Cancer Immunity, Vol. 5, p. 7 (19 May 2005)

CANCER
IMMUNITY
Commentary

Withdrawal of immunosuppression contributing to the remission of malignant melanoma: a case report

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Keywords: human, melanoma, immunosuppression, remission

The withdrawal of immunosuppression is effective in treating lymphoproliferative diseases arising in organ transplant recipients. We report a case of a durable complete response in a melanoma patient following discontinuation of immunosuppression.

A male with aplastic anemia since 1997 was treated with cyclosporine until 2001 when immunosuppression was changed to sirolimus plus tacrolimus to limit nephrotoxicity. In 2003, a shave biopsy of a persistent bleeding and non-healing scalp lesion demonstrated malignant melanoma (Breslow 2.3 mm, Clark's level IV), the presence of ulceration, and 10 mitoses/mm^2. Wide excision with skin grafting and sentinel node biopsy of a left post-auricular lymph node revealed lentigo malignant melanoma (Breslow 5.5 mm, Clark's level V), 14 mitoses/mm^2, neural and vascular invasion, and a lymph node positive for metastatic melanoma. A radical left cervical lymphadenectomy revealed one additional positive lymph node with extranodal extension. The patient soon developed multiple in transit metastases on the scalp, and received radiation therapy followed by re-excision and skin grafting.

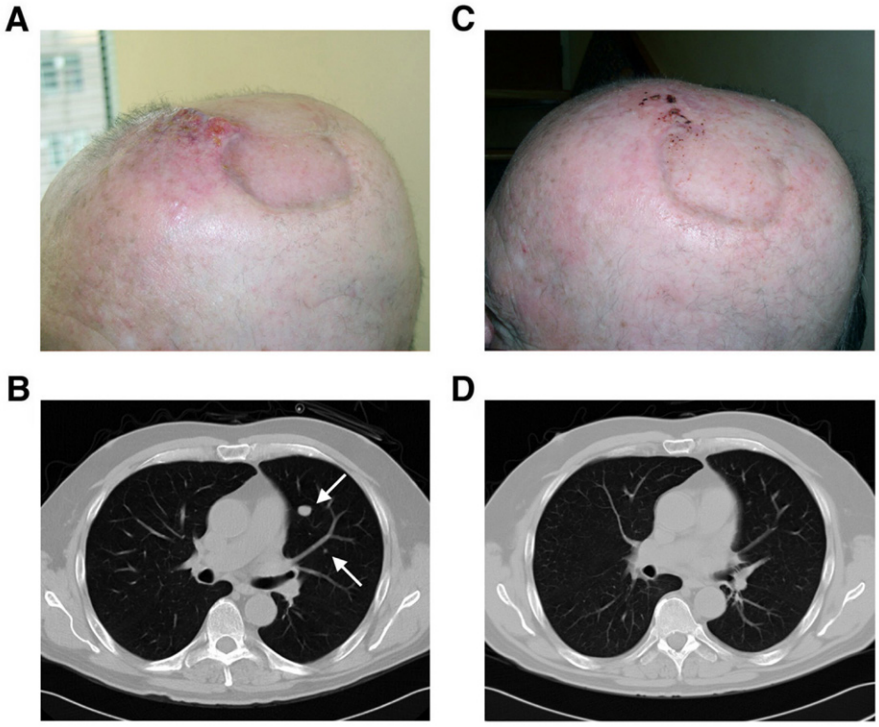
In January 2004, the patient developed new lung and scalp nodules. Immunosuppression was then discontinued. In March 2004, a new inflammatory reaction with extensive erythema and warmth of these scalp lesions was noted (Figure 1, panel A). Due to concern with the lung nodules slightly increasing in size as determined by computed tomography (CT) (Figure 1, panel B), the patient received one cycle of chemotherapy with a reduced dose of dacarbazine at 350 mg/m^2 daily for two days and 250 μg/m^2 GM-CSF daily for 14 days, achieving a clinical (Figure 1, panel C) and radiographic (Figure 1, panel D) complete response. Currently, the patient continues to be treated with 250 μg/m^2 GM-CSF two to three times a week, requires weekly platelet and monthly red cell transfusions, and remains without evidence of melanoma one year later.

To explain the possible role of the anti-tumor immune response in this dramatic clinical response, we analyzed a biopsy of the inflammatory scalp lesion following withdrawal of immunosuppression and before the administration of chemotherapy. Histologic examination revealed focal areas of melanoma cells infiltrated with lymphocytes. Immunohistochemistry demonstrated that these cellular immune responses comprised both CD4+ and CD8+ T cells (Figure 2). With the withdrawal of immunosuppression, the patient's peripheral white blood cell (WBC) count steadily recovered over the period of two months from 4,100/μl (60% polys, 4% bands, 19% lymphocytes, 4% monocytes, and 13% eosinophils) to 12,700/μl (53% polys, 17% bands, 8% lymphocytes, 10% monocytes, 11% eosinophils). Following the administration of chemotherapy, the WBC count has remained between 7,000/μl to 10,000/μl, without a significant change in the differential. The histological examination of the biopsy specimen and changes in peripheral blood counts suggest that the withdrawal of immunosuppression permits the recovering immune system to recognize the melanoma metastases present.

Although the patient did receive chemotherapy with dacarbazine, it is unlikely that this alone is responsible for the dramatic and durable complete response. Dacarbazine is the most active chemotherapy agent used to treat melanoma (1). The reported complete response rate to dacarbazine is less than 5%, and the median durability of responses averages 3 to 6 months (2, 3). The dose of dacarbazine that is typically administered is significantly greater than the dose that this patient received and patients usually receive extended courses of chemotherapy treatment. In light of our pathological findings, this patient's impressive tumor response cannot be explained by chemotherapy alone.

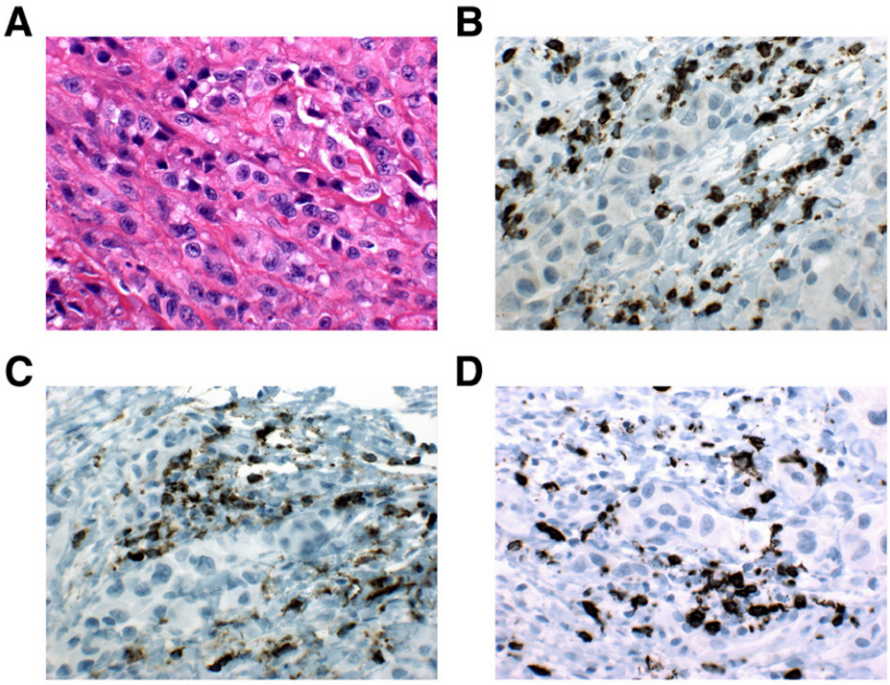
This case reveals a dramatic and durable response to immunosuppression withdrawal and standard therapy for melanoma developing in an immunocompromised host. The risk for melanoma in transplant patients receiving immunosuppression is 1.6- to 4-fold higher than the general population (4). A previous report of fatal melanoma transferred in a donated kidney 16 years after presentation (5) also reveals the significance of immunosuppression permitting some melanomas to become clinically meaningful. Tumor infiltrating lymphocytes present within the vertical growth phase of a primary melanoma (6) or within local regional lymph node metastases (7) offer improved prognoses. In ovarian cancer patients, the presence of intratumoral T cells correlates with improved responses to chemotherapy (8). This suggests that immune competency and tumor recognition by the immune system can offer a survival advantage and potentiate synergistic anti-tumor effects with chemotherapy in patients with solid tumors as evidenced in this current melanoma case. This report poses the basis to better understand the biologic significance of a solid tumor developing in an immunocompromised host as well as the synergies between the recovering innate anti-tumor immune responses and anti-cancer cytotoxic agents.

Figure 1



Evolution of scalp and lung nodules. Inflammatory reaction to in transit scalp melanoma metastases (panel A) and slight increase in the size of lung nodules (panel B) developing two months after discontinuation of immunosuppression. Durable complete resolution of scalp metastases (panel C) and lung nodules (panel D) following one cycle of chemotherapy.

Figure 2



Biopsy of the scalp lesion following withdrawal of immunosuppression and before treatment with chemotherapy. Histological examination reveals focal areas of lymphocytic infiltrate of melanoma cells (panel A). This lymphocytic infiltrate is comprised of CD3+ (panel B), CD4+ (panel C), and CD8+ (panel D) cells.

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