Malignant pleural effusion and mesothelioma

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Abstract: The main difference between patients with pleural effusion (PE) accompanying mesothelioma and patients in whom PE is caused by other malignancies, is that in former group, the presence of effusion does not necessarily mean that patient should be *a priori* rejected from surgery. Although surgery can be offered to selected patients with lung cancer and accompanying effusion, in a great majority of these patients and patients with malignancies of other localisations, nonsurgical treatment is a treatment of choice. Before the era of the widespread use of video-assisted thoracoscopy and video-assisted thoracic surgical procedures, the cytological and biochemical analysis of the pleural fluid had a greater clinical importance. Owing to the aforementioned progress in technology, the focus is nowadays switched from diagnostics to pleural fluid management, so that some aspects of the pleural fluid as an isolated entity remain actual mostly as initial orientation and in patients with mesothelioma and short life expectancy. This chapter gives an evidence based overview of different clinical aspects of the PE accompanying mesothelioma and of the current clinical importance of the analysis of the PE in the era of the widespread use of hi-tech procedures in clinical practice.

Keywords: Effusion; mesothelioma; diagnostics

Malignant pleural mesothelioma (MPM) still represents a major clinical challenge, with most of the main aspects being sufficiently covered by several existing guidelines (BTS, ERS/EACTS etc.). These guidelines gave quite clear diagnostic algorithms and evidence-based recommendations for treatment options, with advantages and draw-backs for each approach. That is why the subject of this chapter are only specificities of the mesothelioma-related pleural effusion (PE): what are the differences *vs.* other malignant pleural effusions (MPEs), what is the reliability of non-invasive and cytological diagnostics, what is its role in follow up and what is the optimal pleural fluid management. In the era of the widespread use of VATS procedures, enabling precise biopsy of any underlying lesion under the eye control, it is clear that the practical significance of MPM-associated PE itself relates mostly to patients being unfit for medical or surgical thoracoscopic biopsies.

Differences between MPM-related PE and other MPE

From the clinical standpoint, the main difference relates to the need for further invasive diagnostics after initial cytological analysis. Unlike patients with PE accompanying primary or secondary lung or mediastinal tumours, in whom pleural fluid cytology may be often enough for diagnosis, in case of MPM-associated effusion, the need for thoracoscopic/VATS biopsy is much more frequent. This because in a quite high proportion of patients with lung cancer, owing to typical radiographic aspect, the histological diagnosis of the underlying malignancy is usually obtained by bronchoscopy, mediastinoscopy or transcutaneous needle biopsy, thus obviating the need for further pleural biopsies to confirm the cause of the PE. In most of these patients, the accompanying pleural fluid frequently means the
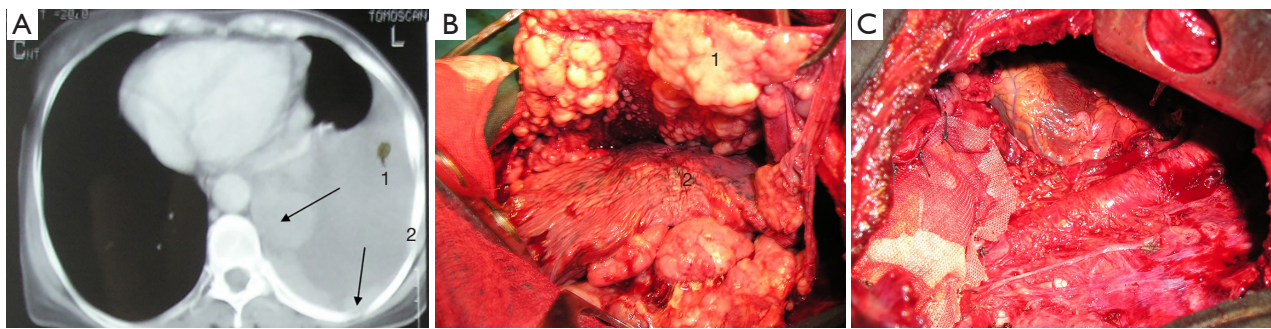
Figure 1 Mesothelioma with dominantly parietal pleural, pericardial and diaphragmatic involvement with direct multifocal lung infiltration. Pleuropneumonectomy with pericardial and diaphragm resection and reconstruction. (A) PA chest radiography on admission; arrows: [1] bulky mesothelioma growth over the aorta; [2] tumour growth over the posterior chest wall; (B) left thoracotomy: [1] tumour tissue detached extrapleurally from the anterior chest wall; [2] lung; (C) aspect after pleuropneumonectomy with reconstructed diaphragm, before the pericardial mesh suture.
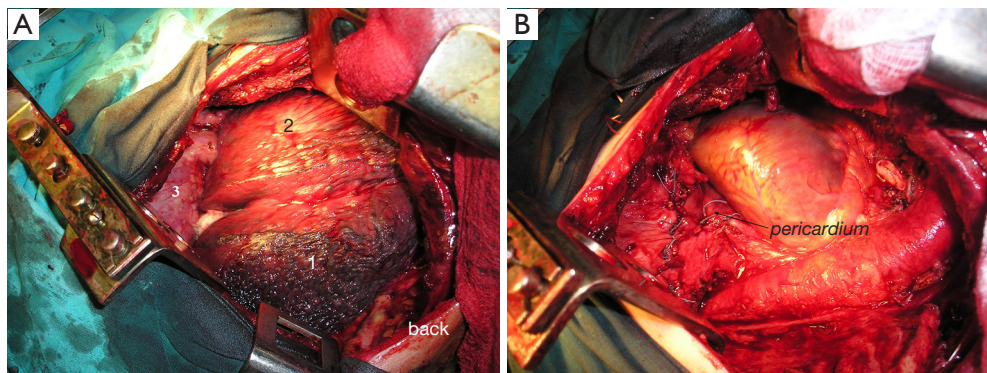
Figure 2 Mesothelioma with parietal pleural and disperse visceral pleural involvement. (A) Left thoracotomy: [1] lower lobe with disperse visceral pleural involvement; [2] upper lobe; [3] diaphragm; (B) aspect after the pleuropneumonectomy with directly reconstructed diaphragm defect, before positioning of the pericardial mesh.

advanced disease, eliminating eventual surgical treatment, thus switching the focus of PE management to the type of pleurodesis as a part of palliative treatment. Unlike that, in patients with MPM, especially in those without the lung and/or mediastinal lesions, the diagnostic possibilities are limited to the region of the pleura and importantly, the accompanying PE itself, independently of size and aspect, does not preclude eventual surgery. In addition, the high operative Mb and Mt require biopsies with sufficient volume of tissue to establish the reliable diagnosis before offering surgery to the patient. Secondly, PE may be present only in the early disease stage, followed by complete resolution synchronously with disease progression in form of the circumferential tumour growth from the parietal pleura. Such a scenario additionally complicates the diagnostics. As the volume of the PE is not of great help in

practice, patients with previous asbestos exposure and PE, even if small, should be carefully monitored, because in some of them MPM will develop (1).

The radiographic aspect of PE does not correlate neither with the mesothelioma growth pattern nor with the disease extent. Two different morphological patterns of mesothelioma, each with PE as initial manifestation, in patients who underwent surgery are presented on *Figures 1* and *2*.

Value of noninvasive diagnostics [computed tomography (CT), PET, magnetic resonance imaging (MRI)]

In patients with any PE, the standard chest radiography can serve only for initial orientation. In the great majority of

them some additional imaging is necessary.

One of the most important practical benefits of CT in patients with MPM, especially in presence of small amount of fluid and/or suspected major pleural adhaesions, is to identify eventual areas on the parietal pleura that are accessible by transcutaneous needle-biopsy. This is also very important in patients unsuitable for thoracoscopy for any reason.

The diagnostic accuracy of CT in patients with a malignant pleural dissemination/involvement ranges between 70% and 97%. The differentiation between MPM and other pleural malignancies is difficult. Features favoring MPM over metastatic pleural malignancy are fissure involvement and the absence of the lung lesions (2). The presence of pleural plaques *per se* is not a reliable sign of malignancy, because the PE may also exist due to benign asbestos-related PE.

The accuracy of CT is quite low for the assessment of invasion of the chest wall and diaphragm. The CT is not so accurate for mediastinal staging, so that more than a third of patients are subsequently upstaged after a PET scan (3).

The use of PET-CT can help to determine a nature of some findings that remain unclear after CT and to better determine the areas for biopsies. It should be mentioned that, even under the thoracoscopic view, it is not always easy to distinguish between sequellar or constitutional lesions and tumour growth. Areas of pleural thickenings containing a malignant tissue have elevated maximal standardised uptake values (SUVmax) (4,5). A SUVmax threshold of >2.0 was demonstrated as reliable to differentiate between malignant and nonmalignant pleural lesions with sensitivity and specificity being 88–100% and 88–92%, respectively (6-8). The false negative results may be due to small tumour diameter and low proliferative index, like in early stage epithelioid mesothelioma. False positive results may be mostly the consequence of different inflammations, tuberculosis, or talc pleurodesis.

In brief, despite the role in identifying targets for biopsies, PET-CT alone cannot differentiate MPM from pleural carcinosis and no causative relationship between SUV_{max} and histological sub-type could be demonstrated (6). In addition, poor spatial resolution of PET-CT, results in low sensitivity for extrapleural invasion.

Despite the limited role of MRI in MPM staging, MRI is superior to CT in detecting invasion of the chest wall, diaphragmatic muscle and mediastinal fat, thus significantly improving the overall diagnostic accuracy (9).

More recently, the diffusion-weighted MRI (DWI-MRI) appeared as potentially useful, in a way that lower values of apparent diffusion coefficient (ADC) exist in pleural malignancy, compared with benign disease (10). That is a consequence of the thickened pleura and may be of help in practice (92.5% sensitivity, 79% specificity (11). It was also demonstrated that epithelioid type of mesothelioma had a significantly higher ADC value than non-epithelioid, with the suggested threshold of 1.1 (sensitivity of 60% and specificity of 94%) (12). The latter finding could be also useful in practice, but these MRI data still need to be prospectively validated.

Role of cytological diagnostics

Although some laboratories are reliable for definitive cytological diagnosis, the International Mesothelioma Interest Group recommends biopsy to establish the definitive diagnosis (13). So, what are the limitations of cytological analysis of pleural fluid in suspected MPM?

First, many currently performed testes can be done on both pleural fluid and biopsy samples, but the sensitivity is reduced if no atypical mesothelial cells are present in pleural fluid (14,15). Although the clinical value of several markers has been analysed, it was limited for many of them, because sarcomatoid type usually does not express typical 'mesothelial' markers. That is why the use of keratins (quite non-specific as a marker), still remains appropriate.

Second, it is difficult to distinguish between sarcomatoid type of mesothelioma and other sarcomatous tumours. The use of GATA3 was reported with promising results (16). Analysis of BAP1 expression (if absent) and of p16 deletion by using the FISH method (fluorescent in-situ hybridization) may suggest the presence of MPM, but are not specific (17,18).

Positive immunohistochemical markers for MPM are calretinin, thrombomodulin, CK5/6, CAM5.2, EMA, vimentin, GLUT-1, HBME-1, WT-1, p53, with 45–100% sensitivity. Negative markers are Ber-Ep4, MOC-31, CEA, Leu-1, CD15, TTF-1, B72.3, with 53–100% overall specificity. By combining two positive mesothelioma and two negative adenocarcinoma markers may increases the diagnostic accuracy according to BTS guidelines (19).

The over-expression of mesothelin also exists in patients with MPM. The values of serum mesothelin increase in patients with MPM compared to control group of asbestos-exposed patients (20,21). A meta-analysis on 460 MPM and 1,046 non-MPM demonstrated the overall sensitivity and specificity of pleural fluid SMRP of 75%,

Table 1 Summary of evidence for Fibulin 3*

Study	Source	Sensitivity	Specificity	Area under the curve	Cut off (ng/mL)
Pass *et al.* (24) 2012.	Plasma	100	100	1	33
	Plasma	95	96	0.99	53
	Pleural fluid	84	92	0.93	346
Agha *et al.* (25) 2014.	Serum	88	81.8	0.776	67
	Pleural fluid	72	80	0.878	150
Elgazzar *et al.* (26) 2014	Serum	100	97	0.98	54
	Pleural fluid	90	97	0.94	520
Creaney *et al.* (27) 2014	Plasma	22	95	n/a	52
	Plasma	48	71	0.671	29
	Pleural fluid	59	52	0.588	346
Kirschner *et al.* (28) 2015	Plasma	14	97		29

*From reference (19).

and 76%, respectively (22). As SMRP correlates with bulky disease, a drop in SMRP levels after surgery (EPP) is to be expected (23). The same meta-analysis showed that this marker has also a role in disease progression monitoring, and differentiation between patients with a progressive and stable disease.

The summary of evidence for Fibulin 3 is presented on *Table 1* (BTS guidelines). Lower values of Fibulin 3 were shown to be favorable in term of survival (28).

Pleural fluid management

Different types of the pleural fluid management in patients with MPM must be analysed in context of the overall therapeutic approach. Having in mind that there is practically no curative treatment for MPM, with controversial role of surgery, the role of palliative treatment, is essential. The PE control is the key part of the palliative treatment for two reasons: first, thoracocenthesis improves or eliminates dyspnea; second, absence of the PE recurrence improves the quality of life (29). In patients unfit for surgery, some kind of pleurodesis should be performed. The prerequisite for any type of pleurodesis is the ability of the lung to expand either by indwelling pleural catheters or chest tube aspiration. The evidence about different types of pleurodesis is given below.

Therapeutic pleural needle-aspiration is usually the first therapeutic procedure. As the fluid re-accumulates, repeated aspirations may be an option, but only in patients with very poor general condition. In other patients, some other procedures are necessary in order to achieve a more efficient control of the PE (30).

Chemical pleurodesis is used the most frequently, usually by applying talc or less frequently, bleomycin or tetracycline (31). Talc can be used either in form of thoracoscopic poudrage or as slurry applied through the chest tube. The success rate is 60–80% in the absence of the trapped lung (32,33).

In a study with a direct comparison of VATS partial pleurectomy (VATS-PP) with talc (poudrage or slurry), despite initial pleurodesis success in favor of VATS-PP group (37% success rate with talc *vs.* 59% with VATS PP), this trend gradually disappeared during the follow-up period reaching 77% success with talc *vs.* 70% with VATS PP at one year follow up) (34). Furthermore, VATS pleurectomy brought neither survival benefit nor the lung function improvement. In the VATS group a higher complication rate (31% *vs.* 14%) and longer hospital stay (7 *vs.* 3 days) were registered.

Concerning the improvement of dyspnea and pleurodesis success, no significant difference between indwelling pleural catheters and talc slurry could be demonstrated in a randomized clinical trial (29).

Concerning the preference between surgical and medical pleurodesis, no clear benefit could be attributed to any of these methods in a retrospective study that included a high number of patients—28.2% *vs.* 29.7% success rate for medical and surgical group, respectively) (35). The

comparison of the success of pleurodesis in patients with MPM with those with PE caused by other malignancies, the success rate was the lowest in patients with MPM—66% *vs.* 63%, 77% and 74% in patients with lung, breast carcinoma and other malignancies, respectively (36).

Indwelling pleural catheters represent an alternative to pleurodesis. They are equally effective against breathlessness as talc slurry applied through the chest tube, being appropriate for patients with trapped lung as well. If both of the aforementioned options are available, the choice the patient's preference should be taken into consideration (37).

In brief, talc pleurodesis, performed in form of any of aforementioned ways, seem to be superior to VATS-PP for PE control in patients with mesothelioma.

Acknowledgments

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal* for the series "Malignant Pleural Effusion". The article has undergone external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://amj.amegroups. com/article/view/10.21037/amj.2020.02.04/coif). The series "Malignant Pleural Effusion" was commissioned by the editorial office without any funding or sponsorship. DS served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *AME Medical Journal* from August 2019 to February 2020 and an unpaid Associate Editor-in-Chief of *AME Medical Journal* from March 2020 to February 2022. The author has no other conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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