Slowly Enlarging Nodule on the Neck

Stacey Pun, MD; Wonwoo Shon, DO

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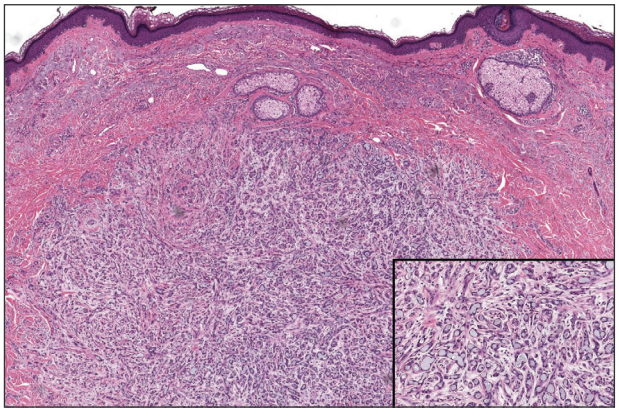

H&E, original magnification ×40 (inset: H&E, original magnification ×200).

A 74-year-old man presented with an asymptomatic nodule on the left neck measuring approximately 2 cm. An excisional biopsy was obtained for histopathologic evaluation.

THE BEST **DIAGNOSIS IS:**

a. cribriform tumor (previously carcinoma)
b. metastatic adenocarcinoma
c. microsecretory adenocarcinoma
d. secretory carcinoma
e. tubular adenoma

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From the Dermatopathology Division, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, Los Angeles, California.
The authors report no conflict of interest.
Correspondence: Wonwoo Shon, DO, Department of Pathology and Laboratory Medicine, Cedars-Sinai Medical Center, 8700 Beverly Blvd, Ste 8612, Los Angeles, CA 90048 (wonwoo.shon@cshs.org).
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THE **DIAGNOSIS:** Microsecretory Adenocarcinoma

Microscopically, the tumor was relatively well circumscribed but had irregular borders. It consisted of microcysts and tubules lined by flattened to plump eosinophilic cells with mildly enlarged nuclei and intraluminal basophilic secretions. Peripheral lymphocytic aggregates also were seen in the mid and deep reticular dermis. Tumor necrosis, lymphovascular invasion, and notable mitotic activity were absent. Immunohistochemistry was diffusely positive for cytokeratin (CK) 7 and CK5/6. Occasional tumor cells showed variable expression of alpha smooth muscle actin, S-100 protein, and p40 and p63 antibodies. Immunohistochemistry was negative for CK20; GATA binding protein 3; MYB proto-oncogene, transcription factor; and insulinoma-associated protein 1. A dual-color, break-apart fluorescence in situ hybridization probe identified a rearrangement of the *SS18* (SYT) gene locus on chromosome 18. The nodule was excised with clear surgical margins, and the patient had no evidence of recurrent disease or metastasis at 2-year follow-up.

In recent years, there has been a growing recognition of the pivotal role played by gene fusions in driving oncogenesis, encompassing a diverse range of benign and malignant cutaneous neoplasms. These investigations have shed light on previously unknown mechanisms and pathways contributing to the pathogenesis of these neoplastic conditions, offering invaluable insights into their underlying biology. As a result, our ability to classify and diagnose these cutaneous tumors has improved. A notable example of how our current understanding has evolved is the discovery of the new cutaneous adnexal tumor microsecretory adenocarcinoma (MSA). Initially described by Bishop et al[1] in 2019 as predominantly occurring in the intraoral minor salivary glands, rare instances of primary cutaneous MSA involving the head and neck regions also have been reported.[2] Microsecretory adenocarcinoma represents an important addition to the group of fusion-driven tumors with both salivary gland and cutaneous adnexal analogues, characterized by a *MEF2C::SS18* gene fusion. This entity is now recognized as a group of cutaneous adnexal tumors with distinct gene fusions, including both relatively recently discovered entities (eg, secretory carcinoma with *NTRK* fusions) and previously known entities with newly identified gene fusions (eg, poroid neoplasms with *NUTM1, YAP1,* or *WWTR1* fusions; hidradenomatous neoplasms with *CRTC1::MAML2* fusions; and adenoid cystic carcinoma with *MYB, MYBL1,* and/or *NFIB* rearrangements).[3]

Microsecretory adenocarcinoma exhibits a high degree of morphologic consistency, characterized by a microcystic-predominant growth pattern, uniform intercalated ductlike tumor cells with attenuated eosinophilic to clear cytoplasm, monotonous oval hyperchromatic nuclei with indistinct nucleoli, abundant basophilic luminal secretions, and a variably cellular fibromyxoid stroma. It also shows rounded borders with subtle infiltrative growth. Occasionally, pseudoepitheliomatous hyperplasia, tumor-associated lymphoid proliferation, or metaplastic bone formation may accompany MSA. Perineural invasion is rare, necrosis is absent, and mitotic rates generally are low, contributing to its distinctive histopathologic features that aid in accurate diagnosis and differentiation from other entities. Immunohistochemistry reveals diffuse positivity for CK7 and patchy to diffuse expression of S-100 in tumor cells as well as variable expression of p40 and p63. Highly specific *SS18* gene translocations at chromosome 18q are useful for diagnosing MSA when found alongside its characteristic appearance, and *SS18* break-apart fluorescence in situ hybridization can serve reliably as an accurate diagnostic method (Figure 1).[4] Our case illustrates how molecular analysis assists in distinguishing MSA from other cutaneous adnexal tumors, exemplifying the power of our evolving understanding in refining diagnostic accuracy and guiding targeted therapies in clinical practice.

The differential diagnosis of MSA includes tubular adenoma, secretory carcinoma, cribriform tumor (previously carcinoma), and metastatic adenocarcinoma. Tubular adenoma is a rare benign neoplasm that predominantly affects females and can manifest at any age in adulthood. It typically manifests as a slow-growing, occasionally pedunculated nodule, often measuring less than 2 cm. Although it most commonly manifests on the scalp, tubular adenoma also may arise in diverse sites such as the face, axillae, lower extremities, or genitalia.

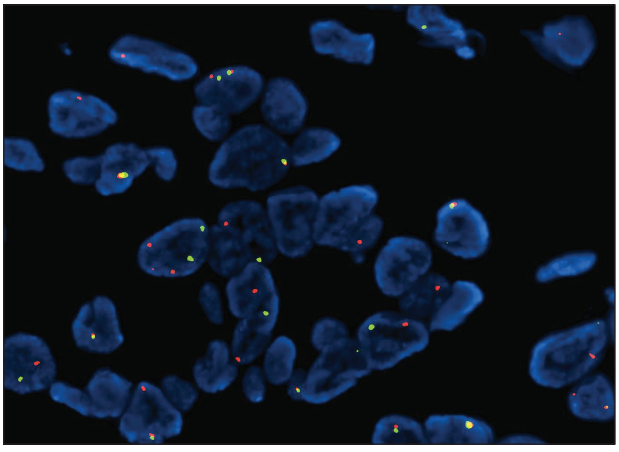

FIGURE 1. *SS18* break-apart fluorescence in situ hybridization (red and green signals split apart) can serve as an accurate diagnostic method for microsecretory adenocarcinoma.

Notably, scalp lesions often are associated with nevus sebaceus of Jadassohn or syringocystadenoma papilliferum. Microscopically, tubular adenoma is well circumscribed within the dermis and may extend into the subcutis in some cases. Its distinctive appearance consists of variably sized tubules lined by a double or multilayered cuboidal to columnar epithelium, frequently displaying apocrine decapitation secretion (Figure 2). Cystic changes and intraluminal papillae devoid of true fibrovascular cores frequently are observed. Immunohistochemically, luminal epithelial cells express epithelial membrane antigen and carcinoembryonic antigen, while the myoepithelial layer expresses smooth muscle markers, p40, and S-100 protein. *BRAF V600E* mutation can be detected using immunohistochemistry, with excellent sensitivity and specificity using the anti-*BRAF V600E* antibody (clone VE1).[5] Distinguishing tubular adenoma from MSA is achievable by observing its larger, more variable tubules, along with the consistent presence of a peripheral myoepithelial layer.

Secretory carcinoma is recognized as a low-grade gene fusion–driven carcinoma that primarily arises in salivary glands (both major and minor), with occasional occurrences in the breast and extremely rare instances in other locations such as the skin, thyroid gland, and lung.[6] Although the axilla is the most common cutaneous site, diverse locations such as the neck, eyelids, extremities, and nipples also have been documented. Secretory carcinoma affects individuals across a wide age range (13–71 years).[6] The hallmark tumors exhibit densely packed, sievelike microcystic glands and tubular spaces filled with abundant eosinophilic intraluminal secretions (Figure 3). Additionally, morphologic variants, such as predominantly papillary, papillary-cystic, macrocystic, solid, partially mucinous, and mixed-pattern neoplasms, have been described. Secretory carcinoma shares certain features with MSA; however, it is distinguished by the presence of pronounced eosinophilic secretions, plump and vacuolated cytoplasm, and a less conspicuous fibromyxoid stroma. Immunohistochemistry reveals tumor cells that are positive for CK7, SOX-10, S-100, mammaglobin, MUC4, and variably GATA-3. Genetically, secretory carcinoma exhibits distinct characteristics, commonly showing the *ETV6::NTRK3* fusion, detectable through molecular techniques or pan-TRK immunohistochemistry, while *RET* fusions and other rare variants are less frequent.[7]

In 1998, Requena et al[8] introduced the concept of primary cutaneous cribriform carcinoma. Despite initially being classified as a carcinoma, the malignant potential of this tumor remains uncertain. Consequently, the term *cribriform tumor* now has become the preferred terminology for denoting this rare entity.[9] Primary cutaneous cribriform tumors are observed more commonly in women and typically affect individuals aged 20 to 55 years (mean, 44 years). Predominant locations include the upper and lower extremities, especially the thighs, knees, and legs, with additional cases occurring on the head and trunk. Microscopically, cribriform tumor is characterized by a partially circumscribed, unencapsulated dermal nodule composed of round or oval nuclei displaying hyperchromatism and mild pleomorphism. The defining aspect of its morphology revolves around interspersed small round cavities that give rise to the hallmark cribriform pattern (Figure 4). Although MSA occasionally may exhibit a cribriform architectural pattern, it typically lacks the distinctive feature of thin, threadlike, intraluminal bridging strands observed in cribriform tumors. Similarly, luminal cells within the cribriform tumor express CK7 and exhibit variable S-100 expression. It is recognized as an indolent neoplasm with uncertain malignant potential.

The histopathologic features of metastatic carcinomas can overlap with those of primary cutaneous tumors, particularly adnexal neoplasms.[10] However, several key

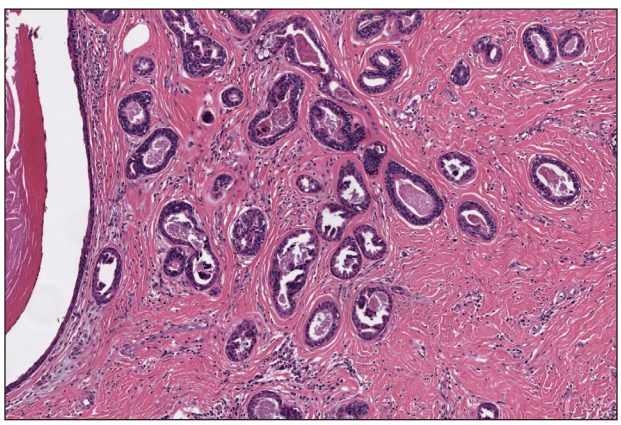

FIGURE 2. Tubular adenoma has a lobular architecture surrounded by fibrous stroma; the lobules contain irregular tubular structures with a multilayered epithelial lining. Some tubules exhibit decapitation secretion, while others display papillary cellular extensions without stroma that project into lumina filled with cellular debris and eosinophilic granular material (H&E, original magnification ×100).

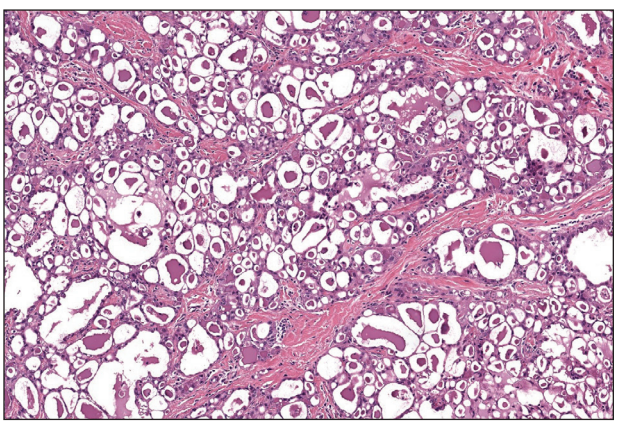

FIGURE 3. The characteristic tumors of secretory carcinoma display tightly clustered, sievelike microcystic glands and tubular cavities enriched with brightly eosinophilic intraluminal secretions (H&E, original magnification ×100).

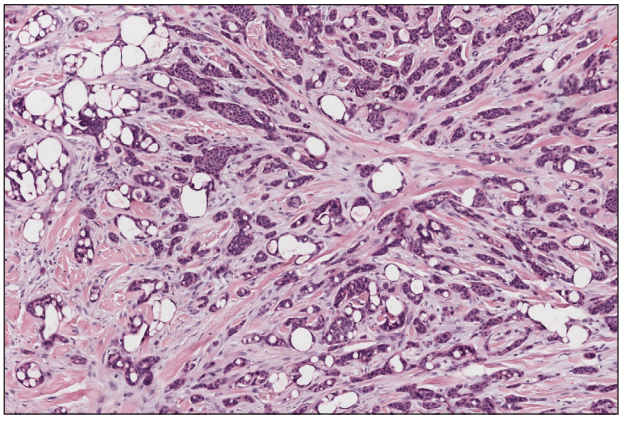

FIGURE 4. Cribriform tumor features interconnected epithelial cell nests with round or oval hyperchromatic nuclei, inconspicuous nucleoli, granular chromatin, and minimal eosinophilic cytoplasm, accentuated by threadlike intraluminal strands (H&E, original magnification ×100).

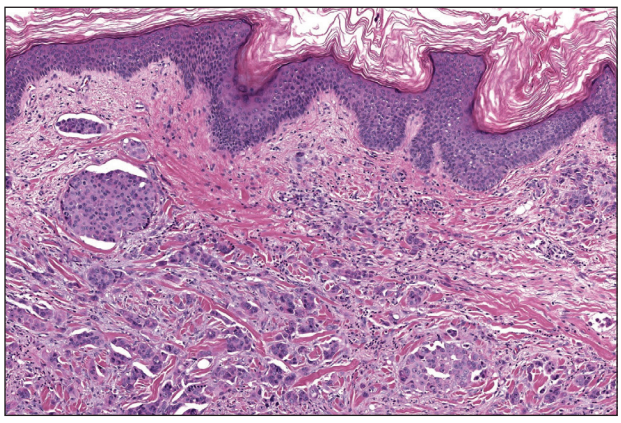

FIGURE 5. Metastatic carcinoma—in this case, metastatic mammary adenocarcinoma—involves the dermis, characterized by diffuse infiltration and dissection of collagen bundles, along with extensive lymphovascular invasion (H&E, original magnification ×100).

features can aid in the differentiation of cutaneous metastases, including a dermal-based growth pattern with or without subcutaneous involvement, the presence of multiple lesions, and the occurrence of lymphovascular invasion (Figure 5). Conversely, features that suggest a primary cutaneous adnexal neoplasm include the presence of superimposed in situ disease, carcinoma developing within a benign adnexal neoplasm, and notable stromal and/or vascular hyalinization within benign-appearing areas. In some cases, it can be difficult to determine the primary site of origin of a metastatic carcinoma to the skin based on morphologic features alone. In these cases, immunohistochemistry can be helpful. The most cost-effective and time-efficient approach to accurate diagnosis is to obtain a comprehensive clinical history. If there is a known history of cancer, a small panel of organ-specific immunohistochemical studies can be performed to confirm the diagnosis. If there is no known history, an algorithmic approach can be used to identify the primary site of origin. In all circumstances, it cannot be stressed enough that acquiring a thorough clinical history before conducting any diagnostic examinations is paramount.

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