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PLEURAL DISEASE

Prognosis of Cancer with Synchronous or Metachronous Malignant Pleural Effusion

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Abstract
Purpose Malignant pleural effusions (MPE) may either coincide with or follow the diagnosis of a primary tumor. Whether this circumstance influences prognosis has not been well substantiated.
Methods Retrospective review of all consecutive patients who were cared for at a Spanish university hospital during an 11-year period and received a diagnosis of MPE.
Results Of 401 patients, the MPE was the first evidence of cancer in 265 (66%), and it followed a previously diagnosed neoplasm in 136 (34%). Lung cancer predominated in the former group (131, 50%), and breast cancer in the latter (55, 40%). MPE that were the presenting manifestation of hematological and ovarian tumors had a statistically significant survival advantage as compared to those which developed in patients from a previously known cancer (respective absolute differences of 41 and 20 months; $p < 0.005$).
Conclusions In hematological and ovarian malignancies, the synchronous or metachronous diagnosis of MPE may have prognostic implications.

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Introduction

Malignancy accounted for 27% of all pleural effusions (and 34.4% of exudates) in a series of 3077 consecutive patients who were subjected to a diagnostic thoracentesis [1]. Among 840 patients with malignant pleural effusions (MPE), lung cancer was the most common primary tumor (37%), followed by breast cancer (16%), unknown origin (10%), and hematological malignancies (10%) [1]. In another study, according to chest radiographs and computed tomography (CT) scans, as many as 16 and 26% of 556 lung cancer patients, respectively, had an MPE on initial presentation [2], while an additional 14% developed pleural effusions during the course of the disease (overall prevalence of 40%). With breast carcinoma, however, the expectation is a time lapse of months or years between the diagnosis of the tumor and the appearance of an MPE [3].

Whether MPE at the time of cancer presentation adversely affects survival rate, as compared to those patients with a previously known primary tumor which subsequently spreads to the pleura, has not been previously addressed. We sought to determine, in the largest series reported to date, the clinical characteristics and survival expectations of MPE patients based on time of occurrence with respect to the diagnosis of the primary tumor.

Patients and Methods

A retrospective review of all consecutive patients who were diagnosed with MPE at the Arnau de Vilanova University Hospital (Lleida, Spain) from January 2006 to January 2017 was conducted. Our 450-bed hospital is the only tertiary care facility in Lleida province, serving a population of approximately 450,000 people. The local ethics committee approved the study protocol (Reference No. CEIC-1780).

The following data were extracted from medical records: age, gender, date of diagnosis for both the MPE and primary tumor, presence of extra-pleural metastases, size and laterality of pleural effusions on chest radiographs, pleural fluid biochemistries, pleural cytohistological studies, palliative pleural procedures (i.e., therapeutic thoracenteses, indwelling pleural catheter, pleurodesis), Eastern Cooperative Oncology Group performance score (ECOG-PS) at the time of MPE diagnosis, oncologic treatments, and survival after the discovery of the MPE.

The diagnosis of MPE was based on the demonstration of malignant cells in pleural fluid or pleural biopsy specimens. Pleural fluid cytological examinations were composed of smears (Papanicolaou) and cell blocks (hematoxylin and eosin as well as immunocytochemical studies) and, for suspected hematological malignancies, Giemsa staining preparations and flow cytometry analyses were also performed.

Quantitative variables are expressed as medians (25th and 75th percentiles) and qualitative ones as numbers (percentages). The Mann–Whitney and Fisher exact tests were used to compare quantitative and qualitative data, respectively, between patients with MPE as a first presentation of cancer (group A) and those with a history of malignancy who secondarily developed an MPE during the course of the disease (group B). The time interval between the diagnosis of cancer and that of the MPE among different primary tumor types was compared using the Kruskall–Wallis test. Survival rates were calculated by the Kaplan–Meier estimation method, using the date of MPE discovery as the starting point, and the date of death or last follow-up as the end point. Survival differences were analyzed using the log-rank test. A multivariate analysis using a Cox regression model was performed to assess whether the metachronous discovery of MPE predicted survival, regardless of the ECOG-PS. All analyses were conducted with SPSS version 24.0 statistical software (Chicago, IL, USA).

Results

During the study period, a total of 644 patients were diagnosed with MPE. A pleural cytohistological confirmation was obtained in 401 (195 males and 206 females, with a median age of 70 (58–79) years), who represented the study population. Of these, group A was composed of 265 (66%) subjects and group B was 136 (34%). As illustrated in Table 1, the diagnosis of the MPE and the primary tumor was made simultaneously (group A) in most patients with lung cancer (84%), unknown primary (94%), and mesothelioma (92%). Conversely, 87% of breast cancer patients developed MPE with a median of 70 (29–135) months after the discovery of the original neoplasm.

The need for palliative pleural interventions was comparable in both groups A and B (57 vs 66%, $p = 0.108$). As anticipated, more patients from group B had previously received some kind of oncology therapy as compared to group A (Table 2), with the notable exception of chemotherapy for those having hematological (94 vs 74%, $p = 0.206$) or ovarian malignancies (88 vs 75%, $p = 0.646$). Also, group B subjects more often had extra-pleural metastases (77 vs 60%, $p < 0.001$) at the time of the MPE diagnosis, although this was not the case in ovarian (100 vs 96%, $p = 1$), gastrointestinal (84 vs 90%, $p = 0.589$), and hematological (50 vs 38%, $p = 0.522$) malignancies. No fluid biochemistries differed significantly between groups (data not shown).

The overall median survival of the study population was 4 (3.2–4.8) months, though patients with breast, hematological malignancies, and mesothelioma had a longer duration of survival (11, 9, and 9 months, respectively) (Table 3). Notably, the duration of survival was longer in group A patients with hematological (44 vs 3 months, $p = 0.004$) and ovarian (22 vs 2 months, $p = 0.001$) neoplasms, as compared to their group B counterpart. The prognostic significance of metachronous MPE from hematological and ovarian tumors on survival was confirmed in a Cox's regression analysis adjusting for the ECOG-PS (respective hazard ratios of 2.83 (95% CI 1.21–6.61) and 3.76 (95% CI 1.36–10.37); both p values 0.01).

Discussion

This study shows that two-thirds of MPE occur as the initial presentation of cancer. Of these, lung cancer accounts for half. Cancer was also first revealed by MPE in most patients with unknown primaries or mesotheliomas. In contrast, 40% of MPE which are secondarily detected in patients with a known history of cancer originate from

Table 1 Synchronous (group A) and metachronous (group B) malignant pleural effusions according to primary tumor types

Tumor type	Group A	Group B	Time lapse from primary tumor and MPE diagnoses, months (group B)
Lung	131 (84)[a]	25 (16)	9 (3.5–16.5)
Adenocarcinoma	100 (84)	19 (16)	9 (4–17)
Squamous cell carcinoma	13 (81)	3 (19)	12 (7–12)
Small cell carcinoma	10 (77)	3 (23)	3 (2–3)
Unspecified NSCLC	8 (100)	0 (0)	NA
Breast	8 (13)	55 (87)[a]	70 (29–135)[b]
Hematological[c]	24 (60)	16 (40)	28.5 (11.5–98.8)
Gastrointestinal[d]	20 (51)	19 (49)	21 (10–32)
Unknown origin	34 (94)[a]	2 (6)	7 (2–7)
Ovary	24 (75)	8 (25)	11 (5.5–51.5)
Mesothelioma	12 (92)[a]	1 (8)[f]	5
Miscellaneous[e]	12 (55)	10 (45)	34.5 (7.8–75.3)
Total	265 (66)	136 (34)	24.5 (10–74)

Data are presented as numbers (percentages) or medians (interquartile ranges), as appropriate

Synchronous MPE was defined as the simultaneous discovery of the pleural metastases and the primary tumor, while metachronous MPE referred to those cases in which the primary tumor had been diagnosed before the pleural metastases

MPE malignant pleural effusion, *NA* not applicable, *NSCLC* non-small cell lung cancer

[a]Significantly higher than the respective values in other tumor types by *Chi* square ($p < 0.001$)

[b]Significantly higher than the respective values in other tumor types by Kruskall–Wallis ($p < 0.001$)

[c]Includes 35 lymphomas, 3 lymphocytic leukemias, and 2 multiple myelomas

[d]Includes 12 pancreas, 10 stomach, 8 colon, 4 esophagus, 3 gallbladder or biliary tree, 1 liver, and 1 appendix

[e]Includes 6 kidney, 5 endometrium, 4 melanomas, 2 bladder, and 5 others

[f]This single case was a peritoneal mesothelioma which subsequently involved the pleural membranes

Table 2 Basal characteristics and clinical data of the study population

Characteristic	Group A ($n = 265$)	Group B ($n = 136$)	p
Age, years	73 (61–81)	64 (55–73)	<0.001
Male sex	142 (54)	52 (38)	0.004
ECOG-PS ≥2	125 (47)	60 (44)	0.59
Large effusions on chest radiographs (≥1/2 of the hemithorax)	170 (64)	96 (71)	0.163
Bilateral effusions on chest radiographs	42 (16)	19 (14)	0.641
Extra-pleural metastases at the time of MPE diagnosis	158 (60)	105 (77)	<0.001
Oncologic treatments			
Surgery	15 (6)	85 (63)	<0.001
Chemotherapy	141 (54)	127 (93)	<0.001
Radiotherapy	18 (7)	63 (46)	<0.001
Hormone therapy	5 (11)	33 (49)	<0.001
Palliative pleural procedures			
Therapeutic thoracentesis	19 (7)	11 (8)	0.842
Pleurodesis	93 (35)	46 (34)	0.825
Indwelling pleural catheters	57 (22)	42 (31)	0.051
Pleurodesis or indwelling pleural catheters	142 (54)	84 (61)	0.168
Any	151 (57)	90 (66)	0.108

Data are presented as numbers (percentages) or medians (25th–75th percentiles), as appropriate

ECOG-PS Eastern Cooperative Group performance score, *MPE* malignant pleural effusion

Table 3 Survival (months) of malignant pleural effusions

Tumor type	Group A	Group B	Overall survival (group A + group B)	p[a]
Lung	4 (2.7–5.3)	2 (0.8–3.2)	4 (2.8–5.2)	0.161
Adenocarcinoma	5 (3.2–6.8)	2 (0.6–3.4)	4 (2.2–5.8)	0.323
Squamous cell carcinoma	3 (0–6.5)	4 (0,7–5.3)	3 (0–6.5)	0.937
Small cell carcinoma	1 (0–2.6)	2 (0–5.2)	2 (0.7–3.3)	0.661
Unspecified NSCLC	2 (0–18.6)	–	2 (0–18.6)	NA
Breast	11 (0–26.4)	11 (3.5–18.5)	11 (4–18)	0.322
Hematological	44 (4.5–83.5)	3 (0.4–5.6)	9 (0–32)	0.004
Gastrointestinal	1 (0–2.1)	3 (1.4–4.6)	1 (0–2.3)	0.84
Unknown origin	1 (0.1–1.9)	4 (NA)	1 (0.03–2)	0.19
Ovary	22 (6.9–37.1)	2 (0–4.7)	6 (0–15.5)	0.001
Mesothelioma	9 (4.8–13.2)	1	9 (4.7–13.3)	0.029[b]
Miscellaneous	1.9 (0.4–3.4)	3 (0–6.7)	1 (0–3.8)	0.817
Total	4 (2.8–5.2)	5 (3.8–6.2)	4 (3.2–4.8)	0.89

Data are presented as medians (interquartile ranges)

NA not applicable, *NSCLC* non-small cell lung cancer

[a] p Values for the comparison between groups A and B

[b] This comparison was considered uninterpretable due to the existence of only one patient in the group B branch

breast tumors. In the few previous series addressing this issue, figures for MPE as the first indication of malignancy were reported to be much lower: 14% of 126 cases [4], 27.5% of 171 [5], and 41% of 209 [6]. This discrepancy correlates with the higher proportion of women with breast cancer that were included.

The interval between the discovery of the primary tumor and the MPE was longer in patients with breast cancer than in those with non-breast neoplasms (median 70 months, 25th–75th percentile 29–135 months vs median 15 months, 25th–75th percentile 6–32 months; $p < 0.001$); the shortest median intervals being observed in patients with lung cancer or unknown primaries (9 and 7 months, respectively), in agreement with an earlier small study [5].

Overall, 56% of MPE were subjected to a definitive pleural therapy to relieve dyspnea, either pleurodesis or the insertion of a tunneled pleural catheter, as described in a previous multicenter study (53.6% of 540 MPE patients) [7]. The likelihood of being treated by any of these procedures was unrelated to the discovery of the MPE, either at the same time or later than the primary tumor.

MPE carried a poor prognosis (median of 4 months), regardless of whether or not they represented the first evidence of malignancy. However, the survival time of MPE which were diagnosed concurrently with hematological and ovarian neoplasms greatly improved in comparison to that of patients in whom these primaries antedated the MPE detection (absolute difference of 41 and 20 months, respectively). The reason behind this is speculative, but the fact that lymphomas and ovarian cancer are very chemosensitive may justify a significant proportion of chemotherapy-refractory disease in relapsing non-responders to the primary therapy (group B in this study), which surely influences survival. The finding of a similar median life expectancy for breast cancer patients belonging to groups A and B, however, seems difficult to reconcile with this hypothesis and should be viewed with caution. The scarce number of patients in breast group A ($n = 8$) did not allow a meaningful comparison between the different cancer phenotypes (i.e., estrogen receptor, progestogen receptor, and *HER2* over expression status), some of which (e.g., triple-negative tumors) are particularly aggressive. Overall, figures concerning survival for the different etiologies of MPE in this study compare with those which have been previously reported [8].

This study is not only limited by its retrospective design, but also the relatively small number of patients with some specific primary tumor types, which, however, reflects current clinical epidemiology and practice. Moreover, the behavior of probable MPE, namely cytologically negative exudative effusions in cancer patients with no other potential explanation for the accumulation of pleural fluid, was not investigated. This subgroup of patients with "false-negative" pleural fluid cytology exams may comprise up to 40% of MPE [9]. Finally, the study was performed at a single center and, therefore, the results must be confirmed by others.

To conclude, in the majority of patients with lung cancer, unknown primaries, and mesotheliomas, MPE are diagnosed synchronically with the corresponding primary tumor. Just the opposite occurs in breast cancer patients, in whom MPE usually follows several years thereafter. MPE as the first presentation of hematological and ovarian neoplasms infer a survival advantage in comparison with those developed during the course of the disease. Even so, this study confirms the overall poor prognosis of MPE regardless of whether it is the initial presentation of cancer or is discovered during follow-up.

Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest with the current study.

Ethical Approval All studies performed in human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration.

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