

Malignant pleural effusion and algorithm management

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ABSTRACT

Involvement of the pleura in lung cancer is a common manifestation accompanying with reduced life expectancy. Symptoms relief and improvement of the quality of life are the primary goals of the management of malignant pleural effusion (MPE). Histological confirmation is essential for optimal patient management. Lung cancer patients, with life expectancy more than 3 months, resistant to chemotherapy should be treated with thoracentesis, intercostal tube drainage and installation of a sclerosant agent or pleurodesis through thoracoscopic procedures or placement of an indwelling pleura catheter. Talc pleurodesis (sterile asbestos-free graded, particle size >15 µm), as "poudrage" or "slurry" still remains the treatment of choice in patients with MPE resistant to chemotherapy.

KEY WORDS

Malignant pleural effusion (MPE); pleurodesis; suicide gene therapy; thoracoscopy

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Background

Normally, 5 to 15 mL of pleural fluid present within the pleural space, formed by the parietal and visceral pleural membranes of hemithorax. About 5 to 10 liters of pleural fluid traverse the pleural space on a daily basis (1-7). Increased pleural fluid production due to increased vascular permeability or reduced reabsorption by lymphatics usually due to disrupted or occluded drainage channels. The presence of malignant pleural effusion (MPE) frequently indicates advanced disease and the primary goal in the management of MPE should be palliation of symptoms (palliative treatment). Bronchogenic carcinomas and breast cancers are the most common metastatic tumors to the pleura (40% and 25% respectively). Nevertheless, about 10% of

all MPEs are due to primary cancers arising from the pleura with malignant mesothelioma as the predominant type (>90%) and cancer of unknown primary results in less than 10%. According to the International Association for the Study of Lung Cancer (IASLC), pleural dissemination of lung cancer, either by pleural effusion or pleural invasion without evidence of other metastatic foci, was revised to M1a categorizing it as stage IV disease (8).

Diagnosis of MPE

Diagnostic tests typically include a chest X-ray (effusions produce a meniscus sign along the lateral chest wall), chest computer tomography (CT) scan, MRI (especially to detect small effusions), thoracentesis, pleural fluid analysis and pleural biopsy. Lateral chest X-ray, lateral view or in case of small effusions a decubitus films can detect 100 cc of free flowing effusion. More than 90% of MPEs are exudatives. The appearance in half of them is hemorrhagic and in 11% is bloody in nature: Exudative properties after pleural fluid thoracentesis are commonly defined on the basis of the Light's criteria (a pleural fluid-to-serum protein ratio of more than 0.5, a pleural fluid-to-serum lactic dehydrogenase ratio of more than 0.6, or a pleural fluid LDH level of 200 IU, pH of less than 7.30, pleural fluid

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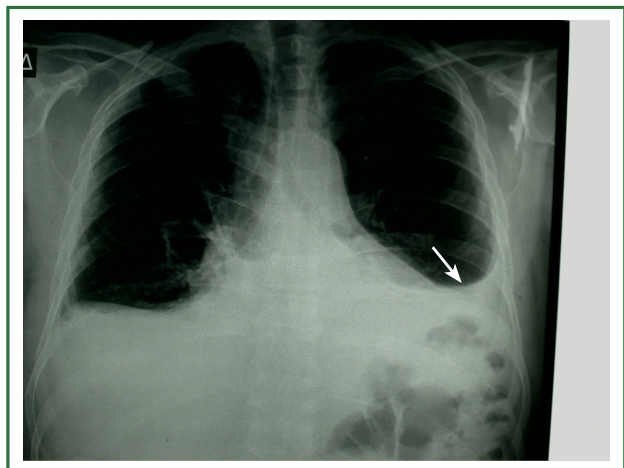


Figure 1. Chest radiograph demonstrating production of a meniscus sign along the left lateral chest wall (arrow).

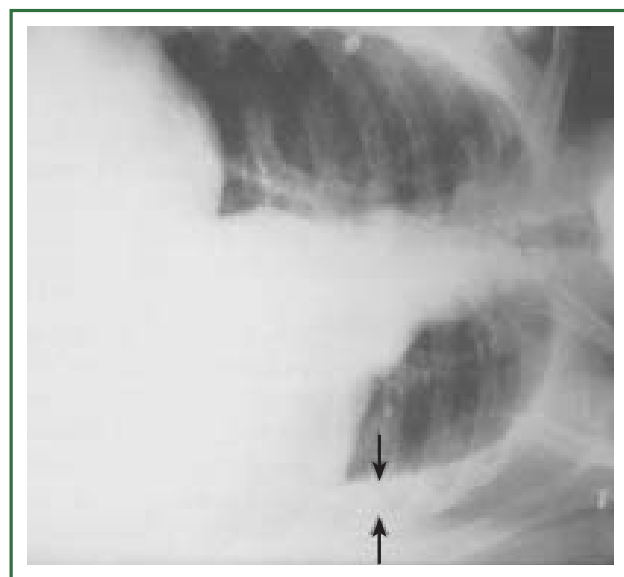


Figure 2. Profile X-ray-decubitus position-demonstrating a free flowing effusion (arrows).

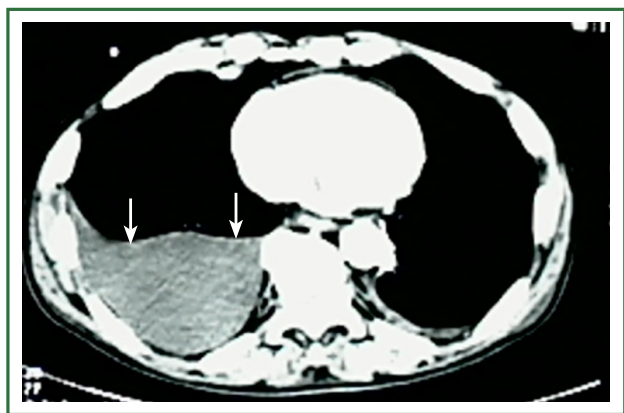


Figure 3. Chest computer tomography demonstrating a right malignant pleural effusion (arrows).

glucose less than 60 mg/dL) (9,10). Cytological examinations of pleural fluid from thoracentesis have a diagnostic yield, ranging from 62% to 90% (11-16). Where the initial cytological evaluation was negative a closed biopsy could be combined with cytology. These diagnostic combinations increase the diagnosis as high as 80% (17).

In case of two negative consecutive, cytologic examinations medical thoracoscopy or Video-Assisted Thoracoscopic Surgery (VATS) are recommended. Diagnostic sensitivity for medical thoracoscopy and for VATS is greater than 90% with specificity of 100% while the operative mortality is less than 0.5% (18,19). Both procedures allow detailed investigation of pleural cavity and for visually detected lesions, directed pleural biopsies could be obtained. Epidermal Growth Factor Receptor (EGFR) mutations analysis of MPE biopsies in cases of non squamous non-small cell lung cancer (NSCLC) offers the benefit of EGFR-targeted therapies (20).

DNA methylation was detected in 59% of MPEs. But in none of the benign pleural effusions (21).

Standard examination of DNA methylation in MPEs may increase sensitivity of cytological evaluation (Figures 1-5).

Treatment

The main goals in the treatment of MPE are the removal of the effusion, the improvement in symptoms and the prevention of re-accumulation. Therapeutic thoracentesis and fluid aspiration should be the first medical procedure in the management of MPE which are useful in determining the effects on breathlessness. Thoracentesis has limited effect as a permanent therapeutic approach. More than 98% of MPE associated with lung cancer will relapse within 30 days from the first thoracentesis. Chemotherapy is effective in controlling the production only in responders NSCLC patients. On the other hand a successful management of MPE usually is observed in small cell lung cancer (SCLC) as many patients respond to chemotherapy.

Chemical pleurodesis

This procedure refers to application of sclerosant agents into the pleural cavity to achieve symphysis between the visceral and parietal pleura. The ideal sclerosant agent for chest catheter pleurodesis still remains controversial. A Cochrane review reported that pleurodesis with talc is superior when compared with other sclerotic agents (Table 1) or chest drainage alone to control an MPE or prevent the re-accumulation of fluid in the pleural cavity. The European Respiratory Society (ERS) and the American Thoracic Society (ATS) recommend not to remove more than 1.5l of fluid on each occasion and to discontinue aspiration in case of signs of rapid pulmonary expansion (dyspnoea, chest pain, persistent cough). Fluid aspiration could

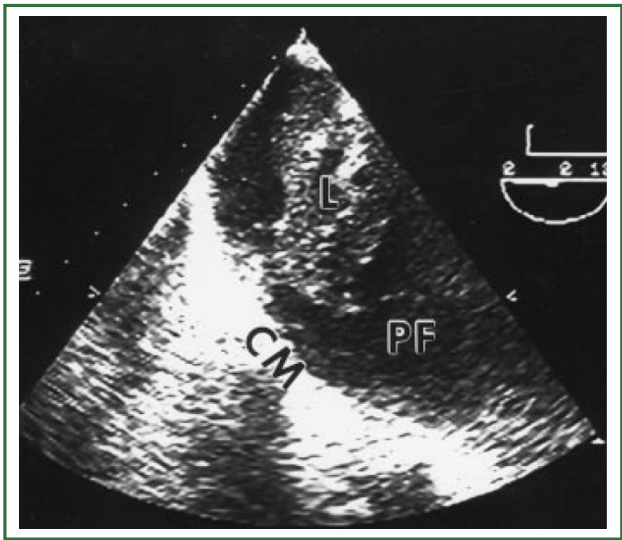


Figure 4. A thoracic ultrasonography detecting pleural fluid PF.

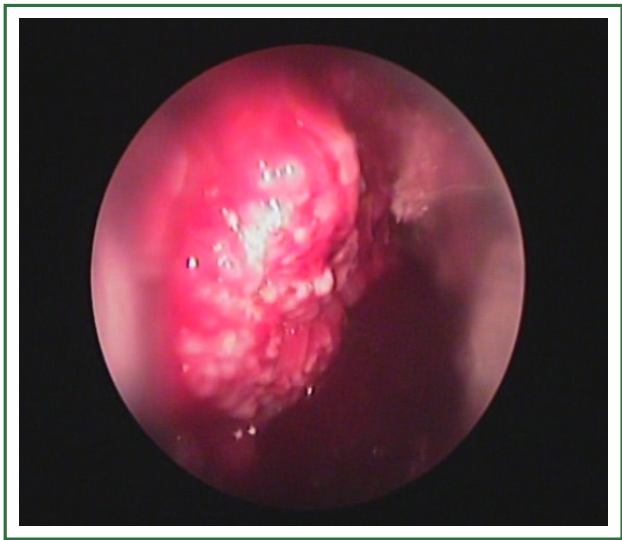


Figure 5. Thoracoscopic view in the right pleura cavity. The chest wall pleura is infiltrated with whities nodular tumor deposits secondary to metastatic lung adenocarcinoma.

Table 1. Sclerosing agents for pleurodesis/success rate.

Agent	Standard dose	Success rate (%)
Talc	2.5-10 mg	70-100 (22-25)
Tetracycline	20 mg/kg	50-92 (26-30)
Bleomycin	60 U in 100 mL, NaCl 0.9%	58-85 (25,26,31-35)
Mitoxantrone	0.4 mg/kg or 25-60 mg	73-88 (36-38)
Cisplatin	100 mg/m ²	65-83 (39-42)
Doxycycline	500 mg in 30mL, NaCl 0.9%	60-89 (39,43-45)
Taxol	120 mg/m ²	85-93 (46,47)
Erythromycin	1 g in 30 mL, 5% glucose	85-88 (48-50)
Corynebacterium parvum	4-14 mg	65-92 (51)
Interferon alpha-2b	3 × 10 ⁶ IU	62-100 (26)
Iodopovidone	20 mL of 10% iodopovidone	64-96 (52)

Table 2. Major adverse of talc pleurodesis.

Chest pain
Atelectasis
Pneumonia
Dysrhythmia
Dyspnoea
Fever
Respiratory failure (significant arterial oxygen desaturation) (53)
Thrombosis
Pulmonary embolism (probably due to coagulation through Interleukin-8 activation)
Empyema (rare)

be repeated at 2 hours intervals in case of persistent, severe dyspnoea due to large pleural effusions (Table 2). Experimental data demonstrated that talc stimulation of mesothelial cells have the capacity to promote intrapleural fibrosis. Talc also affects the angiogenic balance into pleural cavity and produces apoptosis of malignant mesothelial cells but not normal mesothelial cells.

Which talc and which policy?

Sterile asbestos-free graded (particle size >15 µm) talc is used for intrapleural administration in two ways. Either via thoracoscopy using an atomizer formed “talc poudrage”, either via an inter costal tube in the form of a suspension termed “talc slurry”. The

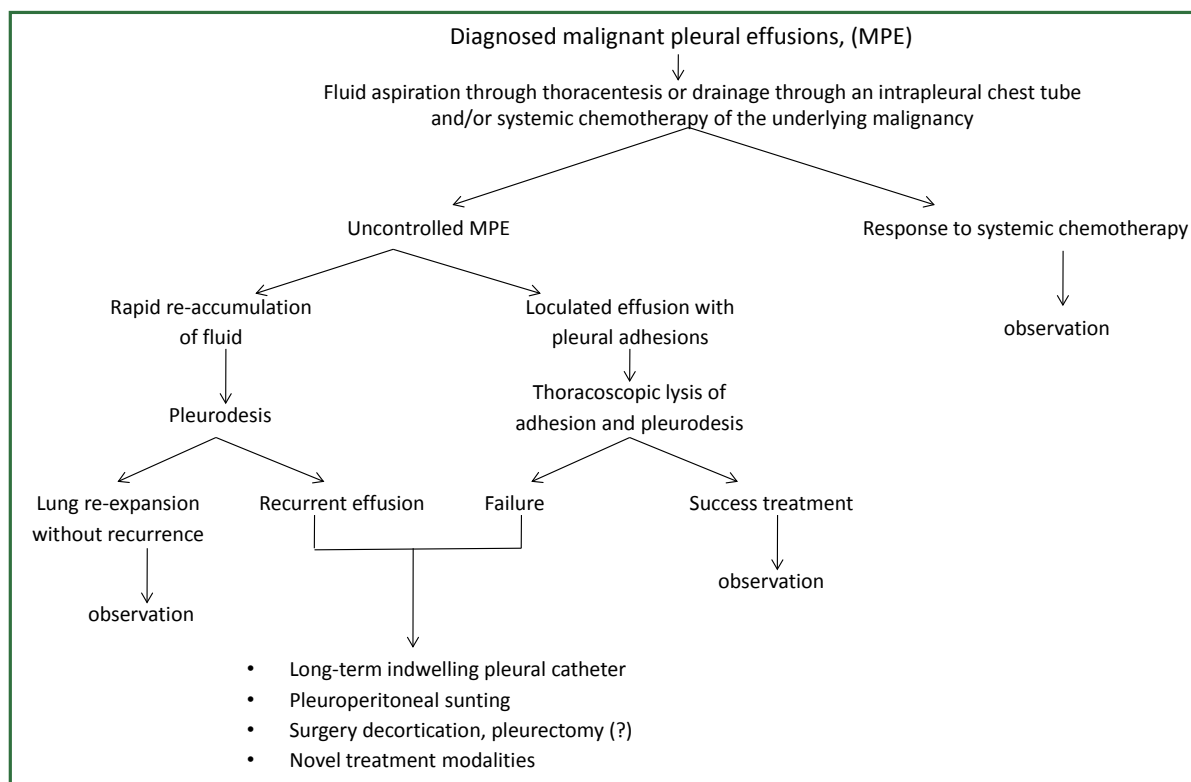


Figure 6. Management algorithm of the of Lung Cancer primary malignant pleural effusions.

majority of similar studies show a slight superiority in “talc poudrage” but with no statistical significance as far as the control and the re-accumulation of the fluid.

Via the indwelling pleural catheter (IPC) prior to pleurodesis, 3 mg/kg lidocaine solution (1%) up to 250 mg should be administered in order to prevent local pain and discomfort. Also the use of sedation to prevent patient's anxiety may be helpful.

Contra-indications

- ❖ Life expectancy <3 months;
- ❖ Failure of opposition of the pleural surfaces (trapped lung).

Trapped lung occurs: when lung expansion is restricted, either by visceral pleura tumour encasement or by endobronchial obstruction.

Successful pleurodesis often defined as no significant fluid re-accumulation in 30 days occurs in about 75% of pts in large clinical studies (54).

Tetracycline

There is some evidence that the sclerosant agent tetracycline stimulates mesothelial cells, releases growth factor, like activity for fibroblasts and this action may play an important role in inducing pleural fibrosis (55).

The reported success rate for control of MPEs with this agent

ranged from 59% to 94% (56). The intravenous form used for intrapleural instillation is no longer commercially available in the United States and Greece.

Long-term IPC

IPC is preferred for patients with a trapped lung or failed pleurodesis or to provide apposition of the parietal and visceral pleural surfaces for subsequent pleurodesis. Three randomized trials investigating the efficacy between small- and large-bone chest tubes, all concluded that they were equivalent, but large-bone tubes are associated with significant discomfort (57). This has led to the assessment of smaller-bone IPC (10-14F) for drainage and administration of sclerosing agents (58-60).

Pleuroperitoneal shunting

For pts with trapped lung or for pts who failed to control an MPE with other interventions, pleuroperitoneal shunting remains an alternative approach (61).

Pleurectomy

There is not sufficient evidence to recommend this as an alternative to pleurodesis or IPC in recurrent effusions or trapped lung.

Suicide gene therapy

Suicide gene therapy is the methodology where viral or bacterial genes are inserted into tumors cells and consequently modify a non-cytotoxic drug into a cytotoxic. The non-cytotoxic agent has already been previously administered either intravenously or locally. The two major systems that have been extensively used are the herpes simplex virus thymidine kinase gene (HSV-tk) and cytosine deaminase (CD) of *Escherichia coli*. The first converts the pro-drug ganciclovir (GCV) to GCV monophosphate and thereafter to GCV triphosphate inside the cells and the second 5-Fluorocytosine (5-FC) to the cytotoxic agent 5-Fluoracil (5-FU). The method of CD has been previously used with positive results in patients with MPE from NSCLC and SCLC. An algorithm regarding the methodology of administration of this therapy along with the criteria of the possible candidates has been previously proposed (62). However, still larger studies still remain to elicit whether this method will be used as a local treatment of lung cancer or it will be used as another method of pleurodesis. Certainly the cost-effectiveness of these two approaches has to be considered along with the effectiveness.

Conclusions

MPE is a common manifestation in patient with advanced lung cancer and other cancers. Therapy primary is directed to control symptoms and improve the quality of life rather than to cure the disease. Careful evaluation of the effusion to establish its etiology and patient treatment customization is required in order to decrease the volume of intrapleural fluid, to control the associated symptoms and to improve the quality of life and the survival. Talc pleurodesis (sterile asbestos-free graded, particle size >15 µm) still remains the treatment of choice in patients with MPE resistant to chemotherapy (Figure 6).

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