March 2017 case:

A 16 year-old female presented with a complaint of left supraclavicular enlarged lymphadenopathy, chest pain, and occasional SOB.

Clinical History:

She underwent CT scan of chest, which showed ~5.0 cm x 8.5 cm anterior chest wall mass abutting anterior to inferior heart border and enlarged lymph nodes measuring ~3.0 cm x 4.0 cm in left subclavicular region. Clinical differential diagnoses include T lymphoblastic lymphoma, Ewing sarcoma, etc. Core biopsy of left supraclavicular lymph node was performed.

Microscopic examination:

Microscopic examination shows aggregates of poorly differentiated round or oval tumor cells with high N/C ratio, relative uniform nuclei (Fig. 1), and central floating clusters of cells in the “alveolar spaces” (Fig. 2). Mitoses and apoptosis are easily identified. Lesional cells are separated and surrounded by a framework of dense, frequently hyalinized fibrous septa that contain dilated vascular channels (Fig. 3).

1

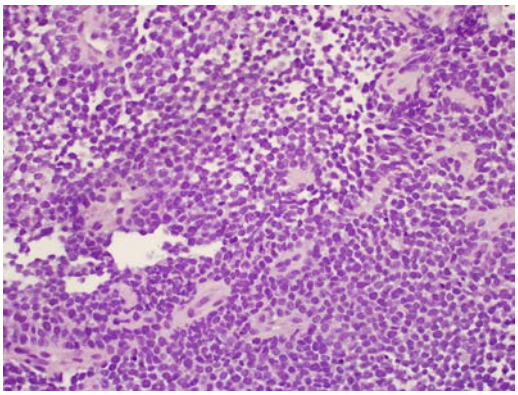

Fig 1: Lesional cells with high N/C ratio and relatively uniform nuclei.

2

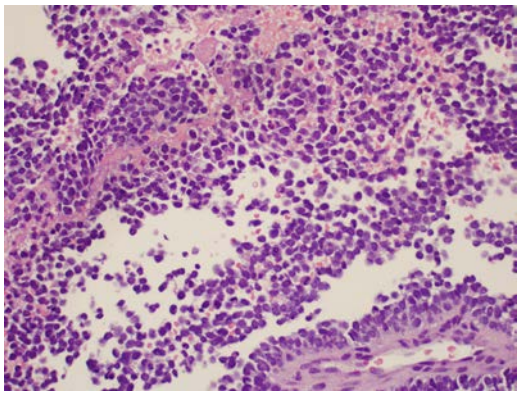

Fig 2: Floating cells in the center of “alveolar spaces”.

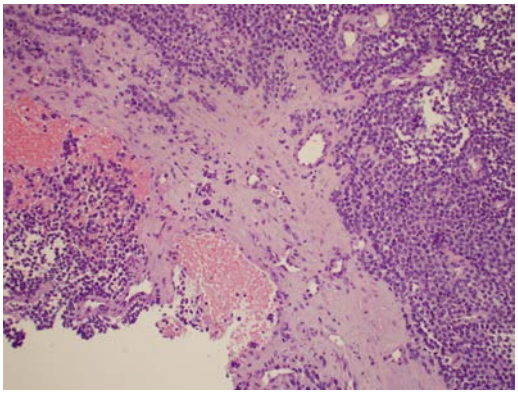

Fig 3: Lesional cells are separated by fibrous septa containing vascular structures.

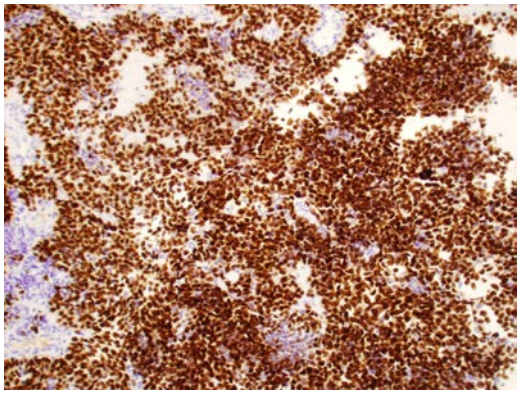

Fig 4: Lesional cells are diffusely and strongly positive for myogenin (nuclear).

Immunohistochemistry:

Lesional cells are diffusely and strongly positive for myogenin (Fig. 4) and myoD1. They are negative for CD99, Fli1, CD3, CD20, and TdT.

Final diagnosis and Discussion:

Alveolar rhabdomyosarcoma (ARMS).

Discussion:

According to the latest version (2013) of WHO classification of tumors of soft tissue, malignant skeletal muscle tumors are classified as Embryonal rhabdomyosarcoma (embryonal RMS), alveolar rhabdomyosarcoma (ARMS), pleomorphic RMS and spindle cell/sclerosing RMS. ARMS occurs less frequently than embryonal RMS and accounts for approximately 20% of all pediatric rhabdomyosarcomas. This variant tends to arise at a slightly older age with a peak incidence of 10-25 years of age. It generally arises in the deep soft tissue of the extremities. But It can occur in other sites include the head and neck, trunk, perineum, pelvis and retroperitoneum. ARMS consists of primitive cells with monomorphous round nuclei and high N/C ratio. Typically lesional cells are separated by fibrous septa into discrete nests or cords with floating cluster of lesional cells in the center of artifactual alveolar spaces. Wreath-like multinucleate cells with rhabdomyoblastic differentiation may be present. The solid variant of ARMS lacks the fibrovascular stroma and consists of sheets of round cells with variable rhabdomyoblastic differentiation. **Immunostaining:** lesional cells show strong and diffuse staining for myogenin (nuclear). Positivity for desmin and muscle-specific actin can be noticed. A subset of cases express cytokeratins or neuroendocrine markers (synaptophysin, etc). **Molecular genetics**: most of ARMS are associated with recurrent chromosomal translocations, including t(2;13) (60%), and less commonly, t(1;13) (20%), which lead to fusion of the *PAX3* and *PAX7* genes, respectively, to the *FKHR* (or called *FOXO1*) gene. Fusion genes can be detected by FISH or RT-PCR routinely. The remaining 20% of ARMS lack the usual translocations. **Prognosis:** ARMS has much worse prognosis compared to embryonal RMS. For ARMS, *PAX7-FKHR* tumors tend to occur in younger patients and are usually associated with lower metastatic rates and better survival compared with those with *PAX3-FKHR* fusions. The most frequent metastatic sites include the lung and lymph nodes.

Main differential diagnoses in the anterior mediastinum include T lymphoblastic lymphoma (T-LBL), Ewing sarcoma, poorly differentiated synovial sarcoma, etc. **T-LBL** frequently shows mediastinal (thymic) involvement, though it may involve any lymph node or extranodal site. The lymphoblasts have a high N/C ratio, thin nuclear membrane, finely-stippled chromatin and inconspicuous nucleoli. Fibrous septa and alveolar-like structure should not be present. The flow was performed and revealed no evidence of lymphoma. Lesional cells were also negative for CD3, CD20 and TdT. **Ewing sarcoma** and ARMS have overlapping clinical and morphological features. Both occur in extremities in patients of the age 10-25 yr and show lesional cells with high N/C ratio and monotonous nuclei histologically. Ewing sarcoma generally express FLI-1 which is absent in ARMS. Ewing sarcoma commonly contains EWSR1-FLI1/ERG fusion genes. **Poorly differentiated synovial sarcoma** can

show high cellularity with nuclear crowding, nuclear irregularity, prominent nuclei or irregular clumping of chromatin. Lesional cells TLE1 staining is positive in most of synovial sarcoma. However, TLE1 can be positive in a subset of MPNST and SFT cases. The t(x;18) translocation is found exclusively in synovial sarcoma. Break-apart FISH and RT-PCR are commonly used to detect fusion transcripts of synovial sarcoma.

References

1. Fletcher C, et al: WHO Classification of Tumours of Soft Tissue and Bone (IARC WHO Classification of Tumours) 4th Edition

2. Sorensen PH, et al: PAX3-FKHR and PAX7-FKHR gene fusions are prognostic indicators in alveolar rhabdomyosarcoma: a report from the children's oncology group. J Clin Oncol. 2002 Jun 1;20(11):2672-9.