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CASE REPORT

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Giant basal cell carcinoma of anterior chest wall reveals metastasis to lungs: A case report

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Abstract

Basal cell carcinoma (BCC) is the most common cutaneous malignancy in the world, and the incidence of pulmonary metastasis is exceedingly rare. We present a case of middle-aged male with findings consistent with BCC with metastasis to the lungs managed with surgical resection and the use of targeted therapy using the hedgehog pathway inhibitor with improvement.

KEYWORDS

basal cell carcinoma, lung metastasis, pathology

1 | INTRODUCTION

The lungs are the second-most frequent site of disease metastasis from extra-thoracic tumors, and is most often related to endovascular spread of tumor cells from the primary site.[1] The most common primary tumors to metastasize to the lungs are breast, colorectal, renal, and head and neck cancers. While basal cell carcinoma is the most common malignancy,[2,3] and the incidence of metastasis is estimated 0.0028%–0.55%,[2,4] pulmonary metastasis is exceedingly rare.

2 | CASE PRESENTATION

A 58-year-old Latino male without significant past medical history presented with a progressively evolving ulcerated lesion on the anterior chest which started draining foul-smelling purulent discharge for a week. He initially noticed a small, pruritic nodule on the left side of his sternum four months prior; and due to repeated scratching and scarring of the lesion, the nodule eventually progressed to a 5 × 7 cm deep ulcer (Figure 1) resulting in worsening discomfort, itching, and malodorous drainage over the course of the previous week. Symptoms were limited to the anterior chest lesion, and a comprehensive review of systems was not suggestive of systemic disease. History was remarkable for 8 years of work on a coffee-farm in which he was routinely exposed to the sun for hours on end, as well as years as a soccer player, both without sunscreen use; and there was no significant exposure to tanning beds, known chemical irritants, tobacco use, or other obvious topical carcinogens. In addition, there was no family history of skin cancer nor any personal history of basal cell nevus syndrome.

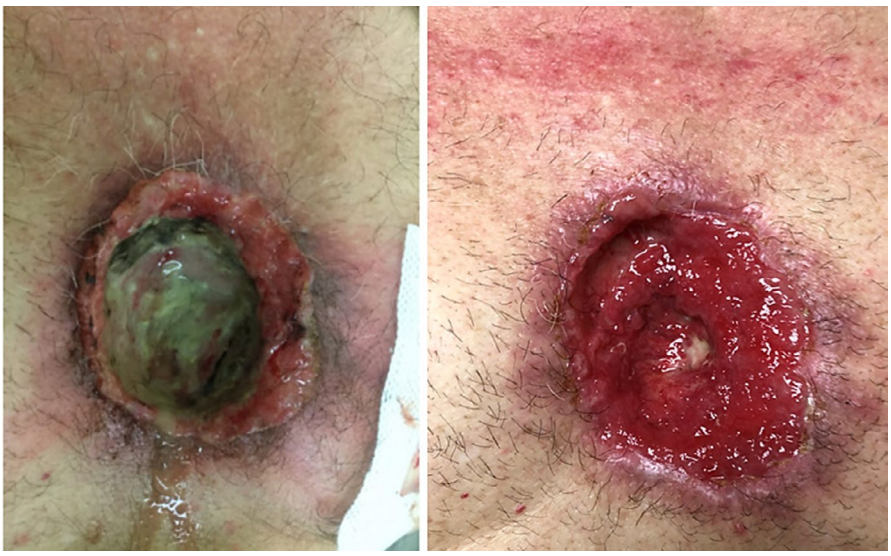

FIGURE 1 (Left) Ulcerated chest wall lesion before surgical debridement with purulent material and fibrinous debris at base. (Right) Ulcerated chest wall lesion after surgical debridement with coverage of clean granulation, minimal turbid fluid at the base of the lesion. Chest skin is notable for likely contact dermatitis in areas where tape was applied for dressing changes

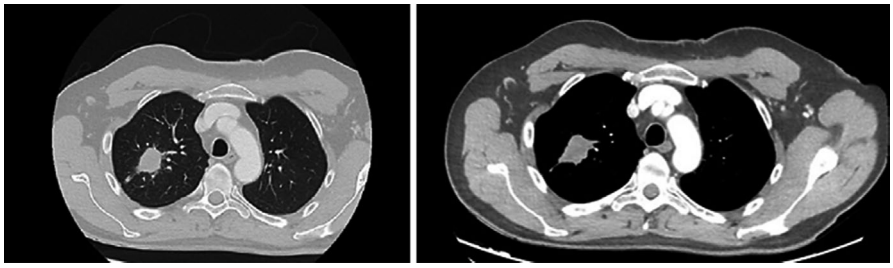

FIGURE 2 CT Chest demonstrating large mass in the right upper lobe of the lung along with some sites of distant metastasis

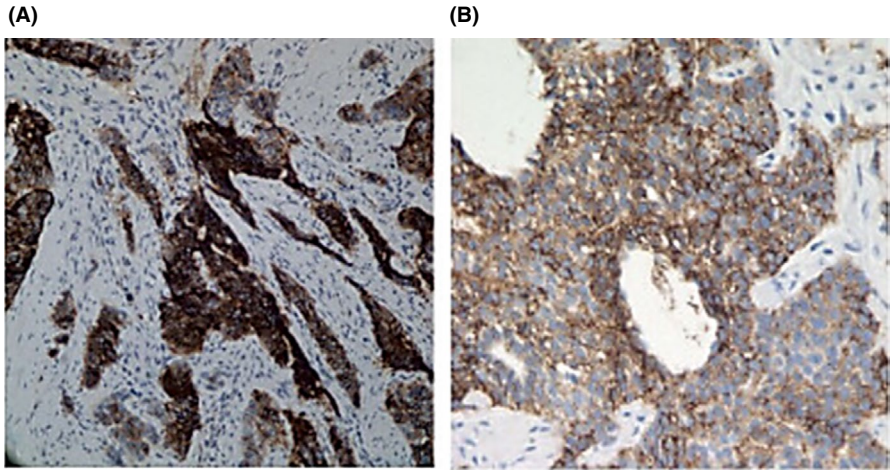

FIGURE 3 (A) Ber-EP4 positive lesion from ulcerated chest wall lesion biopsy. (B) Ber-EP4 positive lung tumor which shares similar morphology with the chest wall lesion showing basal cell features in a desmoplastic background

Aside from the necrotic ulceration of the anterior chest, physical examination revealed two 1-cm occipital subcutaneous nodulations but was otherwise unremarkable. He was afebrile and exhibited no elevated white count, and an HIV test was negative. While blood cultures were negative, wound cultures grew Staphylococcus aureus, beta hemolytic streptococci Group G, and Bacteroides fragilis, for which the patient completed a course of systemic antibiotics.

Chest CT imaging (Figure 2) was negative for evidence of osseous destruction, periosteal reaction, or deeper fluid collections. However, a 3.7 cm spiculated mass in the right upper lobe, 1.1 cm mass in the right middle lobe, along with multiple subcentimeter nodules in the left upper, left lower, and lingual lobes were described. Surgical debridement and biopsy of the chest ulcer revealed basal cell carcinoma extending beyond tissue margins, and CT-guided core biopsy of the RUL lesion showed the

same immunohistochemical profile: positive for Ber-EP4 (Figure 3A), Bcl-2, SMA (focally positive) and negative for EMA and CK20. In addition, the RUL core biopsy was positive for Ber-EP4 (Figure 3B), Bcl-2, CK 5/6, P63, cytokertin AE1/3 (weakly), EMA (rare focally) and negative for TTF-1, napsin A, CK7, PSA, MSA, p16, S-100, chromogranin, and synaptophysin. Thus, a diagnosis of metastatic basal cell carcinoma was made. Further staging done with CT of head and abdomen/pelvis revealed no metastatic disease processes. Bronchoscopy (Figure 4) was negative for endobronchial lesions, and no other metastatic lesions were appreciated on further workup.

After interdisciplinary review, surgical excision of the lesion along with resection of the anterior sternal bone was performed, and targeted therapy using the hedgehog pathway inhibitor vismodejib 150 mg daily for 7 months followed by a reassessment for disease progression.

3 | DISCUSSION

Basal cell carcinoma (BCC) is the most common cutaneous malignancy in the world, accounting for up to 80% of all cancers arising from the epidermis[4] and with 750,000 cases reported annually in the United States.[5] Most cases occur on the head and neck[6] likely due to ultraviolet light exposure.[7] It is characterized by its slow growth, a very low potential to metastasize, and a high cure rate. After local excision, BCC rarely demonstrates metastatic potential.[8]

The first case of metastatic BCC was described by Beadles in 1894 in which a 46-year-old man demonstrated an extensive ulcer on the face that metastasized to his submaxillary lymph node.[9] Due to the rarity of metastasis, all published cases are limited to case reports and retrospective studies[10]; however, over 400 cases have been described, with an annual estimated incidence of 0.0028%–0.55%[11,12] of all cases.

While metastatic lesions can present asymptomatically, they frequently manifest as ulcerations and lymphadenopathy.[13] Most BCC are found on the head and neck, followed by the trunk; and are likely related to significant sun exposure,[14] as was the case in our patient. The clinical morphologies are diverse, with the more common benign lesions following superficial or nodular pattern while the more aggressive subtypes fall into the infiltrative, sclerosing, and metatypical subtypes, the latter of which is most likely to be aggressive and confused with squamous cell carcinoma.[15]

Further classification by size defines giant basal cell carcinomas (GBCCs) as BCC with >5 cm diameter, and are a rare presentation of the disease, accounting for less than 1% of all cases. While the occurrence of metastasis is still low, incidence in the GBCC subgroup is higher.[16] The average size of a primary tumor that metastasizes is 7.5 cm in diameter,[12] and most commonly metastasizes to regional lymph nodes (53%–56%), lungs (33%–36%), and bone (16%–20%). As tumor size exceeds 25 cm in diameter, metastasis in these tumors essentially becomes unavoidable.[17]

The importance of morphologic differentiation of tumor subgroups carries particular importance in this case, as lesions were seen as much on the superficial trunk as in the lungs: sites in which squamous cell carcinoma is also common. For this reason, immunohistochemical analysis of tissue samples from both sites, and concordance or discordance between them, drastically changes diagnostic conclusions and therapeutic approaches.

3.1 | Clinical and microscopic analysis

We believe our patient presented with a nodular basal cell carcinoma, which is a lesion described to be papular or pearly in appearance and bleeds easily from

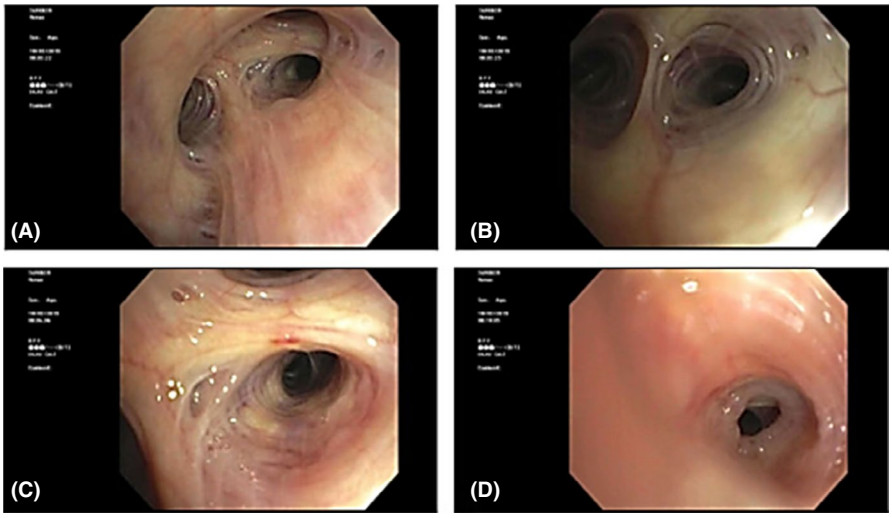

FIGURE 4 (A) Right mainstem bronchus. (B–D) Right Upper Lobe. Bronchial mucosa and anatomy are normal with no signs of endobronchial lesions and secretions

minor trauma.[3] This subtype carries a gradual extension toward micronodular and ultimately metatypical subtypes, which can be confused with squamous cell carcinoma. His initial skin lesion progressed to an enlarging deep ulcer in the setting of repetitive trauma, and presented with heaped-up borders making it difficult to distinguish from squamous cell carcinomas and keratoacanthomas.

The diagnosis of mBCC is largely dependent on the criteria constructed by Lattes and Kessler in 1951: (i) neither the primary tumor nor the metastasis can be predominantly squamous and both must have similar histological appearances showing BCC; (ii) in the case of presumed metastasis, direct extension of the original tumor and new primary growths must be excluded; (iii) the primary tumor must originate from skin and cannot originate from salivary glands, other glands, and mucous membranes.[18] Our patient met all criteria constructed by Lattes and Kessler indicating a diagnosis of mBCC to the lung.

The pathogenic pathway of metastasis of BCC tumor dissemination can be both hematogenous and lymphatic. Given the presentation of our case with multiple small nodules located diffusely between the two lungs, in addition to the large RUL mass, the likely cause of metastasis was hematogenic. Given how highly vascularized the lungs are and the presentation of an ulcerative lesion which was formed by repetitive trauma to the site, the BCC likely seeded the bloodstream by this mechanism. In such cases, there is a high likelihood of other metastatic sites, and a comprehensive exploration is warranted.

The low incidence of metastatic basal cell carcinoma is often the reason why mBCC is not considered clinically for differential diagnoses. Additionally, the characteristics of the tumor may be obscured by small or distorted biopsy specimens resulting in a misdiagnosis. This was particularly important in the present case, in which the initial pathology from lung biopsies was interpreted to be glandular in nature and of pulmonary origin. It was only after a multidisciplinary evaluation of the clinical, histopathological, and immunohistochemical data was a diagnosis of mBCC made.

3.2 | Immunohistochemical analysis

In instances when morphological analysis may lack the architectural clues for a definitive diagnosis, immunophenotyping is the most accurate methodology. In our case, morphological analysis was indicative of mBCC and further confirmed with immunostaining.

While both BCC and SCC tumors may show overlapping features of squamous differentiation by being positive for p63 and CK5/6,[19,20] positivity for both Ber-Ep4 and BCL-2[14,21] are most consistent with BCC. Strong expression of EMA (epithelial membrane antigen) and lack of staining for BCL-2 is more indicative of squamous cell carcinoma (SCC). In addition, TTF-1, napsin, and CK7 are consistent with tumors of pulmonary parenchymal origin. Another type of tumor that can often be misdiagnosed as mBCC is a primary neuroendocrine carcinoma of the lung[22] given the microscopic appearance of nested monotonous basaloid cells in otherwise normal lung parenchyma. However, these tumors are usually positive for both Chromogranin-A and Synaptophysin.

In our patient, the initial impression of primary lung cancer from the pulmonary nodule was re-evaluated given the clinical context. On evaluation of the nested basaloid cells in the lung tissue samples, it was found that strong positivity for both Ber-Ep4 and BCL-2 were consistent with markers from the sternal lesion and supported the diagnosis of metastatic BCC.[21,23] Of note, EMA is not expressed in BCC, but was seen focally in our RUL lung biopsy. Studies have demonstrated that although rare, EMA expression may be present in the squamatized areas of BCC,[24,25] while others have hypothesized that it is possible for basal cell carcinoma to undergo squamous cell differentiation into a basosquamous carcinoma, leading to an intermediate lesion with greater tendency to recur and metastasize.[26]

3.3 | Management

Currently, there are no established guidelines for the management of metastatic basal cell carcinoma, and treatment options depend on the location and extent of metastatic disease. Surgical resection remains the primary modality of treatment for lesions spread locally via direct extension.[27] Radiation and platinum-based chemotherapy drugs are often used for distant metastasis[28]; however, response rates have been poor.[12] More recently, the pathogenesis of BCCs and especially GBCCs has been found to be linked to a mutation of the hedgehog pathway genes on chromosome 9q22.3 encoding patched homologue 1 (PTCH1).[29,30] Microdeletions resulting in dysfunction of PTCH1 can impede the cell cycle resulting in upregulation of growth factors and thereby unregulated growth and differentiation. Treatment of metastatic BCC has since focused on hedgehog inhibitors, vismodegib, or sonidegib,[31,32] with response rates of 37%–49%, and extending survival by 34 months on average.[33] Despite the addition of hedgehog inhibitors, prognosis remains poor with a median survival of 10 months.[12] Further investigation has explored the usage of immunotherapies, and case reports have demonstrated an antitumor response with the usage of PD-1/PD-L1 blockage regardless of the expression of PD-L1 in the hedgehog inhibitor-resistant tumors.[34,35]

3.4 | Conclusion

This case of BCC on the anterior chest wall that developed several distant metastases in different aspects of the lungs highlights the importance of a careful interdisciplinary approach to the clinical evaluation along with histological and immunologic staining techniques in order to correctly diagnose and therefore offer treatment to an uncommon disease. Pulmonary nodules are frequently biopsied, and careful clinical input in the histopathological analysis in the age of ever-increasing immunohistochemical markers can be the difference between a correct diagnosis with prompt and pointed therapeutic intervention or a missed diagnosis and poor patient outcomes. Although mBCC is rare, it is important to include on the differential of any patient with a primary BCC tumor. Additionally, it's imperative to eliminate barriers for the access to care to ensure the best treatment strategy and overall prognosis.

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
SA, DS, JR, RD, and VJ wrote the initial draft of the manuscript; EA reviewed the manuscript; NBP and RA edited the draft and reshaped it into this manuscript; all authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONSENT
Written informed consent was obtained from the patient for publication of this report and any images related to the patient. A copy of the consent is available for review by the Editor-in-Chief of the journal.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES
1. Stella GM, Kolling S, Benvenuti S, Bortolotto C. Lung-seeking metastases. *Cancers*. 2019;11(7):1010. doi:10.3390/cancers11071010
2. Kim DP, Kus KJ, Ruiz E. Basal cell carcinoma review. *Hematol Oncol Clin North Am*. 2019;33(1):13-24. doi:10.1016/j.hoc.2018.09.004
3. Marzuka AG, Book SE. Basal cell carcinoma: pathogenesis, epidemiology, clinical features, diagnosis, histopathology, and management. *Yale J Biol Med*. 2015;88(2):167-179. Published 2015 Jun 1.
4. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005;353(21):2262-2269. doi:10.1056/NEJMra044151
5. Amin SH, Motamedi KK, Ochsner MC, Song TE, Hybarger CP. Mechanisms and efficacy of vismodegib in the treatment of basal cell carcinoma. *Discov Med*. 2013;16(89):229-232.
6. Goldberg LH. Basal cell carcinoma. *Lancet*. 1996;347(9002):663-667. doi:10.1016/s0140-6736(96)91208-8
7. Preston DS, Stern RS. Nonmelanoma cancers of the skin. *N Engl J Med*. 1992;327(23):1649-1662. doi:10.1056/NEJM199212033272307
8. Nehal KS, Bichakjian CK. Update on keratinocyte carcinomas. *N Engl J Med*. 2018;379(4):363-374. doi:10.1056/NEJMra1708701
9. Beadles CF. Rodent ulcer. *Trans Pathol Soc Lond*. 1894;45:176-181.
10. Bellahammou K, Lakhdissi A, Akkar O, et al. Metastatic giant basal cell carcinoma: a case report. *Pan African Med J*. 2016;24:1-4. doi:10.11604/pamj.2016.24.157.9233
11. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. *J Am Acad Dermatol*. 1984;10(6):1043-1060. doi:10.1016/s0190-9622(84)80334-5
12. Wysong A, Aasi SZ, Tang JY. Update on metastatic basal cell carcinoma: a summary of published cases from 1981 through 2011. *JAMA Dermatol*. 2013;149(5):615-616. doi:10.1001/jamadermatol.2013.3064
13. Seo SH, Shim WH, Shin DH, Kim YS, Sung HW. Pulmonary metastasis of Basal cell carcinoma. *Ann Dermatol*. 2011;23(2):213-216. doi:10.5021/ad.2011.23.2.213
14. Piva De Freitas P, Senna CG, Tabai M, Chone CT, Altemani A. Metastatic basal cell carcinoma: a rare manifestation of a common disease. *Case Rep Med*. 2017;2017:1-4. doi:10.1155/2017/8929745
15. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. *Mod Pathol*. 2006;19(S2):S127-S147. doi:10.1038/modpathol.3800512
16. Lackey PL, Sargent LA, Wong L, Brzezienski M, Kennedy JW. Giant basal cell carcinoma surgical management and reconstructive challenges. *Ann Plast Surg*. 2007;58(3):250-254. doi:10.1097/01.sap.0000250842.96272.37
17. Lo JS, Snow SN, Reizner GT, Mohs FE, Larson PO, Hruza GJ. Metastatic basal cell carcinoma: report of twelve cases with a review of the literature. *J Am Acad Dermatol*. 1991;24(5 Pt 1):715-719. doi:10.1016/0190-9622(91)70108-e
18. Lattes R, Kessler RW. Metastasizing basal-cell epithelioma of the skin; report of two cases. *Cancer*. 1951;4(4):866-878.
19. Bircan S, Candir O, Kapucoglu N, Baspinar S. The expression of p63 in basal cell carcinomas and association with

histological differentiation. *J Cutan Pathol*. 2006;33(4):293-298. doi:10.1111/j.0303-6987.2006.00436.x

20. Andruszkow JH, Oll M, Förster S, Knüchel R, Jäkel J. p40 in conjunction with CK20 and E-cadherin distinguishes primary adnexal neoplasms of the skin. *Appl Immunohistochem Mol Morphol*. 2016;24(6):414-421. doi:10.1097/PAI.0000000000000204
21. Saladi RN, Singh F, Wei H, Lebwohl MG, Phelps RG. Use of Ber-EP4 protein in recurrent metastatic basal cell carcinoma: a case report and review of the literature. *Int J Dermatol*. 2004;43(8):600-603. doi:10.1111/j.1365-4632.2004.02192.x
22. Weissferdt A, Kalhor N, Moran CA. Cutaneous basal cell carcinoma with distant metastasis to thorax and bone: a clinicopathological and immunohistochemical study of 15 cases. *Virchows Arch*. 2017;470(6):687-694. doi:10.1007/s00428-017-2121-3
23. Beer TW, Shepherd P, Theaker JM. Ber EP4 and epithelial membrane antigen aid distinction of basal cell, squamous cell and basosquamous carcinomas of the skin. *Histopathology*. 2000;37(3):218-223. doi:10.1046/j.1365-2559.2000.00999.x
24. Kazakov DV, Michal M, Kacerovska D, McKee PH. Lesions with predominant follicular differentiation. In: Kazakov DV, ed. *Cutaneous Adnexal Tumors* (1st edn). Lippincott Williams & Wilkins; 2012:173-328.
25. Heyderman E, Graham RM, Chapman DV, Richardson TC, McKee PH. Epithelial markers in primary skin cancer: an immunoperoxidase study of the distribution of epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) in 65 primary skin carcinomas. *Histopathology*. 1984;8(3):423-434.
26. Martin RCG, Edwards MJ, Cawte TG, Sewell CL, McMasters KM. Basosquamous carcinoma: analysis of prognostic factors influencing recurrence. *Cancer*. 2000;88(6):1365-1369. doi:10.1002/(SICI)1097-0142(20000315)88:6<1365:AID-CNCR13>3.0.CO;2-Y
27. Boswell JS, Flam MS, Tashjian DN, Tschang TP. Basal cell carcinoma metastatic to cervical lymph nodes and lungs. *Dermatol Online J*. 2006;12(6):9. Published 2006 Oct 31.
28. Aldhaban S, Marc S, Eshki M, et al. Giant basal cell carcinoma with regional lymph node and distant lung metastasis. *Eur J Dermatol*. 2011;21(6):972-975. doi:10.1684/ejd.2011.1519
29. Zoccali G, Pajand R, Papa P, Orsini G, Lomartire N, Giuliani M. Giant basal cell carcinoma of the skin: literature review and personal experience. *J Eur Acad Dermatol Venereol*. 2012;26(8):942-952. doi:10.1111/j.1468-3083.2011.04427.x
30. Ingham PW, McMahon AP. Hedgehog signaling in animal development: paradigms and principles. *Genes Dev*. 2001;15(23):3059-3087. doi:10.1101/gad.938601
31. Xie P, Lefrançois P. Efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2018;79(6):1089-1100.e17. doi:10.1016/j.jaad.2018.07.004
32. Jacobsen AA, Aldahan AS, Hughes OB, Shah VV, Strasswimmer J. Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: a systematic review and pooled analysis of interventional studies. *JAMA Dermatol*. 2016;152(7):816-824. doi:10.1001/jamadermatol.2016.0780
33. Sekulic A, Migden MR, Basset-Seguin N, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study [published correction appears in BMC Cancer. 2019 Apr 18;19(1):366]. *BMC Cancer*. 2017;17(1):332. doi:10.1186/s12885-017-3286-5
34. Falchook GS, Leidner R, Stankevich E, et al. Responses of metastatic basal cell and cutaneous squamous cell carcinomas to anti-PD1 monoclonal antibody REGN2810. *J Immunother Cancer*. 2016;4(1):70. doi:10.1186/s40425-016-0176-3
35. Basset-Séguin N, Hauschild A, Kunstfeld R, et al. Vismodegib in patients with advanced basal cell carcinoma: Primary analysis of STEVIE, an international, open-label trial. *Eur J Cancer*. 2017;86:334-348. doi:10.1016/j.ejca.2017.08.022

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