

ORIGINAL ARTICLE

Retrospective analysis of unknown primary cancers with malignant pleural effusion at initial diagnosis

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Abstract

Background: Malignant pleural effusion (MPE) can occur during the progression of various cancers. However, factors, such as the incidence of MPE associated with different types of cancers and its potential for diagnosing previously undetected cancers, are unknown. Moreover, MPE may accompany potentially curable cancers or those with a favorable survival prognosis with adequate treatment. The present study determined the types of cancers accompanied by MPE at initial diagnosis and investigated appropriate related methods for diagnosing previously unknown cancers.

Methods: We retrospectively reviewed the medical records of 35 patients with MPE at initial cancer diagnosis between 2004 and 2012. We evaluated the patient characteristics, final diagnosis, and diagnostic processes.

Results: Of the 35 patients, 10 had lung cancer, seven ovarian or peritoneal cancer, four malignant pleural mesothelioma, one breast cancer, one lymphoma, one pancreatic cancer, and 11 had cancers of unknown origin. Diagnoses of the primary lesions were confirmed using the MPE cellblock method for seven of 11 patients (63.6%), by excisional biopsy or aspiration from other sites in four of nine patients, by exploratory laparotomy in two of three patients, and by peritoneal washing cytology in five patients.

Conclusion: Lung cancer and cancer of unknown origin are major causes of MPE at initial presentation. However, these groups also contain cancers that are curable and those with good long-term prognosis. The MPE cellblock method represents an accurate method for identifying cancer origin.

Introduction

Malignant pleural effusion (MPE) is a common complication in patients with advanced cancers, and occurs in 15% of cancer-related deaths.¹ MPE is thought to be caused by the hyperpermeability of microvascular tissue or invasion of cancer cells into lymphatic vessels. Massive MPE leads to coughing, chest pain, and dyspnea, with potentially serious effects on quality of life. The main cause of MPE is lung cancer (37.5%), followed by breast cancer (16.8%), lymphoma (11.5%), and other malignancies.² It is usually suspected following chest radiography or computed tomog-

raphy, and is diagnosed by evidence of malignant cells in pleural effusion samples from thoracentesis.

Current guidelines recommend repeating thoracentesis until a diagnosis can be made, even if samples are cytologically negative for possible MPE. However, the sensitivity of cytological diagnosis for MPE using thoracentesis is relatively poor, with an accuracy of only 62%, and the primary lesion of MPE is often difficult to identify histologically, even in cytologically positive samples.³ Moreover, half of the patients with MPE are asymptomatic and, therefore, do not undergo any procedures or treatments.⁴ In an era of molecular targeted agents and diverse cancer treatment managements, more

accurate diagnosis and/or identification of the cancer origin is required to allow patients to be treated adequately. Although MPE is generally considered to be indicative of a poor prognosis, prognosis and treatment vary according to the cancer's primary origin, and MPE also occurs with potentially curable cancers and in patients with the possibility of long-term survival following adequate treatment. However, the frequency of associations between MPE and different cancers, and the best diagnostic methods to determine the cancer's origin from MPE are currently unknown. In this study, we retrospectively evaluated the primary lesions responsible for MPE at initial diagnosis to determine if these lesions included potentially curable cancers or malignancies with good long-term prognosis, and to evaluate the diagnostic methods for determining cancer origin from MPE.

Patients and methods

Database

We retrospectively analyzed data of cancer patients with MPE who were definitively diagnosed at the Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan, from July 2004 to July 2012. International Classification of Diseases (9th edition) codes were used. The institutional review board approved this study.

Patients who had not been diagnosed with any disease, underwent thoracentesis of pleural effusion, and were pathologically diagnosed as having MPE, were eligible for the present study. The primary cancer lesion was identified based on data from medical charts. Patients who had been histologically diagnosed with lung, breast, or other cancers in the previous five years were excluded from this study because the primary origin was strongly indicated. We also reviewed patient characteristics including age, gender, cytological examination results of MPE, other metastatic sites, and the diagnostic processes used to clarify the primary lesions. The primary cancer lesion was initially identified using the MPE cellblock method (CBM) in selected patients. Patients with other metastatic lesions underwent biopsies at the physician's discretion.

Cellblock method

Pleural effusion specimens were fixed in 95% ethyl alcohol (34 mL), glacial acetic acid (2 mL), and formalin (4 mL) (AAF) and centrifuged at $2500 \times g$ for 10 minutes. The cell sediment was mixed with $3 \times$ the volume of AAF fixative and one or two drops of the mixture fluid, then centrifuged for 10 minutes at $2000 \times g$. The pellet was then resuspended in AAF fixative and centrifuged for another 10 minutes at $3000 \times g$. The centrifuge tube was left undisturbed for four to six hours, and the pellet was then removed, wrapped in filter paper, and

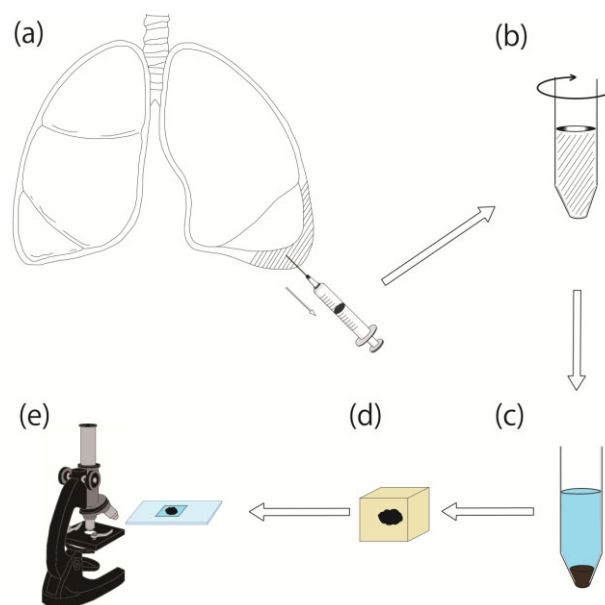


Figure 1 Cellblock method: (a) Pleural effusion is sampled using thoracentesis at the affected thorax site. (b), (c) The pleural effusion specimen is first stabilized using ethyl alcohol with glacial acetic acid and formalin (AAF) fixative and centrifuged several times with the pellet resuspended in AAF fixative. The centrifuged tube is then left undisturbed for four to six hours. (d) The cell pellet is carefully scraped out and processed in an automatic tissue processor for routine histopathology sections. The cellblock is also embedded in paraffin and cut into 4- μ m sections, (e) which a pathologist can examine with a microscope, using immunohistochemistry or specific staining if required.

processed in an automatic tissue processor for routine histopathology sectioning. Cellblocks were embedded in paraffin and cut into 4- μ m sections, which were compared with tissue sections. Sections were stained with diastase-periodic acid Schiff, mucicarmine or Alcian blue, as appropriate (Fig 1).

Results

Patient characteristics

Thirty-five patients were eligible for the present study (Table 1). Their median age was 67 years (range: 44–93 years), and there were 20 men (57%) and 15 women (43%). Cytological examination of pleural aspiration samples revealed that 27 patients (77%) had adenocarcinoma, two (6%) had mesothelial cells, one (3%) had squamous cell carcinoma, one (3%) had lymphoma, and four (11%) had other histological subtypes. Twelve (34%) patients had metastases to the lymph nodes, eight (23%) to the peritoneum, three (9%) to the liver, three (9%) to the bone, one (3%) to the pancreas, one (3%) had pericardial dissemination, and 13 (37%) only had pleural lesions.

Table 1 Patient characteristics

Variables	Number of patients (n = 35)	(%)
Age, median [range]	67 [44–93]	—
Gender		
Male	20	57
Female	15	43
Pathological diagnosis		
Adenocarcinoma	27	77
Mesothelium cell	2	6
Squamous cell carcinoma	1	3
Lymphoma	1	3
Other	4	11
Metastatic sites†		
Lymph node	12	34
Peritoneum	8	23
Liver	3	9
Bone	3	9
Pancreas	1	3
Pericardium	1	3
None	13	37

Pathological diagnosis is based on cytological examination of pleural effusion. †It includes overlapping metastatic sites.

Primary cancer lesions

Ten patients (28.6%) were diagnosed with lung cancer, seven (20%) with ovarian or peritoneal cancer, four (11.4%) with

Table 2 Primary origin results

Diagnosis	Number of patients (n = 35)	(%)
Lung	10	28.6
Ovarian cancer	7	20.0
MPM	4	11.4
Malignant lymphoma	1	2.9
Pancreatic cancer	1	2.9
Breast cancer	1	2.9
Cancer of unknown origin	11	31.4

Diagnosis after detailed pathological examination is shown. MPM, malignant pleural mesothelioma.

Table 3 Diagnostic methods and results

Methods	Positive	Negative	Positive rate	Diagnosis (n)
Cellblock (n = 11)	7	4	63.6%	MPM (3) Lung cancer (2) Malignant lymphoma (1) Breast cancer (1)
Biopsy or aspiration of other metastatic lesion (n = 9)	4	5	44.4%	Lung cancer (2) Pancreatic cancer (1) Peritoneal cancer (1)
Exploratory laparotomy (n = 3)	2	1	66.7%	Ovarian cancer (2)
Total (n = 23)	13	10	56.5%	

Cellblock is made from pleural effusion. Biopsy of other site is performed, such as liver and lymph node. MPM, malignant pleural mesothelioma.

malignant pleural mesothelioma (MPM), one each (3%) with lymphoma, breast, and pancreatic cancer, and 11 (31.4%) with cancer of unknown primary origin (CUP) (Table 2). Patients diagnosed with CUP included those with poor performance status who, therefore, received best supportive care alone. These patients, thus, underwent less invasive examinations for their primary tumors.

Diagnostic method

The primary cancer origin was identified using the CBM of MPE samples in seven of 11 (63.6%) eligible patients, including three MPM, two lung cancer, one lymphoma, and one breast cancer. Specimens from lymph nodes or other organs were obtained from nine patients and examination of these allowed identification of the primary sites in four patients (44.4%; two lung, one pancreatic, and one peritoneal cancer). Three female patients with peritoneal effusion underwent exploratory laparotomy because of suspected ovarian or peritoneal cancer; two were, subsequently, definitively diagnosed with ovarian cancer (Table 3).

Discussion

The results of this study identified lung cancer and CUP as the most common primary cancers associated with MPE (60.0%). Eleven patients (34.3%) were diagnosed with curative disease or tumors associated with potential long-term survival, such as MPM, lymphoma, and ovarian and peritoneal cancers. Cytological examination found adenocarcinoma to be the most common diagnosis (77%).

Among the available diagnostic methods, the CBM and biopsies of other lesions were used to identify primary lesions, with an accuracy of 63.6% for the CBM. The main metastatic sites were the lymph nodes and peritoneum, although a third of the cancer patients with MPE were found by radiological examination to have no metastatic sites.

The diagnostic accuracy of the CBM has been compared with that of tissue samples. The CBM demonstrated

estimated sensitivities and specificities of 87.3% and 100%, respectively, in lung cancer, and 73% and 100%, respectively, for axillary lymph nodes in breast cancer.^{5,6} Furthermore, the accuracy of cytological examination for primary tumor origin was 100% in Müllerian cancers.⁷ These reports suggest that the specificity of the CBM for making a pathological diagnosis is very high. However, the sensitivity in our report was lower than in these previous studies. This may be attributable to patient selection; we excluded patients with suspected primary lung and breast lesions, and the clinical diagnosis of the primary lesion was, therefore, difficult.

The presence of MPE generally predicts a poor prognosis for patients, with median survival times of eight months for lung cancer and 11 months for CUP.^{8,9} Chemotherapy with palliative intent is the main treatment modality in these patients, while patients with MPM, lymphoma, and ovarian and peritoneal cancers can undergo surgery or chemotherapy with curative intent, and are expected to have long-term survival.^{10,11} Pursuing an adequate diagnosis by identifying the primary lesion of MPE is, therefore, of critical importance. Invasive exploratory laparotomy is, thus, usually considered in women with MPE of unknown origin.

The CBM was found to be 16.8–27.2% more sensitive than the direct smear method for diagnosing malignancies associated with MPE.¹² Distinguishing between MPM and reactive mesothelial cells from adenocarcinoma is often difficult by cytological examination alone. Patients in the present study were initially diagnosed incorrectly with adenocarcinoma by cytological examination before eventually being diagnosed with MPM or reactive mesothelial cells. Several recent studies reported that HBME-1, calretinin, desmin, N-cadherin, cytokeratin 5/6, and D2-40 may help to distinguish between MPM and reactive mesothelial cells of adenocarcinoma.^{13–17} The CBM appears to support immunohistochemical staining for these markers.¹⁸ Moreover, several cancers that cause MPE are currently diagnosed using biomarkers and treated accordingly. It has been reported that 81.3% of cases of MPE from lung cancer harbored epidermal growth factor receptor mutations, whereas MPEs from breast cancer were reportedly 100% positive for human epidermal growth factor receptor-2 (HER-2) and 85.7% for hormone receptors.^{19,20} Moreover, MPE associated with gastric cancer was 100% HER2-positive.²¹ These results may not only affect primary lesion diagnosis, but may also influence treatment decisions regarding the use of molecular targeted agents, with the potential for long-term survival.

To the best of our knowledge, this is the first report detailing methods for the diagnosis of primary lesions in patients with MPE from CUP. Pleural effusion samples are easily obtained by thoracentesis, which is less invasive than excisional or endoscopic biopsy, making it an ideal sample for diagnosing primary cancer origin and obtaining biomarkers in patients with MPE. Our results indicate the suitability of

the CBM for achieving both these goals. However, further studies are needed to validate the role of the CBM. It remains unclear which tumor origins should be selected to obtain specimens from biopsy. The initial diagnosis in patients with malignant peritoneal effusion should be ovarian or peritoneal cancer, and these patients should, therefore, undergo exploratory laparotomy.

The key limitations of the present study were its retrospective nature, the small number of patients, and the fact that neither the CBM for MPE nor histological biopsies were performed in all patients. Furthermore, the patients did not all undergo the same diagnostic procedures, because the individual physicians decided these. Moreover, the diagnostic accordance between histological biopsy and the CBM was not confirmed. We were, therefore, unable to conclude which method was more useful for diagnosing the primary lesion.

Conclusion

In conclusion, although MPE may tend to originate from cancers with a poor prognosis, it can also be used to determine potentially curable malignancies in patients with expectations of long-term survival, and may, thus, help to guide the appropriate treatment.

Disclosure

No authors report any conflict of interest.

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