Malignant Melanoma in Transplant Patients: A Case Report and Review of the Literature

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The clinical course and outcome of malignant melanoma (MM) are well-established for immunocompetent groups; however, they are not well-documented for immunosuppressed populations. Specifically, the influence of immunosuppression may result in poorer outcomes, especially in more advanced cases of melanoma. We report a 67-year-old woman who had previously undergone a kidney and pancreas transplant and presented with American Joint Committee on Cancer (AJCC) stage IIIA melanoma with subsequent rapid demise. As medicine advances with greater numbers of organ transplant recipients, a multi-institutional prospective study for this at-risk population would be greatly beneficial to help characterize the incidence, progression, and prognosis of melanoma in posttransplant immunosuppressed populations.

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The clinical course and outcome of malignant melanoma (MM) are well-established in immunocompetent groups; however, they are not well-documented for immunosuppressed populations despite the hypothesis that melanoma is an immune responsive tumor. Important prognostic factors for MM have been established including Breslow thickness, presence of ulceration, mitotic activity, regression, and evidence of tumor-infiltrating lymphocytes.[1] Consequently, survival is best estimated based on the American Joint Committee on Cancer (AJCC) stage of disease with sentinel lymph node status being a primary predictor of outcome.[1,2] With early diagnosis, primary melanomas are highly curable by primary excision and appropriate follow-up, as described in the National Comprehensive Cancer Network recommendations.[3]

Case Report

A 67-year-old woman presented to our melanoma specialty clinic 4 weeks after her initial diagnosis of melanoma. She had a history of insulin-dependent diabetes mellitus that resulted in renal failure and an associated renal transplant 16 years prior to presentation in addition to a subsequent pancreatic transplant 4 years prior to initial presentation. She was immunosuppressed for the prevention of graft rejection and had a history of nonmelanoma skin cancers.

At the time of presentation, she underwent wide local excision of the lesion from the left forearm that revealed a nonulcerated superficial spreading melanoma with a Breslow thickness of 2.6 mm. After finding micrometastatic disease on sentinel lymph node biopsy without further evidence of disease, she was deemed to have AJCC stage IIIA melanoma with expected disease-specific median survival of more than 15 years.[2] Because her transplant status required an immunosuppressed state, interferon adjuvant therapy was contraindicated and the patient opted instead for close observational follow-up with radiation therapy to the left axillary lymph node basin to forestall recurrence. Unfortunately, the patient's condition declined quickly as clinicians observed a rapid expansion of her MM,

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and she died approximately 13 months after initial presentation.

Comment

Little is known about the natural progression of MM in transplant populations; however, MM is thought to be an immune responsive tumor, thus raising questions regarding the incidence, aggressiveness, and overall prognosis of the disease in immunosuppressed populations. There is some evidence to suggest an increased incidence of MM in transplant recipients; however, further studies are necessary for a definitive answer. Currently, there is no consensus on the risk for developing MM in organ transplant populations or the relationship with immunosuppressive therapy. The documented incidence of melanoma in posttransplant populations is limited to a small number of studies (according to a PubMed search of articles indexed for MEDLINE using the terms *malignant melanoma* and *organ transplantation* and then excluding single case reports and other articles for relevance) that report relative incidence widely ranging from 0 to 8 times more frequent than the general population (Table).[4-13]

Furthermore, additional study is necessary to determine if transplant recipients present with MM in more advanced stages because of possible opportunistic aggressiveness of the disease, resulting in what has been reported as considerably worse outcomes. Mostly superficial spreading melanomas with a Breslow thickness less than 1 mm have been reported as the initial clinical presentation in the transplant population[5,7,10,14]; however, 1 study found that 69% (47/68) of transplant patients with subsequent melanoma presented with thicker skin lesions (Breslow thickness, ≥0.75 mm),[15] which is in contrast to 1 report of 31 transplant recipients who presented with de novo primary melanomas at a less advanced stage than the overall cohort of patients used to develop the 2002 AJCC staging system and survival calculations,[16] a cohort considered relatively representative of the general population. However, this transplant population may have been better monitored than at other institutions.[17]

The clinical course of melanoma in transplant patients also is not well-characterized in the literature with widely reported mortality rates ranging from 6% to 50%.[4,5,7,10,11,14,15,17,18] Overall, outcomes of MM in transplant recipients with thin lesions generally are favorable and consistent with data from the general population; however, transplant recipients with thicker melanomas did relatively worse than expected in several of these studies.[7,14,15] One article reported death due to MM in 2 of 13 patients with an identified Breslow tumor thickness less than 0.76 mm.[5] Another article reported no deaths in 11 cases of MM with a Breslow thickness less than 1 mm but also acknowledged that this mortality rate may have been lower than others in the literature due to detection at early stages because of patients' frequent examinations in dermatology clinics. Only 1 patient in this latter study developed a melanoma with a Breslow thickness greater than 1 mm, notably resulting in the only fatality in the study.[10]

Reported Relative Incidence of Malignant Melanoma in Transplant Recipients

Reference (Year)	Sample Size (Transplant Years)[a]	Relative Risk
Bouwes Bavinck et al[4] (1996)	1098	2.0
Brown et al[5] (2007)	861 (8557)	7.0–8.0
Hollenbeak et al[6] (2005)	89,786	3.6
Imko-Walczuk et al[7] (2007)	1958 (16,676.19)	5.5
Jensen et al[8] (1999)	2561	3.0
Kasiske et al[9] (2004)	35,765	5.0
Le Mire et al[10] (2006)	1874 (11,942.2)	8.0
Lévêque et al[11] (2000)	12,477	2.5
Lindelöf et al[12] (2000)	5356	0
Moloney et al[13] (2006)	1558	7.0

[a]Not all studies either reported or provided data that could allow for extrapolation of number of transplant years followed.

Although the clinical course of MM in patients with a tumor with a Breslow thickness less than 1 mm are generally good, the outcomes in transplant recipients with thick MM are not as encouraging. Due to comparable reporting methods, results of 2 published studies on this topic may be combined. In either study, 2 of 9 transplant recipients with a Breslow thickness of 0.76 to 1.5 mm died of melanoma, 8 of 15 patients with tumor thickness of 1.51 to 4 mm died, and 3 of 6 patients with tumor thickness greater than 4 mm died.[10,15]

In response to these studies, another author reported 7 transplant patients with melanoma; 5 of these patients had invasive disease. Of those 5 patients, 3 died because of their melanoma; 2 patients had tumors with a Breslow thickness greater than 2 mm and 1 died because of metastases from a lentigo maligna melanoma with a Breslow thickness of 0.4 mm.[5]

Although the prior reports were largely descriptive, one study assessed 89 cutaneous melanomas in 85 transplant recipients.[14] A 13% melanoma-specific mortality rate was observed along with a mean time from diagnosis to death of 22 months and a mean Breslow tumor thickness of 4.4 mm (range, 0.32–13 mm). In 2 cases that resulted in mortality the primary tumor had a Breslow thickness of less than 1 mm, and 2 fatal cases were due to metastases from an unknown MM primary tumor. It was concluded that the prognosis was significantly ($P<.001$) poorer for posttransplant melanomas with a Breslow thickness greater than 2 mm because of the worse outcome for the combined T3 (2.01–4 mm) and T4 (>4 mm) melanomas observed.[14]

In direct contrast, one study found that there was no significant difference in outcomes for posttransplant patients with MM in a retrospective cohort.[17] Thirty-one posttransplant patients with 34 sites of melanoma were reported. Two of 31 patients died; both patients were initially classified as stage IB or IIA melanoma. It was concluded that the rate of survival seen in the study was consistent with the trend seen in the general population, as it revealed no differences in outcome for the posttransplant population.[17]

Given these contradictory reports, the most helpful method of determining the true outcome of melanoma in the transplant population relative to Breslow thickness and other known disease-modifying factors as determined in the general population would be to conduct a well-powered, multi-institutional prospective study for this at-risk cohort.

Unfortunately, our patient presented with already advanced T3aN1aM0 stage IIIA melanoma. She had a course of short disease-free intervals followed by subsequent rapidly progressive disease resulting in death, despite chemotherapeutic intervention and, importantly, reduction in her immunosuppressive regimen. It is still unknown if melanoma presents with greater incidence, a more advanced stage, and a more aggressive course or poorer outcome in the posttransplant population. As medicine advances with greater numbers of long-surviving organ transplant recipients, a multi-institutional prospective study for this at-risk population would be greatly beneficial. Until then, treatment should proceed with caution in these groups until definitive characterization of the natural course of the disease can be established for the transplant population.[19] More frequent skin cancer screening in the transplant population may be indicated to obtain the relatively good outcomes reported by some studies, but until more data are obtained it remains conjecture.

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