

Lymphadenopathic form of PAX 3-7/FKHR Fusion Gene and ALK Negative, Solid Type of Alveolar Rhabdomyosarcoma in an Infant: A Rare Entity Mimicking Lymphoma with a Review of Literature

Chetan Sudhakar Chaudhari*, Ganesh Ramdas Kshirsagar, Prashant Vijay Kumavat and Nitin M.Gadgil

Dept of Pathology, Lokmanya Tilak Municipal Medical College & General Hospital, Sion, Mumbai, India

Keywords: *Lymphadenopathic form, Solid Alveolar Rhabdomyosarcoma, ALK-Fusion Gene Negative*

ABSTRACT

Alveolar rhabdomyosarcoma is a high-grade neoplasm, which forms about 30% of rhabdomyosarcomas. A rare solid variant has been described. Cervical and axillary lymph node enlargement due to metastatic rhabdomyosarcoma, without an obvious primary tumor, is a rare finding. We report a case of multiple cervical and axillary lymphadenopathies in a 6 month old infant, clinically suspected as lymphoma. On histopathology examination diagnosed to be a case of solid variant of alveolar rhabdomyosarcoma, which was confirmed by immunohistochemical and genetic studies. Tumour was negative for anaplastic lymphoma kinase (ALK) gene aberrations and for PAX 3-7/FKHR fusion gene studies on RT-PCR, a rare subset of alveolar rhabdomyosarcoma. The pediatric and adolescent cases of this rare tumor reported in English language literature are reviewed.

***Corresponding author:**

Dr. Chetan Sudhakar Chaudhari, 11, Jagannath darshan, M.D. Keni Road, Near RBI quarters, Bhandup village(East),Mumbai, India

Phone: +91 9819133606

E-mail: drchetanchoudhari26@yahoo.co.in



Introduction

Rhabdomyosarcoma (RMS) is one of the most common pediatric soft tissue sarcoma, likely results from dysregulation of the precursor cells during skeletal myogenesis. RMS can be classified into three subtypes histologically: the most common embryonal rhabdomyosarcoma (ERMS), the less common but more aggressive alveolar rhabdomyosarcoma (ARMS), and the rare adult variant pleomorphic rhabdomyosarcoma (PRMS).^[1] Although these tumors can arise almost anywhere, the most common locations for these tumors to develop are in the structures of the head and neck (nearly 40% of all cases), the male or female genitourinary tract (about 25% of all cases), and the extremities (about 20% of all cases). Alveolar RMS not otherwise specified (NOS) has a poor prognosis with a 5 years survival rate of about 53%. It occurs frequently in extremities, perirectal and perineal regions mainly in adults. These tumors are composed of sheets of uniform, dyscohesive malignant small rounded cells with a tendency to attach to thin fibrous septae. Multinucleated tumor giant cells with eosinophilic cytoplasm may be seen in some cases. Tumor cells may show a thin rim of eosinophilic cytoplasm. Morphologic evidence of rhabdomyoblastic differentiation including strap cells or cells with cross-striations and multinucleate myoblasts may be seen in 30% of cases. In a rare solid type, predominantly sheets of tumor cells divided by thin fibrovascular septae but without an obvious alveolar pattern seen.^[2] Presentation with multiple peripheral lymph node enlargements without an obvious clinical primary lesion is a rare presentation of alveolar RMS, with only a few cases has been reported in a literature.

Case Report

A 6 month old infant presented with multiple axillary and cervical lymph node enlargement since 1 month. Lymph nodes were measuring from 3x2 cm to 1x1 cm, firm, non-tender and mobile. There was no other significant history or a clinical finding at time of initial presentation. There was no positive family history of similar lesions in past. Hematological and biochemical investigations were within normal limits. Radiological examination on CT scan showed non necrotic bilateral axillary, left supraclavicular & infraclavicular lymphadenopathy which on PET scan showed hyper metabolic nature. Clinically provisional diagnosis of lymphoma was made and lymph node excision biopsy was received for histopathological examination.

On microscopy examination, it revealed tumor was composed of sheets of uniform; dyscohesive malignant small round to oval cells with a tendency to attach to thin fibrous septae at places (Fig 1). Tumor cells showed high

nuclear-cytoplasmic ratio, hyperchromatic irregular nuclei and deeply eosinophilic cytoplasm (Fig 2). Morphologic evidence of rhabdomyoblastic differentiation including strap cells or cells with cross-striations was seen focally (Fig 3). A differential diagnosis of RMS metastatic to cervical lymph nodes was considered along with non-Hodgkin lymphoma(ALCL), extra renal rhabdoid tumor, Ewing's sarcoma (ES)/primitive neuroectodermal tumor (PNET),alveolar soft part sarcoma. Non-Hodgkin lymphoma(ALCL) may often come in the differential diagnosis of Round cell sarcomas such as RMSs. It shows broad spectrum of morphology and small cell type may mimic RMS. The presence of strap cells may help in such cases for establishing the diagnosis of RMS.Extra renal rhabdoid tumour shows sheets of poorly cohesive large polygonal cells with large eccentric vesicular nuclei, abundant eosinophilic cytoplasm with keratin positivity and strict negativity for muscle markers on IHC. Ewing's sarcoma(PNET) is a small cell neoplasm with a spectrum of appearance from undifferentiated to forming rosettes and alveolar pattern.No rosettes were noted in this case.Alveolar soft part sarcoma usually shows distinct regular pseudo alveolar pattern and specific intracytoplasmic crystals,which were not seen in this case. Immunohistochemical staining was performed for leukocyte common antigen (LCA), cytokeratin, desmin and myogenin. LCA and cytokeratin were negative, whereas there was strong nuclear positivity for desmin, myogenin and Myo D1 (Fig 4). Thus, a diagnosis of alveolar RMS, solid variant was made. Based on clinical presentation and histopathology features, supported by Immunohistochemistry, diagnosis of solid variant of alveolar RMS was made. No obvious primary was found at time of diagnosis. Tumor was negative for anaplastic lymphoma kinase gene aberrations (ALK) and for PAX 3-7/FKHR fusion gene studies on RT-PCR, which is a rare subset of alveolar rhabdomyosarcoma and has relatively good prognostic values.

Discussion

Alveolar rhabdomyosarcoma (RMS) is usually found in adolescents with a mean age of 15–20 years, and typically arises in the deep musculature of the extremities. Within the head and neck region, embryonal RMS is the most common RMS, whereas alveolar and pleomorphic tumors are more common in the extremities. It is estimated that RMS accounts for approximately 8% of cancers in children and 2–5% of all adult sarcomas.^[1] Pediatric RMS has been classified by The International Pediatric Sarcoma Working Classification into prognostically useful histological categories, including embryonal botryoid, embryonal spindle, embryonal NOS, alveolar NOS or solid variant and

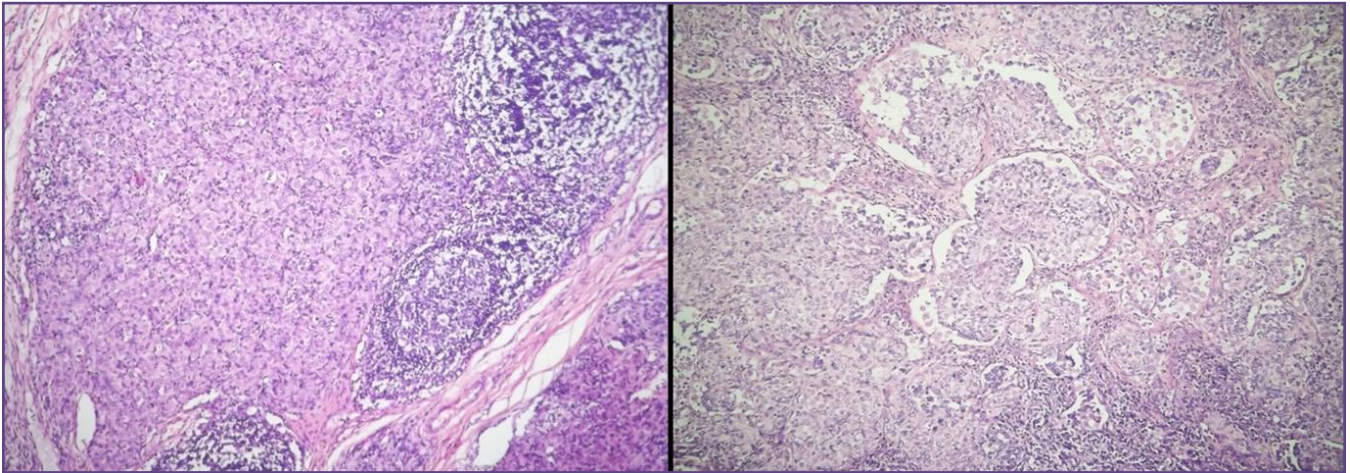


Fig. 1: Tumor was composed of sheets of uniform, dyscohesive malignant small round to oval cells with a tendency to attach to thin fibrous septae at places (H & E 100x).

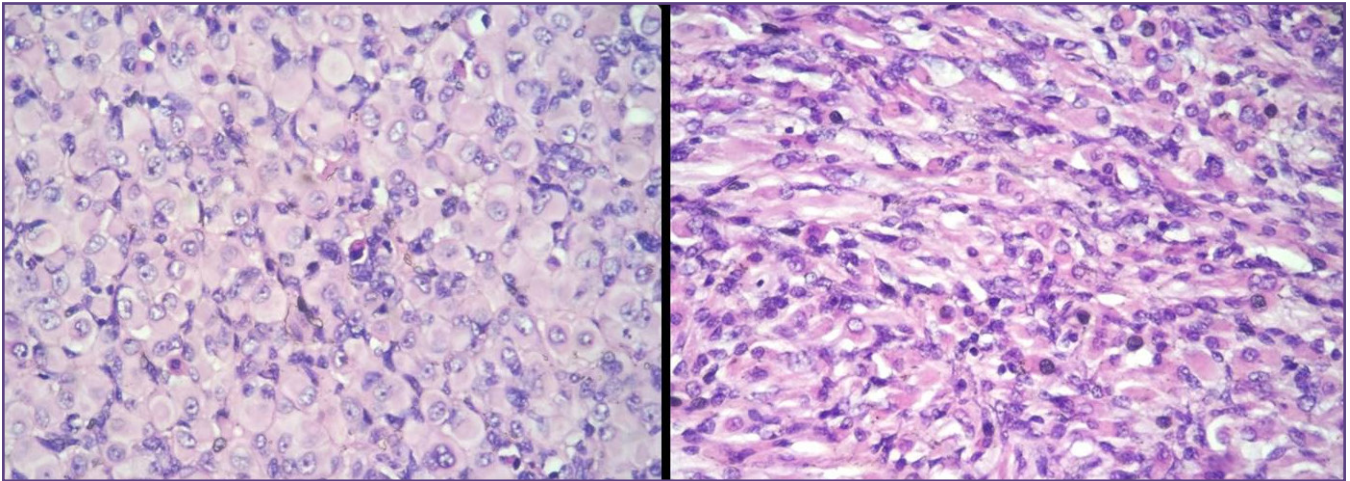


Fig. 2: Tumor cells showed high nuclear-cytoplasmic ratio, hyperchromatic irregular nuclei and deeply eosinophilic cytoplasm (H & E 400x).

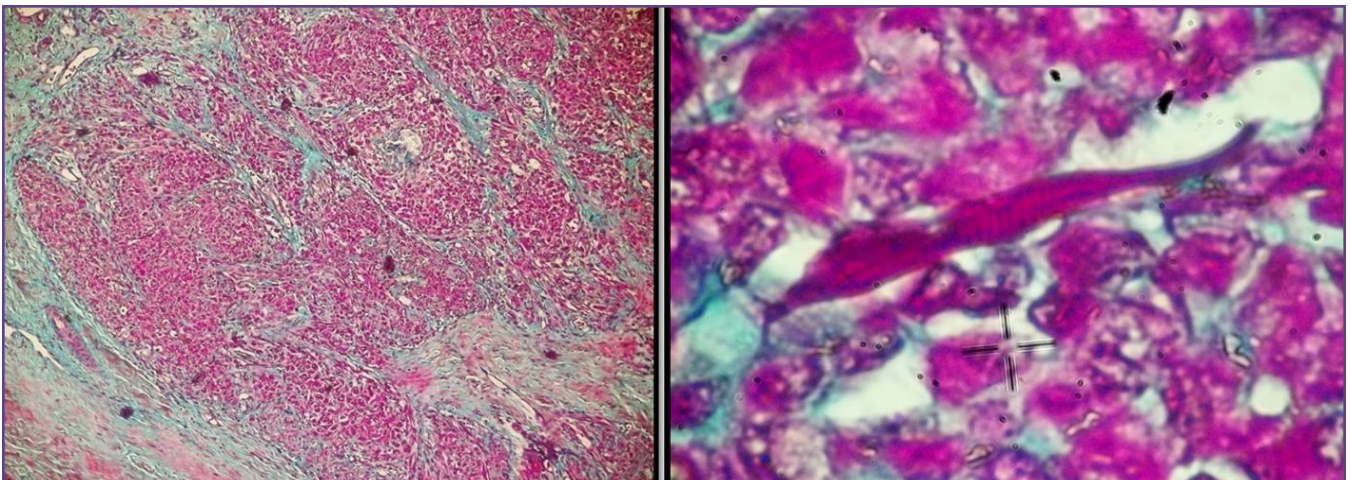


Fig. 3: Morphologic evidence of rhabdomyoblastic differentiation including strap cells or cells with cross-striations was seen focally (Masson's trichrome 400 x).

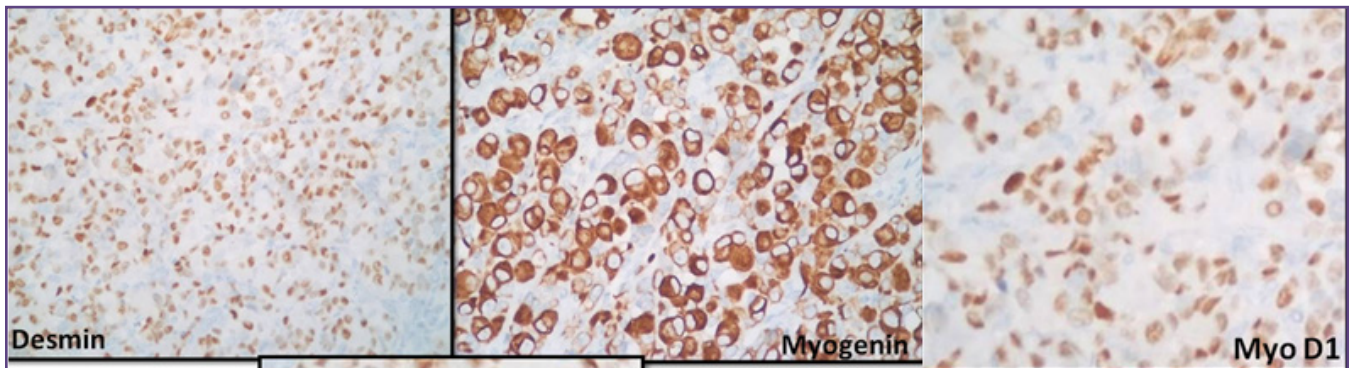


Fig. 4: Immunostaining: strong nuclear positivity for desmin, myogenin and Myo D1.

undifferentiated sarcoma. ^[1,2] Certain genetic conditions such as Li-Fraumeni syndrome, Neurofibromatosis type 1 (NF1), Beckwith-Wiedemann syndrome, Costello syndrome, Noonan syndrome increase the risk of childhood rhabdomyosarcoma. In most cases, the cause of rhabdomyosarcoma is not known. Approximately two-thirds of children with RMS have the more common embryonal type (or the spindle-cell or botryoid variants). These tumors are more common in younger children, particularly those with tumors arising in the head and neck sites (including parameningeal sites) and the genitourinary system (including the bladder and prostate). ^[3] About 20-25% of children with RMS have the less common alveolar type (or solid alveolar variant). These tumors are much more common in teenagers, and most commonly arise in the extremities. The tumor cells tend to be smaller and rounder, often with a denser cellularity, and are so named because of their resemblance to the appearance of the “alveoli”. Alveolar tumors are often considered more “aggressive”, or “higher risk”, than embryonal tumors. Immunohistochemical staining for desmin, MyoD1, and myogenin (myogenic markers) assist in the diagnosis.

The alveolar variant exhibits the greatest propensity for lymph node metastasis; 33% are associated with positive regional nodes on initial examination and 75–85% develops either regional or distant nodal deposits. Recently, there have been case reports of alveolar rhabdomyosarcoma masquerading as hematologic malignancies, and there have been several cases of alveolar rhabdomyosarcoma with lymph node involvement. ^[4, 5] Lymphadenopathic form of alveolar RMS shows lymph node involvement as first clinical manifestation in absence of recognizable primary tumor. There are a few studies reporting this form of alveolar RMS. Solid variant of alveolar RMS is a rare variant in which the alveolar pattern is not seen. Although, this can have a strong resemblance with lymphoma, presence of strap cells and multinucleated giant cells with deeply eosinophilic cytoplasm is a characteristic finding

in alveolar RMS. Solid variant of alveolar RMS with unknown primary has been reported in few studies. ^[6, 7, 8]

In approximately 90% of cases of alveolar RMS, a portion of one of the PAX genes (most commonly the PAX 3 gene located on chromosome 2, less commonly the PAX 7 gene located on chromosome 1) fuses with a portion of the FKHR gene (located on chromosome 13) to create a new “hybrid” gene (PAX-FKHR) that turns on growth-stimulatory genes that would otherwise be “inactive” and turns off growth-inhibitory genes that are normally active. Since this abnormal “hybrid” gene is found only in cases of alveolar RMS, it can be used for diagnostic purposes and, potentially in the future, as a target for immune-mediated cancer therapies. This abnormality is usually tested for using a technique known as RT-PCR (reverse transcriptase polymerase chain reaction). Alveolar RMS have chromosomal translocations (2; 13) (q35; q14) or (1; 13) (p36; q14). Approximately 20% of Alveolar RMS are translocation negative, and have allelic imbalance and Loss of heterozygosity patterns that are indistinguishable from conventional Embryonal RMS cases. ^[9] The clinical behavior and molecular characteristics of Alveolar RMS without a fusion gene are indistinguishable from Embryonal RMS cases and significantly different from fusion-positive Alveolar RMS cases. Thus, fusion gene status may play a role as a factor in risk stratification in RMS, irrespective of histology. The proper treatment and the exact nature of PAX fusion-negative alveolar RMS are currently debated, so that histological diagnosis remains the primary determinant for therapeutic protocol assignment. ^[10]

Conclusion

Our case attempts to highlight the rare occurrence of Lymphadenopathic form of solid alveolar RMS. A possibility of metastatic alveolar RMS must be kept in mind in cases presenting with isolated lymphadenopathy. A rare possibility of solid variant cannot be overemphasized to allow timely diagnosis and management.

Acknowledgements

Nil

Funding

None

Competing Interests

None Declared

Reference:

1. Weiss SW, Goldblum JR. Enzinger and Weiss's soft tissue tumors. 5th edn. Mosby Press, 2008:595–9.
2. Rosenblum MK, Bibao JM, Ang LC. Neuromuscular system: Central nervous system. In: Rosai J, editor. Rosai and Ackerman's Surgical Pathology. 9th ed., Vol. 2. India: Thomson Press, Mosby, Elsevier 2004: 2301-6.
3. Parham DM. Pathologic classification of rhabdomyosarcomas and correlations with molecular studies. *Mod Pathol* 2001; 14:506-14.
4. Reinecke P, Gerharz CD, Thiele KP, et al: Alveolar rhabdomyosarcoma presenting as acute leukemia. *Verh Dtsch Ges Pathol* 1998;82:336-339.
5. Duran Padilla MA, Rodriguez Martinez HA, Chavez Mercado L, et al: Atypical biological behavior of alveolar rhabdomyosarcoma in five patients. *Rev Invest Clin* 1999;51:17-22.
6. Mekni A, Bouraoui S, Boussen H, et al: Lymphadenopathic form of alveolar rhabdomyosarcoma: A case report. *Tunis Med* 2004;82:241-244.
7. Chen L, Shah HO, Lin JH: Alveolar rhabdomyosarcoma with concurrent metastases to bone marrow and lymph nodes simulating acute hematologic malignancy. *J Pediatr Hematol Oncol* 2004;26:696-697.
8. Ganesan P, Thulkar S, Rajan A, Bakhshi S. Solid variant of alveolar rhabdomyosarcoma mimicking non-Hodgkin lymphoma: Case report and review of literature. *J Pediatr Hematol Oncol* 2008;30:772-4.
9. Parham DM, Qualman SJ, Teot L, Barr FG, Morotti R, Sorensen PH, Triche TJ; Soft Tissue Sarcoma Committee of the Children's Oncology Group. Correlation between histology and PAX/FKHR fusion status in alveolar rhabdomyosarcoma: a report from the Children's Oncology Group. *Am J Surg Pathol*. 2007 Jun;31(6):895-901.
10. Egas-Bejar D, Huh WW. Rhabdomyosarcoma in adolescent and young adult patients: current perspectives. *Adolesc Health Med Ther*. 2014; 5: 115–125.