

# Genomic tumor studies aid in diagnosing metastatic basal cell carcinoma: A case series



Kylee J. B. Kus, BS,<sup>a,b</sup> and Emily S. Ruiz, MD, MPH<sup>a</sup>  
*Boston, Massachusetts and Rochester, Michigan*

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## INTRODUCTION

Metastatic basal cell carcinomas (mBCC) are thought to be extremely rare, occurring in 0.003-0.05% of basal cell carcinomas (BCC).<sup>1</sup> However, new data suggests that tumors of 4 cm or greater, located on the head and neck, and extending beyond subcutaneous fat have a high rate of metastasis and death.<sup>2</sup> Given the rarity of the diagnosis, mBCC is often not considered in the differential diagnosis of poorly differentiated carcinomas resulting in misclassification of some cases. The features that distinguish BCC and cutaneous squamous cell carcinoma (CSCC) on pathology and immunohistochemistry are subtle. When available, Ber-EP4 should be diffusely positive in BCC and negative in CSCC; however, poorly differentiated CSCC may exhibit some positivity.<sup>3</sup> Additionally, the presence of mucin deposition is suggestive of BCC.<sup>4</sup> Genomic tumor analysis provides a method to aide in differentiating such tumors. We present 3 cases of patients with no history of Nevoid BCC Syndrome who initially had mBCC misdiagnosed as metastatic CSCC, where review of key features combined with genomics helped elucidate the diagnosis.

## CASE SERIES

### Case 1

A 57-year-old man with chronic lymphocytic leukemia presented with a 2.4-cm right parietal scalp infiltrative BCC. The tumor extended into the fascia, had extensive perineural invasion (diameter >0.025 mm), and could not be cleared with 3 Mohs micrographic surgery stages and wide local excision. Pathology from the wide local excision showed

### Abbreviations used:

BCC:	basal cell carcinoma
CSCC:	cutaneous squamous cell carcinoma
CT:	computed tomography
mBCC:	metastatic basal cell carcinoma

infiltrative BCC with high-grade features and focal clear cell morphology. The patient received salvage intensity-modulated radiation therapy to the right posterior scalp (21 fractions, 52.5 Gy).

One year later, the patient underwent computed tomography (CT) of the neck for a 2.9-cm poorly defined tumor in the sternocleidomastoid muscle that had been enlarging over 9 months. An excisional biopsy showed a poorly differentiated CSCC with basaloid features. Immunohistochemistry was positive for p16, p63, and pan-keratin. A positron emission tomography-CT revealed multiple foci of osseous disease. Biopsy of a 2-cm sternal bone lesion showed carcinoma with basaloid cytomorphology and matrix production. Given the basaloid features on both biopsies, the history of an aggressive BCC, and the pattern of metastasis, tumor genomic profiling was performed on the sternal bone specimen, which revealed a mutation in the *PTCH1* gene, confirming the diagnosis of metastatic BCC.

### Case 2

A 55-year-old man underwent wide local excision for a recurrent 2.3-cm infiltrative BCC of the left back which had been previously treated with 3 electrodesiccation and curettages. The tumor extended beyond 1.0 cm in depth, but the final margins were

From the Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston<sup>a</sup>; and the Oakland University William Beaumont School of Medicine, Rochester.<sup>b</sup>

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Correspondence to: Emily S. Ruiz, MD, MPH, Assistant Professor of Dermatology, Department of Dermatology, Brigham and Women's Hospital, 1153 Centre Street Suite 4J, Boston, MA 02130. E-mail: [esruiz@bwh.harvard.edu](mailto:esruiz@bwh.harvard.edu).

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negative. Nearly 5 years later, multiple lung nodules and a 1.8-cm left axillary lymph node were incidentally noted on CT. Histology from the axillary mass was suggestive of metastatic CSCC. Immunohistochemistry was negative for TTF-1, positive for P40, and focally positive for pan-keratin and PD 16. Since the patient had no history of CSCC, the axillary mass specimen underwent next-generation sequencing, which showed mutations in the *PTCH1* gene (loci Q816\* and F434fs\*1). Review of the histology and genetic profiling confirmed the diagnosis of metastatic BCC.

### Case 3

A 66-year-old with a history of numerous low-risk BCCs and CSCCs underwent Mohs micrographic surgery for a 9-mm ill-defined BCC on his left superior shoulder. The tumor required 4 stages to clear with a final defect size of 3.5 cm; it invaded the muscle and exhibited multifocal small-caliber perineural invasion.

Over 2 years later, the patient noted right axillary lymphadenopathy. An ultrasound-guided core-needle biopsy revealed a poorly differentiated epithelioid neoplasm consistent with metastatic CSCC. Immunohistochemistry was positive for p63, p40, Ber-EP4 (patchy), and pan-keratin, while negative for TTF-1. Positron emission tomography-CT showed metastatic disease in the right axilla, spine, and pelvis. Due to the pattern of metastasis and no history of a high-stage CSCC, tumor genomic profiling was performed on the axillary lymph node specimen, which revealed a dominant mutation in the *PTCH1* gene, confirming the diagnosis of metastatic BCC.

### DISCUSSION

The cases presented herein describe 3 patients with histories of aggressive BCCs who developed metastatic disease initially misclassified as metastatic CSCC. Since the diagnosis of metastatic BCC is thought to be rare, the diagnosis was overlooked until genomic sequencing revealed mutations in the *PTCH1* gene. Genomic profiling of metastatic tumors should be considered for patients with a history of aggressive BCC who have no history of high-stage CSCC to aid in diagnosis.

It is important to appropriately classify mBCCs as vismodegib is approved by the United States Food and Drug Administration as a first-line treatment for this diagnosis. BCC formation is due to constitutive activation of the patched/hedgehog intracellular signaling pathway, which is responsible for regulating cell growth. An inactivating mutation in the *PTCH1* gene (chromosome 9q) or an activating mutation of the *SMO* gene (chromosome 7q) results in aberrant

hedgehog pathway activation.<sup>5</sup> This mutation is present in approximately 73% of BCCs, but absent in CSCCs.<sup>6,7</sup> Vismodegib is a selective hedgehog pathway inhibitor that blocks signaling by binding to *SMO*. Thus, vismodegib is efficacious for mBCCs, but not CSCCs. More recently, cemiplimab was approved for advanced BCC previously treated with a hedgehog pathway inhibitor or for whom these therapies are not appropriate. Although cemiplimab is also approved for CSCC, it is important to differentiate mBCCs from metastatic CSCCs since they have a lower response to cemiplimab and the alternative option of treatment with a hedgehog inhibitor.<sup>8,9</sup>

There are several risk factors associated with an increased risk for metastasis and/or death in BCCs  $\geq 2$  cm in diameter. A 10-year retrospective study found that a tumor diameter  $\geq 4$  cm (OR, 11.9; 95% CI, 2.4-59.4), head/neck location (OR, 5.3; 95% CI, 1.2-23.2), and tumor depth of invasion beyond fat (OR, 28.6; 95% CI, 6.7-121) were significant predictors of metastasis/death.<sup>2</sup> The increased risk of metastasis in large tumors with additional risk factors should warrant additional investigation to ensure proper management.

Although genomic profiling cinched the diagnosis, the metastatic pattern guided diagnosis in these 3 cases. It is common for mBCC to spread to regional lymph nodes, lung, bone, or skin, in order of descending frequency.<sup>1,10</sup> Approximately 42% of mBCC cases metastasize to lung and 20% to bone. In contrast, approximately 70% of CSCC-related deaths are due to locoregional disease, while the remaining 30% are due to distant metastasis, typically the lung.<sup>10</sup>

Discovery of *PTCH1* mutations supported metastatic BCC diagnoses in place of previously diagnosed metastatic CSCCs in the presented cases. Patients who have a history of aggressive BCCs and lack a history of high-stage CSCC should raise suspicion of metastatic BCC and may benefit from genomic profiling. Procuring the appropriate diagnosis is of particular importance as treatment options for metastatic BCC differ from those of other metastatic cutaneous diagnoses.

### Conflicts of interest

None disclosed.

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