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.

We report a case of Gorlin syndrome in a patient with metastatic BCC refractory to SMO inhibitors. Furthermore, clinical responses in this patient’s cutaneous tumors did not parallel the responses in the distant site. However, serial imaging after diagnosis of metastatic disease can be critical to monitor for response to therapy.
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 on this regimen. However, his metastatic BCCs remained stable in size on CT scans, indicating refractory disease. Sixteen months after initiating vismodegib 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.

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 germline 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\textsuperscript{6,10} have suggested sensitivity of nonadvanced BCCs to SMO inhibitors in patients with Gorlin syndrome, patients who have been exposed to conventional chemotherpay 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.\textsuperscript{21} These pathway changes could then be targeted to achieve improved and more durable responses for these high-risk patients.

REFERENCES


ARTICLE INFORMATION

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