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Orbital Malignant Melanoma arising in Cellular Blue Nevus

Clinical History:A 52-year-old male presented on June 30, 2021, with 5 months history of increasing unilateral proptosis, eyelids swelling, diplopia in his RE in addition to a blue periocular pigmentation that he reported having been present since the age of 7.
The past medical history was notable for a right orchifuniculectomy he underwent for seminoma when he was 40.Before referral to our Ocular Oncology Unit, the patient had undergone an orbital MRI, a biopsy, and a PET/CT scan. The MRI of the brain and orbits showed an angioma already known in anamnesis, and two new masses, one of them, a 24 mm intraconal lesion, placed on the orbital floor and displacing the medial rectus muscle and the globe. The other smaller mass was in a superolateral position. The biopsy demonstrated the benign nature of the smaller lesion, consisting with a cellular blue nevus (CBN), and the malignant nature of the other one, consisting with melanoma. Mutational analysis of KIT, BRAF and NRAS genes was negative. PET/CT scans were negative for regional and distant metastasis.
On examination, an area of grey/blue discoloration of the periocular skin associated with swelling of the right upper lid and mild proptosis was evident. Small, pigmented granules in the bulbar conjunctiva were visible, and a pigmented subconjunctival multilobulated mass with an irregular surface extended from the lacrimal gland to the inferior fornix. BCVA was 20/20 in both eyes, IOP was 17 mmHg in both eyes. An incisional biopsy of the conjunctival lesion was performed in July 2021. The histological examination diagnosed a cellular blue nevus. In August, the medical oncologist decided to treat the patient with immunotherapy by nivolumab.
Other cutaneous and orbital biopsies were taken in November, due to worsening of proptosis and growth of the orbital lesion, documented by MRI. The histological diagnosis was invasive melanoma in the orbit and blue nevus in the cutaneous specimen. A PET/TC, a few days later, showedwidespread uptake of the metabolic tracer in the orbital tissue and bones. After sentinel lymph node mapping, an orbital exenteration (Kesting type IIb), together with lymph nodes biopsy, was performed on December 10, 2021. The histological examination revealed spread of melanoma to the orbital soft tissues, while the excision margins, the bone biopsies and the node were infiltrated by cellular blue nevus.
Clinical Course: One month later, in January 2022, MRI scan detected small solid nodules along the edge of the flap and in the retromaxillary tissue, and suggested perineural spread of the disease. A PET/TC, last month, described high metabolic activity in different portions of the facial massif and progression of skeletal and hepatic disease.The patient is now being treated withPembrolizumab for metastatic melanoma, waiting for genomic profiling results.

Ocular Pathology: **Macroscopic examination**: the surgical specimen, measuring 6 x 5 x 5 cm, included ocular globe, tract of optic nerve, superior and inferior eyelid skin, lateral and inferior bones, and orbital soft tissues inside which a brownish lesion of 6 cm is observed.

Microscopic examination: the melanocytic tumour was composed of elongated, slender, slightly wavy, heavily pigmented melanocytes with numerous dendritic processes, that involve the dermis and the orbital fat. The tumour showed a pattern of growthconsisting in islands of deeply pigmented spindle melanocytes alternate with islands of nonpigmented cells that have a neuroid appearance.Nerve hypertrophy was often present with perineural aggregation of cells.Inside the lesion, particularly in the inferior and infero-posterior orbital tissue, nodular areas consisting of hypopigmented, epithelioid and spindle shaped cells were identified. These cells had convoluted nuclei, prominent nucleoli and macronucleoli. Occasional mitotic figures were noted.

Immunohistochemistry revealed positive reactions for Melan-A and negative reaction for VE1, used to detect BRAF V600E mutation.Both melanoma and blue nevus cells were negative for p16.

The morphological findings were consistent with the diagnosis of *primary orbital malignant melanoma arising from a pre-existing cellular blue nevus*. Based on the eighth edition of the American Joint Committee on Cancer Staging, the patient's disease stage was determined to be pT3cN0M0.

Discussion: Primary orbital malignant melanomas (POM)are extremely rare, encompassing less than 1% of orbital neoplasms.While it can develop de novo, a subset of primary orbital melanomas can arise from a pre-existing melanocytic proliferation either in the form of diffuse melanocytosis or a melanocytic naevus, particularly of the blue naevus family. Blue melanocytic naevi, as well as diffuse mucocutaneous melanocytosis (naevus of Ota), are seen not infrequently in the orbital and conjunctival region; however, melanoma arising from such lesions is exceedingly rare. The blue naevus family is a heterogenous group of melanocytic proliferations occurring in the skin and soft tissue, meninges, and mucosa. The exact incidence is not clear. Clinically, these neoplasms manifest as variably pigmented, sometimes very dark/blue lesions, which can be flat or slightly raised. Histologically, blue naevi and melanocytoses are characterised by variably dense proliferation of elongated to dendritic melanocytes with thin bland spindle nuclei, often with cytoplasmic melanin pigmentation.Histologic variations including cellular blue naevi have been described, typically presenting as bulbous to dumbbell-shaped proliferation of fascicles of compacted spindled to ovoid melanocytes with a mild degree of cytologic atypia and limited mitotic activity.At the molecular level, blue naevi and mucocutaneous melanocytoses, like uveal melanocytic neoplasms, harbour somatic mutations in genes encoding G protein, including *GNAQ* and *GNA11* in most cases.A recent review article indicates that the mean age of presentation for POMwas 45.1,whites were predominantly affected, and the most common presentation was painless proptosis. Males were affected slightly more than females.Surgery remains the mainstay of treatment for orbital melanoma. Surgical options include local resection, debulking, or exenteration, and local adjuvant radiotherapy is commonly given.Generally, the disease is associated with poor prognosis.

Our case is quite rare, but not unusual as reported in a case series by Telladoet *al*, in which 47.5% of patients with POM had congenital melanosis and intraorbital blue nevus was present in 90%.The Literature contains isolated cases and only few large series have been reported, and with so few patients described, it is difficult to make conclusive recommendations. It may be that genetic testing provide insight into the prognosis and management of POM. However, any new case may add valuable information to better define this rare tumor.

References

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