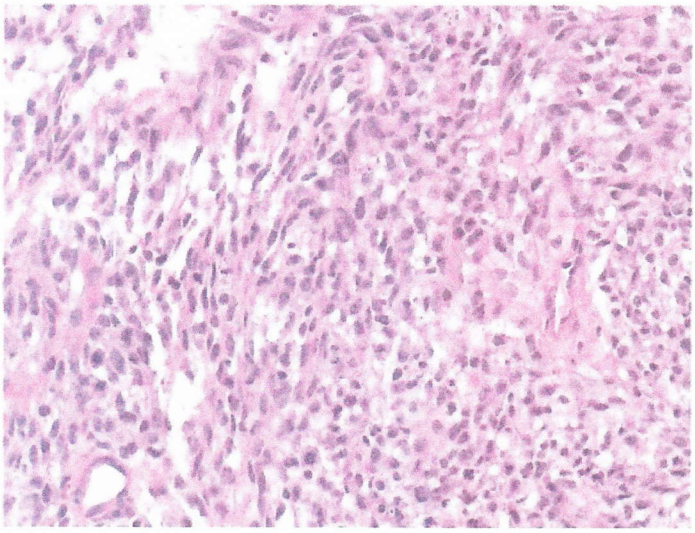
Evaluation of biopsy material of Ms. Lori Reigert

The patient had a presentation of discomfort and pain in the chest. The patient had a history of recent trauma; to which she had attributed the discomfort and pain. Radiologic and clinical evaluation demonstrated features suspicious for possible involvement by a disease process; resulting in subsequent biopsies.

There was no documented history of melanoma; either based on clinical features or on pathologic assessment of surgically excised pigmented/ melanocytic skin lesions.

The materials provided for evaluation consisted of biopsies from the "Right Pleura, and Right Lung Tissue" and "Cytology evaluation of Pleural Fluid" (performed 12/21/2015). Biopsy of the "Right Pleura" was performed again (2/8/2016). Biopsy of the "Left Pleura and Pericardium" and cytologic assessment of "Pericardial Fluid" were performed on 3/4/2016 and 3/5/2016. The first set of biopsies were performed at Lake Health; the second and third were performed at University Hospitals.

The tissue and fluid material evaluated at three different time points show a tumor with similar morphologic features in all the three assessments.



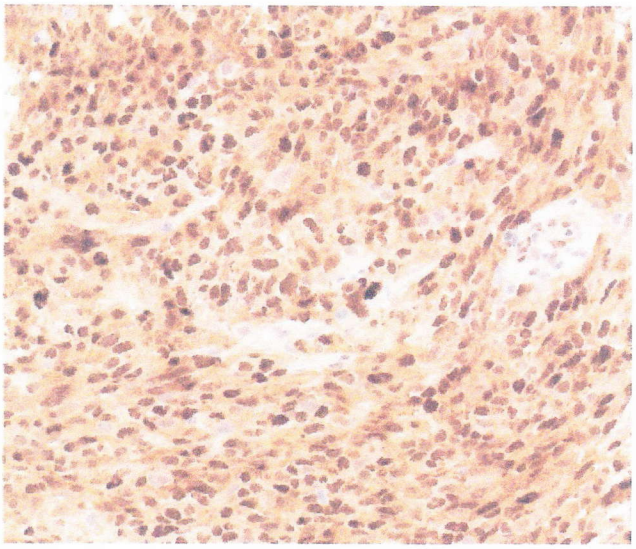
Tumor Cells with Spindle and Epitheloid morphology. Mild atypia is seen. No significant mitotic activity is identified.

The biopsies from the right lung and the right pleura demonstrate a malignant neoplastic proliferation. The tumor cells show both spindle and epithelioid features. Occasional

cells demonstrate presence of melanin. Intranuclear inclusions are also noted.

The tumor cells do show mild pleomorphism and atypia. However, there is a definitive absence of prominent mitotic figures as well as prominent atypia.

According to the information provided in the reports from the two institutions, a battery of immunohistochemical stains were performed by them. These stains demonstrated the tumor cells to be positive for S100, HMB-45, SOX-10 and Melan A. The tumor cells were negative for AE1/AE3, CD34, desmin, actin, calretinin, MOC-31, D2-40, WT-1, TTF-1, p40, cytokeratin 8/18, cytokeratin 5/6, CD68, LCA and CD20. Ki-67 immunohistochemical stains demonstrated a labeling index of approximately 65%.



Tumor Cells show prominent nuclear expression of Cyclin-D1.

Additional immunohistochemical stains were subsequently performed as part of a formal second review consultation done at Shadyside Hospital, UPMC, Pittsburgh PA. These additional stains documented some additional features; notably that the tumor cells were also positive for cyclin-D1 and CD57. The tumor cells are negative for CD68.

Molecular testing was also performed. The molecular tests were done to assess for translocation of the EWSR1 gene. These studies were done utilizing the dual color break-apart

probe for 22q12. The Florescent In-situ Hybridization (FISH) studies demonstrate presence of translocation in approximately 93.3% of tumor cells (56/60 positive for translocation). The FISH studies performed are positive for translocation of the EWSR1 gene.

The light microscopic, immunohistochemical, and molecular studies performed establish that this tumor is a clear cell sarcoma.

It is well known that Clear Cell Sarcomas and Malignant Melanomas can have very similar light microscopic and immunohistochemical features. On light microscopic examination, a malignant melanoma; especially a metastatic malignant melanoma (which this lesion was being considered); typically demonstrates significant pleomorphism and mitotic activity; features that are not prominent in the samples from this patient.

Since the immunohistochemical features in these two entities are very similar, the clinical history is important. In the absence of a documented history of malignant melanoma, it is absolutely essential to assess the lesion using additional molecular tools to definitively establish the exact nature of the malignant neoplasm.

The reciprocal translocation t(12;22)(q13;q12) is observed in more than 90% of clear cell sarcoma cases, with chromosome analysis, reverse transcriptase polymerase chain reaction (RT-PCR), and fluorescent in situ hybridization (FISH). This is well known having been first described in 2001 (Langezaal SM et. al. , Br J Cancer. 2001). Testing for this molecular event is part of standard of care.

The distinction of the two entities is critical. The treatment approach for the two entities is completely different; and obviously significantly impacts outcomes. The mainstay of treatment for a Clear Cell Sarcoma is typically wide excision with negative margins. In addition,

assessment of the local draining lymph node status is also important as 10-20% of patients can have regional lymph node involvement.

Conclusions

1. The expected norm/ standard of care would require definitive establishment of the lineage of the tumor; especially in the absence of a previously documented malignant melanoma.
2. Molecular studies to identify the EWSR1 translocation are considered standard of care in the context of the diagnostic evaluation of the tumor biopsies performed to establish the exact nature of this patient's disease process.
3. These studies were not performed and contributed to the rendering of a wrong diagnosis.
4. One also wonders if any correlation with the clinical scenario was performed, as the absence of a definitive history of malignant melanoma should have raised questions; needing additional assessment for establishing a definitive diagnosis.
5. The wrong diagnosis also resulted in inappropriate and inadequate treatment. As per medical records, the patient received therapies for malignant melanoma with associated severe adverse side-effects.
6. **In summary, the overall approach is negligent and does not meet expected standard of care. In this context it would be considered "malpractice".**

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Dated 9th June 2020

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