A pathological complete response after preoperative chemotherapy with carboplatin and pemetrexed in malignant pleural mesothelioma: A case report.

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ABSTRACT Malignant pleural mesothelioma is an aggressive tumour with poor prognosis and short duration of response probably due to the high chemo-refractoriness. Multimodality treatment based on preoperative chemotherapy, surgery and adjuvant radiotherapy seems to be a feasible and effective therapeutic option in selected patients.We report on a case of pathological complete response in a patient affected by malignant pleural mesothelioma who was treated with four cycles of preoperative chemotherapy based on carboplatin plus pemetrexed followed by parietal pleurectomy and lung decortication. Carboplatin plus pemetrexed was a well tolerated regimen without grade 3-4 haematological toxicity, and this confirm the feasibility of such a treatment as an alternative to the current golden standard based on cisplatin plus pemetrexed.Complete resection allows the pathologist to better describe biological markers of mesothelioma cells, in order to select patients with different treatment outcome and prognosis.

Key Words: mesothelioma; chemotherapy; carboplatin; pemetrexed

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Introduction

Malignant pleural mesothelioma (MPM) is an aggressive tumour with poor prognosis and increasing incidence in industrialized countries as a consequence of the previous widespread exposure to asbestos. Multimodality treatment based on preoperative chemotherapy, surgery and adjuvant radiotherapy seems to be a feasible and effective therapeutic option in selected patients. Currently, the combination of pemetrexed plus cisplatin is the golden standard first-line chemotherapy for MPM patients (1); also pemetrexed plus carboplatin is an active and well-tolerated regimen in the same setting (2). The main clinical problems of MPM management are the short duration of response and the early relapse, probably due to the high chemo-refractoriness of the disease.

No potential conflict of interest.

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Case report

We report on a 75-year-old non smoking man with previous asbestos exposure who presented with a 2-month history of dyspnoea during physical exertion and right thoracic pain. Chest X-ray examination showed right pleural effusion.

The patient underwent multiple pleural biopsies and pleurodesis by video-assisted thoracic surgery (VATS).

All the tissue fragments were fixed in formalin and processed by usual methods. Histological examination showed pleural fragments enlarged by fibrosis and containing nodular infiltration of atypical epithelial cells; single atypical elements among collagen fibers as well as small nodules were present. The cells were medium sized with eosinophilic cytoplasm, central ovoid nucleus and evident nucleolus. The mesothelial origin of these atypical cells was documented by the unreactivity with TTF-1 antibody and by the strong staining pattern of LW-cKeratin (AE1), calretinin and HMBE antibodies. p53 antibody showed a strong reactivity in more than 50% of neoplastic cells and the proliferative fraction as documented by Ki67 labelling index was up to 20% (Fig 1A-C).

Histologic subtype was defined as epithelioid mesothelioma.

Disease staging was performed with a CT-scan that showed

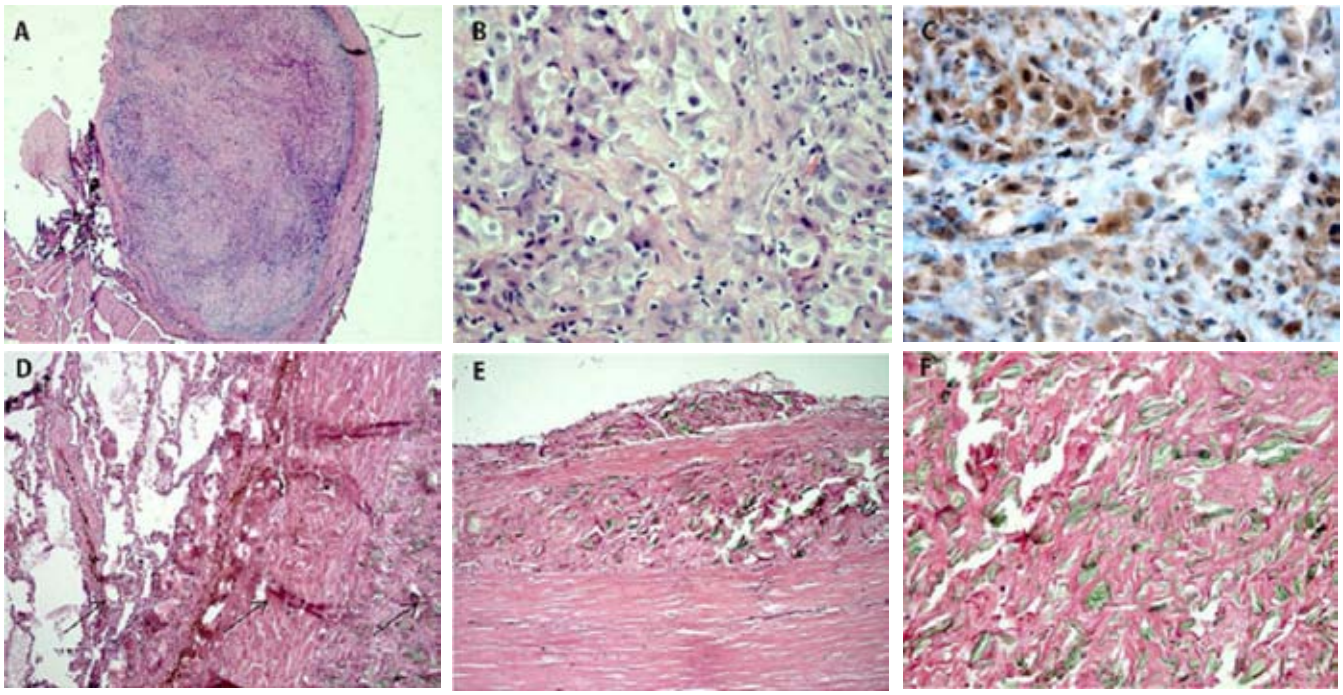

Fig1. Nodule-like pleural lesion (A); atypical epithelial cells without grown pattern, among collagen fibers (B); strong staining pattern of calretinin (C); lung, fibrosis of visceral pleura, pleural surface with granulomas around foreign material and absence of cancer lesions (D); details of chronic granulomas full of giant cells around needle-like birefringent foreign material (E-F).

right pleural thickenings and interlobar septal nodule-like feature without any enlargement of mediastinal lymphnodes (Fig2A-C), defining a stage II according to TNM staging system.

The patient was treated with four cycles of carboplatin administered to target an area under the concentration/time Curve (AUC) of 5 mg/mL/min and pemetrexed 500 mg/m2 on day 1 every three weeks and supplemented with oral folic acid and intramuscular vitamin B12.

No grade 3-4 haematological toxicity has been shown; grade 1 leucopenia, grade 1 anaemia and grade 2 neutropenia were present during the last cycle.

Non-haematological toxicities were grade 1 nausea and constipation. No ECOG Performance Status impairment was shown during the treatment.

Disease re-staging with CT-scan showed no pleural effusion and a massive reduction of pleural thickness (Fig2D-F), classified as a partial response higher than 50% according to modified RECIST criteria for MPM.

The patient underwent a right parietal pleurectomy and lung decortication by open thoracotomy after 8 weeks since the last cycle of chemotherapy.

We defined a complete resection as a resection of all tumoral lesions without macroscopic residues.

The histological examination of the surgical specimen showed pleural tissue without epithelial layer, covered by fibrinous exudate, with many chronic granulomas full of giant cells around needle-like birefringent foreign material, with fibrous-hyaline thickening and focal calcinosis. Sub-pleural lung parenchyma was free from cancer findings with inter-alveolar fibrosis (Fig 2D-F).

No residual malignancy was shown at the right pleura, lung, hilo-mediastinal lymphnodes and the sixth rib; as a consequence, no adjuvant radiotherapy was administered except for the surgical scar (21Gy/3F). Currently the patient is followed-up in our outpatient clinic and is free from relapse after 50 weeks since diagnosis. Data were reported according to the patient informed consent.

Discussion

Trimodality treatment seems to be the best therapeutic option for malignant mesothelioma patients, achieving an overall survival longer than 20 months in some series (3-6). The main effect of chemotherapy in this setting seemed to be disease stabilization (40-70%), whereas response rate was about 30%.

In the multimodality approach, the goal of surgery is to provide a macroscopic complete resection defined as the removal of all tumoral lesions without macroscopic residues.

Preoperative chemotherapy based on the association of cisplatin plus pemetrexed achieved 1.3% of radiological complete

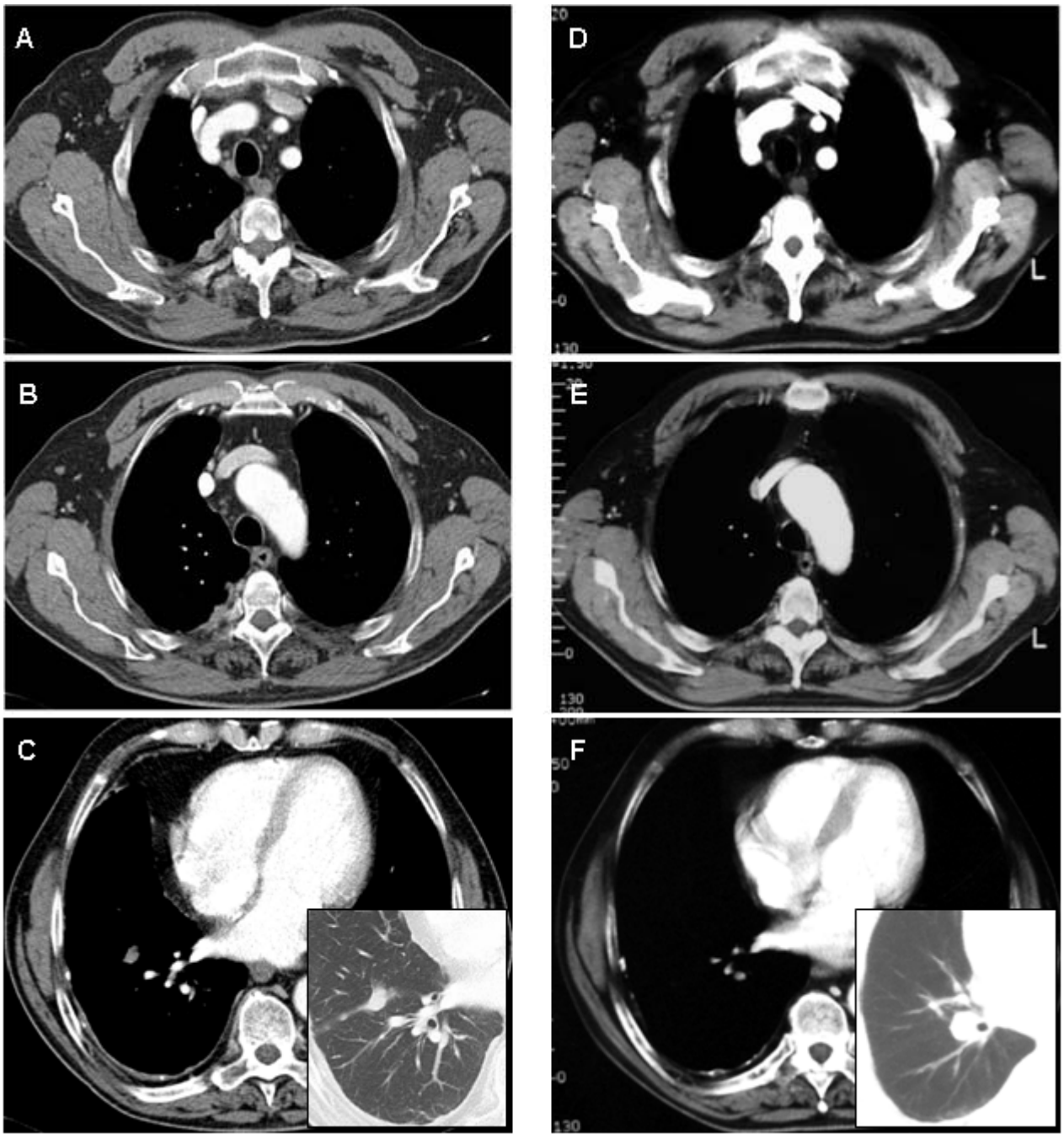

Fig 2 Mediastinal windows of CT-scan before chemotherapy showed right pleural thickenings and interlobar septal nodule-like feature (A-C); disease re-staging with CT-scan at the end of the four cycles of chemotherapy showed the disappearance of most of the lesions (D-F). The involvement of the lung fissure is more evident in the lung window (C, F).

responses and about 5% of pathological complete responses among patients who underwent extrapleural pneumonectomy (5,6). These data underline that induction chemotherapy in mesothelioma patients achieves a lower rate of pathologic complete response compared to other tumor types (e.g. non-small cell lung cancer). Further efforts are needed to improve cytotoxicity of currently used regimens in order to improve the outcome of the affected patients and to get the pathological diagnosis and staging of the disease.

Patients not eligible for radical surgery seem to benefit from carboplatin plus pemetrexed. A phase II trial showed a response rate about 20% (2% complete response, 18% partial response)

and a disease stabilization of 47%. Median time to progression was 6.5 months and median overall survival time was 12.7 months (2), quite similar to the results achieved with the standard regimen of pemetrexed and cisplatin (1). The regimen was well-tolerated and patients with disease control showed a stabilization or improvement of quality of life.

These evidences underline that carboplatin plus pemetrexed could be a valid option as preoperative chemotherapeutic regimen in patients eligible for a multimodality approach.

So far, no prospective trial with carboplatin plus pemetrexed as induction chemotherapy in the context of a multimodality treatment was performed. We have recently analyzed activity and tolerability of pemetrexed plus carboplatin or cisplatin in the first-line treatment of 54 operable patients with resectable MPM. We showed a response rate of 33% (complete response: 3%, partial response: 30%) in patients treated with pemetrexed/carboplatin (AC) vs 17% (no complete response, 17% of partial response) in patients treated with pemetrexed/cisplatin (AP). Moreover, cumulative non-haematological toxicities and PS worsening were commoner in AP-treated patients, and this could impair the clinical conditions of patients undergoing surgery.

Two surgical approaches are possible in operable MPM patients: extrapleural pneumonectomy in case of advanced locally invasive disease with extensive involvement of visceral pleura and fissures, and pleurectomy/decortication in patients with superficial tumors without large involvement of lung and fissures. Moreover, patients with limited disease and a compromised respiratory function test of the tumor-involved lung could benefit from pneumonectomy.

In this particular case, considering the limited stage of disease and the presence of a single nodule-like feature in the interlobar fissure, our patient underwent a parietal pleurectomy with lung decortication.

The surgical specimen of the patient we reported about showed no residual malignancy at the pathological examination, and this seems quite unexpected according to the high chemoresistance of the disease. Favourable factors in this patient were stage II and epithelioid histology. Furthermore, toxicity was moderate and no dose reduction was applied. These factors might have had an effect on improved response to chemotherapy. A good concordance between radiological and pathological response was found: CT-scan showed the persistence of a modest pleural thickening at the rib vertebral angle, but this corresponded to a fibrous-hyaline thickening and focal calcinosis at the pathological examination.

Complete resection allows the pathologist to better describe peculiar biological characteristics of the tumoral sample, in order to select mesothelioma patients with different prognosis and who could benefit from targeted treatments.

The availability of mesothelioma tissue from surgical or bioptical specimens could improve the analysis of anti-apoptotic protein expression, namely Bcl-2 and IAP (inhibitors of apoptosis proteins) family, which seem to be highly expressed in chemo-refractory MPM.

The inhibition of such targets could sensitize mesothelioma cells to apoptosis, and this seems to be a promising strategy to improve cytotoxicity of chemotherapy regimens.

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