Case Report

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# Rhabdomyosarcoma Presenting as Bilateral Cervical Lymphadenopathy in an Adult with Aberrant Expression of Cytokeratin and Synaptophysin: A Potentially Serious Diagnostic Pitfall

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## ABSTRACT

Rhabdomyosarcoma (RMS) is the most common soft tissue malignancy in children and adolescents. Its occurrence in patients more than 18 years of age is rare. Subtypes of rhabdomyosarcoma include embryonal RMS, alveolar RMS, pleomorphic RMS and spindle/sclerosing RMS.

Herein, we report the case of a 42-year-old female patient who presented with bilateral cervical lymphadenopathy of two-month duration. Clinical and radiological examination showed no other significant lesions. Fine needle aspiration cytology and biopsy of lymph node showed diffusely arranged atypical round cells. The clinical findings and morphology pointed to a hematolymphoid malignancy. On immunohistochemical examination, the atypical cells were negative for CD45, CD20, CD3, PAX5 and CD30. The cells showed patchy moderate positivity for cytokeratin, focal weak positivity for synaptophysin and were negative for chromogranin, CD56 and TTF1. On further evaluation, patchy strong positivity for desmin, myogenin and myo D1 were noted. Correlating the morphology and immunoprofile, diagnosis of rhabdomyosarcoma was given.

Multiple peripheral lymph node enlargement without an obvious primary lesion is a rare presentation of alveolar RMS, with only a few cases reported in literature. Unusual clinical presentation complicated with aberrant expression of epithelial markers may make the diagnosis of alveolar RMS difficult. This case demonstrates the importance of considering extensive differential diagnosis for neck masses with poorly differentiated morphology.

***Keywords:*** *Aberrant Antigen Expression, Cervical Lymphadenopathy, Cytokeratin, Rhabdomyosarcoma, Synaptophysin.*

## Introduction

Malignant small round cell tumours are characterised by small, round, relatively undifferentiated cells. Undifferentiated morphology or primitive character of these tumours may cause challenges in accurate categorization. The differential diagnosis of small round cell tumors of the head and neck region in adults include non-Hodgkin lymphoma, metastases from small cell carcinoma, sinonasal undifferentiated carcinoma and esthesioneuroblastoma. Rhabdomyosarcoma is rare in older age group. [1,2] Alveolar rhabdomyosarcoma (ARMS), composed of primitive cells with round nuclei, predominantly arises in the extremities of adolescents and young adults.

The rarity of alveolar RMS in adults can result in misdiagnosis or delayed diagnosis. The initial immunopanel of small round cell tumors in adults may not include myogenic markers. In addition, aberrant expression of epithelial and neuroendocrine markers in alveolar RMS may also lead to misdiagnosis, particularly in adults with atypical clinical presentation. The outcome of rhabdomyosarcoma in adults is poor especially due to difficulties in diagnosis. [1-3] This case report emphasize the importance of an immunopanel that includes desmin, myogenin/MyoD1, in the diagnosis of primitive round cell neoplasms in all age groups and in all locations.

## Case Report

A 43-year-old female patient presented with complaints of rapidly enlarging bilateral neck swellings of 2-month duration with recent onset dysphagia, exertional dyspnea and hoarseness of voice.

On examination there were multiple bilateral enlarged cervical lymph nodes, largest on right level 3 measuring 2x2 cm.

Computerized tomography (CT) scan showed multiple lymph node masses in the neck and superior mediastinum causing compression of trachea and esophagus. In focal areas, the enlarged lymph node masses were infiltrating into adjacent neck muscles and subcutaneous tissue. PET study and imaging studies of the chest, abdomen, and pelvis did not show any significant findings.

Fine needle aspiration cytology of the cervical lymph node showed singly dispersed medium to large sized atypical cells with scant to moderate cytoplasm, enlarged irregular nuclei with 1-2 nucleoli [Figure 1a]. The clinical presentation and cytology findings were suggestive of a hematolymphoid neoplasm. Bone marrow examination was normal.

Wedge biopsy of lymph node was done which showed replacement of nodal architecture by sheets and vague nests of uniform, discohesive atypical small round to oval cells. Tumor cells showed high nuclear-cytoplasmic ratio and hyperchromatic irregular nuclei [Figure 1b, 1c]. On immunohistochemical examination, the malignant cells were negative for CD 45, CD 20, CD3 and CD30. Further study showed granular positivity for cytokeratin [Figure 1d]. To consider/rule out the possibility of metastasis from neuroendocrine carcinoma and thyroid carcinoma we proceeded with next panel of markers. Neoplastic cells showed focal positivity for synaptophysin and were negative for chromogranin, CD56 and TTF1. On further evaluation, the atypical cells showed positivity for desmin indicating myogenic differentiation. Myogenin and Myo D1 showed patchy moderate to strong positivity, confirming the diagnosis of alveolar rhabdomyosarcoma [Figure 2a, 2b, 2c,2d]. The patient received chemotherapy followed by radiation. No other lesions were detected on follow up examinations.

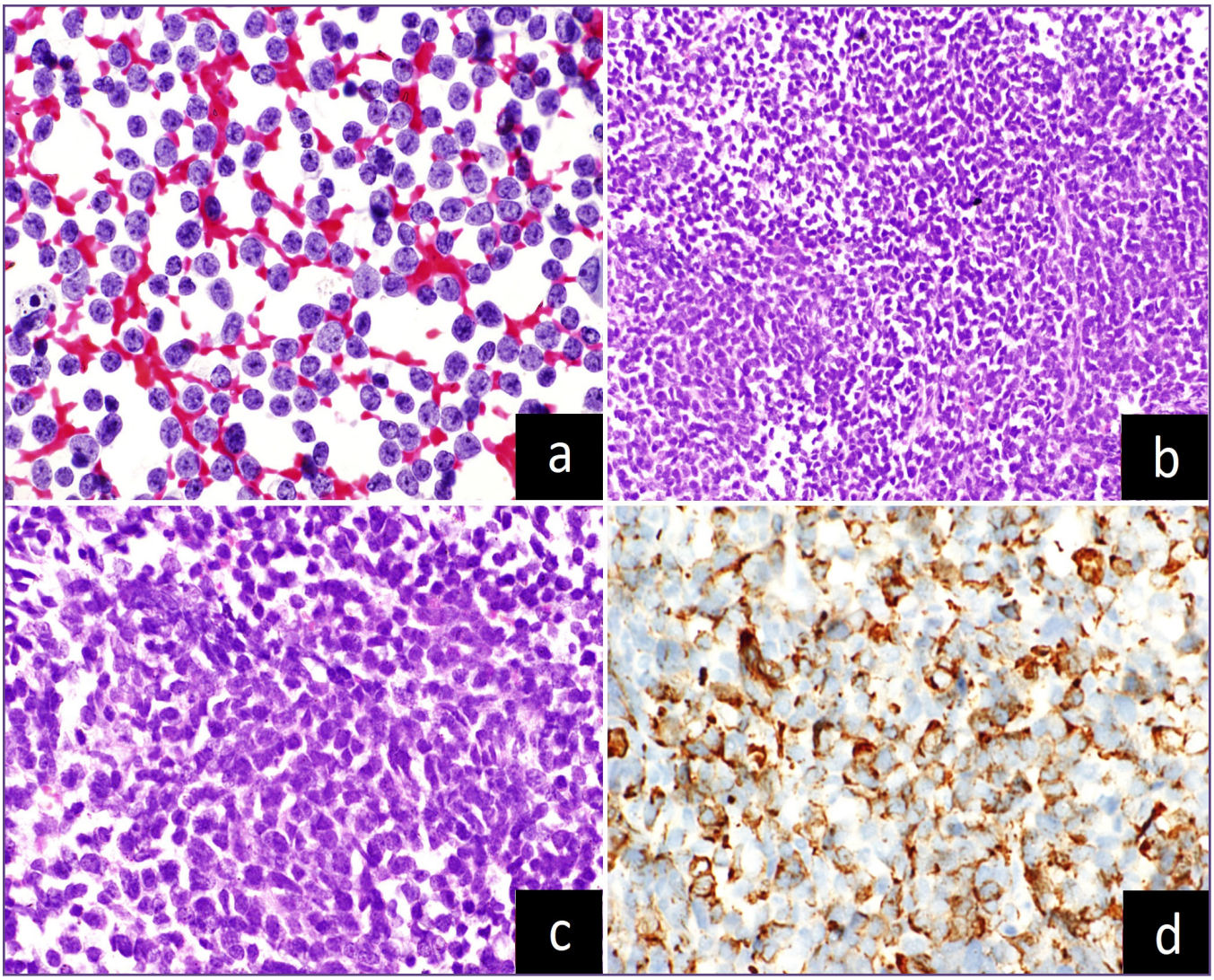


**Fig. 1: a) Aspiration cytology showing cellular smear with singly dispersed atypical cells (Pap, X400), b) Biopsy showing sheets of atypical cells (H&E,X200), c) High power showing atypical cells with high N/C ratio (H&E, X400), d) Atypical cells with cytokeratin positivity (IHC, X400)..**

## Discussion

Malignant small round cell tumours are a group of neoplasms characterized by small, round, relatively undifferentiated cells. Small round cell tumours of childhood generally include lymphoblastic lymphoma, Ewing sarcoma / peripheral neuroectodermal tumour, rhabdomyosarcoma, neuroblastoma, hepatoblastoma, nephroblastoma. In adult patients the differential diagnoses include non-Hodgkin lymphoma, small cell neuroendocrine carcinoma, Merkel cell carcinoma, Ewing sarcoma / peripheral neuroectodermal tumour, poorly differentiated synovial sarcoma, olfactory neuroblastoma and intraabdominal desmoplastic small round cell tumour. In poorly differentiated tumours, the diagnosis will be challenging and need ancillary studies that include extensive immunopanel and molecular studies. [4]

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in childhood and adolescence. The highest incidence is in the age group of one to four years. Its occurrence in adults is rare. [1,5]

Median age of occurrence of alveolar rhabdomyosarcoma (ARMS) is between 7 and 9 years. [5,6,7] Alveolar rhabdomyosarcoma is characterized by distinctive nests of discohesive primitive-appearing round cells, surrounded by hyalinized and vascular fibrous septae.

A rare solid variant has been described. Solid forms of alveolar rhabdomyosarcomas lack fibrovascular stroma and the prominent nested pattern which are the characteristic features of classic alveolar rhabdomyosarcomas. It is characterized by sheets of round cells with variable rhabdomyoblastic differentiation and may closely mimic a variety of other 'small round cell tumors' such as small cell carcinoma, lymphoma and neuroblastoma.

Cervical and axillary lymph node enlargement due to metastatic rhabdomyosarcoma, without an obvious primary tumor, is rarely described. This unusual presentation of lymphadenopathic alveolar RMS may mimic lymphoma. [7,8]

In immunohistochemistry, alveolar RMS typically expresses vimentin, desmin, myogenin and MyoD1. Desmin positivity has been reported as being useful in differentiating between different small round cell tumours of childhood. Myogenin and MyoD1 are specific markers of rhabdomyoblastic differentiation. In a study conducted by Wang et al. nuclear expression myogenin and MyoDl was noted in 91% of RMS cases, whereas neither was detected in any of the neuroblastomas or Ewing sarcomas/ PNETs. [9] Morotti et al. studied 956 RMS cases and observed positivity of MyoD1 and myogenin in 97% of the cases. None of the 96 non-RMS tumours tested in their series showed positivity for these markers. Both alveolar RMS and embryonal RMS showed myogenin positivity, although the number of cells staining in the embryonal subtype were clearly fewer. [10] Thus, MyoD1 and myogenin are specific markers for RMS, and the staining pattern can play role in differentiating alveolar RMS from the embryonal type.

The expression of epithelial marker cytokeratin has been recognized to occur in non-epithelial tumours including Ewing sarcoma/ peripheral neuroectodermal tumour, angiosarcoma, epithelioid sarcoma, malignant peripheral nerve sheath tumor, synovial sarcoma and leiomyosarcoma. Study by Miettinen et al detected cytokeratin-positivity in alveolar rhabdomyosarcomas, with a small number of cytokeratin-positive cells in eight of 12 alveolar rhabdomyosarcomas. [11] Later, study by Bahrami et al identified 42 pure alveolar rhabdomyosarcoma, and two mixed alveolar and embryonal rhabdomyosarcoma expressing cytokeratin and neuroendocrine markers. [12] In their series, they observed at least rare cytokeratin-positive cells in approximately 50% of cases and expression of at least one neuroendocrine marker in over 40% of cases. The authors pointed to the fact that aberrant expression of cytokeratin and neuroendocrine markers is more widespread than has been appreciated. Based on the observations, these authors suggested a subset of alveolar rhabdomyosarcoma may in fact show true epithelial and/or neuroendocrine differentiation. [12]

The most important implication of the aberrant antigen expression is the potential for misclassification of alveolar rhabdomyosarcoma with other tumors that may share cytokeratin and/or neuroendocrine marker expression. In children and young adults, alveolar rhabdomyosarcoma with anomalous immunophenotypes are most likely to be confused with desmoplastic small round cell tumor and Ewing sarcoma/primitive neuroectodermal tumor. In adults, especially in the head/neck location, aberrant expression of epithelial and neuroendocrine markers in alveolar rhabdomyosarcomas are more likely to simulate small cell neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, and esthesioneuroblastoma.

## Conclusion

The expression of cytokeratin and/or neuroendocrine markers in alveolar rhabdomyosarcoma especially in head and neck region in adult patients present a major diagnostic challenge. In the scenario of massive bilateral cervical lymphadenopathy in an adult without any obvious primary lesion, the clinical and pathological differential diagnoses may not include rhabdomyosarcoma. As a result, muscle specific markers like desmin, myogenin and Myo D1 are

usually not included in the immunopanel. In this setting, the positivity of cytokeratin and/or neuroendocrine markers can result in misdiagnosis. The awareness of atypical presentations and aberrant expression of markers in rhabdomyosarcoma will help to solve the dilemmas in the diagnosis.

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