

Review Article

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Malignant mesothelioma: Cytological features

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Abstract

A malignant mesothelioma arises from the serosal surface of the pleural, peritoneal, or pericardial cavity. Although rare, with development of diagnostic techniques, the frequency of this tumor has been increasing. Malignant mesothelioma is classified into three types; epithelioid, sarcomatoid, and biphasic. It is especially important to differentiate epithelioid type from reactive mesothelial cells and another type of carcinoma, with a definitive diagnosis usually obtained based on examination of tissue biopsy or surgical resection specimens. However, pleural effusion is often the first sign of malignancy. For older patients unable to tolerate an invasive procedure such as thoracoscopic surgery to perform a diagnostic biopsy, a cytological examination of pleural fluid is less invasive and can be readily performed. Furthermore, a combination of cytological morphology and immunocytological methods can lead to a definitive diagnosis. In this review, we present cytological features of the epithelioid type of malignant mesothelioma, and also introduce immunocytological markers for differentiating from reactive mesothelial cells or another type of malignant carcinoma including pulmonary carcinoma.

Keywords: Malignant mesothelioma; Immunocytochemistry; Differential diagnosis.

Abbreviations: PAS: Periodic Acid-Schiff; HEG1: HEG homolog 1; GLUT1: Glucose Transporter 1; CEA: Carcinoembryonic Antigen; EPCAM: Epithelial Cell Adhesion Molecule; TTF-1: Thyroid Transcription Factor.

Introduction

A malignant mesothelioma arises from the serosal surface of the pleural, peritoneal, or pericardial cavity [1], and its oncogenesis is related to exposure to asbestos fibers. Of these tumors, the most frequently encountered is malignant pleural mesothelioma and affected patients have a poor prognosis, with an overall survival of less than 18 months [1,2]. Although considered to be rare, the incidence of malignant pleural mesothelioma is increasing.

Malignant mesothelioma is classified into three types; epithelioid, sarcomatoid, and biphasic [3]. A definitive diagnosis of epithelioid type of malignant pleural mesothelioma is usually reached by examination of a tissue biopsy or surgical resection specimen, though pleural effusion is often the first sign of malignancy. Affected patients are usually elderly or unfit to tolerate invasive procedures such as thoracoscopic surgery to obtain a diagnostic biopsy sample. On the other hand, a cytological examination of pleural fluid is far less invasive and can be readily performed [2,4], thus a cytology sample is often the only

material available for establishing a diagnosis. However, the cytological features of malignant pleural mesothelioma are not always straightforward, as reactive mesothelial cells can have an atypical appearance that overlaps with the epithelioid type. Moreover, cytological findings to determine malignant pleural mesothelioma in an examination of effusion can be deceptively bland. Not surprisingly, a cytological diagnosis of mesothelioma based on pleural effusion material was previously believed to be unreliable, with diagnostic sensitivity reported to range from 30% to 75% [5]. Nevertheless, the recent availability of immunocytochemistry with newer biomarkers has greatly enhanced the diagnostic yield of cytology. Macroscopically, pleural involvement of a peripheral adenocarcinoma of the lung is strikingly similar to diffuse type mesothelioma and it is also difficult to discriminate epithelioid type of malignant pleural mesothelioma from other malignant tumors such as pulmonary carcinoma.

The purpose of this review is to present cytological features of the epithelioid type of malignant pleural mesothelioma for differentiation from reactive mesothelial cells or pulmonary carcinoma, including use of immunocytological techniques.

Histological features

Most epithelioid type malignant pleural mesotheliomas are cytologically bland; though show a wide range of histological patterns. In most of these tumors, the cells possess eosinophilic cytoplasm with non-descript vesicular chromatin. Mitoses are infrequent (Figure 1A) [6]. In poorly differentiated forms, the nuclei tend to have a coarse type of chromatin with prominent nucleoli and frequent mitoses (Figure 1B). The most commonly encountered patterns are solid, tubulopapillary, and trabecular, while micropapillary, adenomatoid, clear cell, transitional, decudoid, and small cell patterns are less common [6].

General cytological features of epithelioid type of MPM

Because of differentiation from metastatic carcinoma, it is occasionally difficult to make a diagnosis of malignant mesothelioma with a cytological technique using Papanicolaou, May-Giemsa, or Periodic Acid-Schiff (PAS) stain. Also, cells of a malignant mesothelioma are similar to reactive mesothelial cells, thus cell volume, cluster, nuclear, and cytoplasm findings, as well as evidence of a cellular inter-association are needed for a definitive diagnosis [7]. In addition, an immunocytochemical method the uses a cell transfer process and produces cell

blocks is desirable for cytological diagnosis [8,9]. Following are details regarding the cytological morphology of a malignant mesothelioma, as well as immunocytochemical markers useful for differentiation from other malignant tumors and reactive mesothelial cells.

Numerous clusters composed of more than 10 mesothelial cells and showing sphenoid-formation, aegagropila linnaei, and grape-bunch structures suggest a malignant mesothelioma (Figure 2A) [10]. Type II collagenous stroma can sometimes be seen in the center of these clusters with use of a light green stain. In addition, clusters of mesothelioma cells lacking nuclear protrusion found in a cluster of adenocarcinoma cells indicate mutual cell inclusion and hump formation (Figure 2B). Overlapping of mesothelioma cell clusters is relatively rare as compared to that seen with an adenocarcinoma, as they are generally flat [11]. Mesothelioma cells showing a signet cell-like ring are also occasionally noted [12].

Clusters containing numerous mesothelial cells with scant pleomorphism and a size more than five times that of lymphocyte cells, as well as findings showing cells with a low N: C ratio as compared to that of reactive mesothelial cells suggests mesothelioma (Figure 2C). The cytoplasm of mesothelioma cells varies from a profound to clear tone (Figure 2D,E), while some clusters have a yellow tone (Figure 2F).

The shape of the nucleus of a mesothelioma cell is oval or ovoid, and it is positioned in the center or laterally [13]. Nuclear findings showing prominent pleomorphism suggest carcinoma, whereas a scant pleomorphism condition requires discrimination from reactive mesothelial cells [14]. Chromatin of reactive mesothelial cells tends to be less than that of carcinoma cells, though malignant mesothelial cells show distinctive features, such as hyperchromatism and coarse chromatin clumping of nuclei, prominent nucleoli, multinucleation, and marked variations in cell size [15]. As for the general appearance of a mesothelioma, it is likely to observe various types of cells in a transitional stage to activated mesothelial cells with enlargement and multiplication. Acidophilic stainability around the nucleus is also one of the characteristic properties of mesothelial cells [16]. Furthermore, an intercellular window is another characteristic feature of these cells, though the frequency of cell mutual inclusion in a mesothelioma is higher than that of a carcinoma and reactive mesothelial cells [17]. Also, molding of cells that possess a hump-like process are often seen and suggest malignant mesothelioma.

Immunohistochemistry

Cytological material derived from pleural effusion is often the only available specimen to establish a diagnosis in patients with suspected mesothelioma, and adequate sampling and specimen processing is of paramount importance. Availability of a large amount of material allows for production of cell blocks with higher cellularity, thus enabling immunocytochemistry to be performed, as well as preservation of material for future investigation or biobanking. Mesothelioma guidelines recommended that cell block preparation be performed whenever possible [2]. Investigations have shown a relatively large number of cytological markers for distinguishing between malignant mesothelioma and reactive mesothelial proliferation.

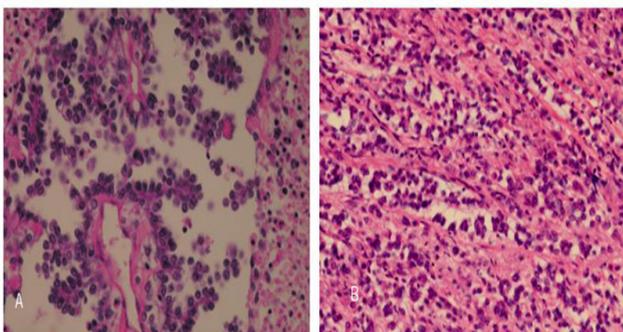


Figure 1: Histological features of epithelioid type of malignant mesothelioma. (A) Well differentiated (papillary type). (B) Poorly differentiated (solid type).

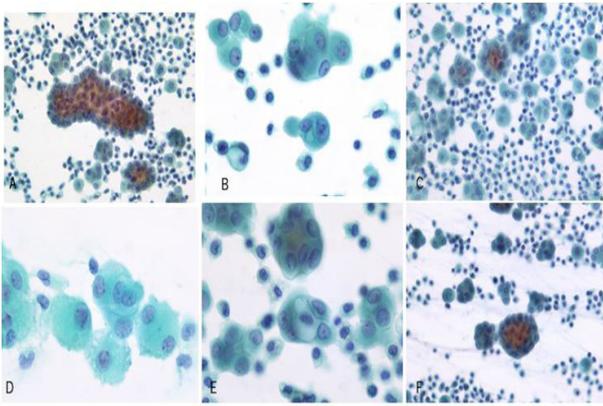


Figure 2: Cytological features. (A) Large cluster showing sphenoid formation composed of more than 10 mesothelial cells. (B) Mesothelioma cells showing mutual cell inclusion and hump formation. (C) Clusters of numerous mesothelial cells with scant pleomorphism and size at least five times greater than lymphocytes. Low N: C ratio, less than that of reactive mesothelial cells, suggests mesothelioma. (D) Cytoplasm of mesothelioma cells with clear tone and obscure membrane. (E) Cytoplasm of mesothelial cells with profound tone and mutual cell inclusion. (F) Mesothelioma clusters with yellow tone. (G) Mutual cell inclusion with mesothelial cells. (H) Collagenous stroma.

Differentiation from reactive mesothelial cells

A pleural biopsy specimen is the gold standard for diagnosis, with which identification of pleural invasion by atypical mesothelial cells is a major criterion. Pleural effusion is usually the first sign of disease, thus a cytological specimen is often the initial or only sample available for examination to determine diagnosis. Recently, new markers indicating malignant mesothelioma have been reported for distinguishing from reactive mesothelial proliferation [18]. Of those, BRCA1-associated protein 1 nuclear staining loss is highly specific for mesothelioma. Also, cyclin-dependent kinase inhibitor 2A /p16 homozygous deletion, assessed by fluorescence in situ hybridization, is more specific for mesothelioma with better sensitivity, while the surrogate marker methylthioadenosine phosphorylase has been found to have an excellent diagnostic correlation with p16 (Figure 3A) [19]. In addition, demonstration of p16 deletion using fluorescence in situ hybridization indicates mesothelioma [18].

Differentiation from other tumors

Immunohistochemistry plays an important role for distinguishing an epithelioid malignant mesothelioma from other tumors involving the pleura, particularly lung adenocarcinoma, and that distinction is greatly facilitated by combined use of a minimum of two mesothelial and two carcinoma markers. Based on their specificity and sensitivity, calretinin (Figure 3B), WT1 (Figure 3C), and D2-40 (Figure 3D) are considered to be the best positive markers to support a diagnosis of mesothelioma. Additionally, a recently described monoclonal HEG homolog 1 (HEG1) antibody has been proposed as a specific marker for a mesothelioma differentiated from another type of malignant neoplasm (Figure 3E) [20]. Glucose Transporter 1 (GLUT1) is also informative, though difficult to interpret when reactive proliferations are aberrantly stained positive (Figure 3F) [21]. In contrast, BerEP4 or MOC31, B72.3, carcinoembryonic antigen, BG8, CEA, EPCAM, TTF-1, napsin A, and claudin 4 are most commonly used to diagnose adenocarcinoma (Figure 4A, B, C) [6,22].

Similar to pulmonary adenocarcinoma, differentiation from other types of metastatic carcinoma is important. Markers useful for distinguishing as compared to other malignant tumors are described below. Estrogen receptor, progesterone receptor, GCDFF 15, and mammaglobin are markers of differentiation from breast carcinoma (Figure 5A,B) [23], PAX8 is a marker of differentiation from renal cell carcinoma, and prostate-specific antigen is useful for differentiation from prostate cancer [23]. Additionally, p40 is helpful for distinguishing epithelioid mesothelioma with a squamous morphology from squamous cell carcinoma [24] and thyroglobulin indicates differentiation from thyroid cancer (Figure 6A,B). Finally, CA125 and ER are helpful for distinguishing epithelioid mesothelioma from adenocarcinoma of the uterine body (Figure 7A,B,C).

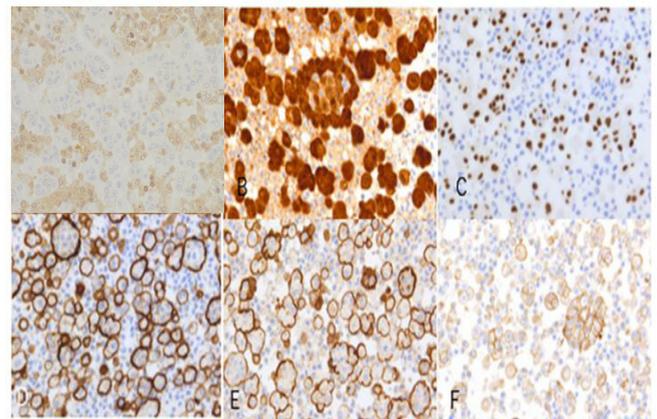


Figure 3: Immunocytochemical images of (A) methylthioadenosine phosphorylase (MTAP), MTAP is negative for tumor cells, (B) calretinin, (C) WT-1, (D) D2-40, (E) HEG2, and (F) GLUT-1.

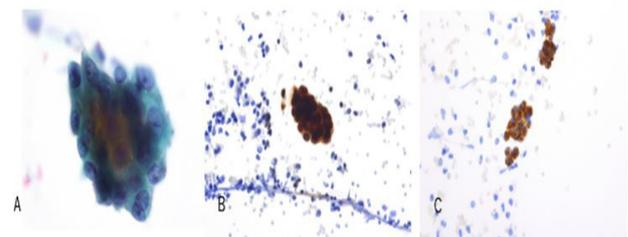


Figure 4: Cytology of pulmonary adenocarcinoma obtained from effusion examination. (A) Papanicolaou stain. (B) Thyroid transcription factor 1. (C) Napsin A.

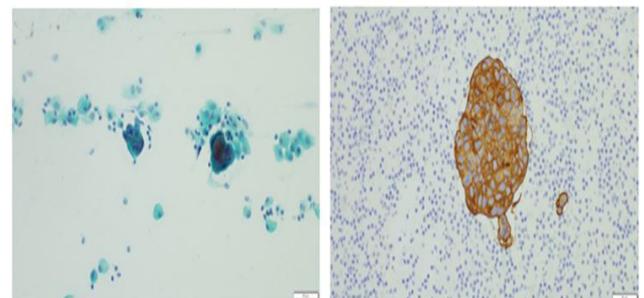


Figure 5: Cytological features of breast carcinoma. (A) Papanicolaou stain. (B) HER2 stain.

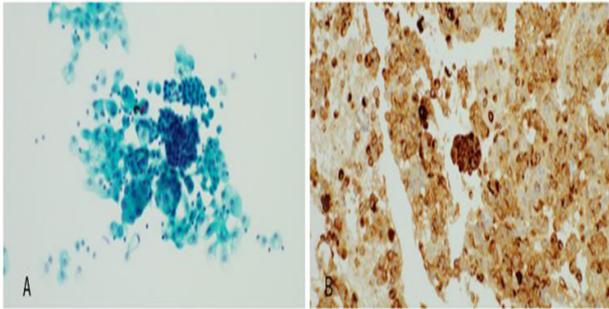


Figure 6: Cytological features of thyroid carcinoma. (A) Papanicolaou stain. (B) Thyroglobulin.

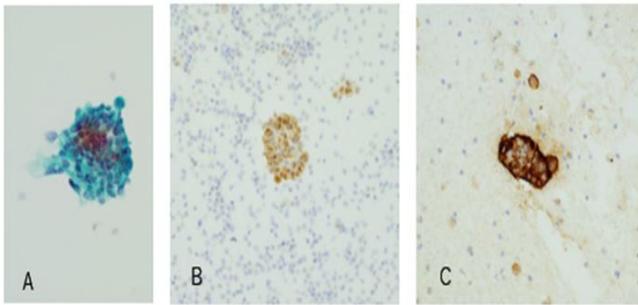


Figure 7: Cytological features of adenocarcinoma of uterine body. (A) Papanicolaou stain. (B) Estrogen receptor. (C) CA125.

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