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ORIGINAL PAPER

Head and Neck Rhabdomyosarcoma: Clinical and Pathologic Characterization of Seven Cases

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Abstract Head and neck rhabdomyosarcoma occurs frequently in children and adolescents, and has been well studied in that population. In contrast, it is rare in adults and is not as well characterized clinically and pathologically. Seven cases of adult rhabdomyosarcoma occurring in head and neck were retrieved from the archives of Department of Pathology and Division of Oral Pathology at University of Washington. Radiologic findings and clinical history, as well as pathologic findings from hematoxylin and eosin slides and immunohistochemistry for myogenic markers were reviewed. A total of seven cases of rhabdomyosarcoma (two embryonal, three alveolar and two pleomorphic subtype) were reviewed. Patient ages ranged from 18 to 57 years (median 21 years). Classic and unique histologic features for each subtype, including post-treatment morphologic changes, were identified. Clinical follow-up information was available for 4 patients. 3 of 4 patients experienced recurrence, including two with distant metastasis. One patient died of disease progression 41 months after presentation. Head and neck rhabdomyosarcoma in adults can manifest both classic and unique histologic features for each subtype. In addition, recurrence and distant metastasis were observed, suggesting aggressive clinical behavior regardless of subtype.

Keywords Rhabdomyosarcoma · Head and neck · Alveolar · Embryonal · Pleomorphic

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Introduction

Rhabdomyosarcoma (RMS) is a soft tissue sarcoma pathologically characterized by abnormal myogenesis. It is the most common soft tissue sarcoma of children and adolescents, with an incidence of approximately 0.44/100,000 per year [1]. About 30% of pediatric RMS occurs in the head and neck [1]. In contrast, RMS is relatively rare in adults and occurs more frequently in the extremities and very infrequently in the head and neck region [2]. Due to the rarity of head and neck RMS in adults, most narratives of this disease have been published only as case reports [3–7].

Major histological subtypes of RMS include embryonal (ERMS), alveolar (ARMS), pleomorphic (PRMS), and spindle cell/sclerosing rhabdomyosarcoma. ERMS and ARMS are the major subtypes seen in the pediatric population. ERMS tends to occur in younger children, and carries a better prognosis. ARMS occurs more frequently in adolescents, and exhibits more aggressive biological behavior [8]. PRMS occurs in both children and adults, but the outcome is significantly worse in adults, with higher rates of recurrence and metastasis [9, 10]. Spindle cell RMS was traditionally included as a variant of ERMS but it is now provisionally listed as a separate spindle cell/sclerosing RMS subtype in the latest World Health Organization (WHO) classification (4th Edition, 2013). Recently, a rare epithelioid variant of RMS mimicking carcinoma or melanoma that frequently occurs in older patients has also been

described [11]. Of the RMS subtypes, ARMS is the only one with known recurrent chromosomal translocations. In about 75% of ARMS cases, chromosomal translocation results in the fusion of two transcription factor-encoding genes: the *PAX3* gene (or less frequently the *PAX7* gene) and the *FOXO1* gene [12, 13]. This fusion results in ARMS tumor cells expressing chimeric *PAX3/7-FOXO1* protein. In contrast, ERMS frequently shows loss of heterozygosity at chromosome 11p15.5 [14], and recurrent mutations affecting the receptor tyrosine kinase/RAS/PIK3CA axis are present in >90% of cases [15]. Recurrent *MYOD1*(L122R) mutation has been identified in a subset of pediatric and adult spindle cell/sclerosing variant of RMS [16–19].

To provide a deeper insight into the clinical and pathologic features of RMS, this study presents seven cases of adult head and neck RMS. Each was treated at the University of Washington Medical Center between 2000 and 2015.

Materials and Methods

Cases were retrieved from the archives of the Department of Pathology and Department of Oral and Maxillofacial Surgery at University of Washington. H&E and immunohistochemistry slides were independently reviewed by 3 pathologists (EC, DO and RR). For immunohistochemical characterization, tissue sections (5 uM thickness) were deparaffinized, and immunochemical staining was performed following standard antigen retrieval procedure. The following antibody dilutions were used: Desmin (1:800, Dako), MYOD1 (1:80, AbCam), Myogenin (1:25, Cell Marque).

Immunohistochemical staining was scored using the 4-point system [20]:

Strong (3+): dark staining in >50% of cells.

Moderate (2+): focal darkly staining areas in <50% of cells.

Weak (1+): focal moderate staining in <50% of cells.

Negative (0): None of the above.

Results

Clinical Findings

Our adult patients with head and neck RMS included three females and four males ranging in age from 18 to 57 years (median 21 years). Three cases occurred in the maxillary sinus, two in the cheek, one in the alveolar ridge, and one in the palate. Bone destruction was observed radiologically on presentation in four cases (cases 1, 4, 6 and 7; see examples in Fig. 1a, b). Tumor sizes at the time of excision ranged from 3.4 to 6.2 cm. Four patients (cases 1, 3, 6 and 7) underwent adjuvant chemotherapy and radiation post-operatively. Post-operative follow-up information was available for 4 patients. ERMS in case 1 recurred 17 months after completion of surgery, radiation and chemotherapy with regional and distant metastasis to the lung. ARMS in case 3 recurred locally 11 months post-composite resection. The patient of PRMS in case 6 was disease free in a limited 3-month follow-up after surgery and adjuvant radiation and chemotherapy treatments. The patient with PRMS in case 7 died of progressive disease after several regimens of chemotherapy, 41 months after presentation. Clinical features are summarized in Table 1.

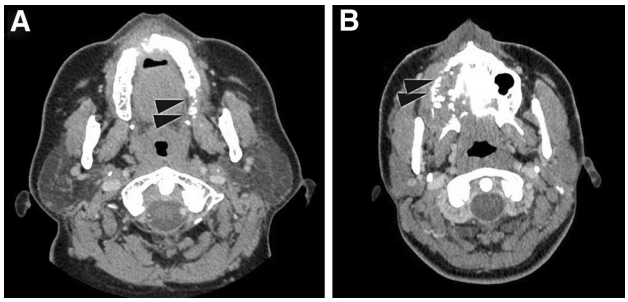

Fig. 1 Radiologic features of RMS. CT scans of **a** ERMS (case 1); **b** ARMS (case 4), showing destructive invasion of bone by tumor cells as indicated by *arrowheads*

Pathologic Findings

There were two cases of embryonal, three cases of alveolar and two cases of pleomorphic rhabdomyosarcoma with spindle cell features. Cases 1 and 2 showed characteristic features of ERMS including primitive mesenchymal cells recapitulating various stages of myogenesis with variable presence of rhabdomyoblasts (example in Fig. 2a). As cytodifferentiation progresses, the rhabdomyoblasts acquire increased amount of eosinophilic cytoplasm. Cytoplasmic striations and multinucleation can be seen occasionally in rhabdomyoblasts, but these features are not evident in the rhabdomyoblasts seen in the ERMS cases of this series. Cases 3, 4 and 5 showed conventional features of ARMS, characterized by fibrovascular septa separating primitive small round cells into discrete nests (example in Fig. 2b). Wreath-like multi-nucleated cells with rhabdomyoblastic differentiation, which may be seen in ARMS, are not present in these cases. Cases 6 and 7 showed features of PRMS characterized by large, atypical and occasionally multi-nucleated cells with prominent eosinophilic cytoplasm (example in Fig. 2c).

In addition to the conventional morphology as described for each RMS subtype, more unusual morphologic features and growth patterns were also present. While most of the ERMS in case 1 showed conventional features of

Table 1 Clinical features

Case #	RMS subtype	Age	Sex	Site	Size (cm)	Treatment	FU Duration (mo)	Recurrence	Metastasis	DOD
1	Embryonal	40	F	Maxillary sinus	3.4	S, C, R	17	Y	Y	–
2	Embryonal	18	M	Cheek	–	S	–	–	–	–
3	Alveolar	19	F	Cheek	–	S, C, R	11	Y	–	–
4	Alveolar	20	F	Maxillary sinus	—	S	–	–	–	–
5	Alveolar	21	M	Alveolar ridge	–	S, C	–	–	–	–
6	Pleomorphic	55	M	Maxillary sinus	4.2	S, C, R	3	N	N	–
7	Pleomorphic	57	M	Palate	6.2	S, C, R	41	Y	Y	Y

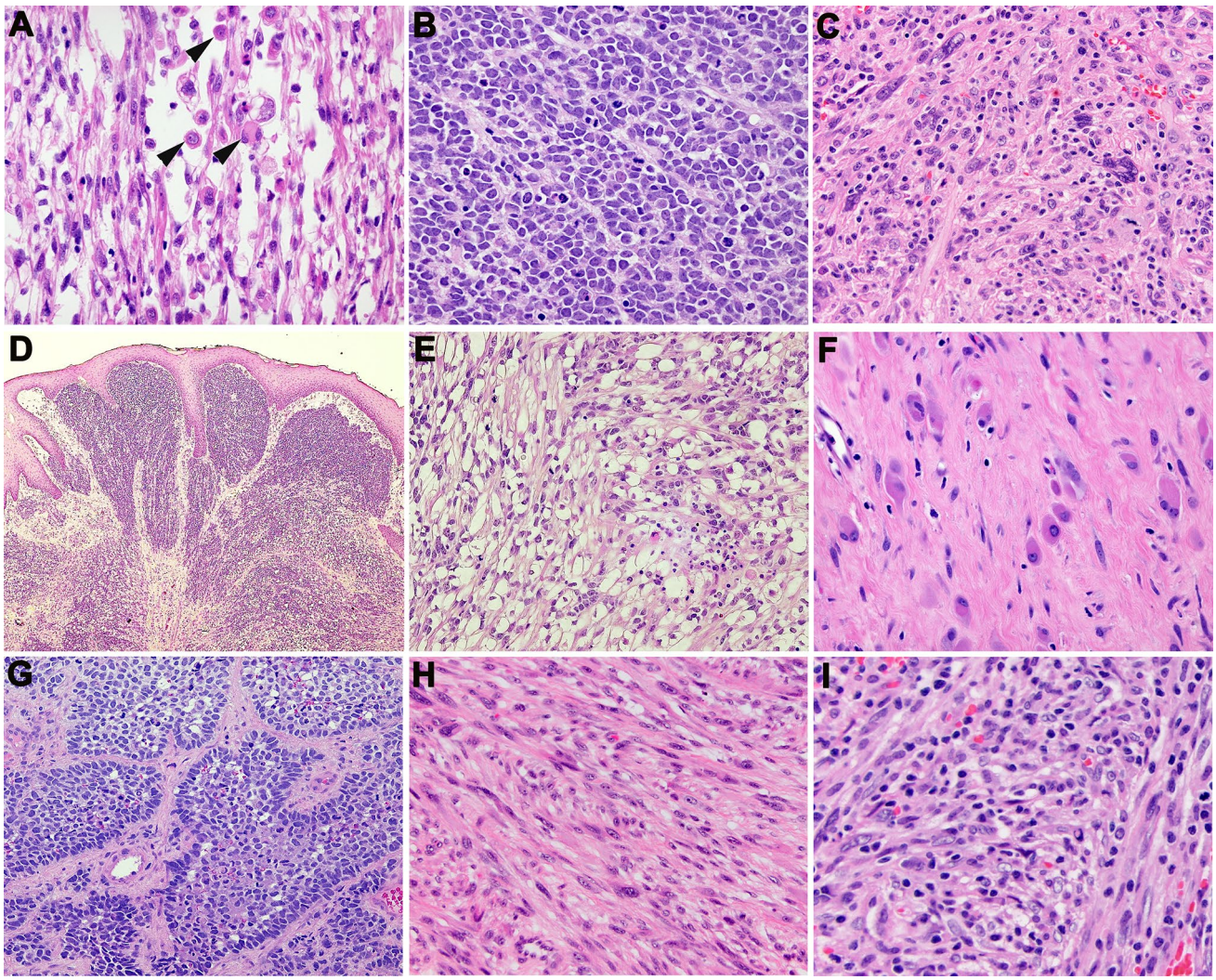

Fig. 2 Histologic features of head and neck RMS. **a** Rhabdomyoblasts (indicated by *arrowheads*) in ERMS (Case 2); **b** ARMS with alveolar arrangement of tumor cells (Case 4); **c** PRMS with pleomorphic cell morphology including multi-nucleated cells (Case 6); **d** ERMS (Case 1) with sub-epithelial condensation of tumor cells, resembling a cambium layer; **e** Nests and clusters of ERMS cells with abundant clear cytoplasm (Case 2); **f** Prominent cytodifferentiation of ARMS cells into myoblast-like cells post-radiation (3); **g** Nests of ARMs with prominent palisading of tumor cells in the periphery (Case 5); **h** PRMS with areas of spindle cell morphology (Case 7); **i** PRMS with pleomorphic tumor cells with prominent lymphocytic infiltrate (Case 6)

ERMS, there were also focal areas of subepithelial condensation of tumor cells beneath the overlying squamous epithelium, reminiscent of the cambium layer seen in the botryoid variant of ERMS (Fig. 2d). The ERMS in case 2 showed an abundance of cells with clear cytoplasm, admixed with rhabdomyoblasts (Fig. 2e). ARMS in cases 3 and case 5 showed the presence of residual differentiated rhabdomyoblasts with eosinophilic cytoplasm, some binucleated, following adjuvant radiation (Fig. 2f). In addition to the characteristic nested arrangement of tumor cells (Fig. 2b), ARMS of case 4 also showed prominent palisading of tumor cells in the periphery of each tumor cell nest (Fig. 2g). In both cases 6 and 7 of PRMS, areas of spindle cell morphology with fascicular growth pattern were present in addition to the classic pleomorphic epithelioid morphology (Fig. 2h), suggesting that these two cases may represent a mixed subtype of pleomorphic and spindle cell RMS. Case 6 also demonstrates brisk lymphocytic infiltrate (Fig. 2i), in contrast to the minimal inflammatory infiltrate seen in other RMS described in this series.

Immunohistochemical Findings

By immunohistochemistry (IHC), all 7 cases demonstrated positive expression of myogenic markers, desmin, MyoD1 or Myogenin. In particular, the ARMS in cases 3–5 showed a diffuse positive staining (3+) of Myogenin or MyoD1, in contrast to the focal Myogenin staining (2+) seen in the cases of ERMS (cases 1 and 2) and PRMS (cases 6–7) (examples of Myogenin IHC in Fig. 3). This is in keeping with the previous findings that strong and diffuse expression of Myogenin is significantly associated with ARMS [21]. PRMS of case 7 with spindle cell areas showed negative Myogenin expression, strong expression of MyoD1 (3+), and focal expression of desmin (2+). The spindle cell/sclerosing variant of RMS has been described to show limited expression of Myogenin, strong MyoD1 expression and focal dot-like desmin expression [22]. The immunoprofile of case 7 further suggests that this tumor may represent a mixed subtype of pleomorphic and spindle cell RMS. Table 2 summarizes quantitative IHC scoring results.

Discussion

This study described clinical and pathologic characteristics of seven cases of adult head and neck RMS, including alveolar, embryonal and pleomorphic subtypes with spindle cell features. In children, RMS occurring in the head and neck tends to have favorable outcome except for tumors arising in parameningeal sites such as the nasal

Table 2 Immunohistochemical study of myogenic markers, MyoD, Myogenin and Desmin

Case #	MyoD	Myogenin	Desmin
1	3+	2+	3+
2	–	3+	3+
3	3+	–	3+
4	–	3+	3+
5	–	3+	3+
6	–	2+	3+
7	3+	0	2+

IHC was scored as the following categories: Strong (3+), dark staining in >50% of cells; moderate (2+), focal darkly staining areas in <50% of cells; weak (1+), focal moderate staining in <50% of cells; negative (0), none of the above. Staining not performed is indicated as "–"

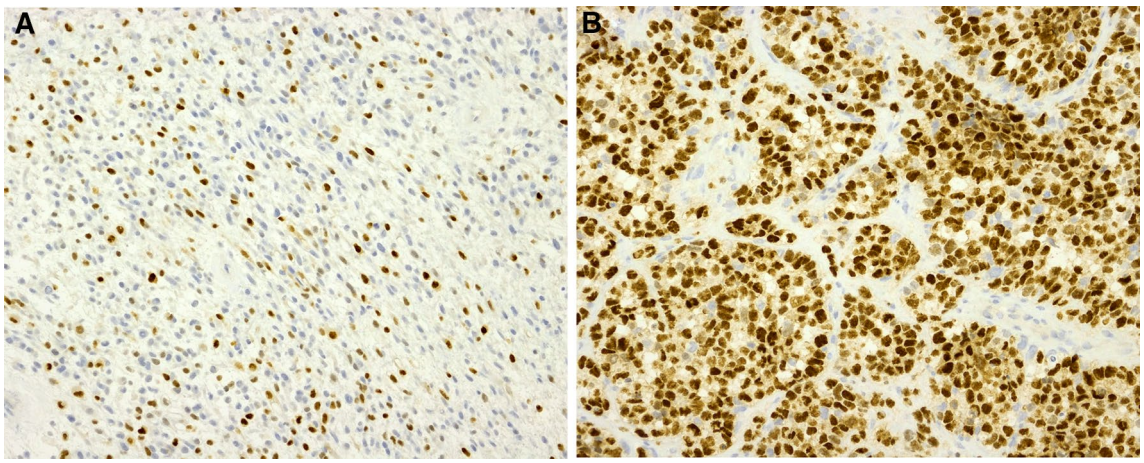

Fig. 3 Immunohistochemistry for Myogenin. **a** ERMS in case 1; **b** ARMS in case 4

cavity, paranasal sinuses, infratemporal fossa and the mastoid. Poorer outcomes for tumors in these sites are due in part to difficulty in achieving complete resection from these areas. In contrast, the cases of head and neck RMS in adults in our study manifested more aggressive biological behavior compared to pathologically similar RMS in pediatric patients. Of our 4 currently described adult cases with available post-operative clinical follow-up, case 1 (ERMS) in the maxillary sinus, case 3 (ARMS) in the cheek and case 7 (PRMS) in the palate showed local recurrence within 3 years. The case 1 ERMS and case 7 PRMS patients also experienced distant metastases, and one patient with PRMS (case 7) died of progressive disease within 4 years from the time of diagnosis.

All adult head and neck RMS cases described in this series showed conventional histologic features for each subtype. Some of the cases demonstrated more unusual morphologic features. In particular, ERMS cells in case 2 showed foci of tumor cells with abundant clear cytoplasm admixed with typical rhabdomyoblasts, a morphologic feature not previously described in ERMS. In cases 3 and case 5 of ARMS, we noted maturation of myogenic tumor cells post adjuvant chemotherapy and radiation. Cytodifferentiation of RMS cells post-treatment has been previously described in a subset of cases, but more frequently in the ERMS subtype and appears to correlate with decreased proliferative activity of tumor cells [23]. Finally, the two PRMS cases (case 6 and case 7) demonstrate focal areas of spindle cells admixed with tumor cells showing the more characteristic pleomorphic morphology. The findings raise the possibility that these cases may represent a mixed subtype of pleomorphic and spindle cell RMS. In all, the additional morphologic features seen in adult head and neck RMS likely reflect tumor heterogeneity in cell differentiation and pathogenesis distinct from their pediatric counterpart.

Other malignant tumors with rhabdomyosarcomatous differentiation need to be considered on the differential diagnosis. For example, malignant peripheral nerve sheath tumor (MPNST) with heterologous rhabdomyosarcomatous differentiation ("malignant Triton tumor") should be considered, particularly in patients with history of type 1 neurofibromatosis (NF1) and in cases where there is gross or radiologic finding showing a close association of the tumor with a peripheral nerve. Histologically, the association with a peripheral nerve or a benign nerve sheath tumor, e.g. neurofibroma, may be seen in a subset of MPNSTs. Immunohistochemistry for S100 and SOX10 can sometimes be helpful diagnostically. However, the staining pattern for these markers is focal and positive expression is seen in approximately 50–60% of MPNST [24, 25].

Sarcomatoid carcinoma of cutaneous, mucosal or salivary gland origin needs to be considered on the differential diagnosis when dealing with a limited tissue biopsy and a mucosal biopsy from an older patient, particularly in the setting of prior carcinoma or radiation. Thorough sampling of the resection specimen to cover the surface component and heterogeneous areas of the tumor is crucial. Immunohistochemistry for multiple cytokeratins and p40/p63 can be utilized to further support the diagnosis of sarcomatoid carcinoma.

RMS, in particular the ERMS and ARMS subtypes, can take on the appearance of small, primitive and round cells, therefore differential diagnosis in this context needs to include other small round cell tumors. Examples are Ewing's sarcoma, small cell melanoma, and lymphoblastic lymphoma. Immunohistochemistry for markers such as CD99 (diffuse membranous pattern in Ewing's sarcoma [26]), S100, Melan A and HMB-45 (melanoma) and TdT, CD43 and CD79a (lymphoblastic lymphoma [27, 28]) will be helpful in the diagnostic work-up. Ancillary tests such as Fluorescent In Situ Hybridization (FISH) or Reverse Transcription Polymerase Chain Reaction (RT-PCR) assays to show the presence of *EWS* gene rearrangement in Ewing's sarcoma and flow cytometry assay to show clonal lymphoid population will also be useful.

In conclusion, we have described a series of 7 adult head and neck RMS. The major subtypes share morphologic features with their pediatric counterpart, but also show more unusual features. The biological behavior appears to be aggressive regardless of histologic subtype.

Compliance with Ethical Standards

Conflict of interest No conflict of interest to disclose.

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