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Non-surgical management of primary invasive melanoma

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Abstract

Surgical excision is standard-of-care for primary invasive melanoma, but best care can be unclear for patients who are surgically high-risk or for whom resection may be excessively morbid. Alternatives to surgical excision have emerged for treatment of metastatic melanoma but have not yet been explored for primary invasive melanoma. Two elderly patients with primary invasive melanoma with many medical co-morbidities who were not surgical candidates were determined to be appropriate candidates for an intralesional IL-2 based regimen. Herein we report their clinical and histological outcome. An intralesional-based regimen (intralesional IL-2, topical imiquimod cream 5%, and tretinoin cream 0.1% under occlusion to the treatment site) was administered over the course of six to seven weeks, followed by two weeks of topical-only therapy. A complete response was seen after eight to nine weeks of treating invasive melanomas that were ≥1.85 mm and 5.5 mm thick. For patients with primary invasive melanoma on high morbidity sites and patients who are poor surgical candidates, a neoadjuvant intralesional IL-2-based approach may be a reasonable alternative. The two cases presented here suggest that alternative intralesional-based treatment modalities may minimize the size of the excision site and can be associated with complete histological clearance of invasive melanoma.

Keywords

Intralesional IL-2; interleukin-2; non-surgical alternatives; imiquimod; tretinoin; primary invasive melanoma; TVEC

Introduction

Although surgery remains the gold standard treatment for primary invasive melanoma, operative intervention can be associated with significant morbidity, especially for lesions at anatomically challenging sites such as the face or acral locations, making wide surgical

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margins difficult to achieve. In addition, patients who are poor surgical candidates due to extreme age or comorbidities may warrant tailored care outside of standard guidelines. Patients presenting with in-transit and locoregionally advanced disease have highlighted the need for improved non-surgical treatment. While these patients were historically treated with repeat surgeries, even amputation, in an era of effective systemic therapy it may be difficult to justify an excessively morbid procedure that is associated with 70–80% risk of additional or distant recurrence when modern alternatives exist.[1,2]

Neoadjuvant and novel regional therapies for advanced and metastatic melanoma are now being evaluated and have demonstrated encouraging results, including conversion of previously unresectable disease, improved survival, as well as non-surgical palliation.[3–7] Applying such an approach to the management of primary invasive melanomas might be advantageous in certain circumstances, especially in those just described. Multimodality treatment for metastatic melanoma is also demonstrating improved response rates and has been especially effective for cutaneous melanoma metastases, with complete response rates reaching 100% for intralesional-based therapies.[7]

The possibility of applying these treatments to primary melanoma may be an appealing progression of our armamentarium for this disease.[7] We envision that, for a select population of patients, the management of primary invasive melanoma will incorporate a neoadjuvant approach. Herein we describe the first reported cases of primary invasive melanoma successfully treated with an intralesional-based approach without surgical intervention.

Patient 1

A woman in her 90’s with multiple medical co-morbidities and full dependence on all activities of daily living (ADLs) presented with an enlarging pigmented nodule found to be a 5.5 mm thick acral melanoma (Figure 1A–D). Previously obtained PET/CT demonstrated only localized diseasented to a multidisciplinary cutaneous malignancy tumor board for discussion of further management. Given her advanced age, multiple co-morbidities, ADL-dependent status, and poor options for tissue coverage, wide local excision and sentinel lymph node biopsy were not recommended. As there has been significant success reported with intralesional-based approaches in treating recurrent and in-transit melanoma,[7,8] the tumor board and patient favored this option. The patient provided written informed consent to initiate an intralesional IL-2-based regimen.

The patient underwent five total rounds of an intralesional IL-2-based regimen over the course of seven weeks following the protocol as previously described[9] with the exception of reducing the dose of IL-2 (5.5 million units, administered every other week) given the patient’s poor performance status. Prior to injections, a posterior tibial nerve block was performed and the lesion was pre-treated with cryotherapy at the initial visit. The patient applied imiquimod cream 5% and tretinoin cream 0.1% under occlusion to the treatment site daily. She was closely monitored for IL-2 associated adverse events, and apart from a decreased appetite and nausea managed by ondansetron, the patient tolerated the therapy well.

Patient 2

A man in his 90's presented to an outside dermatologist with a flesh-colored pearly papule on the right frontal scalp found to be an amelanotic nodular melanoma (Figure 2B–2D). The patient was seen by surgical oncology to discuss standard-of-care treatment with wide local excision with 1 – 2 cm margins and a sentinel lymph node biopsy. During his pre-operative assessment, however, the patient was determined to be a very high risk surgical candidate in light of his multiple co-morbidities and poor cardiac function. He too was determined to be an appropriate candidate for intralesional IL-2-based therapy.

Prior to therapy, a recurrent, symptomatic pearly papule was evident at the initial biopsy site (Figure 2A). He provided written informed consent and underwent 11 total rounds of a reduced-dose intralesional IL-2-based regimen to this site, scheduled at twice weekly visits for a total of six weeks.[9] Apart from chills and minor fatigue, the patient tolerated the therapy well.

Patient Outcomes

Following the last round of injections, both patients continued daily application of topical imiquimod and tretinoin for two weeks, after which the treated site was re-biopsied three to four weeks later for residual melanoma, of which there was no evidence clinically (Figure 1E and 2D) or on histopathology (Figure 1F–1H and Figure 2E–2F). On completion of therapy, both patients returned to their baseline of health and premorbid state of activity. No clinical evidence of tumor recurrence occurred during routine melanoma follow-up. The first patient was followed without recurrence, and expired a year later reportedly from failure to thrive. The second patient declined further treatment but was found to have no complications or evidence of recurrence in the treated area 14 months after his last IL-2 injection.

Discussion

We report herein the first cases of primary invasive melanoma successfully treated with an intralesional-based approach without surgical intervention. A complete response was seen after eight to nine weeks of treating invasive melanomas that were ≥ 1.85 mm and 5.5 mm thick, respectively.

Historically, management of invasive melanoma has been largely surgical in nature. With the rapid evolution of immunologic-based therapies, both local and systemic options have changed dramatically over the last decade. Ongoing trials of neoadjuvant therapy in advanced or metastatic disease have almost uniformly endorsed that surgical intervention has moved into a relatively more adjuvant position, consistent with the general trend of current cancer care. One can imagine that the logical next advancement to translate these findings into the primary disease setting. In other cancer types, this has led to improved outcomes, decreases in unnecessarily morbid procedures, and improved organ preservation.[10,11] Moreover, in an era of personalized medicine, it is increasingly appreciated that one-size does not fit all, and it should be recognized that alternative approaches may be desirable in very select, challenging patients.

Reasonable alternatives to surgical excision including various intralesional-based approaches have recently emerged in the treatment of advanced and metastatic melanoma,[6,7] but have not yet been explored in the setting of primary invasive melanoma. There are a few reports of melanoma (usually melanoma *in situ*) responding to imiquimod monotherapy, but complete response rates are low and thus do not warrant this treatment for primary invasive melanoma.

For patients presenting with primary invasive melanoma on high morbidity sites or are surgically high-risk, we imagine that a neoadjuvant intralesional IL-2-based approach may be a reasonable alternative as it may be possible to achieve complete local control through a better tolerated intervention in patients with excessive surgical risk. Ultimately, in the neoadjuvant setting and for patients who are surgically high-risk, agents that demonstrate potential for local and systemic control from abscopal effect will likely be practice-changing and currently represent an intense area of research.

Our limited experience with two patients cannot be extrapolated to all patients with primary invasive melanoma and in both cases standard alternatives were discussed extensively with patients and family. Long-term outcomes of this approach may be difficult to assess in this population. However, this therapy may be applicable for a select population of patients with primary invasive melanoma desiring local intervention and for whom surgical excision is portended to be excessively morbid. Moreover, these therapies may represent an opportunity for improved neoadjuvant strategies in the management of borderline resectable or high-risk primary lesions. Future efforts should focus on demonstrating the reliability and reproducibility of this approach to further evaluate the role of an intralesional IL-2-based regimen in the treatment of invasive melanoma, as well as defining the subsets of patients who are most likely to benefit from this therapy.

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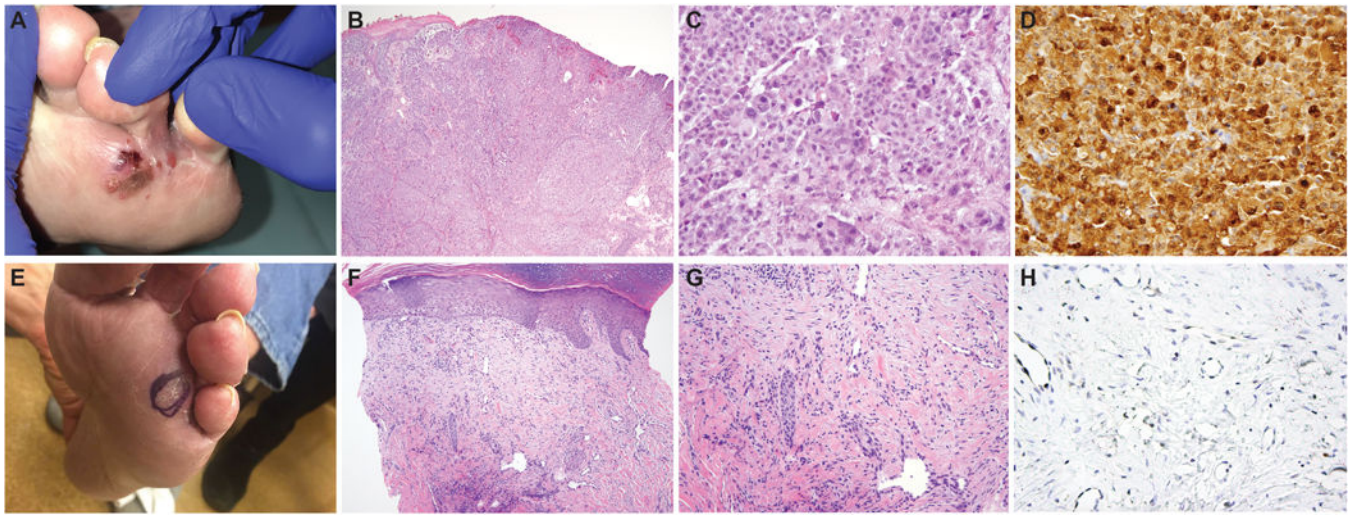

Figure 1. Acral melanoma (stage pT4a Nx Mx) with macroscopic satellite lesions in an elderly patient before and after therapy.

Patient had a recently discovered enlarging pigmented nodule with surrounding scattered pink papules on the plantar aspect of her left foot (A), found on biopsy to be a 5.5 mm thick acral melanoma with ulceration and a mitotic index of 12 (10x magnification) (B). Histopathology demonstrated a large cellular ulcerated tumor of atypical melanocytes with irregular nests of melanocytes found in the epidermis, numerous mitotic figures in the dermis. The atypical cells (40x magnification) (C) stained positive for S100 (D), Melan-a, and HMB45, negative for AE1/AE3, CD45, and CK5/6, supporting the diagnosis of melanoma. Acral site status post completion of therapy (E). Patient had no clinically apparent residual disease or on histopathology, as shown at 4x magnification (F) and at 20x magnification (G). The biopsy showed spongiosis, fibrosis and mild to moderate lymphocytes and was negative for occult melanoma staining positive for SOX-10 (H).

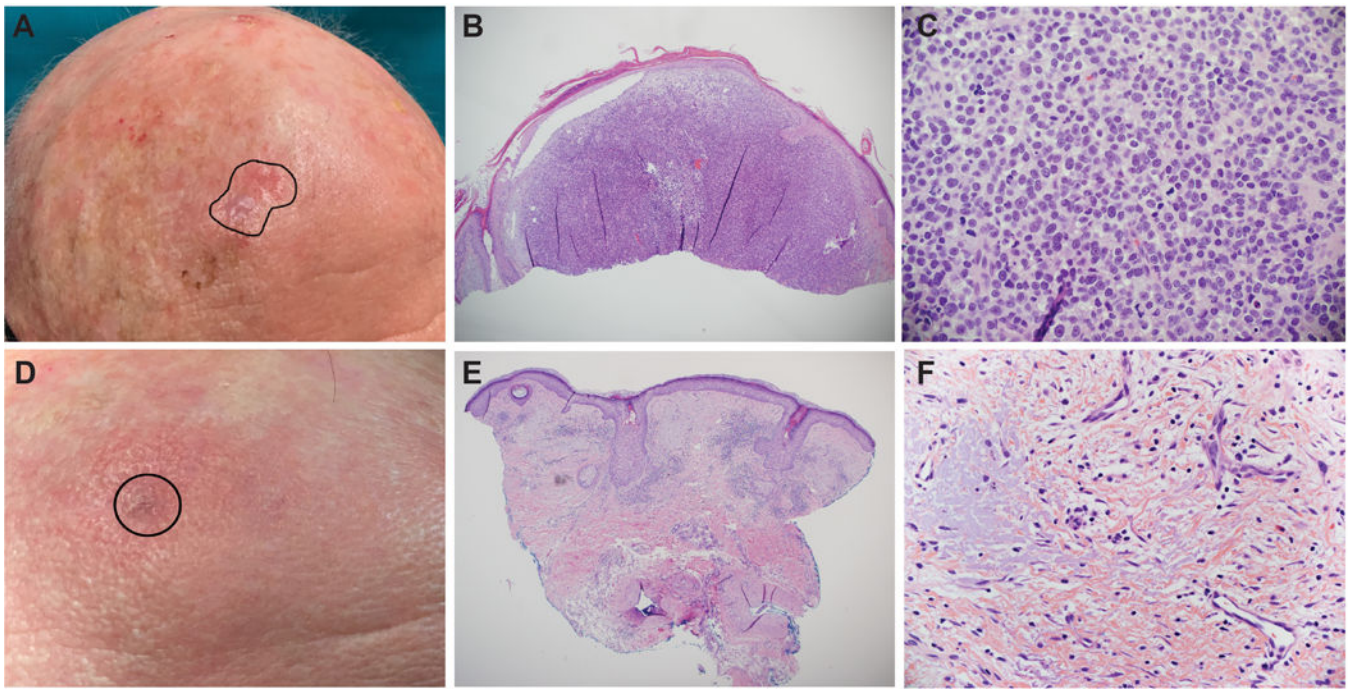

Figure 2. Amelanotic melanoma (at least stage pT2a Nx Mx) in an elderly patient, before and after therapy.

Prior to commencing an intralesional IL-2-based regimen, the patient presented to our team with a pearly papule that recurred after the initial diagnostic biopsy (A). Initially, the patient presented to an outside dermatologist with a 0.6 × 0.7 cm pearly papule that was found on biopsy to be at least a 1.85 mm thick amelanotic melanoma without ulceration (B and C, 4x and 40x magnification) and a mitotic index of 18. On histopathology, the tumor was transected at the base at a depth of 1.85 mm thus preventing accurate pathologic staging (stage ≥ pT2a). Histopathology showed nodular collections of cells with large nuclei and scattered necrotic cells and mitoses. The atypical cells stained positive for SOX-10 and negative for neurofilament and CK-Pan. Treatment site 3 weeks status post completion of therapy had presence of an atrophic scar (D). No tumor or residual disease was found on histopathology, as shown at 4x magnification (E) and at 40x magnification (F). The biopsy showed fibrosis with granulomatous inflammation and was negative for tumor and for occult melanoma staining positive for SOX-10.