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

Nattamol Hosiriluck* and Catherine Jones

Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas, USA

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.

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 PTCH1 or 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 18×15×11 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

*Corresponding author: Nattamol Hosiriluck, Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas, USA, Tel: 8066202092; E-mail: nattamol.hosiriluck@ttuhsc.edu

Author	Age, gender	Initial Diagnosis, Location	Treatment	Last Diagnosis	Treatment
Iarrobino [5]	61,M	BCC, right shoulder	Electrodessication and curettage. Local recurrence was treated with excision and radiation with surgery on axillary node metastasis. Then vismodegib, but the patient progressed.	SCC, strongly positive for p63 and negative for BerEP4	Doxorubicin and cisplatin for two cycles
Gathings [11]	81,M	N/A; suspected locally advance nonmelanoma skin cancer of face trunk and extremities	Vismodegib with 10-week response but developed lesions on left parietal scalp, left zygoma, and left lower leg.	Invasive SCC	Radiation to left parietal scalp and left zygoma
Orouji [6]	84,F	BCC, face, lower lip and forearms	Vismodegib response in 4 weeks. Continued for 16 weeks then new lesion developed at right cheek and forearm.	Moderately differentiated SCC at fore arm and well-differentiated SCC at right cheek	Total excision
Zhu [7]	60,F	BCC, right medial canthus, upper eyelid, lacrimal duct opening, and nasal sidewall	Vismodegib, with 4 months response, but developed hyperkeratotic papule within the prior BCC tumor bed	Invasive acantholytic SCC and no abnormal basaloid cells	Moh Surgery
Zhu [7]	40,F	BCC, scalp with dura extension	Photodynamic therapy and radiation, then vismodegib, responded within 3 months and continued for 2.5 years until MRI demonstrated tumor progression.	Invasive SCC, spindle cell type and no abnormal basaloid cells	Surgical resection of calvarium and dura
Ransohoff [8]	62, F	BCC, back with left axillary lymph node metastasis	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	Keratinizing SCC stained positive for cytokeratins 5 and 6. Genetic study showed NOTCH1/2 and KMT2C, while primary BCC detected PTCH1 mutation.	N/A
Poulalhon [12]	90, M	BCC, right nostril SCC, right cheek	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.	Combining moderately and poorly differentiated SCC. Positive anti-p63, cytokeratin (CK) 5/6, CK7, human epithelial antigen (HEA)/BerEP4, and epithelial membrane antigen (EMA) antibodies	Palliative rhinectomy
Guo [9]	75, M	BCC, right cheek SCC, right cheek The patient had underlying CLL	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.	Peripheral BCC with central SCC with squamoid and spindle histology with dense CLL infiltrates	Complete resection from Moh's surgery
Mohan [10]	12 out of 16 cases of SCC emerging after vismodegib exposure with mean age of 52	N/A	N/A	N/A	N/A

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

coracoid 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 with the tumor composed almost entirely squamous cell carcinoma with one localized region of BCC. Scapula invasion was present with a positive soft tissue margin and one out of thirteen axillary lymph node metastases were reported. It was described as well to moderately differentiated with poorly differentiate foci. Pathological staging was stage III T4N1M0. He was restarted on vismodegib treatment post-operatively. In March 2015, three months after his forequarter amputation, the patient presented with a recurrent left shoulder mass and an infected nonhealing surgical wound (Figure 1). CT scan showed a large fun gating mass involving the base of left neck, extending to the carotid bifurcation with vascular encasement of the left jugular vein and left subclavian vein and artery. Rib erosion and mediastina lymphadenopathy were also noted (Figure 2). Due to the size of the mass with extensive involvement of the vasculature, the patient was not felt to be a candidate for further surgery. He was admitted for intravenous antibiotics and underwent repeat biopsy of the lesion. Biopsy was consistent with invasive moderately differentiated squamous cell carcinoma. Genomic profiling of the lesion identified PIK3R1, PTCH1 and STK11 gene mutations. At the patient's request

he was subsequently transferred to another facility for a second surgical opinion.

Discussion

As in our patient, the appearance of squamous cell carcinoma (SCC) in a previously documented basal cell carcinoma (BCC) treated with vismodigeb 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 therapy with no prior history of KA or SCC [4]. To date, there are eighteen cases of SCC emergence replacing the previous pathological finding of BCC in patients undergoing treatment with vismodegib [5-10], from six different case reports and twelve cases from a cohort study. There also two cases of co-existing BCC and SCC, which SCC only emerging on repeat biopsy after vismodegib treatment [11,12]. Mohan et al. conducted a cohort study to determine secondary non-BCC malignancy after vismodegib exposure, with a hazard ratio of 8.12 (95% CI, 3.89-16.97; P < .001) of secondary cutaneous squamous cell carcinoma, accounting for age and basal cell nevus syndrome status

Figure 1: In March 2015, the patient presented again with a recurrent left shoulder mass and an infected nonhealing surgical wound.
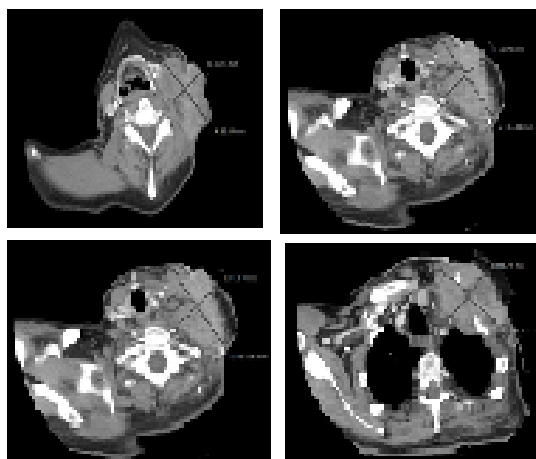

Figure 2: In March 2015, CT scan showed a large fun gating mass involving the base of left neck, extending to the carotid bifurcation with vascular encasement of the left jugular vein and left subclavian vein and artery. Rib erosion and mediastinal lymphadenopathy were also noted.

[10]. The study has confirmed correlation of SCC development from vismodegib exposure. Our case demonstrated a sequential pathological change over two years of vismodegib treatment. Orouji et al. proposed a theory that SCC development could be a coincidental finding related to field cancerization from to prior sun exposure [6], but later opposed the idea because SCC developed only after initiation of SMO inhibitor. The author later hypothesized that vismodegib was the culprit rather than sun exposure. Only Ransohoff reported an associated genetic mutation, NOTCH1/2 and KMT2C (also called MLL3), which were not found in our patient. The author proposed the transition of the cell types was from mechanism of vismodegib selection as a tumor escape [8]. These findings urge clinicians to pay close attention to surveillance for secondary malignancy development in patients initiating vismodegib and could potentially lead to a post-market report.

Genetic mutations detected in our patients were PIK3R1, PTCH1 and STK11. PIK3R1 mutations activate the phosphatidylinositol 3-kinase downstream signaling pathway, which targets multiple intracellular process including cell proliferation, transformation and apoptosis. Somatic mutations of PIK3R1 had been reported in primary colon cancer, but also found in association with breast, ovarian, cervical, endometrium and esophageal cancer [13,14]. While mutations in PIK3CA have been previously reported in association with non-melanoma skin cancers, including SCC, there are no previous reports of PIK3R1 mutations in BCC [15]. However, Herrero-Gonzalez et al. found the effect of PIK3R1 and PIK3R2 in endometrial cancer produced similar downstream signaling to PIK3CA which led to subsequent loss of PTEN (Phosphatase and tensin homologue) as a tumor suppress protein [13]. The up-regulation of PIK3 pathway was thought to be potential mechanism of SMO inhibitor resistance. The study showed an enriched PIK3 targeted gene in SMO-inhibitor resistant samples [16]. We hypothesized that this resistant mechanism could be a potential cause of higher regulation of PIK3 pathway and could probably be accountable for SCC development.

Over 90% of BCC carries either mutations in PTCH1 or SMO, two main proteins in the hedgehog signaling pathway [17]. There were also reports of PTCH1 expression in human tissue studies of medulloblastoma, non-small cell lung cancer, breast cancer, and pancreatic neuroendocrine tumor (PNET) [18-21]. PTCH1 mutation was found in 30% of medulloblastomas in humans [22]. A phase I trial of vismodegib on a medulloblastoma patient showed an initial response, but the patient was later removed from the study due to disease progression [23]. Further molecular analyses reported loss of heterozygosity from amino acid missense mutation of previously detected homozygous PTCH1 mutation [24].

Serine/threonine kinase 11 (STK11), also known as liver kinase B1 (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 LKB1 may 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 LBK1 mutation was prone to development of skin and lung SCC with chemical carcinogen exposure [27]. Presence of STK11 (LKB1) 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.

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