



Malignant pleural effusion and cancer of unknown primary site: a review of literature

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Abstract: Malignant pleural effusions (MPE) are most frequently (50–65%) noted from lung and breast cancers. They are commonly unilateral and are reflective of poorer prognosis. Cancer of unknown primary (CUP) account for 4–5% of all invasive cancers. These are metastatic tumors in which the primary is unknown despite an extensive medical evaluation. About 11% of MPE are from CUP. These MPEs present a clinical dilemma to physicians as there is a paucity of literature on their management and no consensus or guideline statement. This paper provides an overview of MPE from CUP in regard to diagnosis, prognosis, and treatment options. A selective search was performed in Medline and PubMed, with the keywords “Malignant pleural effusion” and “Cancer of unknown primary” up to December 2018. A review of literature would suggest that a thoracentesis is the first step in all cases but additional work up such as thoracoscopy & pleural biopsies is frequently warranted. With advances in immunohistochemical staining and biomarker development, MPE with CUP maybe profiled in a similar manner as lung cancer. Similarly, liquid biopsy or identification of circulating tumor cell free DNA may have a role in the work up of CUP in the future. There is some experience in managing these patients with gene directed therapies and immune checkpoint inhibitors, however, with mixed results. Given the poor prognosis associated with MPE from CUP, symptom alleviating measures such as indwelling pleural catheters should be part of the management strategy.

Keywords: Lung cancer; pleural effusion; cancer of unknown primary (CUP)

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Introduction

Metastatic cancer of unknown primary (CUP) site refers to a heterogeneous group of cancers that are detected histologically at metastatic site but with unknown primary location despite a thorough and extensive medical evaluation (1,2). They account for 4–5% of all invasive cancers. More than half of these patients will be identified to have adenocarcinoma with multiple sites of metastasis (3). Isolated pleural effusion, as the initial presenting site for CUP is uncommon. Most of these patients portend a poor prognosis (3).

A malignant pleural effusion (MPE) is defined as the presence of malignant cells in pleural fluid as noted in cytology or histology of pleural tissue biopsy obtained during thoracotomy, thoracoscopy or autopsy (4). MPE is a very common complication of advanced malignancies and is the most important diagnosis to exclude in unilateral pleural effusions. The leading etiology of MPE in both sexes is lung cancer (35.6%), lymphoma/leukemia (15.9%) and breast cancer (14.8%) (5). In one study evaluating 5888 MPE specimens, the incidence of cancer with unknown primary was 10.2% (5).

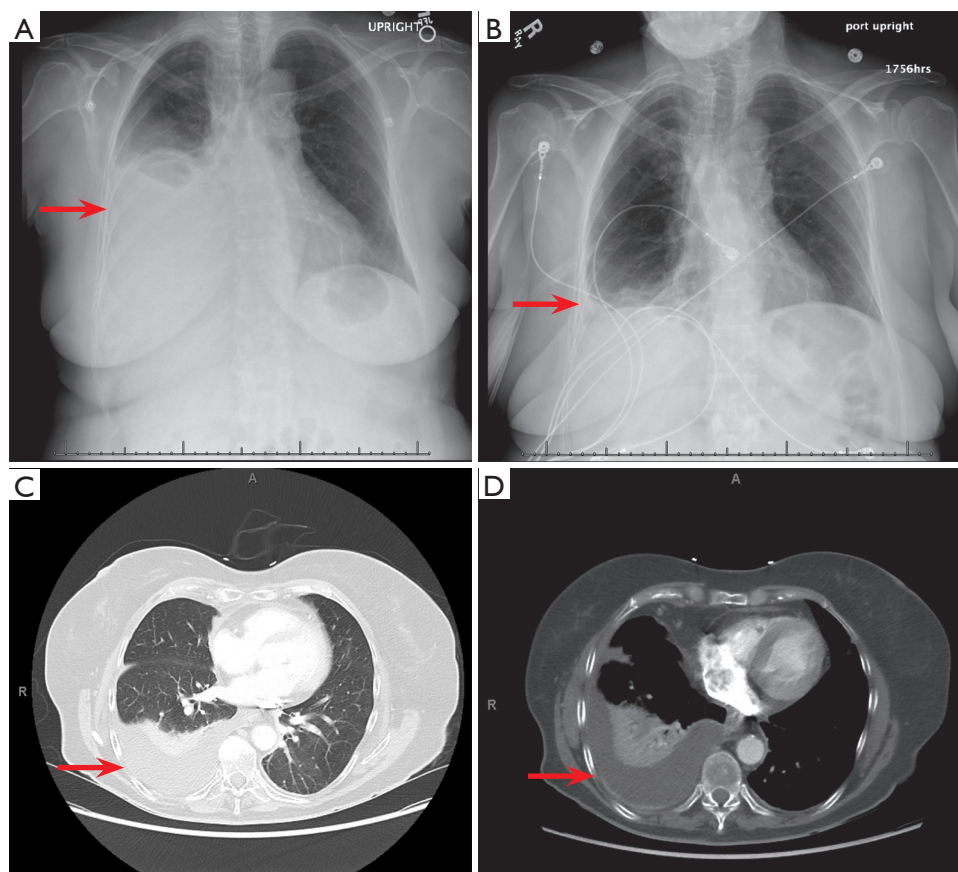


Figure 1 Chest X-ray pre (A) and post (B) thoracentesis & computed tomography images (C,D) of a 61-year-old female with malignant right pleural effusion (arrows).

Despite all the recent advances in Oncology, the diagnosis and treatment of MPE associated with CUP remains a dilemma for physicians with no clear guidelines or consensus.

Discussion

MPE

The most common cause of MPE tends to be lung cancers. In one analysis of 5,888 MPE specimens, 35.6% were of MPE were noted to be from the lung (5). Together, 50–65% of MPE are either from lung or breast cancer (6). Clinically, dyspnea and cough are the most common presenting features of MPE. The degree of dyspnea has a positive correlation with size of pleural effusion and a therapeutic thoracentesis usually results in relief of dyspnea (7). Some patients may also have vague constitutional symptoms,

however none of these symptoms elude to the localization of the primary tumor. Of note, up to 25% of patients with MPE are asymptomatic at the time of diagnosis (8). On chest imaging (*Figure 1*), a majority of MPE present as ipsilateral effusions although 10–13% can be bilateral (9,10). The 3/4th of MPE are moderate to large in size, with volumes ranging between 0.5–2 L (5). These effusions can cause complete opacification of the hemithorax and are termed as a massive pleural effusion. When present, they can be a strong indication of malignancy (11).

Paraneoplastic effusions (also known as paramalignant effusions) are effusions seen in tumors without direct pleural involvement and no evidence of malignant cells in pleural fluid. These effusions are usually caused by conditions that coexist with tumors, such as pulmonary embolism, thoracic duct obstruction, compression of the superior vena cava, pericardial infiltration, hypoalbuminemia, obstructive pneumonia, or atelectasis (4). Paraneoplastic pleural

effusions tend to have a better prognosis than MPE (12). Differentiating between MPE and paraneoplastic effusions is important and always requires a thoracentesis with pleural fluid analysis. MPEs are mostly exudative with a protein concentration of about 4 mg/dL (8). Bloody malignant effusion can result from tumor induced angiogenesis, direct vascular invasion of tumor, venule occlusion and increased capillary permeability by release of vasoactive factors (13). The red cell count of these effusions are usually in the range 30,000–50,000 per microliter (5). The lymphocytes are usually numerous and in the range of 50–70% with a predominance of T cells (5). One third of MPEs have a low pleural fluid pH (<7.3) and pleural glucose concentration (<60 mg/dL) (14,15). Low pleural fluid pH and glucose concentration in MPE is associated with poorer prognosis. They are also indicative of extensive disease and lower chance of successful pleurodesis (14). In one study, shorter survival was noted with pleural fluid pH <7.28 [median survival of 2.5 months and a 3-month survival of 38.9% (95% CI: 31.1% to 46.8%)] versus pH >7.28 [median survival of 4.3 months and 3-month survival of 61.6% (95% CI: 55.7% to 67.4%)] (16).

Pleural biopsy might be necessary if the pleural fluid analysis was insufficient to make a diagnosis or if the tissue yield is inadequate for immunohistochemical staining. The biopsy can be done by several methods including blind-closed percutaneous needle biopsies and image guided needle biopsies. More recently the popularity of local anesthetic thoracoscopy (LAT) (aka medical thoracoscopy) (17,18), or video-assisted thoracoscopic surgery (VATS) has been increasing given their safety profile. When dealing with malignancy, image guided biopsy or thoracoscopy (medical or surgical) are very reliable in obtaining sufficient tissue to facilitate diagnosis (4).

CUP

Metastatic CUP site account for 4–5% of all invasive cancers. More than half of these tumors identified to be adenocarcinoma with multiple sites of metastasis (3). CUP usually lack early clinical symptoms due to the fact of absence of primary tumor which may explain the aggressive behavior seen with them, such as early dissemination and unpredictability of metastatic pattern. Extensive medical evaluation for CUP should include, a detailed medical history, complete physical examination, full blood count and biochemistry, urinalysis and stool occult blood testing, histopathological review of biopsy material with the use

of immunohistochemistry, chest radiography, and CT of the abdomen and pelvis (2). In one study, ~11% of the MPE were deemed to be from CUP despite an extensive work up (5). Unfortunately, the diagnostic yield after a single thoracentesis for malignancy from pleural fluid samples is just 60% (19). CUP typically tend to be poorly differentiated cancers and may not demonstrate typical immunocytochemistry (IHC) stains with clonal evolution of cell lineage. When seen with MPE there is often a need for pleural biopsies to confirm or exclude a primary tumor diagnosis. Finally, while it is important to state the importance of using gene expression profiling to guide suspected site-specific treatment of CUP; site specific treatment based on microarray profiling does not improve 1-year survival (16.7 *vs.* 10.6 months; $P=0.116$) compared to empiric paclitaxel and carboplatin (20). The use of an established algorithm to predict the primary site of CUP does have prognostic value (20).

Hybrid positron emission tomography-computed tomography (PET-CT) should be utilized in the workup of CUP since it aids in the identification of primary site and hence affect management algorithm (21). In a 2006 study, 68 consecutive patients with CUP syndrome underwent whole body FDG-PET/CT as part of diagnostic workup. In this study, the primary tumor site was identified in 35.3% of patients (22). Unexpected metastases were identified in ~13% of these patients resulting in restaging. Overall, the final oncological treatment was influenced by PET-CT in 48.5% of these patients (22). A 2009 systematic review of 11 studies (433 patients with CUP) examined the use of combined FDG-PET/CT in the detection of unknown primary tumors. The overall primary tumor detection rate in this paper was 37% (23); 4/11 studies in this review showed that PET-CT modified therapy in 18.2–60% of patients (23). In a more recent 2016 recent study involving 82 patients with CUP syndrome, PET-CT scan identified the primary tumor site in 57.3% of cases and upstaged the disease in 27% of cases (24). Overall, PET-CT in CUP was found to have a diagnostic accuracy of 78%, sensitivity of 80%, specificity of 74%, positive predictive value of 88.7% and negative predictive value of 59% (24). While there is substantial data to support the use of FDG-PET/CT in the detection of primary tumor sites, but one must keep in mind that this imaging modality is expensive and not always available in some regions. Furthermore, false positive results can lead to unnecessary secondary diagnostic procedures with associated risk of complications.

Recent advances in management of MPE and CUP

The use of immunocytochemistry (IHC) studies and biomarkers of MPE has proven useful in helping to evaluate the primary tumor histology in patients with CUP (25,26).

IHC of a CUP biopsy includes a three-step approach:

- (I) Diagnose the broad type of cancer (carcinoma, sarcoma, melanoma or lymphoma);
- (II) Detect the subtypes (adenocarcinoma, germ-cell tumor, hepatocellular, renal, thyroid, neuroendocrine, or squamous carcinoma);
- (III) Provide information about primary site of cancer (prostate, lung, breast, colon, pancreas or biliary, or ovarian cancer).

Pomjanski *et al.* evaluated the malignant effusions (118 pleural, 53, peritoneal, and 9 pericardial) of 180 CUP patients for the presence of 6 monoclonal antibodies: Cytokeratin (CK) 5/6, CK 7, CK 20, cancer antigen (CA) 125, and thyroid transcription factor (TTF)-1. An algorithmic approach was employed utilizing these 6 antibodies to identify the primary tumor site. This approach correctly identified 85% of the primary tumors (94 % ovaries and 88% lungs) (27).

The identification of specific biomarkers for malignancy, especially in lung cancer, is vital for not only improving the accuracy of diagnosis but also guiding therapy. Evaluating for markers like epidermal growth factor (EGFR), v-Raf murine sarcoma viral oncogene homolog B (BRAF), Kirsten rat sarcoma virus (KRAS), and for translocations in gene rearrangement anaplastic lymphoma kinase (ALK), rat osteosarcoma (ROS1) can predict tumor behavior and assess patient candidacy for gene targeted therapy (26). Also, the presence of one of these markers may help suggest that the MPE in the CUP is of lung origin (28). It has also been shown that pleural fluid oncogenic marker detection correlates well with the markers noted in tissue samples from the primary tumor in lung cancer (29). With the recent advancement of cancer therapy and the introduction of monoclonal antibodies including immune checkpoint inhibitors (ICIs), identification of these targetable oncogenic mutation has gained limelight in research. There have been few reported cases (*Table 1*) of disease control being achieved in patients with CUP treated with monoclonal antibodies that mainly targeted EGFR, HER2 and VEGF antigens (31-33). Similarly, Nivolumab and Pembrolizumab are two immune checkpoint inhibitors (ICI) that are approved by FDA targeting PD-1, while Atezolizumab, Durvalumab and Avelumab are three ICI targeting PD-L1.

Scarce data available on the use of ICI to treat patient with CUP. However, there are cases were reported in literature (*Table 1*) with varying degree of response (34-36). An evolving area is the use of agents such as VEGF inhibitors (Bevacizumab), to improve the pleural permeability of conventional chemotherapeutic agents (37). This could allow for higher bioavailability of the drugs at the site of tumor at potentially lower doses.

Another emerging science in the field of Oncology is liquid biopsy (38). It refers to the development of technology to identify circulating tumor cell free DNA (cfDNA) in the blood. The hypothesis of being able to detect these mutations in blood for patients with CUP is intriguing since these abnormalities will generate from both the metastatic and primary tumor site (39). In one study involving 442 patients with CUP, 80% of the patients had cfDNA alterations detected in the blood and of those 87% had distinct genetic profiles of which 99% had targetable mutations (34). Although interesting, there may not be enough evidence for liquid biopsy to routinely be utilized in patients with CUP (39).

The prognosis of patients with CUP (with MPE) remains poor despite the recent advancement in therapy. The mean survival of these patient (untreated) is estimated to be 4–6 months, with one-year survival rate of around 18% associated with significant symptoms, poor quality of life, and extensive utilization of medical resources (1,2,4). As the focus of therapy should be to alleviate symptoms and improve quality of life, indwelling pleural catheters (IPC) or palliative pleurodesis should be considered in the setting of recurrent symptomatic pleural effusions under controlled with optimal tumor therapy. It is well known that IPC utilization leads to decreased hospital stay, improved quality of life, and reduction of dyspnea while maintaining good safety profile with low complications in long term use (40). Other measure considered included decortication and pleuroperitoneal shunts (41). For patients with very short life expectancy, serial thoracentesis is a reasonable option for dyspnea relief (41).

Conclusions

In this paper, we provided an overview of MPE from CUP including diagnosis, prognosis and treatment options. About 11% of MPE are due to CUP. As with all cases of CUP, the first step should be complete an extensive medical evaluation with appropriate diagnostic testing. A thoracentesis is vital diagnostic step and is required to differentiate neoplastic from paraneoplastic effusion. Additional methods

Table 1 Current experience with advanced treatment strategies for CUP

Author	Pathology	Targetable mutation	Metastatic site	Treatment strategy	Outcomes
Whang <i>et al.</i>	Poorly differentiated adenocarcinoma	HER2, BRCA1	Bone, lymph nodes	Trastuzumab + chemotherapy then maintenance trastuzumab + lapatinib: first line	Partial response
Hainsworth <i>et al.</i>	Adenocarcinoma, signet ring	ALK rearrangement	Ovary, bone, lymph nodes	Bevacizumab + chemotherapy: second line	Partial response
Asakura <i>et al.</i>	Poorly differentiated adenocarcinoma	HER2	Multiple lymph nodes	Trastuzumab + chemotherapy	Complete response
Varadhachary <i>et al.</i>	Poorly differentiated adenocarcinoma	Not reported	Right testis	Bevacizumab + chemotherapy	Partial response
Sonnenblick <i>et al.</i>	Poorly differentiated carcinoma	Not reported	Multiple lymph nodes	Bevacizumab + chemotherapy: first line	Complete response
Shima <i>et al.</i>	Adenocarcinoma	HER2	Multiple lymph nodes	Trastuzumab + chemotherapy: neoadjuvant	Complete response
Kato <i>et al.</i>	Adenocarcinoma	MLH1 mutations and KRAS G12D on ctDNA	Liver and multiple lymph nodes	Nivolumab + trametinib: first line	Partial response
Røe <i>et al.</i>	Malignant epithelioid tumor	BRAF V600E	Skin and lung	Ipilimumab: fourth line	Complete response
Gröschel <i>et al.</i>	Pleomorphic tumor with sarcomatoid features	PDL-1	Diffuse muscular masses	Pembrolizumab: first line	Partial response

HER2, human epidermal growth factor receptor 2; BRCA, breast cancer gene 1; ALK, anaplastic lymphoma kinase; MLH1, MutL homolog 1; KRAS, K-ras or Ki-ras; BRAF, B-raf; PDL, programmed death-ligand 1. Adapted from (30), with copyright clearance from Cancer Treatment Reviews (Order number-4535370589134).

for tissue sampling should be considered if the initial pathology is non-revealing or if the tissue yield is poor. Immunohistochemical testing of fluid cytology and pleural biopsy samples can elude to the primary malignancy and guide therapy, as most of these cases are felt to be from lung cancer. With the advent of gene directed therapies and immune checkpoint inhibitors, there are new therapies being considered for these patients. Overall, MPEs from a CUP has a poor prognosis and symptom alleviating measures should be part of the management plan.

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Footnote

Conflicts of Interest: MR Bowling is a consultant for

Medtronic, Biodesix and Veracyte. The other authors have no conflicts of interest to declare.

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