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Scalp metastasis as initial presentation of neuroendocrine carcinoma

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Abstract

Neuroendocrine carcinomas are a rare, heterogenous group of malignancies that arise from neuroendocrine cells throughout the body. Cutaneous metastasis of neuroendocrine carcinoma is uncommon and they can be easily misdiagnosed as benign epidermal cysts or Merkel cell carcinoma. Collectively, histopathology, immunochemical profile, biochemical markers, and nuclear imaging can guide the diagnosis of neuroendocrine metastasis and localization of primary tumors.

Keywords: cutaneous metastasis, neuroendocrine carcinoma, somatostatin receptor imaging

Introduction

Neuroendocrine carcinomas (NECs) are a heterogeneous group of malignancies that arise from neuroendocrine cells throughout the body, most commonly in the intestines, pancreas, and lungs [1]. Approximately 30% of NEC metastasize [2]. Although metastatic sites frequently involve the liver, lung, and lymph nodes [3], cutaneous metastases of NEC are relatively rare, with even fewer reports of metastasis to the scalp (**Table 1**). Herein, we report a patient with NEC who presented with multiple scalp metastases masquerading as epidermoid cysts as initial clinical manifestation.

Case Synopsis

A 68-year-old woman presented to a dermatology clinic with multiple presumed "cysts" in the scalp that had developed and grown insidiously over the prior six months. Physical examination was significant for three well-circumscribed, minimally mobile, firm subcutaneous nodules on the left frontal, right frontal, and right parietal scalp, ranging between 3-6mm in size (**Figure 1**).

Excisional biopsies revealed poorly defined, diffuse dermal neoplasms extending to the subcutis and sparing the epidermis and papillary dermis (consistent with a Grenz zone), (**Figure 2A**). The tumors were arranged in nests, cords, and strands with vague peripheral palisading (**Figure 2B**). Constituent cells were small-to-medium sized with scant, somewhat granular eosinophilic cytoplasm and round, eccentrically located nuclei with finely dispersed chromatin. Rosette formation, numerous mitoses, and scattered necrotic bodies were also

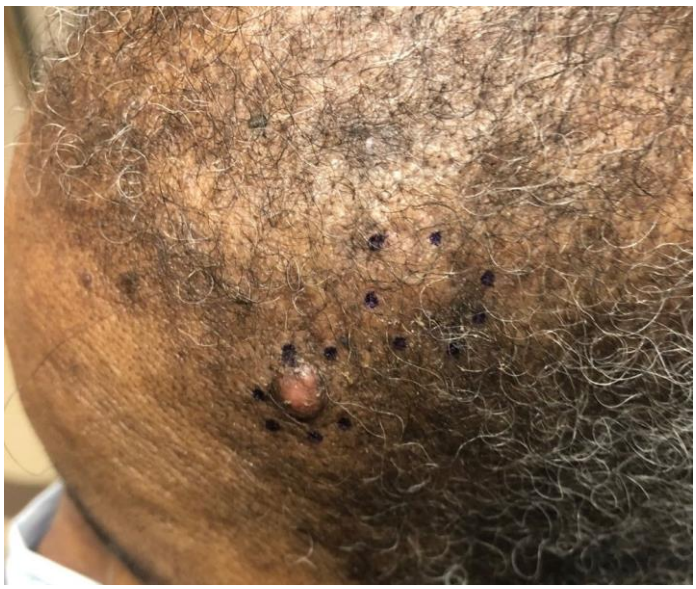

Figure 1. *Clinical image of the left frontal scalp nodule on initial presentation.*

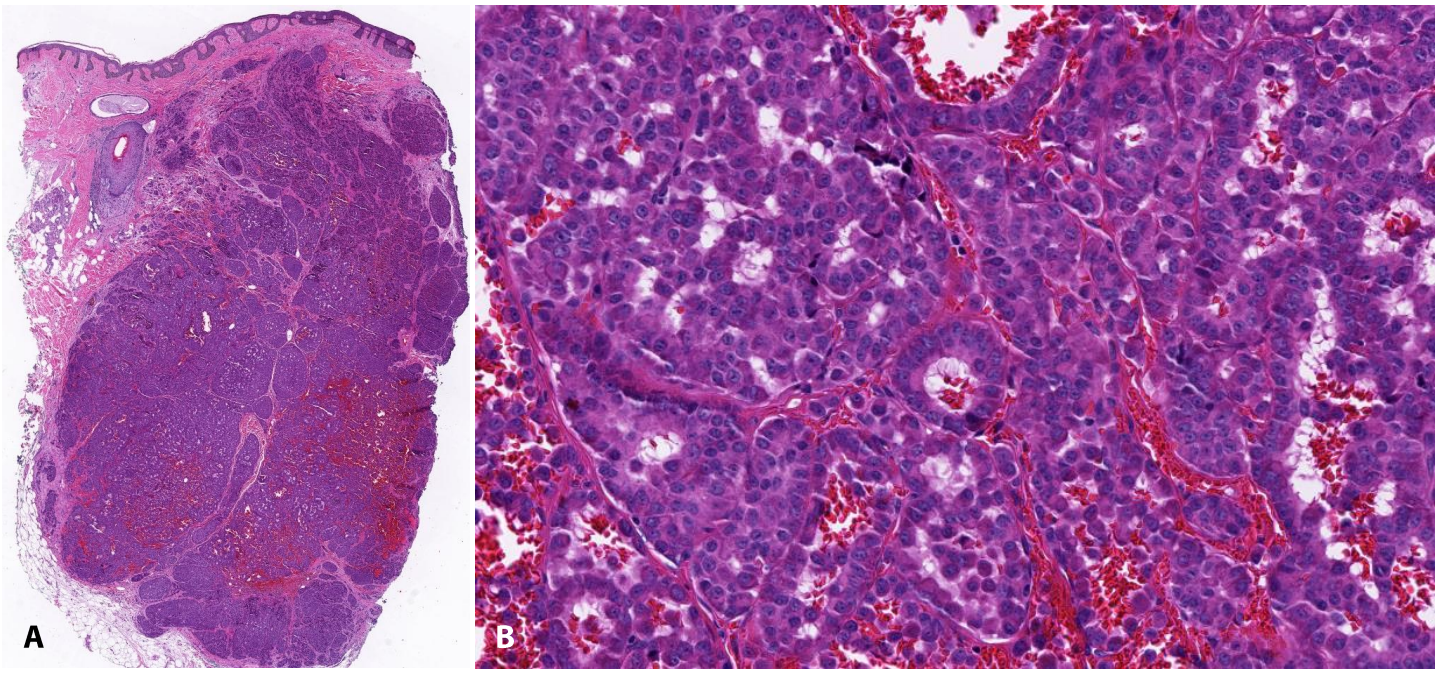

Figure 2. *Pathology images of biopsied scalp nodules.* ***A)*** *Low power magnification reveals a poorly defined diffuse dermal neoplasm extending to the subcutis. H&E, 20×.* ***B)*** *Higher power magnification highlighting tumor cells arranged in nests, cords, and strands. H&E, 200×.*

present. Synaptophysin and pankeratin were diffusely positive. Negative immunohistochemical stains included: cytokeratin 7 (CK7), cytokeratin 20 (CK20), thyroid transcription factor-1 (TTF-1), estrogen receptor (ER), gross cystic disease fluid protein-15 (GCDFP-15), and carcinoembryonic antigen (CEA).

Somatostatin receptor (SSTR) positron emission tomography (PET) revealed widespread SSTR positive tumor metastases within the liver, thoracic lymph nodes, skin/subcutaneous tissue, and bones. Correlating with PET/computed tomography (CT) results, magnetic resonance imaging (MRI) findings confirmed diffuse involvement of the pancreas and retroperitoneal lymph nodes. The patient's laboratory values were significant for markedly elevated pancreatic polypeptide (748pg/ml [normal <418pg/ml]), serotonin (1041ng/ml [normal <420ng/ml]), and 24-hour urine 5-hydroxyindoleacetic acid (234mg [normal <15mg]). The clinical presentation and investigative findings were consistent with a diagnosis of widely metastatic neuroendocrine tumors, likely from pancreatic origin. The patient was initiated on chemotherapy with carboplatin and etoposide and hormonal therapy with octreotide.

Case Discussion

Cutaneous metastases are reported in one to 10% of patients with metastatic cancer [4]. Common origins of cutaneous metastasis include breast, lung, and large intestine carcinomas and melanoma [5]. Although scalp involvement is not uncommon, NEC metastasis to the scalp is a rare phenomenon with few reported cases (**Table 1**). Several reports have described the scalp lesions using terms consistent with our presenting case, including "nodules," "painless," "slowly enlarging," "firm," and "non-ulcerated" [6,7]. Neuroendocrine differentiation is morphologically characterized by small-to-medium sized cells with high nuclear-to-cytoplasmic ratios, coarse granular nuclear chromatin, and inconspicuous nucleoli. Although small cell NECs can be difficult to distinguish from small blue cell tumors, such as lymphomas, Ewing sarcoma, or rhabdomyosarcoma, the histological findings of this patient's lesion, correlated with positive staining for neuroendocrine marker synaptophysin, confirm neuroendocrine differentiation [8].

Table 1 *Case reports of neuroendocrine carcinoma metastases to the scalp.*

Reference	Sex/Age	Primary Tumor	Metastasis to other sites	Scalp metastasis presentation
Jedrych et al. [6]	M/74	Right middle lobe lung	Not reported	Single painless nodule
Jedrych et al. [6]	F/67	Pancreas	Not reported	Single painless nodule
Jedrych et al. [6]	F/50	Right upper lobe lung	Not reported	Single painless, slowly enlarging, flesh-colored nodule
Luh et al. [11]	M/42	Large intestine	Liver, both femurs, left orbit	Two erythematous dome-like nodules
Rekhi et al. [12]	M/35	Stomach	Liver	Two firm, painless, nodules
Bolchin et al. [13]	F/55	Lung	Not reported	Painful, no erythema or induration
Fogaca et al. [14]	F/33	Uterine	Chest, back, abdomen, axilla, neck	Firm, tender, and non-ulcerated and measured from 0.2 to 1.2cm in diameter
Chung et al. [15]	F/31	Uterine cervix	Bones, lungs, pleura, lymph nodes, and spinal cord	Two purplish, nontender nodules
Ishida et al. [16]	M/55	Left upper lobe lung	Left iliac bone	Well-circumscribed subcutaneous nodule
Lee et al. [17]	M/20	Bladder	Lung, retroperitoneal lymph nodes, skin of other sites	Dome-shaped, crater-like, reddish nodule
Wang et al. [7]	M/62	Large intestine	Liver, pancreas, lymph nodes	Erythematous nodules

Immunochemical stains provide further insight into tumor origin. Importantly, the lack of CK20 expression helps differentiate NEC cutaneous metastasis from primary cutaneous NEC, notably Merkel cell carcinoma (MCC). Although CK20 can be positive in rare metastatic NECs of salivary gland origin, MCC is distinguished by its dotlike, perinuclear CK20 staining. TTF-1 can also be useful for excluding MCC in favor of metastatic NEC. For example, metastatic bronchial NECs and small cell lung carcinomas, although lacking CK20 expression, are positive for CK7 and TTF-1, markers that are negative in MCC. Anaplastic thyroid carcinomas are positive for TTF-1 and thyroglobulin. ER and GCDFP-15 are markers of breast differentiation and CEA is an epithelial marker with less specific correlations with various carcinomas [5].

Approximately 20% of biopsied NEC metastases have an unknown primary tumor site despite immunochemical analysis [9]. Somatostatin receptor PET and biochemical markers have shown to be particularly effective in the evaluation of metastatic NEC with unknown primary. Somatostatin is a naturally produced hormone that binds to SSTR, a receptor overexpressed on most neuroendocrine tumors. Somatostatin receptor PET utilizes radioactive ^{68}Ga-DOTATATE, which binds to SSTR, to localize SSTRs and detect neuroendocrine tumors [9]. Synergistically, given NECs are of neuroendocrine origin, specific hormones have been identified as useful biochemical markers for tumor localization [10]. The patient's SSTR PET results, in combination with elevated pancreatic polypeptide, were suggestive of widely metastatic NEC of pancreatic origin.

Conclusion

Cutaneous metastasis of any malignancy confers substantial mortality, with 7.5 months of average survival time after diagnosis [4]. Furthermore, the survival outcome of NEC varies significantly with both primary tumor location and site of metastasis [3]. Thus, early detection of NEC cutaneous metastasis, careful differentiation from benign skin conditions, and prompt identification of primary tumors are important for prognostic implications and management guidance.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia*. 2017;19:991-1002. [PMID: 29091800].
2. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol*. 2017;3:1335-1342. [PMID: 28448665].
3. Trikalinos NA, Tan BR, Amin M, et al. Effect of metastatic site on survival in patients with neuroendocrine neoplasms (NENs). An analysis of SEER data from 2010 to 2014. *BMC Endocr Disord*. 2020;20:44. [PMID: 32245472].
4. Ko CJ, McNiff JM. Cutaneous Metastasis. In: Dermatology. Bolognia JL, Shaffer JV, Cerroni L, editors. 4th ed. Elsevier Limited; 2018. p. 2160-2167.
5. Calonje E, Brenn T, Lazar AJ, Billings SD. Cutaneous Metastases and Paget Disease of the Skin. In: McKee's Pathology of the Skin. Calonje E, Brenn T, Lazar AJ, Billings SD, editors. 5th ed. Elsevier Limited; 2020. p. 1520-1544.
6. Jedrych J, Busam K, Klimstra DS, et al. Cutaneous metastases as an initial manifestation of visceral well-differentiated neuroendocrine tumor: a report of four cases and a review of literature. *J Cutan Pathol*. 2014;41:113-122. [PMID: 24218988].
7. Wang SM, Ye M, Ni SM. Multiple scalp metastases from colonic neuroendocrine 157 carcinoma: case report and literature review. *BMC Cancer*. 2014;14:305. [PMID: 24884973].
8. Scolyer RA, Thomspon JF, Mahar A, Murali R. Metastatic Tumors Involving the Skin. In: Dermatopathology. Busam KJ, Goldblum JR, editors. 2nd ed. Saunders; 2016. p. 675-688.
9. Hope TA, Bergsland EK, Bozkurt MF, et al. Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors. *J Nucl Med*. 2018;59:66-74. [PMID: 29025982].
10. Vinik AI, Silva MP, Woltering EA, et al. Biochemical testing for neuroendocrine tumors. *Pancreas*. 2010;39:117. [PMID: 28760232].
11. Luh JY, Han ES, Simmons JR, et al. Poorly differentiated colon carcinoma with neuroendocrine features presenting with hypercalcemia and cutaneous metastases: case report and review of the literature. *Am J Clin Oncol*. 2002;25:160-163. [PMID: 11943894].
12. Rekhi B, Saxena S, Chintamani. Gastric outlet obstruction and cutaneous metastasis in adenocarcinoid tumor of stomach - unusual presentations with cytologic and ultra structural findings. *Indian J Cancer*. 2005;42:99-101. [PMID: 16141510].
13. Blochin E, Stein JA, Wang NS. Atypical carcinoid metastasis to the skin. *Am J Dermatopathol*. 2010;32:735-739. [PMID: 20595888].
14. Fogaça MF, Fedorciw BJ, Tahan SR, Johnson R, Federman M. Cutaneous metastasis of neuroendocrine carcinoma of uterine origin. *J Cutan Pathol*. 1993;20:455-458. [PMID: 8300931].
15. Chung WK, Yang JH, Chang SE, et al. A case of cutaneous metastasis of small-cell neuroendocrine carcinoma of the uterine cervix. *Am J Dermatopathol*. 2008;30:636-638. [PMID: 19033948].
16. Ishida M, Iwai M, Kagotani A, et al. Cutaneous metastasis from pulmonary large cell neuroendocrine carcinoma in the scalp. *Int J Clin Exp Pathol*. 2014;7:2701-2706. [PMID: 24966991].
17. Lee WJ, Kim CH, Chang SE, et al. Cutaneous metastasis from large-cell neuroendocrine carcinoma of the urinary bladder expressing CK20 and TTF-1. *Am J Dermatopathol*. 2009;31:166-169. [PMID: 19318803].