

## Malignant pleural mesothelioma presenting with symptomatic brain metastases: report of a case

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### Abstract

We describe a unique case of brain metastases presenting as first symptom of a malignant mesothelioma (MM). MM is a highly aggressive tumor of the serous membrane that is generally believed to be rarely metastasizing. Recently, the reports of long surviving cases and larger literature reviews have suggested that cerebral metastases are not so uncommon. An extensive histochemical and immunohistochemical panel is needed to achieve a correct differential diagnosis, especially in the epithelioid type. Pathologists should be aware that brain metastases could have a mesothelial origin.

**Keywords:** pleural mesothelioma, brain metastases, immunohistochemistry.

### Introduction

Malignant mesothelioma, a tumor of the serous membranes that is generally asbestos-related, is highly aggressive and largely unresponsive to current therapies. Survival is related to different mesothelioma subtypes [1–5]. The prognosis is extremely poor and mortality is due to extensive involvement of local structures, mostly in the lung, heart, pericardium, chest wall. Distant metastases (*i.e.*, liver, adrenal glands, kidneys, etc.) are a rare primary clinical presentation and are generally identified at autopsy [6]. The brain is an unusual secondary site and has a reported incidence of only 3% of intracranial metastases [6–16]. Symptomatic metastases are rare and when they are the primary clinical manifestation of a mesothelioma, the histological diagnosis could be difficult.

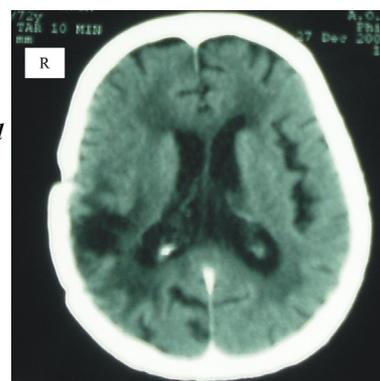
With the steady rise in incidence of mesothelioma over the past years in many parts of the world, ante-mortem brain metastases are expected to be diagnosed more frequently and surgical treatment should be considered.

We report a case of asbestos-related intracranial metastatic mesothelioma, presenting as a primary brain tumor in an older woman treated by surgery, with longer survival.

### Patient, Methods and Results

A 72-year-old Caucasian woman presented to the

Neurological Department in May 2006 with left-sided hemiparesis, headache and general convulsive attacks. Cranial computed tomography (CT) and magnetic resonance (MR) revealed, in the right cerebral hemisphere, a high-density lesion measuring 3 cm in diameter with perifocal edema (Figure 1).



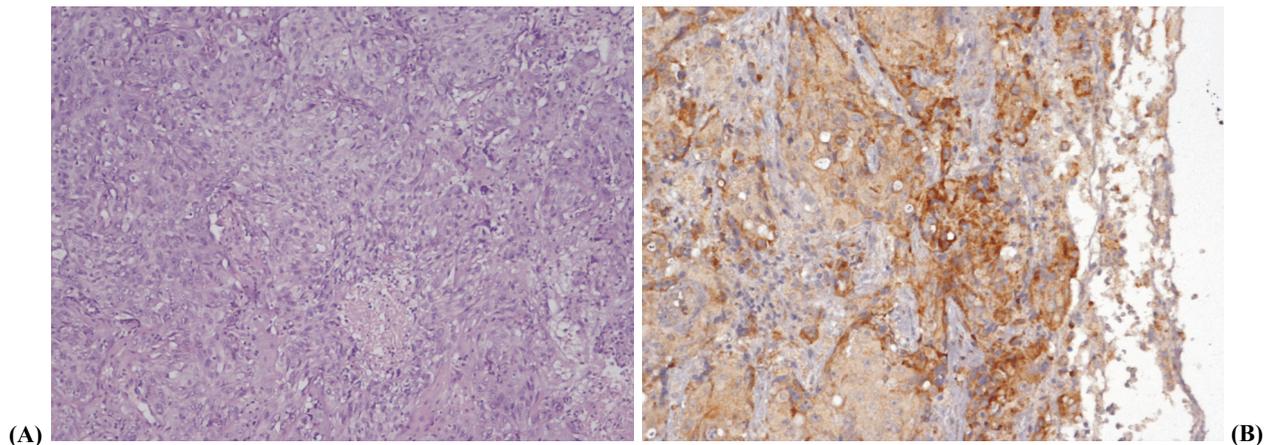
**Figure 1 – Computed tomography scan showing a high-density lesion, 3 cm in diameter, in the right cerebral lobe.**

The patient underwent gross total resection of the lesion. The intraoperative examination revealed a malignant neoplasm with pleomorphic epithelioid cells with comedocarcinoma-like necrosis, initially interpreted as a possible metastatic breast carcinoma (Figure 2A).

Tissue samples were fixed in 10% buffered formalin and embedded in paraffin blocks. Sections were cut at

4  $\mu\text{m}$  thickness, stained with Hematoxylin–Eosin, Periodic Acid–Schiff with and without diastase-digestion and

Alcian Blue with and without hyaluronidase digestion for the initial microscopic evaluation.



**Figure 2 – (A) Photomicrograph of the brain tumor observed in June 2006. Atypical large round epithelium-like cells with large nuclei having prominent nucleoli and a moderate cytoplasm, growing rapidly (HE staining,  $\times 100$ ); (B) Calretinin immunorexpression observed in brain cancer after revision (June 2007) ( $\times 200$ ).**

Subsequently, selected blocks were processed for immunohistochemical analysis (IHC) using the EnVision Flex Detection System (Dako, Denmark), DAB as chromogen substrate and stained with the Dako Auto-stainer after pre-treatment in a steamer at  $99^{\circ}\text{C}$  for antigen retrieval. Positive and negative control tissue specimens were used to evaluate antibody specificity.

Monoclonal antibodies against CK5/6 (Zymed, San Francisco, California, USA; 1:100 dilution), ER (Ventana, Tucson, AZ, USA; prediluted) and PR (Ventana; prediluted), HER-2 (clone CB11, Novocastra, 1:300 dilution) were tested. The tumor cells resulted cytokeratins positive; ER, PgR and HER-2 negative.

Mammography and breast MRI examination did not reveal a tumor and no lesions were found at bone scintigraphy. Then, a total body CT scan was performed, which demonstrated a left basal pleural abnormality, not further investigated. No visceral focal lesions or lymphadenopathies were found. The patient was discharged with no important neurological deficit and treated by adjuvant chemotherapy, CMF-type (Cyclophosphamide, Methotrexate, Fluorouracil) for a possible hidden carcinoma of the breast, and subsequently palliative whole brain radiotherapy.

One year later (June 2007), the woman presented to the Pneumology Department complaining of severe chest pain of sudden onset. A chest X-ray showed a large left-sided pleural effusion (Figure 3).



**Figure 3 – Chest X-ray showed a large left-sided pleural effusion.**

Chest CT-scan confirmed a large left pleural effusion with extensive left pleural abnormalities suspicious for malignancy. Bronchoscopy failed to reveal endobronchial lesions, whereas thoracoscopy showed a diffuse pleural thickening with multiple micronodules (up to 0.8 cm in diameter), which were biopsied.

Histology showed a predominantly epithelioid, poorly differentiated malignant tumor with a solid pattern, admixed with a spindle cell component. Necrotic areas were not observed. There were moderate mitoses ( $5/\times 10$  high-power fields) (Figure 4A).

For immunohistochemistry, tissue samples were tested for AE1/AE3 (Dako, Glostrup, Denmark; 1:50 dilution), CK5/6, calretinin (DBA, Milan, Italy; 1:3000 dilution), human bone marrow endothelial (cell)-1 (HBME-1) (Dako; 1:80 dilution), vimentin (Dako; 1:300 dilution), monoclonal carcinoembryonic antigen (Dako; 1:25 dilution), Ber-EP4 (Dako; 1:500 dilution), ER, PR, HER-2, monoclonal antibody NCL-L-562, WT49 clone (Menarini Laboratories, Newcastle, UK, 1:20 dilution), thyroid transcription factor (TTF-1) (clone SPT24, Novocastra, 1:100 dilution), CD15 (clone BY87, Novocastra, 1:20 dilution), S100 protein (polyclonal, Dako; 1:400 dilution), Leu-M1 (Becton Dickinson, San Jose, CA, USA; 1:40 dilution). The tumor cells resulted positive for CKAE1/AE3, CK5/6, vimentin, EMA, HBME-1, WT-1 and calretinin (Figure 4B).

Histological sections from the brain lesion were reviewed and the morphologic features and immunophenotype (positivity for vimentin, WT1 and calretinin), together with the clinical findings, were consistent with a primary malignant tumor of the pleura, metastasizing to the brain (Figure 2, A and B). However, ultrastructural analysis of both the metastatic and the pleural lesions was performed to support the diagnosis of a biphasic malignant mesothelioma with both solid epithelioid and spindle cell components.

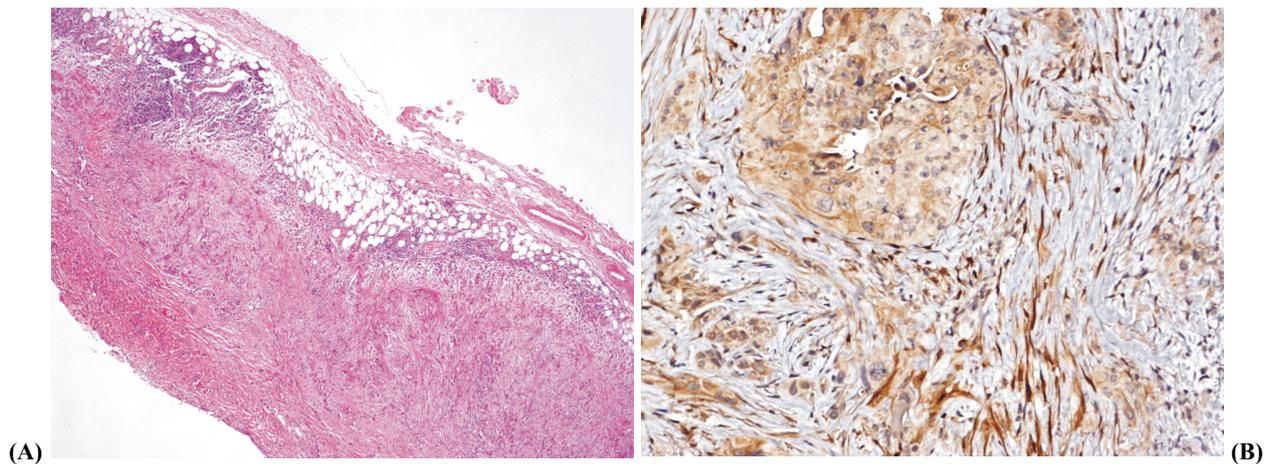
For ultrastructural analysis, a sample of the brain neoplasia, which had previously been examined by light microscopy, was retrieved from a paraffin block, deparaffinated with a mixture of propylene oxide and

xylol, osmicated, and embedded in epoxy resin. Ultrathin sections (50–70 nm) with silver interference were cut, picked up on copper grids and stained with uranyl acetate and lead citrate. The sections were observed under a transmission electron microscope (Morgagni™ 268, FEI Company, Italy).

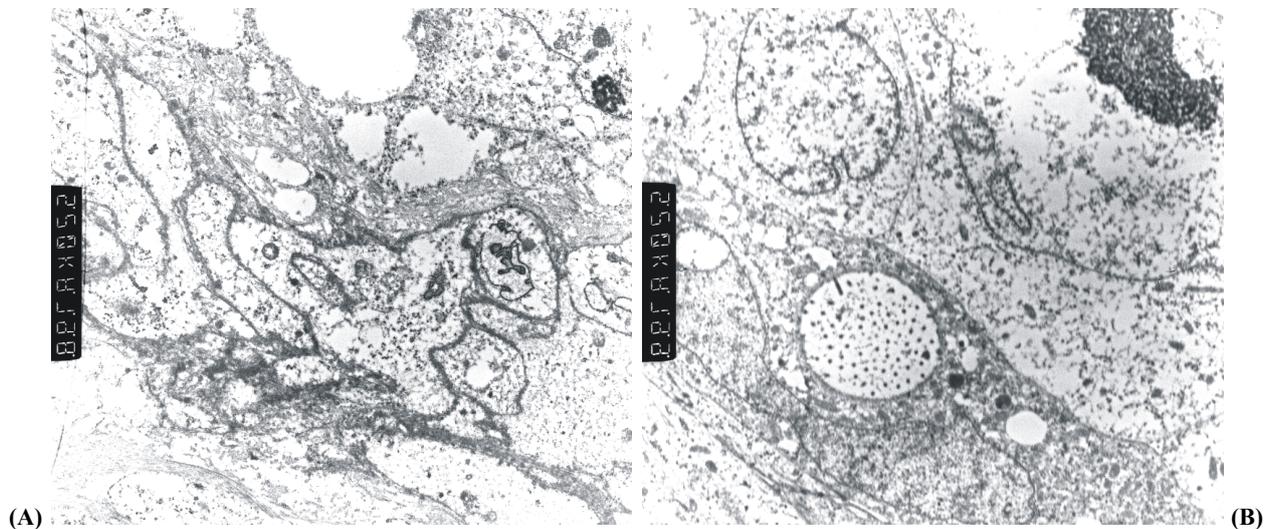
Ultrastructurally, the cells were spindle-shaped, with finely granular chromatin and large nucleoli and with an abundant cytoplasm, and rich organules and vesicles content, admixed with oval cells, with large nucleoli, showing desmosomes and microvilli on the surface,

occasionally with cytoplasmic extroflexions with a Gaucher-like appearance. These findings were consistent with a malignant mesothelioma with a biphasic component (Figure 5, A and B).

Information on a possible asbestos exposure was well documented by the *Apulia Mesothelioma Cancer Registry* and environmental/household exposure was demonstrated [17, 18]. This was confirmed by checking the census records from the City Municipality. The patient died 18 months after the first diagnosis.



**Figure 4** – (A) Poorly differentiated malignant tumor of the pleura with solid epithelioid and spindle cell pattern (HE staining,  $\times 40$ ); (B) Calretinin immunoreaction was observed in both epithelial and sarcomatous components ( $\times 200$ ).



**Figure 5** – (A) Electron microscopy examination of the sarcomatous (cytoplasm more electron-dense) and epithelial component (light cytoplasm with intercellular desmosomal attachments) ( $\times 7000$ ); (B) Intracytoplasmic lumina protruding into microvilli ( $\times 11\ 000$ ).

## Discussion

Conventional mesothelioma is an aggressive malignancy that can be caused by environmental carcinogens (asbestos and erionite), a virus (SV40) and a genetic predisposition [1, 5, 19]. Although this cancer form is not frequent, a dismaying rise in the incidence has been noted in the last three decades. Also, an accurate diagnosis is needed in view of the medico-legal aspects and prognostic and therapeutic implications.

Over 80% of tumors arise from the pleura, although primary mesotheliomas of the peritoneum, pericardium

and tunica vaginalis of the testis have also been reported [19]. MM is a highly lethal tumor with mean survival times from diagnosis ranging from two to 18 months. Moreover, this tumor usually shows resistance to chemotherapy and radiotherapy [18–20].

Studies conducted over the last decades have revised long-standing beliefs that malignant pleural mesotheliomas rarely metastasize outside the chest. Autopsy series clearly document that metastases are a common feature of this neoplasm, although their occurrence is usually late in the natural history of the disease [20, 21]. Early, symptomatic metastases remain uncommon and

symptomatic brain metastases are an unusual phenomenon [22].

Wroński M *et al.* [10] reviewed post-mortem findings and concluded that cerebral metastases are seen post-mortem in about 5–10% of patients.

A few cases of brain symptomatic mesothelioma metastases have been diagnosed ante-mortem and the patients developed cerebral metastases during the course of their illness [7, 10, 14, 15, 23–25]. The epithelioid mesothelioma is the most common type, while the sarcomatous subtype is rare and prognostically poor. Histologically, epithelioid mesotheliomas could mimic metastatic carcinoma, melanoma, sarcoma and glioblastoma multiforme [1]. The risk of metastasis is more evident for this subtype but histological changes are potentially relevant and generally, brain metastases showed features of sarcomatous type mesothelioma [7, 9, 13, 21, 24, 26].

Very few cases of cerebral metastasis presenting as a brain primary tumor have been described in literature; patients undergoing successful resection of brain metastasis from pleural mesothelioma presented a longer survival.

Interestingly, Hortobágyi T *et al.* [14] reported a case of both primary and metastatic tumor in which the histological pattern was epithelioid with few spindle cells elements but no true sarcomatous component. In the present case that presented as a brain primary tumor, histological examination showed almost the same findings and the epithelioid pattern was prevalent.

Although asbestos has been banned in developed countries, an increase in the numbers of cases of malignant mesothelioma is expected in the upcoming years and metastatic spread may occur more commonly. In the case we describe, the brain was the only site of metastasis of a pleural mesothelioma, and disease free-survival was longer after treatment.

## ☒ Conclusions

This study indicates that the central nervous system should be recognized as a possible site of spread of malignant mesothelioma; all three cell-types are associated with metastatic spread. For a correct diagnostic approach, immunohistochemical analysis with a wide panel of antibodies and electron microscopy can be crucial to avoid the diagnostic pitfalls. Finally, in the presence of metastases, surgical treatment with systemic chemotherapy should be considered to improve the life expectancy.

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