Emergence of Squamous Cell Carcinoma during Treatment of Basal Cell Carcinoma with Vismodegib

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Abstract

Introduction: Basal cell carcinoma accounts for 80% of all non-melanoma skin cancer. Vismodegib is the hedgehog signaling pathway inhibitor, which has shown improved outcome in both locally advanced and metastatic basal cell carcinoma. There are, however, reports of cutaneous squamous cell carcinomas developing while on active treatment with vismodegib. We present a case of transition to squamous cell carcinoma after vismodegib treatment in a patient with a 10-year history of basal cell carcinoma.

Case presentation: 44-year-old Caucasian man with 10 year history of basal cell carcinoma on his left chest wall and left shoulder was treated with local resection and actively on vismodegib. He presented with enlarging and infected mass. He underwent left forequarter amputation of his left arm, shoulder and clavicle. Pathology reported basosquamous cell carcinoma with scapula invasion and axillary lymph node metastases. Staging was stage III T4N1M0. He continued on vismodegib post-operation. Three months after his amputation, the patient presented with a recurrent left shoulder mass with nonhealing surgical wound. Imaging revealed vascular invasion. Biopsy of the lesion was consistent with invasive squamous cell carcinoma with genomic profiling of PIK3R1, PTCH1 and STK11 gene mutations. At the patient’s request he was subsequently transferred to another facility for a second surgical opinion.

Conclusion: Biopsy and genetic analyses of basal cell carcinoma lesions should be considered in every case that has treatment plan for hedgehog signaling pathway inhibitor to evaluate for potential secondary squamous cell carcinoma growth. Further study is needed to confirm the mechanism of basal cell resistance to anti-smoothened therapy and eventual squamous cell carcinoma growth.

Keywords: Basal cell carcinoma; Vismodegib; Hedgehog pathway inhibitor; Squamous cell carcinoma

Introduction

Basal cell carcinoma (BCC) accounts for 80% of all non-melanoma skin cancer [1]. Advanced disease is infrequently seen, but when present can be a surgical challenge or even life threatening. Recent studies show that mutations in the hedgehog (HH) signaling pathway are associated with the majority of BCC. Hedgehog protein binds to patched homologue 1 (PTCH1) transmembrane receptor, which prevents inhibition of PTCH-1 signaling by smoothened homologue (SMO). These mutations cause inactivation of PTCH1or activate SMO, which lead to uncontrolled proliferation of basal cell of skin, then development of basal cell carcinomas (BCC). Vismodegib is the first hedgehog signaling pathway inhibitor (SMO inhibitor), which has shown 21% complete response rate and significantly improved outcome in both locally advanced and metastatic BCC (43% and 30% response rates, respectively). Median survival was 7.6 months in both cohorts [2]. There are, however, reports of cutaneous squamous cell carcinomas (SCC) developing while on active treatment with vismodegib. Herein, we present a case of transition to squamous cell carcinoma after vismodegib treatment in a patient with a 10-year history of basal cell carcinoma.

Case Report

44-year-old Caucasian man was admitted to our hospital due to an enlarging mass on his left shoulder. He was known to have basal cell carcinoma on his left chest wall and left shoulder for 10 years. He initially presented in 2003 due to a lesion noted on his left shoulder. At that time this was felt to be a typical nevus. The patient then presented again in 2006 due to gradual increase in the size of the lesion. At that time biopsy confirmed a diagnosis of basal cell carcinoma. Treatment at that time included local resection. Information on the stage at presentation was not available (Table 1).

He followed up with a local oncologist and later had a recurrent lesion with bony involvement that caused clavicle fracture in 2012. Two lesions were surgically removed; however, the type and extent of surgery was unknown. Due to his funding status, he did not receive any chemotherapy until the following year in 2013, when he was started on vismodegib. The mass initially responded well to treatment with significant decrease in size and near complete clinical response after actively on medication for approximately a year. Unfortunately, due to loss of insurance after less than a year on treatment the patient stopped maintenance vismodegib.

In December 2014, the patient was admitted to the hospital due to an infected and rapidly growing left shoulder mass. CT and MRI showed large lobulated fun gating mass size 18x15x11 cm with diffuse skin erosion and dermis involvement. There was extensive involvement of anterior proximal shoulder, anterior lateral chest wall, supraspinatus, subscapular is, lower portion of biceps muscle, including acromion and...
Coracoïd process erosion. Axillary nodal metastasis was also present at that time. CT abdomen and whole body bone scan were unremarkable. He underwent left forequarter amputation of his left arm, shoulder and clavicle. Pathology at that time reported basosquamous cell carcinoma, accounting for age and basal cell nevus syndrome status.

Discussion

As in our patient, the appearance of squamous cell carcinoma (SCC) in a previously documented basal cell carcinoma (BCC) treated with vismodegib has been previously reported. Chang et al. conducted retrospective chart review of 28 patients with regrowth BCC on top of advanced BCC treated with vismodegib [3]. Six out of 28 patients had a tumor regrowth (21%) while actively on treatment at a mean of 56.4 weeks, which accounted for 12 out of 230 lesions (5%). Only one lesion revealed to be basosquamous subtype. There was also a report of a keratoacanthoma (KA) which developed within 2 months while on vismodegib [5-10], from six different case reports and twelve cases of SCC emergence replacing the previous pathological finding of BCC in patients undergoing treatment with vismodegib [5-10].

Table 1: Sixteen cases report of emergence or co-existing squamous cell carcinoma and basal cell carcinoma with vismodegib treatment.

<table>
<thead>
<tr>
<th>Author</th>
<th>Age, gender</th>
<th>Initial Diagnosis, Location</th>
<th>Treatment</th>
<th>Last Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iarrobino [5]</td>
<td>61, M</td>
<td>BCC, right shoulder</td>
<td>Electrodessication and curettage. Local recurrence was treated with excision and radiation with surgery on axillary node metastasis. Then vismodegib, but the patient progressed.</td>
<td>SCC, strongly positive for p63 and negative for BerEP4</td>
<td>Dooxorubicin and cisplatin for two cycles</td>
</tr>
<tr>
<td>Gatting [11]</td>
<td>81, M</td>
<td>N/A; suspected locally advance nonmelanoma skin cancer of face trunk and extremities</td>
<td>Vismodegib with 10-week response but developed lesions on left parietal scalp, left zygoma, and left lower leg.</td>
<td>Invasive SCC</td>
<td>Radiation to left parietal scalp and left zygoma</td>
</tr>
<tr>
<td>Orouji [6]</td>
<td>84, F</td>
<td>BCC, face, lower lip and forearms</td>
<td>Vismodegib response in 4 weeks. Continued for 16 weeks then new lesion developed at right cheek and forearm.</td>
<td>Moderately differentiated SCC at forearm and well-differentiated SCC at right cheek</td>
<td>Total excision</td>
</tr>
<tr>
<td>Zhu [7]</td>
<td>60, F</td>
<td>BCC, right medial canthus, upper eyelid, lacrimal duct opening, and nasal sidewall</td>
<td>Vismodegib, with 4 months response, but developed hyperkeratotic papule within the prior BCC tumor bed</td>
<td>Invasive acantholytic SCC and no abnormal basaloid cells</td>
<td>Moh Surgery</td>
</tr>
<tr>
<td>Zhu [7]</td>
<td>40, F</td>
<td>BCC, scalp with dura extension</td>
<td>Photodynamic therapy and radiation, then vismodegib, responded within 3 months and continued for 2.5 years until MRI demonstrated tumor progression.</td>
<td>Invasive SCC, spindle cell type and no abnormal basaloid cells</td>
<td>Surgical resection of calvarium and dura</td>
</tr>
<tr>
<td>Ranschoff [8]</td>
<td>62, F</td>
<td>BCC, back with left axillary lymph node metastasis</td>
<td>Vismodegib for 9 months, with a complete response in both the primary and lymph node metastasis, then surgical excised on original tumor site. 13 months later, recurrent left axillary lymph node mass on PET-CT</td>
<td>Keratinizing SCC stained positive for cyto-keratins 5 and 6. Genetic study showed NOTCH1/2 and KMT2C, while primary BCC detected PTCH1 mutation.</td>
<td>N/A</td>
</tr>
<tr>
<td>Poulaillon [12]</td>
<td>90, M</td>
<td>BCC, right nostril SCC, right cheek</td>
<td>5-fluorouracil (5-FU) for right cheek lesion with complete clinical response at 4 weeks. Vismodegib was started for right nostril lesion. However, both lesions progressed at 16 week of vismodegib.</td>
<td>Combining moderately and poorly differentiated SCC. Positive anti-p63, cyto-keratin (CK) 5/6, CK7, human epithelial antigen (HEA)/BerEP4, and epithelial membrane antigen (EMA) antibodies</td>
<td>Palliative rhinectomy</td>
</tr>
<tr>
<td>Guo [9]</td>
<td>75, M</td>
<td>BCC, right cheek SCC, right cheek The patient had underlying CLL</td>
<td>Vismodegib for right cheek lesion with clinical respond, but stop at 7.5 months due to intolerable of side effects. Moh’s surgery was performed.</td>
<td>Peripheral BCC with central SCC with squamoid and spindle histology with dense CLL infiltrates</td>
<td>Complete resection from Moh’s surgery</td>
</tr>
<tr>
<td>Mohan [10]</td>
<td>12 out of 16 cases of SCC emerging after vismodegib exposure with mean age of 52</td>
<td>N/A</td>
<td>N/A</td>
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Table 1: Sixteen cases report of emergence or co-existing squamous cell carcinoma and basal cell carcinoma with vismodegib treatment.
with non-melanoma skin cancers, including SCC, there are no mutations in PIK3CA have been previously reported in association with ovarian, cervical, endometrium and esophageal cancer [13,14]. While PIK3R1 encodes a catalytic subunit of the class I PI3K family, which participates in intracellular process including cell proliferation, transformation, and apoptosis. Somatic mutations of PIK3R1 had been reported to contribute to BCC growth in coordination with activated HH signaling [26]. The study also observed upregulation of LKB1/AMPK pathway in human SCC cells. A similar result in another murine study revealed that LKB1 was also present in our patient. A tumor suppressor and upstream kinase of adenine monophosphate–activated protein kinase (AMPK), STK11 plays a role in multiple cellular functions, embryo development, cell cycle arrest, response to DNA damage, cell apoptosis and maintenance of hematopoietic stem cells. Its mutation or deletion is found dominantly in Peutz–Jeghers syndrome (PJS) and also related to various types of cancer including, sporadic non-small cell lung cancer, ovarian, breast cancer, cervical cancer, and pancreatic cancer [25]. In mice, LBK1 expression and AMPK signaling were increased in UVB-induced BCC with positive PTCH-1 mutations. The role of LBK1 may contribute to BCC growth in coordination with activated HH signaling [26]. The study also observed upregulation of LBK1/AMPK pathway in human SCC cells. A similar result in another murine study revealed that LBK1 mutation was prone to development of skin and lung SCC with chemical carcinogen exposure [27]. Presence of STK11 (LBK1) in our patient may contribute to SCC development, however the mechanism is unknown.

Conclusion

Biopsy and genetic analyses of previously responsive or focally progressive BCC lesions to evaluate for SCC should be considered in every case as this could lead to definitive SCC treatment with either surgical excision or earlier combination radiation and chemotherapy for inoperable lesions which otherwise may not be considered. Further study is needed to confirm the mechanism of BCC resistance to anti-SMO therapy and eventual SCC growth.

References


