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Spindle Cell/Sclerosing Rhabdomyosarcoma of the Orbit

Abstract

A three-year-old boy developed proptosis over three weeks. Computed tomography and magnetic resonance imaging disclosed a 3.2 x 1.9 cm soft-tissue mass of the right extraconal and intraconal orbit with right sphenoid bone erosion. After debulking through an upper eyelid crease incision, the tumor was diagnosed as a spindle cell/sclerosing rhabdomyosarcoma. DNA sequencing was negative for an L122R mutation in *MyoD1*. Spindle cell/sclerosing rhabdomyosarcomas are an uncommon variant of this neoplasm, and only two patients with orbital tumors have been reported in two case series. Spindle cell/sclerosing rhabdomyosarcomas confined to the orbit and lacking *MyoD1* mutations have an excellent prognosis when treated with chemotherapy and radiation therapy. Diagnosis and treatment planning rely on histology, immunohistochemistry, and molecular analysis.

Introduction

Rhabdomyosarcoma (RMS) is a high-grade malignant tumor, develops from mesenchymal cells of uncertain origin,[1]and exhibits myogenic differentiation.[2] Approximately 350 new RMS cases are diagnosed per year in the United States[2] with an estimated incidence of 4.5 cases per million population among children ages 0-14 years.[3] RMS, though rare, is the most common malignant orbital tumor in children, accounting for about 40% of cases.[4,5] It is estimated that 37 new cases of orbital RMS occur per year in the USA.[4]

The categorization of RMS into subtypes has changed over the years and is currently based on clinicopathological features and genetic differences.[6,7] The most common subtype is embryonal, which accounts for about 60% to 70% of cases in children less than ten years of age.[3] This subtype is most common in the head and neck region and genitourinary tract,[2]and accounts forabout 70% oforbital RMS.[8-10]Alveolar RMS (ARMS) is the second most common subtype accounting for approximately 20% to 25% of RMS cases.[3] ARMS is equally distributed among all age groups but is the most common type in teenagers and young adults.[2] ARMS is most common in the extremities, less common in the head and neck or torso,[2]and accounts for12% to 25% of orbital RMS.[8-10] Pleomorphic RMS is most common in adults in their 50s, often involves the legs,[2]and is estimated to account for 1-2% of orbital RMS.[4] Jones, Reese, and Krout classified about 20% of their orbital neoplasms as pleomorphic RMS; however, many of their

tumors likely represented ARMS.[10]Spindle cell/sclerosing RMS (SSRMS) accounts for 5% to 10% of RMS,[11] affects all age groups of both sexes,[6,12,13] and is most common in the head and neck, paratesticular area, and the extremities.[6,12,13]Here, I describe a child with orbital SSRMS, a rarely reported site for this neoplasm.[12,13]Collection and evaluation of protected health information complied with the Health Insurance Portability and Accountability Act.

Case Presentation

A three-year-old previously healthy boy developed worsening swelling of his right eye over three weeks. Ophthalmological examination noted "gross" proptosis of the right eye, no injection, normal extraocular movements, the child fixed and followed movements with both eyes, and both pupils were reactive to light and accommodation. The right palpebral fissure did not close completely during sleep. Slit-lamp and fundus examinations were unremarkable. Computed tomography and magnetic resonance imaging (MRI) disclosed a 3.2 x 1.9 cm soft-tissue mass of the right extraconal and intraconal orbit. The tumor wasrelatively isointense to the brain parenchyma, encompassed the lateral rectus muscle, tracked along the periosteum, eroded the adjacent greater wing of the right sphenoid bone, and caused proptosis.

Biopsy and debulking of a majority of the orbital mass through an upper eyelid crease incision revealed interlacing fascicles of spindle-shaped cells with interspersed small scattered foci of brightly eosinophilic collagen. A large majority of the tumor cells (>90%) expressed desmin, approximately 75% of the tumor cell nuclei expressed myoblast determination protein 1 (MyoD1), about one-half of cells stained for smooth muscle actin, 5% had nuclear expression of myogenin, and there was weak focal staining for muscle-specific actin in 1% of cells. The tumor cells did not express S100 protein, calponin, or SOX10. *Forkhead box protein 01*(*FOX01*) gene rearrangement was not detected using fluorescent in situ hybridization break-apart probe, and sequencing was negative for an L122R mutation in *MyoD1*. The pathological diagnosis was SSRMS, French Federation of Cancer Centers Sarcoma Group (FNCLCC) grade G3 (mitotic count = 3, necrosis = 1, and tumor differentiation = 3)and pathological stage pT2. Postoperative positron emission tomography scan disclosed only residual non-avid tissue in the right orbit and no metastatic disease. No metastatic disease was detected using a bone marrow biopsy.

The child is under treatment with vincristine, dactinomycin, cyclophosphamide, and proton beam radiotherapy (Children's Oncology Group protocol ARST0331, subset 1; ClinicalTrials.gov identifier: NCT00075582)[14]for stage 1/group III[15] low-risk rhabdomyosarcoma.He developed periorbital erythema with intermittent serosanguinous drainage after proton beam radiotherapy. MRI after ten weeks of chemotherapy showed a significant decrease in the orbital mass size and no metastases to the chest. MRI following six months of therapy showed a 0.8 x 05 cm residual tumorfocus having less contrast enhancement than before treatment.

Discussion

Spindle cell RMS and sclerosing RMS have been classified together since 2013 as a distinct subtype of RMS based on overlapping morphological features.[6]SSRMS has variable histology ranging from tumors composed of fascicles of spindle cellsto others with prominent hyalinization/sclerosis with tumor cells arranged in cords, nests, small alveoli, or trabeculae.[6,12,13] This case was predominantly fascicles of spindle cells with only small foci of hyalinized collagen. Tumors usually express desmin[13,16] and MyoD1[12,13] in a majority of the cells; myogenin staining may be absent, focal or diffuse;[12,13,16] smooth muscle actin expression may be

absent[13] or present;[12,16] and muscle-specific actin (HHF-35 antibody) staining occurred in all cases of paratesticular and adult spindle cell RMS.[16,17] SSRMS are negative for caldesmon and S100 protein expression.[13,16]

Clinical, molecular, and prognostic data indicate three subtypes of SSMRS: congenital, MyoD1 mutant, and intraosseous.[7] SSRMSs occurring before three years of age are classified as congenital/infantile, exhibit *VGLL2-NCOA2* fusions, and have a favorable prognosis.[7] MyoD1 mutant SSRMSs arise in children and adults and have an unfavorable prognosis.[7] Intraosseous SSRMSs are the rarest subtype, have a predilection for craniofacial bones, display *EWSR1-TFCP2*, *FUS-TFCP2*, and less commonly *MEIS1-NCOA2* fusions, and manifest an unfavorable prognosis.[7]

Treatment protocols for RMS rely on risk stratification based on stage and clinical group.[15] Tumor-node-metastasis (TNM) stage incorporates tumor site and size and the presence or absence of lymph node and distant metastases. Orbital tumors are stage 1 in the absence of distant metastases.[15] The clinical group is based mainly on the extent of residual tumor after surgery and regional lymph node involvement. This child was stage 1 due to the tumor being confined to the orbit and group III due to incomplete tumor resection. Stage 1/group III RMS are low risk with approximately 90% five-year failure-free survival(FFS) for embryonal RMS, including those classified as spindle cell ERMS, treated with the ARST0331 protocol.[14,15]The five-year FFS for patients with orbital tumors was 86%.[14]

The differential diagnosis of SSRMS depends on whether the tumor is predominantly composed of spindle cells or round cell/sclerosing.[11] Embryonal RMS may have a spindle cell component, but "the proportion of sclerosis or spindled cell component necessary to designate a tumor as the SSRMS variant is not currently established." [11] Chen, Rudzinski, and Arnold recommend that any ERMS with even limited spindle cells or sclerosis be tested for molecular aberrations to aid classification and prognostication.[11] The sclerosing variant of SSRMS may mimic alveolar RMS, but most ARMS tumors can be distinguished by fusions of *PAX3/7* to *FOX01*.[11] Fibrosarcomas, which are rare in the pediatric orbit,[4] have a nonspecific immunohistochemical profile with focal desmin expression in some cases[18] and *ETV6-NTRK3* fusions in most cases.[11] Synovial sarcoma, another rare orbital tumor of children, adolescents, and adults,[19]can be differentiated from SSRMS by immunoreactivity for cytokeratins and epithelial membrane antigen and t(X;18)(p11;q11) translocations resulting in *SS18-SSX1/2/4* fusions.[20] Malignant peripheral nerve sheath tumors of the orbit[5] are distinguishable from SSRMS by having markers of Schwann cells differentiation (focal staining for S100 protein and SOX10) and/or loss of H3K27me3 expression.[20] Other soft-tissue tumors are separable from RMS by their immunohistochemical and molecular profiles, with the expression of myogenic markers being the key to the diagnosis of RMS.[20]

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