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Regression of advanced melanoma upon withdrawal of immunosuppression: case series and literature review

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Abstract

We report two cases of stage IV malignant melanoma arising in patients treated with azathioprine for myasthenia gravis. In both cases, the melanoma metastases regressed upon withdrawal of immunosuppression. One patient remains melanoma free at 10 years, and the second patient experienced an 18-month disease free period. There is one prior case report in the medical literature to support full immune reconstitution for treatment in advanced immunosuppression-related melanoma, and one case series suggesting that transplant patients developing melanoma may benefit from a switch to sirolimus. Virtually, no data exist for the medical management of early stage melanoma in the immunosuppressed patients. We review the limited preclinical data in support of immune reconstitution and the data on immunosuppression as a risk factor for melanoma. We conclude that reduction or withdrawal of immunosuppression may be beneficial in patients with advanced stage melanoma and warrants further consideration in patients with early stage melanoma.

Keywords

Melanoma; Immunosuppression; Transplant; Azathioprine; Myasthenia gravis

Introduction

Advanced melanomas arising in immunosuppressed patients are rare. Efforts to define the etiologic association between melanoma and immunosuppression have previously been hindered by low incidence rates and conflicting results in different patient subsets. For treatment of immunosuppression-related melanomas, there is little data for stage IV disease

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and none in early stage disease. There is also no data to stratify risk for melanoma survivors starting immunosuppression. We report two remarkable cases of melanoma regression upon immune reconstitution and suggest a treatment paradigm for immunosuppression-related melanomas. We review the literature on immunosuppression and melanoma, which is primarily limited to defining the etiologic association between the two.

Case 1

A 62-year-old Caucasian with history of Guillan-Barre, polymyositis and myasthenia gravis was diagnosed with cutaneous melanoma of the scalp in 1998. The melanoma had a Breslow depth of 4 mm, with ulceration and a negative sentinel lymph node. The patient had been treated with prednisone and azathioprine intermittently for 10 years, and he was on azathioprine at the time of melanoma diagnosis. Eight months after primary resection, the patient developed a PET avid 5-mm lesion in the thymus and multiple PET avid lung nodules. He underwent surgical excision of the thymus and one of the lung nodules. Pathology revealed metastatic melanoma in the thymus and lung. Following thymectomy, the azathioprine was tapered off over 3 months. The patient had no recurrence of myasthenia symptoms off azathioprine suggesting that the thymectomy may have been curative of the myasthenia. The pulmonary metastases completely resolved within 6 months. The patient continued on close surveillance and is now at 10 years from diagnosis of stage IV disease with no evidence for disease recurrence. The patient continues to work at the age of 72.

Case 2

A 65-year-old Caucasian male with history of myasthenia gravis treated with azathioprine for 11 years was diagnosed with melanoma in 2006. At diagnosis of melanoma, the tumor was Breslow depth 3.45 mm with a positive sentinel node and negative completion lymph node dissection. The patient was not treated with interferon due to the myasthenia. Five months after diagnosis, the patient developed in-transit metastases in the neck and scalp and was treated with wide local excision. Three months later, a second local recurrence was found, but was deemed unresectable due to nerve sheath involvement in the neck. The patient was treated with radiation therapy at a dose of 48 gray with good local response. Four weeks after completion of radiation, multiple new skin deposits were found on the back with largest measuring 4.1 cm. In coordination with neurology, the azathioprine was tapered off. The patient tolerated discontinuation of immunosuppression and was maintained with mestinon for myasthenia symptoms. At 8 weeks off azathioprine, most of the tumors had disappeared completely and the remaining back mass had decreased to 0.3 cm. At 5 months off azathioprine, there was no measurable metastatic disease by examination nor by PET/CT scan. The patient remained melanoma free for 18 months, before a recurrence in a bone site was found. The patient declined further interventions and succumbed to the disease another 12 months later.

Discussion

The link between post-transplant immunosuppression and leukemia/lymphoma is well established [1], but solid tumor incidence post-transplant remains debatable (Table 1). For melanoma, organ transplant recipients have been reported to have incidences of two to ninefold higher than the general population [2-10]. The post-transplant melanomas arise on average 36 months post-transplant and tend to be deeper and worse stage at diagnosis than melanomas in the general population, despite skin surveillance protocols within many transplant programs [11].

In a meta-analysis of 13 transplant studies including 73,284 patients, melanomas occurred 1.6–2.5 times more commonly in transplant patients than in the general population. The

highest melanoma risk seen in any population to date was a renal transplant cohort of 1,874 patients followed in the United Kingdom (UK). In this cohort, 12 incident melanomas were observed, which was a rate eight times the standardized rate for the UK at that time [2]. In Australia, the standardized incidence ratio of melanoma following kidney transplant was 3.18 (95% CI 2.75–3.67) among 13,077 patients transplanted between 1980 and 2003 [12]. In a retrospective renal transplant cohort from Queensland from 1969 to 1994, the relative risk of developing melanoma post-transplant was 2.0 (N = 1098) [13]. It is notable that Australia has among the highest melanoma rates in the world, so the elevated post-transplant melanoma rate may not represent the rates in other parts of the world. In fact, a Swedish trial of 5,356 solid-organ transplant recipients between 1970 and 1994 found no increased melanoma rate despite an average 5-year follow-up [14].

Mirroring the solid-organ transplant experience, the bone marrow transplant (BMT) studies indicate increased secondary malignancies as well as secondary melanomas following BMT [15-22]. Relative risks from 1.85 to 65 have been reported for melanoma post-BMT. We caution that the heavy chemotherapy pretreatment, the high doses of radiation/chemotherapy for marrow ablation, the variable degree of immunosuppression and the rates of graft versus host disease in BMT may confound the relationship between melanoma and immunocompetence in the post-BMT population.

In non-transplant immunosuppressed patients, for example patients with rheumatoid arthritis (RA), there is an increased melanoma risk in some studies that is not replicated in all cohorts. [23-25] One positive study cohort from Australia consisted of 459 methotrexate-treated RA patients and found a threefold increase in melanoma risk among the methotrexate-treated RA patients relative to the general population [26]. In the Netherlands, a study showed no increased malignancy of any type in RA patients treated with cyclosporine and followed for 5 years [27]. A Finnish study of 46,000 RA patients found no melanoma risk, despite an elevated lymphoma risk [28]. In the United States, Wolfe et al. [29] found a significantly increased risk of melanoma (OR 2.3, 95% CI 0.9–5.4) using the US National Databank for Rheumatic Diseases, which included 13,000 subjects and 49,000 patient-years of observation.

Other autoimmune cohorts have been studied for incidence of malignancy. These include lupus, psoriasis, Crohn’s disease, myasthenia gravis, Wegener’s and ocular disorder patients. These studies generally had small numbers and varying degrees of correlation between immunosuppression and melanoma. No conclusion about melanoma risk nor melanoma treatment can be drawn from these small studies [30-33] (Table 2).

In patients with HIV, T-cell immunosuppression is induced by viral replication rather than by immunosuppressants, but the melanoma risk is similar to transplant patients. The effect of HIV-associated immune dysfunction is demonstrated by the frequent development HIV-associated lymphoma, anal cancer, Kaposi sarcoma and cervical cancer. The role of HIV-related immune dysfunction is less well established in other malignancies such as melanoma. A number of case reports suggested a link between HIV and solid cancers, but two larger studies have shown no statistically significant correlation between CD4 count and solid cancer incidence [34, 35]. On the contrary, a large meta-analysis [36] looked at cancer incidences in both transplant recipients and patients with HIV and found positive correlations with cancer in both. The meta-analysis presented standardized incidence ratios from seven studies of patients with HIV/AIDS (n = 444,172) and five studies of transplant recipients (n = 31,977). For 20 of the 28 types of cancer examined, there was a statistically significant increased cancer incidence in both populations. Melanoma had an incidence ratio of 2.34 (1.96–2.77, 95% CI) in transplant patients and an incidence ratio of 1.24 (1.04–1.48, 95% CI) in patients with HIV. This study is compelling evidence for immune dysfunction in

melanoma because it compares two populations that do not share lifestyle and host cancer risk factors, yet experience similar risks for melanoma development.

Worldwide, a consensus about malignancy risks for immunosuppression is lacking. This may be due to differing incidence rates for different solid tumors and the differing rates of cancer in various transplant and non-transplant cohorts. In fact, a possible protective effect may exist for tumors associated with chronic inflammation such as colon cancer, although this has not been fully born out. Nevertheless, in the United States, the Food and Drug Administration added a black box warning to the TNF inhibitors in August 2009 for pediatric and adolescent use warning that increased rates of leukemia and other malignancies are possible.

Harnessing the immune system in melanoma

The histologic finding of infiltrating lymphocytes within most melanomas suggests that immune recognition of melanoma is important to control of disease progression. Importantly, the tumor-infiltrating lymphocytes (TIL) have been shown to have melanoma specificity. Furthermore, the degree of lymphocyte infiltration within a melanoma is shown to be prognostic of melanoma progression [37]. There is a finding that approximately 10% of patients with melanoma will develop vitiligo-like patches, known as melanoma-associated hypopigmentation (MAH). The development of MAH is thought to represent a T-cell-mediated attack against common melanocyte antigens also present on tumor cells. The patients with MAH likely develop effective immunity against the malignant cells [38]. Further confirmation of T-cell specificity has been seen in the related phenomenon of spontaneous regression in melanoma. Evidence of spontaneous regression can be seen both clinically and histologically and is thought to be controlled by $CD8^+$ cytotoxic T-cells [39, 40]. Just like the TIL cells, the lymphocytes from the blood of spontaneous regression patients show T-cell specificity for melanocytes. Interestingly, there may also be a role for B cells in melanoma. Circulating melanoma specific antibodies have been identified in similar studies and are under further investigation [41, 42].

There is clinical evidence that the immune phenomena observed earlier can be harnessed to treat melanoma. For example, interferon alpha treatment in stage III melanoma results in an improved progression free survival compared to placebo [43]. The more compelling aspect of interferon is the disproportionate difference in response among those patients who develop signs of autoimmunity and those who do not while on interferon. The difference is a 50-fold improvement in overall survival for patients developing autoimmune phenomenon ($P < 0.001$) [44]. Clinical support for immune recruitment also comes from the cytokine IL-2, an even more potent stimulator of the immune system than interferon alpha. IL-2 acts through promotion of proliferation, differentiation and recruitment of T and B cells, natural killer (NK) cells and thymocytes as well as increasing the cytolytic activity of CD4 and CD8 tumor infiltrating lymphocytes. IL-2 produces a number of durable responses in stage IV melanoma and is therefore offered for some cases of metastatic disease [45]. IL-2 shows similarly improved efficacy in patients developing autoimmune phenomena.

A further clinical application of T-cell recruitment in melanoma was reported by Rosenberg et al. in 2002 [46]. In their work, they showed that the re-infusion of ex vivo-expanded tumor-infiltrating lymphocytes from advanced melanomas can result in significant tumor reductions. In the study, 6 of 13 patients had objective clinical responses to the “adoptive cell transfer.” Five of the responding patients demonstrated autoimmune melanocyte destruction. Follow-up reports from the National Cancer Institute (NCI) have replicated early findings and improved patient outcomes with the addition of a lymphocyte-depleting pre-conditioning regimen. The adoptive cell transfer therapy has been replicated outside the

NCI [47], confirming the potential roles for T-cell therapies in melanoma and perhaps confirming the risks to T-cell depletion used in transplant and other immunosuppressive regimens.

By a similar mechanism of action, melanoma vaccine work has shown that the immune system can be re-programmed to recognize aberrant melanoma cells. The basic melanoma vaccine approach involves subcutaneous injection of known melanoma proteins with an adjuvant, with the goal of stimulating melanoma specific T cells. A number of reports have suggested potential roles for melanoma vaccines, but to date, no vaccines have reached FDA approval [48]. Similar pharmaceutical approaches to harnessing the T cells in melanoma are in clinical trials. For example, the CTLA4 inhibiting antibodies, which may be close to FDA approval, are enhancers of T-cell activity and proliferation. These antibodies block the T cell co-receptor responsible for preventing overstimulation. The ultimate effect seems to be alteration in the balance of T effector cells in relation to T suppressor cells both within the tumor microenvironment and distantly. The CTLA4 inhibiting antibodies have shown positive clinical activity with manageable side effect profiles. A similar pharmaceutical approach is to target antibodies against PD-1 (programmed death) and PD-1 ligand to increase T-cell activity. Phase I/II trials with both types of antibodies are currently underway and the preclinical work has shown that IL-2 production can be restored following PD-1 blockade [49].

Conclusion

The two cases discussed in this report highlight the role of T-cell function in immune surveillance. The re-constitution of the immune system in both case reports resulted in regression of melanoma metastases. The positive responses to immunosuppressive withdrawal are similar to a previously published case by Hodi et al. [50] and follow the well-established treatment paradigm for post-transplant lymphoproliferative disorders. An additional case series of post-transplant malignancies including two melanomas suggests that switching to sirolimus for immunosuppression may allow improved immune surveillance without graft sacrifice [51]. In addition to the case series and anecdotal evidence, there are plausible immunologic mechanisms to support discontinuation of immunosuppression in the setting of advanced melanoma [52, 53]. Our experience in these and other cases suggests that selected autoimmune-associated melanomas will benefit from withdrawal of immunosuppression. To date, there are no randomized trials to guide treatment in either the early or advanced melanoma patient population and as such we recommend caution when considering a trial of immunosuppressive withdrawal.

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Table 1

Proposed mechanisms that immunosuppressants may contribute to cancer development

Mechanisms suggested for immunosuppressant-related cancers:	
1	Downregulation of immune surveillance, allowing precancerous lesions to progress unchecked
2	Increased susceptibility to infection with oncogenic viruses (i.e., melanoma-associated retrovirus that was detected in murine and human melanoma)
3	Pharmacologic effects of the immunosuppressant on DNA (alkylating agents) or DNA metabolism (antimetabolites)

Table 2

Evidence and case reports for secondary melanoma among specific immunosuppressive agents

Agent class	Specific agent	Evidence/cases of melanoma	References	RR or standardized incidence rate (SIR)	Number of melanomas/total patients
Alkylating agents	Chlorambucil	Yes	Boivin and O'Brien [54]	RR, 4.9 (95% CI 1.6–11.3)	5 of 1,939
			Swerdlow et al. [55]	SIR 4.0 (95% CI 0.7–12.2)	2 of 1,039
	Cyclophosphamide	Yes	Radis et al. [56]	RR 1.5 ($P < 0.05$)	1 of 119
Calcineurin inhibitors	Cyclosporine	Yes	Bouwes Bavinck et al. [13]	RR 2.0 (95% CI 0.9–3.9).	8 of 1,098
	Tacrolimus	Yes	Frezza et al. [57]	Not provided	3 of 3,394
m-Tor inhibitors	Sirolimus	No	Boratynska et al. [51]	n/a	0
Antimetabolites	Azathioprine	Yes	Guenova et al. [58]	n/a	1 case report
	Methotrexate	Yes	Buchbinder et al. [26]	SIR 3.0 (95% CI 1.2–6.2)	7 of 459
			Reutter et al. [59]	n/a	1 case report
			Potter et al. [60]	n/a	1 case report
			Jeannou et al. [61]	n/a	2 case reports
			Barnhill and Wiles [62]	n/a	1 case report
	Mycophenolate mofetil	No	No reports to date	n/a	0
Biologics	Rituxan	No	No reports to date	n/a	0
	Daclizumab	No	Webster et al. [63]	RR 0.67 (95% CI 0.33–1.36)	0 of 4,893
TNF inhibitors (as a group)	Infliximab	Yes	Dreyer et al. [64]	Not provided	3 of 3,688
	Etanercept		Bongartz et al. [25]	Not provided	1 of 3,493
	Adalimumab		Khan et al. [65]	n/a	1 case report
			Fulchiero et al. [66]	n/a	2 cases