**Quiz Case**

**Large lung mass: Cytopathological features**

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**PERTINENT CLINICAL HISTORY**

A Japanese woman in 50s presented with blood-tinged sputum. Chest X-ray and computed tomography scan revealed a large mass lesion in the lung. She had no asbestos exposure. It was considered to be a primary pulmonary malignant tumor because no tumorous lesions were found at any other sites, including the soft tissue. After the preoperative bronchial brushing cytology [Figure 1] was performed, she underwent lobectomy.

**Figure 1:** (a) The cytologic smear is hypercellular and consists of cell clusters with frayed edges and numerous single cells. (b) The cluster is composed of loosely cohesive, small, round to oval, and short spindle to spindle cells surrounding the capillary. The small round cells have scant cytoplasm with hyperchromatic and inconspicuous or absent nucleoli. (c) Most tumor cells are uniformly small, round to oval with high nuclear-cytoplasmic ratio. The nuclear chromatin is finely granular with several small nucleoli.

**QUESTION**

What is your interpretation?

A. Malignant mesothelioma
B. Carcinosarcoma
C. Synovial sarcoma (SS)
D. Malignant peripheral nerve sheath tumor.

See next pages for answer
(Additional quiz questions and answers and brief review of the topic, Page 2).
ANSWER

The correct cytopathologic interpretation is C. Synovial sarcoma

BRIEF DISCUSSION

The resected tumors, measuring 11 cm × 7 cm, were well circumscribed and whitish-yellow in color with extensive hemorrhage and necrosis. Histopathologically, tumor cells showed small, round, oval to short-spindled cells with high nuclear-cytoplasmic (N/C) ratio proliferated in a vaguely intersecting fascicular pattern [Figures 2 and 3]. Focally, hemangiopericytomatous staghorn-like configurations were also observed [Figure 2]. Mitotic figures were frequent. In addition, it showed areas of small round cells in a solid sheet pattern. Pleural or vascular invasion was not detected.

ADDITIONAL QUIZ QUESTIONS

Q1. Which of the following cytomorphologic and histopathological pattern is the most frequent for typical SS?
   A. Biphasic
   B. Monophasic fibrous
   C. Monophasic epithelial
   D. Poorly differentiated.

Q2. What is the most useful immunohistochemistry for diagnosis?
   A. TLE1
   B. STAS6
   C. SOX10
   D. NKX3.1.

Q3. What is the most characteristic gene translocation?
   A. EWSR1-FLI1
   B. NAB2-STAT6
   C. ETV6-NTRK
   D. SYT-SSX.

ANSWERS TO ADDITIONAL QUIZ QUESTIONS

Q1; B, Q2; A, Q3; D

Immunohistochemically, the tumor was positive for vimentin and MIC2 (CD99) and focally for epithelial membrane antigen but negative for CD34. Recently, although the immunohistochemical staining for TLE1 is specific for diagnosis, the SYT/SSX1 fusion gene was detected by real-time polymerase chain reaction and direct sequencing. Finally, she was diagnosed with monophasic fibrous SS, because the poorly differentiated component was focal.

BRIEF REVIEW OF THE TOPIC

SS is usually recognized as a malignant soft-tissue tumor of uncertain differentiation with a predilection for the extremities in adolescents and young adults. However, SS rarely arises at other anatomic sites, including internal organs such as the lung, heart, kidney, liver, gastrointestinal tract, and others. Because of the unusual location, SS of the internal organs is occasionally misdiagnosed.

Primary pulmonary SS should be differentiated from metastatic SS, which depends on whether primary SS at another site is present or not. Histologically, SS is classified into four subtypes: biphasic, monophasic epithelial, monophasic fibrous, and poorly differentiated. SS of the monophasic fibrous type is most common at all sites. The present patient was diagnosed with monophasic SS,

Figure 2: The small round cells and short-spindled cells showed an intersecting fascicular pattern. Focally, hemangiopericytomatous staghorn-like configurations were observed

Figure 3: Small, oval to short-spindled cells with high nuclear-cytoplasmic ratio proliferate in a vaguely intersecting fascicular pattern. Mitotic figures are observed
but small round cells suggestive of poorly differentiated SS of small-cell type were also presented. Including SS of both soft tissue and unusual sites, there are >10 reports describing cytologic features, only a few of which describe primary and metastatic pulmonary SS.\(^2,3,5,6,9-12\) Immunohistochemical staining for TLE1 is considered specific for diagnosis. In addition, SMARCB1/INI-1 expression is reduced in 69% of SS.\(^1\)

Recently, reports of SS at unusual sites have been increasing with the advance of immunohistochemical and cytogenetic techniques. Especially, detection of SS-specific chromosomal translocation t(X; 18) and the subsequent SYT-SSX fusion gene is diagnostic.\(^1\) Primary pulmonary SS is now well recognized, and about 60 cases had been reported in the English literature up to 2005.\(^1\) The clinicopathologic findings of pulmonary SS are similar to those of soft-tissue SS, except for its location and site-specific symptoms.

There are no differences in histologic and cytologic features between SS of the soft tissue and the lung.\(^2-12\) According to the previous reports, SS shows some common characteristic cytologic features, that is, high cellularity and admixture of branching or irregularly shaped clusters with frayed edges and single cells.\(^2-12\) Individual cells are uniformly small to short spindled with high N/C ratio, scant cytoplasm, finely granular chromatin, and small nucleoli. In case, small round cells are mixed, so-called small-round-cell tumors such as small-cell carcinoma, Ewing's sarcoma should be excluded from the study.\(^4,6\)

Actually, small-cell carcinoma was cytologically suspected in the present case because of the small-sized cells and the patient's age (in her 50s). However, upon reviewing the smear, the tumor cells lacked the cytologic characteristics of small-cell carcinoma, that is, nuclear hyperchromasia, nuclear molding, and no nucleoli. A definite cytologic diagnosis of pulmonary SS may be difficult or impossible to make without immunohistochemical and cytogenetic examination, but recognition of this entity is important to avoid misdiagnosis.\(^6\) In cytopathology, there are solitary fibrous tumor, malignant peripheral nerve sheath tumor, or so-called fibrosarcoma for the differential diagnosis of SS (especially monophasic fibrous) in pulmonary [Figure 4]. These tumors’ feature is similar to SS, so the diagnosis of SS may be difficult by the morphological characteristics only. Immunohistochemical panel (TLE1, STAT6) and evaluation of SYT/SSX translocation are useful.

**SUMMARY**

In common with SS of the soft tissue, the cytologic features of pulmonary SS are characterized by hypercellular smears composed of small, oval to short-spindled single cells, and branching or irregular-shaped clusters with frayed edges and thin-walled capillaries. Since the tumor cells of SS are frequently small sized with scant cytoplasm, it is important not to confuse them with so-called small-round-cell tumors. For SS cases with metastasis, the cell block from cytology specimen can help with genetic research.

**COMPETING INTERESTS STATEMENT BY ALL AUTHORS**

The authors declare that we have no competing interests.

**AUTHORSHIP STATEMENTS BY ALL AUTHORS**

All authors have participated sufficiently and took responsibility for the appropriateness of content in this article.

**ETHICS STATEMENT BY ALL AUTHORS**

This study was conducted with approval from the Institutional Review Board of all the institutions associated with this study as applicable.

**LIST OF ABBREVIATIONS** (In alphabetic order)

- CD - Cluster of differentiation,
- ETV6 - ETS variant 6 transcription factor,
- EWSR - Ewing sarcoma,
- FLI1 - Friend leukemia integration 1 transcription factor,
- INI-1 - Integrase Interactor 1,
- MIC2 - Microneme protein 2,
- N/C ratio; nuclear-cytoplasmic ration,
- NAB2 - NGFI-A-binding protein 2,
- NKX3.1 - NK3 Homeobox 1,
- NTRK - Neurotrophic tyrosine receptor kinase,
- SMARCB1 - SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1,
- SOX10 - SRY-related HMG-box 10,
- SS - Synovial sarcoma,
- SSX - Synovial sarcoma, X breakpoint 2,
- STAT6 - Signal transducer and activator of transcription 6,
- SYT - Synovial sarcoma translocation, chromosome 18,
- TLE1 - Transducin-like enhancer of split 1
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EDITORIAL/PEER-REVIEW STATEMENT

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