Endocrine Mucin-Producing Sweat Gland Carcinoma of the Eyelid Associated With Mucinous Adenocarcinoma

Norman C. Charles, M.D.†, Alan D. Proia, M.D., Ph.D.‡, Christopher Lo, M.D.**

Abstract: **Endocrine mucin-producing sweat gland carcinoma, a rare, low-grade neoplasm with predilection for the eyelids, has been posited as a precursor to invasive mucinous adenocarcinoma. Endocrine mucin-producing sweat gland carcinoma and its concurrence with mucinous adenocarcinoma have received little attention in the ophthalmic literature. The combination of the 2 histologic patterns parallels endocrine ductal carcinoma in situ of the breast and its transition to Type B invasive mucinous carcinoma. The authors describe a 59-year-old man who developed a tumor of the right upper eyelid showing endocrine mucin-producing sweat gland carcinoma in the outer dermis and extensive mucinous carcinoma in the deeper tissue. Immunohistochemical analysis showed positivity for endocrine markers chromogranin, synaptophysin, CD56, estrogen, and progesterone in each histologic component of the tumor. This research was conducted in conformity with the Helsinki Declaration and HIPPA regulations.**

REPORT OF A CASE

A healthy 59-year-old man noted an enlarging painless tumor of the right upper eyelid more than 4 months. Examination showed a firm, nontender, nodular skin lesion near the lateral canthus. The mass extended to the eyelid margin with focal madarosis and no ulceration. It measured 1 cm × 1 cm and was fixed to the underlying tissue (Fig. 1A). No lymphadenopathy or ocular abnormalities were present. The general medical and family histories were unremarkable. A complete medical examination, including colonoscopy, was negative.

Surgical excision of a full-thickness pentagonal wedge was achieved with a No. 15 blade, leaving a 40% defect of the upper eyelid. Lateral canthotomy and cantholysis were performed, with creation of a reverse Tenzel semicircular advancement flap. The tarsal defect was closed with buried 5-0 chromic sutures. The gray and lash lines of the eyelid margin defect were closed with 6-0 silk sutures. A 4-0 polydioxanone suture anchored the deep surface of the flap to the inner aspect of lateral orbital periosteal rim. A 7-0 Vicryl suture reformed the lateral commissure. Skin closure was achieved with a running 6-0 silk suture.

Pathologic examination showed a cutaneous intradermal tumor that did not violate the surgical margins. The immediate subepithelial region contained multiple nodules of tumor consisting of medium-sized, bland-appearing, round-to-oval cells containing round nuclei with stippled chromatin and inconspicuous nucleoli. There was abundant, lightly eosinophilic cytoplasm. Some areas showed moderate pleomorphism. Periodic acid-Schiff (PAS), Alcian blue, and mucicarmine stains highlighted intracellular (perinuclear) and extracellular mucin, the latter present within clefts and small cysts (Fig. 1B–F). Mitotic activity was low. This pattern was typical of the solid and cystic patterns of endocrine mucin-producing sweat gland carcinoma (EMPSGC) (Fig. 2A–D). A second architectural pattern that occupied the most of the lesion consisted of abundant pools of mucin within which clumps of tumor cells that resembled those in the EMPSGC appeared to "float." The latter pattern exemplified invasive mucinous adenocarcinoma (Fig. 2E,F).

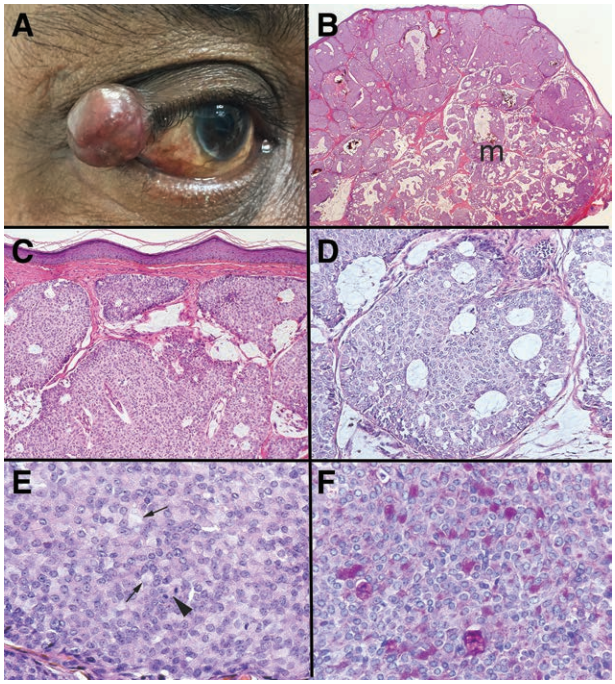

FIG. 1. **A**, Clinical appearance of right upper eyelid tumor. **B**, Low-power view of tumor showing endocrine mucin-producing sweat gland carcinoma (EMPSGC) solid nodules in upper portion and mucinous carcinoma with abundant mucin (m) in lower portion. **C**, **D**, EMPSGC contains mucinous microcysts within solid tumor lobule. **E**, EMPSGC contains rare mitotic figures (*arrowhead*) and barely discernible intracellular mucinous deposits (*arrows*), which are highlighted by periodic acid-Schiff (PAS) stain in **F**. (**B-E**, hematoxylin–eosin, ×20, ×40, ×125, ×200. **F**, periodic-acid Schiff stain, ×250).

Immunohistochemistry showed positivity in each of the biphasic patterns for chromogranin, synaptophysin, CD56, estrogen, progesterone, CK7, CAM5.2, GCDFP-15, and WT1. Negative stains included CK20 and CDX2 (militating against the histologic mimic of metastatic colon cancer). Two cases of purely invasive primary mucinous carcinoma of the eyelid were stained for comparison: tumor cells were positive for expression of CAM5.2, WT1, and ER, and 1 of 2 was positive for CD56.

DISCUSSION

In 2005, a landmark study of EMPSGC noted a preponderance in the lower eyelids of elderly women.[1] "Small foci" of mucinous carcinoma were present in 6 of the 12 cases, unlike the overwhelming portion in the current case. The EMPSGC multinodular patterns included solid, cystic, and papillary varieties. Immunohistochemical endocrine and other markers paralleled those of the current case. Observing the presence of associated

*Departments of Ophthalmology and †Pathology, New York University Langone Medical Center, New York; and ‡Department of Pathology, Duke University Medical Center, Durham, North Carolina

Accepted for publication July 26, 2017.

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

Address correspondence and reprint requests to Norman C. Charles, MD, NYU Langone Medical Center, 550 First Avenue, New York, NY 10016. E-mail: norman.charles@nyumc.org

DOI: 10.1097/IOP.0000000000001002

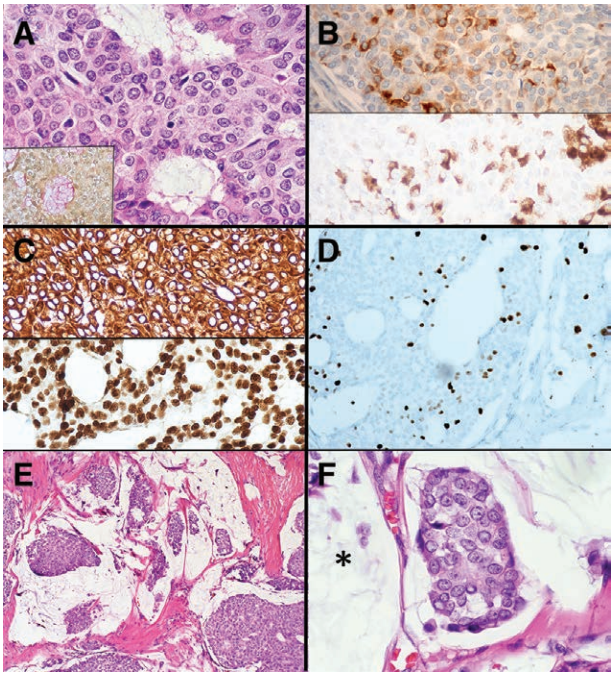

FIG. 2. **A**, Endocrine mucin-producing sweat gland carcinoma (EMPSGC) consists of bland round cells having stippled nuclear chromatin and inconspicuous nucleoli (hematoxylin–eosin, ×400). Inset, mucinous deposits (mucicarmine stain, ×150). **B, upper**, tumor cells positive for synaptophysin. **Lower**, tumor cells react with chromogranin, (both panels, ×200). **C, Upper**, Strong, diffuse tumor reactivity with low molecular weight cytokeratin (CAM 5.2 immunoperoxidase stain, diaminobenzidine chromogen, ×40). **Lower**, Nuclear positivity for estrogen receptors (immunoperoxidase stain, diaminobenzidine chromogen, ×200). **D**, Ki67 nuclear stain shows low percentage of cells in cycle (immunoperoxidase stain, diaminobenzidine chromogen, ×125). **E,F**, mucinous carcinoma with characteristic tumor clusters "floating" in abundant pools of mucin (asterix) (hematoxylin–eosin, ×40, ×400).

eccrine ducts, some showing carcinoma in situ, the authors hypothesized that EMPSGC was a precursor of mucinous carcinoma, a postulate first proposed in 1997 by Flieder et al[2] who noted the resemblance of cutaneous EMPSGC and endocrine ductal carcinoma in situ of the breast.[3] A more recent study supports the derivation of invasive mucinous adenocarcinoma from EMPSGC, demonstrating similar immunohistochemical profiles of "pure" EMPSGC, "pure" invasive mucinous sweat gland carcinomas, and tumors having mixtures of each.[4]

Another study, describing WT1 expression in EMPSCG (positive in the current case) noted co-existent mucinous carcinoma in only 1 of 13 cases, highlighting the variable appearances of these tumors.[5]

Primary mucinous carcinoma lacking its EMPSCG precursor is well recognized to occur on the eyelid[6] as a low-grade tumor with limited capacity for metastasis. While it has been shown to express estrogen and progesterone markers, a trait of many cutaneous adnexal tumors,[7] our case is one of only a few to illustrate neuroendocrine markers chromogranin, synaptophysin, and CD56 in an eyelid mucinous carcinoma. Neuroendocrine immunostains have also been demonstrated in mucinous carcinoma elsewhere on the integument.[8,9] Our case supports the contention that primary mucinous sweat gland carcinomas arise from preexisting EMPSGC even in those cases wherein an EMPSGC component cannot be identified without serial sectioning.

Complete surgical excision is the recommended treatment for EMPSGC and mucinous carcinoma, including their synchronous presentation.[1] Mohs micrographic surgery has been used to ensure complete tumor extirpation.[10]

Periocular sweat gland carcinomas comprise a diverse group of rare tumors and are mostly low grade with slow growth and only exceptional metastases. Among these tumors, only the microcystic adnexal carcinoma subtype exhibits aggressive clinical behavior.[11] The current synchronous tumors may be expected to show a relatively benign course.

REFERENCES

1. Zembowicz A, Garcia CF, Tannous ZS, et al. Endocrine mucin-producing sweat gland carcinoma: twelve new cases suggest that it is a precursor of some invasive mucinous carcinomas. *Am J Surg Pathol* 2005;29:1330–9.
2. Flieder A, Koerner FC, Pilch BZ, et al. Endocrine mucin-producing sweat gland carcinoma: a cutaneous neoplasm analogous to solid papillary carcinoma of breast. *Am J Surg Pathol* 1997;21:1501–6.
3. Tsang WY, Chan JK. Endocrine ductal carcinoma in situ (E-DCIS) of the breast: a form of low-grade DCIS with distinctive clinicopathologic and biologic characteristics. *Am J Surg Pathol* 1996;20:921–43.
4. Hoguet A, Warrow D, Milite J, et al. Mucin-producing sweat gland carcinoma of the eyelid: diagnostic and prognostic considerations. *Am J Ophthalmol* 2013;155:585–592.e2.
5. Shon W, Salomão DR. WT1 expression in endocrine mucin-producing sweat gland carcinoma: a study of 13 cases. *Int J Dermatol* 2014;53:1228–34.
6. Wright JD, Font RL. Mucinous sweat gland adenocarcinoma of eyelid: a clinicopathologic study of 21 cases with histochemical and electron microscopic observations. *Cancer* 1979;44:1757–68.
7. Zhang Q, Wojno TH, Fitch SD, et al. Mucinous eccrine adenocarcinoma of the eyelid: report of 6 cases. *Can J Ophthalmol* 2010;45:76–8.
8. Han SE, Lim SY, Lim HS. Neuroendocrine differentiation of primary mucinous carcinoma of the cheek skin. *Arch Plast Surg* 2013;40:159–62.
9. Kim JB, Choi JH, Kim JH, et al. A case of primary cutaneous mucinous carcinoma with neuroendocrine differentiation. *Ann Dermatol* 2010;22:472–7.
10. Tannous ZS, Avram MM, Zembowicz A, et al. Treatment of synchronous mucinous carcinoma and endocrine mucin-producing sweat gland carcinoma with Mohs' micrographic surgery. *Dermatol Surg* 2005;31:364–7.
11. Baker MS, Yin VT, Ivan D, et al. Epidemiology and prognosis of primary periocular sweat gland carcinomas. *Ophthal Plast Reconstr Surg* 2017;33:101–5.

Acquired Intermittent Pediatric Horner Syndrome due to Neuroblastoma

Liza M. Cohen, M.D., Alexandra Elliott, M.D.†, and Suzanne K. Freitag, M.D.**

Abstract: **A 3-month-old male developed intermittent left upper eyelid ptosis at the age of 1 month that was gradually increasing in frequency and duration. Examination revealed**

*Ophthalmic Plastic Surgery Service, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Massachusetts; and †Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, U.S.A.

Accepted for publication July 26, 2017.

The authors have no financial or conflicts of interest to disclose.

Address correspondence and reprint requests to Suzanne K. Freitag, MD, Massachusetts Eye & Ear Infirmary, 243 Charles St., Boston, MA 02114. E-mail: Suzanne_Freitag@meei.harvard.edu

DOI: 10.1097/IOP.0000000000001001