Abstract. Malignant pleural mesothelioma is a rare tumour. A three-modal strategy, comprising of surgery, radiotherapy and chemotherapy has been shown to be essential for appropriate management. Current literature evidences the importance of radiation therapy in the adjuvant setting for local control of the disease, as part of a multidisciplinary treatment, with increment of progression-free survival rate, but also of disease-free survival. Case Report: At the beginning of 2007, a 26-year-old Peruvian woman was admitted to the hospital referring breathlessness and other non-specific symptoms such as fever and weight loss. After the diagnosis of pleural mesothelioma by thoracoscopic talc insufflation, combined with pleural biopsy, and total body computed tomographic scan, the patient underwent two cycles of neoadjuvant chemotherapy with pemetrexed (500 mg/m²) and cisplatin (75 mg/m²), followed by an extra-pleural pneumonectomy. After 6 months, the patient was treated with three-dimensional external beam radiation therapy to the left hemithorax. Computed tomographic scans, performed after the ending of the radiotherapy, integrated with positron-emission tomography, were all negative for neoplastic pathology. The patient remains in good health and free from recurrence at four years. Conclusion: This clinical case shows a disease-free survival interval of 4 years for malignant pleural mesothelioma. A good staging system and a combined treatment, involving surgery, neoadjuvant chemotherapy and adjuvant radiation therapy, represent a useful strategy not only to contain local disease progression, but even to increase disease-free survival in pleural mesothelioma.

Malignant pleural mesothelioma (MPM) is an uncommon neoplastic disease whose diagnosis is often difficult and prognosis is quite bleak. Over the last few years, its incidence is increasing all over the world (1), due to occupational and environmental factors, particularly those related to exposure to asbestos, and also associated with individual predisposition (2, 3).

During the last decade, the improvement in the accuracy of histological and radiological diagnosis (4) and in new technologies, such as positron-emission tomography (PET), have represented great tools for clinical evaluation of this disease. The introduction of new pharmacological agents (5) and the improvement of surgical techniques and postoperative care (6), with the reduction of the peri-surgical morbidity and mortality, has led to a more advantageous use of both chemotherapy and surgery. Furthermore, the availability of three dimensional (3D) and intensity-modulated radiation (IMRT) treatments make radiation therapy (RT) a fundamental part of the management of a disease considered radioresistant (7, 8).

All the standard approaches for treating solid tumour have been investigated in patients with MPM. Radical surgery has been demonstrated to be an effective intervention in a selected group of patients, even though the local recurrence rate reported was high and there was no survival benefit (7). The role of chemotherapy and RT has been mainly evaluated to palliate symptoms of MPM (7). Currently three-modal treatment is the most successfully strategy for this type of tumour (8). However, the multimodality approach has only shown modest improvement in median survival (7, 9) and patients with long-term survival reported in literature are exceptional. Furthermore, the role of adjuvant RT after surgery is still undefined, even considering the different RT techniques, such as 3D external beam RT (3D-EBRT) and IMRT, and the difficulty in achieving an acceptable toxicity profile (6).

Recently, treatment of a clinical case of MPM with a three-modality strategy at the Polyclinic Umberto I of the Sapienza University of Rome was shown to be associated with long-term disease-free survival (DFS).

Case Report

In February 2007, a 26-year-old Peruvian woman was admitted for severe dyspnoea, cough and low-grade fever.
Her medical history was unremarkable, without recurrent fever, bronchitis or pleuritis during her childhood, except for a suspected tuberculosis event when she was 4 years old. At age 10 she had moved to Rome, Italy, where she lives currently. She referred that she travelled for work, living close to steel plants for about five months, whose industrial activities are associated with a very high prevalence of asbestosis and asbestos-related diseases in Southern Italy. Among her family members there were two cases of breast cancer in her maternal great grandmother and her aunt, but no cases of MPM. The young woman had experienced a previous episode in November 2006, characterized by hyperthermia, pharyngo-tonsillitis and breathlessness.

On admission to hospital, the thoracic X-ray performed evidenced the presence of a pleural effusion in the left lung. The diagnosis of MPM was established by positive pleural fluid cytology on thoracentesis (2500 cc), followed by thoracoscopic talc insufflation, combined with pleural biopsy, demonstrating malignant disease of the epithelioid variety. The total body computed tomography scan (CT) showed neoplastic infiltration of the left mediastinal and diaphragmatic pleura, with no sign of involvement of local lymph nodes or the muscular wall or metastasis. After talc insufflation, dyspnoea decreased but the patient was in a persistent poor general condition.

In May 2007, at the Polyclinic Umberto I Sapienza University of Rome, the patient underwent two cycles of neoadjuvant chemotherapy with pemetrexed (500 mg/m²) and cisplatin (75 mg/m²), ending in July 2007. The main referred side-effect, was a slight grade of hypoacusis. Chemotherapy was followed, in September of the same year, by surgery, extra-pleural pneumonectomy, removing the left parietal pleura along with the pericardium, the ipsilateral diaphragm and the respective lung. The diaphragm and the pericardium were reconstructed with synthetic materials. Surgery was followed by good postoperative care and respiratory physiotherapy.

The histological examination of the surgical specimen was positive for neoplastic cells, of the epithelioid variety according to World Health Organization (WHO) (10), involving pleura, pericardium and diaphragm (pT1b, pN0, pMx, R0 stage I).

In December 2007, the patient was treated with 3D-EBRT, using a 6 MV photon linear accelerator with isocentral technique. The radiotherapy planning included nine conformal fields, two anterior, two lateral and five posterior, directed to the clinical target volume of the left hemithorax, with limiting dose administered to organs at risk, such as the heart, the esophagus and the bone marrow. The prescription was 180 cGy daily, five times per week, distributed in 28 fractions, for a total dose of 50.4 Gy. The side-effects reported were chest pain (G2) at 900 cGy, fever (G1) at 18 Gy, cough (G2) at 30.6 Gy, oral mucositis (G2) at 36 Gy, all treated with pharmacological therapy. RT was terminated in February 2008 and during the first follow-up visit, in June of the same year, the patient was in good health and had resumed her daily activities.

Total body CT, integrated with PET, performed in May of the same year, evidenced pleural-pneumonectomy outcomes with no signs of local tumour relapse, no right lung parenchymatous alterations and no pleural effusion, showing only an inflammatory process at the level of the windpipe and pharynx.

The subsequent total body CT scans, performed after 6, 12 and 28 months from the last CT-PET exam, showed no evidence of local disease relapse. In fact, the patient is in good general health, referring only a slight grade of hypoacusis, probably related to chemotherapy treatment, and remains free from tumour recurrence at four years.

Discussion

Life expectancy in MPM is low, with a median survival of 22, 16.5, 12.5 and 8 months for stage I, II, III and IV respectively (11). Median survival based on histological type is 12.5 months for the epithelial type, 9.4 months for sarcomatous type and 11 months for mixed types. For epithelioid and sarcomatous type, the two-year survival is 65% and 20% respectively, while five-year survival is 27% and 0% respectively (11). The only prognostic factor influencing survival is the histological type (11). Furthermore the absence of lymph node involvement also represents a positive prognostic factor.

The young age of our patient suggests an individual predisposition to this type of tumour (3), associated with exposure to unidentified environmental factors. MPM is more common in men than in women (1). In our case, we did not identify any direct or indirect exposure to asbestos, except for her stay in South Italy, close to steel plants for about five months when she was 21 years old (2). Although there were many cases of MPM among steel factory workers, in our particular case, the incubation period of the disease is too short to ascribe an association with the onset of MPM, which is characterized by a long latency period (13). The development of the tumour in the young patient is probably related to an exposure to asbestos fibres or to other environmental factors (13), during childhood or adolescence, together with a genetic susceptibility to this type of tumour (3).

A multidisciplinary treatment was shown to be an effective first strategy for MPM (9). Surgery is the main treatment for localised mesothelioma, but in the case of advanced-stage disease, the therapeutic options may include a multimodal strategy, with surgery, RT and chemotherapy.

In MPM the role of RT in pain palliation has been validated (8), but as a part of a multimodality approach, it is still undefined for improving local tumour control (9).
case has shown a long DFS of four years, without any local tumour relapse. This surprising result in MPM is not the first, although, unlike Higashiyama et al. (14), we used a trimodality treatment including RT.

For patients who undergo surgical treatment, local recurrence, within the surgically operated hemithorax, is the most common form of relapse (15). Efforts to reduce the likelihood of local recurrence after surgery have included the use of different regimens of chemotherapy, second surgery and EBRT (8, 9). Therefore in our case, the use of RT as part of a multidisciplinary approach could have played a fundamental role in increasing local relapse-free survival, without significant side-effects.

**Conclusion**

This case of MPM shows that in the presence of positive prognostic factors, a good staging system and a multimodality treatment may represent an effective strategy to avoid local tumour relapse, but also to promote long-term DFS.

**Competing Interests**

This manuscript has been read and approved by all the Authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The Authors report no conflict of interests. The Authors confirm that they have permission to reproduce any copyrighted material.

**References**


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