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CASE REPORT

Donor transmission of malignant melanoma in a lung transplant recipient 32 years after curative resection

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Summary

In the current era of organ shortages and long wait times for life-saving transplants, marginal or extended donors are increasingly being considered; one such category of marginal organs is from donors with a previous history of malignancy. Melanoma in particular has been associated with increased risk of developing late recurrence. In this report, we describe a case of fatal donor melanoma transmission to a 64-year-old lung transplant recipient 32 years after surgical excision of the melanoma. Based on this report and review of the available literature, we conclude that a history of donor melanoma, regardless of the stage and time interval from 'curative' surgical resection, should remain a strong relative contraindication to transplantation.

Introduction

Throughout the world, donor organs remain in short supply. For example, there are over 100 000 people on transplant waiting lists in the United States; last year, however, <30 000 solid organ transplant procedures were performed [1]. This shortage has led to prolonged waiting times and unacceptably high death rates on transplant wait lists. Several strategies have been employed to try to widen the donor pool. One approach is to consider donors that do not meet standard acceptance criteria. Nonstandard donors typically are older, have organs with suboptimal function or have a history of infection or malignancy [2,3]. In this report, we describe our experience with a recipient who received a lung allograft from a donor with a remote (>30 years) history of melanoma resection.

Case report

A 64-year-old gentleman with history of advanced pulmonary fibrosis underwent right-single lung transplantation in July 2004. He received postoperative immunosuppression with daclizumab for induction therapy (1 mg/kg every 2 weeks for total of five doses) and a standard regimen that included tacrolimus (goal trough levels ~8–12 ng/ml), azathioprine (2 mg/kg/day) and prednisone (10 mg/day). Postoperative course was complicated by ischemic colitis with colonic perforation requiring emergency laparotomy, transverse colon resection with

end-colostomy. Nevertheless, the patient's respiratory status remained stable and he was discharged to home on postoperative day number 21. After transplantation, the patient had a significant improvement in his pulmonary function. Pretransplant pulmonary function tests showed an FEV1 = 1.22L (43%), FVC = 1.57L (45%), TLC = 1.58L (38%) and DlCO = 37% consistent with severe restriction. Several months after surgery, office spirometry measurements revealed an FEV1 = 2.90L (154%) and FVC = 3.64L (157%).

At the end of August 2005, the patient presented to clinic with new onset dyspnea with heavy exertion, dry cough and a <10% decline in home spirometry measurements. A CT scan of the chest was obtained on August 31, 2005 and showed a new (1.3 cm × 0.9 cm) nodule in the right lower lobe (RLL), enlarging right hilar lymph node and nodular thickening of the bronchus intermedius (RBI) and right middle lobe (RML) bronchus (Fig. 1a). A diagnostic bronchoscopy was performed and showed airway edema and 'greenish/black' plaques in the mucosa of the right mainstem bronchus distal to the anastomosis and in the RBI. Several of these lesions were protruding into the airway lumen and partially occluding the RML orifice. Endobronchial biopsies of these lesions revealed findings consistent with malignant melanoma (immunohistochemical staining positive for HMB-45 and S-100) (Fig. 2a).

Staging workup with PET scan showed increased focus of F18-FDG uptake in the RLL and right hilar region suspicious for malignancy. CT imaging of the upper abdomen did not show evidence for metastatic disease. Skin examination did not reveal lesions suspicious for malignancy raising concern for a donor-derived malignancy. Additional information regarding the donor was requested.

The donor was a 51-year-old woman who had died from complications related to traumatic brain injury. Notably, her medical history was significant for excision of a malignant melanoma in 1972, 32 years prior to death. Unfortunately, the transplant team did not know this information at the time of donor acceptance. However, our practice at that time would not have necessarily excluded consideration of this donor. Bronchoscopic evaluation of the donor showed no findings worrisome for malignancy. Retrospective review of the donor medical record showed no documentation of other treatment for this lesion.

To investigate the origin of the endobronchial malignancy, DNA typing via short tandem repeat polymerase chain reaction (STR PCR) was performed. STR PCR is based on the amplification and analysis of multiple polymorphic markers called short tandem repeats or microsatellites [4,5]. Most individuals can be distinguished by comparing allelic data obtained from a common panel of

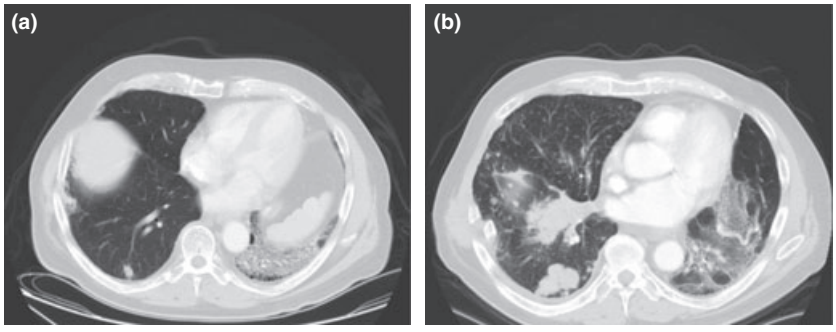

Figure 1 (a) August 30, 2005, chest CT, small nodule RLL. (b) March 3, 2006 – extensive metastatic disease with of right lung pulmonary masses and lymphangitic spread of tumor within the lung.

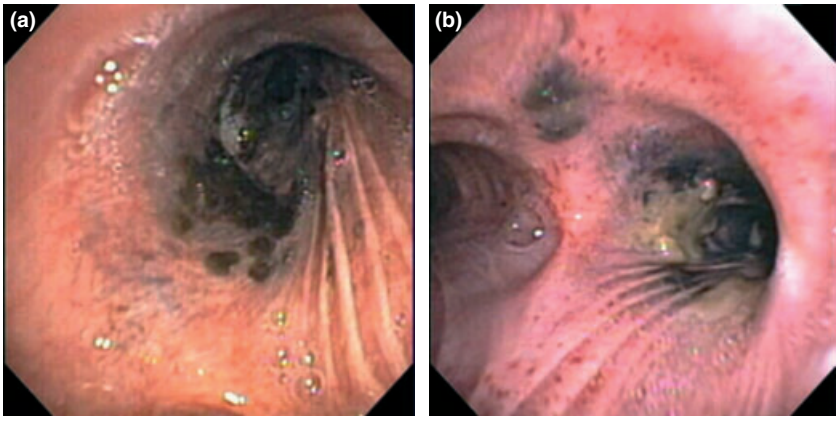

Figure 2 (a) Right mainstem bronchus (September 2005) demonstrating greenish/black deposits. Endobronchial biopsy confirmed the presence of malignant melanoma. (b) Main carina (October 2005). There has been proximal spread of melanoma to now involve the trachea.

STR loci. STR PCR is also quantitative, making this technique useful in the evaluation of chimeric and/or mixed samples (e.g. assessing the degree of engraftment following hematopoietic stem cell transplantation) [6].

Based on visual inspection of the histologic section, malignant cells represented approximately 80% of the endobronchial biopsy tissue. Given this, the origin of the tumor was predicted to correspond with the prevailing STR allele profile in the specimen. DNA was isolated from (i) the recipient's peripheral blood, (ii) the donor's spleen, and (iii) the diagnostic endobronchial biopsy specimen. For each DNA sample, 12 separate STR loci were amplified and evaluated. Nine of the loci were deemed informative for this case; in other words, at nine loci the recipient and the donor alleles could be distinguished. The STR allele profiles from the peripheral blood and the spleen were used as references for the genotypes of the recipient and the donor, respectively. Based on this analysis, it was determined that the endobronchial biopsy specimen consisted of an admixture of recipient and donor cells with 69% being of donor origin when averaged across all nine informative STR loci (range 56% to 88% donor origin, standard deviation 9%). These findings, when taken together with the visual estimations, were most consistent with the tumor being of donor origin.

The patient was subsequently switched to a sirolimus-based immunosuppressive regimen as a result of its potential anti-tumor properties [7]. Overall immunosuppression was reduced by use of only two agents – sirolimus (trough levels 6–8 ng/ml) and prednisone (10 mg/day). Repeat bronchoscopy in October 2005 showed spread of endobronchial melanoma to the trachea (Fig. 2b). Treatment with systemic chemotherapy (Temozolomide) and endobronchial brachytherapy (700 cGy weekly × 5 weeks) for control of endobronchial disease was initiated. Despite these interventions, melanoma progressed rapidly. Imaging studies from December 2005 showed increased right hilar and mediastinal lymphadenopathy and significant progression of right lung tumor. Additionally, metastatic disease was now evident in the liver. Over the next few months, the patient developed increasing dyspnea, recurrent postobstructive pneumonias and cachexia (Fig. 1b). He passed away in April 2006, 7 months after the initial diagnosis of metastatic melanoma.

Discussion

To our knowledge, this report describes the longest interval (>32 years) from 'curative' donor melanoma resection to transmission to an organ recipient. In the general population, the lifetime risk of melanoma is about 1 in 50 for the Caucasian population; thus, a history of melanoma resection would not be unusual in the organ donor population [1]. Donor transmitted malignancy is rare [8–10]. Among all deceased organ donations in 2007 in the United States, donor tumor transmission was documented in only seven recipients from four donors. Although rare, certain tumors appear to pose a higher risk of transmission to the recipient. For example, in a report from the Israel Penn International Tumor Transplant registry, malignant melanoma had an especially high transmission rate of 74% [9].

In the nontransplant setting, malignant melanoma has been described to recur many years after initial 'curative' treatment [11–17]. Approximately 1–7% of melanomas have been reported to recur beyond 10 years, with one report of recurrence occurring after a 35-year disease-free interval [12,18]. Prognosis is based on primary tumor thickness and extent of spread; however, even tumors with the most favorable prognostic features (melanoma <1 mm) can recur many years later [12,13,16,17].

The mechanisms by which metastatic melanoma may remain dormant at distant sites for many years is not well understood. Host anti-tumor immunologic responses have been speculated to play a role in tumor suppression. Support for this theory has included the observation that melanoma may undergo spontaneous regression. In fact, 76 cases of partial or complete regression have been reported in the literature [19]. Spontaneous regression has been associated with the presence of intra-tumoral lymphocytes and the production of pro-inflammatory cytokines. Melanomas also express a number of antigens that can be recognized by T-lymphocytes [20,21]. Unfortunately, despite the immunogenic properties of melanoma, vaccination strategies to enhance anti-tumor immune responses have not resulted in clinical benefit for the majority of patients. Certain clones of tumor cells have the ability to survive by evading or down-regulating the anti-tumor immune response and creating an immunosuppressive microenvironment [19,20]. Several reports of melanoma transmission in the transplant population further support the notion that immune surveillance is important for melanoma suppression [9,10,22–31]. Transplantation and subsequent administration of exogenous immunosuppression may alter the delicate balance between tumor specific immunologic responses and local tumor-derived immunosuppression to favor growth and metastatic spread. However, as this case illustrates, metastatic spread to the transplant recipient was not evident until more than 1 year after the transplant procedure despite continuous use of standard immunosuppression. Thus, other factors that have yet to be identified likely had a role in this transformation.

The association between post-transplant immunosuppression and increased risk of certain types of cancer is well known [32]. For example, post-transplant

immunosuppression has been associated with a 65- to 250-fold increase in the risk of squamous cell skin cancers [33]. Use of induction immunosuppression in the peri- and early post-transplant period with lympholytic agents (e.g. anti-thymocyte globulin) results in profound cell-mediated immunosuppression and has been associated with reduced T-cell responses to Epstein–Barr virus related B-cell proliferation and increased risk of post-transplant lymphoproliferative disorders in solid organ and hematopoietic stem cell transplant recipients [34].

The question of whether or not certain maintenance immunosuppressive regimens are more or less likely to favor tumor growth is unknown. There has been increasing interest in the potential anti-neoplastic properties of the antiproliferative agent rapamycin. Several studies have suggested that a rapamycin based post-transplant immunosuppressive regimen may reduce the incidence of both skin and other types of cancers [32,35]. Unfortunately, transition to a reduced immunosuppressive regimen that included rapamycin did not appear to result in clinical benefit for our patient. However, this change was made after the melanoma was already widespread. It is not known if initiation of rapamycin therapy at an earlier time point would have improved outcome. The liver, right kidney and contralateral lung from this donor were also transplanted at our institution. Their immunosuppressive regimens were reviewed. The liver and kidney recipients remain healthy and do not have evidence of melanoma 5 years after transplantation. Notably, the kidney recipient has been maintained on a tacrolimus, mycophenolate mofetil and prednisone regimen since transplantation and has never received rapamycin. The liver recipient was initially maintained on a tacrolimus and prednisone immunosuppressive regimen, but was transitioned from tacrolimus to rapamycin for 8 months in the first post-transplant year after developing severe headaches attributed to the calcineurin inhibitor. He was eventually switched back to tacrolimus because of the occurrence of severe lower extremity edema thought to be related to rapamycin. The contralateral lung recipient died approximately 1 year after transplantation at home for unclear reasons. Clinical history, physical examination and radiographic imaging obtained shortly before her death did not demonstrate evidence for metastatic melanoma. Unfortunately, an autopsy was not performed. This patient was transitioned from tacrolimus to rapamycin after 8 months because of the development of calcineurin inhibitor-associated hemolytic uremic syndrome. Finally, the heart recipient was transplanted at another institution. Although information regarding this recipient's immunosuppressive regimen is unavailable, this patient is also healthy and does not have evidence of melanoma. Overall, from the two cases in which rapamycin was administered, it is difficult to ascertain whether or not its brief use has contributed to tumor-free survival.

Metastatic melanoma has a poor prognosis in cardiothoracic organ recipients [36,37]. Treatment options are limited and evidence for their effectiveness is lacking. Our patient had progressive disease despite reduction in immunosuppression, systemic chemotherapy and brachytherapy. In renal transplantation, complete withdrawal of immunosuppression has been reported to result in tumor regression and prolonged disease-free survival [25,28]. However, these reports also indicate a high likelihood of developing severe graft rejection and graft loss necessitating dialysis support. Unfortunately, no such option is available for lung recipients.

The potential for donor melanoma transmission and poor prognosis once it has developed in the recipient has generated debate about whether or not organs from these donors should ever be utilized [38,39]. More broadly, this concern applies to all donors with history of high-risk malignancies (e.g. malignant gliomas) [40]. The observation that other solid organ recipients from the donor in this case did not develop melanoma supports the practice of considering a history of melanoma as a very strong relative rather than absolute contraindication to organ donation. Use of donors with history of melanoma or other high-risk malignancies may only be justified for potential recipients deemed to be unlikely to survive the wait for another donor. Prior to donor acceptance, consultation with an oncologist and a rigorous search for metastatic disease should be undertaken. In addition to bronchoscopy, we would recommend obtaining a head, chest and abdomen CT scan to search for lesions suspicious for metastatic disease. Additionally, patients and their families must be counseled about the risk of life-threatening melanoma transmission. Their participation in this critical risk/benefit analysis is essential for obtaining informed consent. Implementation of a reduced immunosuppression strategy (i.e. not administering induction immunosuppression) or use of agents with antineopastic properties such as rapamycin should be considered, although it is not clear whether this approach would reduce the risk of metastatic spread.

Authorship

NSB: first author, wrote the initial manuscript, CW: analyzed data, wrote part of the manuscript, DH: contributed to discussion section of paper, CG: assisted in writing the section on brachytherapy, ARH: assisted in editing the discussion, subm. bronchoscopy pictures, AP: transplant surgeon, involved in all aspects of patient management,

JM: collected data, DHS: assisted in writing discussion, LMS: oncologist, edited manuscript, JDC: transplant pulmonologist, edited case report & discussion section, JCL: transplant pulmonologist, edited case report & discussion section, VNA: senior author, collected data, substantially edited and revised manuscript and managed patient discussed.

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