Pigmented Basal Cell Carcinoma of the Nipple: A Case Report and Review of the Literature

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Although basal cell carcinoma (BCC) of the nipple-areola complex (NAC) is rare, it is important for dermatologists to be aware of this potential malignancy, as it is thought to behave more aggressively than BCC arising in other anatomic locations and also can mimic a number of more serious conditions. A review of the literature failed to generate a consensus regarding staging or treatment of BCC of the NAC; current therapies range from simple excision of the lesion to mastectomy with sentinel lymph node biopsy. We report the case of a 23-year-old man who presented with a pigmented BCC of the nipple to highlight several important aspects of the diagnosis; we also review 49 cases of BCC of the NAC from the literature and give our recommendations for treatment approach.

Practice Points

- Basal cell carcinoma should be considered in the differential diagnosis for any patient presenting with a lesion on the nipple or areola.
- Basal cell carcinoma of the nipple or areola may have increased metastatic potential; therefore, discussing appropriate staging measures with the patient and emphasizing routine dermatologic surveillance are prudent.

The nipple-areola complex (NAC) is an unusual location for basal cell carcinoma (BCC). In 1979, Rahbari and Mehregan1 reviewed 2126 consecutive cases of BCC and reported only 2 involving the NAC. Compared to all other malignancies of the breast, BCC of the NAC is relatively rare, accounting for only 2 in 10,000 cases.2 A PubMed search of articles indexed for MEDLINE using the term basal cell carcinoma or BCC and nipple or areola or chest or breast was performed and pertinent results were cross-referenced to yield 42 reports describing 49 BCCs of the NAC in 48 patients (1 patient had bilateral tumors).1-42 The paucity of reported cases and a general lack of detail in reported cases have prohibited a consensus in the literature regarding the natural history of these lesions and their management. Recommendations for more aggressive staging and treatment of BCC of the NAC have been made in studies citing metastatic rates ranging from 9.1% to 11.5%, but no controlled trials have been performed.35,43 We report the case of a 23-year-old man who presented with a pigmented BCC of the nipple to highlight several important aspects of the diagnosis; we also review 49 cases of BCC of the NAC from the literature and give our recommendations for treatment approach.1-42

Case Report

A 23-year-old man presented with a pigmented lesion on the right nipple of uncertain duration. On
examination edema was noted on the inferior half of the right nipple and the normal architecture was distorted by a well-demarcated, pink, semicircular papule with a diameter of approximately 6 mm. Dermoscopy revealed multiple pin-point pigmented macules that appeared as streaks of uniform pigmentation on the nipple from the 2- to 10-o'clock positions (Figure). Excisional biopsy revealed features that were consistent with pigmented BCC. The biopsy site was subsequently reexcised with 0.2-cm margins. No residual BCC was found on exhaustion of the tissue block. Sentinel lymph node biopsy was not pursued. At 5-year follow-up, the patient was doing well with no evidence of recurrence.

Comment
A review of the literature revealed that BCC of the NAC has a predilection for males (65% [32/49]) over females (33% [16/49]). Although it has been hypothesized that direct sun exposure to the chest accounts for the greater incidence of BCC of the nipples in men, out review only yielded 2 cases attributed to sun exposure. A true association between classic BCC risk factors such as direct sun exposure or exposure to ionizing radiation, arsenic, immunosuppressive medications, trauma, or burns, and formation of BCC on the NAC has never been established. Alternatively, sporadic gene mutations and decreased immune surveillance secondary to UV light exposure at distant sites may play a role in the pathogenesis of BCC in locations that normally are sun protected, such as the nipples, axillae, and groin.

The increase in malignant potential of BCC of the NAC remains largely anecdotal, as the true incidence of BCC of the NAC remains unknown and there likely is a bias toward reporting more interesting or advanced cases in the literature (ie, a publication bias favoring metastatic cases). Of the cases of BCC in the NAC that we reviewed, there were 2 cases of histologically confirmed axillary lymph node metastasis, thus suggesting a histologically confirmed metastatic rate of 4% (2/49). In one case, lymph node metastasis was detected 4 years following nipple resection and adjuvant radiation therapy. The second case report described a tumor that was "most likely" a BCC of the nipple based on immunohistochemical markers (ie, $\alpha$-lactalbumin, mammary epithelial membrane antigen, and non-squamous epithelial keratin intermediate filament negative; squamous epithelial keratin intermediate filament positive). Two additional reports from 1927 and 1965 described clinically positive axillary lymph nodes but made no further comment regarding histologic evaluation. Another case found no histologic evidence of malignancy in clinically enlarged nodes from a patient with BCC of the NAC. It is unknown if the greater reported incidence of metastasis from this anatomic region is a result of a reporting bias in the literature or truly represents the increased potential for malignancy secondary to rich angiolymphatic drainage, invasion of lactiferous ducts by tumor cells, or some other mechanism.

Although wide local excision is the most common surgical intervention for BCC of the NAC, concern of increased metastatic potential or positive biopsy margins led to simple mastectomy in 10 of the cases we reviewed and sentinel lymph node biopsy without clinical lymphadenopathy in 3 cases. More recently, Mohs micrographic surgery (MMS) has been utilized for its tissue-sparing benefits in this cosmetically concerning area. Cosmesis has been preserved with a number of closure techniques following MMS to include island pedicle flaps and healing by secondary intention. Apart from the possible increase in metastatic potential, timely diagnosis of BCC of the NAC is of paramount importance, as these lesions can...
clinically mimic a host of serious conditions, including cutaneous extension of primary breast cancer (Table). Basal cell carcinoma of the NAC comprises only 0.02% of all breast malignancies. In the cases we reviewed, morphologies ranged from eczematous patches to ulcerated fungating tumors. Although rare, primary melanoma of the NAC has been reported in the literature and can mimic pigmented BCC. In a review of 14 cases, Papachristou et al described 4 patients with axillary metastasis from primary NAC melanoma who died within 3 years of surgery. Pigmented BCC can be differentiated from melanoma by routine histologic examination alone, whereas differentiating melanoma from other entities in the differential diagnosis (eg, pigmented Paget disease, pigmented epidermotropic breast metastases) may require immunohistochemistry markers such as S-100, HMB-45 (human melanoma black), MART-1 (melanoma-associated antigen recognized by T cells), microphthalmia transcription factor, cytokeratins, CEA (carcinoembryonic antigen), and EMA (epithelial membrane antigen).52

**Conclusion**

To our knowledge, our patient represents the fifth case of pigmented BCC of the nipple reported in the literature. In general, BCCs in this region represent a diagnostic dilemma because of their variable morphology and broad differential diagnosis. In the cases we reviewed, Paget disease was the leading diagnosis prior to histologic sampling. Although histologic examination is the gold standard for differentiating among cutaneous lesions in the NAC, a biopsy of every lesion is both impractical and unnecessary. Factors that may lower the threshold for biopsy include advanced age, persistent or unilateral lesions, ulceration, pigmentation, pathologic nipple discharge, and lesions commencing on the nipple that spread to the areola. However, the predictive value of these clinical factors has not been prospectively studied in BCC because of its low incidence in this anatomic region.

Preliminary imaging is warranted if there is clinical or histologic concern for underlying primary breast cancer. For localized BCC of the NAC without evidence of parenchymal changes, simple excision likely is adequate; however, MMS can improve cosmesis with its tissue-sparing effects. Although a publication bias almost certainly led to prior artificially inflated metastatic rates of 9.1% to 11.5%, we cannot make any firm recommendations for or against sentinel lymph node biopsy based on these retrospective data and believe staging should be evaluated on a case-by-case basis. Although there has been little to no follow-up reported in most published cases, we know from Shertz and Balogh that clinically evident lymph node metastasis can occur 4 years after initial excision with negative margins. For this reason, we agree with others who have encouraged the detailed reporting of BCCs of the NAC to better understand their natural history. Genetic analysis for UV signature mutations in BCCs arising in unusual locations may help elucidate their pathologic basis.

**REFERENCES**


**Differential Diagnosis of Basal Cell Carcinoma of the Nipple-Areola Complex**

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<th>Differential Diagnosis</th>
<th>Basal Cell Carcinoma of the Nipple-Areola Complex</th>
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<td>Benign nevi*</td>
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<td>Pigmented Paget disease*</td>
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*Pigmented lesions.


42. Williams C, Hussain W. A low-risk tumour, at a high-risk site? basal cell carcinoma of the nipple-areola complex


