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Material submitted:
Protocol and slides

Rhabdomyosarcoma: The dreaded, rapidly progressive orbital mass

Clinical case

History:

An 8-year-old female presented with a rapidly growing right orbital mass over 2 weeks. She had no significant medical, ocular or family history.

Examination:

Ocular examination of the right eye showed fullness of the upper eyelid with 7 mm exophthalmos. Vision was 6/6 bilaterally with normal intraocular pressures and retinal examinations.

Management:

CT orbit with contrast performed 2 weeks later showed a 3.8 x 2.9 x 2.2 cm lobular heterogeneous enhancing right orbital mass causing mass effect mildly deforming the optic nerve, proptosis, and with medial extension to the right nasolacrimal duct and superior extension to the superior rectus muscle. There was no associated bony remodeling or osteolysis.

right anterior orbitotomy was urgently performed. Intraoperative frozen section diagnosis was consistent with rhabdomyosarcoma. The mass could be only be partially separated and excised from its surrounding subcutaneous and soft tissue. Excised tissue was sent for routine processing and cytogenetics.

Final pathology report:

'Right orbital mass, biopsy: Rhabdomyosarcoma of the orbit
The tumor is composed of hyperchromatic ovoid, spindled and focally rounded cells with indistinct cytoplasm. Focally the cells are oval shaped with deeply eosinophilic intracytoplasmic material. Cross striations are not readily visible but focally there are elongated cells with angulations of pink material. The mitotic rate is 1 mitosis/ 10 HPF at 400x in the most proliferative area. Necrosis and lymphovascular invasion are not identified. Intracytoplasmic glycogen is present (PAS and PAS-D stains). The tumor cells are immunoreactive to vimentin, desmin, myogenin and focally with myoglobin. S100 and EMA stains are negative. SMA is only focally positive. The overall findings are consistent with a rhabdomyosarcoma, favor embryonal type.
Cytogenetic analysis: 46, XX normal female karyotype.'

The patient was referred to and treated at another institution and was lost to our further follow up.

Discussion:

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, classified by the World Health Organization (WHO) as a skeletal muscle tumor arising from undifferentiated skeletal tissue.[1] 40% of cases affect the head and neck region in children,[2] while adult RMS is commonly observed in the extremities.

Trunk, paratesticular and genitourinary tract lesions are more common in older children and adolescents.[3] RMS has a male: female ratio of 1.5:1.[4]

Clinical presentations:
Clinical signs and symptoms may vary depending on the affected site, varying from asymptomatic to proptosis, nasal stuffiness, nasal discharge and facial asymmetry. It can also mimic an infectious lesion, further delaying appropriate treatment.
In addition to the orbit, RMS can rarely occur in the eyelid, conjunctiva and uveal tract.
In a small subset, RMS is part of a genetic syndrome such as Beckwith-Wiedemann, Von Recklinghausen disease, Costello, Noonan, Gorlin, Rubinstein-Taybi, Li-Fraumeni, DICER1, Nijmegen breakage, and mismatch repair (PMS2 gene) cancer syndromes.

Histologic subtypes ('WHO Classification of Tumours of Soft Tissue and Bone', fourth edition, 2013):

- Embryonal (ERMS)
- Alveolar (ARMS)
- Pleomorphic
- Spindle cell/ sclerosing

Embryonal (ERMS):
Accounts for 60% of cases. Common in younger patients and has a better prognosis.
Histology: Undifferentiated, small, round, and hyperchromatic cells with variable number of strap, or tadpole-shaped, eosinophilic rhabdomyoblasts which can show bright eosinophilic cytoplasm, peripheral nuclei, cytoplasmic cross-striations and multinucleation.
Genetics: A small subset of ERMS may harbor LOH at 11p15, as well as FGFR4, P53, BCOR, ARID1A and RAS mutations.[5]
Botryoid: Subtype of ERMS. It has a grape-like gross appearance, and can arise in the submucosa of the conjunctiva.
Histology: Sub-epithelial tumor aggregates

Alveolar (ARMS):
Accounts for 30% of cases. Commonly seen in older patients (10-25 years old) and has an unfavorable prognosis.[6]
Histology: Small round rhabdomyoblasts arranged in nests separated by connective tissue trabeculae and focal areas of alveolar architecture. Cells show hyperchromatic nuclei and eosinophilic cytoplasm.
Genetics: 75% of ARMS carry a t(2;13)(q35;q14) or the t(1;13)(q36;q14) chromosomal translocation between PAX3 (or PAX7) and FOXO1 genes, that results in the expression of the chimeric PAX3/7-FOXO1 protein and have a more aggressive clinical course.[7]

Pleomorphic:
Accounts for 5% of cases. Rarely occurs in the pediatric group; commonly seen over the age of 45 years.
Histology: Intensely eosinophilic atypical and frequently multinucleated cells with a wide range of shapes from round to spindle to tadpole-like.
Genetics: Losses of DNA (10q23), gains (1p22-23) and amplifications have been identified.

Spindle cell/sclerosing (SRMS-ScRMS):
Accounts for 5-10% of cases. Occurs in both children and adults.
Histology: Monomorphic spindle cells arranged in intersecting fascicles, lacking overt rhabdomyoblastic differentiation. A subset may display areas of hyaline sclerosis suggesting a morphologic overlap with the less common sclerosing RMS.

Sclerosing RMS may show an undifferentiated round cell component arranged in a pseudovascular or a pseudoalveolar pattern in a prominent hyalinized stroma.[8]
Genetics: SRMS-ScRMS share genetic alterations, recurrent NCOA2 and VGLL2 related fusions in congenital/infantile settings which are associated with a favorable outcome, [9,10] or MYOD1 mutations in older children and adults which are associated with a poor prognosis. [11]

Immunohistochemistry:
RMS is positive for desmin, myogenin, MyoD1

Differential diagnosis:
The clinical differential diagnosis includes progressive rapidly developing masses and inflammatory conditions of childhood, such as neuroblastoma, chloroma, lymphangioma, infantile hemangioma, cellulitis, and nonspecific inflammatory diseases. The histopathologic differential diagnosis of pediatric blue round cell tumors include neuroblastoma, neuroepithelioma, Ewing's sarcoma, angiosarcoma, synovial sarcoma, malignant melanoma, granulocytic sarcoma, alveolar soft part sarcoma, and malignant lymphoma.

Prognosis: Depends on

- Primary location of tumor.

  Poor prognosis:
  Parameningeal areas involving the nasopharynx, nasal cavities, paranasal sinuses, parapharyngeal space, infratemporal and pterygopalatine fossae, and middle ear. These sites have limited surgical accessibility, making it difficult to achieve complete surgical resection with a tendency to invade the skull base and extend intracranially.
  Better prognosis:
  Non-parameningeal areas involving the oral cavity, larynx, parotid region, cheek, scalp and soft tissues of the neck.
  Excellent prognosis:
  Orbital tumors (25%)
- Tumor size

  Poor prognosis: Lesions greater than 5 cm
- Age

  Poor prognosis: Children younger than a year and older than 10 years and adults

Risk group stratification: Depends on
1) TNM staging system which evaluates:
   - Site of primary tumor (orbital, parameningeal or non-parameningeal)
   - Size (diameter greater or lesser than 5 cm)
   - Invasiveness (confined to site of origin, extending or fixed to surrounding tissue)
   - Nodal status (unknown, with or without regional node involvement)
   - Presence of distant metastasis
2) Intergroup Rhabdomyosarcoma Study (IRS) surgical clinical grouping system:
   - Group I: Completely resected tumors with free surgical margins
   - Group II: Grossly resected tumors with microscopic residual disease and /or regional lymph node involvement
   - Group III: Gross residual disease after incomplete resection or biopsy
   - Group IV: Metastasis at onset
3) Histology

Risk prognosis is stratified into low, intermediate and high risk groups, the 5-year event-free survival rate for which are 95%, 65% and 15% respectively.[12]

Treatment: Multimodal approach:

Chemotherapy, radiation and surgery (total resection depending on anatomic location)

Common cause of death:

- Tumor involvement of adjacent vital structures
- Metastasis: Common site- lung

  Others: bone marrow, cerebrospinal and peritoneal fluid[13]

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