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Diverse cutaneous side effects associated with BRAF inhibitor therapy: A clinicopathologic study

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Abstract

Background—Vemurafenib, a novel selective small molecule inhibitor of BRAF, has recently been shown to be effective in the treatment of melanomas harboring the *BRAF* V600E mutation. Similar to the broad-spectrum RAF inhibitor sorafenib, vemurafenib induces development of squamous cell carcinomas and keratoacanthomas as a side effect of therapy.

Objective—We sought to detail additional cutaneous adverse effects of vemurafenib and a similar BRAF inhibitor, dabrafenib.

Methods—We evaluated the clinical and histologic feature of skin side effects developing on vemurafenib or dabrafenib therapy in 14 patients.

Results—Eight patients developed one or more squamous cell carcinomas, and 11 patients formed benign verrucous keratoses. Eight patients developed single lesions and/or widespread eruptions with histopathologic findings of acantholytic dyskeratosis, consistent with warty dyskeratomas and Darier- or Grover-like rashes, respectively. One patient developed palmoplantar hyperkeratosis, and darkening of existing nevi and new nevi within 2 months of starting vemurafenib. Side effects presented as early as 1 week after beginning therapy, with a mean time of onset of 12.6 weeks in our cohort.

Limitations—This study was limited by the small number of cases, all from a single institution.

Conclusion—Selective BRAF inhibitor therapy is associated with the development of malignant and benign growths, including keratoacanthoma-like squamous cell carcinomas, warty

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dyskeratomas, and verrucous keratoses, along with widespread eruptions with histologic features of acantholytic dyskeratosis. Given the potential for malignant lesions to develop on treatment, awareness of potential adverse effects of these agents is necessary, and a low threshold for biopsy of new growths is recommended.

Keywords

acantholytic dyskeratosis; BRAF; drug adverse effects; nevi; squamous cell carcinoma; verrucous keratosis; warty dyskeratoma

Vemurafenib is a recently developed small molecule inhibitor of the serine/threonine kinase BRAF, a component of the RAS–RAF–MEK–ERK (mitogen-activated protein kinase [MAPK]) signaling pathway that effects cellular processes including proliferation, survival, and differentiation.[1] The drug specifically targets tumor cells that harbor activating mutations in *BRAF*, most commonly the substitution of glutamic acid for valine at codon 600 (V600E).[2] Vemurafenib was approved by the Food and Drug Administration for treatment of metastatic melanoma in August 2011, after promising tumor responses to the medication in phase I, II, and III clinical trials.[3–5] A similar selective BRAF inhibitor, dabrafenib (GSK2118436), is currently being tested in clinical studies for treatment of advanced stage and metastatic melanoma, as a single agent and in combination with a MEK inhibitor, trametinib (GSK1120212).[1,6,7]

Several cutaneous adverse effects of vemurafenib have been noted in earlier clinical studies.[3,4] Photosensitivity, sometimes resulting in blistering reactions, has been documented.[3,8] Palmar-plantar dysesthesia occurred in several patients.[4] Keratosis pilaris–like eruptions occur in roughly one third of patients treated.[3,9] Lastly, squamous cell carcinomas (SCCs) and keratoacanthomas (KAs) have been reported in 20% to 30% of patients treated with vemurafenib.[3,4]

Here, we describe in detail the cutaneous side effects observed in 14 patients after initiation of BRAF inhibitor therapy. These findings include the previously noted eruptive SCCs, and several additional skin reactions, which will be discussed in detail.

REPORT OF REPRESENTATIVE CASES

Case 1

A 47-year-old Caucasian woman (patient 1, Table I) was diagnosed with stage IV melanoma with lung involvement, and was found to have V600E mutation in *BRAF*. Vemurafenib 960 mg twice daily was initiated, and 12 weeks after beginning therapy she noticed new scaly papules on the central aspect of her chest (Fig 1, *A*), upper aspect of her shoulders, back, and face. Several biopsies were performed at these sites. A biopsy from a 2-mm, pink, hyperkeratotic papule on the central aspect of her chest revealed an epidermal invagination featuring acantholysis and dyskeratosis and clefting of the suprabasilar epidermis, characteristic of warty dyskeratomas (Fig 1, *B*). Histopathologic examination of a papule on the patient's face demonstrated a benign verrucous keratosis, and samples taken from the shoulder and back revealed SCCs (not shown). After 2 months of treatment with vemurafenib, the patient had a 60% reduction of her tumor burden based on computed

tomography examination, and symptomatically experienced relief of her disease-related chronic cough and fatigue.

Case 2

A 55-year-old Caucasian woman (patient 7, Table I) had a history of multiple primary melanomas on her abdomen, arm, and elbow and developed metastatic disease to her axillary lymph nodes and brain 1 month after detection of her third primary melanoma. Tumor genotyping revealed the *BRAF* V600E mutation. Vemurafenib was started at a dose of 960 mg twice a day, and she developed a new rash on her chest, face, and arms 4 weeks later. Of note, she had no history of nonmelanoma skin cancers. On physical examination, she had many erythematous, 2- to 3-mm scaly papules on her chest and abdomen (Fig 2, *A*), and a 1-cm dome-shaped hyperkeratotic, tender red papule on her arm. Histopathologic examination of the chest lesions demonstrated acantholysis and dyskeratosis consistent with Grover disease (also known as transient acantholytic dyskeratosis) or Darier disease (Fig 2, *B*). An additional biopsy specimen revealed a SCC on her arm (not shown). The acantholytic rash was responsive to treatment with triamcinolone 0.1% ointment, and the SCC was treated with wide local excision.

Coincident with the development of her skin lesions, the patient noted a reduction in size of her subcutaneous lymph nodes. However, her brain disease later progressed on therapy, and she subsequently died.

Case 3

An 83-year-old Caucasian woman (patient 13, Table I) with a history of an aggressive melanoma on her scalp status-post excision was given the diagnosis of metastatic disease involving her lungs and left breast. She was initially treated with temozolomide and radiation therapy, with partial response. Vemurafenib was then started at 960 mg twice daily after detection of *BRAF* V600K mutation in her tumor. After 1 week on the medication, she noticed eruptive growths on her forehead, arms, legs, and back. She denied any history of non-melanoma skin cancers before starting vemurafenib. On physical examination, she had approximately 30 3- to 10-mm inflamed papules and nodules with keratotic cores on the face, back, arms, and legs (Fig 3, *A*), Biopsy specimens taken from multiple lesions demonstrated similar findings of large cup-shaped atypical proliferations of squamous epithelial cells, with central keratin-filled craters, diagnostic of SCC of the KA type (Fig 3, *B*). The patient's SCCs were all well differentiated, and exhibited moderate solar elastosis in the surrounding dermis. The lesions ranged from 2 to 3.5 mm in thickness, extending from superficial to deep reticular dermis.

Marked reduction in size of the patient's scalp melanoma was observed after 4 weeks of treatment. Because of medication-related fatigue, the patient's dose of vemurafenib was subsequently decreased to 720 mg twice daily, but she continued to develop additional SCCs. The patient was prescribed topical 5-fluorouracil to apply twice daily to SCCs indefinitely; several lesions have demonstrated regression clinically on therapy.

Case 4

A 57-year-old Chinese man (patient 14, Table I) had a history of papillary thyroid cancer status-post total thyroidectomy, with involvement in his lymph nodes, jaw, and right parotid gland. He received but was resistant to radioactive iodine and was placed on a clinical trial of vemurafenib for his metastatic disease after confirmation of a *BRAF* V600E mutation. After 8 weeks of treatment, he had a 22% reduction of tumor burden on computed tomography scan. At the same time, he developed several new papules on his face. He also noticed new pigmented macules on his palms. He denied history of nonmelanoma skin cancers.

On physical examination, he had flesh-colored and slightly erythematous verrucous papules on the nose and left cheek (Fig 4, *A*). He was also noted to have two new brown macules on his palm (Fig 5, *A*), and one on the plantar aspect of his foot, on a background of new focal palmoplantar hyperkeratosis. He had multiple evenly pigmented nevi scattered on his trunk and arms (Fig 5, *B*), which had darkened after starting the medication. The darkening was marked, noted both by the patient and the clinician based on pretreatment and post-treatment evaluations. Histopathologic examination of a facial papule demonstrated hyperkeratosis, acanthosis, and papillomatosis without apparent koilocytic change, consistent with a verrucous keratosis (Fig 4, *B*). Biopsy specimen of a dark nevus on the trunk revealed a junctional dysplastic nevus with moderate atypia (not shown).

DISCUSSION

Vemurafenib and dabrafenib commonly induce cutaneous reactions. Each of the 14 patients (13 with metastatic melanoma and one with metastatic thyroid cancer) reported here developed one or more skin side effects after initiation of vemurafenib or dabrafenib treatment, and 13 of the 14 exhibited at least two different types of skin reactions (Table I). Verrucous keratoses were most commonly observed, occurring in 12 of 14 patients. SCCs and acantholytic eruptions each appeared in 8 of the 14 patients (Table II). Patient 14, with metastatic papillary thyroid cancer, experienced darkening of his pre-existing nevi and eruption of several new nevi on acral sites.

Interestingly, only 3 of the 8 patients who developed a SCC on therapy had been given the diagnosis of a SCC before starting vemurafenib (patients 1, 2, and 7). Histologically, the SCCs observed in our patients were well-differentiated lesions. The SCCs biopsied ranged from in situ carcinoma, to invasive SCCs with a greatest thickness of 3.5 mm (data not shown). The thickest lesions extended to the mid to deep reticular dermis, and none demonstrated per-ineural invasion. All lesions occurred on a background of solar elastosis, with most exhibiting moderate sun damage (CSD 2, per the grading scheme devised by Landi et al[10]). In 4 of 8 patients with SCCs, at least one of their tumors exhibited features of a KA, with cup-shaped architecture and central keratin-filled crater. Whereas KAs classically demonstrate microabscesses composed of neutrophils and/or eosinophils within epithelial nests,[11] these features were not observed in the biopsy specimens from this cohort.

Recent evidence suggests that SCCs and KAs arise specifically in the setting of RAF inhibitor therapy.[12,13] Sorafenib, a multikinase inhibitor with pan-RAF activity, has been

demonstrated in multiple reports to induce SCCs and KAs.[14–24] Sorafenib has a much broader spectrum of action than vemurafenib and dabrafenib, exhibiting activity against vascular endothelial growth factor receptor 1, 2, and 3; platelet-derived growth factor receptor-β; FMS-like tyrosine kinase 3; c-kit; RET receptor tyrosine kinase; and all isoforms of RAF.[25] Significantly, the multi-kinase inhibitor sunitinib, which targets many of the same kinases as sorafenib (vascular endothelial growth factor receptor 1, 2, and 3; platelet-derived growth factor receptor; c-kit; FMS-like tyrosine kinase 3; and RET tyrosine kinase) but not RAF, does not result in development of SCCs or KAs.[13,26] Sorafenib is a nonselective inhibitor of wild-type and mutated forms of RAF, with poor activity against *BRAF* V600E tumor cells, and has been demonstrated to be an ineffective treatment for melanoma.[7,27] An estimated 6% to 7% of patients treated with sorafenib develop SCCs and KAs, which stands in contrast to 20% to 30% of patients taking vemurafenib.[3,4]

The mechanism underlying development of SCCs in patients treated with RAF inhibitors is actively being investigated. Recent data suggest that pharmacologic RAF blockade in cells harboring wild-type BRAF paradoxically increases signaling through CRAF, which then increases MAPK signaling overall.[28–30] Arnault et al[31] examined normal-appearing skin biopsy specimens from patients treated with sorafenib, finding increased Ki67 and phosphorylated ERK staining in keratinocytes on histologic sections, compared with normal-appearing skin taken from placebo-treated patients. This suggests that MAPK signaling is in fact increased, presumably leading to increased keratinocyte proliferation. Paradoxical activation of MAPK signaling by itself may not be sufficient to induce SCCs and KAs. To this end, Oberholzer et al[12] determined that *RAS* activating mutations are more frequently found in SCCs and KAs from patients treated with vemurafenib (30%) and sorafenib (11%) compared with those from control patients (3.2%). Pre-existing *RAS* mutations in keratinocytes (possibly induced by sun exposure or viral infection) may therefore receive a “second hit” via RAF inhibitor–driven paradoxical activation of MAPK signaling, which would then be sufficient for tumor development.

A large number of the patients reported here developed either single lesions or widespread eruptions with histopathologic findings of acantholytic dyskeratosis, consistent with warty dyskeratomas and Darier- or Grover-like rashes, respectively. To our knowledge, such findings have not been previously associated with RAF inhibitor therapy. Paradoxical activation of the MAPK pathway in normal keratinocytes may account for the findings of acantholytic dyskeratosis, as it has previously been shown that transfection of rat cardiac myocytes with constitutively active Ras and Raf leads to decreased expression of sarco/endoplasmic reticulum Ca2+-ATPase type 2 isoform (SERCA2), the protein deficient in Darier disease.[32] It remains to be determined whether SERCA2 expression is decreased in the warty dyskeratomas and Darier-like eruptions observed in our patients.

Verrucous keratoses, which we define as benign wartlike growths without apparent viral cytopathic changes, were observed in nearly all cases presented here. HPV immunostaining was performed on several biopsy specimens that had architectural changes suggestive of true verrucae; however, in each case the staining was negative. Lacouture et al[9] also describe the occurrence of wartlike proliferations arising in the setting of vemurafenib therapy. Intriguingly, cutaneous papillomas have been reported to occur in patients with Costello

syndrome, which is most frequently caused by activating germline *HRAS* mutations,[33,34] and in those with cardiofaciocutaneous (CFC) syndrome, in which activating germline mutations in *BRAF*, *MEK1*, *MEK2*, and *KRAS* are the most common underlying genetic alterations.[35] Papillomas are more common in Costello syndrome, occurring most often on the nose and central aspect of the face.[34] Histologically, the papillomas of Costello syndrome resemble the verrucous keratoses observed in our study, demonstrating verrucous epidermal hyperplasia without the koilocytes and clumped keratohyalin granules found in common verrucae.[36] It is interesting to note that most of the verrucous keratoses observed in our study were biopsied from the face (63%).

Eruptive nevi have been described in patients treated with sorafenib, occurring on acral sites in one patient.[37] The patient presented in case 4 not only developed new acral nevi, but also experienced darkening of pre-existing nevi. These findings again warrant comparison with the inherited CFC syndrome, in which a greater than average number of nevi is a characteristic finding. Nevi in patients with CFC syndrome are typically evenly distributed across all body sites, and individually are uniformly pigmented and medium to dark brown in color.[35]

Mild palmoplantar hyperkeratosis, accentuated at pressure points, affected the patient in case 4 after starting vemurafenib, and several other patients in this practice. Palmoplantar hyperkeratosis is a frequent side effect of sorafenib therapy, in the context of the hand-foot skin reaction.[38] Drawing further parallels to Costello and CFC syndromes, focal palmoplantar hyperkeratosis appears in both conditions often, in 76% and 36% of patients, respectively.[34]

Clinical management of the keratotic lesions presents challenges. First, patients frequently present with such a high number of keratotic lesions that surgical management with excision may be impractical or intolerable. For example, our patient who had approximately 30 SCCs of the KA type (case 3) declined excision except for lesions that were either symptomatic or growing quickly. Second, clinical examination could not reliably distinguish benign from malignant lesions, therefore a low threshold for skin biopsy of new growths is recommended. Even under the microscope, distinction between benign and malignant lesions can be challenging. For example, one case demonstrated focal areas of transition to SCC in situ in what otherwise had the histologic appearance of a benign verrucous keratosis.

Practitioners may consider several surgical approaches to manage these keratotic growths. For lesions that are large, tender, growing rapidly, or located in critical anatomic locations, excision or Mohs micrographic surgery is indicated. For small and superficial lesions, destructive modalities such as curettage and electrodessication or cryosurgery may be sufficient. We have used cryotherapy for treatment of small SCCs in case 3, with good results. Before destruction, biopsy to confirm the diagnosis and remove the clinically visible lesion would be prudent.

In cases where surgical treatment is either impractical or undesirable, other strategies may be necessary. We have observed anecdotally regression of lesions after treatment with topical 5-fluorouracil (case 3). Reduction of vemurafenib dose is another potential management

strategy, although this did not prevent development of new SCCs in case 3. Bexarotene was used with apparent success for treatment of KAs in a patient treated with sorafenib, raising the possibility that it and other systemic retinoids may be helpful for vemurafenib-associated SCCs and KAs.[23] Another potential therapeutic modality is the use of a MEK inhibitor in combination with vemurafenib or dabrafenib, with the idea that the MEK inhibitor may block paradoxical MAPK signaling downstream of CRAF in keratinocytes.[13] This is a particularly appealing possibility as combination therapy may also be useful in circumventing at least some forms of resistance to BRAF inhibitors that develop in melanomas.[39–41] In a recent study, SCCs did not develop in any of 45 patients treated with combination BRAF and MEK inhibitor therapy.[42] In our cohort, the two patients treated with dabrafenib and trametinib (patients 6 and 12) did not form SCCs, although they developed benign keratoses.

In summary, we have described several cutaneous side effects associated with selective BRAF inhibitor therapy for metastatic melanoma and thyroid cancer, many of which may be attributed to paradoxical activation the MAPK signaling pathway in nontumor cells. Further investigation will be necessary to elucidate the precise molecular mechanisms underlying these phenomena. Awareness on the part of dermatologists and oncologists of the potential side effects of selective BRAF inhibitors will become increasingly important as these agents are used more widely.

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Abbreviations used

CFC	cardiofaciocutaneous
KA	keratoacanthoma
MAPK	mitogen-activated protein kinase
SCC	squamous cell carcinoma

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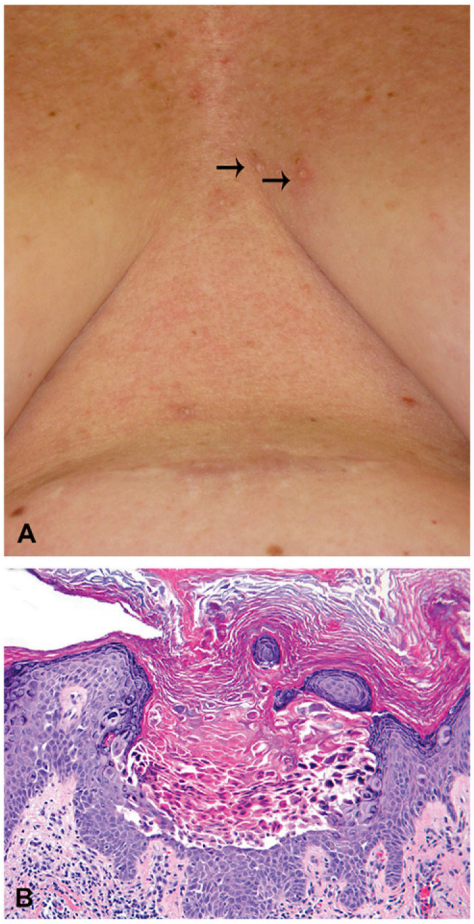

Fig 1.

Warty dyskeratoma (case 1). **A**, New keratotic papules on chest. **B**, Biopsy specimen demonstrating acantholysis and dyskeratosis, consistent with warty dyskeratoma. (Hematoxylin-eosin stain; original magnification: ×200.)

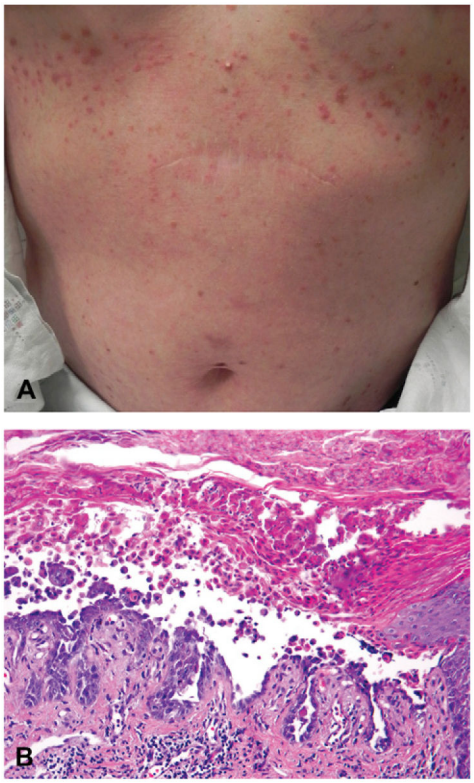

Fig 2.

Acantholytic dyskeratosis resembling Darier disease (case 2). **A**, Eruption of crusted papules on trunk. **B**, Biopsy specimen demonstrating prominent acantholytic dyskeratosis. (Hematoxylin-eosin stain; original magnification: ×200.)

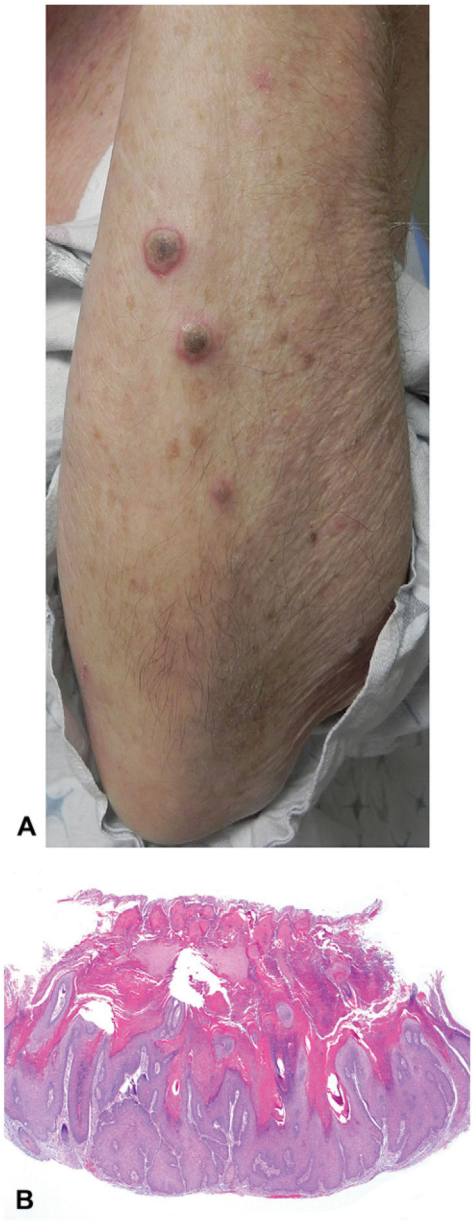

Fig 3.

Squamous cell carcinoma (SCC) (case 3). **A**, Multiple eruptive nodules on forearm. **B**, Histopathologic examination reveals well-differentiated SCC with keratoacanthoma-like features. (Hematoxylin-eosin stain; original magnification: ×20.)

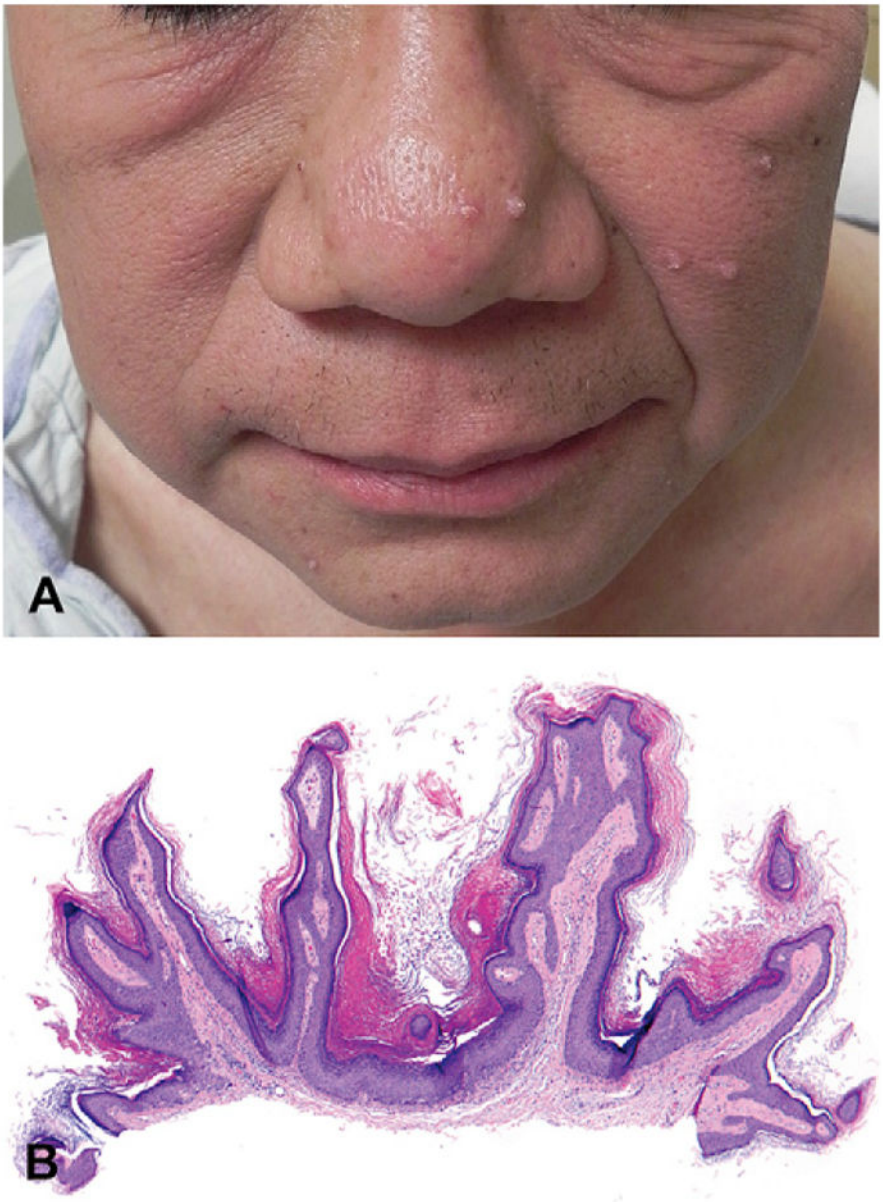

Fig 4.

Verrucous keratosis (case 4). **A**, Multiple verrucous papules on face. **B**, Biopsy specimen of facial papule reveals hyperkeratosis, acanthosis, and papillomatosis in absence of viral changes, all features of verrucous keratosis. (Hematoxylin-eosin stain; original magnification: ×40.)

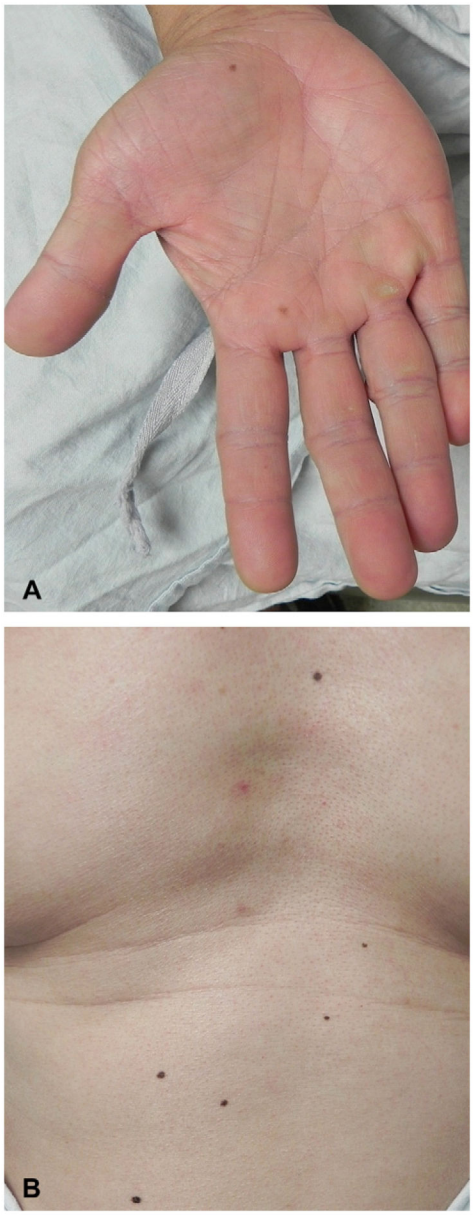

Fig 5.

Eruptive nevi and darkening nevi (case 4). **A**, New nevi on palm developing on treatment with vemurafenib, and focal palmar hyperkeratosis. **B**, Nevi on trunk, which darkened after initiation of vemurafenib.

Table I

Characteristic of patients on BRAF inhibitors

	Patient no.													
Characteristic	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Age, y	46	64	47	60	54	53	55	58	69	77	68	64	83	57
Sex	F	M	F	F	F	M	F	F	F	M	F	M	F	M
Targeted therapy	V	V	V	V	V	D + T	V	V	V	V	D	D + T; V	V	V
Time before first skin lesion, wk	12	5	20	56	12	19	4	10	5	3	8	14	1	8
History of SCC	+	+	−	−	−	−	+	−	−	−	−	−	−	−
Type of lesion														
SCC	+	+	−	+	+	−	+	−	+	−	+	−	+	−
SCC, KA type	+	−	−	+	−	−	−	−	−	−	+	−	+	−
Verrucous keratosis	+	+	+	−	+	+	−	+	+	+	+	+	+	+
Acantholytic dyskeratosis	+	−	+	+	−	−	+	−	+	+	+	+	−	−
Eruptive nevi	−	−	−	−	−	−	−	−	−	−	−	−	−	+

D, Dabrafenib (GSK2118436); F, female; KA, keratoacanthoma; M, male; SCC, squamous cell carcinoma; T, trametinib (GSK1120212); V, vemurafenib.

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Table II

Frequency of lesions observed in patients on BRAF inhibitors

		Distribution of lesions (% of total biopsied)		
Type of lesion	**Total patients affected (%)**	**Face**	**Extremities**	**Trunk**
Verrucous keratosis	12 (86)	12 (63)	2 (11)	5 (28)
SCC	8 (57)	4 (19)	13 (62)	4 (19)
KA type	4 (29)	3 (27)	6 (55)	2 (18)
Acantholytic dyskeratosis	8 (57)	0 (0)	4 (27)	11 (73)
Eruptive nevi	1 (7)	0 (0)	1 (7)	0 (0)

KA, Keratoacanthoma; SCC, squamous cell carcinoma.