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A case report

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Multimodality approach to malignant pleural mesothelioma. A case report

INTRODUCTION: *We report a case of diffuse malignant pleural mesothelioma (DMPM) in a 68 years old male patient who was admitted for right sited pleural effusion. The patient was treated by multimodality approach consisting in surgical treatment with Extrapleural Pleuropneumonectomy followed by chemotherapy with Cisplatin and Pemetrexed. He had a disease free period of one year and survived for 31 months.*
CASE REPORT: *The patient was admitted to our Institute for a right sited pleural effusion diagnosed on chest X ray. Anamnesis revealed professional asbestos exposure and the patient presented dyspnea, dry cough, right sited chest pain, low fever and loss of weight.*
As thoracentesis and CT scan did not reveal pathological findings except of the effusion, we performed videothoracoscopy. Several grey nodular lesions involving the costal, diaphragmatic and mediastinic parietal pleural sheets were found. Histological examination of the specimens extracted revealed the presence of epithelial malignant pleural mesothelioma with sarcomatoid areas. Further examinations staged the lesion as Butchart I. Extrapleural pleuropneumonectomy was performed followed by a chemiotherapic treatment with Cisplatin and Pemetrexed. The patient underwent a follow up program with CT scan every four months. The disease free period was of about one year and the patient died after 31 months from diagnosis for septic complications related to chronic effusion.
DISCUSSION: *Single treatments do not demonstrate an acceptable efficacy on the treatment of DMPM. Multimodality therapy provides good survival improvement and acceptable quality of life for the patients.*

KEY WORDS: Extrapleural pleuropneumonectomy, Multimodality treatment, Pleural mesothelioma.

Introduction

We report a case of diffuse malignant pleural mesothelioma (DMPM) in a 68 years old male patient who was admitted for right sited pleural effusion. The histological examination of a pleural specimen obtained in videothoracoscopy diagnosed a pleural mesothelioma with mixed histological pattern. Further instrumental investigations showed a Butchart's stage I disease. The patient was treated by multimodality approach consisting in surgery with Extrapleural Pleuropneumonectomy followed by chemotherapy with Cisplatin and Pemetrexed. The patient survived 31 months from diagnosis with a disease free period of about one year and died for septic complications related to a chronic pleural effusion.

Case report

A 68 years old male patient with history of prostate carcinoma was found to have a right sited pleural effusion at thoracic X ray done for follow up. Before admission to our Institute he underwent several thoracentesis with negative cytological and microbiological findings. Also

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CT scan did not reveal pathological findings except of the effusion.

At admission to our Institute in January 2005 the patient presented dyspnea, dry cough, right sited chest pain, low fever and loss of weight. Anamnesis revealed professional asbestos exposure as he worked in a shipyard. During physical examination we found diffused decreased breath sounds on the right hemithorax with dull percussion and absence of tactile fremitus. No alteration of neoplastic markers and blood tests was present, even cardiological examination and electrocardiography were within normal parameters.

Chest and abdominal CT scan were repeated, showing compression atelectasis of the right lower lobe caused by abundant right pleural effusion. No pathological findings of lung or parietal pleura were described.

For further investigation we performed right videothoracoscopy with diagnostic and therapeutic intent. After evacuation of 1000cc of a yellow limpid liquid several grey nodular lesions involving the costal, diaphragmatic and mediastinal parietal pleural sheets were found. Specimens for biopsy where extracted.

Cytological examination of the evacuated fluid demonstrated atypical cell elements with voluminous nucleus which seamed to be of neoplastic origin. The histological study of the specimens confirmed the neoplastic nature of the lesions. In fact, the presence of fibroadipous tissue with massive malignant neoplastic infiltration and the positivity for specific tumor markers (Cytokeratin, Vimentin, Calretinin, HMBE 1 resulted positive; TTF 1 and S-100 markers resulted negative) where compatible with diagnosis of mixed (or biphasic) malignant pleural mesothelioma with epithelial and sarcomatoid areas.

Once confirmed the diagnosis, we completed tumor staging. A chest scintigraphy with 99mTc–Tetrofosmin indicated an hyperaccumulation along the right lung profile in correspondence of the pleura. Also parahilar and paramediastinic areas of great uptake were found.

Positron emission tomography (FDG-PET) showed metabolically active areas in correspondence of the pericardium and the right pleura extended to the great fissure, while no suspect areas were detected at the contralateral hemithorax or underneath the diaphragm.

So the patient could be classified in Butchart's stage I and, as he had a good performance status, he was suitable for surgical treatment.

According to our oncologists we decided to perform surgical treatment with radical intent followed by adjuvant chemotherapy as described by Sugarbaker back in 1999.

On February 2005 the patient underwent right Extrapleural Pleuropneumonectomy with resection of the ipsilateral pericardium and diaphragm. We choose a right anterolateral approach with incision at the fifth and seventh intercostal space. Once opened the thorax we observed a diffused neoplastic involvement of the costal, diaphragmatic and mediastinal parietal pleura. We also found visceral pleural involvement and numerous adhesions between lung and parietal pleura. After "en bloc" resection of pleura, hemidiaphragm, right pericardium and lung we proceeded to reconstruction of the pericardium with fenestrated Gore-Tex© patch, while a non fenestrated patch was used for the diaphragm.

The specimen testing described a malignant epithelioid pleural mesothelioma with areas of sarcomatoid aspects and areas of parenchymal lung involvement.

Thirteen days after operation (March 2005) the patient was dismissed and sent to the oncologists. On April 2005 a FDG-PET revealed metabolically active areas in correspondence of the right anterolateral costophrenic sinus, the right hemidiaphragm and right paratracheal lymph nodes. These findings were compatible with postoperative inflammation or tumor recurrence.

Subsequent systemic chemotherapy was started in May 2005 with Cisplatin (130 mg intravenous) and Pemetrexed (875 mg intravenous). After the first administration the therapy was suspended because of the onset of fever (38°C), cough, right sited chest pain and acute leucopoenia (<2000 x 10^3). Chest X-ray showed right thoracic effusion and bronchoscopy revealed a 2mm bronchial leakage of the right principal bronchus. More than once we afforded to endoscopic resolution, also using different types of glue, but we achieved only temporary benefits. The patient refused surgical treatment, and in June 2005 we placed a permanent thoracic drain.

A CT scan performed on January 2006 showed local tumor recurrence at the right paramediastinic area (7cm of diameter) and the right anterolateral chest wall (7cm of diameter). Also peritoneal carcinomatosis and several hepatic lesions (sixth segment and between second and fourth segment) were described.

The patient performance status permitted to restart the chemotherapic treatment with palliative intent on February 2006, using the same regimen as in May 2005 (Cisplatin 130mg i.v. + Pemetrexed 875 mg i.v.). In April 2006, after three cycles of chemotherapy, another CT scan was done and no signs of tumor could be detected. All the recurrences described previously were regressed.

The patient started a follow up program with total body CT scan every 4 months. At the forth CT examination, done in June 2007, recurrences were redetected in correspondence of the chest wall and the liver.

The disease free period, after the chemotherapic treatment, amounts to more than 12 months with an acceptable quality of life. On August 2007, the patient was admitted to an internal medicine department with fever, dyspnea and decadence of the general conditions. The patient died on September 2007 for septic complications related to the right chronic effusion.

Discussion

Diffuse malignant pleural mesothelioma is the most common type of mesothelioma, arising in the pleura from

mesothelial cells and showing a diffuse growth pattern over the pleural surfaces. In most industrialized countries, more than 90% of pleural mesotheliomas in men are related, principally for occupational reasons, to asbestos exposure (especially amosite and crocidolite fibre types). Actually, in the USA every year are diagnosed between 2000 and 3000 new cases and the incidence is expected to increase in future as a result of the high rates of asbestos exposure in the 70's and the disease's latency period of 20 to 50 years [1].

DMPM is an extremely aggressive neoplastic lesion characterized by a high local diffusion rate, with early involvement of the pericardium and the diaphragm, and by the attitude to recur after radical surgical treatment. Median survival time from diagnosis without treatment ranges from 4 to 12 months [2].

Macroscopically there are described local forms (Localized Malignant Pleural Mesothelioma LMPM) which are rare and less aggressive in comparison to the most frequent diffuse forms (DMPM). There are three different histological types of DMPM: Epithelial, representing about 50% of all cases, Sarcomatoid (35%) and Mixed or Biphasic (15%), with the epithelial form having a better prognosis[3]. Occasionally it is possible to reveal patterns of mesenchymal differentiation (chondroid, osteoblastic, fibrosarcomatous etc) or even cell patterns mimicking small cell carcinoma or lymphoma[4]. Differential diagnosis has to be made versus benign forms, adenocarcinoma and pleurisy and there are proposed several immunohistochemical and molecular panels of markers in order to avoid any diagnostic error [5,6].

For a long time it was believed that DMPM, did not respond to chemo or radiotherapies at all. Today, several therapeutic strategies able to provide important results in terms of survival and quality of life are available.

DMPM has a modest sensitivity to radiation [7]. Radiation therapy is an option to be used as a palliative treatment or as an adjuvant treatment after extrapleural pneumonectomy. Its utility is limited by the several side effects related to radio-sensibility of the near vital anatomical structures (risk for pulmonitis, esofagitis etc) [8]. If used alone, as a palliative treatment, radiotherapy is effective when beamed in doses higher than 40 Gy in small groups of selected patients [9]. If used as an adjuvant measure after EPP, it has a good efficacy in controlling local recurrence [10].

DMPM is relatively resistant to chemotherapy, particularly to single agent treatments with no substantial improvements on overall survival. The most effective agents are antimetabolites, platinum and anthracyclines but with poor results in terms of local recurrence control and survival rates and with important toxicity. Pemetrexed in some series used in single modality therapy showed better outcomes in comparison with other single agents[11]. Combination therapies present greater response rates than single agent therapies, in particular way the association of Pemetrexed plus Cisplatin which is accepted today as the standard chemical treatment for mesothelioma [12].

Among the single modality therapies surgery is the most effective treatment for DMPM. The radical surgical approach consists in extrapleural pulmonectomy (EPP): en bloc resection of pleura, lung, omolateral pericardium and hemidiaphragm. Other surgical approaches with palliative intent are pleurectomy, decortication and pleurodesis. The radical approach is indicated for stage I according to Butchart classification. In relation to the histological pattern, all authors accord with the indication to surgery for the epithelioid type; there is not unanimity regarding the other forms. In fact, a multivariate analysis showed that the most important factors for poor results after EPP was non – epithelioid histology, N2 nodal disease and positive resection margins[3]. EPP presents, in comparison with other surgical procedures, higher rates of perioperative mortality and morbidity but recent works report significant reduction of these parameters and longer disease – free survival time, for EPP alone or when associated to adjuvant Chemo or Radiotherapy [14-16].

Failure of single modality treatments, induced several authors to experiment multimodality treatments, associating different types of therapy and creating new treatment strategies: surgery plus radiation, surgery plus chemotherapy and surgery plus chemoradiotherapy. These combinations, called multimodality therapy, had better survival rates and acceptable toxicity compare with the single modality treatments. The therapeutic strategy based on the association of adjuvant chemoradiotherapy to surgery is called Trimodality therapy and actually it can be considered the most effective treatment[16].

Conclusions

Single treatments do not present an acceptable efficacy for the treatment of DMPM. Multimodality therapy provides good survival improvement and acceptable quality of life for the patient. A lot more has to be done to optimise surgical performances, to research more effective chemical agents with greater activity and less side effects and to improve the efficacy of radiation therapy reducing it's toxicity to surrounding anatomical structures.

Riassunto

Descriviamo in questo nostro lavoro un caso di mesotelioma pleurico maligno in un paziente di 68 anni, ricoverato presso il nostro Istituto per versamento pleurico destro, diagnosticato in altra sede con una radiografia del torace. All'anamnesi il paziente riferì esposizione professionale all'asbesto. Il quadro clinico era caratterizzato da dispnea, tosse secca, dolore toracico all'emitorace destro,

febbricola e calo ponderale. Poiché ripetute toracentesi e l'esame TC non hanno mostrato alterazioni patologiche, il paziente è stato sottoposto a videotoracoscopia diagnostica, la quale ha rivelato la presenza di lesioni nodulari multiple a carico della pleura parietale costale, diaframmatica e mediastinica. L'esame istologico condotto sulle biopsie eseguite ha posto diagnosi di mesotelioma pleurico maligno di tipo misto. La stadiazione preoperatoria classificò la malattia come Butchart I. Il paziente è stato sottoposto a trattamento multimodale con pleuropneumonmectomia extrapleurica seguita da chemioterapia adiuvante con Cisplatino e Pemetrexate. Il periodo di sopravvivenza libero da malattia è stato superiore all' anno ed il paziente è deceduto dopo 31 mesi per complicanze settiche legate ad un versamento pleurico cronico residuo. Mentre la sopravvivenza media senza trattamento varia da 4 a 12 mesi per pazienti affetti da mesotelioma pleurico maligno, ed i singoli trattamenti offrono modesti miglioramenti in termini di sopravvivenza e di qualità di vita, le strategie terapeutiche multimodali ottengono risultati migliori e devono essere di prima scelta nel trattamento di questa malattia.

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