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Title: Contemporary Approach to the Diagnosis of Malignant Pleural Effusion

Running Head: Diagnosis of Malignant Pleural Effusion

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ABSTRACT

Advanced malignancy is a prevalent cause of exudative pleural effusion. The management of malignant pleural effusion (MPE) has been the subject of several recent randomized controlled trials and excellent reviews. Less attention has been focused on another controversial and challenging aspect of MPE: establishing the diagnosis. Prior to selecting the optimal management strategy, the presence of an MPE must first be correctly identified with an emphasis on minimizing invasiveness and discomfort in a patient afflicted with late-stage cancer. The aim of the present review is to summarize the current knowledge about MPE diagnostics and to propose an algorithm for the diagnosis of MPE in established or suspected malignancy.

INTRODUCTION

Malignancy is the second most common etiology of exudative pleural effusions (1), leading to over 125,000 admissions in the United States in 2012 with a median cost per hospitalization of more than $42,000 (2). Lung and breast cancer together account for the majority of primary tumors metastatic to the pleural space (3). Malignant pleural effusion (MPE) signifies an advanced stage of malignancy, so unsurprisingly the median survival in cases of lung and breast carcinoma ranges from approximately 2 to 6 months (4). The identification of an MPE may have implications for the staging, management, and prognosis of a patient with established cancer, or it can be the source of initial diagnostic material. A pleural effusion can be definitively called MPE only after the detection of neoplastic cells or tissue in the pleural space. This is important as other types of pleural effusions could occur during a cancer patient's clinical course. So-called "paramalignant effusions," may result from complications of cancer such as endobronchial obstruction or pulmonary embolism but do not represent direct involvement of the pleural space by malignancy. Table 1 summarizes the performance characteristics of these various diagnostic modalities, which are synthesized into a proposed algorithm in Figure 1.

CLINICAL AND RADIOLOGICAL EVALUATION

Clinical Features

The majority of patients with MPE are symptomatic at presentation, typically reporting subacute dyspnea and chest discomfort (5)(6). Ferrer et al (7) studied the following 5 features of 93 patients referred for thoracoscopy and determined that all patients fulfilling ≥4 criteria were eventually diagnosed with MPE, whereas those with one or none of these characteristics invariably had benign effusions:

a) Clinical symptoms (dyspnea, chest pain, constitutional symptoms)
b) Symptomatic period >1month
c) Absence of fever
d) Blood-tinged pleural effusion
e) Chest CT suggestive of malignancy (mass, atelectasis, adenopathy)

Chest Radiography and Computed Tomography

On plain chest radiographs, MPE is usually unilateral, though bilateral effusions are present in about 11% of cases (8) Over half of MPE are large, occupying more than two-thirds of a hemithorax, or massive (i.e., complete opacification) (9). Contrast-enhanced chest CT can contribute valuable predictive information in cases of suspected pleural malignancy. Nodular pleural thickening, mediastinal pleural thickening, parietal pleural thickening >1cm, and circumferential pleural thickening are all highly specific (88-100%) for malignant involvement (10). Porcel et al used a single-center sample to derive a scoring system for identifying malignancy based on chest CT findings that included the following elements and point values (11):

a. Pleural lesion ≥1cm (5 points)
b. Presence of liver metastasis, abdominal mass or lung mass/nodule (3 points each)
c. Absence of pleural loculations, pericardial effusion, or cardiomegaly (2 points each)

A total score of ≥7 points predicted MPE with a sensitivity of 88% and a specificity of 94% in the validation cohort. These encouraging performance characteristics were, however, not replicated when two UK centers correlated radiologists' CT interpretations with subsequent pleural histology (12). In clinical practice, it turned out that the sensitivity and specificity of CT reports for pleural malignancy were 68% and 78%, respectively. These results translated to a negative predictive value of 65%, meaning that one in three patients with MPE would have been missed based on the CT reading. While informative if present, CT features of malignancy cannot by themselves substitute for cytohistological sampling nor should their absence preclude additional evaluation in real-world practice.

Magnetic Resonance Imaging

Using signal intensity as the criterion, magnetic resonance imaging (MRI) performs comparably to CT in the radiological differentiation of benign from malignant pleural disease, though it is less widely available and more challenging to obtain (13). It may have particular value in delineating the presence or absence of invasion in mesothelioma cases, but it currently lacks a defined role in the initial evaluation of suspected pleural malignancy (14).

Positron Emission Tomography

^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) is a functional imaging technique used widely in the field of oncology for characterization of suspected malignancy and in the search for metastases. The avidity of the pleura for ^{18}FDG can be quantified using the maximum standardized uptake value (SUV_{max}) or assessed qualitatively by comparison with normal background activity (Figure 2). The integration of ^{18}FDG-PET with chest CT (PET/CT) raised the sensitivity of CT findings alone from 70% to 93% in a study of 86 patients with metastatic pleural malignancy (15). In this study performed in an endemic area for tuberculosis (TB), the specificity of PET by itself for MPE was limited to 63% primarily by falsely positive TB pleuritis cases. Integrated PET/CT imaging compensated for this shortcoming by allowing concurrent functional and anatomical evaluation of the pleural space with a resultant specificity increase to 93%. The addition of PET did not increase the already very high (>90%) sensitivity and specificity of CT scanning for the identification of pleural mesothelioma. Meta-analysis of 14 publications through the year 2012 yielded a best-case specificity of ^{18}FDG-PET of only 76%, which was reached by pooling just those studies that applied qualitative criteria for ^{18}FDG avidity (16). Of note, a study from an area of low TB prevalence included in this meta-analysis reported a specificity of only 35% for PET/CT despite a population enriched with cases of mesothelioma (17). Many of the false positive studies occurred in patients status post talc pleurodesis. False positivity has thus consistently been the Achilles heel of ^{18}FDG-PET, which severely limits the utility of a test applied to cases of suspected pleural malignancy. Much like CT and other forms of imaging,

^{18}FDG-PET cannot differentiate benign from malignant pleuritis with sufficient accuracy to obviate cytohistology.

In summary, scoring systems and advanced radiological techniques can heighten suspicion for malignant pleural disease. However, given that tissue confirmation is required for definitive diagnosis, clinical features and radiology should be regarded as a triage strategy rather than conclusive evidence of MPE.

PLEURAL FLUID ANALYSIS

Biochemistry

Ultrasound-guided thoracentesis is the initial procedure of choice for the investigation of suspected MPE. Routine pleural fluid (PF) analysis in MPE will typically reveal exudative characteristics with a predominance of mononuclear cells. The differential diagnosis of this laboratory pattern primarily includes TB, collagen vascular disease, and late effusions complicating coronary artery bypass graft surgery. In endemic countries, TB pleuritis poses the biggest diagnostic challenge and is the only one of the aforementioned etiologies that frequently occurs without historical clues. PF adenosine deaminase (ADA) level can help distinguish TB from MPE as it is characteristically much higher in the former median 86 U/L) than in the latter (median 23U/L) (18). The so-called “cancer ratio,” defined as serum lactate dehydrogenase/pleural ADA,

at a value >20 has been shown to identify MPE with a sensitivity of 98% and specificity of 94% (19).While not diagnostic, PF pH <7.30, found in about one-third of patients with MPE, is associated with greater PF cytology yield, reduced pleurodesis success, and shorter survival (20). Care must be taken when interpreting low pleural fluid pH values to exclude the possibility of artifact as may occur with an admixture of heparin or lidocaine (21).

Cytology

The diagnosis of MPE by PF sampling can be considered definitive only if cytology shows malignant cells. From their contemporary series of over 3,000 PF aspirations, Porcel et al calculated the yield of the initial PF cytology specimen in MPE to be 51%, which rose to only 59% even after counting second and third cytology specimens in the overall MPE patient sample (N=831) (3). On its surface, the modest 8% incremental yield appears to negate the utility of performing serial PF cytology testing. Viewed another way, however, of the 214 patients with negative first cytology who underwent a second PF aspiration, 55 additional MPE were diagnosed, corresponding to 26% of that group. Further, 52 patients with two negative cytologies underwent a third thoracentesis, and 12 (23%) of these were diagnostic. In agreement with previous work (22), cytological yield in the study by Porcel et al varied greatly with the primary cell type. More exfoliative cell types such as lung adenocarcinoma and ovarian cancer produced yields in excess of 70%, whereas only 25% of lung squamous cell carcinoma cases were diagnosed by PF cytology.

Even lower utility of serial PF cytology emerged from prospectively collected data on 515 patients with MPE wherein the overall yield was 46% (23). Repeat samples were positive in 6 out of 106 initially negative cases (5.6%) and in none of 30 cases that proceeded to a third collection. Expectedly, PF cytology yields varied dramatically by cell type: 95% in ovarian primaries, 82% in pulmonary adenocarcinoma, and 14% in squamous cell cancer of the lung.

Submitting large PF aliquots (i.e., >250cc) does not appear to increase the cytological yield for diagnosis of malignancy (24). The overall detection rate reaches a plateau at a volume of 75cc (25), but at least 150cc may be required to maximize the utility of the cell block preparation (26). Higher volumes may be of incremental value when extensive immunohistochemical testing or molecular genetic analysis of the fluid is anticipated. Malignant PF usually provides sufficient material for genetic profiling of lung cancer, and for this purpose the cell block preparation can substitute for tissue biopsy with a high but imperfect accuracy of about 80% (27).

Tumor Markers

PF tumor markers have been studied individually and in combination as a tool for MPE diagnosis when cytology is negative with the understanding, of course, that they cannot provide pathological material. It has been argued that, for distinguishing MPE from benign effusions in clinical practice, the threshold for positivity of a given tumor marker ought to correspond to the level of 100% specificity in order to preclude false positivity (28). A panel of 4 tumor markers, including familiar ones such as carcinoembryonic antigen (CEA) and cancer antigen (CA)-125,

identified 23% of cytology-negative effusions eventually proven to be malignant (29). Porcel et al have shown that elevation of either CEA or CA 15-3 correctly predicts malignancy in 41% of false negative PF cytology cases (30). When the results are stratified by cell type, it emerges that these tumor markers have similar sensitivity to PF cytology (approximately 70-80%) in exfoliative malignancies such as lung adenocarcinoma and ovarian cancer, limiting their incremental benefit in such cases. However, in less exfoliative lung squamous cell carcinoma, these tumor markers had a sensitivity of 47%, which exceeds the aforementioned sensitivities of PF cytology when this is the primary tumor. In mesothelioma, another malignancy with low cytological yield, the PF tumor marker mesothelin significantly outperformed PF cytology with sensitivity of 71% versus 35% when studied prospectively, though there were false positive results (specificity 89%) (31). Vascular endothelial growth factor (VEGF) is not a tumor marker but rather a potent mediator of pleural fluid formation in MPE. The level of VEGF in PF correlates inversely with survival in non-small cell lung cancer complicated by MPE (32). As a diagnostic tool, using a PF concentration above 652pg/ml as the threshold value, VEGF elevation correctly identified 12 of 20 (60%) cytologically negative MPE confirmed by thoracoscopy (33). False positives did occur at this cut-off, however, translating to a specificity of 83%. Overall, PF tumor markers can support a malignant etiology if elevated, but they are insufficient in isolation for a confident diagnosis of MPE, especially with regard to planning oncological treatment decisions.

PLEURAL BIOPSY

Needle Biopsy

In contrast to TB pleuritis, in which the pleura is typically diffusely involved by granulomatous inflammation, metastatic malignancy tends to implant on the pleura in a patchy distribution. This difference explains the traditionally high yield of "blind" closed needle biopsy of the pleura in TB and its low yield in MPE. In fact, this type of needle biopsy detected fewer cases of malignancy (43%) than did PF cytology (58%) among 281 patients with MPE, and histology diagnosed only an additional 7% of cases missed by cytology (34). Superior sensitivity of PF cytology over "blind" needle histology in MPE (71% vs. 45%) was also demonstrated by another study (35), wherein biopsy diagnosed only 3 cases with negative cytology. In mesothelioma, the utility of this technique varies widely with reported yields ranging from as low as 16% (36) to as high as 44% (37) compared to less variable but still poor results from PF cytology: 30-35% (31,38). Generally, given the challenges posed by small specimens, acquisition of larger tissue biopsies is preferred for the diagnosis of mesothelioma when thoracoscopic sampling is feasible.

Bedside ultrasonography is available to the respiratory clinician and can increase the yield of needle biopsy in MPE by directing the sampling to areas with overt or more probable malignant involvement, such as the basal pleura (Figure 3, Supplemental Video). Sonographically visible pleural thickening >1cm and pleural nodularity are both highly specific—95% and 100%, respectively—for malignancy (39). Koegelenberg et al performed thoracentesis followed by US-directed pleural biopsies in 100 patients with previously undiagnosed exudates (40). Subjects with a sonographically detected pleural mass lesion (N=11) underwent fine needle aspiration,

which was followed by cutting needle biopsy if the on-site aspirate result was anything but lung cancer. Those with pleural thickening visible on US (N=24) underwent cutting needle biopsy if the thickening was ≥2.5cm and closed needle biopsy if it was <2.5cm. In the absence of sonographic pleural abnormalities (N=65), US-assisted random closed needle biopsies aiming at the low supradiaphragmatic pleura were performed. With this approach, these investigators achieved an overall diagnostic yield for malignancy of 89.7%, a significant improvement over the 31% yield of PF cytology in the same patients. The authors reported only three minor complications, all after closed needle biopsy.

Dynamic CT guidance for needle biopsies of thickened or nodular pleura is usually the domain of radiologists and is not a bedside modality. Its use nearly doubled the sensitivity of "blind" needle biopsy in one study, which was 44% without imaging and 87% with imaging (41). Static CT imaging, on the other hand, can help respiratory clinicians to identify the optimal needle insertion site. When compared to US-assisted (i.e., non-real-time) cutting needle biopsy in a study that included 93 patients with pleural malignancy, CT-assisted closed needle biopsy produced superior sensitivity: 77% vs. 61% (42). Both techniques performed better in the setting of pleural thickening >1cm. Complications were few and minor, comparable between the two procedures. Extrapolating the findings of another group, it is conceivable that the sensitivity gap between CT and US could have been narrowed if real-time US guidance had been used instead of a static technique (43).

Medical thoracoscopy

Medical thoracoscopy (MT) refers to the insertion of a rigid or semi-rigid thoracoscope into the pleural space of a patient placed in a lateral decubitus position and administered a local anesthetic with or without intravenous sedation. This is in contrast to the general anesthesia and single-lung ventilation that characterize surgical thoracoscopy (see below). The procedure allows direct visualization of the pleural space and the performance of forceps biopsies of abnormal sites on the parietal pleura (Figure 4). Because of the obligatory induction of a pneumothorax, a pleural drain is typically left in place at the conclusion of MT. On the other hand, since the visceral pleura is not traversed, the duration of post-procedure pleural drainage could be brief enough to perform MT as an ambulatory case (44). Not every patient with pleural effusion is capable of undergoing this procedure, particularly among the often-debilitated cohort with MPE. Absolute contraindications include lung extensively adherent to the chest wall prohibiting entry into the pleural space and resting hypercapnia, which is likely to worsen during and after the procedure (45). When Rahman et al aggregated data available prior to 2010 from all series reporting the yield of MT in MPE, the pooled sensitivity was 93% (46). Studies published subsequently have corroborated the >90% diagnostic yield of medical thoracoscopic biopsy in pleural malignancy (47), irrespective of whether biopsies are performed through a rigid or semi-rigid instrument (48). Sensitivity approaching 100% has likewise been reported for MT in mesothelioma (49). Comparison of MT to CT-assisted closed needle biopsy in a randomized controlled trial showed numerical but not statistical superiority of the former for diagnosing malignant pleural disease: sensitivity of 95% vs. 87%, respectively(50). Nor did statistically significant differences emerge in subgroup analysis based on primary site. In appropriate

candidates, MT is a well-tolerated procedure with a favorable risk profile. In the literature survey by Rahman et al, diagnostic MT was found to have no associated mortality. More recently, exceptional MT-related fatalities have appeared in print(47). Overall complication rates are low: 1.6% for major events such as empyema or hemorrhage and 7.3% for minor events such as subcutaneous emphysema or skin infection(46).

Surgical thoracoscopy

The "gold standard" for diagnosing pleural malignancy, but also the most invasive means of doing so, remains surgical pleural biopsy, nowadays increasingly performed thoracoscopically via video assisted thoracoscopic surgery. Patients considered for this approach must be capable of tolerating general anesthesia and single lung ventilation, but unlike MT, they are not expected to sustain spontaneous respiration in the face of a partial unilateral pneumothorax. The other traditional differentiating factors between VATS and MT include the performing provider (surgeon vs. pulmonologist), setting and type of anesthesia used, as well as post-operative management (duration of chest tube requirement and pain control). The yield of VATS in MPE ranges from 89-95% with a reported major complication rate of 15-26% in this patient population in older literature (51,52). Recently published retrospective data indicate comparably low major complication rates after both VATS (4.0%) and MT (2.6%) but a significant difference in hospital stay and cost favoring the latter (53). The post-operative pain associated with VATS is less severe than that after thoracotomy, but it can nevertheless be persistent (54).

THE UNDIAGNOSED EFFUSION

Approximately 15-30% of cytology-negative exudative pleural effusions in an unselected population remain without a definable etiology despite histological sampling and are labeled as "non-specific pleuritis" (55,56). In patients with active malignancy, the frequency of "non-specific pleuritis" histology after thoracoscopy has been reported to be as high as 52%, but the majority of these cases could be assigned a clinical correlation such as chemotherapy-induced pleuritis or radiation-induced pleuritis (57). Pleural malignancy is discovered during subsequent surveillance in a small but tangible minority of "non-specific pleuritis" cases (3-12%), thus justifying continued clinical vigilance (56–58).

FUTURE DIRECTIONS

Biomarkers

The current movement towards personalized medicine includes development of biomarkers as diagnostic and monitoring tools. This trend has extended to potential biomarkers of malignancy, among them circulating tumor DNA (ctDNA). The entry of ctDNA into the bloodstream is presumed to occur by way of tumor necrosis or apoptosis, and it is anticipated that its detection may lead to the future development of a so-called "liquid biopsy" (58). The role of ctDNA has

been investigated in breast, colon and most recently in non-small cell lung cancer (59–61). The TRACERx study has demonstrated the utility of this assay for the detection of early stage lung cancer and of disease recurrence (59). Although mutation analysis using ctDNA may already be in use to direct treatment in certain tumors, diagnostic sensitivity, particularly in relation to intrathoracic malignancies, has been limited so far (59,62). Eventually, ctDNA may therefore become a helpful blood-based adjunct in the evaluation of a patient with an undiagnosed exudative pleural effusion. It is doubtful, however, that its use would preclude invasive sampling in cases of suspected pleural malignancy. Notably, the definition of a "liquid biopsy" could be extended to PF such that soluble tumor-derived biomarkers may be part of the future of MPE diagnostics. As an example, a novel technique to identify circulating tumor cells has shown encouraging early results when applied to malignant PF of lung cancer patients (63). The PROMISE study is further cause for optimism with respect to PF biomarkers in MPE (64). Utilizing datasets from five randomized controlled trials, researchers were able to identify four potential PF biomarkers predictive of survival. In the future, it may be possible to apply similar investigative techniques in pursuit of potential diagnostic biomarkers.

Imaging

The utility of PET/CT in malignant pleural disease remains uncertain. The TARGET trial (ISRCTN14024829) has been designed to investigate the role of PET/CT in suspected MPE by assessing whether targeted biopsy based on ^{18}FDG avidity improves diagnostic sensitivity over conventional CT-guided biopsy with the potential secondary benefit of identifying distant

399 metastatic disease. This trial also aims to further clarify the role of serum mesothelin by including
400 this biomarker in the assessment of subjects with mesothelioma (65).
401
402 Narrow band imaging (NBM) is an endoscopic technique that generates two narrow bands of
403 light to enhance the imaging of blood vessels. The detection of irregular vascular patterns is
404 thought to identify the presence of malignant involvement, thus improving selection of biopsy
405 sites and thereby diagnostic yield. Its use has become an established component in the
406 investigation of head and neck, gastrointestinal, urological and some bronchogenic carcinomas
407 (66). One study has suggested a potential role for NBM during thoracoscopy for suspected
408 malignancy. This approach requires further validation (67).
409
410 Thoracic US has become an indispensable tool in pleural disease management due to the high
411 diagnostic sensitivity and improved safety profile when used to facilitate pleural interventions
412 (68). Awaiting confirmation are findings from small-scale feasibility studies indicating that
413 contrast-enhanced US may increase diagnostic accuracy when sampling sub-pleural lesions and
414 may also help to direct pleural biopsy.
415
416
417 **CONCLUSION**
418
419 The diagnosis of MPE can remain elusive after analysis of a single or even multiple PF cytology
420 specimens, especially in relatively non-exfoliative cancer histology. Imaging characteristics and

elevation of PF tumor markers can support ongoing suspicion for MPE despite negative cytology, but both lack the ability to provide pathological material for determination of cell type and molecular genetic profile. The role of serum biomarkers is still at the investigational stage, and they are subject to the same limitations. Depending on availability and the presence or absence of pleural thickening, persistent concern for MPE despite negative PF cytology should prompt imaging-guided needle biopsy of the pleura or MT as the next step, the latter also affording an avenue for therapeutic intervention. In most settings, thoracoscopy is preferable to needle biopsy in suspected mesothelioma. Currently under investigation is the use of PET/CT targeting to improve the utility of needle biopsy in mesothelioma. In appropriate candidates for general anesthesia and single-lung ventilation, surgical thoracoscopy can follow negative PF cytology in centers with limited access to less invasive techniques.

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FIGURE LEGENDS:

Figure 1: Colors correspond to the three modalities capable of definitively establishing the presence of pleural malignancy: green – pleural fluid cytology, red – needle biopsy of the pleura, blue- thoracoscopy.

**In light of challenges posed by small specimens for the confident diagnosis of mesothelioma, acquisition of thoracoscopic tissue biopsies is preferred when such sampling is permitted by local availability and expertise.

MPE = Malignant Pleural Effusion

Figure 2: ^{18}FDG-PET/CT fusion image demonstrating diffusely increased ^{18}FDG uptake in the pleural membranes of the left hemithorax (SUV_{max} 6.84). Needle biopsy of the pleura showed squamous cell carcinoma.

Figure 3: Still image captured during cutting needle (CN) biopsy of pleural thickening (PT). The tip of the needle (CN tip) is located in the accompanying pleural fluid (PF).

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644 **Figure 4:** An image acquired during medical thoracoscopy showing diffuse nodularity of the

645 parietal pleura, a pattern consistent with metastatic pleural malignancy.