Mesothelioma-Hiding Behind the “Community Border”: Case Report and Literature Review

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Abstract
Malignant mesothelioma (MM) is a rare and highly aggressive neoplasm primarily of the pleura with a poor prognosis principally due to its late presentation. Differentiation of malignant cells from reactive benign cells in ascitic and pleural effusions can be challenging and may lead to diagnostic errors. Even after malignant cells are identified, it is equally challenging to differentiate malignant mesothelial from malignant epithelial cells.

Diagnosis should be based on cytological evaluation and confirmation utilizing immunohistochemistry studies. We report the case of a 44-year-old patient diagnosed with malignant mesothelioma. Initial cytology assessment was suggestive of adenocarcinoma (clusters with community border). However, with utility of immunohistochemistry studies for confirmation, the final diagnosis proved to be malignant mesothelioma and not adenocarcinoma. The diagnosis was confirmed using immunohistochemical studies even in the presence of strong cytomorphic features.

ABBREVIATIONS
MM: Malignant Mesothelioma; IHC: Immunohistochemistry

INTRODUCTION
Lung cancer is the leading cause of cancer-related death among men and women worldwide [1]. Many causal risk factors for lung cancer have been identified, including cigarette smoking, radiation exposure and occupational exposure to carcinogenic agents like asbestos [2]. Twenty percent of individuals exposed to asbestos fibers die from lung cancer; six to seven percent die from mesothelioma [3]. Mesothelioma is a rare malignant cancer of the mesothelial serosa that most commonly originates from the parietal pleura and the peritoneum. The typical clinical manifestation is pleuritic chest pain, dyspnea, weight loss and radiographic findings of pleural effusion or pleural thickening [4]. The clinical presentation of malignant mesothelioma can mimic lung adenocarcinoma. Distinguishing between the two poses a great degree of diagnostic difficulty due to the many clinical and cytomorphicologic similarities.

Over the years, several techniques have been used to make the distinction between malignant cells and reactive benign mesothelial cells. The most traditional method involves cytology sampling to analyze the cytology morphology of the expected tumor. However, this approach has shown to have a lot of variability, resulting in low sensitivity depending on the sample and preparation method used [5]. In addition, the coexistence of malignant mesothelioma and pulmonary carcinoma, although rare, has been reported. Adenocarcinomas on cytology material display smooth, low surface area border (community border), a strong cytomorphic feature used by cytopathologist to differentiate it from mesothelioma [6]. In addition to using cytomyology, immunohistochemistry is an invaluable tool in differentiating carcinoma from mesothelial cells. For many years, electron microscopy was the preferred method used to evaluate mesothelioma. However, immunohistochemistry has largely replaced EM as the ancillary technique to not only detects but to differentiate mesotheliomas from adenocarcinomas, which possess the ability to invade the pleura. Due to the poor prognosis of mesothelioma, early detection and accurate diagnosis are of vital importance. Patients with an earlier diagnosis may benefit from a more effective therapeutic regimen leading to higher survival rates [7]. In our case, immunohistochemical studies were essential to establish the correct diagnosis that would have been missed by using cytomorphicologic features alone.

CASE PRESENTATION
We report a case of a 44-year-old man who presented with pleural effusion, ascites, peritoneal implants, and questionable lung nodules. Initial cytomylographic analysis of the pleural fluid and ascitic fluid was negative for malignancy. Subsequent fine-needle aspiration of peritoneal implants showed characteristic cell clusters with smooth outlines (community borders) (Figure 1-A). The cytomylography displayed crowded
3-dimensional groups and single malignant cells with enlarged nuclei and prominent nucleoli with obvious “community border”, suggestive of metastatic adenocarcinoma (Figure 1-C). Confirmatory immunocytochemistry studies were performed on the cytology cellblock preparation. Immunohistochemical profile established a diagnosis of malignant mesothelioma: positive mesothelial markers were WT-1 (Figure 1-B), CK5/6 (Figure 1-D), calretinin, and GLUT-1; negative epithelial markers were MOC-31, BerEP4, and TTF-1; nonspecific CEA positivity was noted, as was the negative histiocytic marker (CD163). The combination of the cytomorphologic features together with the results of immunocytochemistry studies was diagnostic of malignant epithelioid mesothelioma. The lung nodules were evaluated by biopsy and the histomorphology, as well as the immunohistochemistry studies, were consistent with the prior cytology diagnosis of malignant mesothelioma.

The patient was treated with radical pleurectomy/decortication procedures, followed by a high dose of radiation therapy. The patient was disease-free for 23 months after which he expired due to extensive metastatic disease.

DISCUSSION

It is important to utilize a combination of cytology and immunohistochemical markers to make proper diagnoses of malignant mesothelioma. Malignant mesothelioma exhibits a wide range of phenotypic variability, making it difficult to obtain a diagnosis based solely on cytomorphic features [8]. IHC provides pathologists with fundamental information to aid in establishing a differential diagnosis such as 1) identifying if the sample is of mesothelial origin, 2) differentiating between the different phenotypic variants of mesothelioma (epithelioid, sarcomatous and mixed).

A recent study evaluating 12 antibodies to distinguish mesothelioma from adenocarcinoma showed that calretinin, a mesothelial marker, is the strongest marker for correctly identifying mesothelioma [9]. Although the expression of thyroid transcription factor-1 (TTF-1) yielded positive in many lung adenocarcinomas and thyroid carcinomas, the result was negative in several malignant mesotheliomas. A recently published case report showed the positive expression of TTF-1 in mesothelioma, making it an ineffective marker to exclude mesothelioma [10]. Although there is no consensus on a single marker to exclusively identify mesothelioma, the scientific community recommends the use of panels containing a wide variety of markers. New applications of IHC continue to be discovered as new antibodies continue to be developed, but its most important application is in facilitating the diagnostic process of a wide selection of neoplasms.

In cases where cytology and IHC yield inconclusive results, molecular testing can be used to establish an accurate diagnosis. A previous study by Gordon et al., demonstrated the ability to differentiate mesothelioma from adenocarcinoma using gene expression profiling. The study used polymerase

![Figure 1](image-url)
chain reaction (PCR) to measure the expression ratio of certain genes that resulted in an inexpensive yet accurate approach for diagnosis [11]. Gene expression quantification is not the only molecular procedure currently being used aiding in the diagnosis of tumor cells with unequivocal features. Recent studies have utilized fluorescence in situ hybridization (FISH) to locate specific chromosomal rearrangements, deletions, and amplification that are associated with a variety of neoplasms [12]. Malignant mesothelial cells possess distinct chromosomal aberrations such as, polysomy in a combination with a 9p21 deletion, which can be used as a biomarker to identify and distinguish mesothelial cells from other cell lines [6].

Mesothelioma is a rare and aggressive malignant neoplasm of the serosal membranes, posing diagnostic challenges. Our case highlights the importance of using immunohistochemical studies in effusions, even in the presence of strong cytomorphologic features, in order to increase the accuracy of diagnosis and to achieve a better prognosis by early cancer detection. In cases of inconclusive atypical cells, a combination of IHC, morphology, and FISH can be used to make a better distinction between mesothelioma and adenocarcinoma. Further exploration into the role of IHC in cancer is essential. Future investigation will hopefully result in the identification of more efficacious therapeutic targets and improved diagnostic markers. To help in the diagnostic process, the clinician should perform a comprehensive history to evaluate possible exposure to risk factors. However, mesothelioma should not be ruled out simply because of not being exposed to asbestos [13-15].

Cytomorphology sampling alone, with adequate cellblock preparation is sufficient for the diagnosis of malignant mesothelioma utilizing cytomorphology and immunocytochemistry studies. Our case highlights the importance of using immunohistochemical studies in effusions even in the presence of strong cytomorphologic features.

REFERENCES