# **Case Report**

DOI: http://dx.doi.org/10.18203/2349-2902.isj20202854

# Rhabdomyosarcoma of lip - issues of subtyping, morphology and immunohistochemistry versus molecular studies: a case report with review of literature

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Received: 09 May 2020 Accepted: 15 June 2020

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#### **ABSTRACT**

Rhabdomyosarcoma (RMS) is a malignant soft tissue tumour occurring most frequently in younger age groups. Study presented a rare case of spindle cell Rhabdomyosarcoma of the upper lip involving the commissure area. In this case report after successful surgical excision, the patient underwent extensive postoperative histopathological studies including special stains and immunohistochemistry. Genotype studies (reverse transcription polymerase chain reaction) were done to help in subtyping and prognostication, and it turned out to be a surprise as it showed positivity for PAX3-FOXO1 t (2;13) translocation which is almost exclusively seen with alveolar RMS. After that he successfully underwent chemotherapy and radiotherapy as it was an aggressive variant and has been disease free for the past 2 years. The author hopes that this case report will highlight the importance of high clinical suspicion in head and neck masses presenting in pediatric age group and to not rely solely on biopsy reports to confirm diagnosis, so that early detection will lead to successful therapy and outcome as exemplified in this case.

**Keywords:** Alveolar rhabdomyosarcoma, Chemotherapy, Lip, Radiotherapy, Surgical excision, Spindle cell rhabdomyosarcoma

#### **INTRODUCTION**

Rhabdomyosarcomas (RMS) are malignant tumors of skeletal muscle origin found most commonly in pediatric age groups. There are 4 subtypes of rhabdomyosarcoma as per the current WHO classification which includes embryonal, alveolar, spindle cell/sclerosing and pleomorphic subtypes of RMS.<sup>1</sup>

The immunohistochemical (IHC) positivity for vimentin, muscle-specific actin, desmin and myoglobin has been used to distinguish RMS from other soft tissue sarcomas with similar histopathological patterns. Myogenin and MyoD1 are markers more specific for myogenic cellular line.<sup>2</sup>

#### **CASE REPORT**

An 8-year-old boy presented with a rapidly enlarging growth of the left upper lip for 3 months duration (Figure 1). He had associated pain but no discharge or bleeding on touch from the lesion. Pre-operative imaging showed a vascular lesion and a provisional diagnosis of hemangioma lip was made. Surgical excision was done, and the post-operative biopsy report was consistent with a Epitheloid spindle cell neoplasm and Epithelioid hemangioendothelioma was considered as a likely diagnosis based on morphology alone (Figure 2 a and b), however immunohistochemistry was advised to rule out other morphologically similar entities and to reach a specific diagnosis. The tumor was fairly circumscribed,

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located in the submucosal plane with a tiny rim of normal soft tissue as deep margin.



Figure 1: Preoperative image showing tumour in the left upper lip involving the commissure.

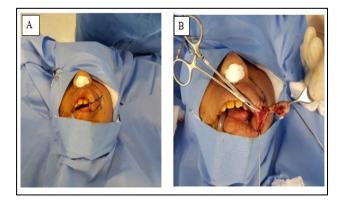


Figure 2: (A) Intra-operative image showing markings for surgical excision and (B) intra -operative image of tumour excision.

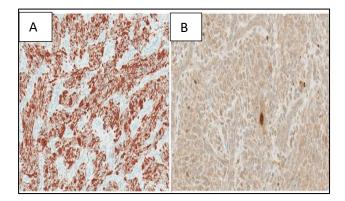


Figure 3: (A) IHC staining for desmin and (B) IHC staining for myogenin.

The cells were showing diffuse strong cytoplasmic positivity for desmin and patchy nuclear positivity for myogenin. Other positive markers were Myo-D1, Epithelial membrane antigen (EMA) and smooth muscle actin (SMA). Tumor cells were negative for CD31 and CD34 ruling out hemangioendothelioma. The cells were also negative for S100 (ruling out malignant peripheral

nerve sheath tumor) and cytokeratin (ruling out sarcomatous squamous cell carcinoma). On reviewing the histology and upon taking deeper sections many cells with eccentrically located nuclei and abundant eosinophilic cytoplasm is noted. Occasional cells also revealed cross striations. Myogenin positivity is generally patchy and weak in embryonal RMS and usually diffuse and strong in alveolar RMS.<sup>3</sup> Myo D1 and nuclear receptor coactivator -2 (NCOA2) is more specifically seen in spindle cell RMS. The histological and immunohistochemical features were consistent with spindle cell RMS (Figure 3 a and b). Spindle cell RMS lacks specific recurrent structural changes. PAX3 and PAX7 – FOXO1 alterations are typically absent.<sup>4-6</sup>

Hence the patient was referred to a Multi-disciplinary team (MDT), who then recommended further IHC studies which again confirmed spindle cell RMS. Metastatic workup including PET-CT was done and the result confirmed no metastasis. After that he underwent 20 cycles of adjuvant chemotherapy with vincristine, dactinomycin and cyclophosphamide (VAC) regime. After completion of chemotherapy further gene testing was done to prognosticate the tumor and it turned out to be a surprise as it was reported as positive for PAX3-FOXO1 with t (2;13) translocations suggestive of alveolar RMS and the presence of this mutation was said associated with unfavorable prognosis. be Subsequently he underwent 20 cycles of radiotherapy (RT) and 2 years post-surgery he is completely free of disease (Figure 4).



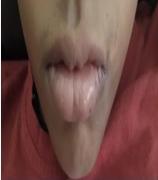


Figure 4: Post-operative results 2 years after surgery.

### **DISCUSSION**

The classification provided by the International Rhabdomyosarcoma study group divides RMS into 4 subtypes - superior prognosis subtypes (embryonal and spindle cell RMS) and poor prognosis (alveolar RMS and pleomorphic RMS). In the past, the prognosis of head and neck RMS was very poor, but now with the introduction of multimodal therapy wherein a combination of surgery, adjuvant chemotherapy with/without adjuvant radiotherapy, the 5 year survival rate of RMS has increased manifold.

The head and neck region are the most common site for RMS, with the orbit being the most frequent primary site. In the oral cavity the most common sites are tongue, palate and buccal mucosa. Oral Rhabdomyosarcoma is a rare neoplasm, and accounts for only 0.04% of all head and neck malignancies. 8.9 In our case the lip was involved with only a handful of cases being reported in literature.

Diagnosis of RMS is based primarily on histopathological studies followed by immunohistochemistry and molecular testing. In our case spindle and epitheloid cells were seen. The morphology and immunohistochemistry favored spindle cell RMS, but genetic studies were positive for PAX3-FOXO1 with t (2;13) translocations which is generally associated with alveolar RMS. This created a dilemma for us, whether to go with morphology or with genetic markers? The prognosis of spindle cell RMS is good, especially in pediatric population (95% survival in 5 years). 10,11 This is in contrast with alveolar RMS where the prognosis is worse especially with PAX3- FOXO1 translocation. 12

Metastases develop during the progression of the disease, and the major sites are the lungs, lymph nodes, and bone marrow. The lungs are involved in at least two thirds of patients with metastasis.<sup>13</sup>

This case is reported due to its rarity and its diagnostic dilemma, as not a single case of spindle cell RMS on the lip has been reported in literature (PubMed search of the term/terms spindle cell rhabdomyosarcoma lip, did not give any matching results.). PAX3-FOXO1 with t (2;13) translocations are never reported in a spindle cell RMS. The prognostic significance of this mutation in spindle cell RMS is yet to be seen, and only time will tell whether this case report will lead to many more of such cases being reported.

Genetic testing and Immunohistochemistry studies must be made mandatory for the diagnosis of these rare tumors in case of clinical suspicion and may also guide therapy for this aggressive tumor thereby improving survival outcomes as a resul.<sup>3</sup> Prognosis of RMS in adults and children with advanced metastatic disease still remains bad, despite a multidisciplinary approach. To improve local response and overcome drug resistance newer treatment options like hyper fractionated radiotherapy and dose intensive chemotherapy with growth factors are under evaluation. Also, with genetic testing becoming more commonplace the culprit genes could be targeted with gene therapy in the future.<sup>14</sup>

## **CONCLUSION**

Primary mixed rhabdomyosarcoma of the lip is a very rare tumor with an insidious onset and requires a multidisciplinary approach to its management with a combination of surgery, radiotherapy and chemotherapy. With the advent of immunohistochemistry and genetic testing, affected patients can be offered an early aggressive multimodal therapy before the tumor spreads, leading to better outcomes as exemplified in this case.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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Cite this article as: Alexander L, Ravindran HK, George J. Rhabdomyosarcoma of lip - issues of subtyping, morphology and immunohistochemistry versus molecular studies: a case report with review of literature. Int Surg J 2020;7:2389-92.