INNOVATIONS JOURNALS

Case Report

Images in Immunotherapy and Precision Oncology: Advanced Basal Cell Carcinoma

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ABSTRACT

A 62-year-old man presented with a slowly growing, painless lesion on his face. This eventually led to a progressive left-eye vision lesion, and the patient was subsequently diagnosed with advanced basal cell carcinoma (BCC). Of note, BCC involving cranial nerves is extremely rare, making this case unique and important to highlight. Standard treatment options for BCC involve surgery, radiation, or platinum-based chemotherapy. However, targeted therapies such as sonidegib and vismodegib – sonic hedgehog pathway inhibitors – have emerged that have been approved for treating BCC, as have anti-PD1 immunotherapies, such as cemiplimab, with their success likely based on the high tumor mutational burden seen in some of these tumors. Epidermal growth factor receptor (EGFR) inhibitors also serve a role in treating this condition as well. Molecular studies on metastatic/advanced BCC and other rare malignancies may inform treatment therapeutic decisions.

Keywords: basal cell carcinoma, sonidegib, vismodegib, cemiplimab-rwlc, case report

CASE SUMMARY

A 62-year-old male had presented 10 years earlier with a slowly growing, painless lesion on the left side of his face. His local treating physicians had initially discussed the option of wide, local excision; however, the patient did not pursue further treatment, purportedly due to a lack of insurance. The lesion continued to grow and eventually became painful (Fig. 1). One year before presentation at our clinic, the patient was evaluated by ophthalmology because of progressive left-eye vision loss. He was subsequently diagnosed with advanced basal cell carcinoma (BCC). The options of surgery or radiation were discussed, but the patient was ultimately referred to a phase I clinic because of the highly advanced nature of the disease. At the time of the initial visit, the patient had lost all vision in his left eye. Informed consent was provided by the patient. He was then noted to have a *PTCH1* mutation and was treated with vismodegib, a hedgehog pathway inhibitor. He was treated with 150 mg of vismodegib daily for 6 weeks; however, his response to treatment was minimal, and he died before additional therapy could be instituted.

DISCUSSION

BCC is the most common type of skin cancer. It arises from the basal cells within the epidermis, and it has an extremely variable clinical presentation. BCC rarely causes death or metastatic disease, but it can

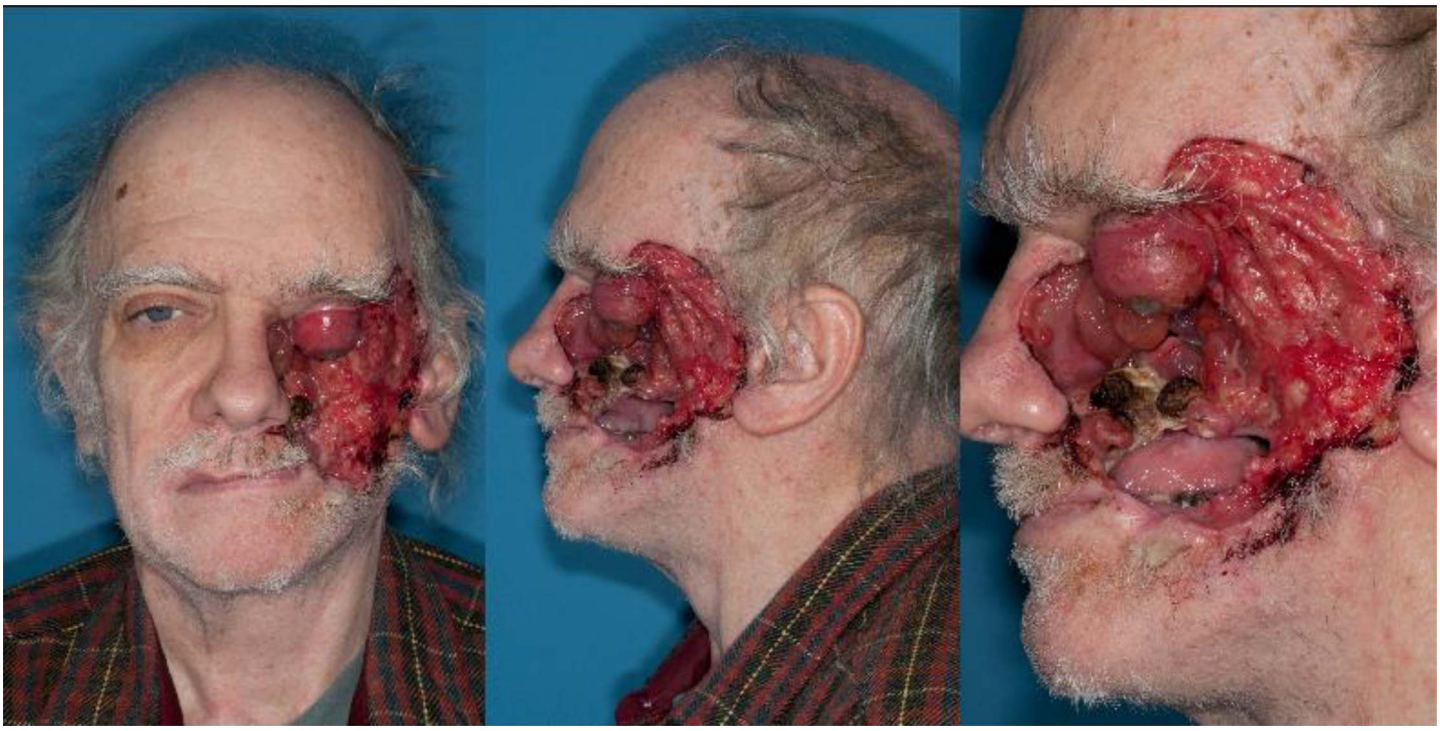

Figure 1. Advanced basal cell carcinoma of the face.

lead to destructive local spread that can be distressing.[1] The most important cause of BCC is UV-ray exposure, with sunlight being the most common source.[1] Other risk factors include having a lighter skin color, using tanning beds, being exposed to ionizing radiation, or being immunosuppressed.[1] There are also some genetic syndromes associated with BCC, such as nevoid BCC syndrome, xeroderma pigmentosum, and acrokeratosis neoplastica syndrome (Bazex syndrome).[1] The main clinical presentations of BCC are as nodular, superficial, or morpheaform lesions.[1] Most of these lesions present on the face with the remaining arising on the trunk or extremities.[1] Although BCCs generally have good outcomes when diagnosed and treated early with local excision, a small minority of patients develop advanced disease because of delays in treatment or aggressive tumor biology.[2] Locally advanced BCCs are typically large, aggressive tumors that can invade the surrounding tissue, including bone, cartilage, nerve, and muscle.[2] Of note, intracranial invasion leading to the destruction of the cranium or cranial nerves is extremely rare, and it has only been reported in about 0.03% of cases.[3]

In the past, treatment for advanced or metastatic BCC involved using platinum-based chemotherapies. One phase I/II study found that two patients with disseminated BCC had a partial and complete response to cisplatin therapy.[4] Further studies have reported overall response rates as high as 77% with cisplatin-based treatments.[5] However, most of these patients eventually relapse and succumb to the disease. In addition, responses were not as high in the metastatic or locally advanced setting.[6]

The treatment landscape for BCC evolved when it was discovered that genetic mutations leading to the upregulation of hedgehog (HH) signaling contributed to the development of BCC. The transmembrane receptor protein, PTCH, functions as a tumor suppressor by binding to HH ligands including Sonic hedgehog (SHH), Indian hedgehog, and Desert hedgehog.[7] Most BCCs have loss-of-function mutations in *PTCH1*, which prevents the suppression of the HH pathway.[7] After this discovery was made, the HH pathway inhibitors, sonidegib and vismodegib, were developed (Fig. 2). The BOLT study evaluated the efficacy and safety of sonidegib in locally advanced and metastatic BCC.[8] At a median 30 months of follow-up, the study found an objective response rate (ORR) of 56.1% and 2-year overall survival (OS) rate of 93.2% in locally advanced BCC.[8] ORR and 2-year OS rates were 23.1% and 69.3%, respectively, for metastatic BCC.[8] On the other hand, the ERIVANCE trial evaluated the same outcomes with vismodegib.[9] The ORRs were 43% and 30% for locally advanced and metastatic BCC, respectively, with 21% of locally advanced disease achieving a complete response.[9] In terms of tolerability, the most common side effects reported with both drugs are fatigue, muscle spasms, alopecia, and dysgeusia.[10] Although there are no direct comparisons between the two drugs, sonidegib appears to have a 10% lower adverse event incidence rate, and the adverse events with sonidegib may be less severe.[11]

It has also been noted that there is a higher level of expression of epidermal growth factor receptor (EGFR)

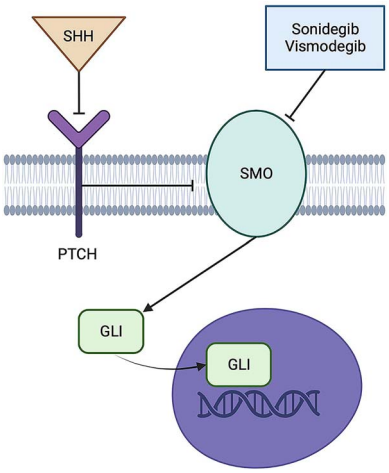

Figure 2. Illustrative depiction of the Sonic hedgehog (SHH) pathway and inhibitors. The SHH signaling pathway involves several key components: SHH ligands (such as SHH), patched receptors (PTCH1 and PTCH2), and glioma-associated oncogene homolog (GLI) transcription factors. SHH is a secreted protein that acts as a signaling molecule. It binds to the patched receptors on target cells. PTCH receptors are transmembrane proteins that inhibit the activity of the transmembrane protein smoothened (SMO) in the absence of SHH. When SHH binds to PTCH receptors, it relieves the inhibition of SMO. SMO activation leads to the activation of GLI transcription factors (GLI1, GLI2, and GLI3). These factors enter the cell nucleus and regulate the expression of target genes involved in important biologic processes. Mutations or dysregulation in the SHH pathway can lead to uncontrolled cell growth and contribute to the development of tumors, particularly in skin cancers such as basal cell carcinomas (BCCs). Vismodegib and sonidegib are small molecule inhibitors that interact with SMO in the drug-binding pocket, where they act as antagonists, preventing downstream activation of SHH pathway signaling. Mutations in BCCs are in the SHH pathway and include inactivating mutations in the negative regulator *PTCH1* or, less often, activating mutations in a positive regulator *SMO*.

GLI: glioma-associated oncogene transcription factor; PTCH: protein patched homolog 1; SMO: smoothened.

in BCC. For this reason, in some cases, clinicians have treated patients with advanced disease with cetuximab, an EGFR inhibitor. At one center, three patients with advanced disease were treated with cetuximab and were found to have a very good response with tumor regression a few weeks after initiating treatment.[12] Another study showed that cetuximab led to continued remission rates in patients with disease refractory to other standard therapies.[13] Sixty-three percent of patients experienced grade 1 or 2 adverse events of skin rashes or hypomagnesemia with no grade 3 or higher adverse events.[13]

Recently, the US Food and Drug Administration approved using cemiplimab-rwlc, a PD-1 inhibitor, for advanced BCC. The pertinent study evaluated the efficacy and safety of this immune checkpoint inhibitor in patients with locally advanced BCC who had progressed on HH inhibitor therapy.[14] The study found an ORR of 29% and complete response rate of 6% with 79% maintaining their response for at least 6 months.[14] Grade 3 or higher adverse events occurred in 48%, and the most common were hypertension or colitis.[14] No treatment-related deaths were noted.[14] Some patients with metastatic basal cell carcinoma achieve durable complete remissions after immune checkpoint blockade.[15–21]

CONCLUSION

In summary, although most BCCs can be treated with local excision, patients with locally advanced or metastatic disease require more aggressive and targeted therapies. There is a role for using the HH inhibitors sonidegib and vismodegib. Furthermore, targeting advanced disease with EGFR inhibitors, like cetuximab, and immune checkpoint inhibitors, like cemiplimab-rwlc, stand as novel precision oncology approaches. Cemiplimab and other checkpoint inhibitors may be active in advanced and/or metastatic BCCs, perhaps because they harbor a high tumor mutation burden or other features such as *PD-L1* amplification, which is predictive of immunotherapy responsiveness. Interestingly, some of these patients, including those with widely metastatic disease, may achieve long-term complete remissions (a "cure") after immune checkpoint blockade.

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