BRIEF ARTICLES

Complete Histologic Response of Regionally Metastatic Melanoma Treated with Intralesional Interleukin 2, Topical Retinoid and Imiquimod

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INTRODUCTION

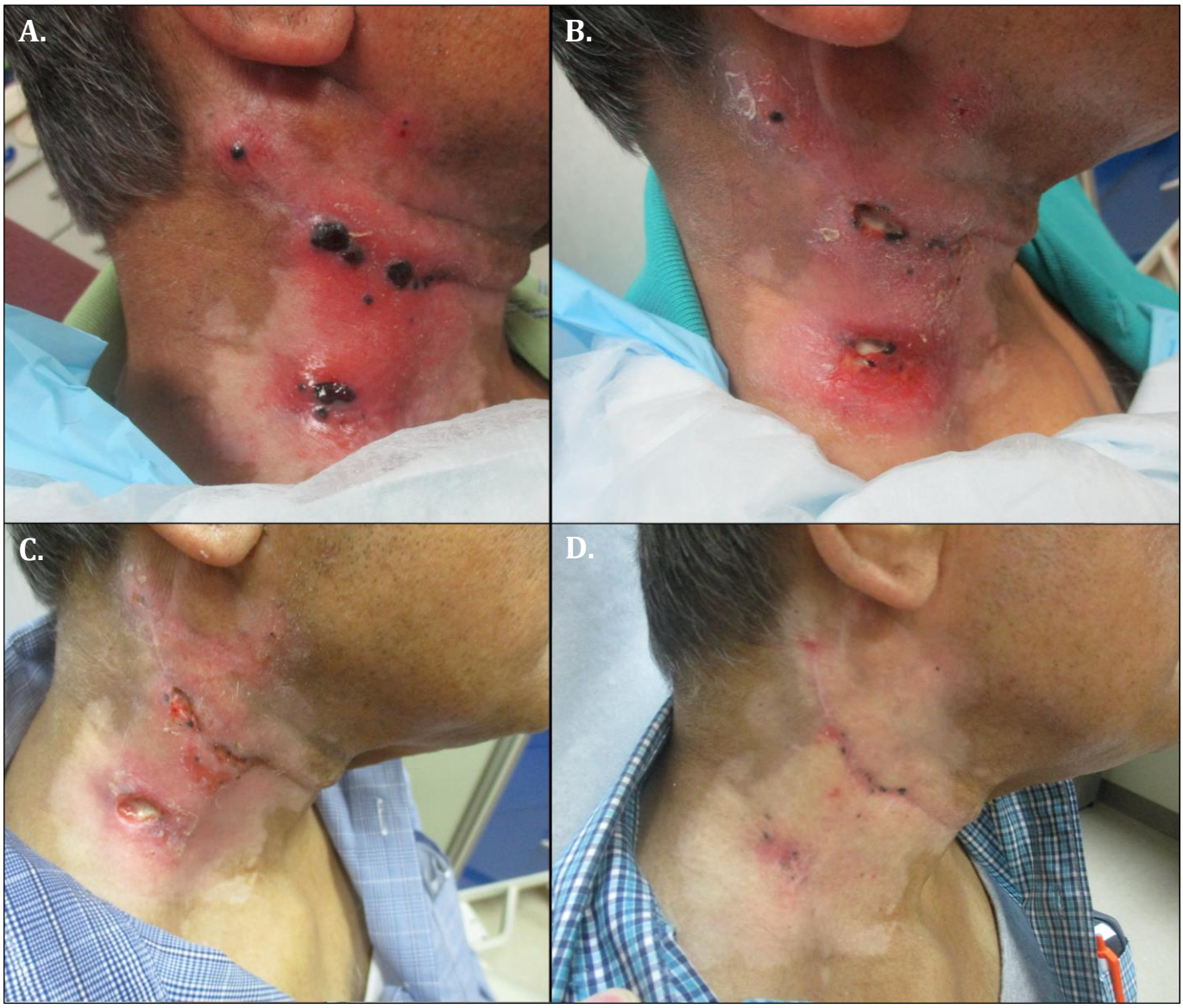
Metastatic melanoma is a difficult malignancy to manage, and the methods used to treat it have significantly changed over the past two decades. We present the use of older medications in a previously successful newer modality that can achieve results suggestive of cure. This method has shown repeated success in patients who desire to avoid surgery, or who lack apparent response to newer standard of care medical treatment. This demonstrates that the method continues to work despite use of check point inhibitor immunotherapy, and check point inhibitor medication side effects requiring further immunosuppression.

CASE PRESENTATION

A 74-year-old Indian man presented with a growing nodule on his right parietal scalp, which biopsy proved to be a 3.8mm invasive melanoma. Histological examination of punch biopsies before treatment showed dermal nodules of heavily pigmented, malignant melanocytes. The dermatopathologist noted that considerations included locally recurrent disease at the site of prior lymphadenectomy and possibly in-transit or distant cutaneous metastatic foci (Figure 2). Further testing revealed a valine to lysine mutation within the BRAF gene (V600K). He was initially treated with wide local excision and sentinel lymph node biopsy which was positive in five levels of lymph nodes. He then underwent right neck lymph node dissection with a free-flap graft from his left forearm to close the scalp defect. Positron emission tomography (PET) showed no evidence of systemic disease. The patient responded to adjuvant monthly nivolumab post-surgically, but was noted to develop persistent adrenal insufficiency, which required daily oral hydrocortisone supplementation.

Nine months later, multiple black papules were noted in and around the surgical scars of his right neck (Figure 1). Multiple biopsies showed melanoma, consistent with possible "surgical seeding" due to lack of epidermal involvement (Figure 2). Repeat imaging showed evidence of only cutaneous disease. The patient was switched from

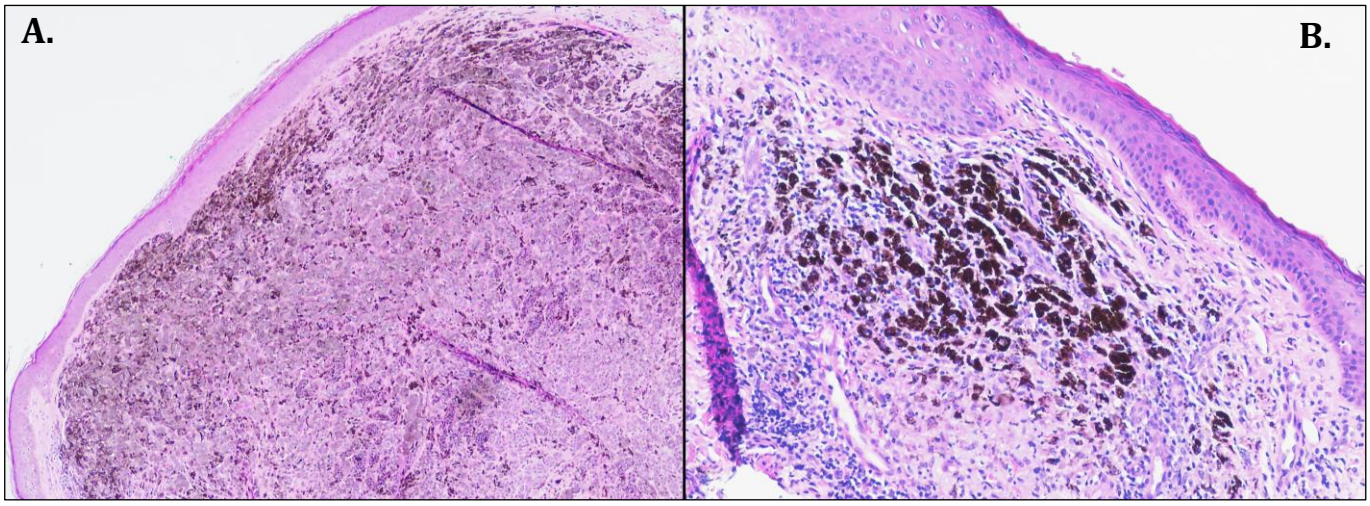
Figure 1. Progression of Cutaneous Melanocytic Lesions over Course of Interleukin Treatment. (**A**) Therapy two weeks into treatment with IL-2; (**B**)Therapy five weeks into treatment with IL-2; (**C**) Therapy one week post therapy with IL-2; (**D**) Therapy four weeks post therapy with IL-2.



nivolumab to pembrolizumab and ipilimumab with a goal of increased immunologic response, but did not gain significant benefit. His daily oral hydrocortisone dependency precluded him from other systemic treatments, such as tumor infiltrating lymphocytes (TIL), or clinical trials.

Due to skin-limited disease, a regimen of imiquimod, tretinoin 0.025% cream (with intermittent increase to tazarotene 0.1% gel as tolerated), and intralesional and perilesional interleukin-2 (IL-2) injections was initiated. The regimen per Shi *et al.* resulted in leukoderma, ulceration and irritation to the area as intended.[1] With daily application of topical treatment, plus biweekly IL-2 injections, the local metastases slowly regressed over the next six weeks (Figure 1). Biopsies of brown-

Figure 2. Comparison of biopsies before (**A**) and after (**B**) treatment, showing no further evidence of abnormal appearing melanocytes with residual melanophages. (H&E, 20X)



black macules post-therapy consistently demonstrated superficial clusters of melanophages with melanin incontinence, melanophages, cicatrix, and evidence of regression, consistent with successful localized treatment (Figure 2). Initial dosing of IL-2 was performed with monitoring in an infusion clinic at a starting dose of 5 million units with subsequent increase in concentration to a maximum of 22 million units over next three injections, which were performed in the dermatology clinic.[1,3]

DISCUSSION

With the advent of immunotherapy, systemic IL-2 treatment has fallen out of favor for treatment of metastatic melanoma due to poorly tolerated side effects, such as rigors, chills, and hemodynamic instability requiring hospital admission. Intralesional delivery has allowed patients to receive much higher localized doses and, depending on disease location, promising results.[1-3] IL-2 is thought to stimulate proliferation and activation of humoral and cell mediated immunologically active cells through the differentiation of $CD4^+$ T cells and to stimulate effector T cell generation and differentiation into memory cells for $CD8^+$ T cells, resulting in tumor lysis.[1,4] Applying topical retinoids increases the rate of keratinocyte maturation and potentiates imiquimod penetration, which in turn upregulates toll-like receptors seven and eight as well as cytokines, such as tumor necrosis factor alpha, and cytotoxic T-cell responses.[1,2] Previous small studies have treated patients with intralesional IL-2 injections, imiquimod and topical retinoids with good results, but many of the participants had not received any immunotherapy prior to treatment, whereas our patient had already been treated with two programmed cell death protein-1 inhibitors (nivolumab and pembrolizumab) and a cytotoxic T-lymphocyte associated protein 4 inhibitor (ipilimumab).[1]

CONCLUSION

This report demonstrates procedural adjunctive therapies that dermatologists can offer to patients with cutaneous metastases as an adjunct to immunomodulatory therapy or for patients whose post-immunotherapy

endocrinopathies limit their candidacy for TIL therapy or clinical trials.

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