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ORIGINAL ARTICLE

Combined serum and immunohistochemical differentiation between reactive, and malignant mesothelial proliferations

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Abstract *Background:* Malignant mesothelioma (MM) carries a poor prognosis and response rates to palliative chemotherapy remain low. The diagnosis of malignant mesothelioma is frequently difficult, the most common differential diagnosis being reactive pleural conditions and metastatic adenocarcinoma. Several studies have used immunohistochemical markers to distinguish between reactive and neoplastic mesothelial cells. Soluble mesothelin levels in serum have recently been shown to be highly specific and moderately sensitive for mesothelioma. A combined detection of serum levels of mesothelin and immunohistochemical expression of desmin and EMA are used in order to differentiate between reactive mesothelial proliferations, and malignant mesothelioma of epithelioid type.

Patients and methods: This prospective study includes 17 cases of reactive mesothelial proliferations, 6 cases of atypical mesothelial proliferations and 13 cases of MM. Cases were collected from the Chest Department, Faculty of Medicine, Benha University and International Medical Center (IMC), in the period 2012–2014. Desmin and epithelial membrane antigen (EMA) immunohistochemical staining were performed in all cases and the pattern of expression was analyzed. Soluble mesothelin related peptide (SMRP) was estimated for all cases.

Results: Desmin expression was positive in 88.2%, 0%, and 7.7% of reactive mesothelial proliferations, atypical mesothelial proliferations and MM respectively. EMA was positive in 5.9% of

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reactive mesothelial proliferation, 100% of atypical mesothelial proliferations and 92.3% of MM cases ($P < 0.01$). The calculated mean SMRP was 6.6 nM. SMRP levels were higher than the calculated mean value in 17.6% of studied reactive mesothelial lesions, 66.7% and 76.9% of atypical mesothelial proliferations and MM respectively, which was statistically highly significant correlation ($P < 0.01$).

Conclusion: Combined estimation of SMRP level and immunohistochemical detection of both EMA and desmin could be a useful tool for differentiation between reactive mesothelial proliferation and malignant mesothelioma.

Introduction

Malignant mesothelioma (MM) is an aggressive asbestos-related cancer of serosal surfaces such as the pleura, peritoneum and rarely the pericardium. The cell of origin is a submesothelial mesenchymal stem cell. It is causally linked to asbestos exposure [1]. According to the Egyptian National Cancer Institute (NCI), MM constituted 13.12% of recorded respiratory system tumors and 0.84% of total recorded malignancy. The ratio between malignant lung tumors and pleural mesothelioma was 1.8:1. Pleural mesothelioma showed a wide age range starting from the 3rd to the 8th decade. However the majority of the cases were between 30 and 70 years. Epithelioid mesothelioma constituted 45.13% of all recorded mesotheliomas [2,3]. Diagnosis of MM is challenging as symptoms and early radiographic signs are often non-specific and their significance can be masked by multiple co-morbidities of this normally older patient. Malignant pleural mesothelioma has a median survival of seven to ten months and a clinical pattern that usually involves substantial pain and dyspnea. It presents at a clinically advanced stage in most patients so there is a need for new methods of early detection [4].

Mesothelial cells frequently show florid reactive changes in response to many benign conditions such as pulmonary infarction, systemic disease (i.e., collagen-vascular diseases), cirrhosis, radiation, underlying neoplasm, chronic inflammation, foreign substance, and infection. The distinction between benign reactive mesothelial proliferations and malignant mesothelioma (MM) may be very difficult based only on histologic and morphologic findings. Because of the difficulty in distinguishing reactive conditions from MM even in tissue specimens, such as small pleural biopsies, several studies have used immunohistochemical markers to distinguish between reactive and neoplastic mesothelial cells [5].

The intermediate filament protein desmin is a known marker for smooth and skeletal muscle differentiation. Several studies have reported positive staining of benign mesothelial cells (reactive mesothelial proliferation) in serous fluid and tissue sections for desmin. The exact etiology for expression of desmin in mesothelial cells is not known; however, the multipotential role of mesothelial cells with possible muscle differentiation and coexpression of desmin has been proposed by some studies [6,7].

Epithelial membrane antigen (EMA) is one of several glycoproteins found in human milk fat globule membranes. The glycoprotein identified with EMA is known to be one of a series of glycoproteins or mucins and is designated MUC1 [5]. It is a high molecular weight transmembrane glycoprotein expressed in cancer cells that suppresses cellular aggregation and cell-matrix adhesion and promotes invasion of extracellular matrix by malignant cells. Moreover, it inhibits T-cell mediated cytotoxicity through either induction of apoptosis in activated T cells or inhibition of cytotoxic lymphocyte-target cell interactions. MUC1 is also a ligand for ICAM-1 immunoglobulin which is expressed on endothelial cells. This allows intravascular tumor cells to adhere to and invade through the endothelial barrier; facilitating metastatic spread [7,8].

Mesothelin is a 40 kDa membrane-localized protein that along with the 31 kDa megakaryocyte potentiation factor (MPF) are cleavage products of a 69 kDa precursor protein encoded by MSLN gene on chromosome 16. In tissue culture, Mesothelin is proposed to play a role in cell adhesion as it binds to the cell adhesion molecule Ca125 (Muc16) and forced over-expression of MSLN leads to increased adhesion to a plastic substrate [9,10]. Also in tissue culture, mesothelin promotes cell proliferation, invasion and apoptosis resistance. Mesothelin may therefore be involved in cancer metastasis and its role as a potential therapeutic target is being actively pursued. It is predominantly expressed in epithelioid subtype mesotheliomas, with little/no expression in sarcomatoid subtypes. MPF and mesothelin isoforms 1 and 3 can be detected as soluble proteins in plasma or serum, which may be detected using a validated commercial dual antibody ELISA platform [11,12].

The small amount of mesothelin shed into the serum could make it a valuable diagnostic tool in cancers that express mesothelin. It has been shown to potentially differentiate between mesothelioma and other conditions, both benign and malignant, and also potentially correlates with response to therapy [1,13].

A study by Marchevsky [14] has demonstrated that the use of many markers does not provide higher diagnostic accuracy than the use of selected single antibodies or various combinations of only 2 markers. In this work a combined detection of serum levels of mesothelin and immunohistochemical expression of EMA and desmin are used in order to differentiate between reactive mesothelial proliferations and malignant mesothelioma of epithelioid type.

Patients and methods

This prospective study included 17 cases of non-neoplastic reactive mesothelial proliferations, 6 cases of atypical mesothelial proliferations and selected 13 cases of malignant mesothelioma; epithelioid type. Thoracoscopic biopsies were collected