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Original contribution

Alveolar rhabdomyosarcoma of the head and neck region in older adults: genetic characterization and a review of the literature☆

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Summary Alveolar rhabdomyosarcoma is remarkably rare in adults older than 45 years. Initial immunoprofiling of a small cell neoplasm of the head and neck region in an older adult may not include myogenic markers. A valuable diagnostic aid and important prognostic parameter in alveolar rhabdomyosarcoma is the identification of *PAX3-FOXO1* [t(2;13)(q35;q14)] or *PAX7-FOXO1* [t(1;13)(p36;q14)] rearrangements. The purpose of this study was to document the clinicopathologic, immunophenotypic, and genetic features of head/neck alveolar rhabdomyosarcoma in older adults. Prior isolated descriptions of 3 patients were included. Five patients were female and 2 male (median age, 61 years). Each neoplasm was composed of undifferentiated, small round cells in a predominantly solid pattern. Initially, ordered immunostains corresponded with early diagnostic impressions of a hematologic malignancy or neuroendocrine carcinoma. CD56 was positive in 5 of 5 tumors and synaptophysin in 1 of 6. Given the virtual absence of other lymphoid or epithelial markers, muscle immunostains were performed and these were positive. Definitive alveolar rhabdomyosarcoma diagnoses were confirmed genetically. This study illustrates the diagnosis of head/neck alveolar rhabdomyosarcoma in older adults is complicated by its rarity, lack of an alveolar pattern, and a potentially misleading immunoprofile (CD56 and synaptophysin immunoreactivity) if myogenic markers are not used. Both *PAX3*- and *PAX7-FOXO1* alveolar rhabdomyosarcomas were identified in these patients. In children, *PAX7-FOXO1* alveolar rhabdomyosarcoma is associated with a significantly

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longer event-free survival. In contrast, adult alveolar rhabdomyosarcoma behaves more aggressively with a worse overall survival than pediatric alveolar rhabdomyosarcoma. Further follow-up and additional cases are required to assess the prognostic relevance of these fusion transcripts in the context of advanced age.

1. Introduction

Rhabdomyosarcoma (RMS) is a morphologically and clinically heterogeneous family of malignant soft tissue tumors related to myogenic lineage [1,2]. Alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS) represent the 2 main histologic patterns and must be differentiated from other small round cell tumors. RMS is the most common soft tissue sarcoma in the pediatric population, comprising approximately 5% of all childhood cancers and nearly 50% of soft tissue sarcomas arising in children 0 to 14 years of age [3,4]. In contrast, RMS is remarkably uncommon in older adults representing merely 2% to 5% of all malignant soft tissue tumors, with the majority of the pleomorphic subtype [5]. Hence, owing to the rarity of ARMS in the older adult and the relatively recent inclusion of molecular approaches in the diagnostic assessment of these neoplasms, very few cases of the head and neck region have been previously analyzed genetically [6-8].

In this study, the diagnosis of 4 ARMSs arising in the head and neck region of patients between 61 and 76 years of age was confirmed by the demonstration of *PAX-FOXO1* fusion gene expression. Identification of the characteristic gene fusions in these tumors allowed for a rapid, definitive diagnosis and commencement of proper therapy. The clinicopathologic and genetic findings of these cases and those of previous isolated reports are reviewed [6-8].

2. Materials and methods

2.1. Clinical cases

A summary of the patient characteristics is presented in Table 1.

2.1.1. Case 1

A 76-year-old woman presented with new onset of left ptosis, dysarthria, and headache. Radiographic studies revealed left ethmoid and sphenoid sinus opacification with contrast enhancement consistent with chronic sinus disease but concerning for neoplasm. Histopathologic evaluation of the surgically excised specimen revealed an infiltrative lesion composed of sheets of small round cells (Fig. 1A). Focally, fibrous tissue bands separated some cell aggregates (Fig. 1B). Examination of individual cells was limited by variable crush artifact and necrosis. The initial clinicohistopathologic impression was malignant undifferentiated tumor; a small cell carcinoma was favored. Immunohistochemistry was performed using the following antibodies: epithelial membrane antigen; diverse keratin antibodies MAK6, AE1/AE3, CK7, CK20, CAM5.2; CD56; chromogranin; synaptophysin; glial fibrillary acidic protein; S-100 protein; melan-A; CD45; Epstein-Barr viral LMP and myeloperoxidase. The tumor cells were positive solely for CD56 (Fig. 1C). Additional immunohistochemical studies demonstrated tumor immunoreactivity for vimentin, desmin, and myogenin (Fig. 1D). At the time of biopsy, a portion of

Table 1 Characteristics of adult patients with head and neck ARMS

Case no.	Age/sex	Location	Size (cm)	Metastases at diagnosis	Treatment	Follow-up (mo)	References
1	76/F	Ethmoid sinus	3	Internal auditory canal	ChemoRT	14 (DOD)	Current study
2	61/M	Nasopharynx	NA	Lymph nodes, bone, lung	ChemoRT	10 * (AWD)	Current study
3	61/F	Palate	7.2	Lymph node	ChemoRT	13 (NED)	Current study
4	64/F	Maxillary sinus	5	None	ChemoRT	12 (AWD)	Current study
5	68/F	Cervical paravertebra	10	Widespread: bone marrow, thoracic wall, stomach, pancreas	Chemotherapy	11 d (DOD)	Stindl et al [8]
6	57/F	Ethmoid sinus	NA	NA	NA	NA	Manucha et al [7]
7	49/M	Nasal sinus	NA	None	Resection, chemotherapy	60 (AWD)	Das et al [6]

Abbreviations: M, male; F, female; ChemoRT, chemotherapy and radiation therapy; NA, not available; DOD, died of disease; AWD, alive with disease; NED, no evidence of disease.

* Patient lost to further follow-up after 10 months.