

Embryonal rhabdomyosarcoma in a 1 year old boy misdiagnosed as myxoma in histopathological examination- A case report

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Abstract

Introduction: Rhabdomyosarcoma (RMS) is a rare tumor, with an annual incidence of 4.3 cases per million children. The orbit is the primary site in approximately 10% of these tumors. RMS is the most common malignant orbital tumor of childhood. It usually appears in the first decade of life. The mean age at diagnosis is 8 years. Boys are affected more than girls. Orbital RMS usually presents as a space occupying lesion in the orbit. The tumor has predilection for the superior nasal quadrant of the orbit. The common histological types include embryonal(60%), alveolar(20%) and pleomorphic (20%).The most common sites being sinuses, head and neck regions, genitourinary tract. CT and MR imaging are important in the evaluation of this tumor. The diagnosis is most rapidly and reliably confirmed by immunohistochemical(IHC) by demonstration of one or more muscle antigens. At times, the myxoid stroma and polypoid configuration of some RMS might be mistaken for nasal polyps or myxoma. Treatment usually consists of a combination of chemotherapy and radiation therapy following surgical excision.

Case Report: In our study, a 1 year old male patient presented to a local ophthalmologist with complain of painless swelling of left orbit. CT scan revealed picture suggestive of venolymphatic malformation (March 17,2016) .Thereby, he was referred to a well known health care centre where MRI was advised which revealed a picture suggestive of rhabdomyosarcoma with differential diagnosis of plexiform neurofibroma. Total excision of the orbital mass was done at the same centre and a diagnosis of orbital myxoma/ angiomyxoma was given in HPE (April 29,2016). After about 2 months following the excision biopsy, patient's parents noticed swelling of the same orbit which was aggressive. He was brought to the pediatric surgery department of AMCH and re-biopsied. One specimen was sent to our department and the other to a private centre. The report from the private laboratory suggested myxoma. The report from our college was given as Embryonal rhamdomyosarcoma and further subjected to immunohistochemistry (IHC). IHC was positive for desmin, myogenin and vimentin. Complete haemogram, ESR were within normal limits.

Conclusion: In our case, the patient deteriorated within a very short span of 8-9 months due to misdiagnosis owing to its histological similarity to myxoma. The histopathologist reporting the case previously missed to observe the huge size of the tumour. The facility of IHC was also not utilized. Thus, histopathology along with IHC should be used as an ancillary test in cases as confusing as ours, thereby saving patients valuable time.

Keywords: Embryonal rhamdomyosarcoma, IHC, Myxoma, Desmin, Myogenin, Tumor, Orbit.

Introduction

Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood, representing 5% of all childhood cancers.⁽¹⁾ It is thought to arise from primitive mesenchymal cells committed to skeletal muscle differentiation and can occur in a variety of organs and tissues, including those that lack striated muscle.⁽¹⁾ A highly heterogenous tumor, rhabdomyosarcoma has several histologic subtypes and occurs in localized or disseminated forms. Patients with rhabdomyosarcoma are classified on the basis of their low, intermediate, or high risk for treatment failure.⁽²⁾ Careful diagnostic imaging of potential disease sites at the time of presentation is crucial in assigning risk-based therapy. The two main histological subtypes of rhabdomyosarcoma are embryonal (with botryoid and spindle cell variants) and alveolar.⁽²⁾ Approximately 60% of all newly diagnosed rhabdomyosarcomas are of embryonal histology.⁽²⁾ This subtype often arises in

mucosa-lined structures of the nasopharynx, auditory canal, and genitourinary and gastrointestinal tracts.⁽²⁾ Twenty percent of newly diagnosed rhabdomyosarcoma is of the alveolar subtype, which most commonly occurs in the trunk and extremities.⁽²⁾ The remainder of cases are of pleomorphic or undifferentiated histology.⁽²⁾

The natural history of RMS is that of a highly aggressive tumor that either kills the patient or is cured by modern chemotherapy. Although the prognosis does depend on factors such as the site (Table 1) and histology, it depends mostly on the group (a type of staging). In general, patients in groups I or II, who have either completely resected disease or microscopic disease remaining, respectively, are frequently cured. In contrast, patients in groups III or IV, who have locally unrespectable or metastatic disease, respectively, frequently die despite chemotherapeutic measures.

Table 1: Characteristics of Rhabdomyosarcoma by Site

	All Cases	Head/Neck (Non-Orbit)	Orbit	Paratesticular	Other GU	Extremities	Retroperitoneal	Trunk
Incidence	—	24%-29%	7%-19%	20%	4%	14%-23%	8%	8%
Average age (yr)	5-7	5-7	5-7	15	5-7	14	6	—
Sex (M/F)	3/2	—	—	—	—	1/1	3/2	—
Histology	—	80%-90% E	70% E	90% E	75% B	40% A	85% E	50% A
LN mets	10%-20%	—	—	40%	High rate	High rate	—	—
2-yr DFS	—	51%	77%	80%	68%	42%	42%	50%

Head and neck tumors in parameningeal locations (middle ear, nasopharynx, sinus) have a worse prognosis than other head tumors. The cure rate for orbital tumors is high (as with paratesticular cases). Paratesticular rhabdomyosarcoma is one of the most favorable types, but it is subject to late relapse; lymphadenectomy is the usual procedure, but this need not be done for cases without pelvic lymphadenopathy. Note that the extremity is the least frequent major site (behind head/neck, orbit, and paratesticular cases); extremity cases have the highest relapse rate and the lowest survival rate. The data are from many intergroup reports. Data are based on Intergroup Rhabdomyosarcoma Study literature from the 1980s to 1990s giving comparative information; current survival may be superior.

- A, alveolar types;
- B, botryoid;
- DFS, disease-free survival;
- E, embryonal;
- F, female;
- GU, genitourinary;
- LN mets, lymph node metastases;
- M, male.

Rhabdomyosarcoma Classification: The Intergroup Rhabdomyosarcoma Study grew dissatisfied with the predictive value of the conventional classification, so it has designated tumors as either favorable (botryoid, well-differentiated or spindle cell, and most embryonal RMS tumors) or unfavorable. The unfavorable tumors are those that have anaplastic features or alveolar histology or those that are very poorly differentiated with monomorphous round cell morphology, such as the solid variant of alveolar RMS. With this designation, the unfavorable category comprises approximately 20% of cases, and its 2-year, disease-free survival rate is 72%, versus 89% for favorable cases.⁽³⁾ If a tumor has any alveolar morphology, it should be classified thus.

Embryonal Rhabdomyosarcoma: Most RMS tumors are classified as embryonal; these tumors consist of sheets of poorly to moderately differentiated cells with a rounded morphology. In contrast to the nucleus in Ewing sarcoma, the nucleus in RMS is eccentric (Fig. 5.36A), and the rest of the cytoplasm appears more granular and eosinophilic. Such cells are present, at least focally, in most cases. As the cells become larger, the cytoplasm may appear fibrillar, and it may encircle the nucleus. Cross-striations are uncommon; they are present in approximately half of embryonal RMS cases (20% of alveolar RMS). Thus, these striations cannot be used as the sole criterion for the diagnosis, and they may actually be found in other tumors disguised in the form of trapped skeletal muscle fibers. Again, in contrast to Ewing sarcoma, RMS exhibits occasional spindling, and in such fields, the characteristic “strap” cells may be identified. The cytoplasmic borders run in parallel for a certain length without tapering. When such cells are present throughout RMS, the tumor mimics the myotubular stage of normal muscle development, and the lesion is considered well differentiated. This occurrence has been called spindle cell RMS or leiomyomatous RMS to call attention to the confusion it may cause. Whereas childhood cases of spindle cell RMS have an excellent prognosis, the rare cases in adults do not. The embryonal pattern is the most common type of RMS in practically all sites.⁽³⁾

Botryoid Rhabdomyosarcoma: RMS cases that occur near a lumen or a space (e.g., genitourinary tract, female reproductive tract, conjunctiva) are most often of the botryoid type. This much more myxoid tumor is a variant of the embryonal type, and it has a very typical low-power appearance in which the density of cells is greatest just below the adjacent epithelium. This area is known as the cambium layer. Usually, the characteristic small strap cells are located at the junction of this layer with the more myxoid underlying regions. In all, this type accounts for approximately

25% of all RMS cases; roughly 75% of all botryoid tumors occur in the genitourinary tract.⁽⁴⁾

Alveolar Rhabdomyosarcoma: Alveolar RMS affects patients at an older mean age than do the other types of RMS, and it is frequently observed in adolescents with lesions on the extremities and trunk. This histologic type has the worst prognosis when all other variables are held constant. The tumor is divided by small fibrous septa between which tumor cells float discohesively in oval or elongated spaces. Cells at the periphery of the alveoli hug these septa. Although the differentiation may vary from case to case, most of the tumors are largely non-cytoplasmic, and only scattered eosinophilic cells can be seen. Multinucleated giant cells with a wreath of nuclei are a frequent finding in alveolar rhabdomyosarcoma but not in the other types. Little in the way of spindle-shaped cells is identified. Muscle markers are often reactive. The solid variant fails to form the nearly pathognomonic alveolar spaces, except in very small foci. This form can be recognized by the presence of the aforementioned tumor giant cells. Alveolar RMS may present with bone marrow metastases or tumor cell leukemia.

Pleomorphic Rhabdomyosarcoma: Pleomorphic RMS is rare; the examples designated as such in the past were more likely UPS/MFH. RMS tumors in children with some pleomorphism are, by current convention, subsumed into the embryonal group. However, unusual childhood and rare adult cases can be found. The cells are reminiscent of those seen in rhabdomyoma, with abundant eosinophilic and granular cytoplasm. The cell shape may be elongated and boxcarlike or round to polygonal. Unlike the nuclei of UPS/MFH, the nuclei in pleomorphic RMS are usually regular, single, and round; if multiple nucleation is seen, the nuclear lobes are nearly the same size. Such cases may possibly be considered variants of the embryonal type with more prominent cytoplasmic differentiation.

Present Case

In our study, a 1 year old male patient presented to a local ophthalmologist with complain of painless swelling of left orbit. CT scan revealed picture suggestive of venolymphatic malformation (March 17,2016). Thereby, he was referred to a well known health care centre where MRI was advised which revealed a picture suggestive of rhabdomyosarcoma with differential diagnosis of plexiform neurofibroma. Biopsy was done at the same centre and a diagnosis of orbital myxoma/angiomyxoma was given (April 29,2016). After about 2 months following the biopsy, patient's parents noticed similar swelling of the same orbit. He was brought to the pediatric surgery department of AMCH and re-biopsied. One specimen was sent to our department and the other to a private

centre. The report from the private laboratory suggested myxoma. The report from our college was given as Embryonal rhabdomyosarcoma and further subjected to immunohistochemistry (IHC). IHC was positive for desmin, myogenin and vimentin. Complete hemogram, ESR were within normal limits. The patient received chemotherapy in paediatric surgery department and was later referred to a higher treatment centre for radiation.



Fig. 1: Clinical picture of the patient

Histopathology

The HPE examination of the small bits of tissue sent for examination revealed tumor cells arranged in trabeculae and sheets. Individual cells were stellate shaped with sparse, amphophilic cytoplasm and central nuclei – known as Rhabdoblaster. Rhabdomyoblasts progressively acquire more cytoplasmic eosinophilia and elongation, manifested by “tadpole”, “strap” and “spider” cells. Some contain abundant, myxoid stroma resembling myxomas.

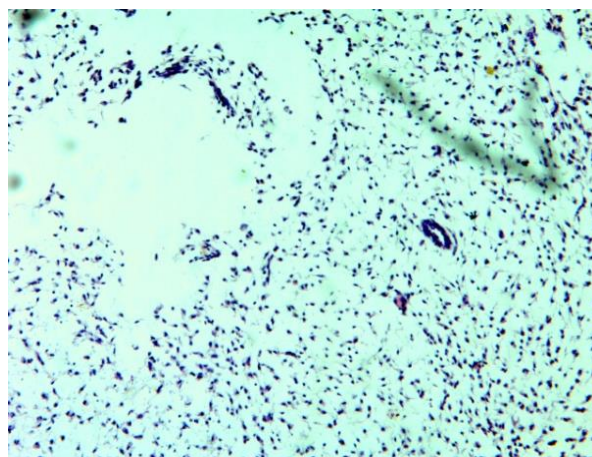


Fig. 2: Low power view of the orbital embryonal RMS

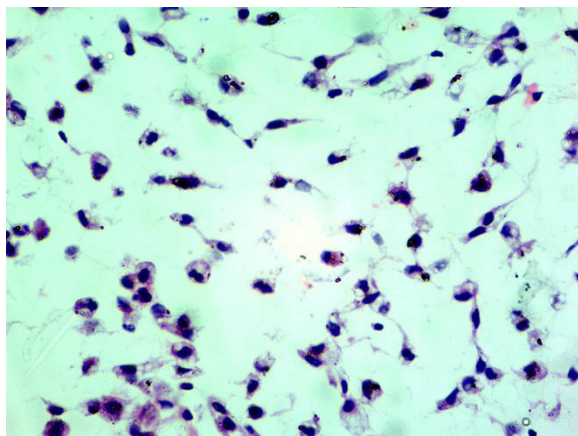


Fig. 3: High power view of the Embryonal orbital RMS

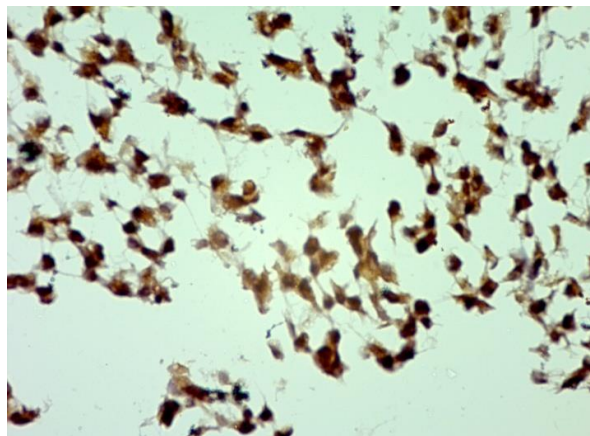


Fig. 6: DESMIN positivity in IHC

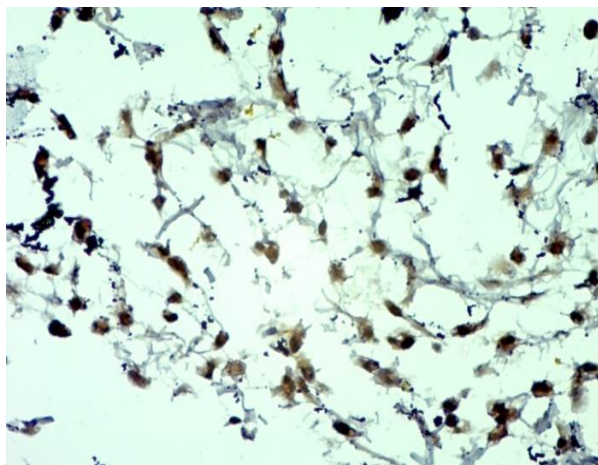


Fig. 4: Myogenin positivity in IHC

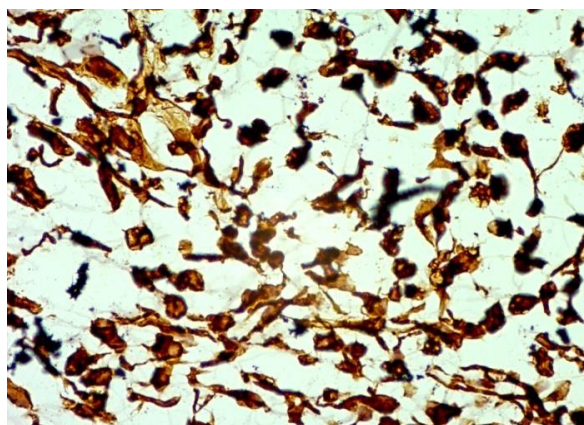


Fig. 5: VIMENTIN positivity in IHC

Discussion

Most RMS tumors are classified as embryonal; these tumors consist of sheets of poorly to moderately differentiated cells with a rounded morphology. In contrast to the nucleus in Ewing sarcoma, the nucleus in RMS is eccentric and the rest of the cytoplasm appears more granular and eosinophilic. Such cells are present, at least focally, in most cases. As the cells become larger, the cytoplasm may appear fibrillar, and it may encircle the nucleus. Cross-striations are uncommon; they are present in approximately half of embryonal RMS cases (20% of alveolar RMS). Thus, these striations cannot be used as the sole criterion for the diagnosis, and they may actually be found in other tumors disguised in the form of trapped skeletal muscle fibers. Again, in contrast to Ewing sarcoma, RMS exhibits occasional spindling, and in such fields, the characteristic “strap” cells may be identified. The cytoplasmic borders run in parallel for a certain length without tapering. When such cells are present throughout RMS, the tumor mimics the myotubular stage of normal muscle development, and the lesion is considered well differentiated. This occurrence has been called spindle cell RMS or leiomyomatous RMS to call attention to the confusion it may cause. Whereas childhood cases of spindle cell RMS have an excellent prognosis, the rare cases in adults do not. The embryonal pattern is the most common type of RMS in practically all sites.⁽⁵⁾

The most common sites of metastatic involvement are the soft tissues, serosal surfaces, lung, bone marrow, and lymph nodes. Cases associated with diffuse bone marrow involvement may simulate acute leukemia. Rhabdomyosarcomas arising from genitourinary sites or extremities are particularly prone to metastasize to lymph nodes, whereas tumors originating in head and neck structures adjacent to meningeal surfaces have a high incidence of direct meningeal extension.

The prognosis of embryonal rhabdomyosarcoma has markedly improved following multimodality treatment with excision, radiation therapy, and multidrug chemotherapy. Over 80% of children now

survive when the disease is localized to the region of origin. Age at diagnosis is an independent predictor of outcome. When growing beneath a mucosal membrane, such as the vagina, urinary bladder, or nasal cavity, it frequently forms large polypoid masses resembling a bunch of grapes – hence the name sarcoma botryoids. This is regarded as a variation in the pattern of growth of embryonal rhabdomyosarcoma and is referred to as the botryoid subtype. The appearance is reminiscent of an allergic nasal polyp, and, as such, is deceptively benign. A highly characteristic feature of these polypoid ('botryoid') tumors is the presence of a dense zone of undifferentiated tumor cells immediately beneath the epithelium, a formation known as Nicholson cambium layer. Tumors examined following multidrug chemotherapy tend to show a greater degree of differentiation than the pretherapy specimen, suggesting that the drugs have either induced maturation or resulted in a selection of the better differentiated components. Very rarely, accumulation of cytoplasmic glycogen or lipids in embryonal rhabdomyosarcoma results in a clear cell appearance that can simulate clear cell carcinoma. Another morphologic variation is represented by tumor cells containing cytoplasmic globular inclusions composed of intermediate filaments and resulting in a rhabdoid appearance.

Occasionally, in infants and children, tumors with a location and appearance otherwise characteristic of embryonal rhabdomyosarcoma are seen to contain collections of cells exhibiting neuronal, melanocytic, and/or schwannian differentiation; these have been interpreted by some as originating from the migratory neural crest (ectomesenchyme) and designated as ectomesenchymomas. Most of these tumors have been located in the head and neck region, but cases have also been reported involving the distal extremities. Tumors with similar appearance have been given the histogenetically less committal name of gangliorhabdomyosarcoma. Little is known about their natural history, which does not seem to differ much from that of the ordinary embryonal rhabdomyosarcoma.⁽⁶⁾

A distinct variant of embryonal rhabdomyosarcoma is represented by the spindle cell type, which is composed of elongated spindle cells arranged in a fasciculated or storiform pattern. Most of the initially published cases were in male children. The most common locations were the paratesticular area and the head and neck region, and their prognosis was favorable. Conversely, spindle cell rhabdomyosarcomas occurring in adults predilect the head and neck region and seem to be more aggressive than their pediatric counterparts. Spindle cell rhabdomyosarcoma bears some resemblance to the tumors described as infantile rhabdomyofibrosarcomas, but it is not clear whether the two are identical. The latter tumors microscopically

simulated fibrosarcoma and were characterized by an aggressive clinical course.⁽⁷⁾

Immunohistochemistry, on the other hand, has proved of great value. Hardly any other tumor type has been described for which the array of markers is as varied as for rhabdomyosarcoma, and the list continues to grow. There is a range of specificity and sensitivity among these markers and this translates into their relative practical utility. Algorithms have been proposed to guide the uninitiated in the search for striated muscle differentiation in a soft tissue tumor. The most important markers are as follows.

1. **Myogenin:** The myogenin gene codes for a phosphoprotein that induces skeletal muscle differentiation in mesenchymal cells. The protein, which has a high degree of specificity, can be demonstrated in the nuclei of the tumor cells in all types and virtually all cases of rhabdomyosarcoma, but it is expressed in a particularly strong and widespread fashion in the alveolar type. Probably because of this very fact, diffuse expression of myogenin is a marker of poor prognosis. MyoD1 is a related nuclear protein with a similar degree of specificity, but – in contrast to myogenin – not well demonstrated in formalin-fixed paraffin-embedded material, and therefore of lesser diagnostic utility. The MyoD1 protein present in these tumors binds DNA but it is relatively nonfunctional as a transcriptional activator, suggesting the lack of a factor needed for its activity.
2. **Desmin:** This intermediate filament is a specific indicator for muscle differentiation, but it is present in both smooth and striated muscle. In general, only tumors with round rhabdomyoblasts or strap cells show positivity for this marker.
3. **Sarcomeric actin:** Rhabdomyosarcomas consistently express sarcomeric actin, which represents one of the best markers for this tumor. The interesting and surprising observation has been made that the specific sarcomeric actin expressed by these tumors is not of the alpha-skeletal muscle but the alpha-cardiac type. Rhabdomyosarcoma cells also express common muscle actin, but little or no smooth muscle actin.
4. **Myosin:** This marker has proved very effective for the identification of skeletal muscle differentiation. Adult sarcomeric and fetal forms of myosin exist; expression of fetal heavy chain skeletal myosin, viewed as the expression of an oncofetal antigen, was found in one series in 81% of rhabdomyosarcomas.
5. **Myoglobin:** This protein appears to be specific for striated muscle differentiation, and it would therefore seem well suited for this purpose. Unfortunately, it is expressed only when the tumor cell has acquired a high degree of differentiation. It is therefore often negative in poorly differentiated

tumors. One should also be careful of diffusion from neighboring injured skeletal muscle fibers.

6. **Tropomyosin a-actinin, titin, and Z protein:** These are constituent proteins of sarcomeric muscle and show a high degree of specificity. Unfortunately, most of them stain only well-differentiated cells in a minority of the tumors, a fact that greatly limits their diagnostic application.
7. **Vimentin:** This antigen is consistently positive, particularly in the lesser differentiated tumors, but of course it lacks specificity as a skeletal muscle marker. It is the first marker to appear in the tumor cells, followed sequentially by actin, desmin, fast myosin, and myoglobin.

Conclusion

Orbital RMS is a life-threatening diseases that presents first to the ophthalmologist. Knowledge of the clinical, histopathological, and radiographic features as well as the more recent advances in the management of this entity is necessary. A multidisciplinary approach for the treatment of orbital RMS is essential. In our case, the patient deteriorated within a very short span of 8-9 months due to misdiagnosis owing to its similarity to myxoma picture histologically. The facility of IHC was not utilized resulting in huge tumor load of the patient. Thus, histopathology along with IHC should be used as an ancillary test in cases as confusing as ours, thereby saving patients valuable time.

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