Chapter 4

Management of Malignant Pleural Effusion

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1. Introduction

Pleural effusions can form basing on the disease of the pleural membranes themselves or thoracic or abdominal organs [1]. The pleura is also important to maintain local fluid homeostasis. The exact mechanisms of pleural fluid production and absorption are complex and not fully understood [2, 3].

The normal pleural space is approximately 18 to 20 μm in width, although it widens at its most dependent areas. It has been shown that the pleural membranes do not touch each other and that the pleural space is a real gap, not a potential space [1].

Classically described; pleural effusion is the accumulation of fluid in the pleural gap that may be caused by any reason [4]. If there is an evidence of invasion by the tumor or any malignant cells detected in this fluid, it is described as malignant pleural effusion. Although there has been no epidemiologic study with respect to pleural effusion yet, it is a common clinic problem which is estimated to be a million cases in the United States of America every year. Malignant diseases account for over 22% of all cases that means; approximately 220 000 new patients in the United States and 40 000 in the United Kingdom [5].

Primary tumours of the pleural space are less common [6]. Pleural metastasis may be caused by any organ. Malignant pleural effusions (MPE) are most frequently produced by carcinomas of the lung (37%), breast (25%), and ovary (10%). Other reasons include malignancies of the genitourinary (7%) or gastrointestinal tract (9%) and lymphoma (10%) [7]. Even today, in up to 10% of the malignant pleural effusions, the origin of tumour is not identified [8].

The incidence and prevalence of mesothelioma may vary from region to region. Interestingly, despite its grim reputation, mesothelioma whose curative treatments are not yet available, offers better survival than does metastatic pleural disease, with a median survival of less than 12 months [6].

Asymptomatic patients with either a malignant or a paramalignant effusion need not be treated initially [9]. Malignant pleural effusion will eventually develop into cancer in the majority of patients. It often recurs challenging the physicians, patients and the patient's family in balancing the benefits of symptomatic improvement with the risk and inconvenience of therapy [10, 11].

2. Pathogenesis

Pathophysiology of MPE has not been fully understood yet and is still on debate. There are many hypotheses on the pathogenesis of MPE in cancer. It commonly results from disruption of normal starling forces regulating pleural fluid absorption by obstruction of mediastinal lymphatics, which drain the pleural space [9]. There is a strong relationship between mediastinal metastasis and development of MPE [12, 13]. Other causes of MPE include direct invasion (e.g. lung cancer, breast cancer, chest wall neoplasms), hematogenous spread of tumor to the pleura (eg, metastasis, non-Hodgkin's lymphoma), or increased capillary permeability caused by tumor invasion-related local inflammatory changes or vascular endothelial growth factor production [14]. Just the presence of metastasis does not seem sufficient to explain the pathogenesis of pleural effusions. In fact, only about 60% of patients with proven pleural metastases develop pleural effusions [15, 16].

Indeed, the accumulation of excess pleural fluid associated with cancer may be the result of a number of separate factors in an individual patient [16]. Postmortem studies have demonstrated a strong relationship between carcinomatous infiltration of the mediastinal lymph nodes and the occurrence of pleural effusion [11,15]. This finding suggests an important role of the impaired lymphatic drainage in the pathogenesis of MPE. However, if this was to be the only mechanism, one would expect MPEs to be transudative, but instead, the majority of these effusions are exudates [16].

Local effects of tumor	Systemic effects of tumor
Lymphatic	Pulmonary embolism
Bronchial obstruction with pneumonia	Hypoalbuminemia
Bronchial obstruction with atelectasis	
Trapped lung	Complications of therapy
Chylothorax	Radiation therapy (Early or late)
Superior vena cava syndrome	Chemotherapy

Table 1. The Causes of paramalignant Effusion [17]

All fluids of pleura may not be malignant in patients with malignancy. The effusion caused by a neoplasm without the evidence of malignant cells in the pleural effusion as well as surrounding tissues is called as "paramalignant" effusion. Presence of paramalignant effusion is not a contraindication for the surgery. Obstructive pneumonia or atelectasia, lymphatic

obstruction, cheilothorax caused by the invasion of thoracic duct, trapped lung, pulmonary embolism, hypoalbuminemia, cachexia, radiotherapy and, chemotherapeutics such as bleomycin, methotrexate and cyclophosphamide are the well known causes of para-malignant effusion [17].

3. Clinical presentations

The first and most common presenting symptom is dyspnea (96%) [12, 18]. The pathogenesis of dyspnea caused by a large pleural effusion has not been clearly elucidated, but several factors may be involved including a decrease in the compliance of the chest wall, contralateral shifting of the mediastinum, a decrease in the ipsilateral lung volume, and reflex stimulation from the lungs and chest wall [19]. After other causes of dyspnea have been excluded; detailed anamnesis, physical examination and radiological monitoring are required. As many as a third of patients with malignant pleural effusions present with weight loss and cachexia and appear debilitated by chronic illness [20]. Malignant causes should be excluded firstly in the list of differential diagnosis in patients diagnosed as exudates. A complete medical history and physical examination should be done considering any potential causes or risk factors of malignancy.

Other bothersome symptoms are cough [44%) and chest pain (56%) [18]. The majority of patients with MPE are symptomatic while less than 25% have no respiratory complaints [12]. Other symptoms include sharp pleuritic pain, dull ache with a feeling of pressure, and heaviness in the chest. A physical examination can reveal decreased breath sounds, and dullness to percussion [12].

4. Imaging techniques

Although standard chest radiographs can detect as little as 50 mL of PF on a lateral view,[21] it provides only suggestive findings for the diagnosis of MPE. A massive effusion increases the probability of a malignant aetiology and commonly produces a meniscus sign with fluid tracking up the lateral chest wall, a shift of the mediastinum to the contralateral side, and an inversion of the diaphragm. Radiographic signs of an MPE include circumferential lobulated pleural thickening, crowding of ribs, and elevation of the hemidiaphragm or ipsilateral mediastinal shift consistent with lung atelectasis due to airway obstruction by a tumor [22]. Due to resembling the other causes of pleural effusion other imaging studies may be necessary such as ultrasound and computed tomography (CT) scan [23].

Ultrasound is an important device during evaluating the presence of an effusion and may be used as a guide during thoracentesis. Ultrasound also may aid in distinguishing an exudates (echogenic) from a transudate (anechoic) although this finding is not definitive [24]. Ultrasound is, in fact, more sensitive than radiography and can detect as little as 5 mL of pleural

fluid and is superior to CT for characterization of collections for the presence of septations and loculations [25].

Computed tomography (CT) scanning is even more accurate in detecting small effusions, including as little as 2 mL of fluid. The volume of the fluid presence can be best determined radiographically by using three-dimensional reconstruction [26]. Currently, the most useful radiographic study is a chest CT scan. CT scans help to establish the presence of a loculated pleural effusion, allow the evaluation of the pulmonary parenchyma if there is not complete lung compression, and distinguish pleural thickening from effusion. It also provides an excellent way to evaluate the mediastinum for the presence of masses or lymphadenopathy and permits detection of pleural-based nodules [27].

The role of magnetic resonance imaging (MRI) in the evaluation of pleural effusions is limited; however, it may be beneficial in better characterizing possible tumour involvement of the chest wall or diaphragm [28]. Neither MRI nor CT scan can distinguish transudates from exudates accurately although both can be helpful in evaluating the pleural contents for masses, nodules, and pleural based thickening once the fluid is removed [29].

Positron emission tomography (PET scan) with 18F-fluorodeoxyglucose provides less anatomic information but has the potential advantage of providing diagnostic information about the effusion. This information may prove useful [30]. The true value of a PET scan would be to provide additional information about disease elsewhere, not to give a diagnosis of malignancy. In addition, diagnosis or treatment of a malignant effusion will depend on the type of cancer, and this cannot be determined with a PET scan [31].

5. Pleura and fluid characteristics

Once a pleural effusion is documented, diagnostic or therapeutic thoracentesis should be performed to establish the nature of the effusion. For adequate separation of transudates and exudates in pleural fluid, protein and LDH levels are determined and also the following tests on pleural fluid are recommended: description of the fluid; cell count and differential; glucose; pH particularly if the patient has a parapneumonic effusion; cytology; smears and cultures for bacteria, mycobacteria, and fungi; and adenosine deaminase (ADA) if tuberculous pleuritis is in the differential [32].

Effusions are classified as either exudative or transudative basing on established criteria and now commonly known as Light's criteria: [33]

1. Ratio of pleural fluid protein to serum protein concentration is greater than 0.5
2. Ratio of pleural fluid lactate dehydrogenase (LDH) to its serum concentration is greater than 0.6
3. LDH concentration in pleural effusion is greater than two thirds of the upper normal value for the serum LDH

This defines an exudate if any one of three criteria are met. The overall accuracy of these criteria is 93% to 95% [34, 35]. Light criteria have commonly misclassify effusions when any one of three criteria has a value close to its cutoff point [36]. Although the majority of malignant pleural effusions are exudates, it is important to keep in mind that a few are transudates [37, 38]. These circumstances result from the defective implementation of diagnostic rules that classify pleural effusions or coexisting conditions with transudates, such as hypoalbuminemia, cirrhosis with ascites, or chronic heart failure [39]. This does not suggest that every individual with a transudative pleural effusion should have pleural fluid cytological examination. However, in the appropriate clinical setting and the absence of congestive heart failure or a pleural fluid LDH level close to the exudative range, determination of pleural fluid cytology is suggested [17].

The primary problem with the Light criteria is that they identify 15% to 20% of transudative effusions as exudative effusions [40]. A re-evaluation of Light's criteria demonstrates that Light's criteria have an overall sensitivity for an exudate of near 100%, but a specificity of only approximately 80% [41]. In the search for the ideal test or improvement of Light's criteria; from the first day of Light criteria that were published the most widely accepted and so far have stood the test of time. Based on a meta-analysis of study in order to find the ideal diagnostic criteria, including 1448 patients, an updated version of Light's criteria, the original light studies a slightly modified by the addition of cholesterol as a marker, recommended as the best way to determine exudate. Judged by these criteria, a patient with any of the following criteria is provided, said to be exudates [42]:

- Pleural fluid protein greater than 2.9 g/dL
- Pleural fluid cholesterol greater than 45 mg/dL
- Ratio of pleural fluid LDH to serum LDH greater than 0.6

The appearance of the pleural fluid obtained by thoracentesis, its consistency and color should be noted. In patients with a known underlying malignancy, it is daily practice not only to obtain the usual tests to differentiate a transudate from an exudate (total protein and lactate dehydrogenase both in the fluid and in the serum) but also to obtain total and differential cell count, pH, glucose level, cholesterol and triglycerides, cytological analysis, hematocrit (if fluid is grossly bloody), and cultures. [37, 38].

Malignant pleural effusions may be serous, serosanguineous, or bloody, and usually are exudative in nature [21]. There are four characteristics features of pleural effusion; suggesting malignancy in patients with undiagnosed pleural effusion: that is to say, [1] a symptomatic period of more than a month, [2] absence of fever, [3] blood-tinged or bloody pleural fluid, or [4] CT findings suggestive of malignancy (pulmonary or pleural masses, pulmonary atelectasis, or lymphadenopathy) [43].

Despite all the progress in the imaging of the chest, for the diagnosis of MPE cytologic or tissue biopsy is required for approval. Cytology is the simplest definitive and most accurate method to diagnose malignant pleural effusion. Recent data suggests that at least 50 mL of pleural fluid should be studied in order to provide optimal cytological analysis [44, 45].

Diagnostic success of cytology can improve with repeated thoracentesis [46]. Fluids should be concentrated first for optimal detection of malignancy. There is a large variation in diagnostic yields of pleural fluid cytology ranging from 62 to 90% [47, 48]. The sensitivity depends on the type of malignancy, extent of disease, and experience of the cytopathologist [49].

Cytology of MPE in breast cancer has a sensitivity of 47% [50]. The diagnosis of adenocarcinomas can be established in nearly all patients whereas patients with pleural effusions secondary to Hodgkin's disease, have a positive cytologic examination in less than 25% of cases [51, 52]. Cytology is superior to blind percutaneous pleural biopsy in the diagnosis of malignant pleural effusion. Blind percutaneous pleural biopsy carries an 8% risk of pneumothorax, and has limited contribution to the diagnosis of patient with suspected malignancy. In a series of 118 patients with pleural effusions and negative cytology, closed pleural biopsy established the diagnosis of malignant pleural effusion in only 17% of the cases [53].

Low diagnostic value of pleural biopsy depends on costal pleural involvement of cancer cells in only half of patients with MPE since initial metastatic disease most commonly occurs on the visceral, mediastinal, and diaphragmatic pleurae [54].

After thoracentesis, pleural biopsy might be indicated in cases with cytological examination undiagnosed or suspected. Diagnostic value of conventional closed pleural biopsy with Abrams or Cope needles is lower when compared with image-guided and thoracoscopic biopsy techniques. The specificity of closed needle biopsy for MPE is high, but case series report sensitivities that range from 7% to 72% [53, 55-57]. However, closed pleural biopsy adds little to the cytological diagnosis in most cases and this is related to the scarce and irregular distribution of the tumour lesions in the pleural cavity when cytology is negative [54]. The yield of blind needle biopsy is higher when the pleural lesions are diffuse, as in tuberculosis and advanced neoplastic disease. In contrast, thoracoscopy has a very high yield in malignant effusions. It can be performed with local anesthesia and a single port of entry, and it has a little more complications than needle biopsy [47]. Contraindications to pleural biopsy include bleeding diathesis, anticoagulation, chest wall infection, and lack of patient cooperation. Important complications include pneumothorax, haemothorax, and vasovagal reactions. A rapid clinical deterioration or increased postprocedure effusion should alert the clinician to a possible haemothorax [58]. Nevertheless, pleural needle biopsy can be performed on outpatient basis [59] whereas thoracoscopy is much more complex and always requires hospitalization.

Normal pleural fluid pH ranges from 7.60 to 7.64. When a diagnostic thoracentesis is performed, pleural fluid pH is measured at any time. Analysis should be via a blood gas machine, not on litmus paper, because the latter is unreliable and not an acceptable alternative [60]. Approximately one-third of malignant effusions have a pleural fluid pH of <7.30 at presentation [61, 62]; this low pH is associated with glucose values of <60 mg/dL [63]. The cause of these low-glucose, low-pH malignant effusion appears to be an increased tumour mass within the pleural space compared with those with a higher pH effusion, resulting in decreased glucose transfer into the pleural space and decreased efflux of the acidic by-products of glucose metabolism, carbon dioxide (CO2], and lactic acid, due to an abnormal pleural membrane [64, 65]. Clinicians should keep in mind that parapneumonic effusions have pH less than 7.3 or puslike looking.

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In general, cell counts obtained from the pleural fluid is rarely useful or pathognomonic. Because most cells are normally neutrophils or monocytes, a predominance of lymphocytes (>50%) should make one more seriously entertain the idea of a carcinomatous pleural effusion, and greater than 85% lymphocytes should make one entertain the diagnosis of lymphoma, sarcoidosis, chylothorax, rheumatoid pleurisy, or yellow nail syndrome [66, 67]. An increase in pleural fluid eosinophilia (>10% of nucleated cells) might be associated with benign disease (hemo- or pneumothorax), but also can be associated with all types of malignancy [68]. The presence of mesothelial cells is not helpful in terms of diagnosis [67, 69]

Several tumor markers have been used in diagnosing of MPE, but their clinical role has not been firmly established [70]. Higher levels of CEA are seen in squamous cell cancer and adenocarcinoma of lung while higher levels of CA 15-3 are observed in breast cancer [71]. The addition of any tumor marker assay would improve the diagnostic value of cytology [70].

Chromosome analysis has low sensitivity and specificity in diagnosing of MPE [71]. It may be helpful particularly with MPE secondary to lymphoma and leukaemia [72]

The molecular biology of pleural effusions has begun to be understood, with vascular endothelial growth factor (VEGF) emerging as a major role player [73]. Because it induces endothelial vasodilatation and enhances the permeability of the mesothelium 50,000 times more potently than histamine, VEGF is thought to be a major, if not the most important, cytokine in the etiology of effusions [74]. VEGF may be a part of the diagnosis of effusion in the future.

6. Diagnosis

MPE has a wide variety of diagnostic methods. Diagnostic methods are often chosen according to health care provider's medical facilities, the clinician's ability and most importantly the patient. In spite of all the advances in today's thoracic imaging confirmation of suspected malignant pleural effusion done by cytological methods or a pleural biopsy, a diagnostic thoracentesis is recommended for any unilateral effusion or bilateral effusion in an individual without obvious evidence of congestive heart failure [75]. Diagnostic thoracentesis is a useful initial approach for patients with MPEs. Thoracentesis takes place in diagnosis of MPE as well as reducing the symptoms. Thoracentesis also helps us in evaluation of the expansion capacity of the lung and relieving acute symptoms.

Traditionally, land selection for thoracentesis is determined by radiographic and physical examination findings [76]. There is no absolute contraindication for thoracentesis. Relative contraindications include a minimal effusion < 1 cm in thickness from the fluid level to the chest wall on a lateral decubitus view, bleeding diathesis, anticoagulation, and mechanical ventilation. There is no increased bleeding in patients with mild-to moderate coagulopathy or thrombocytopenia (prothrombin time or partial thromboplastin time >1.8 times normal, platelets <25,000/mm^3, or creatinine >6 mg/dL) [77]. Although it does not seem to increase the risk of pneumothorax in patients undergoing mechanical ventilation; if a pneumothorax

occurs, the development of tension pneumothorax may be higher. Although the risk of pneumothorax rate is 10% in experienced hands, this risk increases in novices.

Important complications of thoracentesis include pneumothorax, bleeding, infection, and spleen or liver laceration. The amount of fluid drained during thoracentesis should be sufficient to obtain a diagnosis, relieve symptoms of dyspnea, and to avoid re-expansion pulmonary oedema or pneumothorax. The general belief and the guidelines proposed removal of more than 1500 ml in one hemithorax during a single transaction. However, this random number does not consider each patient's height and weight. As a general rule, the amount of fluid discharged from thoracentesis is 20 ml per kilogram of body weight [78]. On the other hand in recent studies, the risk of re-expansion pulmonary oedema was shown to be unrelated to the amount of drained fluid and it has been suggested that no upper limit is required [79].

Diagnostic thoracentesis is also useful in determining a patient's respiratory complaints that can be connected with effusion: Improvement in the patient's symptoms after thoracentesis indicates that the patient can take advantage of more invasive procedures and improve the quality of life. Persistence of respiratory symptoms in patients after thoracentesis, other causes should be investigated and before proceeding, more invasive diagnostic options should be considered twice.

The use of ultrasound guidance is preferred in thoracentesis. Ultrasound guidance, at the time of determining the location of the pleural fluids reduces accidental injury, and this technique to remove the liquid used to assess the degree of lung reexpansion [80].

Thoracoscopy should only be done in patients not diagnosed by less invasive procedures. Actual thoracoscopic techniques include video-assisted thoracoscopic surgery (VATS) [81] and medical thoracoscopy with either a rigid thoracoscope [82] or a semirigid pleuroscope [83, 84]. The advantages of thoracoscopy include visually directed and selective biopsies of parietal, mediastinal, and visceral pleura, direct visualization and examination of the entire hemithorax, and simultaneous lung or lymph node biopsy if required. The procedure is well tolerated with less than 1% mortality [85, 86].

Medical thoracoscopy when compared with surgical thoracoscopy (which is more precisely known as video-assisted thoracic surgery (VATS) has the advantage that it can be performed under local anaesthesia or conscious sedation, in an endoscopy suite, using nondisposable rigid instruments. Physicians skilled in bronchoscopy should find the semirigid pleuroscope easy to use because it has the same light source, video equipment, and manual controls as the fiberoptic bronchoscope [83, 84].Thus, it is considerably less invasive and less expensive than VATS. As an exception: VATS that allows huge biopsy samples can be taken, is preferred to medical thoracoscopy in patients with suspected mesothelioma. For diagnosis of mesothelioma and classification of its subtype, a large pleural biopsy specimen is often necessary. Immunohistochemical staining provides essential information in the diagnostic evaluation [6].

Medical thoracoscopy is primarily a diagnostic procedure [47, 87, 88]. In cases of undiagnosed exudative effusions with a high clinical suspicion for malignancy, some clinicians may proceed directly to thoracoscopy if the facilities for medical thoracoscopy are available. The procedure should be performed for diagnosis and possible talc poudrage [47].

The sensitivity of medical thoracoscopy was higher than that of cytology and closed pleural biopsy combined (96 versus 74%, pv0.001). Similar results have been reported by other investigators [89-92]. The reasons for false-negative thoracoscopy include insufficient and nonrepresentative biopsies that depend largely on the experience of the thoracoscopist [89, 92] and the presence of adhesions that prevent access to neoplastic tissue [87, 89].

The diagnostic yield of bronchoscopy is low in patients with undiagnosed pleural effusions and should not be undertaken routinely [93-95]. However, it is indicated when endobronchial lesions are suspected because of haemoptysis, atelectasis, or large effusions without contralateral mediastinal shift. Thoracotomy for diagnostic purposes is almost never indicated, because less invasive methods can provide diagnosis in up to 97% of cases [89, 96, 97].

7. Prognostic factors

Despite all the recent advances in cancer treatment management, MPE is suggestive of end stage disease with poor prognosis [51]. The mean survival is 3-6 months after diagnosis of malignant pleural effusion. Whereas, this period can take up to 4-12 months depending upon the histological subtype of the primary tumor such as in breast cancer, Hodgkin's disease, or lymphoma [98, 99]. The International Association for the Study of Lung Cancer reclassified MPE to the M1a descriptor, recognizing its prediction for poor long-term survival with an overall 5-year survival rate of 7% [100]. In addition, patients with malignant effusions, and a pH of less than 7:30 with wicked prognosis, shorter median survival, and poorer response to tetracycline pleurodesis and have a high rate of first finding of malignant cells in fluid cytology [61, 101]

On the other hand, malignant pleural effusion significantly affects the quality of life and reduced mobility of patients with malignant disease.The main goals of treatment for pleural effusion are to decrease symptoms and improve the quality of life [11].

8. Treatment

The aims of the treatment include drainage of pleural space, apposition of the visceral and pleural surfaces with complete expansion of the lung, and obliteration of the pleural surface with dispersion of a sclerosing agent throughout the pleural space [78]. Treatment options for malignant pleural effusion (MPE) are varied and often tailored to the clinician's specialty and expertise, the patient's physical performance status, hospitalization status, and individual desires [78].

Selection of optimal treatment for each individual patient requires a careful assessment of the benefits and the risks of the treatment. Primary treatment targets should involve palliation or elimination of dyspnea, improvement of a patient's overall quality of life in order to restore daily activities, and implementation of oncological therapies [102]. Treatment options include repeat thoracentesis, tube thoracostomy with drainage and sclerosis with chemical sclerosant

agents, chronic indwelling pleural catheter, pleuroperitoneal shunt, intrapleural or systemic chemotherapy, thoracoscopy with drainage and talc insufflation, and pleurectomy [78].

8.1. Therapeutic thoracentesis

Therapeutic thoracentesis must be performed in all symptomatic patients with MPE. Up to 50% of patients may not have significant symptom relief due to comorbid conditions, generalized deconditioning from their malignancy, or incomplete re-expansion of the lung. Trapped lung may result from pleural-based malignancy or metastasis, pleural loculations, or bronchial obstruction with post-obstruction collapse [15]. A total of 98%–100% of patients will have reaccumulation of pleural fluid and recurrence of associated symptoms within 30 days of thoracentesis [103,104]. Therefore, recurrent thoracentesis may be a viable therapeutic approach for patients who have limited life expectancy or who are poor candidates for more definitive but invasive interventions [14].

Massive pleural effusions should be drained in a controlled fashion, avoiding evacuation of more than 1.5 l at one time or should be slowed down to about 500 ml/h. A massive evacuation of pleural fluid and rapid re-expansion of the lung can cause discomfort, bothersome cough, and hypotension. Reexpansion pulmonary oedema is a rare complication after rapid drainage of pleural effusion [105]. The mechanism of oedema progression is not fully clarified, but it is believed that it is mostly related to mechanical forces causing vascular stretching or injury, and increasing capillary permeability rather than the absolute level of negative pleural pressure [106].

8.2. Tube thoracostomy and pleurodesis

The aim of tube thoracostomy in MPE is primarily to drainage of the pleural cavity and demonstration of lung re-expansion before instillation of a chemical sclerosant. Typically a large bore chest tube is used though smaller bore tubes [10-14F) have been used for chemical pleurodesis [107-109]. Large bore chest tubes are associated with greater patient discomfort but have traditionally been used because of the concern of obstruction of smaller bore tubes by fibrin plugs. However, several randomized trials have compared small versus large bore chest tubes without significant difference in pleurodesis outcome [107, 110, 111].

Simple small bore drainage catheters have been used effectively. Gravity drainage of the pleural fluid can be accomplished and pleurodesis can be achieved with several agents. In one study, small-bore catheters yielded outcomes equivalent to patients receiving chest tube after diagnostic thoracoscopy, and in addition, they were more comfortable [107]. Additional small studies have been performed with early success using bleomycin or talc sclerotherapy [110, 112, 113].

An earlier randomized trial noted that pleurodesis following rapid drainage (median chest tube duration, 2 days) was equivalent to pleurodesis performed after drainage was less than 150 mL/day (median chest tube duration, 7 days). In summary, drainage of MPE using small bore catheter drainage and rapid pleurodesis achieves results similar to prolonged drainage prior to pleurodesis [78].

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Lung re-expansion is necessary for a successful pleurodesis. A failure of the lung to expand completely after removal of fluid is suggestive of a trapped lung [114]. Radiographic appearance of lung re-expansion can determine an adequate timing for pleurodesis; the amount of pleural fluid drainage is not particularly significant in the timing and outcome of pleurodesis. After pleurodesis, the chest tube can be removed once the pleural fluid drainage is less than 150 ml/day [115, 116]. Failure of pleurodesis may be due to incomplete drainage of the effusion, unequal distribution of a sclerosing agent within the pleural cavity, or trapped lung syndrome [17].

Pleurodesis is performed by mixing the sclerosing agent of choice with 50–100 mL of sterile saline and then instilling it into the pleural cavity through the chest tube or small-bore catheter. The chest tube is clamped for 1–2 h and then reconnected to suction. No benefit in distribution of sclerosant or outcome or has been shown from rotating the patient [118, 119].

A number of antineoplastic and non-antineoplastic agents are used for pleurodesis. Sterilized asbestos-free talc consistently produces the highest success rates regardless of how it is implemented. Talc can be applied as poudrage or slurry. Poudrage is insufflation of talc powder after evacuation of fluid, while slurry is instillation of talc solution through the chest tube after tube thoracostomy and evacuation of an effusion [120]. Walker et al. reported success with the use of talc in 93% (153/165) of patients with MPE [120] Viallat et al. reported a 79% success rate in patients with malignant mesothelioma and an 89% success rate in patients with other malignancies underlying pleural metastasis [121]. Kılıc et al. reported that the success rates with talc insufflation by VATS were 81% in patients with pleural malignant mesothelioma and 91% in those with other malignancies, defined by a reacculumation ratio in 90 days of 19% (6/31) and 9% (2/24), respectively [122].

The video-assisted thoracoscopic talc poudrage with talc slurry via chest tube in patients with MPE has shown similar efficacy [30-day outcome: 78% for poudrage and 71% for slurry). Respiratory complications seem to be slightly higher after talc insufflations (i.e., insufflation 14% vs slurry 6%) [123]. Talc is usually well tolerated, and its most common side effects are pleuritic chest pain and fever. Acute respiratory distress syndrome has been reported with talc pleurodesis, which correlates with higher doses [124-126].

Tetracycline was commonly used in the past in association with tube thoracostomy. Instillation of the tetracycline solution provides a faster pleurodesis and pleural symphysis than chest tube drainage alone; however, it may cause significant pain. Doxycycline is an available alternative to tetracycline and is felt to have roughly equal effectiveness [127].

Bleomycin, an antineoplastic agent, is used in pleurodesis as a sclerosing agent. The precise mechanism of action of bleomycin and other antineoplastic agents is not fully understood, but the optimal dose is 1IU/kg (average 60 IU). In a study on 199 patients with malignant pleural effusion, bleomycin achieved a 54% (108 patients) complete response rate [120]. In the same study, 24% of patients had chest pain, 24% had fever, and 11% suffered from nausea. Hemoptysis, rashes, and diarrhea were also reported. Other rare side effects of bleomycin include alopecia and pulmonary fibrosis. Diacon et al. compared bleomycin with talc poudrage. The

response to bleomycin was 59% whereas it was 87% for talc poudrage [128]. The disadvantages of bleomycin are its lower success rate and higher cost compared with tetracycline and talc.

Other agents tested for use for pleurodesis include cisplatin, cytarabine, doxorubicin, 5-FU, b-interferon, mitomycin C, and Corynebacterium parvum; however, these agents are not commonly used because of their high cost, adverse effects, and low efficacy [129].

8.3. Chronic indwelling pleural catheter

In patients not suitable for pleurodesis, or with recurrent MPE after pleurodesis, chronic intermittent drainage via a subcutaneous tunneled pleural catheter on an outpatient basis has been shown to relieve dyspnea effectively without serious complications [78,130]. A limited number of studies focused on the use of a chronic indwelling pleural catheter in patients with MPE. Putnam et al. summarized their experience with 100 consecutive patients with MPE treated with a chronic indwelling pleural catheter [78]. They concluded that placement of an indwelling pleural catheter was safe, effective and cost-effective. Hospitalization was only one day for patients treated with the pleural catheter, in contrast to 7 days with tube thoracostomy and sclerosis with doxycycline [12].

In a study by Pollak et al., the effectiveness of tunneled pleural catheter's in the treatment of malignant pleural effusions was assessed in 28 patients [130]. Dyspnea improved in 94% at 48th h and 91% on 30th day. Control of the MPE was achieved in 90% of patients. They concluded that the pleural catheter requires a shorter hospitalization and can be placed and managed on an outpatient basis. Other authors concluded that placement of an indwelling catheter was the right procedure in subjects with evidence of a trapped lung [131]. With respect to potential complications of pleural catheters, infections and dislocations of the catheter are seen most often. However, serious complications are uncommon.

8.4. Pleuroperitoneal shunt

The pleuroperitoneal shunt was introduced in 1982 for the management of pleural effusions. Pleuroperitoneal shunts transfer fluid from the pleural space to the peritoneal cavity actively when manually pumped (Denver shunt) or passively (LeVeen shunt). Several series have shown that effective palliation can be achieved in up to 90% of cases [132, 133]. It is used for patients who have failed pleurodesis or systemic chemotherapy, are not surgical candidates, or have trapped lung. The major disadvantage of the pleuroperitoneal shunt is the length of time required to drain the pleural space. The volume of pumping chamber is only 1.5 to 2mL, which translates into the necessity for frequent and protracted pumping sessions, a major inconvenience for patients. Infection and shunt occlusion are the most significant complications, occurring in up to 15% of cases [134].

8.5. Systemic or intrapleural chemotherapy

For the patients with chemosensitive tumors, including small cell lung cancer, lymphomas, and tumors of the breast, prostate, ovary, or thyroid, or those which have arisen from germ cells, systemic therapy can prove to be equally or more effective than local therapy for relieving

malignant effusions. After the initial therapeutic thoracentesis, chemotherapy must be administered and pleurodesis, can be delayed until systemic treatment becomes ineffective [135].

Administration of chemotherapeutic agents directly into the pleural space has the potential to control the underlying malignancy and/or the MPE by producing high drug concentrations localized at the malignancy site while minimizing systemic toxicity [138]. Ideal agents would have a slow clearance rate from the intrapleural cavity, allowing greater exposure of cancer cells to the cytotoxic agent. Doxorubicin hydrochloride, cisplatin, cytarabine, mitomycin C, and 5-FU are some of the agents used.

Several studies have investigated the intrapleural use of several active cytokines. Interleukin-2 and interferon-β have been used. Their success varies but, in general, the results were poorer than that of talc [137, 138]. Staphylococcus aureus superantigen (SSAg) is one of the newer agents. Given current indwelling methods allowing chronic access to the pleural cavity, intrapleural chemotherapy remains a potential mechanism of drug administration, however, further studies are required.

8.6. Thoracoscopy

Tube thoracostomy and drainage with instillation of sclerosing agents is the most common treatment used for malignant pleural effusion. Chest tube drainage and pleurodesis does not allow lysis of adhesions to drain loculated effusions, which are often the reason for failure. The video-thoracoscopic approach allows for breaking of fibrin bridges and consequent loculations, insufflating talc uniformly on pleural surfaces, and full re-expansion of the lung [139].

The video-assisted thoracoscopy (VATS) should replace conventional instillation of talc slurry through tube thoracostomy as a procedure of choice to achieve pleurodesis. VATS pleurodesis offers reasonable palliation of MPE with low morbidity and rapid recovery. It is a safe and effective approach with an efficacy ranging from 88 to 97.5% [139, 140]. The VATS seems to be superior to simple chest tube drainage in management of MPE (92.3% vs 59.3%), with remission rates of 88.5 and 44.4% respectively [42,43]. In a series of 148 patients (VATS pleurodesis in 82 patients and tube thoracostomy with pleurodesis in 66 patients), VATS demonstrated longer recurrence-free survival and improved quality of life [142].

Thoracoscopic mechanical pleurodesis is a parietal pleura abrasion causing inflammation and adhesion of the parietal and visceral pleurae as a result of the healing process. Abrasion of the parietal pleura is initiated to yield uniform oozing. An injury to the visceral pleura should be avoided to reduce the risk of parenchymal injury, which would cause long-lasting postoperative air leak. Its efficacy was re-evaluated in a series of breast cancer patients (n=87) with MPE. Thoracoscopic mechanical pleurodesis and talc pleurodesis demonstrated similar success rates (92 and 91%, respectively) [143].

A VATS pleurectomy can provide excellent pleurodesis with less postoperative discomfort and pulmonary dysfunction compared to thoracotomy. Another benefit of VATS pleurectomy is a reduction of chest pain in patients with malignant tumors of the pleura and lung disease. In addition, it carries a lower risk of postoperative morbidity, less discomfort, and a better quality of life in terminally ill patients [144].

8.7. Pleurectomy

Pleurectomy, which is a palliative debulking procedure, is used to reduce the size of the tumor. However, it can also be done to relieve the lung and provide pleurodesis as a result of severe adhesions between the lung and the chest cavity. A posterolateral thoracotomy provides adequate access to the pleura. The pleura is stripped from the apex to the diaphragm. Dissection is continued in anterior, posterior, and apical aspects of the chest wall [144].

The procedure has a low mortality rate (1.5 to 5%), and it is well tolerated in patients with multiple morbidities [145]. Most authors concluded that thoracotomy was not indicated in patients with malignant effusion because of the high complication rate and prolonged hospitalization [146]. Most authors now agree that VATS is the only surgical approach that can be used in these patients [135, 147].

9. Conclusion

In conclusion, almost any cancer can produce an MPE which is a common clinical problem in thoracic surgery. MPE is prevalent disease and its therapy is essential. The presence of a malignant pleural effusion usually indicates advanced disease that is incurable with surgery alone. At all events, control of malignant pleural effusions is often difficult and inadequate. The risks of the therapy options should be considered meticulously. The survival time is short and expressed with months in patients with MPE. The goal of the treatment is to decrease the symptoms and the duration of hospitalization as well as to improve the quality of life of the patient. Also we aimed to return the patients and their families to daily life as earliest as possible. In order to achieve these targets, the therapy should be established for each patient according to the type, severity, localization and prognosis

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