Quiz Case

An uncommon diagnosis in pleural effusion cytology

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QUESTION

What is your diagnosis?

a. Reactive mesothelial cells
b. Metastatic adenocarcinoma
c. Positive for malignancy, possibly myxoid chondrosarcoma
d. Positive for malignancy, cannot characterize further.

A 50-year-old man presented with complaints of breathlessness of 3-month duration. Computed tomogram (CT) scan of thorax showed a large 4 × 3 cm, predominantly cystic mass in his left anterosuperior hemithorax with necrotic lymph nodes and left-sided severe pleural effusion. Five hundred milliliters of pleural fluid were tapped and cytology examination was performed for the workup. The cytological picture is shown in Figure 1.

Figure 1: (a) Aggregates of tumor cells with round to oval morphology, moderate pleomorphism, and prominent nucleoli (Papanicolaou × 200) (b) Groups of tumor cells embedded in myxoid stroma highlighted by metachromatic magenta (May Grunwald Giemsa × 200) (c) Ultrasonography scan of thorax shows moderate-to-severe left pleural effusion with internal echoes (d) Pleural fluid cell block shows groups of tumor cells within amphophilic hyaline stroma (H and E × 200).

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ANSWER
The correct cytological interpretation is
C. Positive for malignancy, possibly myxoid chondrosarcoma.

EXPLANATION
Grossly, the fluid sample was straw in color. Centrifugation was done at 2000 rpm for 10 min. The supernatant was discarded and the sediment was picked up with the help of a cotton-tipped applicator stick and smears were prepared by rolling the swab stick on glass slides. The smears were fixed in 100% methanol and stained by the routine Papanicolaou (Pap) and May Grunwald Giemsa (MGG) methods.

The smears were cellular and showed atypical cells dispersed singly, in cords and small aggregates with varying amounts of granular, myxoid, and chondromyxoid stroma. The atypical cells were predominantly round to oval in morphology, displaying mild-to-moderate pleomorphism with prominent nucleoli. The cytoplasm was finely vacuolated. Occasionally, the cells showed “rhabdoid” morphology. Atypical cells did not show any specific features of epithelial differentiation. Myxoid stroma was further highlighted by MGG stain as bright magenta (metachromasia). Few reactive mesothelial cells, many red blood cells, neutrophils, and lymphocytes were also noted.

The patient had a history of myxoid chondrosarcoma of his left thigh, which was excised 5 years ago, following which, he received six cycles of adjuvant chemotherapy and radiation therapy.

The cytomorphology of the abnormal cells led to the suspicion of extraskeletal myxoid chondrosarcoma (EMC) and was supported by the clinicoradiological findings. In the given clinical context of known history of EMC of the left thigh and lung mass, pleural fluid cytology was suggestive of metastatic EMC and biopsy/cell block confirmation was advised.

Cell block was prepared from pleural fluid which showed tumor cells arranged in cords within an amphophilic hyaline stroma, consistent with metastatic EMC from a known primary in the left thigh.

Following cytology, a CT-guided biopsy of the lung mass was performed and histopathological examination showed features consistent with metastatic EMC, in a known case. By immunohistochemistry (IHC), the tumor cells were diffusely and strongly positive for neuron-specific enolase (NSE).

Considering the advanced stage of the disease and dismal prognosis, the patient was advised symptomatic treatment.

DISCUSSION
Cytologic examination of pleural fluid is a simple, non-invasive, cost-effective, diagnostic modality used to detect abnormal cells that exfoliate in the fluid. In most of the cases, cytology can recognize the origin of a neoplasm presenting in the fluid on the basis of its morphologic features so as to exclude a second possible primary tumor. When malignant cells are present in the fluid, a definite diagnosis can be made in approximately 90% of the cases. Mostly tumors of the epithelial and non-epithelial origin that metastasizes to the serous membrane are diagnosed in the pleural fluid cytology. Non-epithelial tumor like sarcomas account for only 3–6% of malignant effusions, however, their diagnosis is made in the setting of a known primary tumor. The commonly encountered primary pulmonary malignancies are of epithelial origin. Primary tumors with cartilaginous or osteoid features originating in the lung are extremely rare, and most likely indicate metastatic disease.

Cytological findings of EMC obtained from fine-needle aspiration or imprint smears have been reported previously. However, the cytopathologic features of this rare sarcoma in effusion have not been frequently reported. To the best of our knowledge, only one case report on EMC diagnosed in pleural fluid in a patient presenting with a thigh mass has been published. We report a (rare) case of EMC detected in pleural fluid in a patient presenting with a known history of EMC of the right thigh.

EMC is a rare soft-tissue sarcoma, first described by Stout and Verner and later coined as a distinct clinicopathologic entity by Enzinger and Shiraki. It is usually seen in proximal extremities of middle-aged adults. The median age of patients with this sarcoma is 48.7 years. Lung is the most frequent metastatic and extremely rare primary site of myxoid chondrosarcoma. It is an intermediate to high-grade sarcoma, depending on the degree of nuclear atypia and other histopathologic features, and is associated with late recurrences and lung metastasis. EMC of lung may present as an asymptomatic mass, with clinical symptoms such as hemoptysis, dyspnea, or anemia. The myxoid stroma with varied morphology in EMC can be mistaken for other myxoid neoplasms including chordoma, myxoid liposarcoma, myxomas, low-grade fibromyxoid sarcoma, and myxofibrosarcoma. However, unlike other myxoid sarcomas, EMC is known to be associated with a specific translocation, namely, t(9;22) (q22;q12), resulting in EWS-CHN (TEC) fusion gene product, which can be tested using fluorescent in situ hybridization and is tumor-type specific or pathognomonic for this entity and assumed to play an important role in the development of EMC. Metastasis and the rate of recurrence are related to degree of cellularity and the relative amount of myxoid material. Tumors with the least cellularity and the most myxomatous changes carry the best prognosis.

Detection of tumor cells in the pleural fluid is not possible unless the cells exfoliate in the fluid in large numbers.
In effusion cytology, at times, there is considerable challenge in differentiating reactive mesothelial cells from adenocarcinoma and other metastatic tumors. It is a critical situation, indicative of a high-stage disease. The reported literature on the cytologic features of sarcomas in serous effusions is very scanty. Sarcomas tend to lose the tissue arrangement or the stromal patterns as observed in fine-needle aspiration specimen. They usually tend to round up in the fluids and hence they can be misinterpreted as carcinoma cells, especially in the absence of characteristic myxoid stroma. Massoni and Hajdu pointed out that variable chromatin pattern in nuclei, prominent nucleoli, indistinct cytoplasmic borders, and bipolar cytoplasmic processes have been observed not only in uterine sarcomas but also they appear to be useful in distinguishing these tumors from carcinomas. Accuracy improves when the cytologic findings are correlated with the clinical information and prior history.

Differential diagnoses include reactive mesothelial cells and metastatic adenocarcinoma cells. Reactive mesothelial cells show slightly enlarged nuclei with smooth and regular nuclear membrane, fine chromatin pattern, and moderate amount of cytoplasm. In this case, the atypical cells displayed unequivocal features of malignancy, including enlarged hyperchromatic nuclei, irregular nuclear border, and anisonucleosis. Therefore, the possibility of these cells being reactive mesothelial cells was not considered.

Metastatic adenocarcinoma is the most common diagnosis in effusion cytology. In most cases of adenocarcinoma, tight clusters of tumor cells are observed, including overlapping three-dimensional clusters, papillaroid formations, glandular differentiation, or “signet ring” cell morphology. Extracellular or intracellular mucinous material may be seen in certain cases. Furthermore, the tumor cells exhibit enlarged hyperchromatic nuclei with irregular nuclear membrane, coarse and clumped chromatin pattern, and anisonucleosis. However, the present case did not reveal any of the above features.

Mucinous material in Pap staining appears usually as pale purple amorphous material, while in MGG, it may appear either colorless or pink. The present case showed abundant extracellular ground substance (myxochondroid matrix). This might resemble mucinous material and can be mistaken for a diagnosis of adenocarcinoma. The metachromatic (magenta) effect of the matrix on MGG stain was a useful clue toward the diagnosis.

In the present case, the characteristic features included hypercellular smears with variable tumor cell arrangement and the presence of abundant metachromatic myxoid/chondromyxoid stroma in the background. Small clusters and sheets of markedly pleomorphic cells with vacuolated cytoplasm, enlarged round to oval nuclei, and small nucleoli were noted. In view of previous history of myxoid chondrosarcoma, and presence of malignant cells amidst abundant myxochondroid matrix, a diagnosis of metastatic EMC was rendered. Kumar et al. observed that tumor cells showing “rhabdoid” morphology are more commonly associated with aggressive clinical outcomes, including lung metastasis. The present case did show tumor cells with rhabdoid morphology and also presented with lung metastasis.

Sarcomas do not exhibit a specific immunophenotype. Application of immunocytochemical marker for EMC is not helpful. As per review of literature, diffuse positivity for vimentin and S-100 is of limited value in identifying an EMC; the expression for NSE supports the hypothesis of a possible neural or neuroendocrine differentiation recently reported in a subset of EMC, providing a new insight into their histogenetic nature. Hence, the diagnosis of these tumors in serous effusions relies mainly on morphologic evaluation and clinical correlation.

**ADDITIONAL CME QUESTIONS**

1. **The stromal matrix in EMC in MGG stained smears appear as**
   a. Magenta
   b. Purple
   c. Colorless
   d. Pale pink.

2. **For exact tumor subtyping in effusion, the requirements include**
   a. Detailed clinical history
   b. Pap and MGG stained smears
   c. Cell block and IHC
   d. All of the above.

3. **Chromosomal rearrangements seen in EMC include.**
   a. t(9;22)
   b. t(10;11)
   c. t(8;14)
   d. t(11;22).

**Answers to additional questions**

Q1: A; Q2: D; Q3: A.

**SUMMARY**

During the metastatic workup, effusion cytology can provide a valuable and accurate means of diagnosis. The presence of sarcoma in effusions, including EMC, is extremely rare. Tumor cells with characteristic stroma, cytologic, and immunomorphologic features, in combination with clinical history, are useful in arriving at a correct diagnosis.
COMPETING INTEREST STATEMENT BY ALL AUTHORS
The author(s) declare that they have no competing interests.

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All authors of this article declare that they qualify for authorship as defined by ICMJE http://www.icmje.org/#author.

Each author has participated sufficiently in the work and take public responsibility for appropriate portions of the contents of this article. SD: Conceptualization, drafting of the manuscript, revising it critically for important intellectual content, literature review. SP: Writing of the original draft, cytological workup, data acquisition, revising it critically for important intellectual content, literature review. SY: Critical review, finalization of the manuscript, revising it critically for important intellectual content. BR: Critical review, finalization of the manuscript, cytological workup and revising critically for important intellectual content.

Each author acknowledges that this final version was read and approved.

ETHICS STATEMENT BY ALL AUTHORS
As this is a quiz case without identifiers, our institution does not require approval from Institutional Review Board (IRB) (or its equivalent).

LIST OF ABBREVIATIONS
CT – Computed tomogram
EMC – Extraskeletal myxoid chondrosarcoma
FISH – Fluorescent in situ hybridization
H and E – Hematoxylin and eosin
IHC – Immunohistochemistry
MGG – May Grunwald Giemsa
NSE – Neuron-specific enolase
Pap – Papanicolaou
RBC – Red blood cell
rpm – Revolutions per minute
USG – Ultrasonography

EDITORIAL/PEER-REVIEW STATEMENT
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