Malignant mesothelioma: our experience in the last five years

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Purpose

Malignant mesothelioma is a rare neoplasm, but it is the most common pleural primary tumour. It presents a clear association with exposure to asbestos, a material whose use is prohibited and regulated in Spain since 2001. However, given the long latency period from exposure to onset of the disease, it still presents a high influence nowadays. It has a poor prognosis, with an average survival lower than one year after diagnosis. Our goal is to understand its impact on Spanish population and to study in our cases both typical and atypical radiological manifestations. Other objectives are to review the staging and to study the role of CT in the post-treatment controls.
Methods and Materials

A retrospective study of patients diagnosed from June 2006 to July 2011 with malignant pleural mesothelioma was carried out in the Clinical University Hospital of Valladolid (Spain).

A total number of 40 patients were studied, 30 of which were men and 10 were women. Their age ranged from 56 to 79, with an average age of 67.

Plain chest x-ray studies and CT thoracoabdominal studies were conducted to all patients. A CT with two detectors was used until 2008, while two multislice CT, with 32 and 64 detectors respectively, were used since then. Series from thyroids to iliac crests were obtained. An average of 100 ml of iodinated contrast was administered at 2.5 ml/s with a delay from 30 to 60 seconds. No adverse reactions were observed.

In 14 cases PET was available and in 4 cases MRI was available.

The radiological findings obtained were reviewed, as well as pathologic data and treatment response.
RESULTS:

A total number of 40 patients with pathological diagnosis were studied: 1 with mesothelioma pericardial and 39 with malignant pleural mesotheliomas. 30 of them were men and 10 were women, with an average age of 67. Unilateral involvement was detected in 37 patients (17 on the right side and 18 on the left side) and bilateral involvement in 2 of them.

The referred clinical data was: chest pain (70%), dyspnea, and fatigue and weight loss. According to the clinical history 10 cases recorded past asbestos exposure. The final diagnosis was achieved in all cases by thoracoscopy and/or biopsy.

Radiological findings were pleural effusion in 36 patients (90%), pleural thickening or masses in 34 (85%), diaphragmatic involvement in 6 (15%), mediastinal invasion in 8 (20%), chest wall invasion in 4 (10%), mediastinal lymphadenopathy in 10 (25%), pulmonary involvement in 6 (15%) and extrathoracic involvement in 4 (10%). (fig 1)

Pathology diagnosis was mesothelioma (unspecified) in 20 cases; epithelioid mesothelioma was diagnosed in 12, sarcomatoid mesothelioma in 6 (including 2 desmoplastic) and biphasic mesothelioma in 2. (fig 2)

Average survival was 11 months. At the present time 6 patients are still alive.

DISCUSSION:

Malignant mesothelioma is a rare neoplasm, but it represents the first primitive tumour of the pleura. The most important etiopathogenic factor is exposure to asbestos, although there are speculations about other possible etiologic agents such as the SV40 virus, radiation therapy or genetic factors. Therefore, its impact on the world is very different depending on the exposure to asbestos, being more common in the United States, Canada and Australia (ref 1). In Europe there is a rising trend in recent years, being Britain at the top of the list with an annual average of 15 cases per million inhabitants. In Spain there are approximately 4 cases per million inhabitants/year.

Even if the law prohibits the use of asbestos in Spain since 2001, it is expected that the incidence of the disease in this country will keep rising during many years (ref 2) due to the long latency period from exposure, which varies from 15 to 40 years.
The reference area for Thoracic Surgery Department of the Clinical Hospital of Valladolid covers a population of approximately 800,000. Occupational exposure to asbestos was common in this area due to the presence of cement factories and other industries such as railroads, insulation and building in which asbestos was used. An annual average of 8 cases was detected in this study, which represents a high value compared to the whole Spanish country results (about 4 cases per million population/year).

According to the hospital records occupational exposure to asbestos was present only in 10 cases (25%). This figure is lower than expected, which can be attributed to the fact that work history data was not collected routinely in every report.

The age of disease onset (67 years), the male predominance of the disease (4/1) and the patient's clinical data (chest pain and dyspnea) are similar to most of the publications reviewed.

**RADIOLOGICAL FINDINGS:**

**Plain chest x-ray:**

It was the first test performed, in which unilateral pleural effusion was the most frequently detected finding (up to 90%) (Figure 3), with only 5% of bilateral pleural effusion. Contralateral mediastinal shift is not common as the tumour usually infiltrates parenchyma (Fig. 4). Volume loss on the affected side with widening of intercostal spaces and elevation hemidiaphragmatic is usually found.

Up to 60% of cases present diffuse or lobulated pleural thickening (figure 5) creating a pleural shield, which surrounds the lung and produces ventilatory compromise. Multiple pleural masses can also be observed (Figure 6), as well as enlarged hilar mediastinal widening caused by lymphadenopathy or mediastinal infiltration, and even wall invasion with periosteal reaction, coastal erosion or destruction. (Ref 3 and 4).

**CT scan:**

The CT scan was the next test performed following clinical suspicion of pleural mesothelioma. It provided great anatomical information which is important in patient management. Pleural effusion was observed in 90% of cases, generally unilateral. In some cases this was the only finding. The effusion is usually associated to pleural nodular
thickening (Figures 7, 8 and 9) with lung volume reduction. Fissures affectation are common (Fig 10), and sometimes calcified pleural plaques can be observed. As this is a locally invasive tumour, in some cases chest wall involvement with obliteration of fat planes and intercostal muscle invasion were visualized (fig 11 and 12). Mediastinal, pericardial and diaphragm infiltration can also be observed (Figures 13, 14 and 15 respectively). In 25% of cases lymphadenopathy was detected (Figure 16). Although less frequently, in some cases lung and/or liver metastases were observed (Figure 17). The only case of pericardial mesothelioma was manifested as a single focal mass adjacent to the left ventricle's posterior side (Figures 18 & 19).

The diagnosis is suggested by the findings related to TC, and confirmed by thoracoscopy (Figure 20) and biopsy.

**Differential diagnosis:**

The differential diagnosis is performed with:

- Pleural effusion from other cause
- Metastases
- Lymphoma pleural
- Benign asbestos pleural disease
- Tuberculous pleurisy
- Thymoma with pleural dissemination.

**Pathological diagnosis:**

Pathological diagnosis is histological, being invasion the most important diagnostic criterion (Figures 21 & 22). Immunohistochemical techniques are very useful but none of them are definitive on their own. The association of several positive techniques: calretinin, CK 5/6, WT1, vimentin, HBME-1, etc. and negativity of CEA, MOC 31, TTF-1, Ber-EP4, BG8 are very indicative. (It should be noted that pathologist will sometimes have difficulty in differentiating between epithelioid mesothelioma and metastases, and between sarcoma and sarcomatoid mesothelioma).

**Staging:**
The TNM is the most used classification (Figure 23) (ref 5), (although for some authors is not optimal for mesotheliomas). It helps to categorize patients into groups according to different treatment options. The "T" will condition the therapeutic options, regarding also differences in survival: T3 is considered locally advanced but potentially surgical, and T4 as technically inoperable disease.

**Prognostic factors:**

There are other prognostic factors: histological (non epithelioid have worse prognosis) and clinical (worse prognosis: age> 75 years, elevated LDH, elevated platelets, malaise, chest pain) which, together with the TC, will help choosing among the therapeutic alternatives.

New biomarkers are being investigated (ref 6) in serum and pleural fluid: SMRP (soluble mesothelin-related-peptide-), MPF (megacariocyte-potentiation-factor) and osteopontin whose levels can be used to monitor treatment response.

**PET:**

PET has proven to be useful in improving the staging (with better accuracy in tumoural extension and detection of lymphadenopathy) and the evolutive controls (ref 4) (figures 24 & 25).

**MR:**

MR provides useful anatomical information (especially before multislice CT was available) to assess the diaphragmatic and chest wall extent, as well as cases of allergy to contrast. (ref 4)

**RECIST:**

Multislice CT, in addition to its utility in diagnosis, is essential in post-treatment controls. In oncologic radiology using RECIST criteria is useful (ref 7) in order to assess as objectively as possible the treatment response. In the case of the mesothelioma, the use of the modified RECIST is recommended (ref 8) which consists of measuring target lesions using the perpendicular axis of a fixed structure (rib or vertebrae) instead of using injuries' longest axes. The reason is that in mesotheliomas these longest axes are more difficult
to obtain accurately, so using modified RECIST allows easier comparison in subsequent studies of the patient (Figures 26 and 27).

**Treatment:**

Depending on the staging and the already mentioned clinical criteria, the following treatment options are possible:

- **Surgery:** Radical surgery is extrapleural pneumonectomy (pleura, lung, ipsilateral hemidiaphragm and pericardium block resection). Palliative surgery is pleurectomy (complete or not) and pleurodesis. The recent multicenter MARS (Mesothelioma And Radical Surgery) study limits radical surgery to a few cases, due to the significant surgical morbidity (Ref 9).

- **Chemotherapy:** adjuvant and neoadjuvant. Pemetrexed is currently used (this new chemotherapeutic agent from antifolates group is the most promising) and Cisplatin.

- **Radiotherapy:** adjuvant and palliative for pain treatment.

- **Multifactorial** (surgery, chemotherapy and radiotherapy).

Results are still poor with any of the mentioned treatments, so new alternatives are needed in the future, such as immunotherapy, gene therapy, improving chemotherapeutic agents and therapeutic targets (inhibitors of epidermal growth factor, endothelial factor, etc.). As a result of the legal restrictions to exposure to asbestos, the disease's incidence is expected to decline in the long term.
Fig. 1: Radiological findings frequency for the cases of study in the Clinical University Hospital of Valladolid

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Fig. 2: histological type percentage(%) for the cases of study in Clinical University Hospital of Valladolid

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**Fig. 3:** partially loculated pleural effusion

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**Fig. 4:** Left pleural effusion without mediastinal shift

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**Fig. 5:** lobulated pleural thickening

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Fig. 6: Multiple right hemithorax pleural masses

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Fig. 7: Coronal CT: Right pleural effusion with focal thickening

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Fig. 8: Plain x-ray and coronal CT: left pleural effusion with thickening and multiple pleural masses.

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Fig. 9: Effusion with pleural thickening and rounded atelectasis in underlying lung parenchyma

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Fig. 10: Pleural masses with right major fissure involvement

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Fig. 11: Multiple pleural masses with involvement of intercostal muscles

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Fig. 12: Pleural masses and chest wall invasion (arrows)

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Fig. 13: Pleural masses with mediastinal invasion in two different patients
**Fig. 14:** Pleural masses invading mediastinal fat, pericardium and chest wall

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**Fig. 15:** Diaphragmatic involvement in three different cases

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Fig. 16: mediastinal lymphadenopathy, mass and right pleural thickening are observed

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**Fig. 17:** Liver metastases (black arrows) and right adrenal (green arrow). Right diaphragmatic crura thickening (marked with *).

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Fig. 18: Pericardial mesothelioma. Top row: Axial CT, Bottom row: MRI a) coronal sequence FIESTA b), c) oblique sagittal and IIRR with and without intravenous contrast: pericardial mass in contact with left ventricle.

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**Fig. 19:** Pericardial mesothelioma. (Same case as the previous image) Plain x-ray: cardiophrenic angle mass. a) PET in frontal projection b) lateral projection PET: pathological uptake in heart, adjacent to left ventricle c), d) PET-CT fusion confirms uptake in pericardial mass with greater anatomic resolution

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**Fig. 20:** Thoracoscopy: multiple solid nodules in pleura are observed

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Fig. 21: Epithelioid mesothelioma which presents two components: papillary and solid. a) papillary mesothelium growth with large atypical cells. b) cells are stained with calretinin. c) solid component d) calretinin +.

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Fig. 22: Desmoplastic mesothelioma (included within the sarcomatoid). a) and b) spindle cells proliferation arranged in a swirling shape with mitosis. c) Ki 67: shows the proliferation index which is greater than 40% d) AE1, AE3: cytokeratin expression.

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Fig. 23: Malignant pleural mesothelioma staging.

Fig. 24: a) PET image with left pleura pathologic uptake. b) PET-CT fusion with higher resolution and a good anatomic correlation.

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Fig. 25: Mesothelioma with mediastinal and diaphragmatic involvement, with high uptake in PET. a) coronal CT b) PET-CT fusion c),d) Axial CT.

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Fig. 26: Modified RECIST: red line indicates the correct way to measure injuries perpendicularly to a rib. Black line indicates incorrect measuring.

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**Fig. 27:** Top row: multiple pleural masses. Bottom row: 6 months after treatment: There are partial remission.

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Conclusion

The incidence of malignant mesothelioma is not so low in Valladolid (Spain) population. CT is still the preferred method for disease diagnosis and monitoring. MRI and PET have proved to be useful.

Specific mesothelioma staging and modified RECIST method have to be known in order to evaluate the treatment response.
References


