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Malignant Peripheral Nerve Sheath Tumor (MPNST) Arising from Orbital Plexiform Neurofibroma in a Small Child With Neurofibromatosis Type 1

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Abstract

Background/Aim: Neurofibromatosis type 1 (NF1) is an autosomal dominant hereditary tumor predisposition syndrome. In approximately 30% of cases, plexiform neurofibromas (PNFs) are identified, which are precursor lesions for malignant peripheral nerve sheath tumors (MPNSTs). MPNST is a major cause of the reduced life expectancy of NF1 patients.

Case Report: The patient, a two-year-old at the time of surgical treatment, had been diagnosed with an orbital nerve sheath tumor causing lid swelling and ptosis since birth. The tumor showed disproportionately rapid growth, leading to increasing functional (mechanical) restrictions in lid elevation. Surgical exploration of the orbit indicated a PNF with areas of a MPNST. Two months later, a new biopsy confirmed the MPNST. The tumor was treated with multimodal chemotherapy. After completion of chemotherapy, orbital exenteration was performed. The tissue specimens only comprised tissue of a benign PNF. However, within six months, the patient developed an intracranial recurrence and died from a rapidly growing intracerebral tumor fraction, which histologically proved to be a MPNST.

Conclusion: Orbital PNF is a rare and characteristic manifestation of facial NF1. Typically, tumors in this localization are associated with severe functional disabilities and aesthetic disfigurement, resulting from invasive tumor growth and skeletal deformities. Histological classification of the tumors may be challenging due to varying histological differentiation in different tumor locations. Thus, early diagnosis with representative tumor sampling and complete histological work-up of the specimen together with multimodal therapy are essential prerequisites to overcome the poor prognosis of these tumors.

Keywords: Neurofibromatosis type 1, malignant peripheral nerve sheath tumor, orbit, optic pathway glioma.

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Introduction

Neurofibromatosis type 1 (NF1), an autosomal dominant hereditary tumor predisposition syndrome, occurs in approximately one in 2,500 to 3,000 live births. The gene locus is located on chromosome 17q11.2 and encodes the protein neurofibromin, which, according to current knowledge, is primarily involved in the regulation of the rat sarcoma (RAS) gene (1). RAS is a key regulator in various signal transduction pathways that regulate growth and differentiation processes. The permanent loss of a suppressor of RAS activation leads to a reduced control of RAS signaling, resulting in the amplification of RAS-driven proliferation and cell division signals that increase the risk of cell degeneration. The signaling pathways altered by RAS are among the most frequently detectable molecular prerequisites for the development of malignant diseases (2). However, NF1 is associated with various other findings, such as dysmorphic bones (3). A characteristic feature of the physical appearance in NF1 patients is the presence of tumors known as neurofibromas. These benign tumors originate from the nerves' sheath cells (or their precursors) and can vary greatly in number, primarily appearing on the skin of post-pubertal patients (1). The size of these tumors is typically limited to a diameter of a few centimeters. Another type of neurofibroma appears to develop early in ontogenesis, may interfere with the development of adjacent organs, and can become conspicuous at birth or in early childhood, particularly due to their frequent involvement of larger sections of the peripheral nervous system and the tissues supplied by the affected nerves. These tumors show a characteristic growth pattern, which can infiltrate the tissue macroscopically. Enlarged nerves display pronounced caliber changes and an intertwined, interconnected growth of the nerve cords, which early observers likened to vine tendrils (4). These tumors are called plexiform neurofibromas (PNF). In the orbital region, the combination of a neoplasm with a dysplastic phenotype limited to the extent of the tumor is characteristic of this case (5, 6).

When a PNF is diagnosed, in most cases the patient is affected by NF1 as a whole, except for segmental/mosaic forms of the disease. PNFs are classified as premalignant neoplasms that can develop into malignant peripheral nerve sheath tumors (MPNSTs). However, MPNSTs in NF1 patients preferentially develop in the trunk and extremities and not the face (7). PNFs of the face regularly cause severe disfigurement and functional impairment due to the often-considerable size of the tumors and the bone and soft tissue malformations associated with them (8). MPNSTs of the maxillofacial region of NF1 patients resulting from dysplastic PNFs have been rarely reported (9, 10). Orbital MPNSTs in patients with a confirmed diagnosis of NF1 are usually individual reports (11-15), eventually requiring extensive surgical measures (16). The present case report exemplifies the unusual occurrence of an MPNST arising from an orbital PNF in a small child affected with NF1. The article intends to raise awareness in the care of young NF1 patients with tumorous dysmorphic orbit and rapidly growing PNF.

Case Report

Medical history and treatment. This child, born to non-consanguineous parents, has had a right-sided swelling of the upper eyelid since birth. The swelling extended parallel to the upper orbital rim and increased in size as the child developed. During tumor progression, reclination of the head became necessary for consensual vision to circumvent the tumor-induced ptosis and visual field restriction. A magnetic resonance imaging (MRI) was performed to diagnose the orbital space-occupying lesion at the age of one year and 5 months. The MRI revealed an extensive orbital tumor with sphenoidal dysplasia and a glioma of the visual pathway. Additional findings included significant widening and tortuosity of the left optic nerve, a considerable increase in volume and signal enhancement in the optic chiasm, and extensive myelination disorders and gliosis affecting both visual pathways (more pronounced on the right), the pedunculi cerebri, and the medullary canal. The

orbital tumor was diagnosed as a PNF with involvement of the lacrimal gland. These findings, along with the presence of over 10 cafe-au-lait spots larger than 5 mm on physical examination, justified the diagnosis of NF1 in the child.

The MRI examination three months later showed slightly increased signal-intensive gliosis of the medullary canal and a slightly increased volume of the optic chiasm. In the anterior orbital conus below the orbital roof, there was strong contrast enhancement of the suspected PNF with continued unremarkable visualization of the normal sized right optic nerve in the post-bulbar section. At that time, the head circumference of 52 cm was 2.5 cm above the 97th percentile (at the age of 12 months: 1 cm above the 97th percentile). Prompt pupillary reaction to standardized light stimuli of the right eye, fixation with parallel eye globe position, and free pupils as well as parallel tracking of close objects on both sides with adapted head position was possible. Chemotherapy to treat the orbital tumor was initially considered. However, over the next few months, the orbital mass continued to increase in volume and raised concerns about ptosis-related amblyopia, therefore, surgical tumor reduction in the eyelid region was attempted.

At the time of the first examination at the Clinic for Oral and Craniomaxillofacial Surgery, the 2-year-and-2-month-old child had a confirmed diagnosis of NF1 (spontaneous mutation) and a congenitally noticeable asymmetry in orbital size with a right-sided enlargement (Figure 1). The patient was found to have developed appropriately for her age with an orbital tumor on the right side. The tumor largely covered the bulb, and no pain was reported. The tumor was palpably coarse and non-compressible/firm, and the covering skin over the mass was slightly displaceable. The tumor was primarily filling the outer upper quadrant of the orbit, whose increase in volume and ptosis had led to a lateral depression of the upper eyelid.

Tumor reduction was carried out two months later, primarily removing the tumor from the orbital roof and the lateral area of the globe. Since the histological examination revealed parts of a MPNST in the PNF, extended resections of the tumor were carried out. However, these only comprised PNF. Due to these findings, the child was initially treated as an outpatient and a new biopsy was performed two months later. A MPNST was diagnosed again. Based on the histological diagnosis, the decision was made to treat the MPNST with organ preservation and the child received chemotherapy. After two cycles of chemotherapy (CWD guidance; ifosfamide, vincristine, actinomycin-D and adriamycin) a third cycle was added (ifosfamide, vincristine, actinomycin). During chemotherapy, stable tumor volume was recorded (MRI). Tumor resection was recommended (pediatric oncology board) after completion of chemotherapy and patient's recovery from the medical treatment. Positron emission tomography-computed tomography (PET/CT) performed one week prior to ablative surgery showed no evidence of local fluorine-18 fluoro-deoxy-glucose (18-F FDG) enrichment in the orbital and cerebral regions, nor any indication of distant metastasis. The patient was referred for surgery (Figure 1C). The progression of tumor development in the MRI, leading up to the surgical intervention, is shown in Figure 2.

Ablative surgery of the right orbital contents including eye lids was performed in the two-year-and-10-month-old child. The tissue findings of the entire specimen showed a plexiform-diffuse PNF without signs of malignant degeneration. Healing was uneventful by secondary intention during the next two months. Sample biopsies of the orbital apex were performed 1, 2, 4, and 5 months after exenteration and in all cases demonstrated either residual plexiform/diffuse neurofibroma or tumor-free scar tissue. Due to the initially positive course of the disease, epithetic treatment of the defect was planned. Four months after resection, implants were placed in the orbital rim to anchor the epithesis (Figure 1D-G). The three-dimensional reconstruction of the skull performed in preparation for the epithetic restoration clearly shows the enlargement of the orbit with sphenoid dysplasia on the right side, typical of orbital PNF.

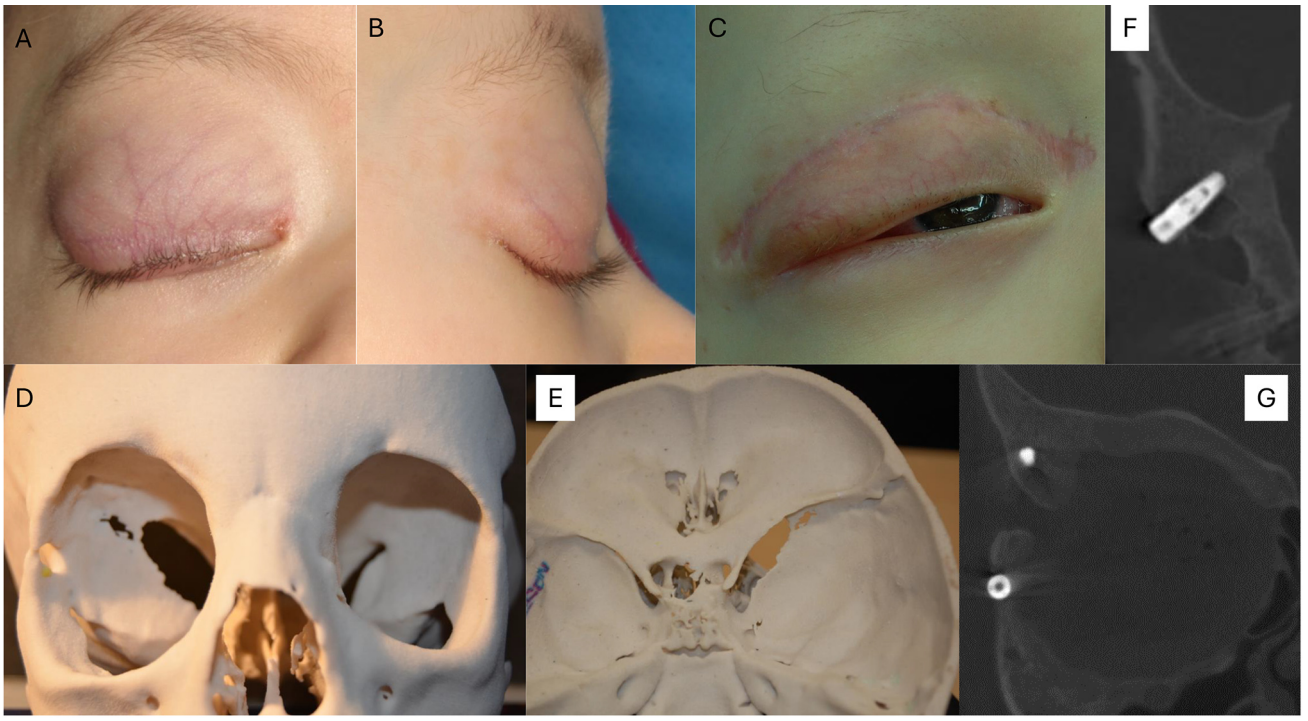

Figure 1. *En-face image of the affected right eye (A) and lateral view at the first examination (age: two years and two months) (B). Notable findings include ptosis, an enlarged upper eyelid, and clear vascularization of the upper eyelid. (C) Image of the eye after tumor debulking, reduction of the upper lid's vertical dimension, and completion of chemotherapy, prior to orbital exenteration. (D) Three-dimensional model of the skull in frontal view, showing the typical enlargement of the orbit commonly found in congenital/infancy orbital plexiform neurofibromas. The superior orbital fissure is significantly enlarged, and the infraorbital rim is dislocated caudally. (E) The top view of the skull model shows enlargement of the middle cranial fossa on the right side, an enlarged superior orbital fissure, and dysplastic sphenoid wings. The dysplasia of the sella with an enlarged left optic canal is noticeable. The width of the spheno-occipital suture is within the normal range for the patient's age. (F) Intraoperative radiographic verification of the orbital implant positions for the planned epithesis retention is shown in the lateral and anterior-posterior (G) projection of the right orbit.*

Five and a half months after tumor resection, a control MRI showed tumor recurrence from the orbital apex to the internal and medial cerebral arteries. An MRI was carried out again two weeks later due to a significant deterioration in the general condition, mainly due to neurological deficits. This imaging revealed a rapid increase in the size of the tumor. The MPNST recurrence was confirmed by a biopsy of the tumor growing into the defect cavity. Due to the tumor progression and the lack of surgical and chemotherapeutic treatment options, further treatment was carried out with palliative intent. The child died eight months after the ablative surgery with signs of cerebral tumor progression.

Molecular genetics. Molecular genetic testing of a blood sample identified a pathogenic heterozygous mutation c.1028deIT (p.Phe343SerfsX33) in exon 7 of the *NF1* gene. *Histology.* First orbital biopsy. Cell-dense, spindle cell-type, mesenchymal differentiated tumor with cord-like growth. The oval cell nuclei had an eosinophilic cytoplasm. The tumor cells had numerous mitoses, and fresh bleeding was noticeable in the tissue sections. Within the tissue there were numerous nerve fascicles in which the normal nerve tissue was displaced by parts of the PNF. Within the tissue samples, the malignant tumor cells lacked immuno-reactivity for the S-100 and CD34 antibodies but exhibited moderate vimentin positivity

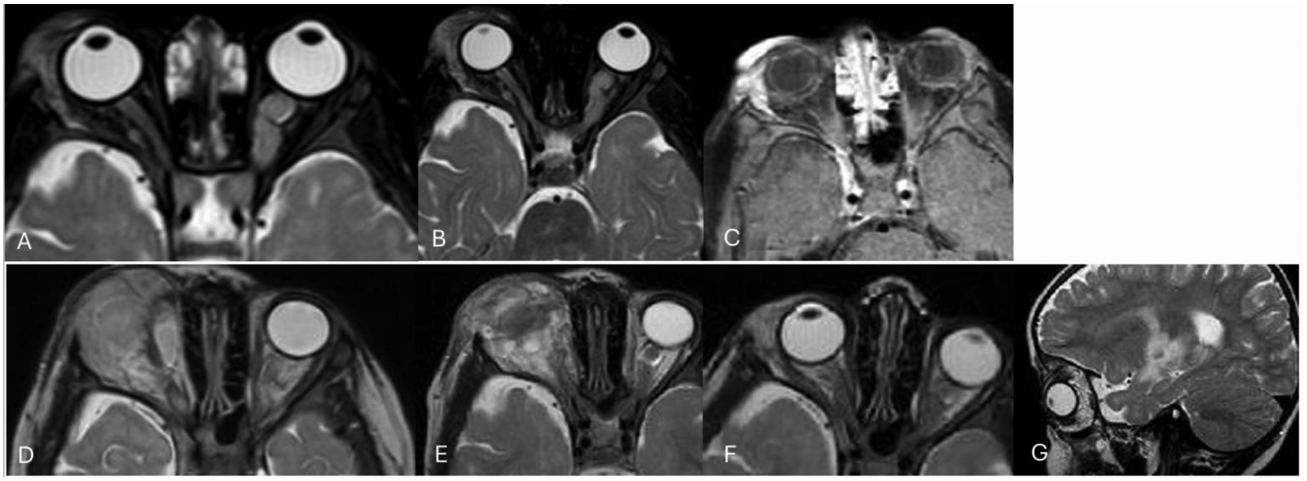

Figure 2. *Axial magnetic resonance imaging (MRI) of the patient over time. (A) First image of the mass at the age of one year and five months shows the tumor under the roof of the orbit and predominantly in the lateral area of the cavity. The left-sided optic glioma is shown. (B) Three months later, a similar finding was noted. (C) The tumor appeared unchanged in size but somewhat inhomogeneous three months later. (D) After considerable reduction of the tumor, tumor recurrence appeared just two months later. (E) Four weeks later, shortly before the start of chemotherapy, imaging revealed an inhomogeneous tumor occupying the upper area of the orbit, exiting from the lateral to the medial border. (F) Images of the orbit after two cycles of chemotherapy. The tumor has regressed significantly (two months prior to exenteration; compare with Figure 2A). (G) Sagittal view prior to exenteration.*

and strong expression of p75. The proliferation rate (Ki-67 index) was 60%. In the PNF areas, there was S100 positivity (Ki-67 negative). Only parts of normal nerves in the resected specimen expressed neurofilament. The diagnosis was MPNST grade III, according to the FNCLCC, arising in an orbital PNF (Figure 3).

Orbital exenteration. The specimen showed a globe with adnexa and eyelid skin as well as parts of a neoplasia close to the orbital optic system. The tumor showed no necrosis and had grown partly diffusely but predominantly in nodules surrounded by the perineurium. The tumor was of low to medium cellularity. The neoplasm had grown mainly in the eyelids, but was also detectable in all border regions of the specimen (temporal, nasal, caudal, cranial). A predominantly plexiform, partly diffusely grown neurofibroma (PNF, WHO grade I) without areas of a MPNST was diagnosed. The tumor did not infiltrate the sclera. In the specimen's border section near the orbital apex, parts of the optic nerve were identified, which were not infiltrated by the surrounding PNF (Figure 4).

Discussion

The case report describes the fatal outcome of an infant with unilateral congenital orbital PNF and malformation of the orbit who developed MPNST in the PNF, underwent combined surgical and medical treatment, and died from the intracranial spread of the tumor. MPNSTs of the orbit are rare, and their association with neurofibromatosis was documented early on (13).

Orbital PNF. Orbital benign peripheral nerve sheath tumors as single findings are relatively common (13). Sporadic neurofibromas are well documented in the literature on orbital pathology and surgery. They are usually characterized as solitary or present in small numbers, with nodular tumors that are generally small in size (13).

In contrast, orbital nerve sheath tumors in NF1 usually occur as plexiform or diffuse-plexiform tumors, infiltrating a larger area of the cavity and involving various structures such as the muscles, lacrimal gland, or globe (7). A

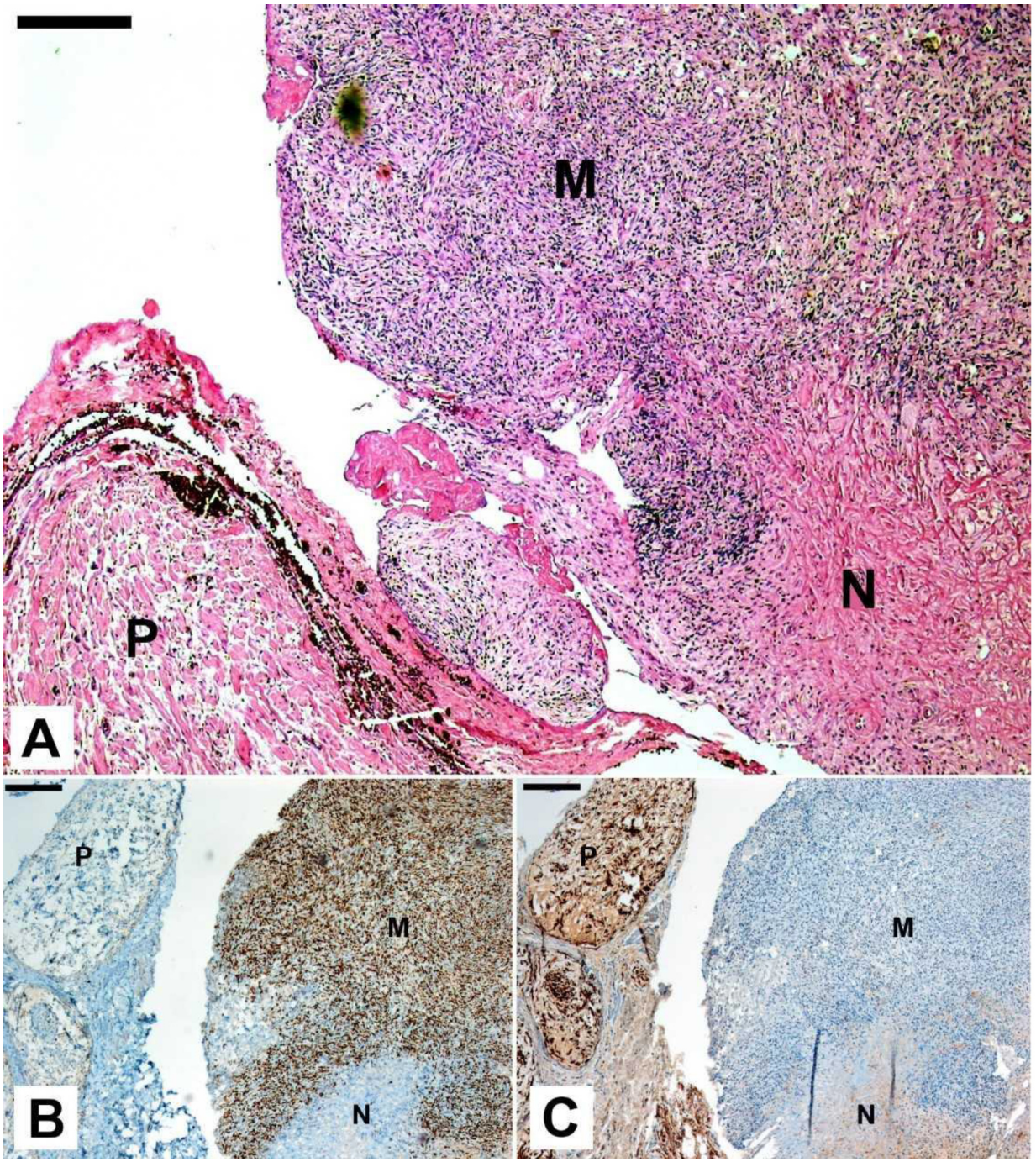

Figure 3. *Histology of the first biopsy. (A) Spindle cell tumor with high cellularity (M) and areas of necrosis (N), indictive of MPNST. Sections revealed a tumor of low cellularity with a myxoid matrix growing within the perineurium (P), typical for a plexiform neurofibroma (PNF) (H&E stain, scale bar 200 µm); (B) The same tumor as in (A): immunohistochemical staining with the proliferation marker Ki-67 shows a high percentage of positive nuclei in the MPNST (M) and a low number of stained nuclei in the PNF (P); (C) Same tumor as in (A): immunohistochemical staining for the S100 antigen highlights labelling in the PNF (P) and loss of S100 expression in the MPNST (M). Chromogen used in (B) and (C): diaminobenzidine; counterstain: alum hematoxylin; Scale bar 200 µm.*

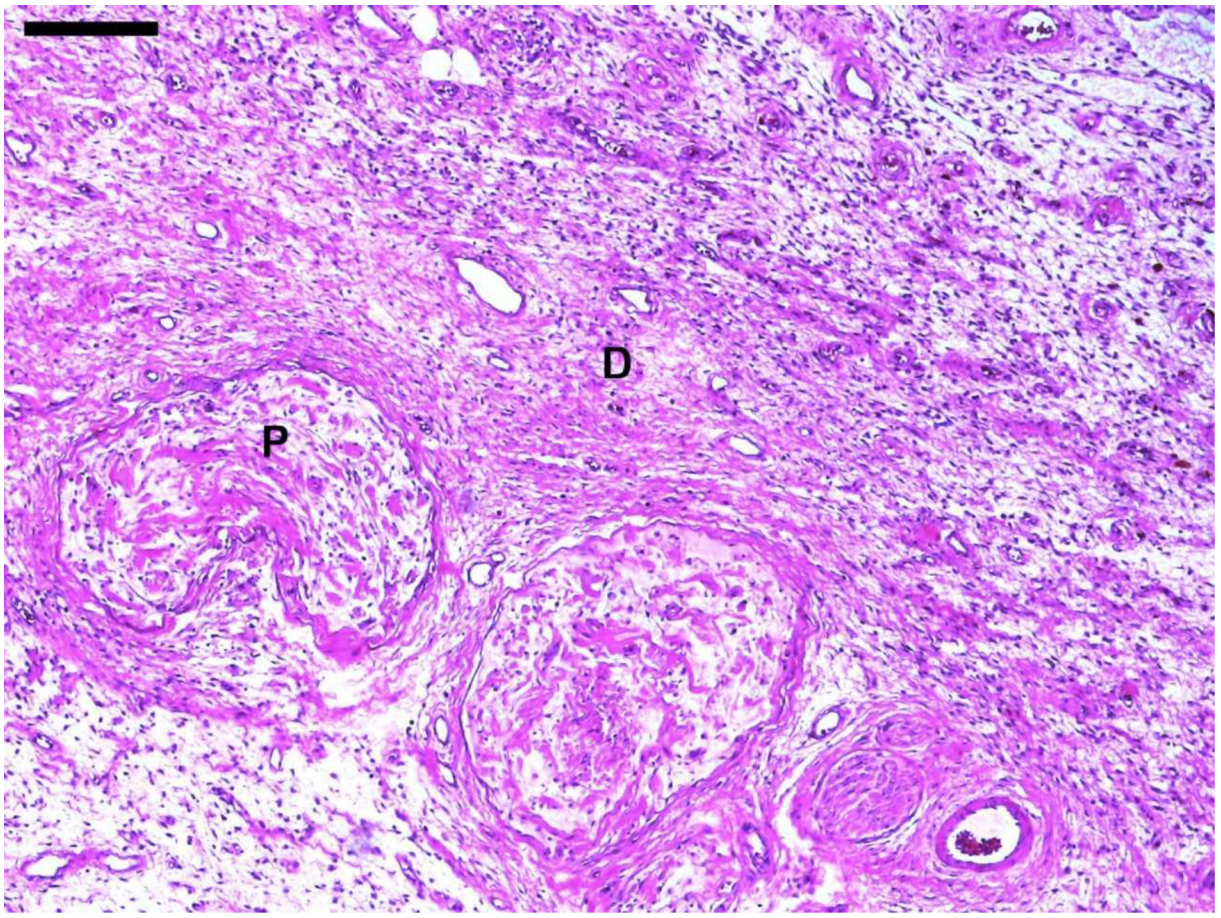

Figure 4. *Tumor tissue from the orbital exenteration showing a tumor of low cellularity with myxoid matrix focally growing as plexiform neurofibroma within the perineurium (P) and diffusely infiltrating the neighboring tissue as diffuse neurofibroma (D) (H&E stain, scale bar 200 µm).*

predilection for the upper outer quadrant in NF1-associated PNF often causes lateral drooping of the upper eyelid due to the tumor's mass and weight. This presentation should raise suspicion for an orbital tumor, especially in pediatric patients (17).

Orbito-facial PNFs often behave aggressively, resulting in the invasion and destruction of adjacent tissues. However, unlike some characteristics of a malignant disease, the extent of orbital PNF is usually limited to the segment of the body from where they originated (7). In the orbit, the assessment of the tumor biology is complicated by the fact that although the bone shows typical and thus categorically rationalizable changes, such as defects and deformations of the orbital frame, these changes can intensify over time, especially during childhood (18). Changes in the meninges and temporal lobe may be additional factors that characterize tumor biology and phenotype (19, 20). The spread of the tumor in the orbital region and neighboring regions (temporal, frontal, cheek) can often be recognized in early childhood (17). However, individual cases with later and more extensive tumor manifestations challenge the general validity of this predictive assessment (21). In fact, PNFs are slowly progressive tumors that cause lifelong dysmorphia, particularly evident in the delicate structures of the orbital contents and adnexa (19). Transformation into MPNST is exceedingly rare (7).

MPNST in children. MPNST is a rare malignancy in the pediatric population. The first signs of MPNST are usually uncharacteristic. The diagnosis should be considered in children who develop an enlarging and/or painful soft-tissue mass (22, 23). NF1 is identified in up to half of the MPNST patients (24). Topographical association of PNF and MPNST in NF1 patients is a serious diagnostic problem. The transition of PNF into a MPNST is a histologically well-defined process in NF1 patients (25, 26). MPNST is one of the main reasons for the lower life expectancy of this patient group compared to the normal population (24). MPNST develops preferentially in the extremities and trunk irrespective of the syndrome-associated or sporadic origin (27). The head and neck regions are rarely affected, except for MPNST of the deep cervical nerves, namely the vagal nerve (22).

MPNST of maxillofacial regions. A comprehensive analysis reporting on 3,267 patients with MPNST noted 449 (13.7%) primary manifestations in the head and neck and 167 (5.1%) in the cranium (27). A meta-analysis restricted to oral and maxillofacial MPNST analyzed 57 cases (28). Only in 23 of 57 patients it was possible to clarify whether the patients had had NF1 (23=100%). For the remaining cases where NF1 was excluded, 91.3% (n=21) showed no evidence of NF1, while 8.7% (n=2) demonstrated evidence of NF1. Despite the limited number of reports investigating the potential genetic background (NF1) of malignant development, this analysis found that the syndrome was significantly associated with a lower survival rate (28). MPNST of the maxillofacial region develops mainly in the paranasal cavities and can infiltrate the orbit in the case of tumor progression. The spread of maxillary MPNST into the orbit is a common progression of this tumor (10) and is difficult to treat (9). In the analysis of maxillofacial MPNSTs (n=43), 13 patients (30.2%) were affected by NF1 (10). The authors of the study emphasized that a significantly larger proportion of patients developed sporadic MPNST compared to those with NF1. Notably, the orbit was not included among the regions of origin for maxillofacial MPNSTs in this study (10).

MPNST of orbit. MPNSTs that arise primarily in the orbit are rare (11, 13, 29). A current literature review of orbital MPNSTs describes evidence of NF1 in 10 of a total of 38 cases [26.3% (30)]. The age of the patients was 29.9 years (range=5-75 years; male: n=6; female: n=4). Only four of the 10 NF1 patients with orbital MPNST survived tumor-free for more than two years. Two of the NF1-associated MPNSTs were identified as post-radiogenic MPNSTs, arising following radiotherapy for an optic pathway glioma (OPG) (30). Sporadic MPNSTs of the orbit can arise from a neurofibroma (31, 32), challenging the earlier assumption that sporadic PNFs are not precursors of MPNSTs (33). This finding has important implications for the diagnosis and management of these tumor patients.

Reviews analyzing the proportion of NF1-associated MPNSTs show that the rate is significantly higher when the selection criterion is a tumor arising in the orbit, compared to analyses focusing on MPNSTs of the maxillofacial region.

The apparently unique case of NF1-associated orbital MPNST with glandular differentiation in a 9-year-old boy (14) is an important reminder to carefully examine the entire orbital contents for changes in shape and structure. It also highlights the morphological mutability of this highly malignant tumor.

Optic pathway glioma. The most common neoplasm of the CNS in NF1 patients is the optic nerve glioma (34, 35). The association of OPG and PNF is less frequent (13). The simultaneous diagnosis of OPG with orbital rhabdomyo-sarcoma in NF1 is probably unique (36), but confirms the need for prompt and detailed diagnosis of orbital masses in these patients (37).

In the present case, a symptomatic orbital tumor was the reason for a comprehensive imaging diagnosis, which revealed the extent and initial characteristics of the orbital tumor. In addition, the MRI showed tumor involvement in adjacent organs (lacrimal gland), as well as skeletal abnormalities (macro-orbit, sphenoid bone defect). Changes were also observed in the brain, specifically in the temporal lobe on the side of the tumor. While the findings

on the tumor-affected side, in connection with the pigment disorder, can provide a clinical suspicion, the diagnosis of the OPG was based solely on imaging, which also revealed a pathology on the opposite side. Irrespective of the importance of MRI in the oncological care of such patients, the multiple pathologies of the brain and skull base identified here underscore the demand for early and adequate imaging in patients with suspected NF1.

Advanced imaging in NF1 patients. Attla *et al.* (38) evaluated the whole-body MRIs (WBMRI) of 83 consecutive NF1 patients for the detection of PNF and the association of these tumors with the subsequent development of MPNST. Eight patients were diagnosed with MPNST, out of a total of nine identified tumors. Only one patient in this group (11%) developed MPNST four years after WBMRI. The authors conclude that there is no predisposition to the development of MPNST from PNF in patients with NF1. The case presented highlights that, while MRI can offer valuable insights, it currently provides only approximate indications of malignancy developing within a PNF (39, 40). However, WBMRI makes a significant contribution to the assessment of tumor burden to design targeted clinical and imaging follow-up in the event of tumor detection (37). Larger tumor conglomerates with conspicuous local differences in differentiation, indicated by signal changes or volume increases, are probably easier to interpret for this prophylactic diagnosis. In contrast, malignancies that arise in small areas with high invasive potential and fail to produce diagnostically useful signals remain challenging to detect and assess (40). The clinical and radiological findings of MPNST on MRI may initially be indistinguishable from those of a peripheral nerve sheath tumor (41). Comparison with preliminary radiographs of the region is valuable, as rapid tumor growth and evidence of soft tissue or bone destruction are strong indicators of malignancy (42). However, the application of these criteria to orbital PNF is sometimes difficult, because the plexiform-diffuse growth pattern of these tumors can be invasive and destructive, affecting structures such as the orbital muscles, lacrimal gland, and orbital bones (7). Additionally, the most significant growth phase of the benign tumor typically occurs during the first decade of life (17, 37).

18 FDG PET has significantly improved the differential diagnosis and follow-up of peripheral nerve sheath tumors in NF1 patients (43). However, its utility in identifying tumor biology is limited due to the overlap of threshold values that can be measured in both PNF and MPNST, making it challenging to distinguish between the two entities reliably (44). In the PET-CT performed prior to orbital exenteration in the presented case, no signal abnormalities were detected. Histological examination of the specimen confirmed the presence of a PNF in all analyzed sections.

Conclusion

This report describes the fatal course of an NF1-associated orbital MPNST that had arisen from a congenital PNF. Despite undergoing chemotherapy and orbital exenteration with histologically confirmed R0 resection, the tumor led to a fulminant intracranial recurrence. Although orbital MPNST in NF1 is very rare and the manifestation of the malignancy in a small child is an exceptional event to date, the news should support current recommendations to include NF1 patients and orbital PNF in regular, standardized monitoring (37).

Conflicts of Interest

The Authors have no conflicts of interest related to this work.

Authors' Contributions

Treatment of patient: REF; Histological evaluation: CH; Drafting the article and final approval: REF, CH.

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