Invasive Basal Cell Carcinoma of the Skin Treated Successfully with Vismodegib: A Case Report

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ABSTRACT

Introduction: Basal cell carcinoma (BCC) is the most common skin cancer. It is primarily a local disease, and it very rarely causes metastatic disease. Chemotherapeutic agents had limited success in management of metastatic disease until the introduction of vismodegib. In this case report, we describe the presentation of a metastatic BCC that was not amenable to surgical resection or local treatment options and was treated successfully with vismodegib.

Case Presentation: A 69-year-old white man was referred to our surgical clinic for evaluation of an erosive left shoulder lesion. Biopsy in the clinic showed BCC with evidence of metastases on positron emission tomography-computed tomography scan. Tumors had invaded multiple bony structures and multiple organs, making surgical resection not an option. The decision was made to treat the patient with vismodegib. At 1-year follow-up, the patient's left shoulder lesion had improved with no evidence of metabolically active distant metastasis.

Discussion: Although BCC is the most common skin cancer, it is usually a local disease and treated with local measures. Metastatic BCC is extremely rare, and in cases when surgical resection or local radiation are not viable options, chemotherapeutic agents typically offer very limited improvement. Vismodegib is an oral selective sonic hedgehog pathway inhibitor that shows benefit in patients with locally advanced or metastatic disease.

INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer though usually not a lethal or metastatic disease. BCC can be associated with significant morbidity secondary to local invasion and destruction.[1] Incidence of BCC is 226 per 100,000, and age-adjusted prevalence is up to 343 per 100,000 people.[2] Ultraviolet light exposure is the main risk factor for developing BCC. Other risk factors include psoralen and ultraviolet A therapy, radiation therapy, immunosuppressive medications, and chronic arsenic toxicity.[1]

On the basis of histopathologic features, BCC is classified into two major categories: Indolent growth subtypes and aggressive growth subtypes.[1] The indolent growth subtypes include nodular and superficial subtypes. Aggressive growth subtypes include morpheaform, micronodular, infiltrative, and basosquamous subtypes. Befitting the name, aggressive growth subtypes are associated with higher rates of recurrence, more aggressive local invasion, and greater possibility of distant metastasis.[1] Various histologic subtypes can be present in a single lesion. Both patient and tumor characteristics, such as location and size of the tumor, aggressive pathologic subtypes, recurrent lesions, lesions appearing in areas of previous radiation therapy or with poorly defined borders, or BCC in immunocompromised patients, determine the risk of recurrence.[3]

Biopsy is needed for accurate diagnosis, especially in cases with pigmented BCC because it can be confused with melanoma. Surgical excision and local destructive measures are the pillars of treatment of nonmetastatic and nonlocally advanced BCC. Surgery is either by local excision or Mohs micrographically controlled surgery, which is the preferred surgical treatment for high-risk cases.[1] Local treatment modalities for superficial tumors include topical imiquimod, 5-fluorouracil, and photodynamic therapy. Imiquimod was noted to have the best results in a comparative study of patients with superficial BCC.[4] Local radiotherapy is another therapeutic modality used when a patient is a poor surgical candidate or when surgery would be disfiguring.[4]

Until approval of targeted systemic therapy, there was no effective systemic therapy for metastatic or locally advanced disease, with most therapies depending on platinum-based chemotherapy.[3,4]

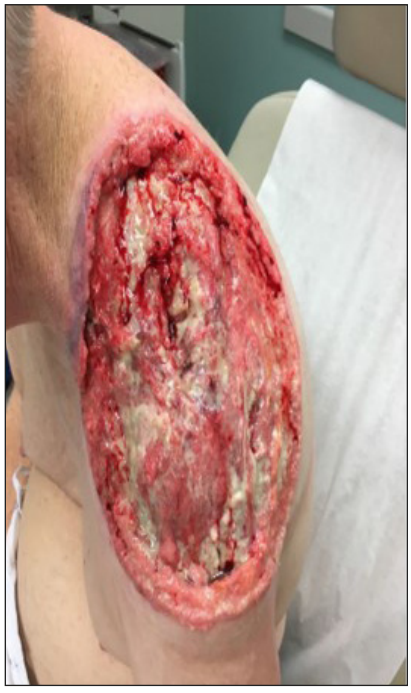

Figure 1. Left shoulder lesion at presentation showing exposed muscle, indurated borders, and surrounding edema.

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CASE PRESENTATION

Presenting Concerns

A 69-year-old white man was referred to our surgical oncology clinic in April 2016 for evaluation of an erosive lesion of the left shoulder. The patient reported that the lesion appeared as an ulcerative lesion 9 years earlier and had been progressive since then. On physical examination the patient had a large ulcerative lesion of the left shoulder that was actively exuding blood on exposure, with visible muscle underneath and retraction of the left platysma and indurated borders (Figure 1). The lesion was surrounded by edema and loss of sensation on the surrounding skin, and the patient experienced impaired motility around his left shoulder and elbow joints.

Four biopsies were performed at the surgical oncology clinic, and the patient was referred to medical oncology. Pathology was consistent with BCC nodular and infiltrative types with positive margins (Figure 2). A positron-emission tomography-computed tomography (PET-CT) scan performed in April 2016 (Figure 3) showed evidence of locally invasive disease with invasion of the left clavicle, glenoid, and humeral head, as well as distant metastases to skin, left axillary lymph nodes, bilateral pulmonary nodules, and the skin of mid-lower back and bilateral lower extremities. Because of multiple organ involvement and involvement of multiple bone and joint structures, surgical excision would have resulted in severe morbidities and disfigurement. The decision was made to treat the patient with vismodegib.

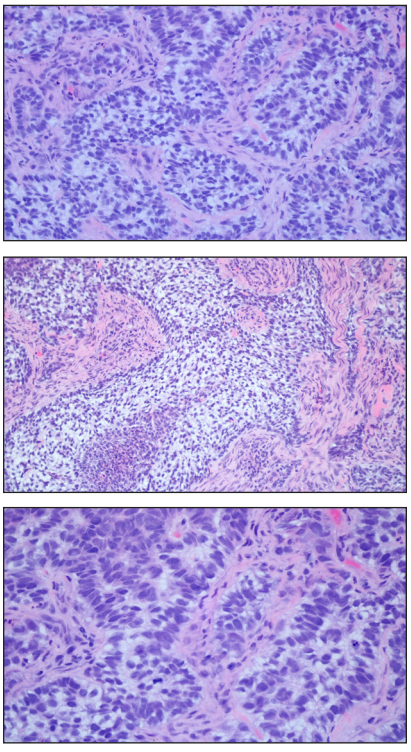

Figure 2. Pathology photos from biopsy performed at presentation, showing nodular and infiltrative types with positive margins (top = x200 magnification; middle = x40 magnification; bottom = x400 magnification).

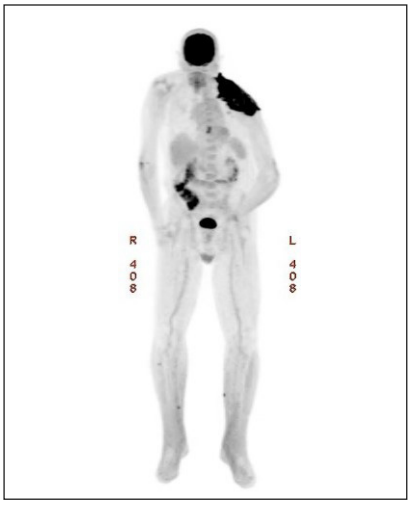

Figure 3. Initial positron-emission tomography-computed tomography image taken April 2016 showing the metabolically active left shoulder lesion, left axillary and chest wall lymph nodes, bilateral pulmonary nodules, and bilateral lower extremity skin lesions.

Therapeutic Interventions and Treatment

The patient was approved for treatment with vismodegib. Treatment was started in April 2016, with a dose of 150 mg daily and continued until July 2017. Clinical follow-up and PET-CT scan in July 2016 (Figures 4 and 5), showed improvement in skin and bone lesions of the left shoulder, improvement in the size of the axillary lymphadenopathy, near complete resolution of distant skin lesions, and stable pulmonary nodules. The patient continued to receive vismodegib.

On a follow-up visit in January 2017, the patient continued to have improvement of the original skin lesion, but a new fungating nodule was noted inferior to it (Figure 6). A PET-CT scan showed a stable left shoulder lesion but showed interval development of nodular excrescence with intense hyper metabolism in the inferior aspect of the area and stable pulmonary nodules (Figure 7). Biopsy was not repeated because the patient was still on treatment; however, the patient was

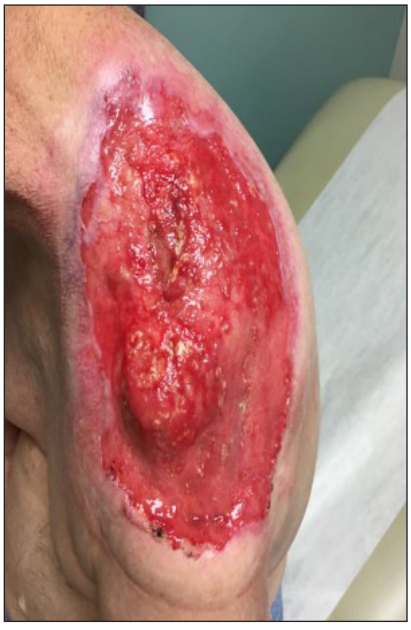

Figure 4. Left shoulder lesion in July 2016, after initiation of treatment.

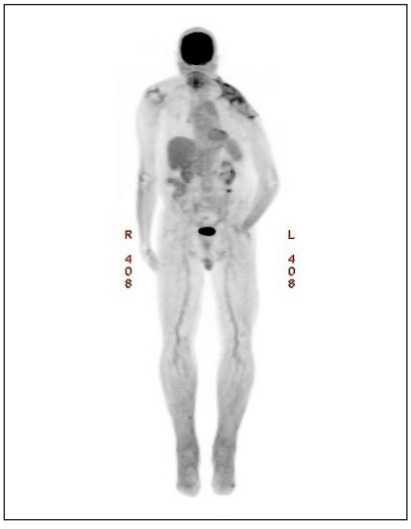

Figure 5. Follow-up positron-emission tomography-computed tomography image taken July 2016 showing improvement in skin and bone lesions of the left shoulder, improvement in the size and metabolic activity of the left axillary lymph nodes, near complete resolution of distant skin lesions in both lower legs, and stable pulmonary nodules.

referred to radiation oncology for evaluation for local radiation therapy of the new lesion. The patient was treated with radiation therapy from January 26 to February 6, 2017, with a total dose of 800 cGy.

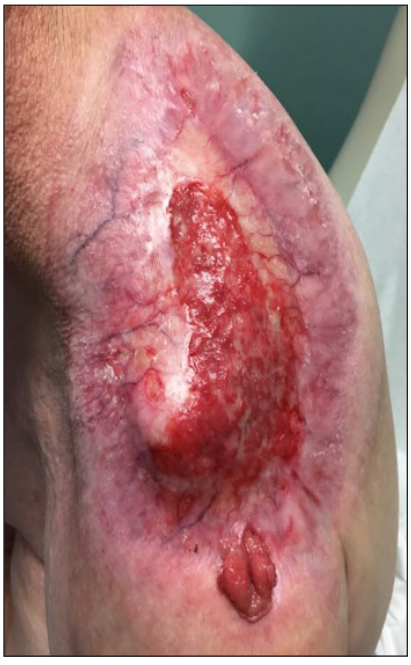

Figure 6. Left shoulder lesion at follow-up in January 2017, showing partial healing of the original skin lesion and a newly developed ulcerative lesion at the inferior border of the original lesion.

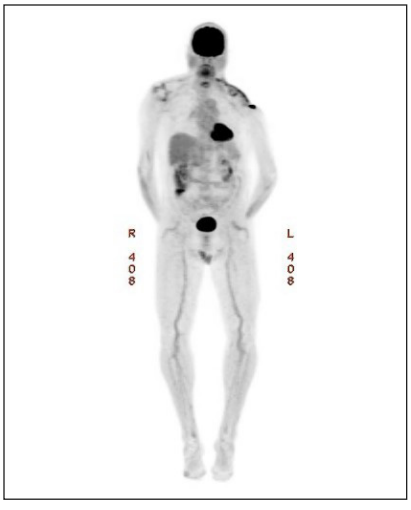

Figure 7. Positron-emission tomography-computed tomography image taken January 2017, showing a stable left shoulder lesion and stable distant metastatic lesions with development of nodular excrescence with intense hypermetabolic signal at the inferior border of the original lesion.

Follow-up and Outcomes

On a subsequent follow-up visit in July 2017, the patient was noted to have near complete resolution of the new nodule and continued improvement of the original skin lesions with no lesions reported and no significant side effects other than sense of taste changes. A follow-up PET-CT scan on July 2017 showed near resolution of the new nodule, stable-to-improved soft tissue at the left shoulder lesion, and no evidence of metabolically active distant metastasis (Figure 8). Clinical evaluation showed near-complete healing of the left shoulder lesion (Figure 9). Table 1 presents a timeline of the case.

DISCUSSION

Metastatic disease in BCC is extremely rare; the incidence ranges from 0.003% to 0.01% of all BCC.[1] Systemic treatment is required in cases of distant metastases or locally advanced disease in which neither surgical nor topical treatments are possible, but the various chemotherapeutic agents previously used have shown only limited success.[4]

Understanding of the sonic hedgehog (SHH) pathway allowed development of vismodegib, a first-of-its-class drug approved by the US Food and Drug Administration in 2012 for management of metastatic and locally advanced BCC. SHH pathway signaling plays a role in differentiation, patterning, and growth during embryogenesis.[1,5] Inactivating mutations affecting the *PTCH* gene, which encodes a receptor for the SHH pathway, were found in 90% of sporadic cases of BCC,[4] which leads to loss of inhibition of the Smoothened protein receptor and overexpression of glioma-associated oncogene transcription factors.[1,5]

Vismodegib is an oral selective SHH pathway inhibitor that showed clinical benefit in patients with locally advanced or metastatic BCC. In the study that led to vismodegib's approval, 43% of study patients with locally advanced disease and 30% of patients with metastatic disease showed objective clinical response, by independent review, during a period of 30 months' follow-up[5] and with a median progression-free survival of 9.5 months.[6] Interim analysis of data from a multicenter

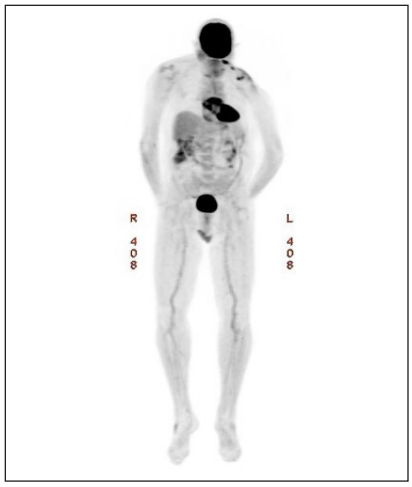

Figure 8. Positron-emission tomography-computed tomography image taken July 2017, showing near resolution of the described new hypermetabolic lesion of the left shoulder area and improved hypermetabolic signal of the original lesion.

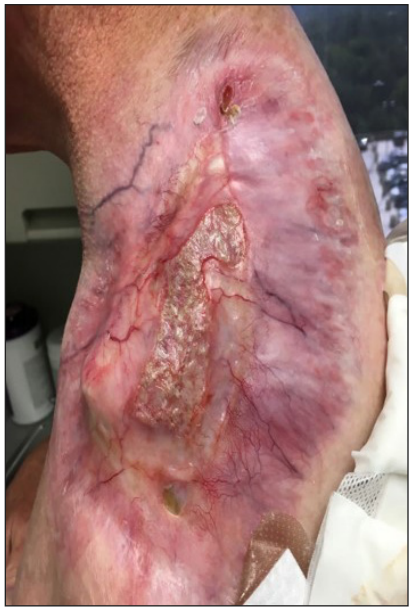

Figure 9. Near-complete healing of the left shoulder lesion at follow-up in July 2017.

open-label trial of 500 patients with the primary end point of safety showed that the most common adverse events associated with vismodegib use are muscle spasms, alopecia, weight loss, dysgeusia, diarrhea, nausea, fatigue, and decreased appetite. Muscle spasms (9%), dysgeusia (6%), weight loss (5%), and asthenia (4%) were the most common adverse events leading to discontinuation of the drug.[5] The long-term safety and final investigator-assessed

Table 1. Timeline of the case

Date	Presentation, treatment, and outcomes
4/4/2016	Patient presented to Surgical Oncology complaining of an erosive skin lesion on the left shoulder; four biopsies were taken in the office
4/8/2016	Pathology report confirmed diagnosis of invasive basal cell carcinoma
4/11/2016	Patient was evaluated by Medical Oncology, and PET-CT was performed that showed locally invasive and metastatic disease
4/15/2016	Patient approved for vismodegib and therapy was started
7/16/2016	Follow-up PET-CT was done and showed improvement in size of left shoulder lesion, left axillary lymph nodes, and distant skin lesions
1/17/2017	At follow-up, patient was noted to have a growing nodule at the inferior aspect of the left shoulder lesion; PET-CT showed interval development of hyperintense nodular excrescence at the inferior aspect of the left shoulder skin lesion
1/20/2017	Patient referred for radiation oncology; patient started on local radiation to the new lesion between 1/26/2017 and 2/6/2017
7/28/2017	Follow-up visit showed near-complete resolution of the new lesion, which was confirmed with follow-up PET-CT

PET-CT = positron-emission tomography-computed tomography.

efficacy results revealed overall response rates of 48.5% for metastatic BCC and 60.3% for locally advanced BCC. Median duration of response was 14.8 months and overall survival was 33.4 months in metastatic BCC compared with 26.2 months and an unestimable overall survival in locally advanced BCC. Safety results showed higher incidences of treatment-related adverse events in patients receiving vismodegib for more than 12 months; however, safety results showed no difference in incidence of grade 3 toxicities (mainly decreased weight, muscle spasms, diarrhea, fatigue, and arthralgia) between the 2 groups and showed that some patients required breaks from the medication to avoid discontinuation secondary to adverse events.[7] Some of the studies on treatment of metastatic and locally advanced BCC are summarized in Table 2.[8-10]

In conclusion, metastatic BCC is an extremely rare and difficult-to-treat disease that had no good treatment options until SHH pathway inhibitors vismodegib and sonidegib were approved. These drugs offer hope to patients with metastatic or locally advanced BCC when surgery is not an option. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Author Contributions

Ramez Awad, MD, had full access to all data and takes full responsibility for the integrity of the data and the accuracy of data analysis. All authors were involved in the development of the manuscript. Fade Mahmoud, MD, and Juan Camilo Barreto Andrade, MD, were involved in the care of the patient.

How to Cite this Article

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Table 2. Studies on treatment of metastatic and locally advanced basal cell carcinoma (BCC)

Author, year	Patients enrolled	Treatment	Dose	Duration of study	Response rate
Basset-Séguin et al,[8] 2017	N = 1215; 1119 locally advanced, 96 metastatic BCC	Vismodegib	Oral vismodegib 150 mg/d	Median treatment duration was 8.6 mo (range, 0-44 mo)	68.5% in patients with locally advanced BCC; 36.9% in patients with metastatic BCC
Chen et al,[9] 2017	N = 230; 194 locally advanced, 36 metastatic BCC	Sonidegib	79 patients were randomized to receive oral sonidegib 200 mg; 151 patients were randomized to receive oral sonidegib 800 mg	30-mo follow-up	36% in the 200 mg treatment group; 34% in the 800 mg treatment group
Rizzo et al,[10] 2017	N = 4; all metastatic BCC	Vismodegib; photodynamic therapy	Oral vismodegib 150 mg/d; photodynamic therapy 1-3 sessions	4 wks	100% response