EUROPEAN OPHTALMIC PATHOLOGY SOCIETY
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Case Number:
Material submitted: 1 histology H&E slide
Title of Case Presentation:
Reddish eyelid nodule in a 60-year-old woman

CLINICAL HISTORY:
A 60-year-old female was referred to our institution for a suspicious growing lesion of the right superior eyelid noted 6 months ago. The patient described the sensation of growth into the lid, with shear stress with ocular movement, sensitive to palpation. Slit lamp examination revealed a nodular pinkish to reddish mass with telangiectatic vessels, measuring 4 x 4 mm, partially translucent, arising above the temporal ciliary margin of the right superior eyelid. Her oncological medical history was unremarkable. Best corrected VA of RE was 0.8 and 1.0 OS. An excision of the mass was performed.

OCULAR PATHOLOGY:

Macroscopy:
There was a whitish mass measuring 6 x 5.5 x 3 mm that was completely included.

Microscopy:
Excision of the mass revealed solid and cystic spaces with papillary projections lined by cuboidal cells with an eosinophilic cytoplasm containing round nuclei with some small nucleoli and a few prominent nucleoli in some areas. In the solid areas, packed small ducts could be found. Some cells contained intracellular mucin, but not all clear intracytoplasmic vacuoles stained positive with Alcian Blue. Intracellular PAS and Alcian blue positive round, globoid secretory material could be found in some cells. In several places, cells had a hobnail appearance. There was no necrosis. There was no mitosis/ 10 HPF (400x, 1.8 mm^2). The lesion was in contact with margins.

Immunohistochemistry:
The tumor cells expressed cytokeratin 7, EMA, GATA-3, MUC4, S100 and NTRK (Neurotrophic Tyrosine Kinase Receptor), but not chromogranin, synaptophysin, estrogen and progesterone receptors, GCDP-15 and cytokeratin 20.

FISH:
FISH analysis demonstrated a rearrangement of ETV6 (E26 Variant Transcription Factor 6)-NTKR confirming the diagnosis of secretory carcinoma.

Diagnosis:
Eyelid skin secretory carcinoma

DISCUSSION:
Secretory carcinoma of the skin is a rare carcinoma similar to secretory carcinomas arising in the breast and in the salivary glands. This tumor was initially described in 2009 in the axilla of a 13-year-old girl[1]. In skin, the most common location seems to be the axilla[2-5] (56%), followed by the neck[3, 5, 6] (13%), but other locations such lip[7] or breast[8] have been described. In the eyelids, 5 cases[8-12] have to best of our knowledge been reported so far, more commonly affecting women (60%), with a mean age of 51 yd (SD 14.8).
In the eyelids, secretory carcinoma presented as a non-painful, slightly pinkish to reddish nodule[8, 9], or as cystic like lesion [10], as in our case. Symptoms duration lasted 9 months in one case[11] and in another case[12], a presumed unrelated metachronous carcinoma developed in the ipsilateral parotid gland 2 years after the diagnosis of the eyelid tumor.
This tumor is characterized by cystic to microcystic spaces with papillary projections lined by cuboidal cells. More solid areas contain closely packed tubes with intraluminal secretory material. The mitotic activity is limited and there is no necrosis, nor lymphatic or perineural invasion. Secretory carcinoma is usually unencapsulated[8]. By immunohistochemistry, secretory carcinoma expresses GATA3[8], Cytokeratin 7[12], mammaglobulin[8, 9, 12], S100[8, 11], EMA[11], STAT5[8, 11] and NTRK[8, 9]. In secretory carcinoma arising outside the eyelids, the expressions of oestrogen receptors and SOX10 have been reported in a minority of cases[13].
The histopathological differential diagnosis may encompass in the skin cribriform carcinoma where the cells are not cuboidal and the tubes not so closely packed as well adenoid cystic carcinoma. It is important to rule out a metastatic secretory carcinoma from another location, especially from the salivary gland, breast or thyroid.
In the ocular adnexa, a retrospective analysis of 350 lachrymal gland tumors led to the identification of one secretory carcinoma[14]. Another case in the lachrymal gland has also been reported in 52- year-old male[15]. In a secretory carcinoma arising in the eyelid[11], the authors speculated that the tumors might have arisen from Wolfring gland. In our situation, as the

tumor was in contact with the margins, a secondary pentagonal resection was performed: this analysis did not identify any tumor residues and no tumor was arising from Wolfring gland.

Secretory carcinoma harbours a translocation involving the N-terminal domain of ETV6 (E26 Variant Transcription Factor 6) on chromosome 12 and the C-terminal tyrosinase domain of NTKR3 (Neurotrophic Tyrosine Kinase Receptor 3) on chromosome 15, leading to ETV6-NTKR3 fusion gene. The ETV6-NTKR3 translocation is not specific for secretory carcinoma and can also be found in congenital fibrosarcoma[16], congenital mesoblastic nephroma[17], thyroid carcinoma[18], leukemia[19], inflammatory myofibroblastic tumor without ALK rearrangements[20]. In secretory carcinomas, this translocation fuses the ETV6 gene up to exon 5 to NTRK3 from exon 13 onward, but other breakpoints have been described in other tumors, resulting in shorter fusion gene in acute myeloid leukemia[19] or longer or shorter fusion genes in irradiated papillary thyroid carcinoma[18]. ETV6-NTKR3 translocation results in downstream activation of the MAP Kinase and PI3K/mTOR pathways partly through an interaction with c-Src[21]. More recent interactome analysis [22] revealed that the ETV6-NTKR3 fusion detected in secretory carcinoma resulted in activation of ABL kinases and STAT5. In our case, we assessed the consequence of the ETV6-NTKR3 fusion gene on MAP kinase and Pi3K pathways downstream activation: there was a nuclear activation of ERK in the majority of the tumor cells, while pS6 was less frequently found.

Secretory carcinoma arising in the skin is believed to have an indolent course without metastasis[23], but metastasis to the lungs has been described 4 years after initial diagnosis of an axillary secretory carcinoma in a 31-year-old female[24]. The follow up of several reported cases is either unknown or limited[13]. It is also the case for secretory carcinoma arising in skin eyelid with a maximum follow up of 6 months[8]. In our situation, the patient experienced no recurrences, nor metastasis after a follow up of 4 months. A global better awareness of this tumor with longer follow up will allow a better appraisal of the presumed indolent behavior of this tumor.

Surgical excision with free margins is the treatment of choice. Although to the best of our knowledge not reported yet in advanced secretory carcinoma of the skin, the presence of ETV6-NTKR3 fusion may allow a treatment with TRK inhibitors[25]. In 13 patients with salivary gland carcinoma with ETV6-NTKR3 fusion, the overall response with Larotrectinib, a TRK inhibitor, was 88% including 3 complete responses with mild sides effects and durable response over months[26].

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