molecular testing of parents for more accurate recurrence risk counseling.[4]

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Management of orbital rhabdomyosarcoma in a child with Li-Fraumeni syndrome

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This case highlights the management of orbital rhabdomyosarcoma in a child with Li Fraumeni syndrome (LFS). Treatment with chemotherapy and eventual orbital exenteration enabled margin-free control of the tumor. Radiation therapy was avoided to reduce the risk of inducing additional malignancy. Reactive orbital hyperostosis was observed postoperatively and was confirmed with surgical biopsy of the orbital roof. In this case, systemic surveillance imaging, which is necessary in patients with LFS, revealed an adrenal cortical carcinoma.

An 18-month-old-boy presented with a 5-week history of nontender, progressive right periorbital swelling (Figure 1A). Examination showed fullness of the right upper eyelid, proptosis, and hypoglobus with limited supraduction. He was otherwise well, with no evidence of fever or systemic illness. Maternal family history was significant for brain, esophageal, and breast cancer.

Magnetic resonance imaging (MRI) with gadolinium demonstrated a multilobulated right orbital mass that involved both intraconal and extraconal spaces surrounding and displacing the right globe anteriorly and occupying the anterior superior and medial aspects of the orbit (Figure 1B). The lesion was isointense to muscle on T1-weighted images with heterogeneous enhancement. There was erosion of the lateral margin of the orbit without intracranial extension.

An incisional biopsy confirmed a diagnosis of rhabdomyosarcoma with anaplasia. A focal nesting pattern of reticulin staining suggested the alveolar histologic subtype. Immunohistochemistry did not demonstrate either the t(1:13)(p36:q14) or t(2;13)(q35;q14) reciprocal translocations typical of alveolar histology, although 23% of alveolar rhabdomyosarcoma may be PAX-fusion negative.[1] Bone marrow biopsies showed no evidence of malignant infiltration. Genetic testing of the patient and his mother revealed heterozygosity for a *TP53* germline mutation (exon 8: c.880dup [p.Glu294fs]), confirming the diagnosis of Li-Fraumeni syndrome.

Orbital radiation was avoided because of the risk of inciting a secondary malignancy. The patient received neoadjuvant chemotherapy with vincristine, dactinomycin, and cyclophosphamide, according to the Children's Oncology Group ARST0331 protocol for low-risk RMS. Subsequent neuroimaging studies demonstrated a reduction in the tumor size. After undergoing a surgical debulking procedure elsewhere that did not provide margin-free control, he underwent a right orbital exenteration. Histopathological examination showed residual viable rhabdomyosarcoma with features of rhabdomyoblastic/cytic maturation. The margins of resection were tumor free. To enable postoperative monitoring, no reconstructive flap was placed over the bone. Subsequent postoperative examinations demonstrated a healing right orbital socket, with no evidence of discharge or recurrence.

Four months after exenteration, computed tomography revealed expansion of the right orbital roof (Figure 2A). Suspicion was raised for tumor recurrence or a second primary malignancy such as osteosarcoma. Biopsy of the right orbital roof was aided by intraoperative imaging

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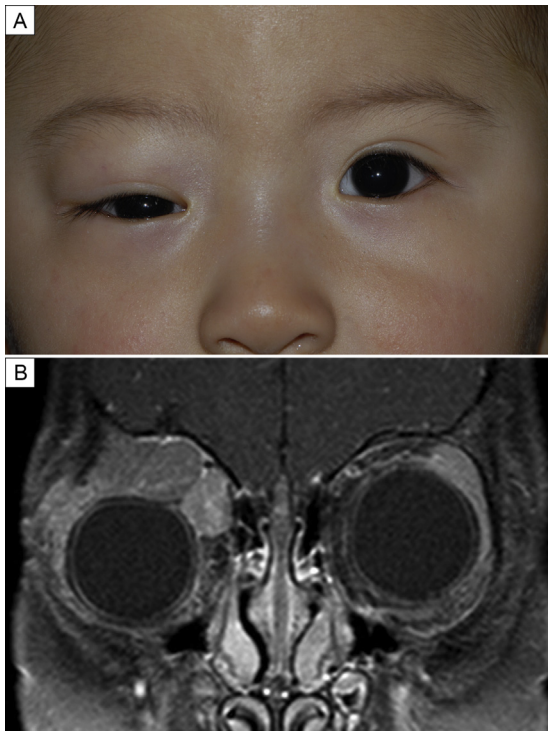

FIG 1. A, Clinical image at presentation demonstrating right proptosis, superior orbital fullness and hypoglobus. B, Magnetic resonance imaging of the brain and orbits showing a 1.3 × 2.6 × 2.1 cm multilobulated infiltrative right orbital mass, with bony erosion of the lateral orbital wall. The lesion was isointense to muscle on T1-weighted images and demonstrated heterogeneous contrast enhancement.

(Figure 2C). Histopathological examination showed anastomosing trabeculae of woven bone as well as focal osteoid formation and permeation (Figure 2D). There was mild pleomorphism and atypia, osteocyte crowding, and a lack of osteoblast rimming, which raised concern for a low-grade osteosarcoma, though an atypical reactive condition was also considered. The bony changes along the orbital roof have remained stable over 4 years of monitoring, with no evidence of tumor recurrence. Whole-body MRI identified a large adrenal mass, which was subsequently resected and found to be an adrenal cortical carcinoma, for which he received modified chemotherapy, according to the COG ARAR0332 protocol, with complete surgical resection.

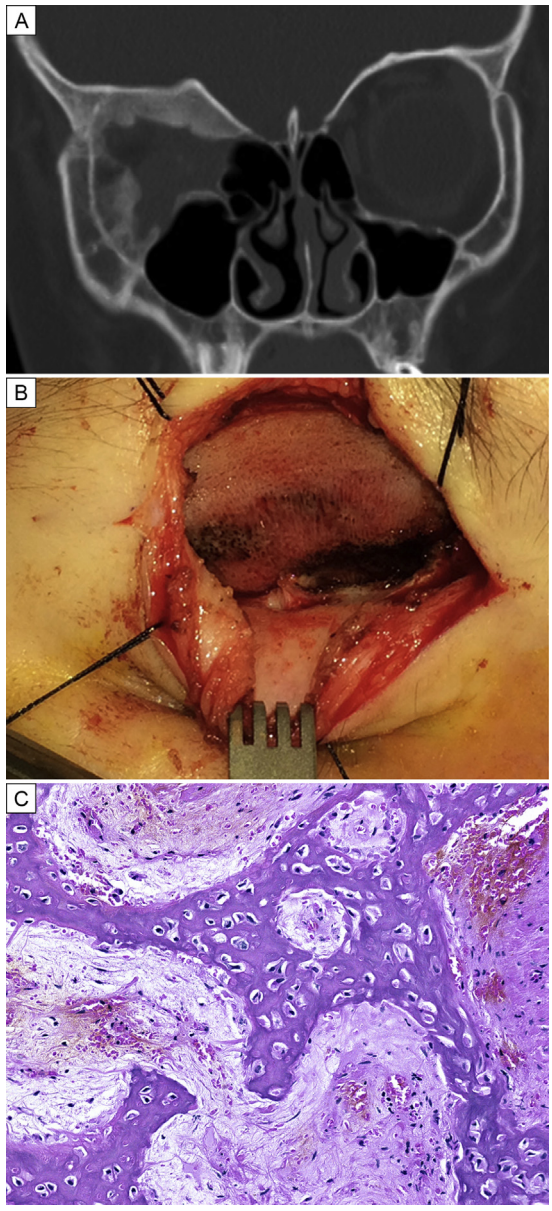

FIG 2. A, Four months after orbital exenteration, computed tomography revealed progressive expansion of the right orbital roof. B, Surgical photograph of the abnormal superior orbital bone in the previously exenterated right orbit. C, Pathology of superior orbital bone revealed mild pleomorphism and atypia, osteocyte crowding, and a lack of osteoblast rimming, which raised concern for a low-grade osteosarcoma or an atypical reactive condition.

Discussion

Orbital rhabdomyosarcoma is the most common malignant orbital neoplasm in children. Current management of primary orbital rhabdomyosarcoma involves systemic chemotherapy and radiotherapy, with the particular combination being tailored to the location, extent, and stage of the tumor.[2] Orbital exenteration, the treatment of choice for rhabdomyosarcoma until the 1970s, was not associated with significant improvements in mortality and is a disfiguring operation. The Intergroup Rhabdomyosarcoma Studies examined the outcomes of various combinations of chemotherapy and radiation for rhabdomyosarcoma and demonstrated improved outcomes; therefore, the present role of exenteration is limited to extremely advanced presentations such as compromise of the eye or tumor resistance to irradiation or chemotherapy.

Li-Fraumeni syndrome (LFS), an autosomal dominant disorder most commonly resulting from germline mutations involving tumor protein 53 (TP53), is associated with characteristic tumors including sarcomas, premenopausal breast cancer, adrenocortical carcinomas, brain tumors (particularly choroid plexus carcinomas), and leukemia.[1,3] LFS must be considered when patients present with rhabdomyosarcoma at a young age. Ognjanovic and colleagues[4] found that *TP53* germline mutation carriers presented with rhabdomyosarcoma at a mean of 4.3 years. Sporadic cases, such as those with no germline mutation, present at 8.0 years.[4] Patients harboring *TP53* mutations may lack a family history of cancer; de novo mutations occur in up to 20% of patients who therefore fail to meet clinical criteria for LFS. It has been suggested that all patients presenting with rhabdomyosarcoma before 5 years of age be considered for *TP53* testing.[5] Children with LFS require additional oncologic screening as outlined in the "modified Toronto protocol."[6] Our patient required surgical resection of an adrenal cortical carcinoma which was discovered on surveillance whole-body MRI. Genetic counseling and testing should be offered to family members.

Management of rhabdomyosarcoma in the context of LFS poses a unique clinical challenge, particularly with respect to radiation therapy. A systematic review of patients with LFS treated for choroid plexus carcinoma found that the survival of patients treated with adjuvant radiation was inferior to that of patients receiving surgical resection and chemotherapy.[7] There are reported cases of patients with LFS who developed sarcomas within the field of radiation. To our knowledge, two other cases of orbital rhabdomyosarcoma occurring in patients with LFS have been described. In the first, initial chemotherapy and radiation were unsuccessful in controlling tumor proliferation.[8] In the second, surgical debulking of the orbital tumor was performed, but additional treatment and follow-up were not described.[9] We believe that the present evidence, while limited, does not support the role of adjuvant radiotherapy in patients with LFS and orbital rhabdomyosarcoma.

Progressive expansion of the right orbital roof was identified four months after exenteration. The primary diagnostic considerations included tumor recurrence, a second primary malignancy, or reactive postoperative bone proliferation. Histopathologic analysis of the orbital roof biopsy could not distinguish between low-grade osteosarcoma and atypical reactive proliferation. The stability of our patient's clinical and radiologic examinations after 3 years' follow-up supports a benign etiology.

To our knowledge, this is the first reported case of hyperostosis following orbital exenteration in a child. Fleming and colleagues[10] described three cases of diffuse uniform orbital hyperostosis in adults following exenteration surgery after the socket was left to heal by secondary intention, each with a prolonged granulation period. The authors postulated that low-grade chronic osteitis developed as a result of recurrent episodes of inflammation and prolonged healing led to reactive orbital hyperostosis.[10] Elkhamary and colleagues[11] published a retrospective case series of 27 patients who underwent unilateral orbital exenteration, of whom 17 (73.9%) had evidence of postoperative hyperostosis. Immediate intraoperative socket rehabilitation with musculocutaneous flaps was significantly associated with reduced odds of developing hyperostosis. It is likely that our patient's exenterated socket, which was left to granulate to monitor for recurrence, developed a chronic osteitis, prompting new bone formation.

Ophthalmologists should be aware of the possibility of LFS and perform genetic testing when rhabdomyosarcoma presents early in life (≤5 years) or when there is a family history of atypical malignancies. Additional cancer surveillance and radiotherapy-related morbidity must be considered in the management of children with LFS. Hyperostosis may be observed after orbital exenteration and may be more likely when the socket is left to heal by secondary intention.

Literature Search

PubMed was search.ed on October 12, 2018, without date restriction, for English-language results, using the following terms singly and in combination: *rhabdomyosarcoma*, *orbit*, *Li Fraumeni*, *hyperostosis*, and *exenteration*.

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Acquired monocular nystagmus in chiasmal glioma—a video-oculographic study

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We report the case of a 9-year-old girl with chiasmal glioma and longstanding monocular nystagmus, in whom video-oculography showed a disconjugate binocular nystagmus indistinguishable from spasmus nutans. The "acquired monocular nystagmus" associated with chiasmal glioma is actually a binocular nystagmus that is indistinguishable from spasmus nutans, except that it lacks the associated head nodding and torticollis. Superimposed visual loss in one eye predisposes to acquired monocular nystagmus and explains the absence of the other components of the spasmus nutans triad.

Spasmus nutans is a benign, self-limiting clinical entity characterized by an asymmetric nystagmus, head nodding, and torticollis.[1] It generally begins between 6 and 12 months of age and resolves over months to years.[1] The nystagmus is of low amplitude and high frequency, and is asymmetrical in the two eyes. Most cases are idiopathic, but some children are found to have congenital retinal dystrophies.[2] It is the critical association with chiasmal glioma that dictates clinical management.[3-6] In most cases, chiasmal glioma is signaled by associated findings, such as a relative afferent pupillary defect, optic atrophy or disk swelling, large head size, café au lait spots, and coexistent neurological dysfunction.[4] Rarely, however, these associated neurological abnormalities are absent.

In some children, chiasmal glioma can present as acquired monocular nystagmus.[5] Farmer and Hoyt[5] described 10 children with monocular nystagmus in infancy or early childhood. Neuroimaging revealed that 6 of these patients had chiasmal glioma, whereas 4 had no tumor and were diagnosed as having spasmus nutans. Acquired monocular nystagmus can also accompany unilateral congenital visual loss and resolve following successful treatment of associated amblyopia.[6]

To our knowledge, eye movement recordings have not been performed in children with acquired monocular nystagmus due to chiasmal glioma. Pathogenetically, these high-resolution measurements are critical, because there is no known mechanism by which the human ocular motor pathways can generate a purely monocular nystagmus. To elucidate the true nature of this condition, we obtained video-oculography for a 9-year-old girl with chiasmal glioma who had longstanding isolated monocular nystagmus.

Case Report

A 9-year-old girl with chiasmal glioma had been followed at the Mayo Clinic Department of Ophthalmology for a monocular nystagmus of the left eye that was first noted at 6 years of age. She had no stigmata of neurofibromatosis 1, no family history of nystagmus, and was neurodevelopmentally normal.

On ophthalmologic examination, visual acuity was 20/20 in the right eye and 20/250 in the left eye (reduced from 20/60 at age 6). She had a normal pupillary response to light in the right eye and a sluggish pupillary response to light, with a 2+ relative afferent pupillary defect, in the left eye. A pendular vertical nystagmus of moderate amplitude and frequency was noted in the left eye only (Video 1, available at jaapos.org). SensoMotoric instruments (SMI) video-oculography showed a disconjugate binocular pendular nystagmus of low amplitude and high frequency in the right eye and high amplitude and low frequency in the left eye (Figure 1). Retinoscopy showed a mildly hyperopic refractive error (+1.00 sphere) in both eyes. Retinal examination disclosed small optic disks, with a bilateral band atrophy that was worse in the left eye. Humphrey 30-2 visual field testing disclosed bitemporal hemianopia.

Magnetic resonance imaging revealed enlargement of a homogeneously enhancing mass involving the optic chiasm, with extension along the intracranial optic nerves bilaterally (Figure 2). The superior aspect of the tumor was larger on the left, corresponding to the more severe visual loss and optic atrophy in the left eye. The tumor exerted a local downward mass effect on the pituitary gland, but no extension to the hypothalamus was found, endocrinologic testing disclosed no abnormalities.

Discussion

Gottlob and colleagues[7] used eye movement recording to define the electro-oculographic waveform of spasmus nutans as a disconjugate binocular pendular nystagmus with the two eyes oscillating out of phase. In our patient with a longstanding chiasmal glioma, video-oculography showed the isolated monocular nystagmus to be a subclinical binocular nystagmus that conformed to the waveform

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