BRIEF ARTICLE

Demodicosis Mimicking Papulopustular Eruption in the Setting of Targeted Therapy

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ABSTRACT

Here we discuss the dramatic cutaneous reactions of two patients receiving targeted therapies for cancer (one on a MEK inhibitor/BRAF inhibitor and the other receiving carfilzomib). Demodicosis was the underlying cause in both cases, though the infection was mistaken for a reaction to the patients' complex malignancy therapies. Given the prevalence of cutaneous side effects of chemotherapy and targeted cancer therapies and the protean nature of demodicosis, it follows that demodicosis may be easily mistaken as a drug reaction to a chemotherapeutic agent. Demodicosis in the setting of chemotherapy and immunosuppression must thus remain an important diagnostic consideration in patients undergoing cancer treatment to allow for appropriate diagnosis and management of cutaneous findings without discontinuation of essential chemotherapy.

INTRODUCTION

Here we discuss the dramatic cutaneous reactions of two patients receiving targeted therapies for cancer (one on a MEK inhibitor/BRAF inhibitor and the other receiving carfilzomib).

CASE REPORTS

A woman in her 50s receiving vemurafenib 480mg twice daily and trametinib 2mg daily for anaplastic astrocytoma presented to oncodermatology clinic with a 6-month history of persistent papulopustular eruption involving the face and scalp. Pink papules and pinpoint pustules were noted on the forehead, nose, cheeks, upper lip and chin one week after beginning targeted therapy (Figure 1a). Inflamed papules were scattered across the lateral and posterior neck and scalp. The lesions were not pruritic nor painful. She received doxycycline 100mg twice daily and triamcinolone 0.1% cream for the face and fluocinonide 0.05% solution for the scalp for suspected cutaneous reaction to MEK inhibitor/BRAF inhibitor (BRAFi/MEKi) therapy. Her eruption persisted over the next five months despite treatment with various oral antibiotics, topical antibiotics, and topical steroids. While mineral preparation of scrapings of active facial pustules did not reveal any organisms, the patient began treatment for presumed *Demodex folliculorum* folliculitis using ivermectin 15mg (two doses, 1 week apart). Remarkable improvement of the eruption was seen 10 days later. She then started a topical compounded cream including metronidazole 1%, ivermectin 1%, and azelaic acid 15% for daily use until complete resolution. One month later, her face was clear (Figure 1b).

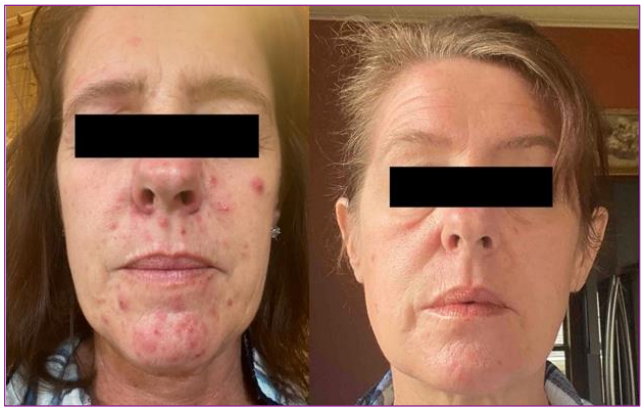

Figure 1. Patient receiving vemurafenib and trametinib daily for anaplastic astrocytoma A) One week after starting targeted therapy. Pink papules and pinpoint pustules noted on the forehead, nose, cheeks, upper lip and chin B) Remarkable improvement of cutaneous events 10 days after starting ivermectin for demodicosis.

A man in his 50s receiving proteasome inhibitor carfilzomib 54mg/m^2 one dose every two weeks for multiple myeloma presented with a new onset facial rash consisting of 2-4 mm pink follicular papules on the face, neck, and scalp. The patient endorsed temporary improvement with 1g doses of methylprednisolone with every carfilzomib infusion. He initiated treatment with clobetasol 0.05% cream twice daily for 2 weeks with some improvement. Two months later, approximately two weeks after switching therapy to daratumumab, he was hospitalized for cancer-related complications and worsening pruritic facial eruption. His physical exam revealed excoriated, erythematous, folliculocentric papules, deep nodules, and pustules on the bilateral temples, cheeks, ears, scalp, forehead, and posterior neck (Figure 2a). Mineral scraping of pustules revealed no organisms. Punch biopsy showed deep suppurative inflammation with dermal neutrophilic infiltrate, and *Demodex* mites (Fig 3). He received 15mg of oral ivermectin (two doses, 1 week apart) for the treatment of demodicosis, achieving complete resolution at two-week follow-up (Fig 2b).

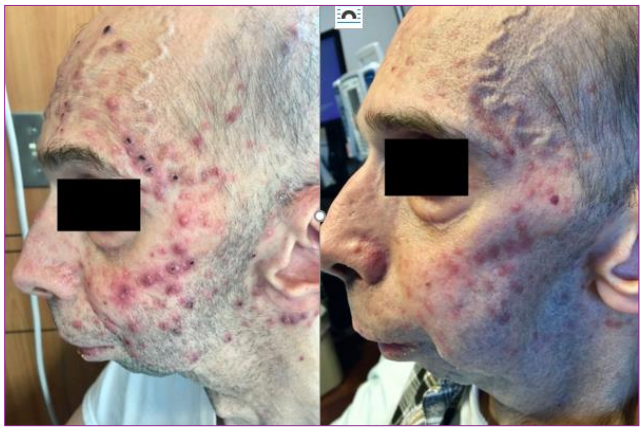

Figure 2. Patient receiving carfilzomib, one dose every two weeks, then daratumumab for multiple myeloma A) Two weeks after starting daratumumab. Erythematous, folliculocentric papules, deep nodules, and pustules on the bilateral temples, cheeks, ears, scalp, forehead, and posterior neck B) Significant resolution seen two weeks after starting ivermectin for demodicosis.

DISCUSSION

Demodex mites (*Demodex folliculorum* and *brevis*) are commensal organisms that colonize sebaceous areas. A range of facial inflammatory eruptions may be seen when the mites proliferate, including pustular folliculitis and conditions that mimic pityriasis folliculorum[1], papulopustular rosacea, granulomatous rosacea, periorificial dermatitis, acne, blepharitis, and papulopustular scalp eruptions[2]. Infection incidence increases among the elderly or immunocompromised patients, including those with HIV and those receiving immunosuppression for cancer treatment[3]. Demodicosis has been associated with several immunomodulatory agents, including topical or systemic steroids, monoclonal antibody therapies like cetuximab and panitumumab[4], and biologics like dupilumab[5]. These therapies are hypothesized to reduce the body's defense against mite proliferation while simultaneously upregulating chemokines

that recruit mast cells and macrophages, potentiating an inflammatory response[4].

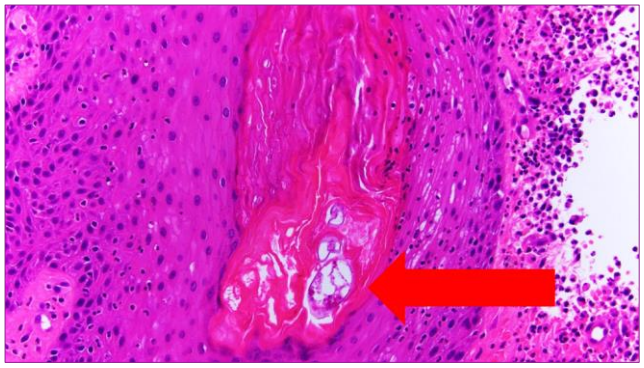

Figure 3. Results of punch biopsy from the patient seen in Figure 2. Biopsy shows deep suppurative inflammation with dermal neutrophilic infiltrate, and Demodex mites.

Our cases add to the literature of demodicosis following immunomodulatory therapy. The combination of BRAFi/MEKi has revealed distinct dermatologic toxicities, potentially due to BRAFi's action on MAPK signaling and increased BRAF signaling[6]. The co-administration of a MEKi has been speculated to limit adverse effects by reducing MAPK/CRAF pathway activation[7]. However, patients on dual therapy still experience maculopapular eruptions, papulopustular eruption, epidermal hyperkeratosis in the form of verrucous keratoses[8] and keratosis pilaris[9], and keratoacanthomas. Proteasome inhibitors like carfilzomib have also been reported to cause cutaneous eruptions, including papulonodular eruptions, urticaria, cutaneous vasculitis[8], and Sweet syndrome[9]. These exanthematous reactions are believed to be the result of cell-mediated delayed hypersensitivity[10]. To our knowledge, demodicosis mimicking papular eruptions associated with BRAFi/MEKi or proteasome inhibitors has previously been reported.

The diagnosis of demodicosis can be made via skin scraping with mineral or KOH preparation or skin biopsy showing organisms within hair follicles (see Fig. 3)[11]. The diagnostic value of microscopic examination of sebaceous secretions versus standardized skin surface biopsy is debated. Treatment options include topical or oral ivermectin, topical permethrin, benzoyl benzoate, and metronidazole[12]. The long-term use of mid-potency or stronger topical corticosteroids on the face should be highly discouraged, as these have the potential to exacerbate this condition or can result in periorificial dermatitis which has a similar clinical presentation. Bacterial superinfection in the setting of *Demodex* infection has also been observed.

CONCLUSION

Few reports exist that causally link BRAFi's or proteosome inhibitors to *Demodex* infection. We suspect a potential relationship between the immunomodulatory effects of targeted therapy and susceptibility to *Demodex*, resulting in our patients' cutaneous eruptions. Demodicosis in the setting of chemotherapy and immunomodulation must remain a diagnostic consideration in cancer patients to allow for appropriate management of cutaneous findings without discontinuation of essential cancer therapy.

Conflict of Interest Disclosures: None

Funding: None

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