Pilomatricomas secondary to treatment with vismodegib

Jorge Magdaleno-Tapial, MD, Cristian Valenzuela-Oñate, MD, José María Ortiz-Salvador, MD, Daniela Subiabre-Ferrer, MD, Macarena Giacaman-von der Weth, MD, Blanca Ferrer-Guillén, MD, José Luis Sánchez-Carazo, PhD, and Víctor Alegre-de Miquel, PhD
Valencia, Spain

Key words: basal cell carcinoma; pilomatricoma; vismodegib.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common type of skin cancer. Vismodegib has emerged as a new therapeutic option in metastatic or locally advanced BCC.[1] Vismodegib has several side effects including alopecia, mucosal involvement, and tumor formation. The tumorigenicity potential of vismodegib has been identified only in rats and is limited to benign hair follicle tumors, including pilomatricomas and keratoacanthomas. However, these tumors have not been reported in humans. We present the case of a vismodegib-treated patient who developed a pilomatricoma in a residual scar.

Abbreviations used:

BCC: basal cell carcinoma
Hh: Hedgehog

CASE REPORT

A 63-year-old woman presented with a 2-month-old pearly and telangiectatic lesion in the left infraorbital area characteristic of nodular BCC. Complete clinical examination found an ulcerated lesion in her right helix, which was partially hidden under her wig. Wig removal showed a giant ulcerated plaque, 21 cm in its greatest diameter, which occupied almost the entire right side of her scalp, from the occipital area to the outer canthus of her right eye (Fig 1). Destruction of the upper half of her right ear was present. Histopathology mapping with multiple punch biopsy was performed with samples from periphery and central areas of tumor (Fig 1, asterisk). All samples were consistent with nodular BCC involving reticular dermis. Vismodegib therapy was started. After 9 months of therapy, 80% clinical remission was observed. A 5-cm ulcer persisted. Histopathologic mapping was performed with 8 samples from the periphery and central areas. Only one sample showed persistent BCC (Fig 2, arrow). One peripheral biopsy done in the same area previously biopsied (Fig 2, asterisk) showed fibrotic scarring and 2 epithelial nodules. These nodules consisted of basaloid matrical cells showing abrupt transition to central eosinophilic, cornified matrical cells in which barely discernible nuclear outlines remained (shadow cells). Foci of calcification were also detected (Fig 3). These findings were compatible with the diagnosis of pilomatricoma. Stains for cytokeratin AE1/AE3 (Fig 4) and p63 were positive in epithelial component and supported our diagnosis. These areas of pilomatricoma were not associated with areas of BCC. Initial biopsies were reviewed, but no areas of pilomatricoma associated with BCC were observed.

DISCUSSION

Vismodegib is a novel small-molecule inhibitor of the Hedgehog (Hh) signalling pathway, which is currently approved for the treatment of metastatic or locally advanced BCC in humans. The aberrant activation of this pathway can result in inappropriate cell proliferation and has been related to the development of several types of cancers such as BCC.[2] In addition, it is also known that the Hh pathway interacts with multiple other pathways like Wnt/β-catenin.[3] The activation of β-catenin mutations has been reported to be often associated with the

From the Department of Dermatology, Hospital General Universitario de Valencia.
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Jorge Magdaleno-Tapial, MD, Department of Dermatology, Hospital General Universitario de Valencia, Av. Tres Creus, 2, 46014, Valencia, Spain. E-mail: jormagta@gmail.com.

JAAD Case Reports 2019;5:12-4.
2352-5126

https://doi.org/10.1016/j.jdcr.2018.09.016

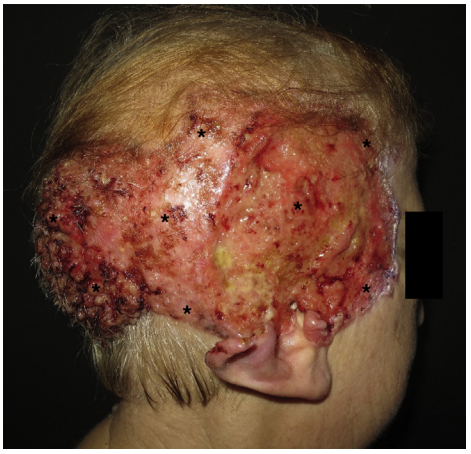

Fig 1. Ulcerated lesion in right hemisphere of her scalp. Asterisks mark the areas biopsied.

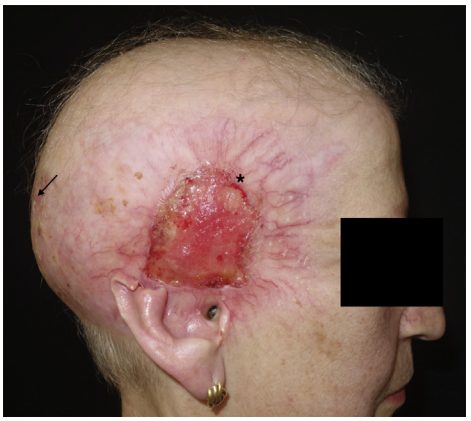

Fig 2. Decrease in the size of BCC 9 months after starting the treatment with vismodegib. The arrow marks the biopsied section in which areas of BCC were observed, and the asterisk marks the biopsied section in which areas of pilomatricoma were found.

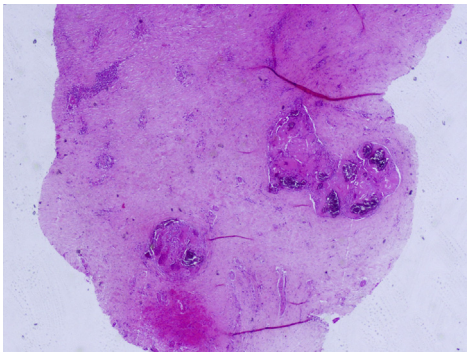

Fig 3. Fibrotic scarring and underlying pilomatricoma areas were observed in the biopsy. (Hematoxylin-eosin stain; original magnifications, ×10.)

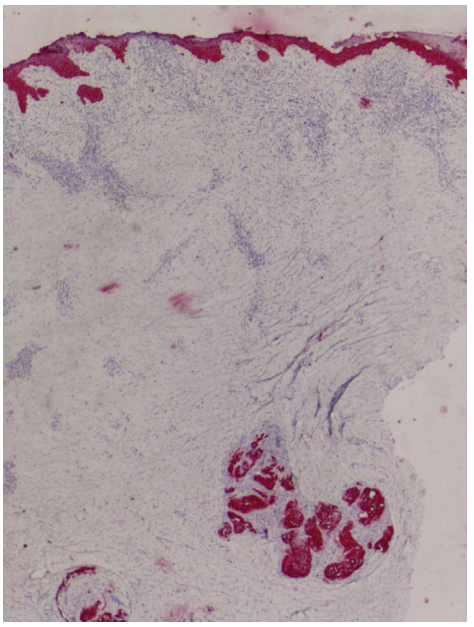

Fig 4. Epidermis and epithelial component of pilomatricoma were positive for AE1/AE3 cytokeratin staining. (Original magnifications, ×10.)

disruption of adequate Hh signalling, which could lead to abnormal hair matrix cell proliferation and to the formation of pilomatricoma in humans. The tumorigenicity potential of vismodegib had been identified so far in rats only and was limited to benign hair follicle tumors, including pilomatricomas and keratoacanthomas, at exposures equivalent to the recommended human dose.[4] However, these tumors had not yet been reported in vismodegib-treated patients. No vismodegib-related malignant tumor findings were identified in either species.

The pathogenic mechanism that causes the development of pilomatricomas is unclear. These tumors may originate from an altered growth of the hair follicles caused by the activation of β-catenin mutations caused by a disruption of the Hh signals.[5] It has been demonstrated that mutations in *CTNNB1*, the gene that encodes β-catenin, a component of a key signalling pathway that influences cell differentiation and proliferation, are generally present in matrical neoplasms, including pilomatricomas.[6]

We present the first case, to our knowledge, of pilomatricomas secondary to treatment with vismodegib in humans. We believe that reports of this type of lesion will be more frequent with time because of the increased use of vismodegib, both for locally advanced or metastatic BCC and for any other new indications. We do not know if the appearance of pilomatricomas has prognostic implications. Further studies are required to demonstrate whether the low carcinogenicity potential of vismodegib is only limited to hair follicle tumors.

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