

# Primary Cutaneous Apocrine Carcinoma Arising Within a Nevus Sebaceus

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## PRACTICE POINTS

- Nevus sebaceus (NS) in the centofacial region has been correlated with a higher risk for neurological abnormalities, including intellectual disability and seizures.
- Historically, basal cell carcinomas (BCCs) were considered a common occurrence arising from an NS, prompting prophylactic surgical excision of such lesions.
- More recently, it has been recognized that the most common tumor to arise from NS is trichoblastoma rather than BCC; in fact, BCC and other malignancies have been found to be relatively rare compared to their benign counterparts.
- In light of this discovery, observation of NS may be a more prudent course of treatment versus prophylactic surgical excision.

Nevus sebaceus (NS)(organoid nevus) is a benign follicular neoplasm that commonly occurs on the scalp, face, or neck. With time, it may give rise to benign or malignant tumors such as trichoblastoma, syringocystadenoma papilliferum, and basal cell carcinoma (BCC). Rarely, other types of neoplasms may develop. We present a 76-year-old woman with several trichoblastomas as well as a primary cutaneous apocrine carcinoma arising within a preexisting NS that was treated with frozen section excision.

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**N**evus sebaceus (NS) is a benign hair follicle neoplasm present in approximately 1.3% of the population, typically involving the scalp, neck, or face.<sup>1</sup> These lesions usually are present at birth or identified

soon after, during the first year. They present as a yellowish hairless patch or plaque but can develop a more papillomatous appearance, especially after puberty. Historically, the concern with NS was its tendency to transform into basal cell carcinoma (BCC), which prompted surgical excision of the lesion during childhood. This theory has been discounted more recently, as further research has suggested that what was once thought to be BCC may have been confused with the similarly appearing trichoblastoma; however, malignant transformation of NS does still occur, with BCC still being the most common.<sup>2</sup> We present the case of a long-standing NS with rare transformation to apocrine carcinoma.

## Case Report

A 76-year-old woman presented with several new lesions within a previously diagnosed NS. She reported having the large plaque for as long as she could recall but reported that several new growths developed within the plaque over the last 2 months, slowly increasing in size. She reported a prior biopsy within the growth several years prior, which she described as an irritated seborrheic keratosis.

Physical examination demonstrated 4 distinct lesions within the flesh-colored, verrucous plaque located on the left side of the temporal scalp (Figure 1). The first lesion was a 2.5-cm pearly, pink, exophytic tumor (labeled as A in Figure 1). The next 2 lesions were brown, pedunculated, verrucous papules (labeled as B and C in Figure 1). The last lesion was a purple papule (labeled as D in Figure 1). Four shave biopsies were performed for histologic analysis of the lesions. Lesions B, C, and D were consistent with trichoblastomas, as pathology showed basaloid epithelial tumors that displayed primitive follicular structures, areas of stromal induction, and some pigmentation. Lesion A, originally thought to be suspicious for a BCC, was

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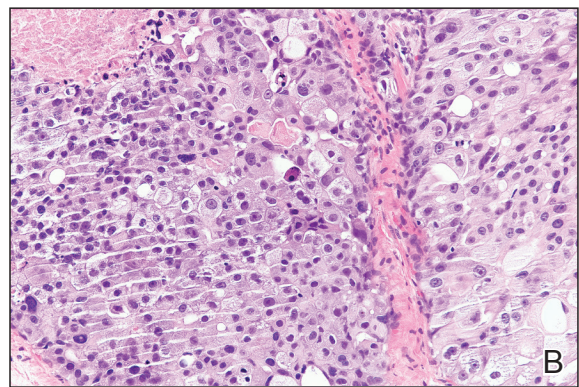
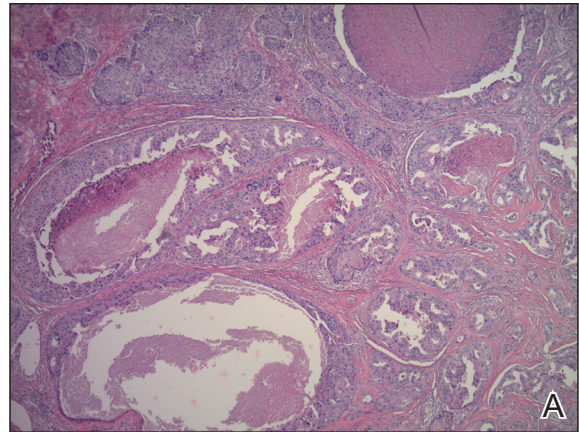
**FIGURE 1.** Verrucous plaque and 4 distinct neoplasms (labeled A–D) on the left side of the temporal scalp.

determined to be a primary cutaneous apocrine adenocarcinoma upon pathologic review. The pathology showed a dermal tumor displaying solid and tubular areas with decapitation secretion. Nuclear pleomorphism and mitoses were present (Figure 2), and staining for carcinoembryonic antigen was positive (Figure 3). Immunoreactivity with epithelial membrane antigen and cytokeratin 7 was noted as well as focal positivity for mammaglobin. Primary apocrine carcinoma was favored over metastatic carcinoma due to the location of the lesion within an NS along with a negative history of internal malignancy. Dermatopathology recommended complete removal of all lesions within the NS.

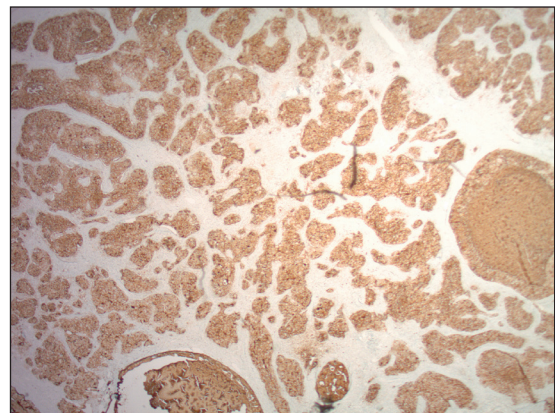
Upon discussing biopsy results and recommendations with our patient, she agreed to undergo excision with intraoperative pathology by a plastic surgeon within our practice to ensure clear margins. The surgical defect following excision was sizeable and closed utilizing a rhomboid flap, full-thickness skin graft, and a split-thickness skin graft. At surgical follow-up, she was doing well and there have been no signs of local recurrence for 10 months since excision.

### Comment

**Presentation**—Nevus sebaceus is the most common adnexal tumor and is classified as a benign congenital hair follicle tumor that is located most commonly on the scalp but also occurs on the face and neck.<sup>1</sup> The lesions usually are present at birth but also can develop during the first year of life.<sup>2</sup> Diagnosis may be later, during adolescence, when patients seek medical attention during the lesion's rapid growth phase.<sup>1</sup> Nevus sebaceus also is known as an organoid nevus because it may contain all components of the skin. It was originally identified by Jadassohn in 1895.<sup>3</sup> It presents as a yellowish, smooth, hairless patch or plaque in prepubertal patients. During adolescence, the lesion typically becomes more yellowish, as well as papillomatous, scaly, or warty. The reported incidence of NS is 0.05% to 1% in dermatology patients.<sup>2</sup>



**FIGURE 2.** Apocrine carcinoma histopathology demonstrating solid and tubular areas with decapitation secretion (A)(H&E). On high power, marked nuclear pleomorphism and increased mitotic activity were observed (B)(H&E).



**FIGURE 3.** Apocrine carcinoma demonstrating carcinoembryonic antigen staining positivity.

**Differential**—Nevus sebaceus also is a component of several syndromes that should be kept in mind, including Schimmelpenning–Feuerstein–Mims syndrome, which presents with neurologic, skeletal, genitourinary, cardiovascular, and ophthalmic disorders, in addition to cutaneous features. Others include phacomatosis

pigmentokeratotic, didymosis aplasticosebacea, SCALP syndrome (sebaceous nevus, central nervous system malformations, aplasia cutis congenita, limbal dermoid, and pigmented nevus), and more.<sup>4,5</sup>

**Etiology**—The etiology of NS has not been completely determined. One study that evaluated 44 NS tissue samples suggested the presence of human papillomavirus (HPV) in NS formation, finding that 82% of NS lesions studied contained HPV DNA. From these results, Carlson et al<sup>6</sup> suggested a possible maternal transmission of HPV and infection of ectodermal cells as a potential cause of NS; however, this hypothesis was soon challenged by a study that showed a complete absence of HPV in 16 samples via histological evaluation and polymerase chain reaction for a broad range of HPV types.<sup>7</sup> There were investigations into a patched (PTCH) deletion as the cause of NS and thus explained the historically high rate of secondary BCC.<sup>8</sup> Further studies showed no mutations at the PTCH locus in trichoblastomas or other tumors arising from NS.<sup>9,10</sup>

More recent studies have recognized *HRAS* and *KRAS* mutations as a causative factor in NS.<sup>11</sup> Nevus sebaceous belongs to a group of syndromes resulting from lethal mutations that survive via mosaicism. Nevus sebaceous is caused by postzygotic *HRAS* or *KRAS* mutations and is known as a mosaic RASopathy.<sup>12</sup> In fact, there is growing evidence to suggest that other nevoid proliferations including keratinocytic epidermal nevi and melanocytic nevi also fall into the spectrum of mosaic RASopathies.<sup>13</sup>

**Staging**—There are 3 clinical stages of NS, originally described by Mehregan and Pinkus.<sup>14</sup> In stage I (historically known as the infantile stage), the lesion presents as a yellow to pink, smooth, hairless patch. Histologic features include immature hair follicles and hypoplastic sebaceous glands. In stage II (also known as the puberty stage), the lesion becomes more pronounced. Firmer plaques can develop with hyperkeratosis. Hormonal changes cause sebaceous glands to develop, accompanied by epidermal hyperplasia and maturation of apocrine glands. Stage III (the tumoral stage) is a period that various neoplasms have the highest likelihood of occurring. Nevus sebaceous in an adolescent or adult demonstrates mature adnexal structures and greater epidermal hyperplasia.<sup>2,4,15</sup>

**Malignancy**—By virtue of these stages of NS development, malignant transformation is expected most often during stage III. However, cases have been reported of malignant tumor development in NS in children before puberty. Two case reports described a 7-year-old boy and a 10-year-old boy diagnosed with a BCC arising from an NS.<sup>16,17</sup> However, secondary BCC formation before 16 years of age is rare. Basal cell carcinoma arising from an NS has been commonly reported and is the most common malignant neoplasm in NS (1.1%).<sup>2,3</sup> However, the most common neoplasm overall is trichoblastoma (7.4%). The second most common tumor was syringocystadenoma papilliferum, occurring in approximately 5.2% of NS cases. The neoplasm rate in NS was found to be proportional to the patient age.<sup>2,18</sup> Multiple studies

have shown the overall rate of secondary neoplasms in NS to be 13% to 21.4%, with malignant tumors composing 0.8% to 2.5%.<sup>2,15,19</sup> Other neoplasms that have been reported include keratoacanthoma, trichilemmoma, sebaceoma, nevocellular nevus, squamous cell carcinoma, adnexal carcinoma, apocrine adenocarcinoma, and malignant melanoma.<sup>19-21</sup>

It is argued that the reported rate of BCC formation is overestimated, as prior studies incorrectly labeled trichoblastomas as BCCs. In fact, the largest studies of NS from the 1990s revealed lower rates of malignant secondary tumors than previously determined.<sup>4</sup>

The identification of apocrine adenocarcinoma tumors arising from NS is exceedingly rare. A study performed by Cribier et al<sup>19</sup> in 2000 retrospectively analyzed 596 cases of excised NS from 1932 to 1998. No apocrine carcinomas were reported in this study.<sup>19</sup> Approximately 12 cases have been previously reported throughout the literature.<sup>20-26</sup> Apocrine carcinomas occur most frequently in apocrine-rich areas such as the axillae, external ears, eyelids, and anogenital area. However, in the cases with apocrine carcinomas that developed from NS, the carcinomas have been located almost exclusively on the scalp.<sup>23</sup>

**Histopathology**—Histopathologic examination reveals considerable variation in morphology, and an underlying pattern has been difficult to recognize. Unfortunately, some authors have concluded that the diagnosis of apocrine carcinoma is relatively subjective.<sup>26</sup> Robson et al<sup>26</sup> identified 3 general architectural patterns: tubular, tubulopapillary, and solid. Tubular structures consisted of glands and ducts lined by a single or multilayered epithelium. Tubulopapillary architecture was characterized by epithelium forming papillary folds without a fibrovascular core. The solid morphology showed sheets of cells with limited ductal or tubular formation.<sup>26</sup> The most specific criteria of these apocrine carcinomas are identification of decapitation secretion, periodic acid-Schiff-positive diastase-resistant material present in the cells or lumen, and positive immunostaining for gross cystic disease fluid protein-15.<sup>27</sup>

Robson et al<sup>26</sup> reported estrogen receptor positivity and androgen receptor positivity in 62% and 64% of 24 primary apocrine carcinoma cases, respectively. However, whether these markers are as common in NS-related apocrine carcinomas has yet to be noted in the literature. One study reports a case of apocrine carcinoma from NS with positive staining for human epidermal growth factor-2, a cell membrane receptor tyrosine kinase commonly investigated in breast cancers and extramammary Paget disease.<sup>22</sup>

These apocrine carcinomas do have the potential for lymphatic metastasis, as seen with multiple studies. Domingo and Helwig<sup>21</sup> identified regional lymph node metastasis in 2 of its 4 apocrine carcinoma patients. Robson et al<sup>26</sup> reported lymphovascular invasion in 4 cases and perineural invasion in 2 of 24 patients studied. However, even in the context of recurrence and regional metastasis, the prognosis was good and seldom fatal.<sup>26</sup>

**Treatment**—The most effective treatment of NS is excision of dermal and epidermal components. Excision should be completed with a minimum of 2- to 3-mm margins and full thickness down to the underlying supporting fat.<sup>28</sup> Historically, the practice of prophylactic excision of NS was supported by the potential for malignant transformation; however, early excision of NS may be less reasonable in light of these more recent studies showing lower incidence of BCC (0.8%), replaced by benign trichoblastomas.<sup>19</sup> In the case of apocrine carcinoma development, excision is undoubtedly recommended, with unclear recommendations regarding further evaluation for metastasis.

Excision also may be favored for cosmetic purposes, given the visible regions where NS tends to develop. Chepla and Gosain<sup>29</sup> argued that surgical intervention should be based on other factors such as location on the scalp, alopecia, and other issues affecting appearance and monitoring rather than incidence of malignant transformation. Close monitoring and biopsy of suspicious areas is a more conservative option.

Other therapies include CO<sub>2</sub> laser, as demonstrated by Kiedrowicz et al,<sup>30</sup> on linear NS in a patient with Schimmelpenning-Feuerstein-Mims syndrome.<sup>31</sup> However, this approach is palliative and not effective in removing the entire lesion. Electrodesiccation and curettage and dermabrasion also are not good options for the same reason.<sup>4</sup>

**Occurrence in Children**—Nevus sebaceus in children, accompanied by other findings suggestive of epidermal nevus syndromes, should prompt further investigation. Schimmelpenning-Feuerstein-Mims syndrome includes major neurological abnormalities including hemimegalencephaly and seizures.<sup>32</sup>

## Conclusion

Apocrine carcinomas are malignant neoplasms that may rarely arise within an NS. Their clinical identification is difficult and requires histopathologic evaluation. Upon recognition, prompt excision with tumor-free margins is recommended. As a rare entity, little data is available regarding its metastatic potential or overall survival rates. Further investigation is clearly necessary as new cases arise.

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