BRIEF ARTICLES

TP53 Mutated Metastatic Basal Cell Carcinoma Responsive to Sonidegib

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ABSTRACT

Basal cell carcinoma (BCC) is the most common nonmelanoma skin cancer (NMSC) with the potential of local invasion and distant metastasis. Our patient presented with an enlarging four-centimeter subcutaneous nodule over the right clavicle. An incisional biopsy demonstrated the unexpected findings of a nodular and infiltrative BCC. Definitive treatment was a radical neck dissection with adjuvant radiation therapy. Negative margins were confirmed on the excision and lymph node evaluation demonstrated no lymphatic spread. Surveillance chest computed tomography revealed new bilateral pulmonary nodules and a subsequent biopsy showed metastatic BCC. A genetic panel demonstrated TP53 mutations and no mutations in SMO. The patient was started on sonidegib and after ten months of therapy his disease was stabilized on repeat imaging. This case report demonstrates a rare presentation of a TP53 mutated, metastatic BCC responsive to sonidegib.

INTRODUCTION

Recent estimates report approximately 5.4 million cases of nonmelanoma skin cancer (NMSC) per year.[1] Basal cell carcinoma (BCC) is the most common NMSC, and the most common skin cancer overall. BCC is commonly linked directly to excessive sun exposure and considered to constitute 80% of NMSCs.[2] It has several histopathological presentations including nodular, superficial, infiltrative, and mixed subtypes.[2] With respect to advanced cases, BCC tends to involve aggressive local invasion rather than distant site metastasis. Distant metastasis, however, can occur, and has a reported prevalence of less than 0.55% of all BCC cases.[2] Tumor genetics play a significant role in the prognosis and subsequent treatment of metastatic BCC. We present the case of a 60-year-old male with *TP53* mutated metastatic BCC responsive to sonidegib.

CASE PRESENTATION

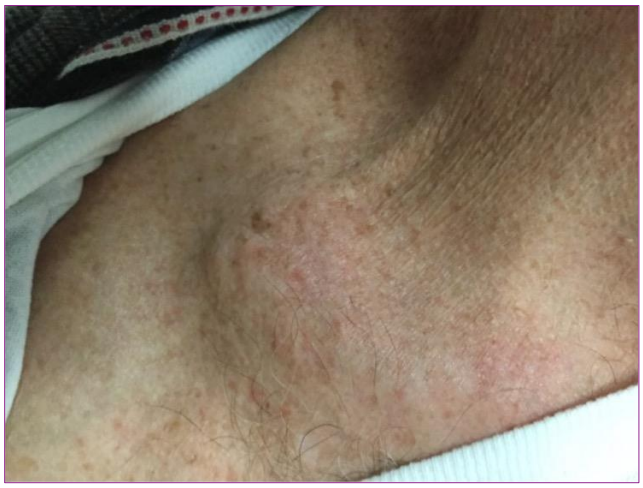
A 60-year-old male with history of a left shoulder superficial BCC (status post electrodessication and curettage [ED&C] 10 years prior) presented with a four-centimeter subcutaneous nodule over the right clavicle (Fig. 1). He was referred to dermatology after a previous biopsy of the lesion showed evidence of a cystic basal cell carcinoma. Of note, a chest computed tomography (CT) scan prior to initial biopsy showed pulmonary nodules of minimal significance. No other concerning lesions were identified on full skin exam and his previous ED&C site had no evidence of recurrence. The

patient was referred to a dermatologic surgeon for incisional biopsy which demonstrated basaloid cells with peripheral palisade, focal clefting, mucin deposition, large caliber perineural invasion, and extension to peripheral and deep tissue edges (Figure 2a and 2b). The findings were consistent with BCC, nodular and infiltrative types. Immunohistochemistry demonstrated weak BerEP4 expression (Figure 3) and negative CK20 and TTF1. He was referred to an otolaryngologic surgeon for mass excision, neck dissection, and adjuvant radiation therapy. Negative margins were confirmed on mass excision, and all 63 lymph nodes were negative for malignancy. Surveillance chest CT revealed significant growth in previously described bilateral pulmonary nodules. Biopsy of the right lung nodule revealed a non-small cell carcinoma with histopathological findings favorable of metastatic BCC. He was referred to medical oncology and started on sonidegib 200 mg daily with reduction to 6 days a week. Subsequent genetic analysis revealed no mutation in *SMO*, however, biallelic *TP53* mutations were present. Eight months after initiating sonidegib therapy, the patient complained of worsening muscle cramps which improved after decreasing sonidegib dosing to three times a week. Ten months after starting therapy, chest CT scan ensured no further growth or increase in the number of lung nodules.

DISCUSSION

In the described case, there was no evidence of a primary BCC despite several skin exams. Due to his history of BCC on the left shoulder, metastasis from this lesion seems possible. However, with no evidence of recurrence at the ED&C site, metastasis from this area is uncertain. As present in this case, a common site of metastasis for BCC is the lungs.[3]

Figure 1. Metastatic BCC presenting as a subcutaneous nodule.

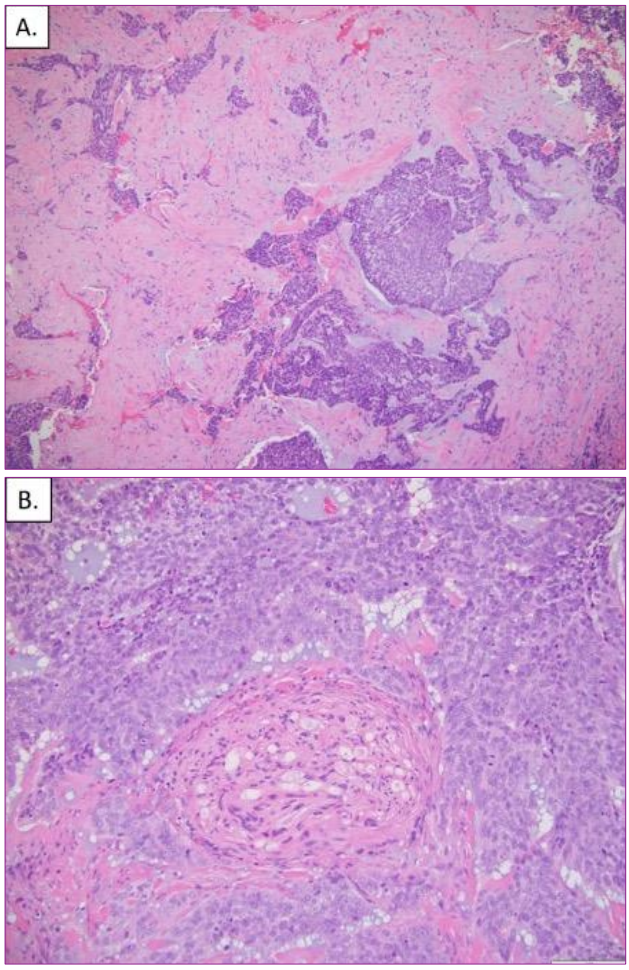


Advanced BCC can be described as either “locally advanced” (laBCC) or “metastatic” (mBCC).[4] LaBCCs extend beyond the skin into the local tissue but do not extend far from the primary lesion. Metastatic BCC is differentiated by noncontiguous spread to organs or structures distant from the primary lesion.[4] The following factors have been associated with increased mortality and metastasis of BCC: tumors > 2cm, tumor depth beyond fat, perineural invasion, infiltrative type on histology, and location on the head and neck.[5]

With recent advances in the molecular understanding of mBCC, more information is available to determine likelihood of metastasis and response to treatment. Currently, mutations in the *PTCH1* (produces patched) or *SMO* (produces smoothened) genes of the hedgehog signaling pathway (HH) are known to lead to carcinogenesis.[6] Patched constantly inhibits smoothened preventing further transcription and translation of pathway end products. Inactivating mutations of *PTCH1*, or activating mutations of *SMO*, create an unchecked formation of downstream products leading to BCC formation.[6] The patient described above was negative for a

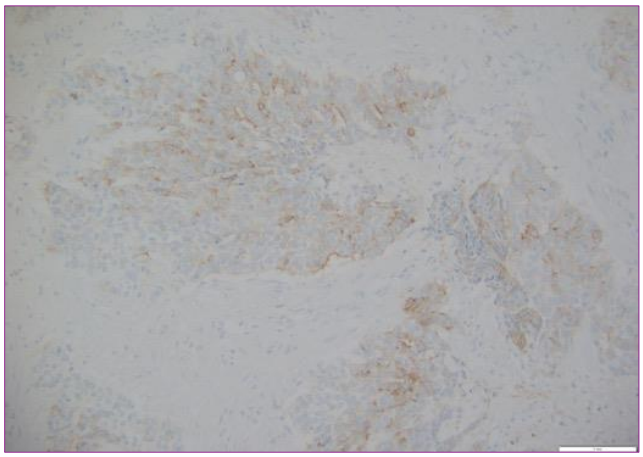
SMO mutation, but positive for biallelic *TP53* mutations. *PTCH1* testing was not performed.

Figure 2: (A) Hematoxylin and eosin stain showing nodular and infiltrative BCC (H&E, 20x) with (B) perineural invasion (H&E, 40x).



The tumor suppressor gene *TP53* can play a significant role in BCC formation. *TP53* is considered the "guardian of the genome" and is the second most frequently mutated gene in BCCs.[6] Interestingly, Pelligreni et al. demonstrated loss of *TP53* in murine models led to significant upregulation in the HH pathway, specifically in *SMO* products (i.e. smoothened). Consequently, the above patient's successful response to sonidegib (a smoothened inhibitor) might be attributed to this pathway. Unfortunately, testing for *PTCH1* was not performed for this patient.

Figure 3: Immunohistochemical stains demonstrating weak expression of BerEP4 (BerEP4 stain, 40x)



Despite the efficacy of smoothened inhibitors, there are relevant adverse effects which commonly lead to treatment discontinuation. Common side effects include muscle spasms, weight loss, dysgeusia, alopecia, and fatigue.[7] Mitigating these side effects while maximizing treatment potential is challenging. A recent study demonstrated reducing treatment frequency can lessen adverse effects and increase compliance.[7] They demonstrated a 5-day dosing regimen with a weekend holiday can improve adverse effects and maintain successful treatment.[7] Similar findings were seen in our patient after adjusting treatment from 6 days a week to 3 days a week.

In review, we present a case of a 60-year-old male with node-negative, metastatic BCC to the lungs. On genetic analysis, his tumor was positive for a *TP53* mutation and negative for *SMO* mutations. He has shown continued improvement on oral sonidegib three days a week.

Limitations

No epidemiological quantities can be generated from a single case report. Additionally, the findings from a case report cannot be generalized and pose a risk for misinterpretation. This case is also hindered by a lack of testing for *PTCH1* gene mutations which could also explain the efficacy of sonidegib in this patient.

Abbreviation List
BCC - Basal Cell Carcinoma
NMSC - Non-Melanoma Skin Cancer
LaBCC - Locally advanced Basal Cell Carcinoma
mBCC - Metastatic Basal Cell Carcinoma
NSCC - Non-Small Cell Carcinoma
HH - Hedgehog Signaling Pathway
PTCH1 - Patched 1
SMO - Smoothen
ED&C - Electrodessication and Curettage

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