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Case Presentation

Regression of cutaneous invasive squamous cell carcinoma in a patient with chronic cutaneous graft versus host disease

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Abstract

Numerous complications can be observed in the post-transplant period among recipients of hematopoietic stem cells including graft-versus-host disease (GVHD), which is associated with significant morbidity and mortality. On the other hand, graft versus tumor (GVT) effect is a well-described phenomenon in patients with hematologic malignancies and has also been reported in renal cell cancer, ovarian cancer, breast carcinoma, and melanoma. We describe spontaneous regression of a cutaneous invasive squamous cell carcinoma and multifocal atypical intraepidermal proliferations in a patient with chronic graft-versus-host disease following initiation of extracorporeal photopheresis (ECP). This observation raises questions regarding the GVT in cutaneous neoplasms and potential immunomodulatory effects of ECP.

Case synopsis

Our patient is a 62-year-old man with a history of Philadelphia chromosome- negative pre-B cell acute lymphocytic leukemia (ALL) status post induction, consolidation and maintenance therapy. During the sixth cycle of maintenance therapy, he was found to have a relapse of Philadelphia chromosome-positive ALL approximately 2 years following his initial diagnosis. This was treated with 3 months of entinostat and imatinib followed by 1 month of dasatinib, during which he was found to have two squamous cell carcinomas (SCC) on the left forearm and left thigh that were subsequently excised. Owing to disease progression, he underwent a matched unrelated donor stem cell transplant with post-transplant cyclophosphamide for graft versus host disease (GVHD) prophylaxis. However, his clinical course was complicated by the development of a skin-limited Grade II (of IV) acute GVHD, which was initially treated with systemic corticosteroids, tacrolimus, and 15 sessions of psoralen Ultraviolet A (PUVA) therapy. Over a course of 1 to 2 months, he developed a 1-cm verrucous papule on the left anterior lower leg and several 6-10mm keratotic papules with overlying scale on the face. Biopsy of the lesion on the lower leg revealed an invasive squamous cell carcinoma (SCC) (Figure 1), which grew in size over the next month (Figure 2). Subsequent biopsies of the two lesions on the

right cheek and chin demonstrated well-differentiated squamous cell proliferations concerning for evolving keratoacanthomas superimposed on a background of GVHD (Figure 3). Although his 60-day bone marrow biopsy demonstrated no evidence of leukemia and full donor chimerism, he progressed to develop chronic GHVD with sclerodermoid changes. For this reason, therapy with extracorporeal photopheresis (ECP) was initiated 4 months following the transplant and 1 month after histological diagnosis of the lower extremity SCC. Owing to concerns with adequate wound healing, definitive treatment for his cutaneous tumors has been postponed. During this time however, spontaneous significant clinical regression was noted following initiation of ECP. Subsequent excision of the residual clinical lesion on the left leg approximately 3 1/2 months after ECP initiation and 4 1/2 months following initial diagnosis demonstrated only focal actinic keratoses and dermal hemosiderin without any evidence of malignancy (Figure 4). Similarly, the two facial lesions clinically completely regressed and no further medical or surgical treatments were administered. His medications during this time period included tacrolimus, trimethoprim and sulfamethoxazole, valaciclovir, potassium, magnesium, omeprazole, insulin glargine, and hydrochlorothiazide.
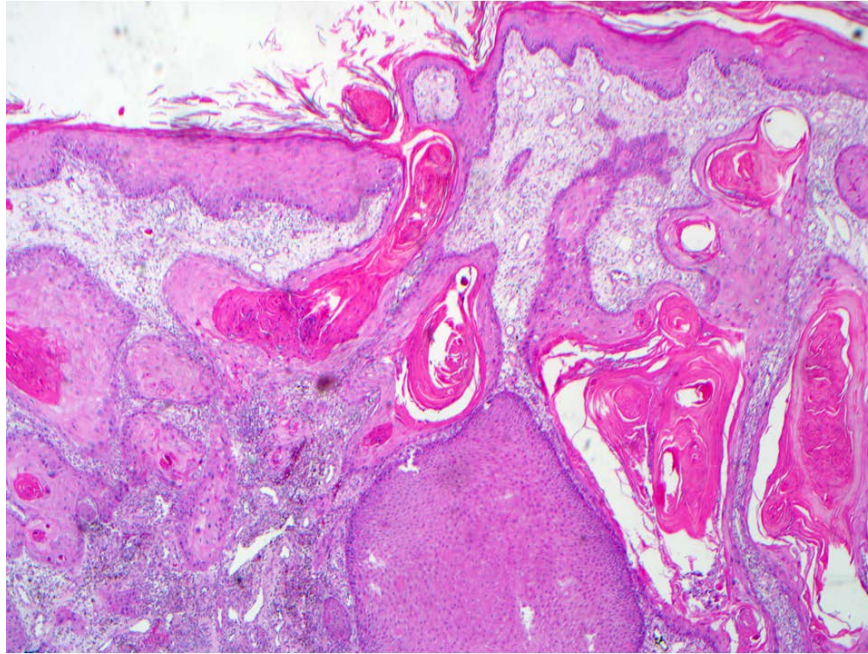

Figure 1. Well-differentiated invasive squamous cell carcinoma H&E, Original magnification, 40x

Figure 2. Biopsy-proven squamous cell carcinoma presenting as a thick, hyperkeratotic plaque on the anterior aspect of the left anterior lower leg
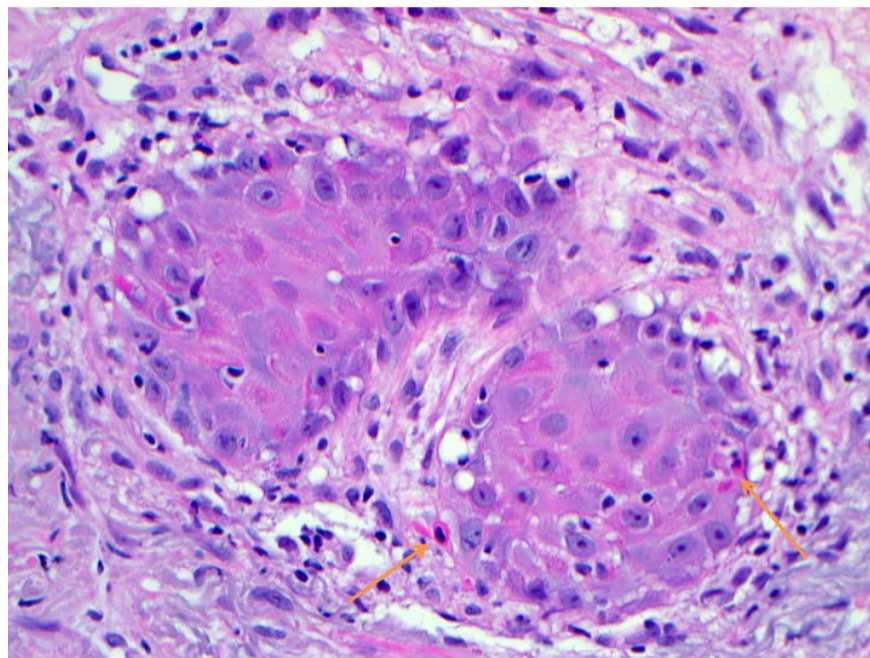
Figure 3. Nests of atypical squamous epithelium with features of graft vs. host disease: Orange arrow points to dyskeratotic keratinocytes at the dermal-epidermal junction, which were identified throughout the proliferation. H&E, Original magnification, 400x.
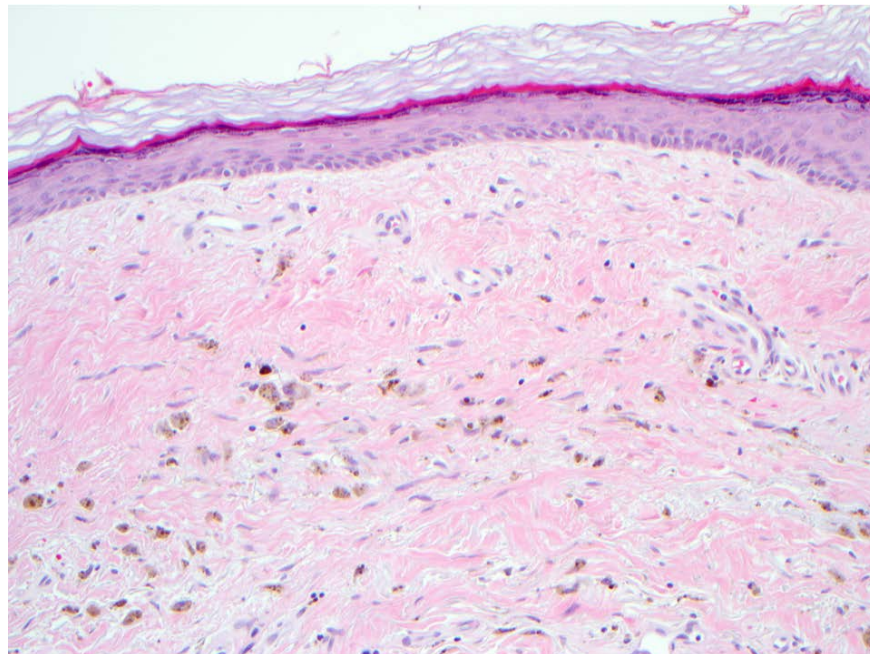

Figure 4. Prominent dermal hemosiderin deposition and early dermal fibrosis with no evidence of residual squamous cell carcinoma H&E, Original magnification, 200x

Discussion

To our knowledge, we describe the first case of spontaneous regression of a cutaneous invasive SCC and multifocal atypical intraepidermal proliferations in a patient undergoing ECP for chronic cutaneous GVHD following a matched unrelated donor stem cell transplant. This observation raises several interesting questions that may have clinical relevance. One potential explanation for tumor regression in this patient is the recovery of the immune system following the transplant and a graft versus tumor (GVT) effect. GVT effect is a well-described phenomenon in patients with hematologic malignancies and serves as a major contributing factor in eliminating cancerous cells [1]. It has also been reported in various advanced solid malignancies including renal cell cancer, ovarian cancer, breast cancer, liver carcinoma, and melanoma [1,2]. It has been postulated that GVT effect is potentiated by the presence of full donor chimerism [1], which was seen in our patient. GVT effect in various solid malignancies is usually delayed and observed several months following the transplantation and discontinuation of immunosuppressive therapy [1,2]. The observed timeline in our patient was in accordance with these previous reports. On the other hand, it has also been established

that skin GVHD and its treatments play a critical role in both cutaneous and mucosal SCC development. Based on the results of a case control study, duration of chronic GVHD therapy, the use of azathioprine and severe chronic GVHD are major risk factors for the development of SCC, which usually develops 7 years (range: 0.9-22.9 years) following the transplant [3]. Chronic immunosuppression, ongoing inflammation, and an autoimmune aspect of chronic GVHD have been proposed as potential mechanisms, which promote skin cancer development in the post-transplant period [3]. In fact, one study demonstrated that inflammation and repeated division of keratinocytes in skin with ongoing or previous cutaneous GVHD results in karyotypic abnormalities such as tetraploidy, which is associated with poor prognosis of SCC [4]. In this investigation, the timing of the skin biopsy ranged from 7 months to 7 years following transplantation. If GVT effect is indeed responsible for the regression of epidermal tumors in our patient, there are important differences in the impact of a reconstituted immune system and associated GVHD on SCC behavior at different time points following the transplant.

Additionally, the continued growth of the SCC prior to initiation of ECP therapy with gradual regression after the start of photopheresis suggests that ECP may be inhibiting tumorigenesis. In contrast to our findings, our review of the literature revealed 4 cases of either multiple, aggressive and/or metastatic SCCs in patients with cutaneous T-cell lymphoma (CTCL) that were attributed to treatment with ECP [5-7]. However, tumor development was observed approximately 1-2 years [6,7], 2-5 years [7], and 11 years [5] following ECP initiation. Furthermore, 2 patients received two [7] and eleven [5] years of PUVA therapy, one patient had limited PUVA exposure (11.1 J/cm^2), and the last patient was treated with topical mechlorethamine [7]; both PUVA and mechlorethamine are associated with increased risk of skin cancer. Three patients had significant pre-existing photodamage with multiple actinic keratoses and/or basal cell carcinoma (BCC) [5,7]. The presence of these additional established risk factors make the interpretation of the proposed association of ECP with aggressive SCCs difficult.

The exact mechanisms by which ECP can induce an immune response against CTCL cells and paradoxically immunosuppress alloreactive cells in GVHD are unknown. However, several hypotheses have been proposed including induction of T-cell apoptosis, formation of immature dendritic cells, generation of T-regulatory (Treg) cells, and immunomodulation [8,9]. Considering currently available data, the role of Treg cells and their relationship to skin cancer deserves a closer examination. Treg cells are a subpopulation of T lymphocytes characterized by CD4+ and CD25+ cell markers and the transcription factor Foxp3, which exert a negative effect on the immune system and play an important role in promoting cutaneous carcinogenesis [10]. Their immunosuppressive effects are mediated via secretion of IL-10 and TGF-β with subsequent induction of T-cell anergy and inactivation of dendritic cells [10]. Levels of circulating Treg cells have been shown to be significantly elevated in patients with stage IV melanoma [11]. Aggregates of Treg cells have also been shown to surround human cutaneous BCCs [12] and infiltrate SCCs [13], contributing to evasion from immune response. Increased circulating levels of Treg cells were also identified in renal transplant recipients and were associated with increased risk of subsequent SCC development [14]. Imiquimod, used to treat cutaneous SCCs and BCCs, has been shown to decrease the number of Treg cells and production of Foxp3, IL-10 and TGF-β [14]. Interestingly, ECP in patients with GVHD significantly increases Treg levels, which interfere with alloreactive cells and correlate with clinical improvement [15]. Therefore, considering their critical role in skin cancer development, ECP-induced increase of Treg cells could theoretically potentiate development of SCC and would not explain the observed regression in our patient. On the contrary, it may support previously described cases of aggressive SCCs that were attributed to ECP therapy. Nevertheless, ECP is not currently considered immunosuppressive and increased risk of malignancy or opportunistic infections has not been observed [8].

We describe a case of spontaneously regressing invasive SCC and intraepidermal atypical squamous cell proliferations suggestive of keratoacanthomas in a patient with chronic and treatment-resistant GVHD. The initial growth and subsequent regression of these tumors were observed within approximately 3 1/2 months of ECP initiation and 7 1/2 months following bone marrow transplant. Although the predominant factor driving these changes is not clear, GVT effect and immunomodulation related to ECP are possible explanations. Current data on mechanisms of ECP and specifically its effect on Treg cells dispute our hypothesis and may suggest that it may act to promote skin carcinogenesis. However, continuing accumulation of safety data would argue otherwise [8]. Keratoacanthomas are known to undergo spontaneous regression following the initial stage of growth and at least the two facial lesions may reflect this phenomenon unrelated to transplant or ECP. However, this process would not explain resolution of the invasive SCC on the lower leg. Although patients with chronic GVHD are at increased risk of developing SCCs [3], the potential impact of ECP in modulating this risk is unknown. Further research is needed to elucidate the interrelationship and individual contribution of cutaneous GVHD, GVT effect, and ECP on the risk of the development of cutaneous malignancy and the roles of these factors at different time points in the post-transplant period.

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