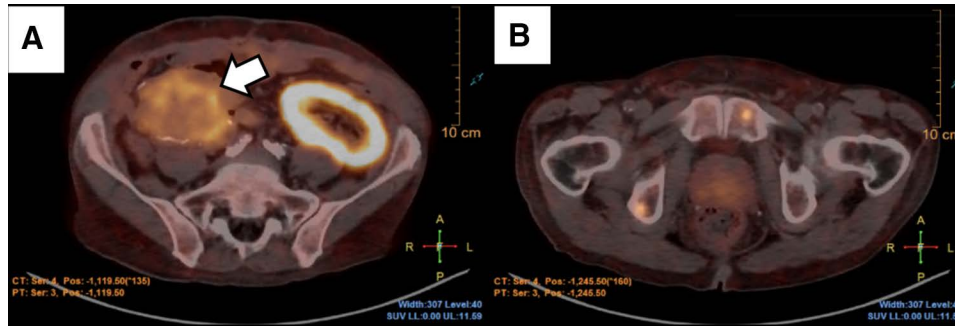

FIGURE 2. PET scan superimposed on CT scan with (A) mild DOTA-TATE uptake in the pancreatic mass consistent with moderately differentiated malignancy (arrow). B, High DOTA-TATE uptake noted in the innumerable bone lesions, consistent with well-differentiated malignancy. CT, computed tomography.

insulin, but his renal function was stable and did not need to resume renal replacement therapy.

After completing 6 cycles of carboplatin and etoposide, restaging imaging showed a decrease in the size and number of the pulmonary lesions with the persistence of the bone and liver metastatic disease as well as the donor pancreatic mass. The patient's chromogranin A showed response to therapy of 429 ng/mL. The patient was started on lanreotide for somatostatin suppression while being referred to nuclear medicine for Lutetium 177 radioactive therapy for the Gallium 68 avid lesions. Before being able to schedule Lutetium 177 treatment, the patient's overall health deteriorated with a spike in chromogranin A level to 16 000 ng/mL and renal failure. He was admitted to home hospice and passed 5 y and 8 mo after transplantation.

DISCUSSION

Cancer-related deaths in patients with solid organ transplants are the number 2 cause of death in patients with functioning grafts, higher than infections and second only to cardiovascular disease.[4] Two large subclassifications of DOC are donor-transmitted cancers (DTCs) and donor-derived cancers (DDCs). DTCs are defined as cancers transplanted into the recipient at the time of transplantation, whereas DDCs are felt to be cancers that arise later from donor tissue.[5] The risk of developing cancers in transplant recipients is estimated to be between 2 and 4 times higher in comparable patients without transplantation. These risks refer to all cancers and not just DOCs and are related to the immunosuppression patients receive after solid organ transplantation, limiting

the recipient's immune system to find cancerous cells in their infancy and remove them before tumors develop.[1-4,5] Studies suggest cancers caused by viral illnesses also occur higher in patients with solid organ transplantation, lending credence to the idea that a dampened immune system plays a significant role in carcinogenesis.[2]

Donor selection is a balancing act between risks associated with the transmission of diseases and the risk of delayed transplantation, possibly leading to death. A thorough history is a crucial part of cancer screening in donors. Given the clinical condition of most donors, history needs to be obtained from family and caregivers. Current cancer surveillance guidelines in the United States are to perform a chest X-ray (CXR) in the screening of potential donors. Different regions could require further imaging based on history. Chotkan et al looked at global radiologic screening for malignancies guidelines and found that 41% of 32 countries responded to perform CXR in addition to abdominal ultrasound. Eleven respondent countries performed a combination of CXR and enhanced or unenhanced abdominal CT scan ± chest CT scan.[6]

Given an overall donor shortage, guidelines have been developed regarding transplantation from donors with a history of cancer to help mitigate further donor shortage. Desai et al reviewed the donor registry in the United Kingdom between 1990 and 2008 to evaluate risk of DOC from donors with a cancer history. Of the 17 639 donations, 202 donors had a malignancy history, with 61 of them deemed to have a high or unacceptable risk of malignancy. These 61 donors donated 140 organs to 133 recipients, and only 8 developed a malignancy. However, none of the 8 recipients developed the same cancer as their donor.[7] Buell et al also performed a review of the international transplant tumor registry to review DDC. In this series, they found that the most common misdiagnosed cause of brain death associated with malignancy transmission was ICH. Misdiagnosed brain death attributed to malignancy postmortem occurred in 42 donors and was associated with 31 cases of DDC (74%).[3] This suggests that the underlying catastrophic ICH may have been associated with a primary or metastatic tumor.

Desai et al reviewed the risk of DTC in transplant recipients from 2001 to 2010 in the United Kingdom. They found that out of 30 765 solid organ transplants, there were only 18 incidences of DDCs, with 3 incidences occurring at least 5 mo from transplantation and were felt to be DOC as opposed to DTC. The risk of DTC was associated with patients aged >45 y, without any other statistically significant risk factor identified. This report found that the risk of DTC was as high as 0.06%, compared with earlier reports of 0.01%. The same report did find that the risk of DDC was lower at 0.01%.[1]

The management of DOC requires a multidisciplinary approach involving oncology, the medical transplant team, and the surgical transplant team. Because the DOC has donor tissue, removal of immunosuppression with the possibility of explantation of the organ needs to be considered.[8] Given the donor-derived tissue malignancy, reconstitution of the recipient immune system theoretically would result in rejection of the donor organ as well as all donor tissue, including the malignant tissue. Reports of DOCs in liver transplant recipients with localized disease do well after undergoing explantation and retransplantation, whereas kidney transplant recipients with DOCs show good response with cessation of immunosuppression.[5,9,10] There is a paucity of data regarding the management of SPK DOC, but in a systematic review of renal transplant recipients, Xiao et al found that the most common management for DOC was the withdrawal of immune suppression and nephrectomy. These strategies appeared to work in patients with more localized diseases.[11]

Ultimately, DOC is a rare phenomenon that needs to be considered when discussing organ transplantation with patients. The risk of DOC must be weighed against the benefits of organ transplantation. If a DOC does occur, management is complex and needs a multidisciplinary approach with surgery, medical oncology, and transplant medicine to provide the best treatment option for the patient.

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