Gorlin syndrome, also known as basal cell nevus syndrome, is a rare autosomal dominant genetic disorder with an estimated birth incidence of 1 in 19,000 that leads to predisposition for multiple basal cell carcinomas (BCCs). The most frequently mutated gene in this syndrome is \( PTCH1 \), accounting for more than 90% of all patients with Gorlin syndrome. The disease also produces characteristic physical findings, including palmar pits, jaw cysts, hypertelorism, and frontal bossing. Only 3 cases of distantly metastatic BCC have been reported in the literature in patients with Gorlin syndrome. The BCCs in patients with Gorlin syndrome have been reported to have sensitivity to targeted therapy against the SMO protein, the downstream effector of \( PTCH1 \). Although it is known that locally advanced BCC in patients with Gorlin syndrome can be refractory to (primary resistance) or regrow (secondary resistance) after Smoothened (SMO) inhibitors, neither primary nor secondary resistance has been described in distantly metastatic tumors in this high-risk group.

We report a case of Gorlin syndrome in a patient with biopsy-proven metastatic BCC in his lungs that was refractory to 2 different SMO inhibitors despite responses in his cutaneous tumors. Because this is a single case report, no institutional review board approval was required. The patient provided written consent to have his case reported.

Report of a Case

A man in his 50s with Gorlin syndrome presented with innumerable cutaneous BCCs on his head, neck, trunk, and 4 extremities. The largest BCC had been present for 18 months and was a locally advanced, ulcerated, left postauricular lesion (6.4 × 6.0 cm) that encased the facial nerve. The area of the locally advanced BCC had been exposed to radiation therapy 20 years earlier to treat other BCCs in that region. The lesion had continued to grow despite topical treatments with fluorouracil and nitrogen mustard. Computed tomography (CT) revealed that the underlying bone was not involved with the tumor. However, the patient reported that his surgeons had recommended against excision because of the extent of his disease and the risk of facial nerve damage and hearing loss.

The patient's metastatic BCC was first discovered 16 months earlier when he presented to his local emergency department for chest pain. As part of his evaluation, he underwent chest CT, computed tomography (CT), and magnetic resonance imaging (MRI) of the neck and chest. The MRI revealed a left periauricular lesion with enhancement consistent with a metastatic BCC. The patient was then referred to our hospital for further evaluation and treatment.

The patient's medical history was significant for stage 2 testicular cancer, diagnosed 10 years earlier, which was successfully treated with bleomycin sulfate, etoposide, and cisplatin. During this treatment, the patient noted incidental shrinkage of all his BCCs. However, this combination chemotherapy left him with persistent shortness of breath, neuropathy, and chronic renal compromise.

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which revealed nodules in the lung. Follow-up positron emission tomography-CT revealed increased fludeoxyglucose uptake in these lung nodules. Findings from a biopsy specimen of the nodules confirmed metastatic BCC (Figure 1). Because of the lack of good treatment options, the patient enrolled in a clinical trial (NCT00761696) of the SMO inhibitor saridegib (IPI-926) at 130 mg/d.10 All of his cutaneous BCCs shrank with saridegib. However, his metastatic BCCs remained stable in size on CT scans, indicating refractory disease. Sixteen months after initiating saridegib therapy, a new 1.1-cm, right, apical lung nodule was discovered on a CT scan, and he was discontinued from the study because of disease progression.

Because of his comorbidities and lack of treatment options, the patient enrolled in a second clinical study (NCT01160250) using a different SMO inhibitor, vismodegib, after a protocol-mandated 1-month washout from saridegib. He received 150 mg/d, and his cutaneous lesions continued to shrink with saridegib. However, his metastatic BCCs remained stable in size on CT scans, indicating refractory disease. Sixteen months after initiating saridegib therapy, a new 1.1-cm, right, apical lung nodule was discovered on a CT scan, and he was discontinued from the study because of disease progression.

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After discussion with his medical oncologist and presentation at a multidisciplinary head and neck tumor board, the consensus was that the new nodules were likely metastatic BCC and an additional biopsy of the lung was not needed. The patient was discontinued from the study because of disease progression but continued to receive vismodegib as part of his dermatology care to control his numerous cutaneous BCCs. The patient is currently considering other clinical trials for his refractory metastatic BCCs.

Discussion

This case illustrates 4 clinical teaching points. First, patients with Gorlin syndrome can develop distantly metastatic BCCs. Only 3 cases of distant metastatic BCCs have been reported in patients with Gorlin syndrome, suggesting either the rarity of this phenomenon or detection bias because of a lack of surveillance by health care professionals.5-7 The prevalence of metastatic BCCs in patients with Gorlin syndrome compared with patients with sporadic BCCs is not known.

Second, this case highlights the importance of tissue biopsy after a positive finding on imaging to confirm the diagnosis of BCC at a distant site. The patient's history of testicular cancer put a testicular cancer metastasis in the differential diagnosis for the lung nodules. In older patients, more common cancers, such as colon or breast cancer metastases, should be considered as well.
Third, this case demonstrates that the treatment responses of distant metastatic BCCs may not reflect the treatment responses of cutaneous BCCs in patients with Gorlin syndrome. Although this patient’s cutaneous BCCs responded to SMO inhibitors, his metastatic BCCs never responded and eventually progressed with the development of new nodules.

Fourth, serial imaging of metastatic BCCs is important to monitor for disease progression and response to treatment, even in patients with Gorlin syndrome.

Conclusions

The differential clinical response to SMO inhibitors suggests that BCCs in patients with Gorlin syndrome may not be genetically identical despite the patient possessing a germ-line mutation (such as in \textit{PTCH1}). We speculate that this patient may be predisposed to BCCs, with multiple mutations conferring chemoresistance to SMO inhibitors because of his history of systemic chemotherapy for testicular cancer and/or radiation to his head region. Although some studies\cite{8,10} have suggested sensitivity of nonadvanced BCCs to SMO inhibitors in patients with Gorlin syndrome, patients who have been exposed to conventional chemotherapy or radiation treatment may have a greater propensity for resistance to SMO inhibitors.

The molecular basis of BCC chemoresistance to targeted therapy is currently the subject of active investigation and may lead to insights on downstream or collateral molecular pathway alterations responsible for chemoresistance.\cite{11} These pathway changes could then be targeted to achieve improved and more durable responses for these high-risk patients.

REFERENCES