Sweat gland carcinoma with neuroendocrine differentiation of the scalp with elevated serum chromogranin A levels

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INTRODUCTION

Sweat gland carcinoma with neuroendocrine differentiation (SCAND), previously called low-grade neuroendocrine carcinoma of the skin, is a primary cutaneous neoplasm with neuroendocrine differentiation typically found on the trunk.[1] Due to their rarity and ability to mimic other neoplasms, not much is known about this primary neuroendocrine carcinoma. Here, we present a case of a primary cutaneous SCAND on the scalp of a 76-year-old woman with negative full-body imaging ruling out other sources of primary malignancy with particular attention to elevated serum chromogranin A (CgA) levels.

Abbreviations used:

CD-56:	cluster of differentiation
CK:	cytokeratin
CT:	computed tomography
EGD:	esophagogastroduodenoscopy
EpCAM:	epithelial cell adhesion molecule
ER:	estrogen receptor
GATA3:	GATA binding protein 3
MOC-31:	monoclonal antibody 31
MRI:	magnetic resonance imaging
MYB:	myoblastosis
PAN:	pan-cytokeratin
PET:	positron emission tomography
PR:	progesterone receptor
SOX-10:	Sry-related HMg-Box gene 10
US:	ultrasound
w/wo:	with and without

CASE REPORT

A 76-year-old woman initially presented in October of 2021 with a firm nodule on the central frontal scalp. On physical examination, the lesion was a 0.4 cm flesh-colored firm nodule suspected to be a cyst. At both the 6-month and 12-month follow-ups, her physical exam showed a 0.7 cm mobile nodule consistent with a pilar cyst and the patient declined biopsy or removal. Five months later in April 2023, the patient presented for evaluation of the nodule which had grown to be a 1.2 cm erythematous plaque (Fig 1). At this time, an excisional biopsy of the plaque was taken, and initial pathology suggested a sweat gland carcinoma with neuroendocrine differentiation. Staining was positive for ER, PR, GATA3, MYB, synaptophysin, chromogranin, EpCAM (weakly positive), PAN keratin (strongly positive), and MOC-31 (weakly positive), and negative for SOX-10, P40, CK 5/6, and CD-56.

On April 27th, 2023, the 1.2 cm plaque was excised and histomorphologically, the tissue showed solid tumor nests and cords infiltrating the dermis and superficial subcutis with no involvement of the epidermis (Fig 2). The tumor cells were fairly uniform and round with ample pale amphophilic cytoplasm, oval nuclei, and smooth chromatin. Mild nuclear pleomorphism and sparse mitoses were also seen. The differential diagnosis based on these features was SCAND (also known as low-grade

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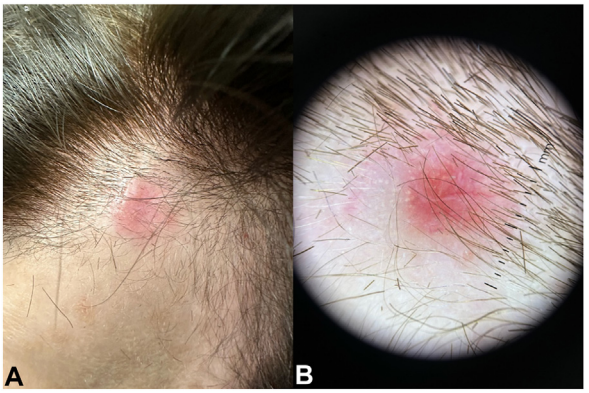

Fig 1. A, 1.2 cm erythematous scaling plaque. **B,** Dermoscopy of plaque showing *pink* and *white* structureless areas with polymorphous vessels.

neuroendocrine carcinoma of the skin) and metastatic papillary carcinoma of the breast. To rule out other tumor origins, a thorough work-up was conducted and comprised of a: head magnetic resonance imaging w/wo contrast, positron emission tomography of skull apex through mid-thigh, US and mammogram of the breasts, esophagogastroduodenoscopy, head computed tomography w/wo contrast, abdominal and thoracic computed tomography w/wo contrast with biopsy of a retroperitoneal mass showing adipose and fibrovascular tissue with no evidence of malignant pathology, and a colonoscopy with a lesion biopsy showing a tubular adenoma. Altogether this work-up revealed no malignant or visceral primary lesions, aiding in the final diagnosis of a SCAND. Lab workups taken on May 4th, 2023, showed normal urinary 5-HIAA of 3.6 mg/24h, normal serum serotonin of 142 ng/mL, and elevated serum chromogranin A of 2793 ng/mL, with normal levels less than 311 ng/mL. The patient was started on sandostatin in June 2023 for constitutional symptoms of dizziness, flushing, and loose stools, the latter symptom starting around the time of surgery and the former 2 symptoms starting roughly 18 months prior to the surgery. Follow-up serum CgA in September of 2023 was 131 ng/mL and subsequent levels stayed within the reference range. The patient is still taking sandostatin with resolvent of her symptoms and is being followed by medical oncology.

DISCUSSION

In this case report, we present a primary cutaneous SCAND with elevated serum chromogranin A levels. Being rare, little is known about the origins of a SCAND making it difficult to distinguish from other dermatologic conditions. They often present as flesh colored nodules and are commonly mistaken for

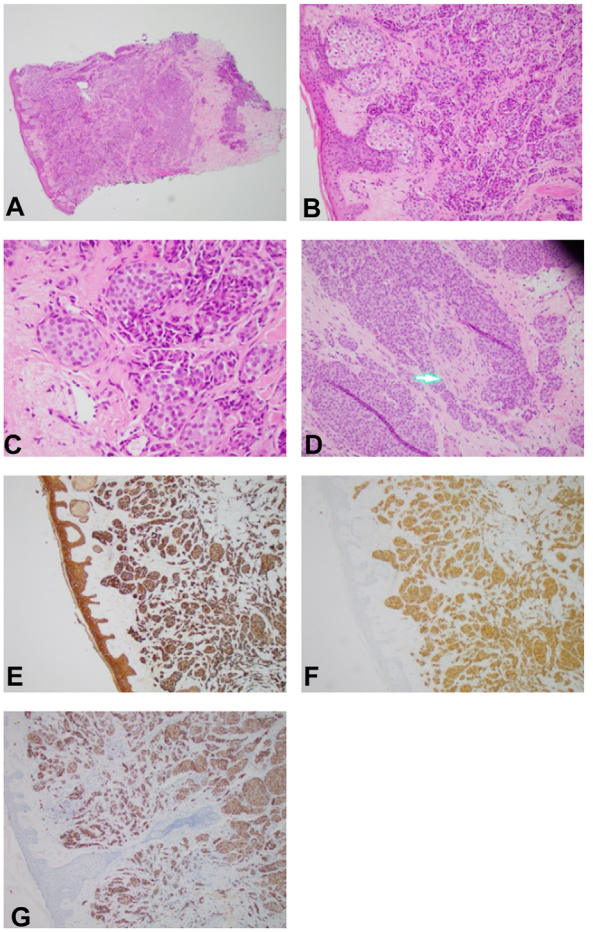

Fig 2. A, Punch biopsy histology showing tumor cells within the dermis and superficial subcutis (original magnification ×40). **B,** Tumor cells in the dermis as cords and nests. The epidermis in uninvolved (original magnification ×100). **C,** Tumor cells are fairly uniform and round with ample pale to eosinophilic cytoplasm, oval nuclei, mild pleomorphism, and sparse mitosis (original magnification ×200). **D,** Tumor cells with perineural/intraneural invasion (original magnification ×100). **E,** Tumor cells positive staining with pan-cytokeratin (original magnification ×100). **F,** Tumor cells positive staining with synaptophysin (original magnification ×100). **G,** Tumor cells positive staining with chromogranin (original magnification ×100).

pilar and epidermal inclusion cysts.[2,3] Differential diagnosis upon biopsy includes pilar cysts, sebaceous neoplasms, Merkle cell carcinomas, and neuroendocrine metastases.[4] While it is more common for a cutaneous neuroendocrine tumor to be a visceral metastasis rather than a primary cutaneous lesion, the patient's thorough systemic workup by medical oncology has yet not revealed a visceral primary lesion.

Previous case reports have emphasized the immunohistologic staining of SCAND which has been shown to express classic neuroendocrine

tumor markers.[3] Our case is unique in which we describe an elevated serum chromogranin A level over 10 times above normal and following excision of the tumor, decreased to normal range over the next 4 months.

CgA is a protein found in granules of neuroendocrine tissue and is widely used as an immunohistochemical marker and serum marker for neuroendocrine carcinomas.[5] Despite its controversial role as a biomarker for neuroendocrine tumors, CgA has important clinical applications in nonfunctioning neuroendocrine tumors as there are no specific hormone markers secreted by the tumors.[5] A study by Nobels et al found that elevated CgA levels were frequently observed in patients with peripheral neuroendocrine tumors without detectable hormonal secretion, similar to our patient. They also mention that CgA levels have a better correlation for the well-being of patients than 5-HIAA in gastroenteropancreatic neuroendocrine carcinomas.[6]

Common causes of falsely elevated CgA levels include the use of proton-pump inhibitors, atrophic gastritis, and reduced renal function.[7] While the patient was taking lansoprazole 15 mg as needed and proton-pump inhibitors can cause roughly a 2.5-fold elevation in serum CgA, it is unlikely that this medication falsely elevated CgA levels to nearly a 10-fold increase from normal range.

Lastly, the carcinoid symptoms in our patient were well controlled with sandostatin. While CgA and serotonin levels are known to be independently affected by sandostatin, with serotonin levels being reduced by more than 70% and CgA being less affected, the drastic decrease in CgA from 2793 ng/mL to 131 ng/mL is better attributed to the complete excision of the carcinoma rather than sandostatin.[8]

In conclusion, we present a rare case of primary SCAND found on the scalp with elevated serum chromogranin A levels. Our case is unique in both the location of the primary lesion and the elevated serum CgA values following excision of the carcinoma which shows levels decreasing to normal range 4 months postexcision. To determine if there is an association between serum CgA levels and SCAND, we propose tracking serum CgA levels in suspected and confirmed SCANDs as this could potentially be a useful marker and adjunct for predicting primary SCAND response to therapy and recurrence.

Conflicts of interest

None disclosed.

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