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Abstract: Cutaneous squamous cell carcinoma (cSCC) is the most common tumour entity that grows secondarily into the orbital area, while basal cell carcinoma (BCC) is the most common periocular and eyelid tumour. Diagnostic delays are common and may increase post-treatment complications. The therapy is challenging and must be discussed at an interdisciplinary tumour board. We discuss four cases of cSCC with orbital invasion treated with immune-checkpoint inhibitors with variable responses. What does this study add? - cSCC is the most common tumour entity that grows secondarily into the orbital area - Diagnosis often may be delayed due to vague complaints - Numbness and pain were the most common symptoms - A rapid response rate is usually seen with anti-PD1 therapy

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CASE REPORT

Cutaneous SCC with orbital invasion: case series

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Abstract
Cutaneous squamous cell carcinoma (cSCC) is the most common tumour entity that grows secondarily into the orbital area, while basal cell carcinoma (BCC) is the most common periocular and eyelid tumour. Diagnostic delays are common and may increase post-treatment complications. The therapy is challenging and must be discussed at an interdisciplinary tumour board. We discuss four cases of cSCC with orbital invasion treated with immune-checkpoint inhibitors with variable responses.

Conflict of interest
Mirjam Nägeli has intermittent project focused consulting and/or advisory relationships or/and travel-congress support with Sanofi and SunPharma outside the submitted work. Prof. Dummer has intermittent project focused consulting and/or advisory relationships with Novartis, Merck Sharp & Dhome (MSD), Bristol-Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome outside the submitted work. Johanna Mangana has intermittent, project focused consulting and/or advisory relationships with Merck-Pfizer, MSD, Novartis, Sanofi, Pierre Fabre, Amgen and BMS outside of submitted work. She reports also travel-congress support from L’oreal, MSD, Ultrasun, BMS and Pierre Fabre. Karla Chaloupka has no conflict of interest.

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What does this study add?
• cSCC is the most common tumour entity that grows secondarily into the orbital area
• Diagnosis often may be delayed due to vague complaints
• Numbness and pain were the most common symptoms
• A rapid response rate is usually seen with anti-PD1 therapy

Introduction
Cutaneous squamous cell carcinoma is the second most common periocular and eyelid cutaneous malignancy, but SCC (including starting from the paranasal sinus) is the most common tumour entity that grows secondarily into the orbital area,1–3 and perineural orbital invasion of cSCC is a well-described phenomenon, usually occurring along the supraorbital or infraorbital nerves.4,5 The incidence of perineural spread is about 2.5%–14%.5 Over 60% of patients with perineural spread may be initially asymptomatic,6 and diagnosis may be delayed either due to vague complaints or due to significant lag of several years between initial removal of the cSCC and perineural invasion, and the patients may simply not recall having had cutaneous cancer.5,7,8 If local therapy with surgery, radiotherapy or combination is no more possible or inadequate, systemic medications are indicated in order to achieve adequate tumour control or cure.

We describe four cases of orbital invasion with partly also strongly delayed diagnosis.

Cases
Patient Nr. 1
71-year-old male patient with cutaneous carcinogenesis while taking azathioprine for many years for Crohn’s disease showed a rapidly growing nodule in the right medial eyebrow area in February 2020. One year earlier, a proliferating epidermoid cyst had been removed at this site. MR in April 2020 showed extension in the orbital area along the superior rectal muscle
and palpebral levator muscle to the superior orbital fissure. Clinically, he suffered from foreign body sensation and watery eye. Biopsy was compatible with squamous cell carcinoma. The interdisciplinary tumour board advised against mutilating surgery and systemic therapy with anti-PD1 (programmed-cell death protein1) cemiplimab. After 4 cycles of 350 mg each every 3 weeks (May-June 2020), the lesion unfortunately progressed. The patient tolerated the immunotherapy very well except for immune-related agranulocytosis. Molecular analysis with FoundationOneCDx (FOne®CDx) of the tumour detected a tumour mutational burden (TMB) of 38 muts/mb and ERBB2 amplification. FOne®CDx is an FDA-approved ‘next-generation sequencing’-based test that identifies genomic alterations in over 300 cancer-related genes. Therefore, an immune histochemical staining of the tumour was performed, which could further confirm the findings of ERBB2 amplification (score of 3+), so that a therapy with trastuzumab (herceptin®) was also recommended in the molecular tumour board. We treated with trastuzumab combined with radiotherapy, which showed a stabilization over 7 months; then, unfortunately the tumour was progressive, so we switched to chemotherapy with carboplatin/paclitaxel in March 2021. In May, he had the 3rd cycle (Table 1 and Fig. 1).

**Patient Nr. 2**

In 2013, the 76-year-old male patient underwent excision of multiple poorly differentiated cSCCs on the right forehead. In 2017, he developed severe orbital and trigeminal right pain with diplopia. At that point, there was no radiologic correlation to the symptoms by MRI, ultrasound and PET-CT. Lumbar puncture was unremarkable and likewise inconspicuous PET-CT in January 2018. The patient presented a right facial palsy in May 2017, he developed severe orbital and trigeminal right pain with multiple poorly differentiated cSCCs on the right forehead. In 2018 started. In May 2019, PET-CT and MRI showed an intraorbital recurrence with ingrowth into the cavernous sinus as well as protrusion bulbi and optic nerve compression. Clinically, he had an incomplete lid closure, supraorbital pain and exophthalmus. Chemotherapy with carboplatin/paclitaxel in July/August 2019 was given with tumour progression in PET-CT in September. Therapy was changed to anti-PD1 therapy with cemiplimab 350mg flat dose every 3 weeks was begun in March 2019. Three-month surveillance with MRI showed a slow tumour response with only inactive tumour portions/scarring. He had no reported adverse events under this immunotherapy. The patient stopped the therapy after more than 1 year in June 2020 suffering from severe intermittent pain, which limited his quality of life so much that he decide to suicide via Exit organization (Association for humane dying, which support if people decide at some point to exercise your right to self-determination, www.exit.ch).

**Patient Nr. 3**

76-year-old male patient with previous excision of cSCC in the left temporal area in 2013, presented 5 years later in June 2018 with subcutaneous soft-tissue metastasis at the inner–upper orbital angle on the left. A biopsy could detect a cSCC, R1-resection was performed and postoperative radiotherapy until November 2018 started. In May 2019, PET-CT and MRI showed an intraorbital recurrence with ingrowth into the cavernous sinus as well as protrusion bulbi and optic nerve compression. Clinically, he had an incomplete lid closure, supraorbital pain and exophthalmus. Chemotherapy with carboplatin/paclitaxel in July/August 2019 was given with tumour progression in PET-CT in September. Therapy was changed to anti-PD1 therapy with cemiplimab 350mg flat dose every 3 weeks. TMB showed 63 muts/mb in August 2020, the intraorbital tumour showed a complete response (CR), so therapy was stopped 6 months beyond CR in March 2021. He had no reported adverse events under this immunotherapy, but development of culture-negative lymph node tuberculosis supraclavicular. Clinically, there was complete regression of his exophthalmos and pain.

| Patient | Sex | Age | Risk factors | Location primary cSCC, year of discovery | Orbital metastasis, treatment | Therapy anti-PD1 duration, response |
|---------|-----|-----|--------------|-----------------------------------------|-------------------------------|----------------------------------|
| 1 (m, 71y) | IS with azathioprine | Eyebrow right 2/2020, orbital metastasis 4/2020, anti-PD1 (4x), RT, trastuzumab (10x), carboplatin/paclitaxel ongoing | PD (after 3mt) |
| 2 (m, 76y) | None | Frontal right 2013, orbital metastasis 5/2018, photon irradiation, anti-PD1 3/2019–6/2020 (21x) | PR |
| 3 (m, 76y) | None | Temporal left 2013, orbital metastasis 6/2018, surgery and RT till 11/2018, intraorbital metastasis 5/2019, carboplatin/taxol till 8/2019, anti-PD1 5/2019–3/2021 (26x) | CR (after 11 mt) |
| 4 (f, 94y) | None (advanced age) | Frontal median SCC12/2019 not therapy (misdiagnosed as AV malformation), orbital metastasis 5/2020, anti-PD1 6/2020–6/2021 | CR (after 6 mt) |

CSCC, cutaneous squamous cell carcinoma; RT, radiotherapy; PD, progressive disease; PR, partial response; CR, complete response; IS, immunosuppression.

Table 1 Four patient cases with orbital metastatic cutaneous squamous cell carcinoma
Patient Nr. 4

94-year-old female patient present with a mass on the forehead left since at least December 2019. It was assessed as an AV malformation on CT. No cSCC was pre-described. In May 2020, a new nodule appeared at the glabella with the development of ptosis on the left with numbness at the forehead left. Biopsy of this nodule showed a poorly differentiated cSCC. MR showed a hypervascularized tumour on the left mid-supraorbital forehead that grew intraorbitally to the apex of the orbit and infiltrated the cavernous sinus. A therapy with anti-PD1 cemiplimab was decided (high risk of visual loss with radiotherapy), which was started in June 2020 with 350 mg flat dose every 3 weeks. Clinically and radiologically, the patient showed a rapid response with CR in December 2020, so that treatment cessation is planned for June 2021. She had no reported adverse events under this immunotherapy.

Discussion

Treatment of orbital lesions with deep perineural invasion (PNI) is challenging, and excessive surgery including a disfiguring exenteration at that stage is in vain. Early diagnosis and uncompromised treatment of PNI before entering the orbital area are crucial for the survival of the patient. Histologic detection of PNI can be difficult on routine sampling, and neural involvement is often not addressed in pathology reports. Numbness and pain were the most common symptoms, whereas ophthalmoplegia, ptosis and facial palsy were the most frequent signs. As an initial symptom, patient 1 suffered from foreign body sensation, patient 2 had severe orbital and trigeminal pain with diplopia, patient 3 had an incomplete lid closure, supraorbital pain and exophthalmus and patient 4 showed ptosis and numbness. Missing the early primary treatment of an extraorbital PNI will cause a hidden
spreading. At that stage, MRI imaging might not show the perineural invasion and, therefore, not guide to a targeted biopsy until it is too late.

Wide surgical excision alone or in combination with radiotherapy is the primary treatment of choice before the perineural invasion enters the orbit. The number of orbital exenterations due to carcinoma differs in the literature with SCC being the largest subgroup. In most cases, recurrence occurs within the first 2 years, despite exenteration. Promising results compared with previous local and systemic treatment options such as radiotherapy, chemotherapy, radiochemotherapy or antibody therapy with an EGFR inhibitor are currently seen with anti-PD1 as a newly approved first-line therapy. A rapid response rate is usually seen with anti-PD1 therapy. The metastatic cSCC group showed an objective response in 47% of patients with emerging evidence of durable response and disease control.

This therapy leads to an improvement in quality of life, which is often very poor in advanced or metastatic cSCC, as seen in patient number 2. The management of patients with cSCC in high-risk locations such as periorbital area is demanding and integrates various disciplines. Interdisciplinary case discussion for treatment planning is of utmost importance in these cases. This includes dermatologists, dermatooncologists, oncologists, ophthalmologists, radiologists, pathologists, radiooncologists, surgeons from various specialties and psychologists.

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