Diagnostic procedure in patients with neoplasm and malignant pleural effusion – our experience

Diagnostyka nowotworu i nowotworowego wysięku opłucnowego – doświadczenia własne

Grzegorz Kacprzak[1], Vladimir Bobek[1,2], Konrad Pawełczyk[1], Jerzy Kolodziej[1]

[1]Wroclaw Thoracic Surgery Centre, Department of Thoracic Surgery, Lower Silesian Centre of Lung Diseases, Medical University Wroclaw, Poland
[2]Department of Tumor Biology, Third Faculty of Medicine, Charles University Prague, Czech Republic

Kardiochirurgia i Torakochirurgia Polska 2012; 1: 58–62

Abstract

Introduction: Malignant pleural effusion (MPE) is a serious diagnostic problem. The proper diagnosis of the cause of the effusion allows the appropriate treatment to be applied.
The aim of this study was to assess the usefulness of diagnostic procedures in patients with MPE.
Material and methods: Between January 1996 and June 2008, 237 patients (ages 23-84) were diagnosed with and treated for MPE in the Department of Thoracic Surgery. They belonged to the following groups: Group I: 121 (51.1%) patients with a previously diagnosed neoplasm, when the MPE occurred in the course of disease; 116 (48.9%) patients required invasive diagnostic methods, because of the lack of a clearly established cause of pleural effusion. These patients underwent either thoracoscopy (videothoracoscopy) (group II, n = 108) or diagnostic thoracotomy (group III, n = 8).
Results: There were 65 patients with lung cancer, 26 with breast cancer, 6 with ovarian cancer, 6 with lymphoma or Hodgkin's disease, 1 with mesothelioma pleurae, and 17 with other malignancies in group I. Neoplastic cells in pleural effusion were diagnosed in 66 (54.5%) patients. From among 108 patients (group II) who underwent thoracoscopy (videothoracoscopy), malignancies were diagnosed in 107 (99.1%) of them. In 1 patient the malignancy was diagnosed in a later period. In 5 patients with diagnosed adenocarcinoma the primary focus was not established. In all patients who underwent diagnostic thoracotomy (group III) malignancy was established. There were 2 patients with lung cancer, 4 with mesothelioma pleurae, 1 with metastases of melanoma, and 1 with an unknown primary tumor.
Conclusions: Examination of the neoplastic cells in pleural effusion is a valuable element in diagnosis of MPE. Thoraco-

Streszczenie

Wstęp: Nowotworowy wysięk w opłucnej (NWO) stanowi poważny problem diagnostyczny. Rozpoznanie przyczyny wysięku umożliwia zastosowanie odpowiedniego leczenia.
Cel pracy: Celem pracy było określenie przydatności stosowanych badań i metod diagnostycznych u chorych z NWO.
Materiał i metody: Od stycznia 1996 r. do czerwca 2008 r. we Wrocławskim Ośrodku Torakochirurgii diagnozowano i leczono z powodu NWO 237 pacjentów w wieku 23–84 lat.
W badanej grupie znajdowali się chorzy z wcześniej rozpoznaną chorobą nowotworową, którzy byli leczeni operacyjnie lub systemowo i u których w późniejszym okresie pojawił się płyn w opłucnej, oraz pacjenci, u których płyn był pierwszym objawem choroby. Grupę I – liczącą 121 osób (51,1%) – stanowili pacjenci, u których rozpoznano wcześniej proces nowotworowy. Pozostałych 116 (48,9%) pacjentów wymagało pogłębienia diagnostyki inwazyjnej z powodu nieustalonej jednoznacznie przyczyny wysięku w jamie opłucnej. Tych pacjentów poddano torakoskopii (wideotorakoskopii) (grupa II; n = 108) lub torakotomii diagnostycznej (grupa III; n = 8).
Wyniki: W grupie I znalazło się 65 pacjentów z rakiem płuca, 26 z rakiem piersi, 6 z rakiem jajnika, 6 z chłoniakiem lub ziarnicą, 1 z międzybłoniakiem, 17 z innymi nowotworami. Potwierdzenie komórek nowotworu złośliwego w płynie opłucnowym w całej grupie uzyskano u 66 (54,5%) pacjentów. Na 108 wykonanych torakoskopii (wideotorakoskopii) (grupa II) uzyskano rozpoznanie procesu nowotworowego u 107 (99,1%) chorych. U jednego chorego poddanego torakoskopii potwierdzono proces nowotworowy w okresie późniejszym. U 5 pacjentów z rozpoznanym rakiem gruczołowym nie ustalono ogniska pierwotnego. U wszystkich 8 chorych (grupa III) poddanych torakotomii dokonano rozpoznania lub uzyskano potwierdzenie procesu no-

Address for correspondence: dr n. med. Grzegorz Kacprzak, ul. Ożynowa 39, 53-009 Wrocław, Poland, tel. +48 608 29 57 70, Email: grzegorz-kacprzak@interia.pl

scopy (videothoracoscopy) is the essential invasive diagnostic procedure in the case of suspicion of neoplastic disease with malignant pleural effusion.
Key words: malignant pleural effusion, diagnostic procedures, thoracentesis, thoracoscopy.

wotworowego złośliwego. U 2 chorych rozpoznano nowotwór płuca, u 4 międzybłoniaka opłucnej, u jednego potwierdzono przerzuty czerniaka do opłucnej, u jednego nie udało się ustalić miejsca pierwotnej choroby nowotworowej.
Wnioski: Badanie płynu opłucnowego pod kątem obecności komórek nowotworowych jest cennym elementem w diagnostyce NWO. Torakoskopia i wideotorakoskopia są podstawowymi inwazyjnymi metodami diagnostycznymi w przypadku podejrzenia procesu nowotworowego z wysiękiem do jamy opłucnej.
Słowa kluczowe: nowotworowy wysięk opłucnowy, metody diagnostyczne, punkcja, torakoskopia.

Introduction

Pleural effusion occurs in the course of many diseases, often in the course of malignancy. It may be the first manifestation of a neoplasm or its complication at a later stage. Malignant pleural effusion (MPE) is a serious diagnostic problem. The diagnosis of the cause of pleural effusion allows one to apply the proper anti-neoplastic treatment (chemotherapy) or palliative procedure. Lung cancer, breast cancer and lymphoma account for approximately 70% of all MPE. In 7% of patients, the primary focus is unknown [1-6]. The diagnosis of accumulation of fluid in the pleural cavity is an indication for thoracentesis. An examination of the pleural fluid is necessary to establish the proper diagnosis, as well as the proper treatment. The goal of the thoracentesis is the removal of fluid to reduce the constriction symptoms, especially dyspnea [1, 2]. Fluid which is taken from the pleural cavity is examined to establish the character of the fluid (if it is exudative or transudative fluid). Cytological and bacteriological examination is also performed [1, 2, 5-13]. Tumor of the pleura and MPE is the indication for transthoracic biopsy of pleura. The value of the blind transthoracic biopsy is limited because of the focal character of lesions. But some scientific investigations demonstrate that 7-12% of patients with MPE and a negative cytological pleural examination of the fluid may be diagnosed using this method [1, 2, 7, 8]. If the diagnosis is not established using non-invasive methods, the investigation should be complemented with a morphological examination of the lesion tissue. Thoracoscopy or videothoracoscopy should be performed in such situations [1, 7, 8, 14-21]. The final diagnostic procedure to determine the cause of pleural fluid is thoracotomy. Thoracotomy is performed when thoracoscopy or videothoracoscopy is unfeasible. Videothoracoscopy or diagnostic thoracotomy is performed in patients with oncological history, in whom we suspect the occurrence of another neoplasm, but the diagnosis was not established using non-invasive methods.

Material and methods

Between January 1996 and June 2008, 237 patients (aged 23-84) were diagnosed with and treated for MPE in Wroclaw Thoracic Surgery Centre. There were 113 (47.7%) women and 124 (52.3%) men. In this group, there were patients with diagnosed pleural fluid accumulation with previously diagnosed neoplasm who were treated surgically or conservatively (chemotherapy) in the past. Furthermore, there were patients in whom the pleural effusion was the first manifestation of the neoplasm. Examination of the pleural fluid was performed in all patients. Biochemical examination was performed to distinguish between exudative and transudative fluid. Cytological examination was performed as well. Sometimes the diagnosis of neoplasm was achieved using several different methods.

Patients were divided into three groups. Group I with 121 patients (51.1%) consisted of patients with an earlier diagnosed neoplastic disease, and a later diagnosed malignant pleural effusion which was connected with neoplasm treated before. The rest of the patients (116; 48.9%) required a broadened diagnosis due to either unknown causes of pleural effusion; finding neoplastic cells in pleural effusion without establishing the kind of neoplasm or place of primary tumor; or a suspicion of a new neoplasm in patients treated because of another neoplasm in the past. These patients underwent either thoracoscopy (videothoracoscopy) (group II; n = 108) or diagnostic thoracotomy (group III; n = 8).

Results

There were 65 patients with lung cancer, 26 with breast cancer, 6 with ovarian cancer, 6 with lymphoma or Hodgkin's disease, 1 with mesothelioma pleurae, and 17 with another malignancy (melanoma, rectal cancer, tonsil cancer, synovial sarcoma glutei, bladder cancer, uterus cancer, paranasal sinus cancer, gastric cancer, renal cell cancer, gall bladder cancer, colorectal cancer, testis cancer) in group I. Neoplastic cells in pleural effusion were diagnosed in 66 (54.5%) patients. Diagnosis of neoplasm with pleural effusion or resumption of neoplasm with pleural effusion in the remaining patients was established during an examination of a sample of the pleura, cytological or histological examination of samples taken during bronchoscopy, examination of samples from other organs or lymph nodes or clinical diagnosis of MPE in the course of neoplasm (tab. I).

From 108 patients (group II) who underwent thoracoscopy (videothoracoscopy) malignancies were diagnosed in 107 (99.1%) patients. In 1 patient the malignancy was not

established during thoracoscopy. In the later period diagnosis of lung cancer (adenocarcinoma) was established from the samples taken during bronchoscopy. In 5 patients with diagnosed adenocarcinoma the primary focus was not established. Primary neoplasm in this group was established in 102 (94.4%) patients (tab. II).

In all the patients who underwent diagnostic thoracotomy (group III) malignancy was established. There were 2 patients with lung cancer, 4 with mesothelioma pleurae, 1 with metastases of melanoma, and 1 with unknown primary tumor. Primary neoplasm in this group was established in 7 (87.5%) patients (tab. III).

Tab. I. Results of pleural fluid investigation and results of cytological and histological examinations from material taken during diagnostic procedures and operation (group I)

	Pleural effusion		Diagnostic procedure and operation			
Group I (*n* = 121)	Positive cytological result	Positive result of pleural biopsy	Positive cytological result from sputum, bronchial lavage or brush bronchial biopsy	Positive histological result from bronchial samples	Positive histological result from postoperative organs	Positive histological result from samples taken from other organs and peripheral lymph nodes
lung cancer (*n* = 65)	41 (63.1%)	2 (3.1%)	48 (73.8%)	24 (36.9%)	9 (13.8%)	2 (3.1%)
breast cancer (*n* = 26)	12 (46.2%)	0 (0%)	0 (0%)	0 (0%)	23 (88.5%)	3 (11.5%)
ovarian cancer (*n* = 6)	4 (66.7%)	0 (0%)	0 (0%)	0 (0%)	6 (100%)	0 (0%)
lymphoma/Hodgkin's disease (*n* = 6)	1 (16.7%)	0 (0%)	0 (0%)	0 (0%)	4 (66.7%)	2 (33.3%)
mesothelioma pleurae (*n* = 1)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
other malignancies (*n* = 17)	7 (41.2%)	0 (0%)	2 (11.8%)	0 (0%)	12 (70.6%)	5 (29.4%)
total	66 (54.5%)	3 (2.5%)	50 (41.3%)	24 (19.8%)	54 (44.6%)	12 (9.9%)

Tab. II. Results of pleural fluid investigation and results of cytological and histological examinations from material taken during diagnostic procedures and operation (group II – patients who underwent thoracoscopy or videothoracoscopy)

	Pleural effusion		Diagnostic procedure and operation			
Group II (*n* = 108)	Positive cytological result	Positive result of pleural biopsy	Positive cytological result from sputum, bronchial lavage or brush bronchial biopsy	Positive histological result from bronchial samples	Positive histological result from postoperative organs	Positive histological result from samples taken from other organs and peripheral lymph nodes
lung cancer (*n* = 35)	12 (34.3%)	34 (97.1%)	4 (11.4%)	2 (5.7%)	0 (0%)	4 (11.4%)
breast cancer (*n* = 13)	8 (61.5%)	13 (100%)	0 (0%)	0 (0%)	12 (92.3%)	1 (7.7%)
ovarian cancer (*n* = 6)	0 (0%)	6 (100%)	0 (0%)	0 (0%)	6 (100%)	0 (0%)
mesothelioma pleurae (*n* = 29)	9 (31.0%)	29 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (3.4%)
others (*n* = 20)	7 (35.0%)	20 (100%)	0 (0%)	0 (0%)	19 (95.0%)	1 (5.0%)
unknown primary tumor (*n* = 5)	4 (80%)	5 (100%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)
total	40 (37.4%)	107 (99.1%)	5 (4.6%)	2 (1.9%)	37 (34.2%)	7 (6.5%)

Tab. III. Results of pleural fluid investigation and results of cytological and histological examinations from material taken during diagnostic procedures and operation (group III – patients who underwent thoracotomy)

	Pleural effusion		Diagnostic procedure and operation			
Group III (*n* = 8)	Positive cytological result	Positive result of pleural biopsy	Positive cytological result from sputum, bronchial lavage or brush bronchial biopsy	Positive histological result from bronchial samples	Positive histological result from postoperative organs	Positive histological result from samples taken from other organs
lung cancer (*n* = 2)	1 (50%)	2 (100%)	0 (0%)	1 (50%)	1 (50%)	1 (50%)
mesothelioma pleurae (*n* = 4)	2 (50%)	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
others (*n* = 1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
unknown primary tumor (*n* = 1)	1 (100%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
total	4 (50%)	8 (100%)	0 (0%)	1 (12.5%)	2 (25%)	1 (12.5%)

Discussion

Diagnosis and effective treatment of malignant pleural effusion is a difficult clinical problem. The most essential and most important step in diagnosis of MPE is thoracentesis. The samples of pleural fluid are taken for biochemical, bacteriological and cytological analysis. The American Thoracic Society states that there are no absolute contraindications for puncture of the pleural cavity. The diagnosis of MPE depends on such factors as type and extent of malignancy. Therefore, the results of cytological examinations of pleural fluid reported by authors are very varied. This type of examination allows one to find malignant cells in between 62 and 92% of patients [7]. Lynch reports positive cytological results in 70-80% of patients with MPE, but emphasizes that diagnostic difficulties appear mainly in patients with unknown primary tumor [4]. Erasmus reports only 50% of cases with positive cytological examination [22]. Antony presents, on the grounds of literature, 42-77% positive cytological results in patients with MPE [7]. Boutin, on the grounds of his cytological examination, reports 40.6%, and Anderson 67% positive cytological results [23, 24]. In our material, we diagnosed malignant cells in pleural fluid in 110 patients (46.4%). These results do not differ from results which have been reported in the literature.

Patients with suspected malignancy and negative cytological examination of pleural fluid taken during thoracentesis are subjected to pleural biopsy or biopsy of the tumor through the chest wall, videothoracoscopy, and finally subjected to diagnostic thoracotomy. The European Respiratory Society and American Thoracic Society recommend performing biopsy of pleura in patients with suspected MPE using the biopsy needle or thoracoscopy if pleural biopsy did not give positive result [25]. Thoracentesis was performed in 236 from 237 patients who were diagnosed and treated in our Thoracic Centre. The number of thoracenteses which were performed before the operative procedure ranged from 1 to 16. Our patients had more punctures of the pleural cavity than is recommended by the European and American societies. It is connected with the treatment of patients with malignancy and MPE in a different hospital before being admitted to our centre. The experiences of treatment of these patients are different and diagnostic procedures and therapeutic management are also different in different facilities, as there is no universally agreed upon procedure scheme.

Because of the relatively low sensitivity of transthoracic biopsy of pleura, due to the prolongation of the time of diagnostic malignancy and the need to immediately stop the increase of fluid in the pleural cavity, the biopsy was performed in only 4 patients. An explicit diagnosis was not established.

A very sensitive diagnostic method is thoracoscopy (videothoracoscopy), which is performed especially when the plural effusion is the first manifestation of neoplastic disease. Morphological assessment of tissue and cell changes with cytochemical and immunological examination allows one to establish an unequivocal diagnosis [1, 7, 8, 20, 21, 24-27]. Boutin reports that thoracoscopy was performed in 215 patients with an unknown etiology of pleural effusion. In 150 patients malignancy was diagnosed. In 115 patients pleural effusion was connected with metastasis of malignancy, and in 35 patients, mesothelioma was diagnosed. In 131 patients, on these grounds, primary tumor was established. The sensitivity of this method was 87% [23]. Loddenkemper in his prospective examination found that diagnosis on the grounds of thoracoscopies, which were conducted in 208 patients with MPE, was established in 95% of cases, while a positive cytology result from pleural effusion was established only in 62% of cases [16]. In our material thoracoscopy (videothoracoscopy) was performed in 108 (45.6%) patients: malignancy was established in 107 (99.1%). In 5 patients metastatic adenocarcinoma was diagnosed, but the primary focus of neoplasm was not established, despite broadened diagnostic investigation. In 1 patient the samples taken during thoracoscopy did not confirm neoplastic processes, but after three months adenocarcinoma was diagnosed from samples taken during bronchoscopy. The diagnosis of primary neoplasm was established in 102 (94.4%) patients. This result is comparable with the results in other centers.

When the neoplastic disease was not established using conservative procedures and there were contraindications for thoracoscopy, diagnostic thoracotomy (mini-thoracotomy) was performed. Antony recommends open biopsy (diagnostic thoracotomy) when the patient either does not tolerate ventilation of one lung during the operation (patients after previous resection of contralateral lung) or there are a lot of adhesions in the pleural cavity, which prevent safe introduction of the thoracoscope [7]. Lynch allows the possibility of performing diagnostic thoracotomy but prefers, like most of the doctors, to conduct thoracoscopy [4]. In our center diagnostic thoracotomy was performed in 8 patients, in whom thoracoscopy was not performed because of massive adhesions. In all these patients the diagnosis of neoplastic disease was established (100%). In 2 patients lung cancer (adenocarcinoma), and in 4 mesothelioma were diagnosed. In 1 patient pleural metastasis of melanoma was established. The primary focus of neoplasm was not established only in one patient.

Diagnosis of MPE is still a big diagnostic problem. Because of relatively low sensitivity and specificity of pleural fluid investigation, invasive diagnostic procedures are necessary.

Conclusions

1. Diagnosis of suspected neoplastic disease and malignant pleural effusion should be performed using different invasive and non-invasive methods.
2. Examination of the neoplastic cells in pleural effusion is a valuable element in the diagnosis of MPE.
3. Thoracoscopy (videothoracoscopy) is an essential invasive diagnostic procedure in the case of suspected neoplastic disease with malignant pleural effusion.

References

1. Droszcz W. Choroby opłucnej. Wydawnictwo Lekarskie PZWL, Warszawa 1997.
2. Sahn SA. Malignant Pleural Effusion. In: Bouros D (ed.). Pleural Disease. Marcel Dekker New York 2004; 411-438.
3. Kacprzak G, Kołodziej J, Rzechonek A, Majewski A, Pawlak I, Spytkowski L. Management of malignant pleural effusion. In: Second International Congress of Thorax Surgery. June 24-26, 1998, Bologna, Italy. Editrice Compositori 1998; 325-330.
4. Lynch TJ. Management of Malignant Pleural Effusions. Chest 1993; 103: 385S-389S.
5. Payne KD, Owens D. Differentiating Between Benin and Malignant Pleural Effusion. In: Bouros D (ed.). Pleural Disease. Marcel Dekker New York 2004; 253-261.
6. Kacprzak G, Kolodziej J. Diagnostic of Malignant Pleural Effusion. Pol J Surg 2003; 1011-1017.
7. Antony VB, Loddenkemper R, Astoul P, Boutin C, Goldstraw P, Hott J, Rodriguez Panadero F, Sahn SA. Management of malignant pleural effusions. Eur Respir J 2001; 18: 402-419.
8. American Thoracic Society. Management of Malignant Pleural Effusions. Am J Respir Crit Care Med 2000; 162: 1987-2001.
9. Droszcz W. Badania mikrobiologiczne, immunologiczne, biochemiczne i alergologiczne. In: Droszcz W, Kowalski J, Pawlicka L, Szymański A (eds). Diagnostyka chorób układu oddechowego. Wydawnictwo Lekarskie PZWL, Warszawa 1987; 207-211.
10. Light RW. Useful tests on the pleural fluid in the management of patients with pleural effusions. Curr Opin Pulm Med 1999; 5: 245-249.
11. Joseph J, Badrinath P, Basran GS, Sahn SA. Is the pleural fluid transudate or exudate? A revisit of the diagnostic criteria. Thorax 2001; 56: 867-870.
12. Cakir E, Demirag F, Aydin M, Erdogan Y. A review of uncommon cytopathologic diagnoses of pleural effusions from a chest diseases center in Turkey. Cytojournal 2011; 8: 13.
13. Dağli AF, Küçük S, Sezer M, Uçer O. Cytopathologic diagnosis in pleural effusion and cyto-histopathologic correlation. Turk Patoloji Derg 2011; 27: 12-16.
14. Little AG. Thoracoscopy: current status. Curr Opin Pulm Med 1996; 2: 315-319.
15. Lewis RJ, Caccavale RJ, Sisler GE. Imaged thoracoscopic lung biopsy. Chest 1992; 102: 60-62.
16. Loddenkemper R, Boutin C. Thoracoscopy: present diagnostic and therapeutic indications. Eur Respir J 1993; 6: 1544-1555.
17. Weatherford DA, Stephenson JE, Taylor SM, Blackhurst D. Thoracoscopy versus thoracotomy: indications and advantages. Am Surg 1995; 61: 83-86.
18. Yap KP, Tan NC. Video-assisted thoracoscopy: role in the management of intrathoracic pathology. Ann Acad Med Singapore 1999; 28: 816-818.
19. Stella F, Ansaloni L, Bini A, Grani G, Grazia M, Mastrorilli M, Pagani D, Bazzocchi R. VATS value in the diagnosis, staging and pallative treatment of malignant pleural mesothelioma. In: Second International Congress of Thorax Surgery. June 24-26, 1998, Bologna, Italy. Editrice Compositori 1998; 325-330.
20. Sakr L, Maldonado F, Greillier L, Dutau H, Loundou A, Astoul P. Thoracoscopic assessment of pleural tumor burden in patients with malignant pleural effusion: prognostic and therapeutic implications. J Thorac Oncol 2011; 6: 592-597.
21. Noppen M. The utility of thoracoscopy in the diagnosis and management of pleural disease. Semin Respir Crit Care Med 2010; 31: 751-759.
22. Erasmus JJ, Patz EF. Treatment of malignant pleural effusions. Curr Opin Pulm Med 1999; 5: 250-255.
23. Boutin C, Viallat JR, Cargnino P, Farisse P. Thoracoscopy in malignant pleural effusions. Am Rev Respir Dis 1981; 124: 588-592.
24. Anderson CB, Philpott GW, Ferguson TB. The treatment of malignant pleural effusions. Cancer 1974; 33: 916-922.
25. Rodriguez-Panadero F. Malignant pleural diseases. Monaldi Arch Chest Dis 2000; 55: 17-19.
26. Chhieng DC, Ko EC, Yee HT, Shultz JJ, Dorvault CC, Eltoum IA. Malignant pleural effusions due to small-cell lung carcinoma: a cytologic and immunocytochemical study. Diagn Cytopathol 2001; 25: 356-360.
27. Braunschweig R, Guilleret I, Delacrétaz F, Bosman FT, Mihaescu A, Benhattar J. Pitfalls in TRAP assay in routine detection of malignancy in effusions. Diagn Cytopathol 2001; 25: 225-230.