Thieme

Proton Therapy of a Conjunctival Carcinoma in the Anophthalmic Socket, 41 Years after Enucleation for a Sporadic Retinoblastoma. A Case Report and Review of the Literature

Protonentherapie für Bindehautkarzinom in der anophthalmischen Höhle 41 Jahre nach Enukleation wegen sporadischen Retinoblastoms

Précis

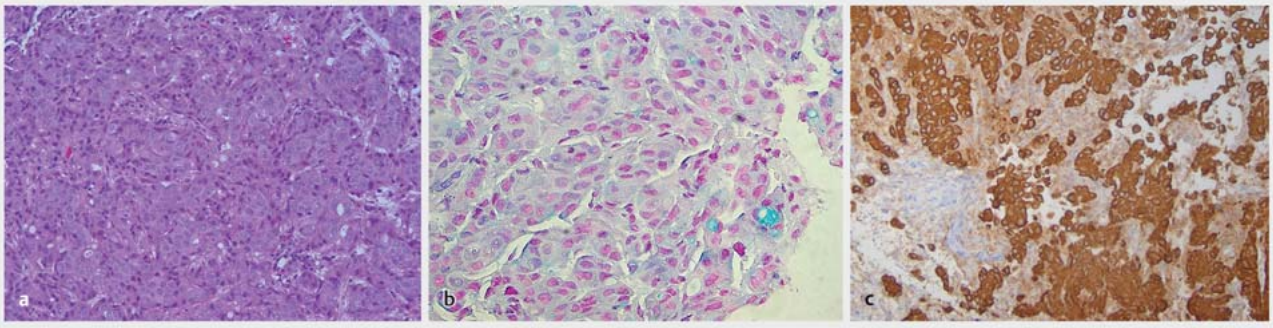
We document here an aggressive carcinoma arising in the conjunctiva of an anophthalmic socket, 41 years after enucleation for a sporadic, non-hereditary unilateral retinoblastoma. This tumor was treated for the first time with proton beam irradiation of the orbit. Investigations revealed an extensive metastatic spread to the locoregional lymph nodes, requiring complementary parotidectomy, chemotherapy, and radiation therapy.

The incidence of conjunctival carcinoma arising in the bulbar conjunctiva peaks in Africa (3.4/100 000/year) and has been linked to factors contributing to its development, such as UV light exposure, as well as HIV or HPV infections [1]. On the contrary, carcinomas arising in the conjunctiva of anophthalmic sockets are extremely rare and, so far, only 23 cases have been documented, usually occurring a long time after enucleation. We document here the clinicopathological findings of a conjunctival carcinoma identified in the anophthalmic socket of a patient enucleated 41 years ago for a sporadic, unilateral retinoblastoma.

Case Report

A 43-year-old man, known for a retinoblastoma enucleated at the age of 3 without complementary orbital radiotherapy, experienced discomfort with his ocular prosthesis for several weeks. Histopathological analysis of the left enucleated eye demonstrated 41 years ago an exophytic, mostly poorly differentiated retinoblastoma, not associated with any known histologic risk factors. Past medical history included smoking, and a scuba diving accident without actual clinical consequences. Examination of the anophthalmic socket showed a retraction syndrome with entropion of the lower eyelid. During revision of the anophthalmic socket with an oral mucosa graft, thickened hyperemic areas were biopsied. Histopathological analysis revealed fibrous tissue with chronic inflammation and cords of atypical cells with rare intracytoplasmic mucin (▶ **Fig. 1 a, b**). In some areas, there were isolated small clumps of cells that were diffusely infiltrating the adipose tissue. By immunohistochemistry, the cells were expressing cytokeratin 19 and 7, consistent with a moderately differentiated conjunctival carcinoma (▶ **Fig. 1 c**). Orbital MRI imaging revealed a thickening around the lateral and superior part of the anophthalmic socket, extending into the ocular muscles, with contrast enhancement (▶ **Fig. 2 a, b**). A thoracoabdominal scan did not show any secondary lesions. No *RB1* mutations were identified in his blood nor in the ipsilateral orbital tissue.

Proton therapy of the left orbit was initiated (66 Gy RBE in the tumor bed and 60 Gy RBE in the rest of the orbit) (▶ **Fig. 2 c, d**). During that treatment, homolateral pretragal and cervical adenopathies were noted and an ^{18}FDG-PET CT demonstrated nodular hypercaptations in the cervical and retromandibular regions (▶ **Fig. 3**), consistent with metastatic adenopathies. A parotidectomy and extensive cervical lymph node resection



▶ **Fig. 1** Histopathological analysis. **a** Cords of epithelioid cells diffusely infiltrate the stroma (hematoxylin and eosin). **b** Some cells contain intracellular mucin (Alcian Blue). **c** By immunohistochemistry, the cells expressed cytokeratin 19 (normally expressed in the conjunctival epithelium). Magnification: **a** and **c**, 126 ×; **b** 252 ×.

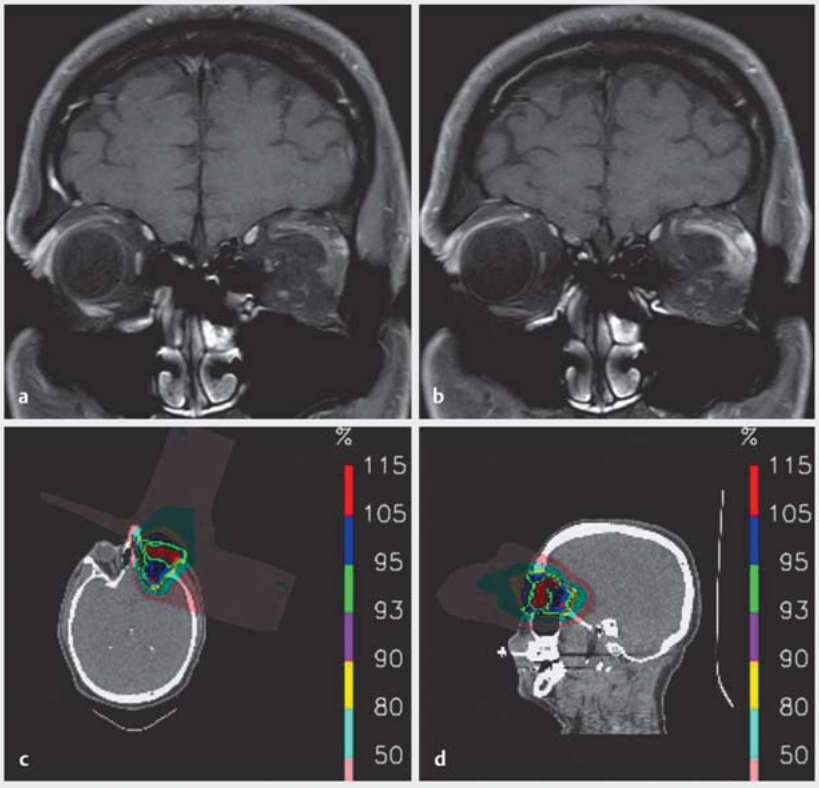
were performed, revealing tumoral lymph node involvement in 31 out of 61 resected lymph nodes, with capsular effraction in some cases. Complementary radiotherapy (photons) in the cervical area (52.8 Gy in the whole cervical region and 66 Gy in the areas with capsular effraction) and chemotherapy (cisplatin followed by carboplatin) were undertaken. There was no clinical tumor recurrence after 6 months of follow-up.

Discussion

Conjunctival carcinomas arising in the anophthalmic socket are extremely rare and, to the best of our knowledge, 23 cases have been documented so far. The mean age at presentation, including our patient, is 56.67 years (SD: 14.09). There were 19 males and 5 females. The reasons for enucleation were traumatic in 17 cases [2–10], tumoral in 6 cases (5 retinoblastomas [11, 12], 1 uveal melanoma [4]), and, in 1 case, a microphthalmia [12] was reported. The interval between enucleation and diagnosis of conjunctival carcinoma ranges from 10 to 63 years, with a mean of 41.67 years (SD: 13.78).

Patients have presented with a mass (54%) [4, 6–8, 10–14], complained of poor prosthesis fit (32%) [2, 3, 6, 14, 15], discomfort (42%) [2, 4, 6], and experienced a local discharge (50%), either serosanguineous [2, 4], mucoid [14], or mucopurulent [3]. The aspect of the tumors ranged from hyperemic, papillomatous areas to a tan, pink [4], or reddish mass, sometimes with "tufts of hairpin loop vessels" [12] or telangiectatic vessels [3, 14]. Some authors have pointed out the difficulties in delineating the tumor within the anophthalmic socket where the contrast with the underlying white sclera does not exist [3, 12]. In some cases, a leukoplakia [2, 11, 14] could be identified and, very rarely, a large, exophytic mass [7] has been documented. Ulceration [5, 14] and madarosis [3] as well as an entropion [9], as observed in our situation, have not been commonly reported.

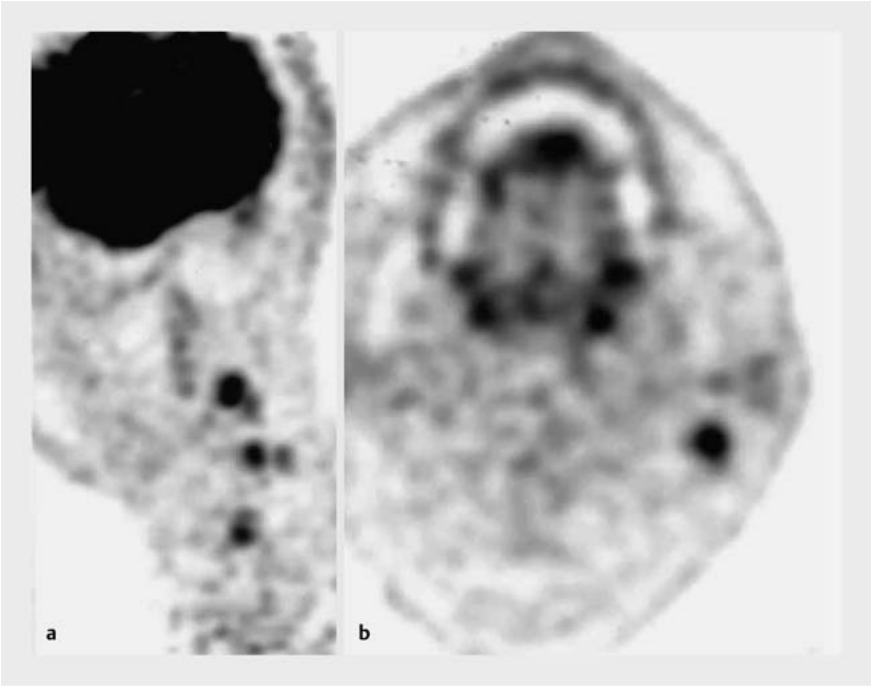
The occurrence of a conjunctival carcinoma in the anophthalmic socket, 40 years after enucleation, has been attributed to chronic irritation due the ocular prosthesis [4–6, 9, 10, 14]. A cytological comparative analysis of the conjunctiva of 40 anophthalmic sockets and conjunctiva of their control eye revealed that the use of an ocular prosthesis was associated with squamous metaplasia and a reduction of goblet cells [16]. It is possible that chronic irritation leads to squamous metaplasia that may ultimately transform into dysplasia and carcinoma. In the oral mucosa, ill-fitting dentures increased the risk of developing cancer and it has been hypothesized that chronic irritation might trigger increased tissue repair, mitosis, and risk of DNA damage as well as a release of oxidative chemicals [17]. Recently, several studies assessed the presence of HPV as a contributing factor to the development of squamous carcinoma in anophthalmic sockets: HPV16 was detected in 4 out of 6 cases [3, 13, 14]. Similar to ocular surface neoplasia, where vitamin A deficiency leads to microabrasions [18], the traumatic use of an ocular prosthesis might be a cofactor, allowing HPV to invade the basement membrane and epithelial cells [14]. As the absolute excess risk of secondary epithelial malignancies increases to 13.3 per 1000 after more than 40 years of follow-up in hereditary retinoblastoma [19], we also assessed the presence of *RB1* mutations in the conjunctiva from the anophthalmic socket, but no *RB1* mutations could be identified in our situation.



▶ **Fig. 2** Orbital MRI and proton therapy plan. **a** T1-weighted, coronal orbital imaging demonstrates a thickening in the superior and temporal left orbital socket, with contrast enhancement (**b**). **c, d** Dose distribution with the proton therapy planning system in the axial plane (**c**) and sagittal plane (**d**).

The extent of the carcinoma has led to exenteration in 50% of the cases [2–4, 6, 8, 13, 15], associated with adjuvant local radiotherapy in 16.6% of the cases [3, 6, 8, 13]. Complete regression was achieved in two multifocal tumors with intralesional interferon α2b injections and topical interferon α2b [12]. Interferon α2b combined with cryotherapy was effective in one *in situ* carcinoma, but not in another one, which recurred as a moderately differentiated carcinoma, ultimately requiring exenteration [14]. To the best of our knowl-

Klin Monatsbl Augenheilkd 2021; 238 |



▶ **Fig. 3** PET-CT. ^{18}FDG-PET CT demonstrates nodular hypercaptations in the cervical (**a**) and retromandibular (**b**) regions, consistent with metastatic adenopathies.

edge, proton beam irradiation of the entire orbit in order to prevent exenteration, as performed in our situation, has not been described in the past.

Possibly due to their localization in the anophthalmic socket and their late discovery, some carcinomas manifested an aggressive behavior with metastatic involvement at the time of diagnosis in two reports [4, 6] or during treatment [3], as observed in our case. Based upon the limited number of reported squamous cell carcinomas arising in the anophthalmic socket (24), the metastatic rate of 16.6% seems to be slightly higher than that of squamous cell carcinomas arising in the bulbar conjunctiva, ranging from 0.7 to 13% [20, 21].

Although no genomic studies have been undertaken on carcinomas of the anophthalmic socket, it is likely their genomic landscape might be different from that of conjunctival carcinomas in the bulbar conjunctiva exposed to UV light. The long time period for the development of a conjunctival squamous carcinoma in the anophthalmic socket as well as the delay in its diagnosis might also be associated with more advanced tumors, possibly with a more aggressive behavior. To the best of our knowledge, we describe the first conjunctival carcinoma of the anophthalmic socket in a unilateral sporadic retinoblastoma, as well as the first time use of orbital proton therapy in its management. In case of poor prosthesis fitting and ocular discomfort, a careful examination of the anophthalmic socket, with biopsies, is recommended.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors

Alexandre Moulin[1], Alessia Pica[2], Francis Munier[1], Ann Schalenbourg[1], Antoine Nobile[3], Aliaksandr Asana[4], Christoforos Astaras[5], Mehrad Hamedani[1]

1 Jules-Gonin Eye Hospital, Lausanne University, FAA, Switzerland
2 Ophthalmology, Paul Scherrer Institut, Villigen, Switzerland
3 Pathology, Promed SA, Marly, Switzerland
4 Otorhinolaryngology, Fribourg Hospitals, Fribourg, Switzerland
5 Oncology, Fribourg Hospitals, Fribourg, Switzerland

Correspondence

Dr. Alexandre Moulin, PD, MER
Jules Gonin Eye Hospital
Ophthalmology
15 Avenue de France
1004 Lausanne
Switzerland
Phone: + 41 2 16 26 85 41
Fax: + 41 2 16 26 81 38
alexandre.moulin@fa2.ch

References

[1] Gichuhi S, Sagoo MS, Weiss HA et al. Epidemiology of ocular surface squamous neoplasia in Africa. Trop Med Int Health 2013; 18: 1424–1443. doi:10.1111/tmi.12203

[2] Nguyen J, Ivan D, Esmaeli B. Conjunctival squamous cell carcinoma in the anophthalmic socket. Ophthalmic Plast Reconstr Surg 2008; 24: 98–101. doi:10.1097/IOP.0b013e31816381fa

[3] Gaier ED, Jakobiec FA, Stagner AM et al. PV16-Positive Invasive Conjunctival Squamous Cell Carcinoma in an Anophthalmic Socket. Ophthalmic Plast Reconstr Surg 2017; 33: S2–S4. doi:10.1097/IOP.0000000000000521

[4] Campanella PC, Goldberg SH, Erlichman K et al. Squamous cell tumors and ocular prostheses. Ophthalmic Plast Reconstr Surg 1998; 14: 45–49. doi:10.1097/00002341-199801000-00010

[5] Whittaker KW, Trivedi D, Bridger J et al. Ocular surface squamous neoplasia: report of an unusual case and review of the literature. Orbit 2002; 21: 209–215. doi:10.1076/orbi.21.3.209.7173

[6] Endo T, Hata J, Togashi S et al. Conjunctival squamous cell carcinoma of the orbit 40 years after enucleation. Ophthalmic Plast Reconstr Surg 2006; 22: 299–301. doi:10.1097/01.iop.0000222521.92518.ee

[7] Chaudhry TA, Memon M, Ahmad K. Use of artificial eye and conjunctival squamous cell carcinoma. J Postgrad Med 2006; 52: 234–235

[8] Hsu VJ, Agarwal MR. Re: "Conjunctival squamous cell carcinoma in the anophthalmic socket". Ophthalmic Plast Reconstr Surg 2009; 25: 257–258. doi:10.1097/IOP.0b013e3181a41faf

[9] Barrett RV, Meyer DR, Carlson JA. Conjunctival squamous cell carcinoma in situ in the anophthalmic socket. Ophthalmic Plast Reconstr Surg 2010; 26: 52–53. doi:10.1097/IOP.0b013e3181b8e3bc

[10] Espana EM, Levine M, Schoenfield L et al. Ocular surface squamous neoplasia in an anophthalmic socket 60 years after enucleation. Surv Ophthalmol 2011; 56: 539–543. doi:10.1016/j.survophthal.2011.06.005

[11] Oka S, Tsuboi S, Morita C et al. Two cases of conjunctival squamous cell carcinoma in the anophthalmic socket after treatment of retinoblastoma. J Dermatol 2018; 45: e346–e347. doi:10.1111/1346-8138.14490

[12] Shields CL, Kancherla S, Bianciotto CG et al. Ocular surface squamous neoplasia (squamous cell carcinoma) of the socket: management of extensive tumors with interferon. Ophthalmic Plast Reconstr Surg 2011; 27: 247–250. doi:10.1097/IOP.0b013e318203d605

[13] Hayashi A, Komoto M, Matsumura T et al. Conjunctival Squamous Cell Carcinoma due to Long-term Placement of Ocular Prosthesis. Plast Reconstr Surg Glob Open 2015; 3: e325. doi:10.1097/GOX.0000000000000299

[14] McGrath LA, Salvi SM, Sandramouli S et al. Squamous cell carcinoma in the anophthalmic socket: a series of four cases with HPV-16 profiling. Br J Ophthalmol 2018. doi:10.1136/bjophthalmol-2018-311916.

[15] Jain RK, Mehta R, Badve S. Conjunctival squamous cell carcinoma due to ocular prostheses: a case report and review of literature. Pathol Oncol Res 2010; 16: 609–612. doi:10.1007/s12253-010-9251-0

[16] Kim JH, Lee MJ, Choung HK et al. Conjunctival cytologic features in anophthalmic patients wearing an ocular prosthesis. Ophthalmic Plast Reconstr Surg 2008; 24: 290–295. doi:10.1097/IOP.0b013e3181788dff

[17] Manoharan S, Nagaraja V, Eslick GD. Ill-fitting dentures and oral cancer: a meta-analysis. Oral Oncol 2014; 50: 1058–1061. doi:10.1016/j.oraloncology.2014.08.002

[18] Gichuhi S, Ohnuma S, Sagoo MS et al. Pathophysiology of ocular surface squamous neoplasia. Exp Eye Res 2014; 129: 172–182. doi:10.1016/j.exer.2014.10.015

[19] Marees T, Moll AC, Imhof SM et al. Risk of second malignancies in survivors of retinoblastoma: more than 40 years of follow-up. J Natl Cancer Inst 2008; 100: 1771–1779. doi:10.1093/jnci/djn394

[20] Cruzado-Sanchez D, Tellez WA, Villarreal-Aguilar B et al. Conjunctival squamous cell carcinoma: prognostic factors for the recurrence and metastasis and clinicopathological characteristics at an oncological hospital in Peru. Br J Ophthalmol 2020; 104: 1010–1015. doi:10.1136/bjophthalmol-2019-314058

[21] Miller CV, Wolf A, Klingenstein A et al. Clinical outcome of advanced squamous cell carcinoma of the conjunctiva. Eye (Lond) 2014; 28: 962–967. doi:10.1038/eye.2014.79

Bibliography

Klin Monatsbl Augenheilkd 2021; 238: 361–364
DOI 10.1055/a-1384-1159
ISSN 0023-2165

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany