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Case Report

Nipple Inflammation: An Unusual Adverse Effect from Vemurafenib, av600e Braf Inhibitor during off-lable Treatment for Anaplastic Thyroid Carcinoma

Daniel G Chong[1], Richard H Schwartz[2], Robert A Silverman[3]

[1]Virginia Cancer Specialists Fairfax Virginia, USA

[2]Inova Inova Children's Hospital Falls Church, Virginia, USA

[3]Section on Dermatology Inova Fairfax Hospital for Children, Virginia, USA

[*]**Corresponding author:** Richard H Schwartz, Advanced Pediatrics100 East St SE, Suite 301Vienna, VA 22180; Virginia, USA, Tel: 703 938-5555; Fax: 703 319-8580; E-mail: rhs738@aol.com

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Abstract

Background: Anaplastic thyroid cancer is regarded as one of the most aggressive of all solid malignant tumors. Until recently the prognosis for patients with these cancers was almost universally bleak with an expected median life expectancy of about 5-months. Although traditional chemotherapy or radiation therapy offers little chance of cure, targeted therapy against mutant tyrosine kinase inhibitors such as BRAF-V600, may give some hope in treatment of these aggressive cancers. The following case report adds information to the well-known cutaneous adverse effects associated with targeted therapy with vemurafenib, an inhibitor of BRAF-V600.

Main observation: A 77-yearold man recently diagnosed with metastatic anaplastic thyroid carcinoma was treated with vemurafenib, noted grade 3 cutaneous toxicity consisting of facial sensation of warmth and flushing, pruritis, extensive xerosis, folliculocentric exanthums, and painful, nipples accompanied by an uncomfortable burning sensation exacerbated by contact with undershirts and bed sheets. Administration of triamcinolone cream (0.1%, twice daily) rapidly eliminated the pain and burning sensation from his nipples.

New Findings: Nipple inflammation should be added to the list of adverse dermatological effects of vemurafenib. The annoying and painful symptoms respond quickly to topical triamcinolone cream.

Introduction

Vemurafenib is a monoclonal inhibitor of a mutant tumor tyrosine kinase protein, V600 E, produced by certain malignant tumors such as advanced cutaneous melanoma, adenocarcinoma of the colon, and anaplastic thyroid cancer. Rashes occur in 68% of patients taking recommended doses of vemurafenib [1]. Annoying pruritic skin rashes and B-RAF-induced new-onset skin tumors such as squamo-proliferative growths are common adverse effects, nipple inflammation (mamillary papillitis) is an unusual dermatologic adverse effect of targeted immunotherapy for selected solid malignant tumors, Recommendations to consult a dermatologist when patients receive vemurafenib for advanced melanoma have been published [2].

Case Presentation

The patient is a 77-year-old pediatrician who was in his usual state of good health when, while shaving, he noticed a large 9 cm mass (measured longitudinally), in his right supraclavicular area. An expedited comprehensive evaluation was undertaken which included contrast-enhanced computed tomography (CT) of his neck, chest, and abdomen. The mass was shown to be located above and below his right clavicle. A fusion CT/positive emission tomogram (PET scan) revealed showed several bright uptake areas in two ribs and in the right adrenal gland, neither of which were visible

on contrast-enhanced CT alone. A large bore core biopsy of the lesion was completed under sedation anesthesia. The final pathology report was highly disorganized, aggressive, anaplastic carcinoma of the thyroid gland. Specimens were sent to the pathology laboratory at Johns Hopkins Hospital where the diagnosis was confirmed. The presence of metastatic lesions distant from the primary site negated the possibility of surgical intervention and, as such, a meeting of the tumor board at the University of Virginia concluded that radiation therapy was not advisable for several reasons.

Six days after discovery of the tumor mass One week after initiation of vemurafenib (ZelborafTM, Genentech, Hoffman La Roche, Switzerland), adverse dermatologic effects, toxicity grade 3, believed secondary to the therapeutic agent were noted. These included a pruritic folliculocentric rash,flushing and a sensation of warmth in face, auricles, and neck regions, pruritis of several areas on the body, and a strange sensation of burning, itching, and hypersensitivity to light touch of both nipples which became engorged (Figure 1).

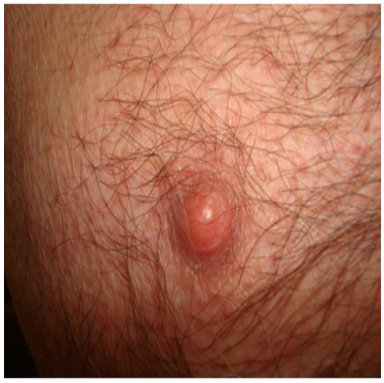

Figure 1: Very inflamed mammillary nipple during early stage of vemurafenib targeted therapy for anaplastic thyroid cancer.

Even skin-to-bedsheet or undershirt provoked moderate pain which did not radiate. Emollient moisturizing solutions were applied to both nipples with mild to moderate benefit. A therapeutic trial of triamcinolone cream (0.1 %, applied twice daily gave considerable relief from nipple pain, pruritis, and burning 12-hours after first application which further improved after subsequent supplication over four days.

Discussion

B-RAF tyrosine kinase inhibitors such as vemurafenib act as targeted therapy against metastatic melanoma and additional solid tumors that possess the B-RAF marker gene. The use of vemurafenib significantly increases progression-free survival in these patients. However, numerous adverse dermatologic effects have been reported. One of the more frequent of adverse effects involves skin rashes. These toxicities are usually not preventable and they rarely require permanent treatment discontinuation. In a series of 42 patients treated with vemurafenib all patients presented with at least one adverse skin reaction. The most common cutaneous side-effects consisted in verrucous papillomas (79%) and hand-foot skin reaction (60%). Other common cutaneous toxic effects were a diffuse hyperkeratotic folliculocentric rash (55%), photosensitivity (52%) and alopecia (45%). Flushing of ears and face, pruritis, burning sensation, and macular and popular rashes are annoying, and may interfere with sleep [3]. Additional common and annoying adverse dermatological effects include xerosis and panniculitis. Keratoacanthomas and squamous cell carcinoma occurred in 14% and 26% of the patients, respectively, in that study. Warty dyskeratomas, and keratoses, along with widespread eruptions of acantholytic dyskeratosis are also common [3]. Vemurafenib-induced side effects generally tend not to be severe or life threatening. Most patients can be managed by dose interruptions, dose reductions, topical therapies such as emollients, moisturizing creams or lotions, and judicious use of corticosteroid ointments or creams. In more severe cases judicious use of oral corticlsteroids are indicated and effective [4]. Squamous cell carcinomas and keratoacanthomas associated with vemurafenib therapy are easily treated by simple excision of the lesion, without discontinuation of vemurafenib. A low threshold for biopsy of new growths is recommended [5]. Additional common adverse dermatologic effects include flushing of face with sense of warmth even without exposure to the sun, generalized of localized pruritis, and granulomatous dermatitis [6]. Recently, a combination of B-RAF inhibitor (B-RAFi) with MEK inhibitor (MEKi) was found to effect a significant reduction in cutaneous adverse effects and longer cutaneous adverse event-free interval, compared to B-RAFimonotherapy [7]. If this can be verified by additional studies annoying and sometimes serious adverse dermatologic effects can be reduced or eliminated. Although Kramkimel et al. suggests that there seems to be a correlation between clinical response to vemurafenib when used to treat high grade malignant melanoma, and severity of toxic rash, this observation was not noted in the large case series of 107 patients by Sinha, et al [4-8].

Conclusion

Mamillary papillits (nipple inflammation) should be added to the list of adverse dermatological effects of vemurafenib. The annoying and painful symptoms respond quickly to triamcinolone cream.

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