Date of meeting:	Basel, June 11th-14th 2025
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Case number:	Unknown
Material distributed:	1 H&E slide of the periorbital lesion

Sebaceous carcinoma

Clinical history

An 50-year old male patient, known with a retinoblastoma concerning the left eye as a 2-year old boy, received radiotherapy many years ago. Five years ago the conjunctiva of the left eye revealed conjunctival squamous intraepithelial neoplasia, with severe dysplasia, which was treated with mitomycin. One year ago the eye was enucleated. A periorbital mass was found, pT4a. Short after lymphatic dissemination the patient presented with a mass in the liver and development of paraneoplastic dermatomyositis.

Pathology

Microscopy: the liver biopsy revealed stroma infiltrated by cords ofcells with scant non vacuolated cytoplasm and enlarged, hyperchromatic nuclei. These cells showed expression of EMA, CK8/18 and CK7, without expression of AR, synaptophysin, INSM1, CD99 and PRAME. This lesion was compared to the biopsy of the orbita socket, which showed two components, i.e.nests of cells with scant cytoplasm and vesicular nuclei, with prominent nucleolus, intermingled with basaloid cells similar to the malignant cells in the liver biopsy. Also perineural invasion was noted. Other high-risk histopathological features, including a pagetoid pattern or lymphovascular invasion, were not observed. All the lesional cells revealed expression of EMA, CK8/18 and CK7 as well as BerEP4 expression and RB1 loss. A subset of the lesional cells showed AR expression. There was no expression of p63 and p40. Her2Neu score 0. The lesions in both the liver and orbita socket were

compared using molecular diagnostics with both lesions revealing *TP53* and *KIT* mutations and *NOTCH3* amplification. The lesion did not reveal a mutational signature associated with ultraviolet radiation. Also, no germline mutations of mismatch-repair genes were found.

Discussion

This case is considered a sebaceous carcinoma. This malignant adnexal neoplasm arises from the sebaceous glands and mostly develop in regions with a higher density of sebaceous glands, including the head and neck region and the periocular region.[1,2,3,4]Periocular sebaceous carcinoma mostly arise from the Meibomian glands of the eyelid, but may also arise in the Zeiss glands[1,5,6]or Moll glands[1]and are described in the caruncle, conjunctivaand eyebrows[1,5]and cornea.[7]Also, rarely, the lacrimal gland is suggested to be the source of sebaceous carcinoma.[7]Periorbital sebaceous carcinoma comprises 1-5.5% of all eyelid malignancies, with an incidence of 2 cases per 1 millionindividuals per year,[8]with increased incidence in India and China.[1,3,5]Risk factors include previous irradiation,[1,5,7,8] immunosuppression,[1,3–5,7]sun exposure,[1,8] HIV infections,[5,8]HPV infections[8,9] and (rarely) Muir-Torre syndrome.[1,4,5,7,8] Also older patient age is described as a risk factor[3,8,10] (median age at diagnosis 73 years[8]). However,patients with hereditary retinoblastoma, treated with irradiation,tend to develop sebaceous carcinoma at a younger age,[5,7,10,11]with the development of sebaceous carcinoma not necessarily associated with radiation.[10]

Clinical presentation may resemble benign disorders, including inflammatory conditions, and malignant skin lesions, including basal cell carcinoma and squamous cell carcinoma,[1,12] which may result in delayed diagnosis.[3,5,7,10]

On microscopic examination these tumors may have various architectural patterns, with variable cytonuclear aspect, with a basaloid, squamoid, sarcomatoid as well as a neuroendocrine aspect being described.[8] Frequently pagetoid spread is observed.[6–8] The various patterns and cytonuclear aspect may result in a differential diagnosis of sebaceoma, squamous cell carcinoma, basal cell carcinoma with sebaceous differentiation and clear cell tumors,[3,8] including a hidradenocarcinoma and a clear cell sarcoma,[3] balloon cell melanoma, Merkel cell carcinoma and metastatic clear cell carcinoma.[8]

The molecular make up of sebaceous carcinoma is reported to be influenced by the anatomical site of origin,[2] with periocular tumors and extraocular tumors having different genetic signatures and a different clinical course and clinical approach.[11] Ocular sebaceous carcinomaare reported to harbor mutations in the PI3K/Akt pathway[2]andfrequently reveal alterations in *TP53*[1,2,8,9,13] and *RB1*,[1,2,8,9,13]and alsogain of the *MYC*locus,[8]*CDKN2A* and *TERT* promoter mutations[9]are reported to contribute to the oncogenesis. Moreover, these lesions are described to harbor aberrationsin the Notch family[8]and

ZNF750 transcription factor.[2,8]Additionally PTEN, ERBB2 and NF1 mutations are described.[13]Thispauci-mutational signature differs from sebaceous carcinoma with microsatellite instability signature or UV damage signature.[2]Moreover, also deregulated microRNAs are suggested to contribute to the pathogenesis of ocular sebaceous carcinoma.[9]

Although immunotherapy[1]and targeted therapy have been described,[1,7] surgical excision and topical chemotherapy and cryotherapy for a pagetoid growth pattern is considered the optimal treatment modality,[7,8] with radiation therapy suggested for adjuvant treatment for locally advanced or high risksebaceous carcinoma, nodal metastasis or palliative care.[7]

The prognosis is influenced by different parameters, including size of the tumor, tumor stage and treatment approach,[12] differentiation grade and resection margins, with a less favorable course for (peri)ocular sebaceous carcinoma compared to extraocular sebaceous carcinoma.[4]Local recurrent disease is reported in 5-25% of the cases.[1,8] Metastatic disease is described in the lymph nodes, especially parotid lymph nodes occurring in 9-42% of the cases[1,5,8]and/or preauricular[5,10]and dissemination to distant organs, including liver, lung and bones developing in 8% of the cases,[1] with also metastases in the brain being described.[5]The sebaceous carcinoma associated with Muir-Torre syndrome have a less favorable clinical course compared to sporadic sebaceous carcinoma.[1]On the contrary HER2 protein positivity may be associated with a more favorable clinical course,[1,3,14]with AR negativity being described as a poor prognostic factor.[14]

1. Dini, F. *et al.* Periocular sebaceous carcinoma: updates in the diagnosis, treatment, staging, and management. *Int J Dermatol***63**, 726–736 (2024).
2. North, J. P. *et al.* Cell of origin and mutation pattern define three clinically distinct classes of sebaceous carcinoma. *Nat Commun***9**, 1894 (2018).
3. Knackstedt, T. & Samie, F. H. Sebaceous Carcinoma: A Review of the Scientific Literature. *Curr Treat Options Oncol***18**, 47 (2017).
4. In ’t Veld, E. H. *et al.* Outcome after treatment for sebaceous carcinoma: A multicenter study. *J Surg Oncol***125**, 730–735 (2022).
5. Shields, J. A., Saktanasate, J., Lally, S. E., Carrasco, J. R. & Shields, C. L. Sebaceous Carcinoma of the Ocular Region: The 2014 Professor Winifred Mao Lecture. *Asia Pac J Ophthalmol (Phila)***4**, 221–7 (2015).
6. Takeuchi, D., Ishida, M., Yasuda, E., Ueda, K. & Hirose, Y. Ocular and extraocular sebaceous carcinomas: A retrospective study with emphasis on the presence of in situ lesion and discussion and review of the histogenesis of extraocular sebaceous carcinoma. *Oncol Lett***26**, 337 (2023).

7. Xu, Y., Li, F., Jia, R. & Fan, X. Updates on the clinical diagnosis and management of ocular sebaceous carcinoma: a brief review of the literature. *Onco Targets Ther***11**, 3713–3720 (2018).

8. Mudhar HS *et al.Sebaceous Carcinoma. In: In: WHO Classification of Tumours Editorial Board. Eye Tumours Lyon (France): International Agency for Research on Cancer; 2023* .

9. de Keizer, R. O. B. *et al.* miR-196b-5p and miR-107 Expression Differentiates Ocular Sebaceous Carcinoma from Squamous Cell Carcinoma of the Conjunctiva. *Int J Mol Sci***23**, (2022).

10. Kivelä, T., Asko-Seljavaara, S., Pihkala, U., Hovi, L. & Heikkonen, J. Sebaceous carcinoma of the eyelid associated with retinoblastoma. *Ophthalmology***108**, 1124–8 (2001).

11. Owen, J. L. *et al.* Sebaceous carcinoma: evidence-based clinical practice guidelines. *Lancet Oncol***20**, e699–e714 (2019).

12. Dowell-Esquivel, C., Lee, R., DiCaprio, R. C. & Nouri, K. Sebaceous carcinoma: an updated review of pathogenesis, diagnosis, and treatment options. *Arch Dermatol Res***316**, 55 (2023).

13. Tetzlaff, M. T. *et al.* Next-generation sequencing identifies high frequency of mutations in potentially clinically actionable genes in sebaceous carcinoma. *J Pathol***240**, 84–95 (2016).

14. Na, H. Y. *et al.* Proposal of a Provisional Classification of Sebaceous Carcinoma Based on Hormone Receptor Expression and HER2 Status. *Am J Surg Pathol***40**, 1622–1630 (2016).

This case describes a 50-year-old male with a history of hereditary retinoblastoma and prior radiotherapy, who developed periorbital sebaceous carcinoma with subsequent liver metastasis and paraneoplastic dermatomyositis. The orbital and liver lesions shared histological and molecular features, including **TP53 and KIT mutations, NOTCH3 amplification, and RB1 loss**. The tumor showed **EMA, CK7, CK8/18, and BerEP4 expression**, with partial **AR positivity** and absence of **UV or MSI signatures**.

Sebaceous carcinoma is a rare malignancy typically arising in sebaceous-rich regions like the periocular area, commonly from Meibomian or Zeiss glands. It can mimic benign or other malignant skin lesions, often delaying diagnosis. Risk factors include prior **radiation, immunosuppression, and hereditary retinoblastoma**. These tumors display **diverse histologic patterns** and **site-specific molecular alterations**, with **TP53, RB1, and PI3K/Akt pathway mutations** being common in ocular cases.

Management involves **surgical excision**, with **topical or adjuvant therapies** for high-risk cases. Prognosis is influenced by **tumor size, differentiation, margins, and spread**, with **periocular cases having a worse outcome**. Metastasis may involve **lymph nodes, liver, lungs, bones**, or brain. **AR negativity and Muir-Torre syndrome** are associated with poorer outcomes.