Editorial

Current perspective on the diagnosis of malignant pleural effusion

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Malignant pleural effusion (MPE) is diagnosed by the presence of malignant cells in the pleural fluid or a pleural biopsy. The presence of MPE is classified as M1a in the 8th edition of the tumor-node-metastasis staging for lung cancer (1). Therefore, the diagnosis of MPE is important for disease staging and establishing a treatment plan in lung cancer patients. Thoracentesis is the first step in diagnosing MPE; however, its reported sensitivity varies from 40% to 87% (2,3). A pleural biopsy may be necessary in cases where the pleural fluid cytology shows a negative or indeterminate result. When pleural thickening or nodularity are noted on contrast-enhanced computed tomography (CT) images, an image-guided percutaneous pleural biopsy is recommended as the standard diagnostic method (4,5). However, these disease-related abnormalities on the pleura are not always observed on chest CT scans, and the pleural biopsy can result in false negatives.

Thoracoscopy is advantageous because it directly visualizes the entire pleural surface to maximize the diagnostic yield from abnormal lesion biopsies (6). However, a significant drawback of the procedure is that it requires general anesthesia. Medical thoracoscopy is feasible under local anesthesia and appropriate method for patients with comorbidities, who are expected to have limited survival or be intolerable to general anesthesia. In previous studies, pleural biopsy via medical thoracoscopy was reported to have a sensitivity that exceeded 90% (7,8). Nevertheless, the procedure requires specialized expertise and is uncommon in clinical practice.

Diagnostic imaging, including contrast enhanced chest CT or fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET), is a potential ancillary tool to provide additional information for diagnosing MPE. Characteristics of MPE on a chest CT scan are as follows: nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening (>1 cm), and circumferential pleural thickening. Although the presence of these features is associated with high diagnostic specificity for MPE (94%, 94%, 88%, and 100%, respectively), they show limited sensitivity (51%, 36%, 56%, and 41%, respectively) (9,10). With respect to PET as a diagnostic tool to distinguish between benign and malignant states, MPE is known to have a high standardized uptake value (SUV). However, widespread application of diagnostic PET for MPE is hindered by false positives in patients with pleural inflammation, including pleural infection and talc pleurodesis (11-13). Therefore, there is a clinical need to develop a non-invasive diagnostic tool for MPE.

Recently, Brun *et al.* reported on a retrospective study that included 101 patients with MPE. Within the study cohort, 76 MPEs were diagnosed at the time of lung cancer diagnosis and 25 MPEs were diagnosed during the follow-up (14). Although they reported no correlations between pleural fluid cytology, chest CT, and PET-FDG, the overall diagnostic yield was improved by 90% when all three methods were combined.

This study can provide valuable information on techniques to non-invasively diagnose MPE. However, the results should be interpreted with caution. There was a high proportion of adenocarcinoma within the study population that may have affected the diagnostic yield. Notably, pleural fluid cytology has a higher sensitivity for detecting adenocarcinoma compared to other cell types (2,15). Therefore, it is necessary to analyze the diagnostic yield

for each cell type. In addition, the inclusion of a control group would strengthen the diagnostic yield evaluation. For example, a patient population receiving a benign pleural effusion could be added.

Biomarkers can be an important asset that contributes to a non-invasive diagnosis. In prior studies, a combination of biomarkers including, carcinoembryonic antigen, carbohydrate antigen (CA) 125, CA 15-3, CA 19-9, cytokeratin 19 fragments, and neuron-specific enolase were used to diagnose MPE when malignant cells were not present in the pleural fluid cytology (16,17). Recently, driver mutations, including *EGFR*, *BRAF V600E*, *ALK*, and *ROS1* were identified as having clinical utility for guiding MPE treatment (18,19). Interestingly, concordances of these biomarkers between primary tumor and pleural metastases were reported to be high (20). Further studies are warranted to elucidate whether biomarkers can potentiate the diagnostic yield and be used as a non-invasive diagnostic method for MPE. Independent validation of the diagnostic yield will be required to ultimately determine the clinical potential of MPE biomarkers.

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Footnote

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