Approach to Management of Giant Basal Cell Carcinomas

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PRACTICE **POINTS**

- Unusually large basal cell carcinomas (BCCs) present a therapeutic challenge.
- A number of therapeutic options exist. Wide excision with margin control and complex reconstruction remains an excellent treatment option for BCC.

Basal cell carcinoma (BCC) is a common nonmelanoma skin cancer with increasing incidence in the United States and worldwide. It is strongly linked to UV radiation exposure and typically is slow growing. Malignancy in BCCs is due to local growth and invasion rather than metastasis, and the prognosis is generally favorable. We report the case of a 60-year-old man with a large, locally destructive giant BCC on the right side of the upper back that was successfully treated via complete surgical excision (SE) and did not recur in the subsequent 36 months. We review the indications, evidence, advantages, and disadvantages associated with multiple surgical and nonsurgical treatment modalities available for the management of giant BCCs.

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Nonmelanoma skin cancer is the most common malignancy in the United States, with basal cell carcinoma (BCC) being the major histological subtype and accounting for approximately 80% of all skin cancers.[1-3] The age-adjusted incidence of BCC in the United States between 2004 and 2006 was estimated at 1019 cases per 100,000 in women and 1488 cases per 100,000 in men, and an estimated 2.8 million new cases are diagnosed in the United States each year.[3,4] Rates have been shown to increase with advancing age and are higher in males than females at all ages.[3] Exposure to solar UVB radiation generally is considered to be the greatest risk factor for development of BCC.[3,5,6] Severe or frequent sunburn and recreational exposure to sun in childhood (from birth to 19 years of age), particularly in individuals who tend to burn rather than tan, have been shown to substantially increase the risk for developing BCC as an adult.[7] Additional risk factors include light skin color, red or blonde hair color, presence of a large number of moles on the extremities, and a family history of melanoma or painful/blistering sunburn reactions.[3,7] Exposure to certain toxins, immunosuppression, and several genetic cancer syndromes also have been linked to BCC.[5]

Eighty percent of BCC cases involve the head and neck, with the trunk, arms, and legs being the next most common sites.[5] Basal cell carcinoma can be classified by histologic subtype including nodular, superficial, nodulocystic, morpheic, metatypical, pigmented, and ulcerative, as well as other rarer forms.[8] Elder[9] recommended that it may be most clinically practical

to divide BCC into subtypes that are known to have low (eg, nodular, nodulocystic) or relatively high risk for local recurrence (eg, infiltrating, morpheic, and metatypical).[9,10] The most common histologic subtype is nodular BCC, with an incidence of 40% to 60%, which typically presents as a red to white pearly nodule or papule with a rolled border; overlying telangiectasia; and occasionally crusting, ulceration, or a cyst.[5,11,12]

Basal cell carcinoma generally is a slow-growing and highly curable form of skin cancer.[5,13,14] Compared to either squamous cell carcinoma or melanoma, BCC is generally easier to treat and carries a more favorable prognosis with a lower incidence of recurrence and metastasis.[15] Malignancy in BCC is due to local growth and destruction of the primary tumor rather than metastasis, which is quite rare (estimated to occur in 0.0028% to 0.55% of cases) but carries a poor prognosis.[5,11,16] Basal cell carcinoma grows continuously along the path of least resistance, showing an affinity for the dermis, fascial planes, nerve sheaths, blood vessels, and lymphatic vessels. It is through these pathways that certain locally aggressive tumors can achieve great depths and distant spread. Tumors also are known to spread along embryonic fascial planes, which allows cells to extend in a direction perpendicular to the skin surface and achieve greater depths.[13] Metastasis has been found to occur more frequently in white men, arising from large tumors larger than 7.5 cm on the head and neck with spread to local lymph nodes. The median survival rate in this group, even in patients receiving adjuvant chemotherapy or radiation, is 10 months but is lower in patients with larger tumors and those who neglect to seek medical care.[16] Although mortality is low, its high and increasing prevalence makes BCC an important and costly health problem in the United States.[2,17]

Case Report

A 60-year-old white man with a history of diabetes mellitus presented to the dermatology clinic with concerns about a nonhealing sore on the right upper back that had been present for more than 10 years and had gradually increased in size. The patient reported he did not have health insurance and thus did not seek medical care. Despite the size and location of the lesion, he was able to maintain an active lifestyle and worked as a janitor without difficulty until shortly before presentation when the lesion began to ooze and bleed, requiring him to change the dressing multiple times each day. The patient had no systemic symptoms and described himself as an otherwise healthy man.

On evaluation, the patient was noted to have a 20×15-cm ulcerated tumor on the right side of the upper back and shoulder with no satellite lesions (Figure 1). There were no palpable lymph nodes or satellite lesions and the rest of the physical examination was unremarkable. An 8-mm shave biopsy was collected on the day of presentation and sent for pathology to evaluate for suspected malignancy. On histology, BCC was present with islands of tumor cells extending from the epidermis into the dermis (Figure 2). These nests of cells displayed classic peripheral palisading of hyperchromatic, ovoid-shaped, basaloid nuclei at the periphery. Clefting around islands of tumor cells in the dermis also was apparent. Several foci suggested squamous differentiation, but the bulk of the lesion suggested a conventional nodular BCC.

The patient was referred to a surgical oncologist who recommended a wide surgical excision (SE) and delayed split-thickness skin graft (STSG) due to the size and location of the lesion. Eighteen days after receiving the diagnosis of BCC, the patient was taken to the operating room and underwent wide en bloc resection of the soft tissue tumor. Upon lifting the specimen off the underlying muscles, it was found to be penetrating into portions of the trapezius, deltoid, paraspinal, supraspinalis, and infraspinatus muscles. As such, the ulcerated tumor was removed as well as portions of the underlying musculature measuring 21×18 cm. The wound was left open until final pathology on margin clearance was available. It was covered with a wound vac to encourage granulation in anticipation of a planned delayed STSG. There were no complications, and the patient returned to the recovery unit in good condition where the dressing was replaced with a large wound vac system.

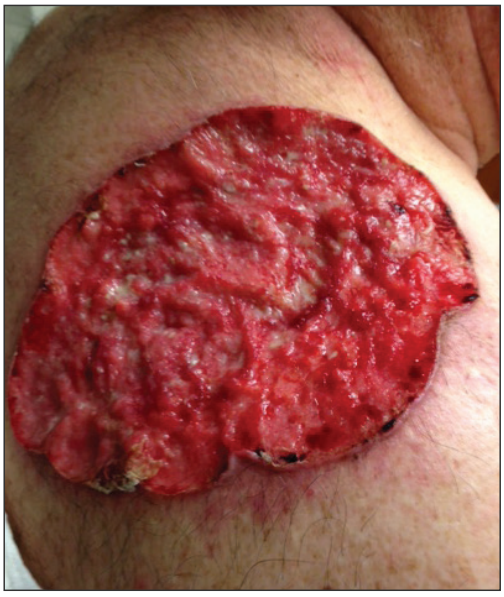

Figure 1. Ulcerated, 20×15-cm giant basal cell carcinoma on the right side of the upper back and shoulder.

Final histologic examination showed negative deep and peripheral margins. More extensive examination of histology of the excised tumor was found to have characteristics consistent with metatypical and morpheic-type BCC. In addition to islands of tumor cells noted in the dermis on original biopsy, this sample also revealed basaloid cells arranged in thin elongated trabeculae invading deeper into the reticular dermis without peripheral palisading, suggestive of the morpheic variant (Figure 3A).[8,9,10] Other areas were found to have focal squamous differentiation with keratin pearls and intercellular bridges (Figure 3B). These findings support the diagnosis of a completely excised BCC of the metatypical (referred to by some authorities as basosquamous)[8,9] type.

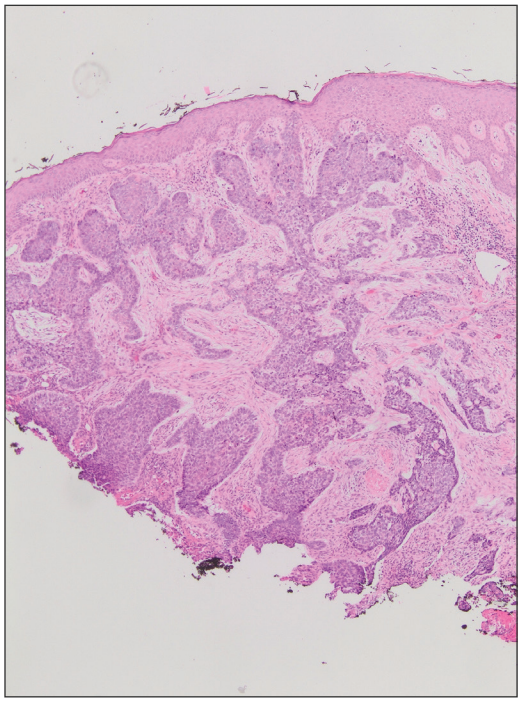

Figure 2. Initial biopsy showing classic basal cell carcinoma with a nest of tumor cells with peripheral palisading of hyperchromatic basaloid cells within the dermis and at deep margins (H&E, original magnification ×4).

The patient was seen for postoperative evaluations at 2 and 3 weeks. Each time granulation was noted to be proceeding well without signs of infection, and the wound vac was left in place. One month after the initial SE, the patient returned for the planned STSG. The skin graft was harvested from the right lateral thigh and was meshed and transferred to the recipient site on the right upper back, sewn circumferentially to the wound edges. Occlusive petrolatum gauze was placed over the graft followed by the wound vac for coverage until the graft matured.

The patient returned for follow-up approximately 7 months after his initial visit to the clinic. He reported feeling well, and his only concern was mild soreness of the scapular muscles while playing golf. The site of tumor excision showed 100% take of the STSG with no nodules in or around the site to suggest recurrence (Figure 4). The patient denied experiencing any constitutional symptoms and had no palpable lymph nodes or physical examination findings suggestive of metastatic disease or new tumor development at other sites. At 36 months after his initial clinic visit, he remained free of recurrence.

Comment

Typical BCC lesions are indolent and small, occurring primarily on the head and neck.[5,11,12,17] We report the case of a locally advanced, extremely large and penetrating lesion located on the trunk. This

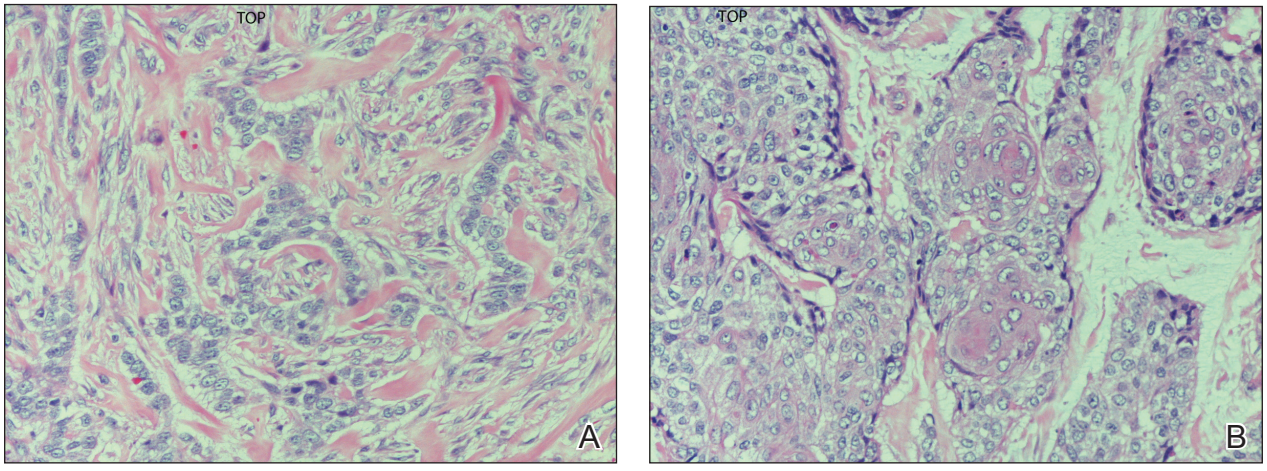

Figure 3. Excisional biopsy of a giant basal cell carcinoma demonstrating invasion of the reticular dermis by trabeculae of basaloid cells, with the absence of islands and peripheral palisading (A) and a focal area of squamous differentiation. Note the formation of keratin pearls in the center (B)(both H&E, original magnification ×20).

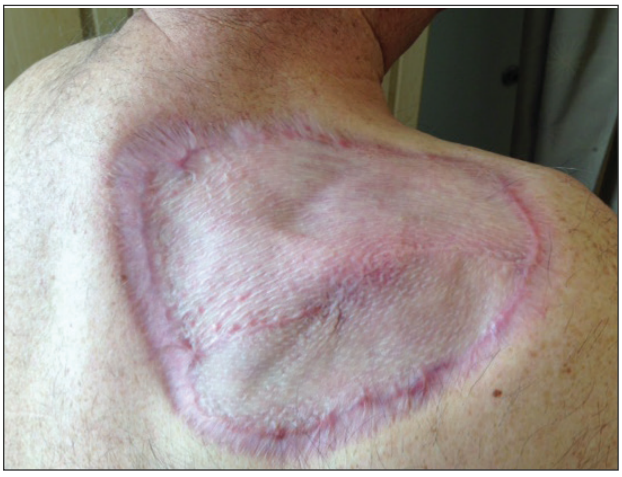

Figure 4. Site of giant basal cell carcinoma 7 months after surgical excision showing 100% take of a split-thickness skin graft.

relatively unique case provides for an interesting comparison between available treatments for BCC as well as several of the generally accepted principles of management previously described in the literature.

Treatment Considerations—The approach to management of BCC considers factors related to the tumor and those related to the patient and practitioner. Telfer et al[6] recommended that tumors be categorized as relatively low or high risk based on prognostic factors including size, site, histologic subtype and growth pattern; definition of margins; and presence or absence of prior treatment. Characteristics of high-risk tumors include size greater than 2.5 to 3 cm in diameter; location on the midface, nose, or ears; aggressive histologic subtype including morpheic, infiltrating, and metatypical; deep extension; perineural invasion; neglected or long-standing lesions; incomplete SE or Mohs micrographic surgery (MMS); and recurrence of tumor after prior treatment.[13,14,18] Although rare, tumors of the metatypical subtype are particularly important to identify, as they are known to be more aggressive and prone to spread than other forms of BCC.[19,20] The clinical appearance of metatypical BCCs often is identical to lower-risk subtypes, reinforcing the importance of careful histologic examination of an adequately deep biopsy, given that metatypical features often are present only in the deep tissue planes.[19]

The practitioner also must consider patient-related factors such as age, general health, immunocompromised states, coexisting medical conditions, and current medications. The skills, experience, and recommendations of the physician also are expected to influence treatment selection.[6,21]

Surgical Versus Nonsurgical Treatment Approaches—Treatment of large, locally advanced, primary BCCs can be divided into surgical and nonsurgical approaches.[5,6] Surgical approaches include MMS and SE. Mohs micrographic surgery, electrodesiccation and curettage, and cryosurgery may achieve high cure rates in lesions that are low risk but generally are not recommended for use with recurrent or high-risk large and aggressive tumors.[5,6] Nonsurgical approaches include radiotherapy; chemotherapy; and vismodegib, an oral inhibitor of the hedgehog pathway involved in the development of many BCCs.[5,6,22] Topical photodynamic therapy with 5-aminolevulinic acid, topical imiquimod (immune-response modulator) and 5-fluorouracil, and intralesional interferon are other nonsurgical options that are primarily effective for small superficial BCCs. These modalities are not indicated for high-risk tumors.[5,6,23]

For small tumors, MMS is regarded by most practitioners as the gold standard due to the high cure rate and cosmetic results it provides.[5,6,18,24] This procedure allows for precise mapping of tumor location on frozen sections and, unlike surgical excision, examination of close to 100% of the deep and peripheral margins.[18] Excision and evaluation of thin horizontal sections for tumor extension also allows for a greater degree of tissue conservation than other modalities.[6,25] Mohs micrographic surgery is particularly useful for tumors of the midface, aggressive histologic subtype (eg, morpheic, infiltrating, basosquamous, micronodular), deep invasion, and perineural spread.[6,8,18,25] In a large review of 3 studies including a total of 7670 patients with primary BCC treated by MMS, Rowe et al[26] reported a 5-year recurrence rate of 1.0%, which was 8.7 times less than the weighted average of all non-MMS modalities. Similarly, in a large prospective review by Leibovitch et al,[18] the 5-year recurrence rate of BCC treated with MMS was 1.4% in primary cases and 4.0% in previously recurrent cases.[18] They reported that the main predictors of recurrence included longer tumor duration, more levels of excision required to obtain clear margins, notable subclinical extension, and prior recurrence. Interestingly, tumor and postexcision defect size did not predict recurrence.[18] Margin-controlled excision with MMS was associated with higher success rates than modalities based on clinical margins without histologic control (eg, surgical excision, electrocautery, curettage) and potentially incomplete excision.[12,18]

Although MMS has been demonstrated to have a high success rate, it has relative disadvantages. Tumors that are multicentric or have indistinct borders are more difficult to treat with MMS, and cure rates with MMS have been shown to decrease with

increasing tumor diameter.[13,25] For example, reported cure rates are greater than 99% for MMS in BCCs less than 2 cm in diameter compared to 98.6% for those between 2 and 3 cm, and only 90.5% for those greater than 3 cm.[27] Mohs micrographic surgery requires a highly trained surgeon and can be extremely time consuming and labor intensive, particularly with large and locally aggressive tumors.[6,25] Tumors that involve fat and cartilage require modifications to standardized processing techniques, and deep wounds involving muscle and bone create technical challenges in maintaining orientation.[25] In the past, MMS was more expensive than other treatment modalities; however, cost analyses have demonstrated a near-equal cost of MMS compared to surgical excision with permanent section control and lower cost as compared to radiation therapy for selected cases.[28]

Surgical excision also is considered a highly effective treatment of primary BCC and is the most commonly used treatment modality for BCC.[5,18,29] In this procedure, the peripheral and deep margins of excised tissue can be examined by a pathologist.[6] Telfer et al[6] recommended SE as the preferable treatment of choice for both large and small tumors in low-risk sites (ie, those that do not include the face) with nodular histology, tumors with morpheic histology in low-risk sites, and small (<2 cm) superficial tumors in high-risk sites. It is recommended that the size of surgical margins correlate with the likelihood of the presence of subclinical tumor extensions. Larger and morpheic-type BCCs require wider margins to achieve complete excision. In these cases, a 3-mm margin yields only a 66% cure rate, while 5-mm margins yield an 82% cure rate and 13- to 15-mm margins yield cure rates higher than 95%.[6,29,30] In a series examining recurrence rates of primary BCC, Rowe et al[26] reviewed 10 studies (2606 patients treated by SE) and calculated a 5-year recurrence rate of 10.1%. Silverman et al[31] reviewed 5-year recurrence rates in 588 cases of BCC treated with SE. They concluded that BCC on the neck, trunk, arms, and legs of any size may be effectively treated with this modality, with 1 case of recurrence among 187 cases (0.5% recurrence rate). Multivariate analysis identified 2 independent risk factors for recurrence: anatomic site (head) and patient sex (male). Analysis of BCCs on the head distinct from other body sites demonstrated a moderately significant trend (P=.196) of increasing diameter with increasing recurrence rates. Age at treatment, duration of lesion, and length of treatment were not significantly associated with an increased risk of recurrence.[31] Similarly, a review of 1417 cases of BCC by Dubin and Kopf[21] demonstrated an increased risk with tumors located on the head and larger lesions.

Radiotherapy (RT) is a commonly employed nonsurgical approach to management. Its use has been declining in recent years due to relative disadvantages and side effects. Similar to MMS, it can be extremely effective for carefully selected patients.[11,31] Radiotherapy is most effective for use with aggressive, rapidly growing BCC subtypes that are more sensitive to radiation, as replicating cells undergo mitotic death when radiation is applied.[15] Radiotherapy is considered a viable option for patients who are not candidates for surgery, tumors in locations difficult to access for SE, and for rare unresectable tumors as a primary therapy.[5,11] In a randomized comparison between RT and SE approaches to the treatment of primary BCCs on the face, RT was found to be inferior to SE both in efficacy (4-year recurrence rate, 7.5% vs 0.7%) and cosmesis (rate of good results, 69% vs 87%).[32]

The major disadvantages of RT as compared to other treatment modalities such as MMS or SE are the lack of control at margins and compromised inferior cosmetic outcomes. Hair loss, hyperpigmentation or hypopigmentation, telangiectasia, keloids, cutaneous necrosis, and RT-induced dermatitis have been reported as side effects of RT.[6,11,32-34] Other disadvantages of RT include the inconvenience of multiple visits to the hospital for treatment, and high cost as compared to other modalities such as MMS.[35] Finally, use of RT even for relatively benign disease has been linked to an increased risk for both squamous cell carcinoma, BCC, and sarcomas.[15,36]

Vismodegib is an oral drug approved by the US Food and Drug Administration in 2012 for the treatment of locally advanced BCC. It is a first-in-class small-molecule systemic inhibitor of the intracellular hedgehog signaling pathway, which has been implicated in the growth and development of several types of cancer, including BCC.[36-38] Most patients with BCC carry loss-of-function mutations that affect *PTCH1* and result in unregulated reactivation of the hedgehog pathway and uncontrolled cell growth.[38-40] Vismodegib is a small molecule that selectively deactivates the hedgehog pathway. It currently is indicated for the treatment of metastatic BCC or patients with locally advanced BCCs who are not candidates for SE or RT.[38-41] An open-label nonrandomized phase 2 study by Sekulic et al[42] evaluated the effectiveness of vismodegib for treatment of metastatic or inoperable BCCs. In 33 patients with metastatic BCCs, the response rate was 30% (10/33) with a 9.5-month median progression-free survival. All responses were partial, with 73% (24/33) showing tumor shrinkage. In 63 patients with locally advanced BCCs, the response rate was 43% (27/63). Most patients demonstrated visible reductions

in tumor size and improvement in appearance, but 13 patients (21%) in this group were noted to have a complete response (ie, absence of residual BCC on biopsy). Both cohorts had a median response time of 7.6 months.[42]

Conclusion

Our patient presented with an extremely large and ulcerating lesion on the upper back that met the criteria for classification as a high-risk tumor. In light of the tumor location and size as well as the involvement of deep tissues and muscles, we elected to pursue SE for management. This modality proved to be extremely effective, and the patient continues to be free of residual or recurrent BCC more than 36 months after surgery. Two large systematic reviews lend support to this management approach and report excellent outcomes. In a review article by Rubin et al,[5] SE was shown to provide cure rates greater than 99% for BCC lesions of any size on the neck, trunk, and extremities. Moreover, Thissen et al[43] performed a systematic meta-analysis of 18 studies reporting recurrence rates of primary BCC after treatment with various modalities and concluded that when surgery is not contraindicated, SE is the treatment of choice for nodular and superficial BCC. Both groups agree in their recommendations that MMS should be used for BCCs in cosmetically compromised zones (eg, midface), sites where tissue sparing is essential, aggressive growth patterns (eg, perineural invasion, morpheaform histology), and when high risk of recurrence is unacceptable.[5,43] In contrast, MMS is not recommended for tumors of large diameter or with indistinct borders due to decreased cure rates.[13,25,27] Vismodegib is an interesting new option in development for management of metastatic and aggressive nonresectable BCCs. It was not an option in our patient. Although consideration for use of vismodegib as a neoadjuvant treatment to shrink the tumor prior to surgery is reasonable, the decision to proceed directly with SE proved to be the superior option for our patient.

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