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REVIEW

Orbital rhabdomyosarcoma: Review

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Abstract

Orbital rhabdomyosarcoma is the most common malignant orbital tumor of childhood originating from mesenchymal cells. The presenting symptom is usually acute onset unilateral proptosis. The rapidly progressive course of the findings may resemble infectious and inflammatory orbital diseases. Radiological imaging and histopathological examinations are crucial for differential diagnosis. The main goal of treatment with a multidisciplinary approach is to control both local and distant spread of the tumor and to prevent further damage. With the introduction of chemotherapy and radiotherapy in the treatment, the overall survival rate has increased. Thus, aggressive surgical approach for complete removal of the tumor has been abandoned.

Keywords: Orbital rhabdomyosarcoma; orbital tumor; proptosis.

Rhabdomyosarcoma is a soft-tissue tumor originating from mesenchymal cells. It is the most common primary malignant tumor of the orbit in childhood and accounts for approximately 5% of all pediatric malignancies.^[1,2] Although it might be seen in different parts of the body such as the genitourinary tract, extremities, and abdomen, approximately 40% of rhabdomyosarcomas occur in the head-and-neck region.^[3,4]

The tumor arises from indifferent pluripotent mesenchymal cells that can differentiate into skeletal muscle during the embryonic period.^[5] Rarely, it occurs after a traumatic

incident.^[6] Histologically, there are four types: Embryonal, alveolar, pleomorphic, and spindle cell/sclerosing rhabdomyosarcoma.^[4] Embryonal rhabdomyosarcoma (EMRS) is the most common variant with a favorable prognosis. Approximately 50–70% of orbital RMS are of the embryonal type. Alveolar rhabdomyosarcoma (ARMS) is the second most common variant that occurs mostly in adolescents and young adults. Pleomorphic and spindle cell rhabdomyosarcomas are extremely rare in the orbit.^[5,7]

This review aims to report the clinical features and current treatment of orbital rhabdomyosarcoma in a multidisciplinary



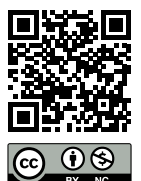
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plinary manner, along with radiological and histopathological findings.

Clinical Characteristics

Orbital rhabdomyosarcoma is usually seen in the first decade of life, especially between the ages of 5–7.^[8,9] Although some have reported male predominance in the literature, no gender or race predilection was found in most series.^[3,10] Approximately 25% of rhabdomyosarcomas involving head-and-neck region originate from the orbit. Primary orbital rhabdomyosarcoma is usually located superiorly to the orbit.^[2] In addition, the presenting symptom is unilateral proptosis with slight downward displacement of the globe (Fig. 1). The acute onset and rapidly progressive nature of the disease may mimic infectious or inflammatory etiologies.^[9] Occasionally, a palpable mass or blue-purple discoloration can be seen under the eyelid. Other clinical signs include red eye, chemosis, ptosis, eyelid swelling, and facial asymmetry.^[8,11] Posteriorly located rhabdomyosarcoma is likely to present with choroidal folds, ocular motility defects and optic nerve compression. Rarely, the orbit may be involved secondary to metastasis from a distant organ or direct invasion from the paranasal sinuses and nasopharynx.^[2,4]

Primary orbital rhabdomyosarcoma itself carries the risk of involvement of surrounding tissues and distant metastasis. Occasionally, intracranial or paranasal sinus invasion may occur. The most common distant metastasis of orbital rhabdomyosarcoma is to the lung. The presence of locally invasive or metastatic tumors at onset is associated with recurrence and poor treatment response.^[2]

Differential Diagnosis

Various benign and malignant etiologies present with

acute progressive proptosis in childhood. Infectious (orbital cellulitis, etc.), inflammatory (orbital pseudotumor, etc.), and neoplastic (granulocytic sarcoma with or without acute myeloid leukemia, non-Hodgkin's lymphoma, neuroblastoma metastasis, Langerhans cell histiocytosis, etc.) etc.) causes should be considered in the differential diagnosis.^[12,13] Orbital rhabdomyosarcoma is frequently misdiagnosed as orbital cellulitis, which is a common cause of proptosis in children. Shared symptoms and clinical findings such as pain, eyelid swelling, and ocular motility defects complicate the accurate diagnosis.^[14,15] However, the absence of systemic findings such as fever and lethargy are more suggestive of orbital rhabdomyosarcoma. Detailed laboratory examination including complete blood count, erythrocyte sedimentation rate, and C-reactive protein levels also helps to differentiate when orbital cellulitis is suspected. Nevertheless, radiological imaging is usually indicated to confirm the diagnosis.^[15]

Radiological Imaging

Orbital tumors may present with symptoms similar to those of orbital infectious and inflammatory diseases. Radiological imaging is useful in revealing the precise location, size, and characteristics of the orbital mass as well as the underlying etiology.^[16] Computed tomography (CT) is one of the first step imaging techniques in orbital masses.^[17] On CT, orbital rhabdomyosarcoma appears as a well-defined homogeneous mass isodense to the extraocular muscles. Occasionally, erosion of adjacent bones may be observed and this CT finding indicates the aggressive nature of the tumor.^[1] Heterogeneous appearance may occur due to intramass hemorrhage.

Although CT is a quick imaging technique that allows detailed imaging of the surrounding bone tissues, exposure

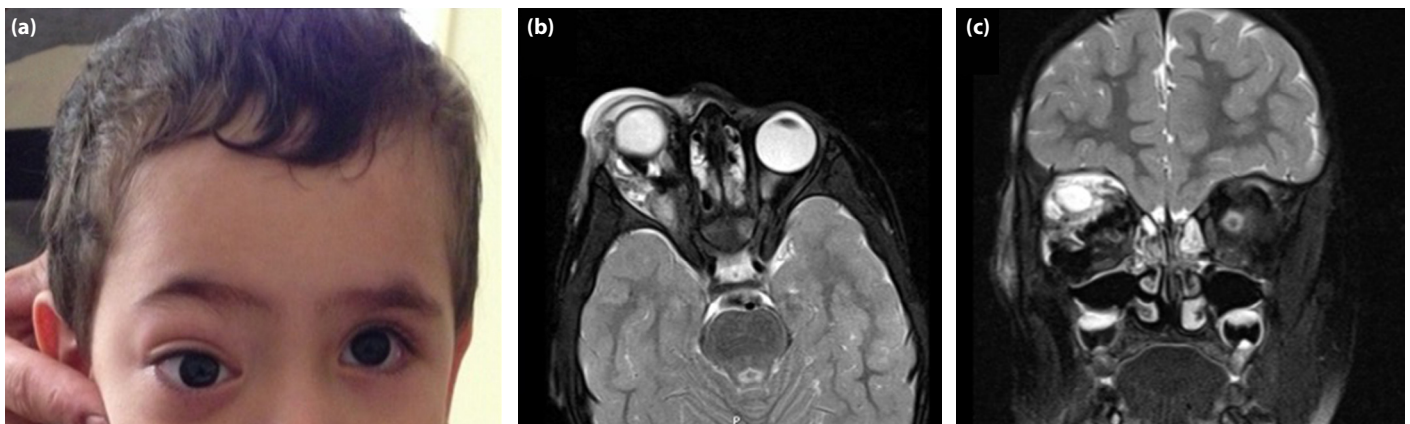


Fig. 1. (a) Rhabdomyosarcoma presenting with anterior and inferior displacement of the right globe in a 3-year-old male (b) axial and (c) coronal T2-Weighted MRI images show a heterogeneous hyperintense mass in the superior extraconal part of the right eye.

to ionizing radiation is a significant drawback.^[17] On the other hand, magnetic resonance imaging (MRI) is better at showing the orbital soft tissues in detail without any ionizing radiation risk. However, it is contraindicated in the presence of a metallic foreign body or implant.^[16,18] Orbital rhabdomyosarcoma appears as a contrast-enhancing mass isointense to the extraocular muscles on T1-weighted MRI. It shows a hyperintense appearance on T2-weighted images. The use of a fat-suppressing technique with a gadolinium contrast agent provides better visualization of the lesion.^[2,19,20] Glob displacement might also be distinguished (Figs. 2 and 3).

Orbital rhabdomyosarcoma may occasionally mimic capillary hemangioma on radiological imaging, especially in patients diagnosed around 1–2 years of age, and this leads to misdiagnosis.^[21]

Although ultrasonography has limited diagnostic efficiency, it usually shows a well-circumscribed heterogeneous mass with low-to-moderate echogenicity.^[22]

Histopathological Assessment

A biopsy is required for the definitive diagnosis of orbital rhabdomyosarcoma. Depending on the localization and spread of the tumor, either incisional or excisional biopsy is preferred. Fine-needle aspiration biopsy is not recommended as only a limited amount of cells can be obtained and further immunohistochemical and/or molecular studies can be needed.^[12,23]

Although orbital rhabdomyosarcoma is classified as a striated muscle tumor, it principally originates from mesenchymal stem cells. On histopathological examination, the tumor is characterized by rhabdomyoblastic/small round/spindle cells in a loose syncytial pattern with striated muscle differentiation.^[24,25]

EMRS, the most common variant, consists of cells with round, oval, elongated, or stellate nuclei and large eosinophilic cytoplasm, arranged in a loose syncytial pattern. It resembles fetal skeletal muscle. In well-differentiated tumors, these cells may have cross striations. At mucosal tissues, a

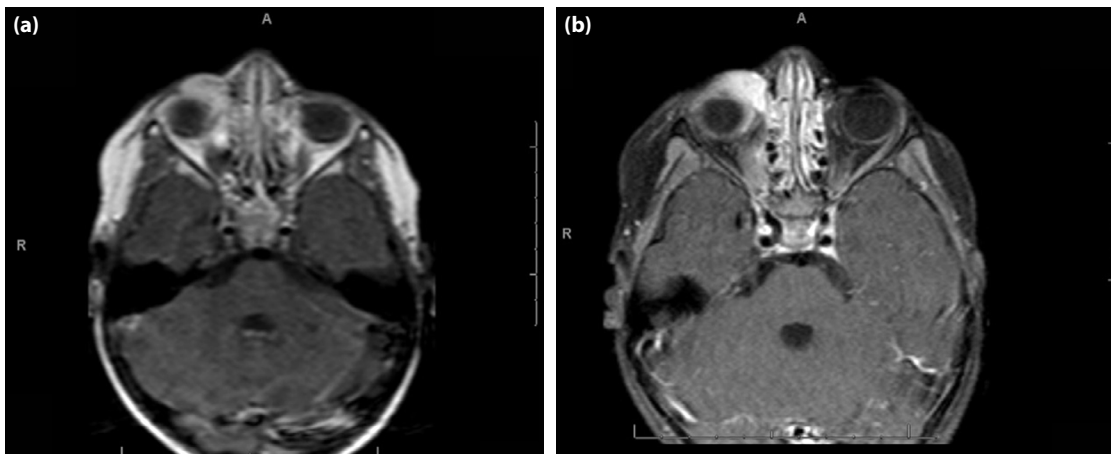


Fig. 2. Embryonal rhabdomyosarcoma presenting with right proptosis in a 5-year-old male. **(a, b)** Axial T1-weighted MRI images show a mass involving the medial rectus and superior oblique muscle and extending into the intraconal space in the right. Significant contrast-enhancement is present.

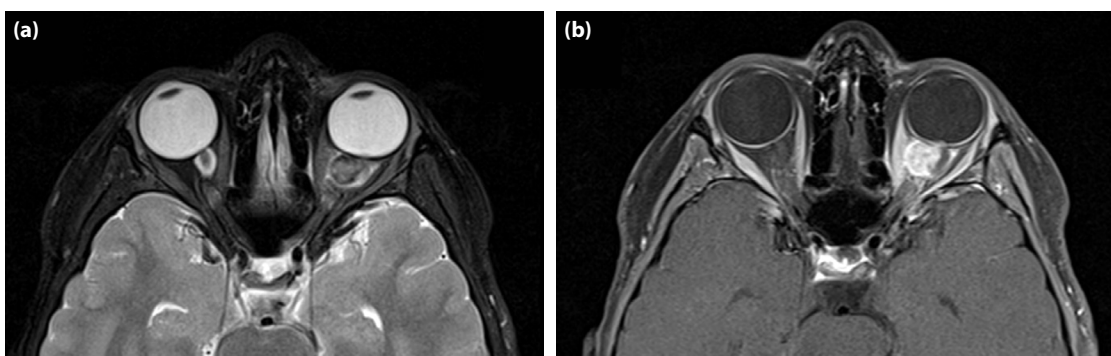


Fig. 3. Orbital rhabdomyosarcoma in a 10-year-old female. **(a)** T2-weighted MRI and **(b)** T1-weighted post-contrast MRI images show a retrobulbar, intraconal mass adjacent to optic nerve. The lesion has a heterogeneous appearance and shows contrast enhancement.

subepithelial concentration of cells referred to as the cambium layer is shown in (Fig. 4).^[24,25]

ARMS is a less common variant associated with poor prognosis, regardless of localization and extent. Histopathologically, ARMS is composed of small round cells with scant cytoplasm, the cellular features resemble EMRS. Differently, it has a cellular arrangement surrounding the fibrous septa, similar to lung alveoli.^[5] Molecular studies have revealed that at least 80% of ARMS tumors have one of the two translocations. One is the gene rearrangement $t(2:13)(q35;q14)$ involving the *FOXO1* and *PAX3* genes. The other translocation $t(1:13)(q36;q14)$ is between the genes *PAX7* and *FOXO1*.^[4,24,25] *PAX3* and *PAX7* govern the expression of the transcription factors myo-D1 and myogenin.

Immunohistochemically, the tumor cells have skeletal muscle cytoplasmic proteins, such as myoglobin, desmin, and muscle-specific actin. Myogenin and myo-D1 are nuclear transcription factors expressed in early skeletal muscle differentiation and are highly sensitive and specific for both ERMS and ARMS. By immunohistochemistry, myogenin is usually heterogeneous and spotty in ERMS, whereas in ARMS the staining is usually uniform and strong.

In the differential diagnosis of rhabdomyosarcoma, small round blue tumors, such as neuroblastic tumors, granulocytic sarcoma with or without acute myeloid leukemia, non-Hodgkin's lymphoma, and Ewing sarcoma family tumors, are to be considered. Alveolar soft part tumor is also histopathologically in the differential diagnosis of ARMS, whereas it involves the head-and-neck region and is most commonly located in the orbit and tongue.

Management and Outcome

The main goal in the management of orbital rhabdomyo-

sarcoma is to prevent further damage by controlling the local spread of the disease and avoiding possible systemic metastasis.^[26,27] In the past, the aim of treatment was the complete removal of the tumor, which is usually possible by either enucleation or exenteration.^[28] However, this aggressive approach has been abandoned with the introduction of chemotherapy and radiotherapy (RT) into the treatment of rhabdomyosarcoma with its favorable outcomes.^[29] Nowadays, a multidisciplinary approach that includes surgery, chemotherapy, and RT is generally preferred in the treatment of orbital rhabdomyosarcoma.^[3] Exenteration is performed only in resistant and recurrent cases.^[29]

Since the definitive diagnosis of orbital rhabdomyosarcoma is made histopathologically, a biopsy is required before treatment. However, there is no consensus in the literature on whether an incisional or excisional biopsy should be performed.^[20] With advances in chemotherapy and RT, some authorities recommend an only incisional biopsy to confirm the preliminary diagnosis.^[22] On the contrary, some concluded that maximal removal of the tumor tissue enhances the response to chemotherapy and RT.^[30] Consistently, Zhang et al.^[30] reported that surgical resection is associated with a better prognosis, with 5.7 times more survival time.

Anatomical location and the extent of the tumor are significant predictors of post-surgical visual outcome. Tumors located posteriorly or adjacent to vital structures are more prone to cause visual and functional impairment. In these cases, the excision area should be limited to preserve visual functions as well as cosmetic appearance. Treatment planning should focus on chemotherapy and RT rather than achieving tumor-free surgical margins.^[22,27,29]

Chemotherapy and RT protocol is usually planned based

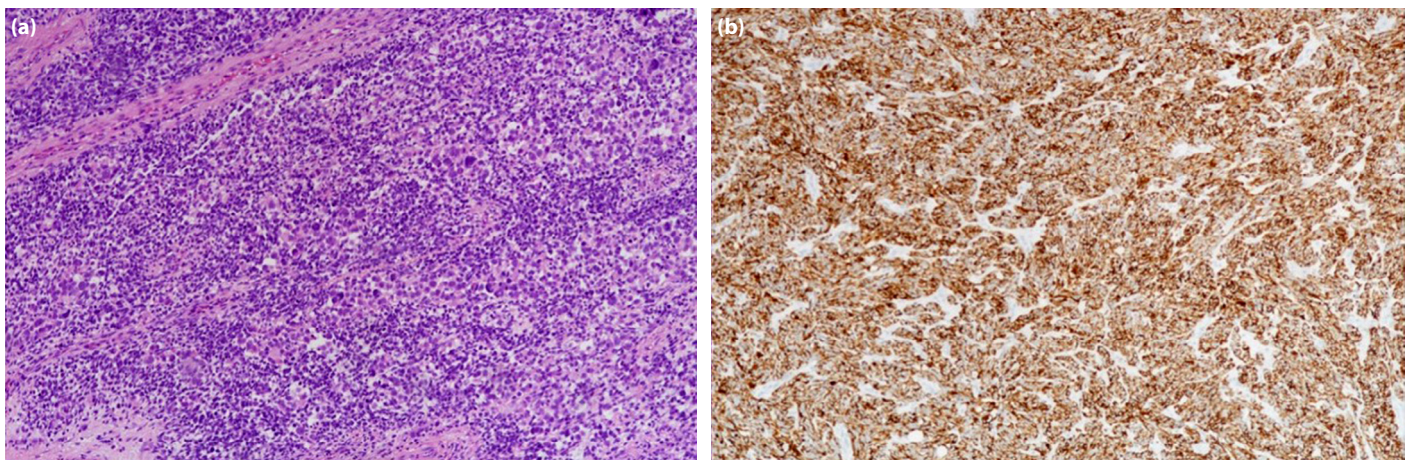


Fig. 4. (a) Histopathological image of orbital embryonal rhabdomyosarcoma (HE; $\times 100$) (b) Immunohistochemically desmin positivity is present (HE; $\times 100$).

on the internationally accepted staging system of the “Intergroup Rhabdomyosarcoma Study Group.” Accordingly, staging after biopsy is as follows: Group 1 – a localized disease in which the lesion is completely excised; Group 2 – microscopic residual disease after biopsy; Group 3 – gross residual disease after biopsy; and Group 4 – the presence of distant metastases.^[22,29,31] Based on this staging, the recommended treatment is only chemotherapy for Group 1, and a combination of chemotherapy and RT for Groups 2, 3, and 4. The intensity of chemotherapy and RT in Groups 2, 3, and 4 varied.^[22] Commonly used chemotherapeutic agents are vincristine, actinomycin-D and cyclophosphamide (VAC protocol).^[32] Arndt et al.^[32] reported well-known systemic side effects of the VAC protocol including febrile neutropenia (85%), anemia (55%), leukopenia (60%), and thrombocytopenia (51%) in patients with rhabdomyosarcoma. However, despite their undesirable systemic effects, chemotherapeutic agents are still the backbone of the therapy in rhabdomyosarcoma.

RT is an important adjunctive treatment modality since rhabdomyosarcoma is sensitive to it. However, depending on the radiation modality and dose, RT has side effects such as enophthalmos, facial asymmetry, tear duct stenosis, xerophthalmia, cataract, and retinopathy.^[27,33] Today, alternative RT methods including intensity-modulated RT, fractionated proton RT and interstitial brachytherapy are used to limit the radiation dose reaching the adjacent tissues. Unlike conventional radiation, these alternatives minimize functional and cosmetic damage by sparing the surrounding normal tissue.^[22]

With the support of adjuvant therapy and a multidisciplinary approach, the overall survival rate has increased to approximately 90%.^[34] However, the presence of selected clinical and histopathological findings affects prognosis and survival rate. Alveolar type, tumor size, involvement of periorbital structures, and distant organ metastasis are considered as poor prognostic factors.^[35]

A recurrence rate of 15–20% is reported in orbital rhabdomyosarcoma and its management is quite challenging. Although there is no consensus, additional chemotherapy, conventional RT, and exenteration are the options for the treatment of recurrent cases.^[20,22]

Conclusion

Orbital rhabdomyosarcoma, which is the most common primary orbital malignancy in childhood, often presents with acute unilateral proptosis. Due to the rapidly progressing course of the findings, distinguishing from infectious and inflammatory orbital diseases is challenging. A multi-

disciplinary approach along with radiology and pathology is required for early diagnosis and accurate management. With the widespread use of chemotherapy and RT in treatment, recurrence-free survival rates have increased with favorable functional and cosmetic outcomes.

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