Review Article

Pleural carcinosis caused by extrathoracic malignancies

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Abstract: Most of malignant tumors at an advanced stage can affect the pleural cavity creating malignant pleural effusion (MPE). Pleural carcinosis secondary to extrathoracic malignancies has not been extensively reported, and different treatments have been described. Although 40% of all cases of MPE are due to lung cancer, the second-most common is breast cancer (25%), lymphoma (10%), ovarian cancer (5%), and gastro-intestinal cancers (5%). For approximately 5% to 10% of MPE, no primary tumor can be found (cancer of unknown primary). Definite evidence of a MPE can be obtained by cytological or histological confirmation of cancer cells. taken using Uniportal surgery increases diagnostic accuracy as large biopsies could be taken and used to perform supplementary tests for more advanced management such as immunotherapy or hormone receptor status for breast cancer. Conventional thoracic treatments such as thoracocentesis, chest tube drainage, pleurodesis, video-assisted thoracic surgery (VATS) procedure have shown extremely limited effect on quality of life and long-term survival which ranges between 4–12 months. New technology procedures such as hyperthermic intrathoracic chemotherapy (HITHOC) or immunotherapy have shown some potentiality. With an eye toward the future, the main aim of this article is to provide a summary of the well-known treatments for pleural carcinosis caused by extrathoracic malignancies with the main intention to contribute to clarify decisions making.

Keywords: Malignant pleural effusion (MPE); uniportal video-assisted thoracic surgery (VATS); extrathoracic malignant effusion; Talc pleurodesis; hyperthermic intrathoracic chemotherapy (HITHOC); hyperthermic chemotherapy

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Introduction

Pleural carcinosis is caused by the implantation of malignant cells to the visceral and/or parietal pleura, and the most common result is the development of malignant pleural effusion (MPE). Metastasis to the pleura (carcinosis), along with pleural effusion, is a late event in the course of many malignancy. Almost all malignant tumors at an advanced stage can affect the pleural cavity; however, certain malignancies are more prone to involve the chest. These are malignancies of colon, breast, kidney, stomach, pancreas, prostate, soft tissues, and genital tracts. It has been estimated that 15% of all kinds of cancer patients will develop pleural effusion as a result of pleural metastasis of the primary cancers (1). Patients with metastatic lung cancers may present clinically with signs and symptoms related to pleural involvement or may be initially asymptomatic. Diagnosis is never simple and treatment is unfortunately only symptomatic and palliative. Established praxis for treatment of MPE is well known, based on standardised guidelines (2,3). It is evident that all the conventional thoracic treatments such as thoracocentesis,

Table 1 Clinical experience with 23 patients with extrathoracic cancers

Metastatic cancer	Number (n=23)
Breast	9
Thymus	2
Malignant lymphoma	2
Bladder	2
Rhabdomyosarcoma	1
Kidney	1
Larynx	1
Idiopathic	5

chest tube drainage, pleurodesis, video-assisted thoracic surgery (VATS) procedure have highly limited effect. Mechanical decompression and creation of adhesions in case of pleurodesis result in a 4 to 12 months length of life, and some improve of QOL, according to most published data.

This article provides a summary of the well-known treatments for pleural carcinosis caused by extrathoracic malignancies with the main intention to contribute to clarify decisions making for this common clinical problem.

Incidence

The incidence of MPE with pleural carcinosis in Europe is approximately 375,000 to 400,000 new patients/year, and has been found at autopsy in 15% of patients with malignant tumors and in 42–77% of exudative pleural effusion. Although 40% of all cases of MPE are due to lung cancer, the second-most common is breast cancer (25%), lymphoma (10%), ovarian cancer (5%), and gastro-intestinal cancers (5%). For approximately 5% to 10% of MPE, no primary tumor can be found (cancer of unknown primary). In our previous experience with 23 patients with malignant disease and pleural effusion due to extrathoracic disease 39.1% were due to breast cancer and 21.7% were idiopathic (*Table 1*).

Pathophysiology

The parietal pleura has a more significant impact to pleural fluid exchange than the visceral pleura, and this is probably secondary to the closeness of the parietal pleura to microvessels and lymphatics. The regular volume of pleural fluid is around 0.26 mL/kg body-weight. When in the chest the balance between production and absorption of the pleural fluid is compromised, pleural effusion is unavoidable. Pleural carcinosis creates an irritation of the pleura leading to increase development of interstitial pleural fluid as a consequence of augmented permeability.

Clinical symptoms

The extent of the effusion is the main responsible for the symptoms and signs, progressive dyspnea, accompanied or not by chest pain, and cough is a common symptom. Nevertheless, symptoms of the underlying malignancy are frequently associated, and the patent's overall physical condition is often reduced.

Diagnosis

The main question is if histopathological confirmation of pleural carcinosis is mandatory in a patient with previous cancer elsewhere. In the real life when MPE is suspected a chest X-ray is the first diagnostic step, and patients with pleural carcinosis usually have medium-large pleural effusions. For some authors ultrasound (US) is not only complementary to radiological investigations of the chest but often provides better results, and therefore, should be the first imaging examination method after chest radiography in presumed pleural disease. Nevertheless, recently, US has been demonstrated to be unreliable for establishing this method as the first diagnostic tool (4).

Computed tomography scan (CT) and magnetic resonance offer more data in many patients with suspected tumors of the chest. Moreover, MPE is not rare findings on the follow up HRCT in final stage of malignant diseases, even yet in asymptomatic patients. In case of massive effusion, thoracocentesis should performed to confirm the presence of bloody MPE, and to permit the lung to expand as it is important to evaluate the presence of a trapped lung or lobe to individualize the treatment. Nevertheless, definite evidence of a MPE can be obtained only by cytological or histological verification of cancer cells. The accuracy of cytological proof of cancer cells range, from 50% to 90%. Diagnostic accuracy increases by a large biopsy taken using uniportal video-assisted thoracic surgery (U-VATS) (5-7). Moreover, the large biopsy can also be used to perform supplementary tests for more advanced management such as immunotherapy or hormone receptor status for breast cancer.

Table 2 Medical and surgical procedures

Thoracocentesis
Indwelling pleural catheter
Chest drain
VATS pleurodesis
Cytoreductive surgery P/D
HITHOC

HITHOC, hyperthermic intrathoracic chemotherapy.

Prognosis

In general, patients with pleural carcinosis and MPE have poor quality of life, prognosis is dismal, with a mean survival of approximately 4–12 months survival rate of around 18%. Karnofsky performance status (KPS) represents the only statistically significant predictor of survival, and it is useful in choosing the type of treatment/palliation in patients with MPE. A limit of 40 or more KPS shown better outcomes for patients planning pleurodesis (8). Prognosis is influenced by biological aggressivity of malignancy, histology of the tumor, timely diagnosis, and the success of relatively narrow field of therapeutic thoraco-surgical procedures. In particular, the survival is longer in patients with breast cancer compared with patients with stomach or ovarian tumor.

Treatment

There is no doubt that the main objective of surgery in patients with pleural carcinosis is palliation with the intention to improve length and quality of life, and decreasing the recurrence of the effusions. The first step of the treatment for patients with MPE is the fully evacuation of the pleural effusion and, if the lung expands, pleurodesis. Possible operative treatments options are summarized in *Table 2*. Although at an initial stage minor pleural effusions can be monitored, in case of progression with increasing dyspnea, pleural effusion must be evacuated before a trapped lung develops. Malignant diseases cause besides MPE also paramalignant pleural effusion, which is categorized by the absence of malignant cells. The distinction between those two is of paramount importancy because they greatly differ in prognosis and treatment (9).

Cytoreductive surgery has the main aim to reduce tumor mass but it's value in the management of pleural carcinosis need confirmation. In presence of a chemo-sensitive primary tumor (e.g., lung, breast, prostate cancer, lymphoma), systemic chemotherapy may be used while the effects of such therapy on pleural metastases is highly questioned in case of synchronous or metachronous cancer. Furthermore, radiotherapy may further improve survival. Pleurodesis and permanent pleural catheters have been showed in retrospective studies to improve quality of life in patient with MPE. Nevertheless, there exist only one prospective randomized trial comparing indwelling pleural catheters to talc pleurodesis (10).

Thoracentesis

Thoracentesis is fundamental for two reasons. Firstly, because it is useful to perform an accurate diagnosis in two-thirds of patients with pleural carcinosis and malignant effusion, and secondly because it alleviates dyspnea. Patients with complete post thoracocentesis pulmonary expansion are eligible for future pleurodesis.

Chest drain insertion

The insertion of a chest drain is suggested in case of fast recurring pleural effusions following a thoracentesis, and to give antineoplastic drugs (e.g., bleomycin) or talc for pleurodesis. Recurrent MPE, usually after two complete thoracentesis indicate the need for insertion of chest drain. Chest tube insertion carries with its own risks. Because it is a pathway for potential infection, patients with chest drain require monitoring of inflammatory parameters. In the case of prolonged secretion, despite pleurodesis, a thoracic tube with Heimlich valve may also represent a definite option for palliation.

Indwelling pleural catheters

When the lung does not expand after a thoracentesis or general conditions are poor, indwelling pleural catheters can be used as an outpatient procedure (11). Several authors have shown safety and effectiveness with a success rate of 91%, and low complications. Moreover, because it has been shown that the use of this type of catheter achieves spontaneous pleurodesis in 26-58% of patients, in many circumstances it is likely to eliminate the catheter (12). In another case controlled and cohort study it has been shown that median survival was 3.4 months and did not differ significantly between breast (n=39, 23%), lymphoma (n=12, 7%), or other extrathoracic

cancer (n=56, 34%). One or more complications such as erroneous placement of tools or iatrogenic lesions occurred in 19 patients (19%). Some authors performed a randomized trial comparing the efficacy and safety of indwelling tunneled pleural catheters and traditional doxycycline pleurodesis showing a short hospital stay and low recurrence rates for indwelling pleural drain (13).

VATS talc pleurodesis

Although minimally invasive surgery can be performed with 1, 2 or 3 ports, since 20 years we prefer uniportal VATS (14,15) which can be performed under local anesthesia and sedation or under general anesthesia using single or double lumen tube (5,16). Pleural biopsy, drainage of simple or complex effusion and lung decortication can be easily performed before talc pleurodesis/poudrage. Success ranges between 85% and 93%, depending on the local findings and the primary tumor. In our previous experience with extrathoracic pleural malignant effusion we performed uniportal talc pleurodesis as a spray powder in 51 patients with a success rate at 30 days of 90% (46 out 51 patients). Chest tubes were removed at 5±2 days (range, 2–9 days) and hospital stay was 6±2 days (range, 2–10 days). Morbidity was present in 12 (22%) patients (atrial fibrillation and hyperpyrexia) (5) (*Table 2*). Among patients with MPE and no previous pleurodesis, the TIME2 Randomized Controlled Trial showed no significant difference between IPCs and talc pleurodesis at relieving patient-reported dyspnea (17).

Debulking surgery

Pleurectomy and decortications are the main surgical steps of debulking surgery which have been used mainly for mesothelioma surgery. This type of surgery is associated with high complication rates such as bleeding or empyema (25%) and mortality rates which range, from 10% to 19% (18,19). When numerous pleurodeses have failed, pleurectomy could be a possible option for highly selected symptomatic patients with better prognosis (e.g., breast cancer). Although EBM proofs for such intervention for pleural effusion do not exist, at the moment pleurectomy is not an alternative to pleurodesis or the insertion of an indwelling pleural catheter. British Thoracic Society (BTS), the European Society of Thoracic Surgeons (ESTS) and the European Respiratory Society (ERS) do not recommend pleurectomy as an alternative to pleurodesis or indwelling pleural catheter in recurrent malignant effusions (2,20).

Hyperthermic intrathoracic chemotherapy (HITHOC)

The use of HITHOC has the main goal to sterilized the chest by injecting a chemotherapeutic agent into the cavity which leads to increased exposure of tumor cells to the agent itself. Hyperthermia improvs the efficacy of chemotherapy. Ried *et al*. have shown under *ex vivo* hyperthermic conditions, that cisplatin penetrates into human lung tissue with a median penetration depth of approximately 3–4 mm (21). Other authors (22) performed VATS biopsy and HITHOC in 54 patients with MPE with 74.1% 1-year survival rate (23).

Cytoreductive surgery and HITHOC

In the chest, pleurectomy/decortications combined with HITHOC has been used for pleural mesothelioma and secondary tumors such as thymoma with pleural involvement (24-27). HITHOC has already been performed in individual patients with pleural carcinosis detected intraoperatively during elective lung cancer resection and resulted in improved survival (28-31). To date, cytoreductive surgery and hyperthermic perfusion is not recommended as treatment for patients with secondary pleural carcinosis, unlike peritoneal carcinosis. This is because no curative approach exists, as tumor growth is usually advanced and generalized. The significance of this combination therapy for pleural carcinosis might be demonstrated in the future. Nevertheless, it is interesting to remember that already in 1972, the concept of immune system activation in the scenery of thoracic cancers was introduced by investigators who noted enhanced survival in patients with empyema after resections for lung cancer (32).

Pleural carcinosis secondary to metastatic breast cancer

A review showed that 119 out 660 patients with breast cancer developed thoracic metastases, which was also the initial site of tumour recurrence. Metastases were most often intrathoracic or intra-extra thoracic. In general the median survival after diagnosis of MPE is less than and a solitary thoracic metastasis which was 42 months (33). A randomized study was performed in patients with breast cancer with MPE. Patients underwent to VATS abrasion or bedside

talc slurry (5 g). Pleurodesis was not significantly different, but hospital stay was shorter in the surgical group (5.5 *vs.* 7.5 days, P<0.05), and complication rate and mortality were also better (16% *vs.* 26% and 0% *vs.* 9.5%) (34).

Pleural carcinosis secondary to hematologic malignancies

Although all hematologic malignancies can present with or develop pleural effusions, Hodgkin and non-Hodgkin lymphomas present malignant carcinomatosis with a frequency of 20% to 30%. A study on 833 patients with pleural effusions of unknown etiology demonstrated that pleural biopsy through medical thoracoscopy achieved a definite diagnosis of B-cell NHL in 9 out of 10 (90%) patients with MPE. The authors concluded that MT is a useful method for diagnosing MPE induced by NHL. In most cases, pleurodesis is necessary (35-37).

Pleural carcinosis secondary to ovarian cancer

Ovarian cancer is the 5th most common malignancy which metastasis in pleura. From 2012–2018, according to GLOBOCAN, mortality rate of ovarian cancer become a higher with 0.1%, from 4.3–4.4%. Approximately 75% of patients with ovarian cancer are diagnosed in advanced stages (III–IV), which include spreading the tumor into the pleural space. Cervical cancer they encompass 10% of all new cases in 2018. Cervical cancer with an estimated over 500,000 cases and over 300,000 deaths in 2018 worldwide, ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women. Endometrial cancer is the most common cancer of the female genitals. Hematogenous spreading are very rare, and most common way of spreading is through pelvic and para-aortic lymph nodes, pelvic viscera or adnexa. Incidence of extra-pelvic, pulmonary metastasis is 2.3–4.6%.

Pleural carcinosis secondary to gastro-intestinal cancers

Pleural carcinosis and MPE from gastrointestinal carcinoma are not frequent, and involve about 5% of all MPE. Advanced stage in colorectal cancer (CRC) is characterized by distant metastasis usually in liver and lung. Pleural manifestation is rare and reserved for end stage of mCRC disease. Because the colon is drained by the portal system metastatic disease is not expect in other organs without the presence of the tumor in the liver. Rectal cancer, on the other site, can be spread through the portal and systemic venous system and can be present in pleural space in majority of cases of mCRC. The presentation of CRC as pleural effusion and isolated pleural metastasis without the involvement of lung parenchyma is very rare. Theoretically tumor cells can be spread via pulmonary circulation and then involve parietal or visceral pleura. The data of pulmonary metastasis of gastric cancer are very limited. The most common way of spreading is hematogenous (52.3%) followed by pleural (35.2%) and lymphangitic (26.4%). Pancreatic cancer is also a possible cause of MPE, but extremely rarely in the final stages. Checking the amylase in the pleural effusion can confirm the etiology of such effusion. Portal hypertension of every, even malignant etiology, is a possible cause of pleural effusion. Mechanism is well known and presented with movement of ascites fluid trough diaphragmatic defects. Bacterial superinfection with enterobacteriaceae is most common complication in such liquidothorax.

Pleural carcinosis secondary to renal carcinoma

MPE secondary to renal cell carcinoma is rare and constitutes only about 1% to 2% of all MPEs. Moreover, even though the lung is one of the most common sites of metastasis of renal cell carcinoma the involvement of pleura has been reported in about 12% of the autopsies of patients with metastatic renal cell carcinoma. There are only few case reports published to date that document the pleural metastasis as initial presentation of renal cell carcinoma.

The presentation of renal cell carcinoma as pleural effusion and isolated pleural metastasis without the involvement of lung parenchyma is very rare (38,39).

Pleural carcinosis secondary to cancer of unknown primary (CUP)

In some circumstances MPE is due to a CUP. We recall that CUP could be defined as an mysterious cancer proved histologically from a metastasis when after a thorough diagnostic work-up no certain primary tumor is identified. Patients with CUP develop usually fast metastases with a poor response to chemotherapy and miserable survival (40).

Immunotherapy

Although many efforts have been done to provide effective

systemic and localized cytotoxic and immune-based therapies, there is currently no effective treatment for MPE, and according to the recent published data of the PulMiCC trial, we could expect an increasing number of MPE (41). Nevertheless, there is a contrast of opinions on the role of immunotherapy in MPE. In fact, recently some authors used immunohistochemical and transcriptional methods to explore the predictive influence of immune cells and expression difference of associated immunomodulatory particles in MPE. They found that the state of the immune system in MPE permits to offer extra information on prognosis (42). In contract other authors noted that the attempt to treat MPE have shown a resistance to almost all forms of drug treatment (43). The reason for the development of drug resistance of MPE is probably at the heart of the process that leads to the formation of metastatic deposits on the pleura. This process involves complex interplay establishing host-to-tumor signaling through mechanisms that stimulate pleural inflammation, tumor angiogenesis and vascular hyperpermeability (44). Moreover, it seems that immunotherapy not only does not lead to cure from MPE but appear to be in a complex process where T-cell effectors are suppressed and killed, and macrophages are reprogrammed to assist the development of anger and invasiveness of the tumor phenotype (45).

It is evident that more data are necessary for the development of immunotherapy directed to treat pleural carcinosis, but it remains the fact that tailor immunotherapy in tumor environments is desirable (46).

Conclusions and future perspective

Pleural carcinosis with symptomatic MPE is one of the most common scenario in clinical practice for physicians and surgeons. The correct decision making is mandatory and differential diagnosis is imperative in order to guarantee the best possible chance of success. Certainly, the treatment of dyspnea using a thoracocentesis is the primary treatment. Different procedures have been used to prevent re accumulation of the effusion, between them talc pleurodesis and indwelling pleural catheters are commonly used depending on the general clinical condition and the presence or not of a trapped lung. Uniportal VATS is a good way to apply talc, and is recommended when intraoperatively pleural carcinosis is detected and confirmed at frozen section.

More aggressive surgical therapies such as VATS pleurectomy has not been suggested by several guidelines. Nevertheless, the "need to do something" for patients with extrathoracic MPE lead many physicians and surgeons to test new modalities, and recent studies have shown that HITHOC alone or in combination with pleurectomy decortication could achieve longer survival maintaining a good quality of life. Despite of all existing controversy in the context of efficiency and effectiveness, HITHOC seems to be at present the only "promising" method, but it needs EBM proofs of effectiveness, reduction of side effects and standardization.

In the future it is evident that treatment for pleural carcinomatosis should be individualised, and therefore based non only on the patient's symptoms and quality of life, but also according to the immunology of the primary tumour and mood of the patient (47).

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