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Case Study

A Donor Transmitted Melanoma in Pancreatic Islet Cell Transplantation

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Key Learning Points

Mr James Gilbert (Transplant Surgeon):

Patients with Type 1 diabetes are prone to a range of complications but perhaps one of the more serious is that of Hypoglycaemic Unawareness which leaves patients susceptible to life threatening hypoglycaemia and often the need for 3rd party assistance or hospitalisation as a result. Such patients may benefit from the treatment of either Islet cell transplantation or solid organ pancreas transplantation. Whilst transplantation has a wide range of benefits to recipients including improved quality and quantity of life, it is a treatment option that carries risks not just from the procedure itself but also from life time immunosuppression which can render the patient susceptible to a range of opportunistic infections and cancers of skin and lympho-proliferative system. In addition, there can be risks associated with the donor organ and the transmission of diseases during the process of implantation. To mitigate this risk a range of guidelines are in place to aid clinicians when they accept potential donor organs for transplantation. These guidelines include information around transference risks of infections and cancers from donors who may have both an active or past history of such. We report a case of islet cell transplantation from a donor with a past history of localised melanoma 8 years prior to donation and who was deemed very low risk, but which resulted in transmission to the recipient non-the less.

Dr Nick Coupe (Oncologist):

This case depicts a tragic but fortunately rare case of melanoma arising as a direct consequence from organ transplantation. Despite stringent donor requirements the risk of transplanting malignant cells can never be completely nullified and is currently 0.05%. Specifically in melanoma, circulating tumour cells can remain dormant for many years, only to execute their malignant potential once in an appropriate context, as described in this unfortunate case. Appreciating the global shortage of transplantable organs, methods with sufficient sensitivity and specificity are required to identify donor tumour cells whilst concurrently minimising false positives and organ wastage. No appropriate method currently exists. With respect to the individual case described above, physicians are hopeful that by stimulating the patient's immune system with immunotherapy they will mount an strong anti-melanoma response against a known immunogenic cancer.

Background:

The benefit of organ transplantation to recipient patients is well established[1], serving as the only long-term treatment for many end stage organ failure diseases. The benefits must be considered against the numerous short- and long-term risks of transplantation to determine if it is an appropriate treatment option. The most common complications of transplant recipients are those from surgery and the physiological effects of immunosuppression[2]. Less common complications may arise from diseases carried by the host being transmitted to the recipient. Microbiological screening allows clinicians to avoid transmission and appropriately manage the prophylactic treatment of infective diseases. Although considerably less common in occurrence, cancer can also be transmitted by organ transplantation. This case report will detail one such case and explore the literature to determine whether donor-transmitted cancer poses a risk to the average transplant recipient. Presentation:

The patient in this case is a 54 year-old female

who presented to the emergency department of her local hospital in early July 2020 with a three week history of progressively frequent vomiting, abdominal pain, rigors and general tiredness. The pain had a stabbing character, centred around the right upper quadrant, becoming more intense over time, and relieved by careful positioning of the abdomen when lying down.

The patient had a history of Type 1 Diabetes Mellitus since the age of 12, which was controlled by exogenous insulin for the majority of the patient's life (initially by multiple daily injection therapy and later by continuous subcutaneous insulin infusion). The patient had previously received two pancreatic islet cell transplantations due to absent hypoglycaemia awareness and severe hypoglycaemic episodes. The first of these was received in June 2018 after which the patient experienced a decrease in insulin dependency and overall improvement in quality of life. Unfortunately, transplant function started to decline in November 2018, resulting in an increasing reliance on exogenous insulin. A second transplant was arranged in December 2019, from a male DBD donor with HLA matching '2-0-1' and CMV status 'donor negative; recipient positive'. The donor had a history of melanoma, with complete curative surgical resection over 7 years prior to donation.

At time of presentation the patient was taking many medications to safely maintain her immunosuppressed state- tacrolimus 2.5mg BD; mycophenolate mofetil 250mg OD; cotrimoxazole 480mg OD; aspirin 75mg OD. The patient was also prescribed citalopram 20mg OD for depression; folic acid 5mg OD for anaemia; and atorvastatin 10mg ON for hypercholesterolaemia. She also had a continuous subcutaneous insulin infusion pump delivering 15 units insulin as background with bolus at mealtimes.

Upon admission the patient received ondansetron 4mg TDS for her nausea and started a course of tazocin 4.5mg IV TDS, micafungin 100mg IV TDS antimicrobial treatment as sepsis was suspected. Cultures were taken but came back negative. Appropriate VTE prophylaxis was administered after risk assessment. The patient had no known drug allergies.

The patient worked as a staff nurse at her local hospital and lived at home with her husband and pets (dog and parrot). She reported no smoking history and no significant alcohol intake, rarely exceeding 2 units per week. She had no family history of T1DM as far as she is aware, although may possibly have had distant relative with Type 2 Diabetes Mellitus.

Whilst under the care of her local hospital the patient received a CT scan of the abdomen and pelvis which revealed multifocal liver lesions (Figure 1), presumed to be abscesses although other potential sources of liver lesions were discussed, with suggestions of malignancy and hyperplasia of the transplanted islet cells.

The patient stabilised but was transferred to the Churchill Hospital 8 days after admission due to declining liver function and decreased urine output. Upon admission to the Churchill Hospital the patient was imaged using an MRI scan which reconfirmed numerous bi-lobar multiseptated liver lesions, consistent with liver abscesses. Antimicrobial therapy was continued, and biopsy of the lesions planned for 5 days later.

Upon examination the patient reported feeling tired and low mood, but otherwise generally well. The patient was mildly jaundiced and had bilateral dupuytren's contractures. Inspection of the abdomen revealed considerable distention and palpation revealed generalised right sided tenderness. Shifting dullness test was positive and peripheral oedema was present bilaterally up to the knee.

Initial investigations showed repeat negative blood culture, and ultrasound guided aspiration of the liver revealed the lesions to be solid and poorly defined. Histological assessment identified the lesions as tumours of metastatic melanoma and HLA typing determined the cancer to be of donor origin. MRI and CT imaging showed no intracranial or pulmonary spread of disease.

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Donor Transmitted Cancer:

Malignancy is a common long-term complication in transplant recipients[3]. Most cancers in transplant recipients are de novo, with an overall two- to three-fold increased risk compared to the general population[4], likely due to the immunosuppressive regimen and exposure to viral infections[3]. However, the focus of this report is on the much rarer incidence of cancer transmission from a transplant donor to a transplant recipient.

The SaBTO (Safety of Blood, Tissues and Organs) Advisory Committee published a document in April 2014 highlighting the risks associated with donor-transmitted cancers (DTCs). SaBTO defines a DTC as "[a cancer] that was present in the donor, perhaps unknown, which spreads to the recipient using the transplanted organ as the vector. It may appear first in the donor organ, or remote from it"[5]. Time of diagnosis is important in DTC prognosis, separating them into two categories: early DTC (before or within 6 weeks of transplantation) and late DTC (6 or more weeks post-transplant)[6].

In many cases, organs from donors with a history of cancer are rejected due to the risk of DTC to the patient, but if the patient and doctor feel the benefit of the transplanted organ is great enough, they may still proceed with the transplant. Using a sample period of 01/10/2009 to 31/03/2013 of the 27,465 potential DBD/DCD donors, 4,208 (15.3%) were contraindicated due to 'any malignancy within the past 12 months, excluding brain tumour'. From a sub-sample from 01/04/2013 to 31/08/2013 of 452 contraindicated donors, the majority (338; 74.8%) were contraindicated due to 'evidence of spread outside the affected organ within the three years preceding death', while only 5 (1.1%) were due to melanoma (Figure 2)[5].

From 01/04/2003 to 31/03/2013, 506 consented and eligible donors were identified to have a past medical history of cancer, of which 358 donated at least one organ[5]. These donors contribute a small but notable proportion of the transplanted organs received by patients each year (approx. 2.5%).

In this case the melanoma is a late DTC, due to presentation 7 months post-transplant. It is assumed the donor pancreatic tissue contained previously undiagnosed metastatic melanoma cells which were seeded into the liver by transplantation. It is likely that the transplanted melanoma cells were present from the melanoma removed 7 years previously and had remained as an occult malignancy in the bloodstream of the patient[7]. Constant immunosurveillance prevented the donor from developing metastatic melanoma themselves, but transplantation of the cells to an immunosuppressed individual allowed the tumour to grow in the hepatic tissue. Occurrence of the tumour in the liver is not surprising, as the liver is one of the most common sites of melanoma metastases[8], and transplanted islet cells are typically implanted into the liver of the recipient, via the main portal vein[9].

DTC Incidence and Risk Assessment:

A study in 2012 of the UK Transplant Registry to investigate incidences of DTC and DDC across all 30,765 organ donations (14,986 donors) from 01/01/2001 to 31/12/2010. A total of 15 cases of cancer transmission were identified (0.05%), and in each case the presence of cancer was not known at donation[6]. These figures are in line with studies from other countries[10–12]. The 15 organs came from 13 donors who donated organs to another 19 recipients, all of whom remained cancer free. Statistical analysis revealed the only factor showing a strong association with DTC (when adjusting for all others) was a donor age of 45 years or older (p=0.004). There were no incidences of DTC from living donors[6].

All potential donors are screened for transmissible diseases under ECOT[13] and BTS[14] guidance including assessment of history; examination; imaging; blood tests; and consultation with family, close acquaintances, and healthcare professionals. Currently, tumour specific imaging and blood tests are not typically requested before donation but will be assessed if reports from previous investigations are available. Reports from an autopsy must be immediately communicated to the organ procurement organisation if performed. Additional SaBTO guidance on minimising risk of DTC was published with the 2014 report, including full exploration of the thoracic and abdominal cavities during retrieval and urgent histological examination of unexplained lesions[5]. The SaBTO report also made recommendations on how to classify the risks of different cancer types (Table 1).

Since no cases of DTC from 2001-2010 were from a previously diagnosed cancer[6], the current system of review makes cases like the one reported in this case study highly unusual. Furthermore, the fact that all cases of DTC are from undiagnosed cancers opens the potential for tumour screening to detect occult malignancies in donors. The guidelines are thorough for CNS tumours after a detailed publication in 2010[15], but the guidelines are limited in scope for non-CNS cancers due to a lack of evidence for many cancer types. Melanomas are generally considered to be high risk (risk of transmission >10%), and some evidence suggests a transmission rate as high as 74%[16]. However, in cases where the melanoma was a superficial spreading type with a >5 year cancer free period after curative surgery, the risk is downgraded to low (risk of transmission 0.1-2%)[5]. This would place the risk of DTC for the patient in this case at 0.1-2% as the donor was 7 years cancer free at time of donation.

The occult nature of malignancies such as melanoma will always pose a risk of DTC in donors with a history of such cancers, as full remission of the disease does not eliminate the possibility for circulation of tumour cells in the body. It is thought these circulating tumour cells are prevented from seeding metastatic disease by

immunosurveillance, but that does not always eliminate their presence[7]. As such there is a reasonable argument to treat most organs from donors with a history of cancer as high risk and contraindicated to transplantation. Novel tests exist to predict the risk of recurrence of melanoma after surgical removal of the primary tumour. By performing a reverse transcription-PCR tyrosinase assay on the blood of the melanoma patient it is possible to detect tyrosinase (an enzyme needed for melanin biosynthesis) in the blood, a marker for circulating melanoma cells[17]. New approaches to the test using multiple time points and larger blood draws, have allowed the development of a 72% accurate (62% sensitivity, 78% specificity) prognostic test for melanoma recurrence after primary tumour removal[18]. If adapted to use in potential donors this could allow surgeons to better understand the risk of DTC following transplantation. However, use of a predictive serological test needs to be considered with the context of DTC rates. Current measures sufficiently eliminate DTC risk, as seen by a DTC rate of 0.05% (from which none of the donors had a history of cancer) and not a single case of donor transmitted melanoma[6]. Even when using a generous overestimation of 0.2% donor transmitted melanoma from a Danish study in 2002[12], the tyrosinase assay would have a number needed to predict (number of patients/donors needed to be examined to correctly predict the diagnosis of one person[19,20]) of 270 (Table 2). Considering the test would have a 22% false positive rate, no useful information would be provided if used to screen for occult melanoma in the donor population. These findings reassure our confidence in the current assessment of DTC risk, and emphasise the rarity of incidences such as the one presented in this report.

Treatment and Prognosis:

Evidence that transplant recipients who develop DTC (compared to non-DTC recipients) have a worse prognosis is unconvincing, showing a statistically insignificant 10% decrease in five-year survival (93% to 83%)[6]. However, it must be noted that in the same study, the 3 DTC recipients that later died as a direct consequence of cancer were all cases of late DTC.

In this case of late DTC, the patient was assessed by oncology and transferred to the team's care for treatment of the melanoma. Previous cases of DTC recommend changing immunosuppression to an mTOR inhibitor (e.g. sirolimus) for combined immunosuppressive and anti-neoplastic effects, however this is typically in cases where transplant function is vital to patient survival[5]. Furthermore, there is no clinical evidence supporting the use of mTOR inhibitors in advanced melanoma. The patient in this case was prescribed pembrolizumab immunotherapy to generate a strong immune response against the tumour, a treatment with an estimated 41% 5-year overall survival in clinical trials[21]. The immune response will be aided by the stopping of all immunosuppressive medication and highly immunogenic nature of a donor melanoma. Unfortunately, the immune response will likely destroy the transplanted tissue, but this is of minor concern to the health of the patient.

Conclusions:

Risk of DTC is minimised by evaluative screening of organs typically relying on documentation of previous cancer diagnosis[13,14]. However, due to existence of previously undiagnosed cancers in donors there is always a small risk of DTC in donation[6]. Furthermore, a previous history of cancer is not always a complete contraindication. Transplantation of a high risk organ may represent good practice when a compelling argument is made that the organ will sufficiently improve the patient's length or quality of life, and the consequences of declining the organ (to wait for a lower risk donation) would detrimentally impact the patient's health. An important judgement must be made by the surgeon and potential transplant recipient together, balancing the benefits and risks of organ transplantation, including the risk of cancer transmission from a potential donor[13]. Patient education is critical in this process. Without a good understanding of their current disease progression and the potential harm imposed by transplantation of a high-risk organ the patient cannot give informed consent. It is crucial these aspects of the procedure are discussed in detail with the patient before obtaining consent and the discussions are well documented[14]. Furthermore, issues of equal access need to be considered as those who are sickest will be least able to wait for a low risk organ, potentially influencing their decision and resulting in health inequality. Due to this, it must be made explicitly clear to a potential high-risk organ recipient that refusal of the organ will in no way impact their ability to receive a lower risk organ in the future[22].

The rarity of the event discussed in this report makes it hard to contextualise within the current literature. Over a 10-year period not a single case of donor transmitted melanoma was recorded in the UK Transplant Registry6. Nor is there record of DTC from a previously diagnosed cancer . Furthermore, pancreas and islet cell transplants contribute a very small proportion of annual recipients when compared to kidney, liver, heart, and lung. None of DTC cases from the 2012 study were from pancreatic transplantation[6] and there appears to be no previous reports of DTC from pancreas and islet cell transplants in the literature. To best understand the context of this case I have instead investigated the incidence of donor transmitted melanoma from all types of transplant, which is also a rare occurrence, and the subject of numerous case reports[23]. A common issue throughout the literature is underreporting of DTC, with many authors believing the true incidence to be higher, and a presumption of post-transplant cancer being de novo causing cases of DTC to be missed[5,13]. This results in the current guidance for DTC risk assessment having limited scope and therefore does not provide clinicians and patients with much useful information when making a difficult decision. As such, very cautious decisions are made, typically rejecting potential donor organs. This may protect recipients from DTC, but an overcautious approach may not be in the patients' best interest, especially when considering the benefits of organ transplantation. A better understanding of DTC risk is required, which will be achieved by more study and analysis of post-transplant malignancies, with an increased awareness of DTC.

When comparing donor-transmitted diseases, it is tempting to assume a screening programme for occult malignancy may prevent DTC much in the same way we manage transmission of infectious diseases. However, the success of organ screening for infective diseases is due to the high prevalence of diseases such as CMV (20-100%); EBV (>90%); HBV (>10%); HCV (0.5-18.5%)[13], and highly sensitive tests for rare infective diseases. As shown previously, the use of currently available serological tests for occult malignancy screening is impractical and may in fact be detrimental to patient health, by falsely contraindicating life-saving organs. Despite this, practical application of serological testing may be found in risk stratification and organ allocation. Testing may be used to determine the

DTC risk of organs which are presumed higher risk due to the donor medical history. This would allow more informed decisions to be made by the clinical team and patient regarding DTC risk, potentially preventing cases such as the one in this report and expanding the organ donation pool.

There is an ever-increasing demand for transplant in patients with end stage organ failure[24]. Malignancy risk factors such as age and obesity are also increasing in the donor population[25], making use of organs from donors with a history of cancer necessary to meet the transplantation demand in the future. Literature already exists suggesting the use of organs from higher risk donors to satisfy increasing demand, with a focus on low grade breast, ovarian, colonic and melanoma cancers[26]. Furthermore, serological tests similar to the melanoma tyrosinase assay[18] already exist to detect circulating tumour cells from breast[27], colon[28], ovarian[29] and prostate[30] cancers. In addition to making more informed clinical decisions, the information gathered from these assays could be used to stratify risk and influence organ allocation. Cohorts of older patients with end stage organ disease receive great benefit to quality of life from organ transplantation[31,32] and are at a lower risk of developing general malignancies post-transplant[33]. The information gained from circulating tumour cell assays could be used to allocate organs from donors with a history of cancer to appropriate recipients, ensuring young organ recipients receive lower risk organs, mitigating the complications of late DTC. Unfortunately, the prognostic tests currently available are impractical for use in an organ retrieval setting, with results taking up to 96 hours to process[27,28,30]. The demand for organs will always be increasing as the general population ages, and with recent legislature making organ donation an 'opt-out' process[34], clinical teams are likely to face the dilemma of DTC transplantation risk increasingly in the future. It is urgent that the true nature of this rare event is investigated, and diagnostic tools are developed to help patients and clinical teams make the best decision for the patient.

Conflicts of interest
None.

Funding
None.

Consent
The patient has consented to the publication of this case study.

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