Alveolar Rhabdomyosarcoma of the Paranasal Cavity in an Adult Woman

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Abstract

Alveolar rhabdomyosarcoma (RMS) is extremely rare in adults older than 45 years and may be very difficult to distinguish from other primitive round cell neoplasms without immunohistochemistry and/or genetic studies. In adults, the differential diagnosis of small round cell tumors of the head and neck region includes small cell carcinoma, lymphomas and neuroepithelial tumors, such as esthesioneuroblastoma and, as last choice, rhabdomyosarcoma. Initial immunoprofiling may not include myogenic markers. Moreover, aberrant expression of epithelial and neuroendocrine markers in alveolar RMS may be a potentially serious diagnostic pitfall. In this report, we describe the clinico-pathological features of a case of paranasal alveolar RMS in a 61-year-old woman with no previous history of neoplasia and discuss the differential diagnosis of small round cell tumor in the nasal/paranasal cavity.

Keywords: Alveolar rhabdomyosarcoma; Adult; Nasal cavity; CD56; Myogenin

Introduction

Rhabdomyosarcomas are a morphologically and clinically

heterogeneous family of malignant soft tissue tumors related to the myogenic lineage [1, 2]. Alveolar rhabdomyosarcoma (RMS) and embryonal RMS represent the two main histological 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 tumors and nearly 50% of soft tissue sarcomas arising in 0 - 14 years old children [3-5]. In contrast, it is remarkably uncommon in elder adults, representing merely 2-5% of all malignant soft tissue tumors, mostly of the pleomorphic type [6].

Alveolar RMS may involve the head and neck region (40%), the genitourinary system (20%), the extremities (20%), the trunk (10%) and other sites (10%) [7-10].

Here we report an uncommon case of alveolar RMS in the paranasal cavity of a 61-year-old woman, with emphasis on the differential diagnosis of small round cell tumors in this location and the potential immunohistological diagnostic pitfalls.

Case Report

A 61-year-old female presented for onset of otalgia and a lump in the right neck.

A computed tomography (CT) scan revealed a right ethmoidal sinus lesion extending to the homolateral maxillary sinus and medial turbinate, with radiological features suspicious for a neoplasia (Fig. 1A, B).

A biopsy was performed and histological evaluation revealed an infiltrative neoplastic proliferation composed of sheets and solid nests of atypical small round cells (Fig. 2A), displaying hypercromatic nuclei, scant eosinophilic cytoplasm and brisk mitotic activity (Fig. 2B). Examination of the individual cell morphology was often limited by variable crush artifacts and necrosis. On the basis of the sole morphology, an initial diagnosis of malignant undifferentiated neoplasia was made, being a small cell carcinoma the favored diagnostic hypothesis. Immunohistochemistry was performed using an antibody panel (Table 1) that could confirm the hypothesis of small cell undifferentiated carcinoma (EMA, cytokeratins AE1/AE3, CK7, CK20), including neu-
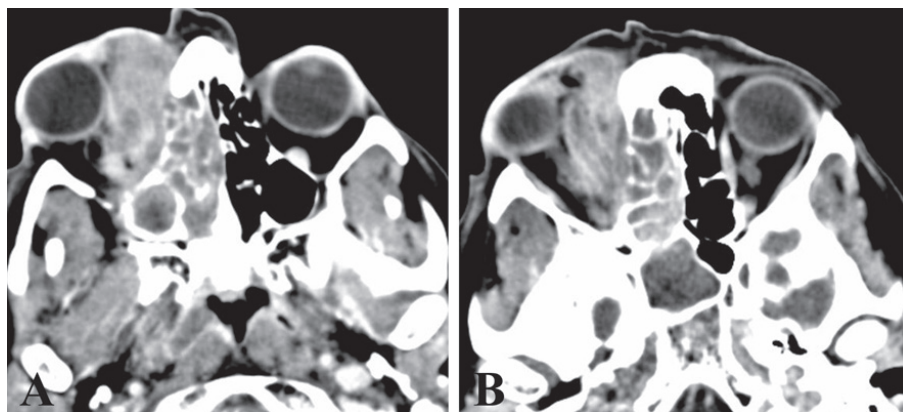
Figure 1. CT scan reveals a right ethmoidal sinus lesion (A), 30 mm in diameter, extending to the homolateral maxillary sinus and medial turbinate, and infiltrating the right orbital cavity (B).

roendocrine markers (CD56, chromogranin, synaptophysin) and GFAP, s-100 protein, HMB45, melan-A, CD45, EBV-LMP1 and myeloperoxidase (for excluding neuroectodermal tumors, melanoma and lymphohemathopoietic neoplasms).

The tumor cells showed a positive immunostain only for CD56 (Fig. 2C). A sarcomatous nature of the lesion was suspected and appropriate additional immunohistochemical studies were performed. The neoplastic cells displayed a positive immunoreaction for vimentin, desmin (Fig. 2D), MyoD1 and myogenin (Fig. 2E), suggesting a rhabdomyosarcomatous differentiation.

A cytogenetic analysis revealed the t(2;13) translocation, a chromosomal rearrangement typical of alveolar RMS.

On the basis of immunohistological and cytogenetic findings a final diagnosis of alveolar RMS was made.

In January 2010, the patient underwent the first cycle of polichemotherapy treatment (VAC scheme: vincristine 2 mg/day 1, adriamicine 108 mg/day 1, cyclophosfamide 3,024/days 1-2).

One month later the patient received the second cycle (75% of VAC scheme: vincristine 1.5 mg/day 1, adriamicine 80 mg/day 1, cyclophosfamide 2,268/days 1-2). The third cycle was at 66% of VAC scheme for progressive mielotoxicity side effect.

CT scan and magnetic resonance imaging (MRI) performed in April revealed a good local response with 80% of tumor regression. From May to July the patient was treated with external beam radiation therapy (69.3 Gy/33 fraction). One month later MRI revealed the presence of local residual disease.

The case was discussed by the Head and Neck Tumor Management Team that scheduled the patient for surgery. Before the operation, the patient presented with a new onset of pain at the right arm and scapula. PET-CT scan and bone scintigraphy revealed the presence of multiple bone metastases. The patient was referred to palliative chemotherapy and

unfortunately died for disease complications one year after the initial consultation.

Discussion

Alveolar RMS is composed in its classical form of distinctive nests of primitive-appearing round cells, which grows in a discohesive fashion, surrounded by hyalinized and highly vascular fibrous septa producing a pattern reminiscent of the alveoli of the lung. Obvious rhabdomyoblastic differentiation, in the form of strap cells and cytoplasmic cross striations, is rarely identified.

Solid forms of alveolar RMS lack the prominent nested pattern and cellular discohesion seen in the classical histotype and may closely mimic a variety of other small round cell tumors, such as small cell carcinoma, lymphoma, neuroblastoma and malignant melanoma [11].

In immunohistochemistry, alveolar RMS typically expresses vimentin and muscle-specific antigens, such as desmin, muscle actins (including smooth muscle isoforms), myogenin and MyoD1 [12, 13]. Aberrant expression of epithelial and neuroendocrine markers, a potentially serious diagnostic pitfall, has been recently described [14, 15].

Alveolar RMS is a very aggressive tumor with a poor prognosis and requires a histotype-specific aggressive therapy. Therefore an accurate diagnosis and its distinction from other small round cell tumors are of crucial clinical importance.

While some cases of alveolar RMS have been described in young adults, the occurrence of this neoplasm in adults over the age of 45 years is extremely uncommon, being pleomorphic RMS, characterized by different microscopic features and biological behavior, the most common histotype in this category of patients [8-10, 16]. For this reason, the inclusion of alveolar RMS in the differential diagnosis of

Table 1. Details on Antibodies Used for the Immunohistochemical Study

Antibody	Clone	Source	Dilution	Pretreatment
GFAP	6F2	Dako	1:50	Microwave
Chromogranin A	DAK-A3	Dako	1:100	Microwave
Vimentin	3B4	Ventana	No	Pressure cooker
Desmin	D33	Dako	1:50	Microwave
CD56	123C3	Dako	No	Microwave
CK20	K20.8	Dako	No	Microwave
CK7	OV-TL 12/30	Dako	1:50	Microwave
Cytokeratin	AE1/AE3	Dako	1:50	Pressure cooker
S-100 protein	Polyclonal	Dako	1:400	Microwave
HMB45	HMB45	Novocastra	1:30	Microwave
MART1	A103	Dako	1:25	Microwave
Synaptophysin	SY38	Dako	No	Microwave
EMA	GP1.4	Novocastra	No	Microwave
CD45	2B11 + PD7/26	Dako	No	Microwave
Myogenin	F5D	Dako	No	Microwave
EBV-LMP1	CS.1-4	Dako	No diluition	Microwave
Myeloperoxidase	Polyclonal	Dako	1:300	Microwave
MYOD1	5.8A	Dako	1:50	Pressure cooker

small round cell tumors of the head and neck region is often neglected. Other malignancies such as small cell undifferentiated or neuroendocrine carcinoma, lymphoma, olfactory neuroblastoma and melanoma are more likely to be considered in this location in elder patients.

In our case, the initial diagnostic work-up for an undifferentiated tumor arising in the head and neck region in a 56-year-old female patient did not include myogenic markers. The neoplastic cells were positive for CD56 immunostain and only as a consequence of no immunoreaction for the other epithelial, lymphoma, or malignant melanoma markers, the differential diagnosis was expanded to include RMS and additional immunostains for a myogenic differentiation were pursued.

The differential diagnosis of CD56 positive small round cell tumors includes natural killer (NK)-cell tumor, rhabdomyosarcoma, small cell carcinoma, neuroblastoma, primary neuroectodermal tumor, malignant peripheral nerve sheath tumor, desmoplastic small round cell tumor, synovial sarcoma and malignant melanoma.

CD56 expression has an established role in the diagnosis of non-Hodgkin lymphoma/NK cell type and other hematological malignancies. The sinonasal region is notably a common location for NK/T-cell lymphomas, in particular in some areas of the world [17].

CD56 immunostain is of limited value in the differential diagnosis of sarcomas because it is widely expressed in these neoplasms. However, it may be useful in combination with the assessment of CD99 expression in the differential diagnosis with Ewing's sarcoma. Only 10-25% of Ewing's sarcomas are CD56 positive in contrast to 100% embryonal and alveolar RMSs [18, 19].

CD56 is also commonly expressed in neuroendocrine tumors and the co-expression of synaptophysin and/or chromogranin is highly suggestive of neuronal or neuroendocrine differentiation.
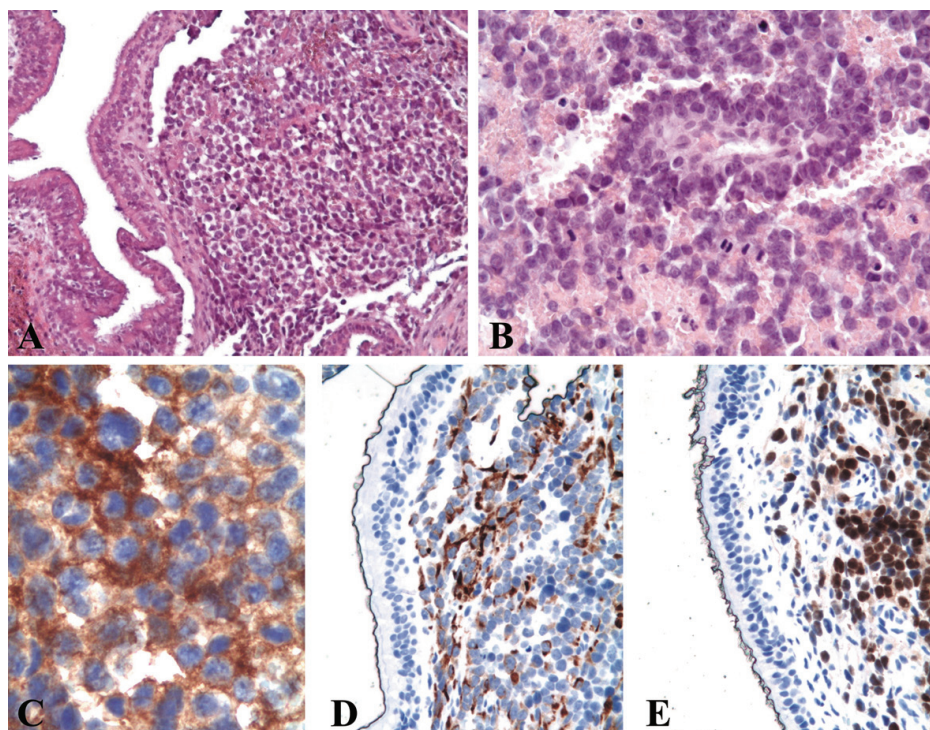
Figure 2. Histological examination of the biopsy shows a submucosal infiltrative lesion composed of sheets of small cells (A, hematoxylin and eosin, original magnification × 200) displaying round hyperchromatic nuclei with nucleoli, scant eosinophilic cytoplasm and brisk mitotic activity (B, hematoxylin and eosin, original magnification × 400). At immunohistochemistry, the neoplastic cells show a diffuse cytoplasmic positivity for CD56 (C, original magnification × 630) and desmin (D, original magnification × 400) and diffuse nuclear positivity for myogenin (E, original magnification × 400).

Indeed, some cases of synaptophysin positive immunoreaction in alveolar RMS have been reported [14, 15]. Conversely, rhabdomyoblastic differentiation may occur in olfactory neuroblastoma [20].

The differential diagnosis of poorly differentiated round cell neoplasms represents a common problem. In most cases morphologic evaluation is not sufficient and further investigations are required. The study of the immunohistochemical profile of the tumor is mandatory and the evaluation of the right combination of immuno-markers may have very important prognostic and therapeutic implications. In doubtful cases, cytogenetics and molecular biology studies can be useful in establishing the right diagnosis or to confirm the diagnostic hypothesis. The most common chromosomal rearrangements in alveolar RMS are t(2;13)(q35;q14), which is seen in 55% of cases, and t(1;13)(p3;q14), which is encountered in about 22% of cases [11].

Our case suggests that in cases of undifferentiated round cell neoplasms of the head and neck region in elder patients, alveolar RMS should be taken into consideration in the differential diagnosis, along with lymphoma, small cell carcinoma and estesioneuroblastoma that are commonly encountered in such clinical spectrum. Therefore, the immunohistochemical differential diagnosis should always include

a myogenic marker, such as desmin, myogenin or MyoD1. The performance of one more immunostain can avoid a diagnostic pitfall and provide a more rapid and correct diagnosis. Moreover, the demonstration of specific chromosomal rearrangements may be a very helpful diagnostic tool in doubtful cases.

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