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CASE REPORT

# Vemurafenib-associated neutrophilic panniculitis in a patient with metastatic amelanotic melanoma presenting as cancer of unknown primary origin

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ABSTRACT

The treatment of metastatic melanoma is challenging. *BRAF* gene mutation is found in 40–60% of melanoma cases, the most common being the V600E mutation. Vemurafenib was approved by the Food and Drug Administration in 2011 as target therapy for the treatment with BRAF V600 mutation-positive metastatic melanoma. We report a case of metastatic amelanotic melanoma with unknown primary cancer as the initial presentation. The patient presented with neutrophilic septal panniculitis 1 week after vemurafenib treatment, which is a rare cutaneous toxicity of BRAF inhibitor. We also review the current literature on management of BRAF inhibitor-related adverse skin effects.



## Introduction

The treatment of metastatic melanoma is challenging. *BRAF* gene mutation is found in 40–60% of melanoma cases, the most common being the V600E mutation. Vemurafenib was approved by the Food and Drug Administration in 2011 as target therapy for the treatment with *BRAF* V600 mutation-positive metastatic melanoma. In this report, we present a case of metastatic amelanotic melanoma with unknown primary cancer as the initial presentation. The patient presented with neutrophilic septal panniculitis 1 week after vemurafenib treatment, which is a rare cutaneous toxicity of *BRAF* inhibitor (BRAFi). We also review the current literature on management of BRAFi-related adverse skin effects.

## Case Report

The patient was a 75-year-old woman, a retired farmer, with a medical history of hypertension under regular control. She was diagnosed as having metastatic melanoma with unknown primary tumor, cTxNxM1, by excision of right axillary lymphadenopathy. Serum tumor marker surveys, including carcinoembryonic antigen, squamous cell carcinoma antigen, cancer antigen 153, cancer antigen 125, and alpha-fetoprotein, were all within normal limits. The pathology report of right axillary lymphadenopathy revealed infiltrating epithelioid malignancy with solid growth pattern, abundant cytoplasm, enlarged and vesicular nuclei, prominent nucleoli, and brisk mitotic activity (Figure 1A). The immunohistochemical studies showed negative reactivity for cytokeratin AE1/AE3, inhibin, calretinin, leukocyte common antigen, CD34, and CD30. Expressions of S-100 protein, HMB-45 (human melanoma black-45; Figure 1B and D), Melan-A (Figure 1C), and MiTF-1 (microphthalmia-associated

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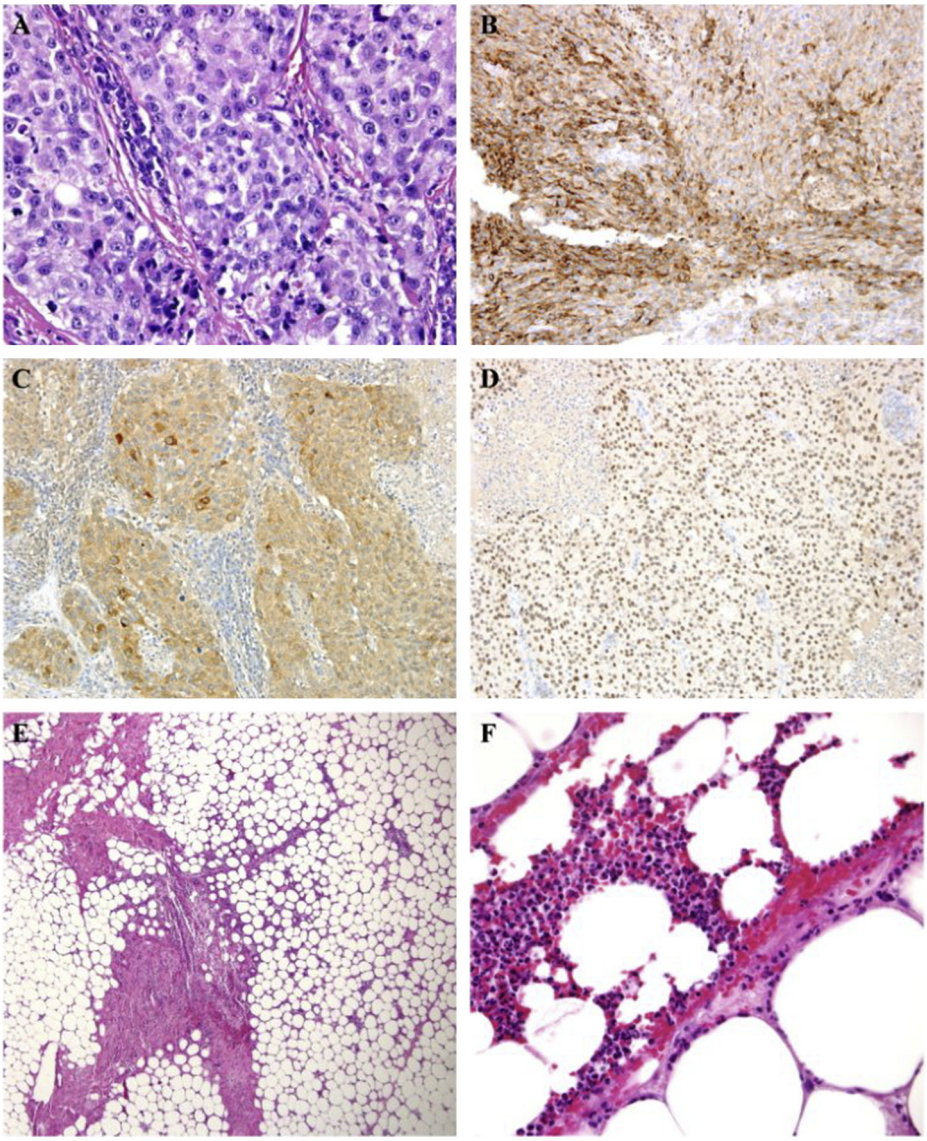


**Figure 1** (A) Pathology shows infiltrating epithelioid malignancy with solid growth pattern, abundant cytoplasm, enlarged and vesicular nuclei, prominent nucleoli, and brisk mitotic activity (hematoxylin and eosin; original magnification, ×400). (B) Positivity for HMB-45 of tumor cells (original magnification, ×200). (C) Positivity for Melan-A of tumor cells (original magnification, ×200). (D) Positivity for MiTF-1 of tumor cells (original magnification, ×200). (E) Pathology shows mainly septal pannuculitis with red blood cells extravasation (hematoxylin and eosin; original magnification ×40). (F) Inflammatory cell infiltrates along septa and focal lobular area of subcutaneous fat, which is predominantly composed of neutrophils (hematoxylin and eosin; original magnification, ×400). HMB-45 = human melanoma black-45; MiTF-1 = microphthalmia-associated transcription factor-1.

transcription factor-1) were diffusely positive. The final diagnosis was metastatic malignant amelanotic epithelioid melanoma. On physical examination, no obvious primary skin tumor was noted. Whole-body positron emission tomography showed metastases to the right axillary area, right supraclavicular area, right shoulder, the mediastinum, and bilateral pulmonary hili (Figure 2B). She also had progressive dysphagia and dyspnea, which are probably related to the metastases with initial upper airway compression. The presence of a v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) gene point mutation at codon 600 from valine to glutamate was confirmed by the LightCycler HybProbe real-time polymerase chain reaction assay for the right axillary lymphadenopathy specimen (Figure 2A). Under a diagnosis of metastatic melanoma with *BRAF* V600E mutation, she received oral vemurafenib (720 mg daily), a specific inhibitor of mutant *BRAF*.

About 1 week under vemurafenib treatment, she noticed several painful skin lesions on her abdomen and bilateral lower limbs. She denied fever, arthralgia, or other symptoms of discomfort. On physical examination, there were several tender erythematous subcutaneous nodules with infiltration over the abdomen and four limbs (Figure 2D and E). Laboratory investigations showed the following results: white blood cell count, 10,600/cumm; hemoglobin, 12.5 g/dL; platelet count, 380,000/cumm; other serum chemistry, urinalysis, and serologic evaluations of thyroid and renal functions yielded results that were all within the normal ranges. Mildly elevated levels of C-reactive protein level (3.99 mg/dL) and erythrocyte sedimentation rate of 94 mm in the 1$^{st}$ hour were noted. Complement 3 and 4 levels, antinuclear antibody titers, antineutrophil cytoplasmic antibody titers, and procalcitonin level were assessed to rule out other possible causes for the erythema nodosum (EN), and all values were entirely within normal limits. Results of her serologic test for rapid plasma reagin and treponema pallidum hemagglutination were negative. Her chest roentgenogram