Evaluation of Pleural Effusions: Malignant and Paramalignant

Plevral Effüzyonların Değerlendirilmesi: Malign ve Paramalign

Miktat Arif HABERAL[1], Ozlem SENGOREN DIKIS[2], Erkan AKAR[1]

[1]Health Sciences University, Bursa Yuksek Ihtisas Education and Research Hospital, Thoracic Surgery Clinic, Bursa, Turkey
[2]Health Sciences University, Bursa Yuksek Ihtisas Education and Research Hospital, Chest Diseases Clinic, Bursa, Turkey

Correspondence Address
Yazışma Adresi

Ozlem SENGOREN DIKIS
Health Sciences University, Bursa Yuksek Ihtisas Education and Research Hospital, Pulmonary Diseases Department, Bursa, Turkey
E-mail:
ozlemsengoren@hotmail.com

Received \ Geliş tarihi : 01.02.2019
Accepted \ Kabul tarihi : 07.03.2019
Online published : 06.09.2019
Elektronik yayın tarihi

Cite this article as:
Bu makaleye yapılacak atıf:
Haberal MA, Sengoren Dıkıs O, Akar E. Evaluation of pleural effusions: Malignant and paramalignant. Akd Med J 2020;2:203-8.

Miktat Arif HABERAL
ORCID ID: 0000-0002-1051-094X
Özlem ŞENGÖREN DİKİŞ
ORCID ID: 0000-0001-7005-3333
Erkan AKAR
ORCID ID: 0000-0002-9113-8237

DOI: 10.17954/amj.2019.1894

ABSTRACT

Objective: Malignant pleural effusions (MPE) are characterized by the presence of malignant cells in the pleural fluid. Paramalignant pleural effusions (PMPE) are caused by the accumulation of fluid due to secondary causes such as bronchial obstruction and lymphatic obstruction. PMPE does not contain malignant cells. We aimed to compare the results of patients with MPE and PMPE.

Material and Methods: 176 patients (MPE: 145 PMPE: 31) were analysed retrospectively. Patients were divided into 2 groups as MPE, and PMPE. The patients' age, sex, symptoms, vital signs, comorbid disease, disease location (the place where surgical procedures were performed was taken into account in patients with bilateral effusions), diagnostic procedures, surgical procedures, complications, length of stay, mortality and morbidity were examined. Results were analysed. P<0.05 was considered significant.

Results: Eighty-four of the patients with MPE had malignant mesothelioma (MM), while 64 of them had pleural metastasis. Thirty one of the patients had PMPE. Male gender, right localization and exudative feature were found to be significant for patients with MPE. On the other hand, pleural effusion having exudative feature was significant for patients with PMPE. MM, chondrosarcoma, lung and liver cancer (ca) were found to be more effective in the development of MPE. Mortality was higher in patients with MPE (n=4). Tube thoracostomy was found to be the primary method in the treatment of patients with MPE.

Conclusion: MPE and PMPE are caused by underlying malignant diseases. The mortality rate is higher in patients with pleural metastasis. Tube thoracostomy is the primary treatment method.

Key Words: Pleural effusion, Malign, Paramalignant, Surgery, Video-assisted thoracic surgery

ÖZ

Amaç: Malign plevral effüzyonlar (MPE) plevral sıvıda malign hücre görülmesi ile karakterizedir. Paramalign plevral effüzyonlar (PMPE) ise bronş tıkanması, lenfatiklerin obstrüksiyon gibi sekonder sebeplere bağlı sıvı birikimi ile oluşur. PMPE malign hücre içermez. Çalışmamızda MPE ve PMPE'lu hastaların sonuçlarını karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Yüz yetmiş altı hasta (MPE: 145 PMPE: 31) retrospektif olarak incelendi. Hastalar MPE ve PMPE olarak 2 gruba ayrıldı. Hastaların yaşı, cinsiyeti, semptomları, yaşamsal belirtileri, komorbid hastalığı, hastalığın yeri (iki taraflı efüzyonlu hastalarda cerrahi işlemlerin yapıldığı yer), tanı prosedürleri, cerrahi işlemler, komplikasyonlar, kalış süresi, mortalite ve morbidite incelendi. Sonuçlar analiz edildi. P<0.05 anlamlı kabul edildi.

Bulgular: MPE'li hastaların 84'ü malign mezotelyoma (MM), 64'ü plevral metastaz idi. Hastaların 31'i PMPE idi. Erkek cinsiyet, sağ lokalizasyon ve eksüdatif özellik MPE hastaları için anlamlı bulundu. Öte yandan, eksudatif özellik gösteren plevral efüzyon PMPE'li hastalar için anlamlıydı. MM, kondrosarkom, akciğer ve karaciğer kanseri (ka) MPE oluşumunda daha etkili bulunmuştur. MPE hastalarında mortalite daha yüksekti (n=4). MPE hastalarının tedavisinde tüp torakostomi primer tedavi yöntemi olarak bulundu.

Sonuç: MPE ve PMPE altta yatan malign patolojilerden kaynaklanmaktadır. Plevra metastazı olan hastalarda mortalite daha yüksektir. Tüp torakostomi başlıca tedavi yöntemidir.

Anahtar Sözcükler: Plevral effüzyon, Malign, Paramalign, Cerrahi, Video yardımlı toraks cerrahisi

INTRODUCTION

Malignancy-induced pleural effusions can be either malignant pleural effusions (MPE) or paramalignant pleural effusions (PMPE). The former is characterized by carcinoma (ca) cells in the pleural fluid or tissue samples. The latter, on the other hand, is caused by an ectopic ca focus elsewhere in the body, and there is no sign of pleural involvement or seeding of ca cells in the pleural fluid or tissue samples (1).

PMPE is a result of a variety of ca-related events, including tumor tissue invading mediastinal lymph nodes or obstructing the bronchi, pulmonary embolism, radiochemotherapy, superior vena cava syndrome, and reduced oncotic pressure (2).

Any malignant lesion in the human body has the capability of causing pleural metastases and pleural effusion. However, lung ca, breast ca, and lymphoma are the most common ca types metastasizing to the pleural space (3-5). Nevertheless, malignancies affecting the gynecologic, gastrointestinal and genitourinary systems rarely cause MPE. The exact origin cannot be detected in 12% of MPE cases (6).

In addition, pleural effusions are divided into 2 as transudative and exudative according to their biochemical properties. MPEs have exudative properties (7).

MPE most notably causes respiratory difficulty of varying levels, which depends on the amount of effusion and pleura-pulmonary interaction. Chest pain is also an important symptom, and is caused by the parietal pleural, costal and chest wall involvement. Although fever is seldom present, signs and symptoms of malignancy, including weight loss, malaise, anorexia, nausea, and vomiting can exist. Additionally, ca-induced cachexia and lymphadenopathy may occur (8,9).

The diagnosis can be made with the anamnesis, chest radiography, ultrasonography (USG) and computed tomography (CT) (10). In general, magnetic resonance imaging (MRI) and 18-fluorodeoxyglucose positron emission tomography (FDG-PET) have no use in the diagnosis of MPE. However, they may provide important information regarding whether malignant pleural mesothelioma exists (11).

The main treatment methods of pleural effusions are observation, thoracentesis, chest tube drainage, video-assisted thoracoscopic surgery (VATS) and thoracotomy (12).

In this study, our aim was to compare the results of the patients with malignant or paramalignant pleural effusions treated with surgery in accordance with the related literature.

METHODS

The files of 176 patients who were hospitalized with a diagnosis of pleural effusion and treated surgically between 2006 and 2016 were analysed retrospectively. The patients that did not undergo surgery were not included.

The patients were divided into 2 groups as MPE and PMPE. The presence of malignant cells being positive for patients with MPE and being negative for patients with PMPE was used as a criterion. In addition, patients were classified as those that underwent tube thoracostomy, those that underwent VATS, and those that underwent thoracotomy. The procedure effective in grouping and producing results was taken into consideration. Tube thoracostomies performed before VATS or thoracotomy were excluded.

The patients' age, sex, symptoms, vital signs, comorbid disease, disease location (the place where surgical procedures were performed was considered in patients with bilateral effusions), diagnostic procedures, surgical procedures, complications, length of stay, mortality and morbidity were examined. The significance of gender, localization, type of concomitant diseases, and treatment methods in patients with MPE and PMPE were evaluated.

Ethics committee approval was received for this study from the ethics committee with decision number 2018-2/12/ KAEK Uludag University Faculty of Medicine Ethics Committee.

Statistical Analysis

Quantitative study data were presented as percentages, and qualitative data were expressed as median (25^{th} and 75^{th} percentiles). The Kolmogorov-Smirnov as well as Shapiro-Wilk tests were used to test the normality of distribution of the quantitative data. The Mann-Whitney U test was used for determining the relationship between 2 groups. The non-parametric binominal test was used for comparison of two group rates. A p value less than <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 21, IBM, Chigago, IL, USA).

RESULTS

Between January 2006 and December 2016, a total of 411 patients with pleural effusion who had undergone surgical intervention were found. 145 patients (82%) were MPE, whereas 31 (18%) were PMPE. 81 of the patients with malignant pleural effusion (56%) were malignant mesothelioma (epithelial types: 51, sarcomatoid types: 12, mixed: 18), while 64 (44%) had pleural metastasis.

In patients with MPE (n=145), the mean age was 54.13 ± 4.71. 99 (68%) were male and 46 (32%) were female. In 92 patients (63%), effusion was on the right, while in 53 patients (37%), it was on the left. One hundred and

thirty-six of the effusions were exudative (94%), whereas 9 (6%) were transudative. Male gender (p=0.0001,<0.05) and right localization (p=0.0076,<0.05) were found to be significant in patients with MPE (Table I).

The mean age of the patients with PMPE (n=31) was 54.53 ± 5.62. 20 (65%) were male and 11 (35%) were female. Effusion was on the right in 19 patients (61%), while it was on the left in 12 patients (39%). All of the effusion was exudative. In patients with PMPE, male gender (p=0.0715,>0.05) and localization (p=0.5429,>0.05) were not found to be significant in patients with PMPE (Table I).

Comorbid malignancies in patients with MPE were malignant mesothelioma (n=81, 100%), lung ca (n=25, 89.29%), breast ca (n=15, 53.57%), liver ca (n=8, 80%), chondrosarcoma (n=5, 100%), osteosarcoma (n=3, 100%), larynx ca (n=2, 40%), pancreas ca (n=2, 33.33%), adrenal ca (n=2, 40%), and colon ca (n=2, 100%) (Table II).

Comorbid malignancies in PMPE were breast ca (n=13, 46.43%), pancreatic ca (n=4, 66.67%), adrenal ca (n=3, 60%), lung ca (n=3, 10.71%), larynx ca (n=3, 60%), and liver ca (n=2, 20%) (Table II).

The most common comorbid malignancies in patients with MPE were malignant mesothelioma, lung ca, breast ca and liver ca, whereas the most commonly encountered comorbid malignancies in patients with PMPE were breast ca and pancreatic ca. Moreover, mesothelioma, lung ca and chondrosarcoma were found to be significantly effective in MPE development (respectively, P=0.001-0.0065-0.0439,<0.05) (Table II).

The most common symptoms of the patients were shortness of breath, chest pain and cough. Other symptoms were fatigue, fever, nausea, vomiting and palpitation. While the first diagnostic method used in patients was chest radiography, other methods were CT and USG.

In the treatment of patients, a total of 101 (57%) underwent tube thoracostomy under local anesthesia; under general anesthesia, 17 (10%) underwent thoracotomy and 58 (33%) underwent VATS. Eighty-one (56%) of the patients with MPE underwent tube thoracostomy, 17 (12%) underwent thoracotomy and 47 (32%) underwent VATS. On the other hand, 20 (65%) of the patients with PMPE underwent tube thoracostomy, and 11 (35%) had VATS. In the treatment of patients with MPE, tube thoracostomy (under local anesthesia) was found to be much more effective than thoracotomy or VATS (under general anesthesia) (P=0.001,<0.05) (Table III).

Thoracotomy indications in patients with MPE were expansion defect in 5 (29%) patients and empyema in 12 (71%) patients. VATS indications in patients with MPE were expansion defect in 7 (15%) patients and loculated fluid collection in 40 (85%) patients. It was seen that enucleation of empyema and decortication were applied through thoracotomy, and drainage of loculated collections, partial

Table I: Distribution of patients with pleural effusion.

Effusion	Male	Female	P*	Right	Left	P*
MPE	99	46	**0.0001**	92	53	**0.0076**
PMPE	20	11	0.0715	19	12	0.5429

PMPE: Paramalignant pleural Effusion, **MPE:** Malignant pleural effusion, **P*:** Non-parametric binominal test.

Table II: Distribution of malignant and paramalignant pleural effusion.

Concomitant malignancy	Total	PMPE n (%)	MPE n (%)	P*
Malignant mesothelioma	84	-	84 (100)	**0.001**
Lung cancer	28	3 (10.71)	25 (89.29)	**0.0065**
Breast cancer	28	13 (46.43)	15 (53.57)	0.7385
Liver cancer	10	2 (20)	8 (80)	0.2815
Chondrosarcoma	5	-	5 (100)	**0.0439**
Osteosarcoma	3	-	3 (100)	0.1035
Laryngeal cancer	5	3 (60)	2 (40)	1
Pancreatic cancer	6	4 (66.67)	2 (33.33)	0.2416
Adrenal cancer	5	3 (60)	2 (40)	1
Colon cancer	2	-	2 (100)	0.1025

PMPE: Paramalignant Pleural effusion, **MPE:** Malignant Pleural Effusion, **P*:** Non-parametric Binominal test, **n:** Number.

Table III: Treatments of patients with malignant and paramalignant pleural effusion.

Effusion	Local anesth.	General anesth.**	P*
MPE	81	64	**<0.001**
PMPE	20	11	0.0879

PMPE: Paramalignant Pleural Effusion, **MPE:** Malignant Pleural Effusion, **P*:** Non-parametric Binominal test, **Anesth:** Anesthesia General anesth.**: Thoracotomy (**MPE:** 17, **PMPE:** 0) or VATS (**MPE:** 47, **PMEP:** 11)

decortication and abrasion were applied by VATS. VATS indications for patients with PMPE were the presence of loculated collections in 3 (27%) patients and for both diagnosis and treatment in 8 (73%) patients.

The most common problems of patients were expansion defects, prolonged air leak and atelectasis. The mortality rate of our study was 2.27% (n=4). Two patients with MPE (50%) died due to lung ca, 1 (25%) died due to larynx ca and 1 (25%) died due to breast ca. The average length of stay for the patients was 7±4 days.

DISCUSSION

The pleural space generally contains a trace amount of fluid (about 0.3 mL/kg), the function of which is to create space for lungs to expand and deflate, causing negligible friction during normal respiration (13). The capillary vessels found in the parietal pleura create the pleural fluid, which is filtrated into the pleural cavity and ultimately absorbed by lymphatics of the pleura. When the rate of formation overwhelms the rate of reabsorbtion, pleural fluid begins to accumulate in the pleural space; there is usually impairment in both processes in most pleural effusion cases (13).

The differential diagnosis of pleural effusions starts with the distinction of its character, namely transudate or exudate (14). The former is a result of increased hydrostatic pressure (e.g., heart failure), reduced oncotic forces (e.g., hypoproteinemia), augmented negative intrapleural pressure (e.g., atelectasis), or intradiaphragmatic displacement of ascites (e.g., hepatic hydrothorax). Exudate fluids originate from proliferative (e.g., malignancy) or inflammatory (e.g., parapneumonic effusions) events that result in capillary permeability increase and/or lymphatic drainage reduction (14). In our study, exudates were dominant in patients with both MPE and PMPE.

Lung ca, malignant mesothelioma, and breast ca are reportedly the most common causes of malignant pleural effusions. The most common causes for females were breast, gynecologic, and lung ca. On the other hand, for males, the most common causes were lung, lymphoma, and gastrointestinal ca (15). The most common cause of MPE for our patients was malignant mesothelioma, and the most common reason of PMPE was breast ca.

Pleural effusion develops only in 60% of patients with pleural metastasis. It has been reported that the reasons why malignant pleural effusions develop are tumor embolisms to visceral pleura, direct invasion from cancerous tissue, hematogenous metastasis to the parietal pleura, lymphatic blockage due to mediastinal lymph node invasion. In such cases, treatment is planned according to the etiology, prognosis and condition of the patient (3,4,16). In our study, the pleural metastasis rate was 44%. Furthermore, lung ca and chondrosarcoma were found to be significantly effective in MPE development.

Malignant mesothelioma is a common primary pleural tumor seen especially in males in the 5th and 7th decades. It is divided into 3 as epithelial, sarcomatoid and mixed. The most common type is epithelial, while the least common one is sarcomatoid. It often causes one-sided pleural effusion and thickening. Diagnosis is made by biopsy of the pleura. In treatment, surgery, radiotherapy and chemotherapy may be used separately or in combination (17,18). In our study, there was pleural effusion in all patients with malignant mesothelioma, and malignant mesothelioma was found to be significantly effective in MPE development.

Past and current history of the clinical status as well as physical examination may greatly aid in determining the likely causes of pleural effusion or may indicate further indications to be done (19). Although small effusions may cause no symptoms at all, massive effusions may invariably lead to development of dyspnea or trepopnea although chest pain and dry cough are absent. Whereas dyspnea and the amount of effusion are generally in close correlation, it is not a rule. This is because small-to-moderate sized pleural effusions may lead to severe dyspnea among patients with lung diseases (COPD, carcinomatous lymphangitis, pulmonary embolism). Trepopnea denotes a type of positional dyspnea where dyspnea is relieved when the patient is lying on the same side with the pleural effusion. Pleural invasion may cause pain that may be sharp (e.g., pulmonary embolism, pneumonia) that is generally exacerbated during deep respiration or coughing or may be described as dull in character (e.g., malignancy) (20). Sometimes pleuritic chest pain radiates to the abdomen or ipsilateral shoulder, the latter occurring when the central diaphragmatic pleura is inflamed. Our patients most commonly complained of dyspnea, chest pain, and coughing.

In the diagnosis, chest X-ray is the first imaging method for the evaluation of the pleura. USG is superior in determining the location of the liquid. CT is usually used in displaying the parenchyma with pleural effusion, and in the evaluation of a nodular mass or structure (10).

MRI is of limited use in pleural disorders. MRI can visualize blood and the timing of any bleeding and thus delineate a hemithorax. MRI has the sole superiority over CT of telling if a pleural malignancy has also involved the thoracic wall and diaphragm (21).

FDG-PET with metabolic imaging is of unclear significance for pleural effusion diagnosis and characterization. Employing a visual or semi-quantitative analysis, it has a general sensitivity of 90% and a specificity of 75-80% for differentiation of malignant from benign pleural effusions (22, 23).

In the treatment of pleural effusion, thoracentesis, tube thoracostomy, the removal of adhesions by thoracoscopy or thoracotomy, decortication and open drainage methods are used (12). In patients with MPE, it was found that surgical interventions with local anesthesia were more significant than surgeries with general anesthesia.

Malignant pleural effusions have a high mortality, poor prognosis and a mean survival of 4-6 months (3, 16). Kookoolis et al. demonstrated that 15% of patients with a pleural effusion were dead within 30 days of admission (24). This increased to nearly 1 in 3 patients with a pleural effusion within 1 year of admission (31% of patients who did not undergo thoracenteses and 36% of those who did). For perspective, a recent analysis of more than 28 million hospital admissions demonstrated a 3.1% mortality for adult patients (25). The rate of mortality in our study was 2.27% (n=4). All of the patients were MPE patients with pleural metastasis. This result was consistent with the literature.

CONCLUSION

Pleural effusion is a group of disease that may occur due to many reasons, and can be recognized, and planned and managed according to the underlying disease. The data obtained from the effusion may vary according to the region where the underlying disease exists. Although tube thoracostomy is the primary treatment method, diagnostic and therapeutic thoracotomy and VATS may be preferable.

REFERENCES

1. Ozdulger A, Ulubas B. Plevral efuzyonlar ve plevra tuberkulozu. In: Yuksel M, Balcı AE, eds. Göğüs cerrahisi, 2th ed. Istanbul: Nobel Tıp Kitabevi, 2015: 529-39.
2. Bielsa S, Martin-Juan J, M. Porcel J, Rodriguez-Panadero F. Diagnostic and prognostic implications of pleural adhesions in malignant effusions. J Thorac Oncol 2008; 3:1251-6.
3. Sahn S. The value of pleural fluid analysis. Am J Med Sci 2008; 335:7-15.
4. Light RW, Hamm H. Malignant pleural effusion: Would the real cause please stand up? Eur Respir J 1997; 10:1701-2.
5. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: An analysis of 96 patients. Am J Med 1997; 63:695-702.
6. Detterbeck FC, Jones DR, Morris DE. Palliative treatment of lung cancer. In: Detterbeck FC, Rivera MP, Socinski MA, Rosenman JG, eds. Diagnosis and treatment of lung cancer. Philadelphia: WB Saunders Company, 2001: 428-33.
7. Medford A, Maskell N. Pleural effusions. Postgrad Med J 2005; 81:702-10.
8. American Thoracic Society. Management of malignant pleural effusions. Am J Respir Crit Care Med 2000; 162: 1987-2001.
9. Light RW. Clinical practice. Pleural effusion. N Engl J Med 2002; 346:1971-7.
10. Soysal O. Plevral efuzyonlar. In: Okten I, Gungor A, eds. Göğüs cerrahisi. Ankara: Sim Matbaacılık Ltd. Şti, 2003: 791-815.
11. Antony VB, Loddenkemper R, Astoul P, Boutin C, Goldstraw P, Hott J, Rodriguez Panadero F, Sahn SA. ERS/ATS Statement: Management of malignant pleural effusions. Eur Respir J 2001; 18:402-19.
12. Molnar TF. Current surgical treatment of thoracic empyema in adults. Eur J Cardiothorac Surg 2007; 32: 422-30.
13. Noppen M. Composition of normal pleural fluid. Int Pleural Newsl 2006; 4:13.
14. Light RW. Pleural effusions. Med Clin North Am. 2011; 95:1055-70.
15. Soysal O, Ziyade S. Benign plevra sıvıları. In: Okten I, Kavukcu HS, eds. Göğüs cerrahisi. Istanbul: Istanbul Tıp Kitabevi, 2013: 1585-601.
16. Sahn SA. Pleural effusion of extravascular origin. Clin Chest Med 2006; 27:285-308.

17. Harber P, Gee JBL. Clinicians' approach to mesothelioma. In: Pass HI, Vogelzang N, Carbone M, eds. Malignant mesothelioma. New York: Springer, 2005: 266-364.
18. Baldini EH. Radiation therapy options for malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 2009; 21:159-63.
19. Porcel JM, Light RW. Diagnostic approach to pleural effusion in adults. Am Fam Physician 2006; 73:1211-20.
20. Brims FJH, Davies HE, Gary Lee YC. Respiratory chest pain: Diagnosis and treatment. Med Clin North Am 2010; 94:217-32.
21. Helm EJ, Matin TN, Gleeson FV. Imaging of the pleura. J Magn Reson Imaging 2010; 32:1275-86.
22. Duysinx B, Nguyen D, Louis R, Cataldo D, Belhocine T, Bartschet P, Bury T. Evaluation of pleural disease with 18-fluorodeoxyglucose positron emission tomography imaging. Chest 2004; 125:489-93.
23. Duyxinx BC, Larock MP, Nguyen D, Corhay JL, Bury T, Hustinx R, Louis R. 18-FDG PET imaging in assessing exudative pleural effusions. Nucl Med Commun 2006; 27:971-6.
24. Kookoolis AS, Puchalski JT, Murphy TE, Araujo KL, Pisani MA. Mortality of hospitalized patients with pleural effusions. J Pulm Respir Med 2014; 4(3):184.
25. Steiner CA, Friedman B. Hospital utilization, costs, and mortality for adults with multiple chronic conditions, Nationwide Inpatient Sample, 2009. Prev Chronic Dis 2013; 10:E62.