EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY

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Breakthrough of an aggressive tumor into the orbit

Clinical History:
A 28-year-old female patient presented in July 2021 with retrobulbar pain of the right eye for 2 months. She also had a nosebleed for the last 2 weeks. As a child she had a haemangioma above the right eye.
The initial ophthalmological examination revealed best corrected visual acuity of 1.0 OU, normotensive intraocular pressure and normal biomicroscopic findings except for hyperaemia of the right conjunctiva. The OCT of the optic disc and macula as well as the visual field examination were unremarkable.
For further clarification, an extended laboratory check was performed. Blood count and chemogram were completely normal, immunoglobulins including IgG subclasses were normal except for an unspecific increase in IgE. ANA, ANCA, rheumatoid factors, anti-glomerular basement membrane IgG and anti-phospholipase A2 receptor IgG were unremarkable. The patient was HIV, HCV and HBV negative. cMRI revealed a relatively well defined, lobulated, T1 hypointense, T2 isointense and inhomogeneously contrast-enhancing lesion in the right cavum nasi and the right ethmoid cells measuring 2.7 x 3.6 x 3.0 cm. There was a questionable contact with the right olfactory nerve and anintraorbital tumour extension with compression of the musculus rectus medialis and lateral displacement of the bulbus oculi. The mass showed osteodestructive growth and was in close contact with the lamina cribrosa. FDG-PET/CT showed an intensely hypermetabolic lesion. Lymph node or distant metastases could not be detected. With good accessibility, a biopsy was obtained by ENT.

Ocular pathology:
Macroscopic examination:
Multiple reddish tissue fragments of a transnasal ethmoidal biopsy.

Microscopic examination:
Histologically, diffuse infiltrates arranged in nests and sheets of a partly lobular growing tumor with intervening desmoplastic stromaand evidence of bone destruction were seen. The tumor showed mainly medium-sized, polygonal, basaloid and malignant appearing epithelial cells with pleomorphic large nuclei and prominent nucleoli. Scattered among the basaloid cells, a distinct tumor cell population withprominent eosinophilic cytoplasmand large round nuclei were

identified,suggestingarhabdoid differentiation. Focally, phagocytosis of erythrocytes was seen.
Immunohistochemistry showed positivity for CK22, p16, SOX2, p40 (focal), p63 (focal), and very focally also for CK7. The cellswere negative for CK5/6, CD117 NUT and MyoD1as well as for EBV non-coding RNA (EBER). The tumor showed a consistent loss of INI1 expression with a preserved internal control.

Diagnosis:
SMARCB1-deficientsinonasal carcinoma of the right cavum nasi and ethmoidal cells with infiltration into the right orbit, TNM stage cT4a cN0 cM0.

Clinical Course:
In collaboration with the oncologists, a multimodal therapy was performed starting on 30.7.21 with induction chemotherapy (IC) with cisplatin, docetaxel and 5-FU (3 cycles: 30.7.; 6.8.; 13.9.21). During this therapy, the patient suffered from a passive thoracic pain syndrome (vasospasm), so the treatment with 5 FU (5.9.21) had to be stopped
FDG-PET/CT performed on 7.9.21 showed clear tumor regression with good partial remission.
Radiotherapy with protons was performed concomitantly with chemotherapy (cisplatin, 3 cycles) from 4.10.21 to 25.10.21 (total dose high-risk area: 74 Gy (RBE), intermediate-risk area: 56 Gy (RBE), and low-risk area: 54 Gy (RBE)). During radiotherapy, the patient suffered from radiation dermatitis, dysphagia, and oropharyngeal pain. Otherwise, the posttherapeutic course was encouraging.
FDG-PET/CT examination performed 3 months after the end of therapy (24.1.22) could not yet distinguish between postradiogenic changes and tumor persistence. Further, there was no evidence of lymph node or distant metastases.
On 9.3.22 a follow-up cMRI was performed, which showed a slightly expansive protein-rich retention (10x9mm) with marginal contrast enhancement in the area of the former tumor area in the posterior ethmoid on the right side, without macroscopic evidence of residual tumor.
The periorbital edema had subsided. The current ophthalmologic findings with a BCVA bds of 0.8, Tensio on RE 12, LE 10 showed with inconspicuous bulbus status, more mild chemosis and hyperemia of the conjunctiva bulbi on the right than on the left. The cornea, lens and ocular fundus as well as ocular motility were unremarkable.

Discussion
Sinonasal undifferentiated carcinoma (SNUC) is a rare and aggressive tumor of the nasal cavity and paranasal sinuses. The incidence rate of SNUC is 0.02 per 100’000, higher in male (0.03) than in female individuals (0.01)[1]. SNUC is often diagnosed at an already advanced stage with extensive locoregional invasion. The proportion of SNUCs with infiltration into the orbit is reported differently in the literature. Musy et al. described an orbital invasion rate of 30% [2]. Gray et al.showed orbital invasion in 63% of patients in his study [3]. At initial presentation, 10-30% of patients have metastases to the cervical lymph nodes whereasperipheral metastases are uncommon[4].
The mortality rate is high across all SNUC stages.Overall 5- and 10-year relative survival ratesof 34.9% and 31.3%, respectively, have been reported[1].
The treatment of patients with SNUC is challenging because of aggressive biologic behavior, advanced stage at presentation and early invasion of critical structures

such as the orbit/eye and the brain. A multimodal therapy is currently considered the standard of care.
In the review by Faisal et al., analysis showed that with trimodal therapy, local control was 63.9% compared with bimodal therapy at 49.2% and surgery alone at 31.3%[5]. Locoregional recurrence is associated with poor prognosis. There is much controversy regarding the implementation of prophylactic therapy of the neck region at the N0 stage [5].
In a retrospective study Amit et al. could show the role of an IC in patients with SNUC before definitive locoregional therapy [6]. Analysing 95 Patient who achieved a favorable response to IC, definitive chemoradiotherapy (CRT) results in improved the 5-year disease-specific survival of 81% compared with those who undergo definitive surgery and postoperative radiotherapy or CRT (54%) after IC. In patients who do not achieve a favorable response to IC, surgery if feasible seems to provide a better chance.

SNUC is a high-grade epithelial neoplasia. According to the World Health Organization classification, SNUC is definedas amalignantepithelial tumorwithout any identifiable line of differentiation (including squamous, glandular and neuroendocrine).
The differential diagnosis includes lymphoma, non-keratinizing squamous cell carcinoma, basaloid squamous cell carcinoma and neuroendocrine carcinoma. Whereas poorly differentiated non-keratinizingsquamous cell carcinoma and nasopharyngeal-type carcinoma frequently express CK5/6, p63 and p40,SNUC shows only lowmolecularweight keratin expression (such as CK8, CAM5.2) [7]. CK7 isexpressed in half of SNUC and squamous cell carcinoma cases [7]. Focal and patchy staining for chromogranin and synaptophysin may be seen as in our case. This isnot considered as a realneuoendocrinedifferentiationin the absence of histological features such as palisading, speckled chromatin or rosette formation of tumor cells [8].
Data on the role of HPV and p16 in SNUC have been heterogeneous and controversial. The frequency of p16 expression in SNUC range from 20% to 100% but does not correlate with HPV infection(HPV-positive SNUCs are very rare) [9,10]. SNUC is consistently Epstein-Barr virus (EBV)-negative andEBV RNA (EBER1) could not be identified also in our case. A NUT carcinoma was excluded immunohistochemically by the lack of NUTexpression.

SMARCB1-deficient sinonasal carcinoma has formerly been considered to belong to the spectrum of SNUC but according to the new WHO classification (5^{th} ed) is now defined as a distinct tumor subtype[11,12]. To date, some 70 cases have been reported in patients over a wide age range (19-89 y; median 52)[12,13]. Slightly more than half of the patients died at a median of 15 months (range 0 to 102 months).Histologically the majority (60%) of sinonasal SMARCB1-deficient carcinomas displayed undifferentiated basaloid or plasmocytoid/rhabdoid (33%) cell morphology as in our case.The immunophenotypeof sinonasal SMARCB1-deficient carcinoma is heterogenous with the consistent expression ofpan-cytokeratin (97%) but with variable reactivity for CK5 (64%), p63 or p40 (56%), CK7 (48%), and neuroendocrine markers[13].Complete loss of SMARCB1 (INI1) is a defining feature and can be identified reliably by by immunohistochemistry.

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