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DIAGNOSIS IN ONCOLOGY

Cutis Verticis Gyrata in Association With Vemurafenib and Whole-Brain Radiotherapy

Case Report 1

A 33-year-old man presented to an outside hospital with a 2-month history of lower back pain, fever, chills, and anorexia. Physical examination revealed subcutaneous nodules on the chest, abdomen, and back. Cross-sectional imaging demonstrated multiple masses throughout the paraspinal tissue, vertebrae, liver, and subcutis. A magnetic resonance imaging scan of the brain showed four brain metastases ranging from 2 to 12 mm in size. An excisional biopsy of a subcutaneous lesion revealed metastatic melanoma characterized by a $BRAF^{V600E}$ mutation.

The patient initiated external-beam whole-brain radiotherapy (WBRT, 30 Gy over 10 daily fractions with 6 MV photons) and vemurafenib at a dose of 960 mg orally twice per day. After seven of 10 fractions of WBRT (21 Gy), the patient developed pain and erythema of the ears and scalp, resulting in a diagnosis of grade 2 radiation dermatitis. The patient temporarily stopped WBRT and received topical emollients. Vemurafenib was continued without a dose reduction. After slight improvement in his symptoms, WBRT was reinitiated to complete the 10 fractions. The patient subsequently noted recurrence and worsening of his symptoms, which reached their maximum severity approximately 3 weeks after completion of WBRT. Photographs (Figs 1A and 1B) of his head and neck demonstrate a severe confluent erythematous and hyperkeratotic plaque limited to the radiation field. Tortuous skin folding

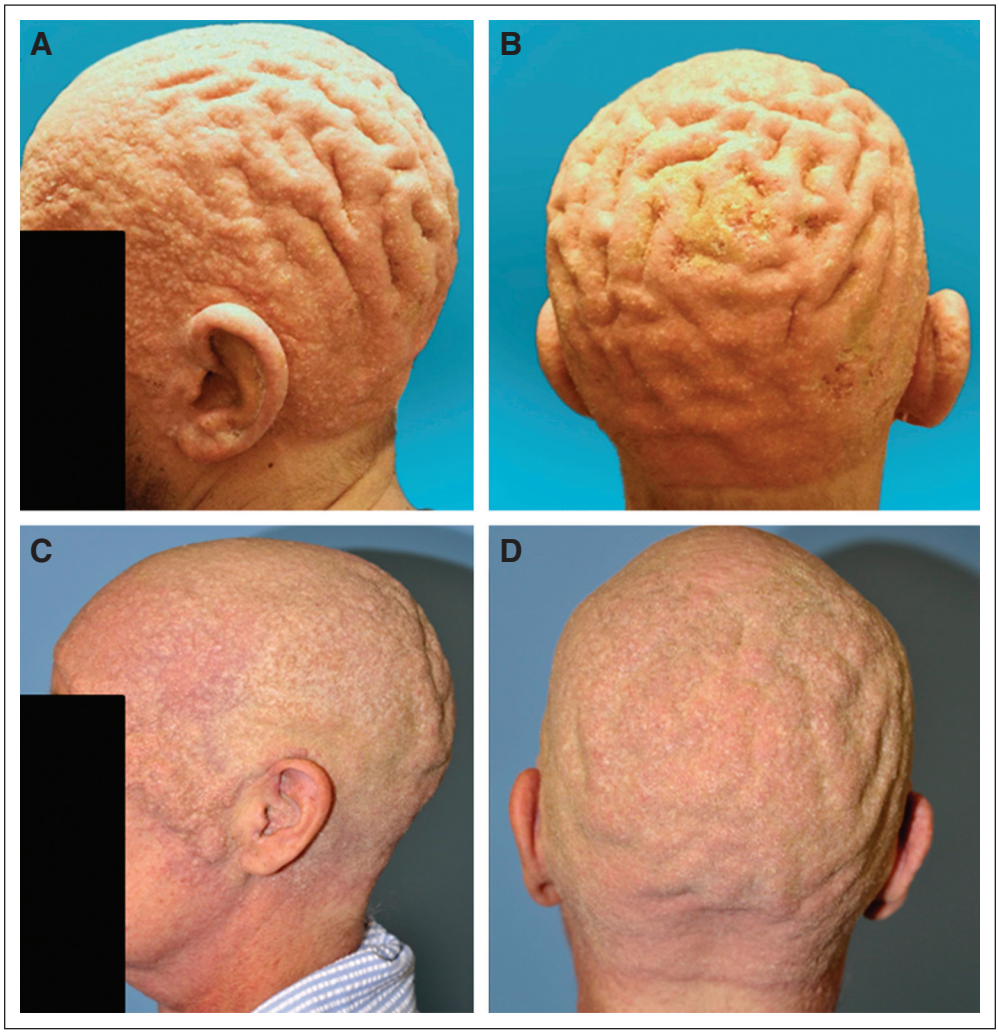

Fig 1.

and thickening of the scalp with induration of the ears, not observed previously, are also notable.

The patient received treatment with topical corticosteroids, retinoids, and antibiotics with slow improvement of this toxicity. Two months later, the patient presented to our Center for further evaluation. Physical examination revealed resolution of the previously noted hypertrophic scalp changes. However, the confluent erythematous and hyperkeratotic plaque persisted. Cross-sectional imaging demonstrated a partial response to vemurafenib therapy. We recommended continuation of vemurafenib and prescribed a topical corticosteroid (alclometasone) for the patient's scalp. One month later, he had a continued clinical response to vemurafenib with complete resolution of his scalp eruption.

Case Report 2

A 53-year-old woman with a history of stage IIIB (T2bN1aM0) cutaneous melanoma (American Joint Committee on Cancer staging system, edition 7) originating on the trunk was treated initially with wide local excision, completion lymph node dissection, and a clinical trial with an adjuvant DNA vaccine. The patient did well clinically and was without radiographic evidence of disease for nearly a decade. Two months before presentation at our center, she complained of fatigue, unintentional weight loss, confusion, and an unsteady gait. Cross-sectional imaging showed extensive pulmonary, splenic, hepatic, mesenteric, and osseous masses that were consistent with widespread metastatic disease. A magnetic resonance imaging scan of the brain demonstrated a left posterior orbital metastasis and innumerable bilateral brain metastases ranging from 1 to 28 mm in size. A computed tomography–guided liver biopsy confirmed the presence of metastatic melanoma.

The patient completed a course of WBRT with the radiation portal including the left posterior orbital metastasis (35 Gy over 14 daily fractions with 6 MV photons) concurrent with temozolomide. After progression of disease, she then presented to our center for further therapeutic options. While tumor sequencing for a *BRAF* mutation was in progress, the patient received one dose of ipilimumab. Once a $BRAF^{V600E}$ mutation was identified, the patient began receiving vemurafenib at a dose of 960 mg orally twice per day. This treatment was begun 3 weeks after the completion of WBRT. Within 3 weeks of initiating vemurafenib, the patient complained of scalp pain, swelling, and redness. Physical examination of the head and neck demonstrated diffuse erythema and hyperkeratosis limited to the radiation field (Figs 1C and 1D). A diagnosis of grade 1 radiation recall was made, with furrowing and ridging of the scalp. She continued vemurafenib with several dose reductions. Her rash persisted, but did not worsen, and was treated with topical salicylic acid. The patient ultimately died as a result of her disease approximately 11 weeks after the initiation of therapy.

Discussion

Herein we present two cases of a cutaneous eruption of the scalp that occurred in the context of vemurafenib and WBRT. Both patients developed a cutaneous reaction that was characterized by pain, erythema, hyperkeratosis, and hypertrophy of the scalp. The observed tortuous skin folding and convoluted furrowing that resembles the sulci and gyri of the cerebrum is descriptively termed cutis verticis gyrata (CVG).[1]

CVG is an uncommon and typically innocuous dermatologic condition that occurs either in isolation (ie, primary essential CVG) or in association with a number of medical conditions (ie, primary nonessential or secondary/acquired CVG).[2] On histopathologic examination, the appearance of CVG is variable and depends on the underlying etiology. In isolated cases of CVG, dermal biopsy may reveal normal skin architecture. In patients with acquired CVG, dermal collagen thickening and hypertrophy of the sebaceous structures (as in acromegaly), inflammation and edema, and, in some cases, malignant conditions (leukemia and sarcoma) are observed on pathologic review.[2-4] Irrespective of the underlying cause, the galea aponeurotica limits the soft tissue expansion and/or overgrowth of the scalp, which in turn leads to the unique and characteristic cerebriform pattern. Spontaneous resolution of acquired CVG can occur with treatment of the underlying medical cause; however, in many patients, the cutaneous changes are permanent.

Dermatologic adverse events occurring with the RAF kinase inhibitors vemurafenib and dabrafenib are common and include rash, photosensitivity, alopecia, and hyperproliferative cutaneous eruptions (ie, verrucae, papillomas, hyperkeratosis, keratoacanthomas, and squamous cell carcinomas).[5] The mechanistic basis for the development of hyperproliferative skin lesions, particularly squamous cell carcinoma, is thought to be the result of paradoxical activation of extracellular signal-regulated kinases (ERK) signaling in *BRAF* wild-type cells in response to RAF kinase inhibition.[6-9] This in turn leads to cellular hyperproliferation of *BRAF* wild-type cells. Like RAF kinase inhibition, radiotherapy can also cause multiple dermatologic complications. Acute radiation-induced skin changes include erythema, mild edema, and dry and moist desquamation, and occur within days to weeks of treatment.[10] Ionizing radiation induces direct DNA damage in developing keratinocytes, which leads to inflammation, cell cycle arrest, and apoptosis.[11] To our knowledge, such dramatic cutaneous reactions characterized by erythema, hyperkeratosis, and CVG have not been reported with WBRT or with the RAF kinase inhibitors alone.

The molecular effects of concurrent RAF kinase inhibition and radiotherapy on *BRAF* mutant melanoma are incompletely understood; preclinical data suggest that RAF inhibitors are radiosensitizers.[12,13] Little is known about their effects on normal tissue. It is possible that RAF inhibitor therapy can enhance the cutaneous toxicity of radiation therapy. RAF inhibitors paradoxically increase ERK signaling and cellular proliferation in *BRAF* wild-type keratinocytes.[8,9] Additionally, ionizing radiation increases ERK signaling in a number of cell lines through the activation of receptor tyrosine kinases, RAS, and the preferential activation of CRAF.[14] Concomitant radiotherapy and RAF inhibitor therapy may each activate the mitogen-activated protein kinase pathway in keratinocytes, leading to hyperkeratosis and hypertrophy within the radiation field.

In summary, we present these cases to familiarize medical and radiation oncologists with CVG and to point out the need for further evaluation of the effects of RAF inhibition and radiotherapy, particularly with concomitant administration. The clinical experience with RAF kinase inhibition and radiotherapy is limited, and presently, it is difficult to ascertain whether or not their combination will lead to improvement in outcomes or greater toxicity.[15-18] The potential for cutaneous toxicity that is associated with combination therapy certainly exists. As illustrated in the cases presented, such events (albeit likely rare) can be intolerable to patients, profoundly disfiguring, and

affect quality of life. Our institutional practice is to discontinue RAF kinase inhibitors 5 to 7 days before the initiation of any form of radiotherapy. On completion of radiotherapy, we resume the RAF inhibitor as dictated by the clinical situation. We avoid concurrent radiotherapy with RAF inhibitors in routine clinical practice and recommend their combined administration only in the context of a clinical trial.

James J. Harding, Christopher A. Barker, Richard D. Carvajal, Jedd D. Wolchok, Paul B. Chapman, and Mario E. Lacouture

Memorial Sloan-Kettering Cancer Center, New York, NY

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REFERENCES

1. Schons KR, Beber AA: Images in clinical medicine: Cutis verticis gyrata. N Engl J Med 367:e23, 2012

2. Walia R, Bhansali A: Cutis verticis gyrata. BMJ Case Rep doi: 10.1136/bcr.01.2011.3763 [epub ahead of print on June 3, 2011]

3. Cheson BD, Christiansen RM: Cutis verticis gyrata: Unusual chloromatous disease in acute myelogenous leukemia. Am J Hematol 8:415-418, 1980

4. Kim JE, Choi KH, Kang SJ, et al: Angiosarcoma mimicking cutis verticis gyrata. Clin Exp Dermatol 36:806-808, 2011

5. Lacouture ME, Duvic M, Hauschild A, et al: Analysis of dermatologic events in vemurafenib-treated patients with melanoma. Oncologist 18:314-322, 2013

6. Callahan MK, Rampal R, Harding JJ, et al: Progression of RAS-mutant leukemia during RAF inhibitor treatment. N Engl J Med 367:2316-2321, 2012

7. Hatzivassiliou G, Song K, Yen I, et al: RAF inhibitors prime wild-type RAF to activate the MAPK pathway and enhance growth. Nature 464:431-435, 2010

8. Poulikakos PI, Zhang C, Bollag G, et al: RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. Nature 464:427-430, 2010

9. Su F, Viros A, Milagre C, et al: RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. N Engl J Med 366:207-215, 2012

10. Sitton E: Early and late radiation-induced skin alterations: Part I. Mechanisms of skin changes. Oncol Nurs Forum 19:801-807, 1992

11. Bentzen SM: Preventing or reducing late side effects of radiation therapy: Radiobiology meets molecular pathology. Nat Rev Cancer 6:702-713, 2006

12. Sambade MJ, Peters EC, Thomas NE, et al: Melanoma cells show a heterogeneous range of sensitivity to ionizing radiation and are radiosensitized by inhibition of B-RAF with PLX-4032. Radiother Oncol 98:394-399, 2011

13. Dasgupta T, Haas-Kogan DA, Yang X, et al: Genotype-dependent cooperation of ionizing radiation with BRAF inhibition in BRAF V600E-mutated carcinomas. Invest New Drugs [epub ahead of print on January 26, 2013]

14. Dent P, Yacoub A, Fisher PB, et al: MAPK pathways in radiation responses. Oncogene 22:5885-5896, 2003

15. Rochet NM, Dronca RS, Kottschade LA, et al: Melanoma brain metastases and vemurafenib: Need for further investigation. Mayo Clin Proc 87:976-981, 2012

16. Lee JM, Mehta UN, Dsouza LH, et al: Long-term stabilization of leptomeningeal disease with whole-brain radiation therapy in a patient with metastatic melanoma treated with vemurafenib: A case report. Melanoma Res 23:175-178, 2013

17. Long GV, Trefzer U, Davies MA, et al: Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): A multicentre, open-label, phase 2 trial. Lancet Oncol 13:1087-1095, 2012

18. Wang CM, Fleming KF, Hsu S: A case of vemurafenib-induced keratosis pilaris-like eruption. Dermatol Online J 18:7, 2012

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