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Malignant Mesothelioma

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Abstract

The major pathogenetic factor for a malignant mesothelioma is asbestos exposure. Cases have recently been increasing, thus clinicians are faced with more instances where a correct diagnosis is required and require information regarding features of this tumor. A malignant mesothelioma can be classified into three subtypes; epithelioid, sarcomatoid, and biphasic, with differential diagnosis varying for each subclass. There are two categories for the differentiation of an epithelioid mesothelioma depending on whether the cells are benign or malignant. The former is mesothelial cell proliferation and the latter malignant epithelial neoplasm, which includes a metastatic carcinoma arising from a site other than the pleura.

Various types of sarcomas are listed under sarcomatoid mesothelioma, while associated with biphasic carcinoma are carcinosarcoma and synovial sarcoma, biphasic type. Furthermore, it is important to understand rare features of a malignant mesothelioma. This review presents the pathological features of malignant mesothelioma including rare histological subtypes.

Keywords: Malignant mesothelioma; Immunohistochemistry; Differential diagnosis

Introduction

The major pathogenetic factor of a malignant mesothelioma is asbestos exposure and cases have recently has been increasing. As a result, clinicians have more instances where a correct diagnosis is required and require information regarding characteristics of this tumor. Presented here are pathological features of malignant mesothelioma including rare histological subtypes.

Clinical Features

Imaging

The imaging methods used for viewing a diffuse pleural mesothelioma are complex because of its rind-like circumferential growth, with the tumor usually arising from the diaphragmatic surface of the pleura and extending along pleural reflections, and demonstrating a propensity to simultaneously invade multiple structures [1]. Radiographic assessment should include characterization of pleural involvement, as well as determination of disease extent and invasion of adjacent structures so as to conclude respectability and clinical staging, and predict response to therapy [2]. A diffuse pleural mesothelioma showing by imaging generally consists of a circumferential ring of nodular pleura that is usually associated with ipsilateral effusion (Figure 1A), while pleural effusion nodular pleural density is less commonly seen. Rarely, an isolated nodular pleural density with or without effusion is revealed (Figure 1B) [3].

Symptoms

The initial presenting symptoms of a diffuse malignant mesothelioma often include dyspnea, unilateral chest pain or discomfort, coughing, unintended weight loss, low-grade fever, and night sweats. A frequent initial manifestation is symptomatic unilateral pleural effusion, with dyspnea and a cough, which can be resolved with effusion drainage [4]. Patients presented with only pleural effusion or when that is shown in screening may have a more indolent clinical course. As pleural thickening advances, chest wall contraction occurs and chest pain can become prominent, which often includes neuropathic characteristics from involvement of adjacent intercostal nerves, and bone pain from rib invasion or pathological fractures [5]. The symptoms then worsen along with stage advancement.

Pathological Features

Macroscopic appearance

Early findings of a diffuse pleural mesothelioma show as multiple small nodules scattered

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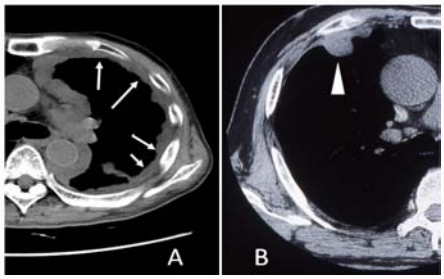

Figure 1: CT, mediastinum widow.
A) The tumor consisting of a circumferential ring around the pleura (arrow).
B) Isolated nodular density attach to the pleura (triangle).

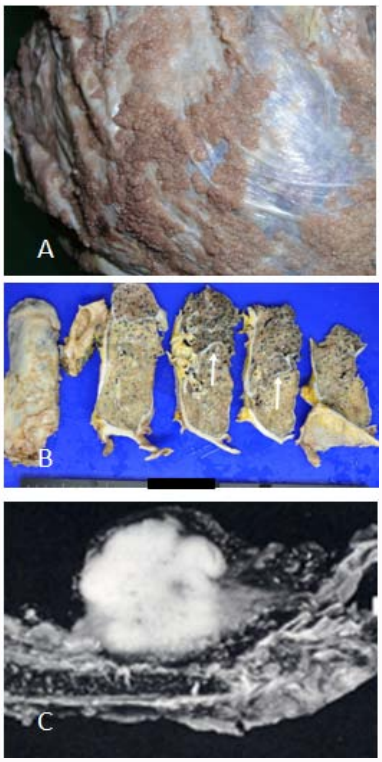

Figure 2: Macroscopic appearance.
A) Multiple small nodules scattered throughout parietal pleura.
B) Gray-white tumor forming a rind encasing underlying lung tissue Tumor growth along the interlobular fistula (arrow).
C) Round nodule attached the vesicular pleura.

throughout the parietal pleura (Figure 2A). As the disease progresses, the nodules coalesce to form a rind encasing the underlying lung (Figure 2B). Growth typically occurs along interlobar fissures leading to invasion of the lung parenchyma, chest wall skeletal muscle, or skin [6]. Occasionally, the mesothelioma forms a nodule that becomes attached to the vesicular pleura (Figure 2C).

Microscopic appearance

Arising from mesothelial cells, a parietal pleura shows various histological features. The WHO classification notes the following subtypes; epithelioid, sarcomatoid, and biphasic mesothelioma [6]. As for histological variants of an epithelioid mesothelioma, tubulopapillary, micropapillary, acinar, trabecular, adenomatoid tumor-like, solid, and adenoid cystic have been reported, while cell morphological variants include epithelioid mesothelioma, clear cell, deciduoid, lymphohistiocytosis, small cell, rhabdoid, pleomorphic,

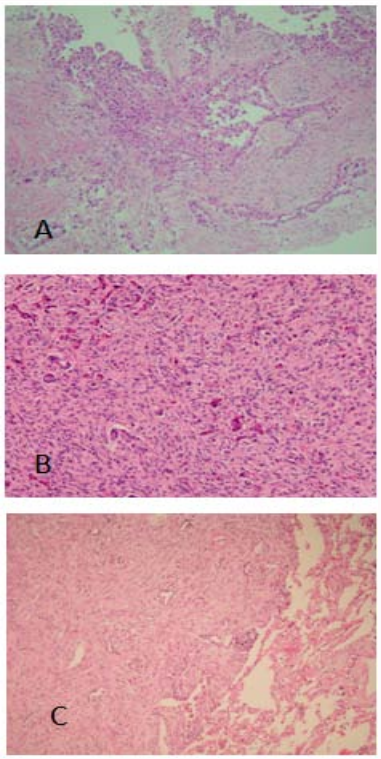

Figure 3: Microscopic features of malignant mesothelioma (HE stain).
A) Epithelioid mesothelioma. Cells with eosinophilic cytoplasm, round nuclei with vesicular chromatin and small nucleoli can be seen.
B) Sarcomatoid mesothelioma. Proliferation of spindle cells arranged in fascicles or in haphazard patterns.
C) Biphasic mesothelioma. Composed of both epithelioid and sarcomatoid morphology.

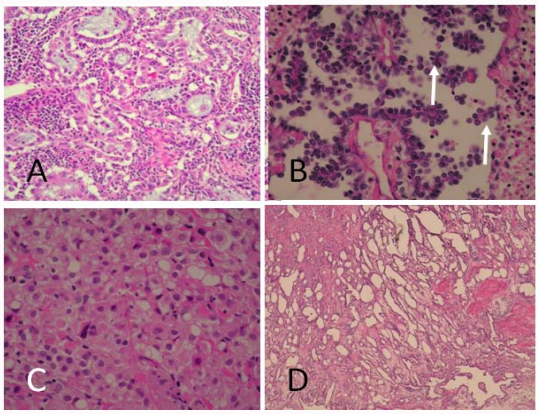

Figure 4: Histological architecture of epithelioid mesothelioma (HE stain).
A) Tubulopapillary pattern. Varying combinations of tubules and papillae.
B) Micropapillary. Papillary structures lacking fibrovascular cores (arrow).
C) Decidua-like appearance.
D) Adenomatoid pattern.

and transitional types are also known. Additionally, a desmoplastic mesothelioma of the sarcomatoid type has been reported [7].

Therefore, it is important to differentiate an epithelioid mesothelioma from a pulmonary adenocarcinoma, pulmonary large cell carcinoma, and thymic carcinoma, as well as a metastatic carcinoma in the pleural originating from breast or kidney tissue [8]. Differential diagnosis should include sarcomatoid mesothelioma,

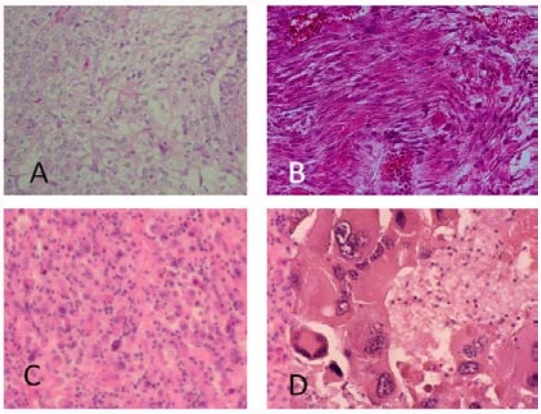

Figure 5: Cytological features of epithelioid carcinoma (HE stain).
A) Clear cell features, including large cells with clear cytoplasm and round central nuclei.
B) Rhabdoid features are tumor cells with cytoplasmic eosinophilic globules, resembling a rhabdomyoblastic tumor.
C) So-called deciduoid mesothelioma demonstrating cells with abundant eosinophilic cytoplasm, resembling deciduoid cells associated with pregnancy.
D) Pleomorphic features include tumor cells with prominent anaplastic and bizarre nuclei, occasionally containing multinucleated giant tumor cells.

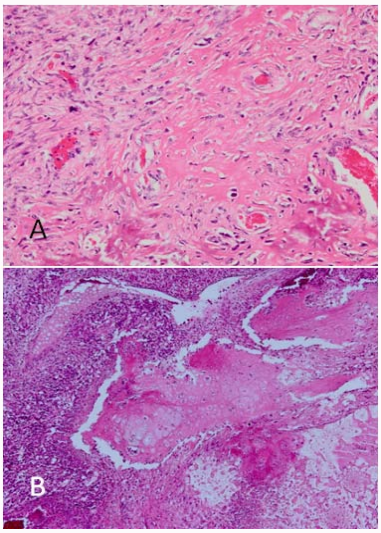

Figure 6: Heterogenous elements of sarcomatoid mesothelioma (HE stain).
A) Osteoid formation.
B) Chondroid formation.

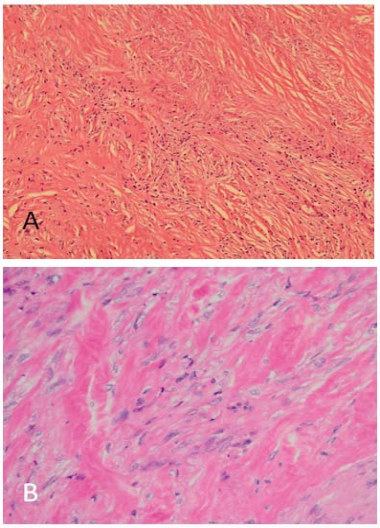

Figure 7: Microscopic features of desmoplastic mesothelioma.
A) So-called patternless pattern.
B) Dense hyalinized stroma with neoplastic cells with minimal atypia.

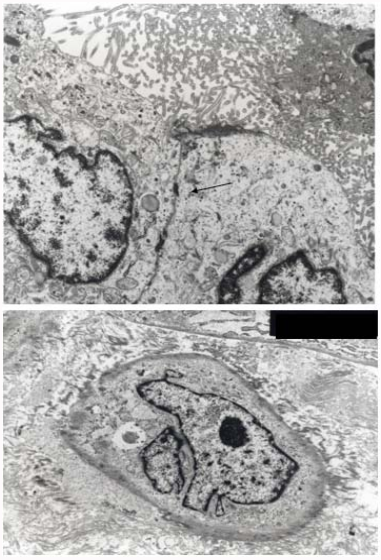

Figure 8: Ultra-structural features.
A) Epithelioid mesothelioma. Long, often branching surface microvilli and desmosomes (arrow).
B) Sarcomatoid mesothelioma. Scarce, short microvilli.

synovial sarcoma [9], leiomyosarcoma, malignant solitary fibrous tumor, and pulmonary carcinosarcoma [10].

An epithelioid mesothelioma is often cytologically bland, though marked cytological atypia can occur [6]. The cells typically display eosinophilic cytoplasm, round nuclei with vesicular chromatin and small nucleoli (Figure 3A). There are a wide range of architectural patterns and several are often observed in the same tumor (Figure 4A), with trabecular, micropapillary (Figure 4B), and solid patterns seen (Figure 4C), with an adenomatoid less common (Figure 4D). The solid pattern is composed of solid sheets of cohesive tumor tubules and papillae, and a tubulopapillary pattern also exhibits varying combinations of tubules and papillae. The trabecular pattern consists of relatively small, uniform cells forming thin cords, or sometimes a single-file arrangement, while the adenomatoid pattern presents microcystic structures with a lace-lake or signet ring appearance. Finally, the micropapillary pattern consists of papillary structures lacking a fibrovascular core and psammoma bodies may be seen.

Cytologically, clear cell type features large cells with clear cytoplasm and round central nuclei, mimicking a renal cell carcinoma or another type of clear cell carcinoma (Figure 5A). A rhabdoid features tumor cells with cytoplasmic eosinophilic globules that express cytokeratin and but not muscular markers, and resembles a rhabdomyoblastic tumor (Figure 5B) [11]. A so-called deciduoid mesothelioma shows cells with abundant eosinophilic cytoplasm, resembling deciduoid cells associated with pregnancy (Figure 5C) [12]. Pleomorphic type features are characterized by tumor cells with prominent anaplastic nuclei as well as bizarre nuclei that often contain multinucleated tumor giant cells (Figure 5D).

A sarcomatoid mesothelioma is characterized by proliferation of spindle cells arranged in fascicles or with a haphazard pattern, and invasion of adipose tissue and/or lung parenchyma (Figure 3B). This tumor shows a wide range of morphologies. Spindle cells are elongated (>2 times longer than as wide) and tapered, with nuclei that range from relatively bland to highly atypical/pleomorphic. Nucleoli may be prominent and multiple, with variable mitoses, and necrosis is frequent [6]. Significant traditional features are elongated yet plump cells with an appearance intermediate between epithelioid and sarcomatoid tumors in morphology results, that contain moderate cytoplasm and prominent nucleoli. These cells appear more round than sarcomatoid cells, though are more discohesive than epithelioid cells, similar to those seen in a sarcomatoid mesothelioma. The presence of transitional features is associated with worse prognosis [13]. A mesothelioma with transitional features is now classified under sarcomatoid mesothelioma.

Occasionally, heterologous elements, such as rhabdomyosarcoma, osteosarcoma, or chondrosarcoma, are present, for which the term 'with heterologous elements' is applied [14]. These elements must be differentiated from those of osteoid (Figure 6A) and chondroid metaplasia (Figure 6B), and any of these patterns can sometimes contain benign osteoclast-like giant cells.

A biphasic mesothelioma shows both an epithelioid and sarcomatoid morphology (Figure 2C). In definitive resection specimens, consensus findings state that more than 10% of each component must be present. When transitional features are observed in an epithelioid mesothelioma, the tumor should be classified as a biphasic mesothelioma [6].

A desmoplastic mesothelioma shows the pattern of a sarcomatoid mesothelioma and is characterized by spindle cells with minimal atypia arranged haphazardly in a so-called patternless pattern within a dense, hyalinized stroma (Figure 7A, 7B). That tumor can be diagnosed using definitive resection specimens and more than 50% of the mass shows desmoplastic features [15].

Immunohistochemistry

A malignant mesothelioma shows various histological features related to an epithelioid and/or sarcomatoid element, thus the use of immunohistological markers differs among the subtype elements.

For differentiation from an epithelioid mesothelioma, WT-1, D2-40, and CK5/6 are recommended as mesothelial markers, whereas claudin-4, BerEP4 or MOC31, B72.3, CEA, CD15 (LeuM1), and BG8 are commonly used as carcinoma markers [16]. Distinguishing epithelioid mesotheliomas from other tumors involving the pleura, most commonly metastatic carcinoma, can be facilitated by use of a minimum of two mesothelial and two carcinoma markers.

Generally, a sarcomatoid mesothelioma is at least focally positive for pan-cytokeratin antibodies, including AE1/AE3, OSCAR, and KL1, as well as CAM5.2, which reacts with CK8 and CK18 [17]. Approximately 30% of sarcomatoid mesotheliomas express calretinin [18], though are more often positive for D2-40 [19], while other mesothelial markers, including CK5/6 and WT1 are relatively uncommon [17]. Sarcomatoid mesotheliomas are often vimentin-positive, whereas epithelioid mesotheliomas are often negative for vimentin. Occasionally, sarcomatoid mesotheliomas express actin, desmin, or S-100. Also, TTF-1 (clone 8G7G3/1) and/or p40 expression supports a diagnosis of sarcomatoid carcinoma [6].

Ultra structure

Ultra structural features may be useful for diagnosis of serosal membrane tumors. The most striking features of an epithelioid mesothelioma is the presence of long, often branching, surface microvilli that are devoid of glycogen (Figure 8A) [20]. Scanning electron microscopy may well reveal the morphology of the microvilli as well as perinuclear tonofibril bundles, cytoplasmic glycogen, basal lamina, and long desmosomes. A sarcomatoid mesothelioma resembles a fibrosarcoma or myofibroblastic tumor [5], though epithelial differentiation may be seen in some cases, with the latter manifesting occasional microvilli (Figure 8B), or incomplete basal lamina, intercellular junctions, or tonofilaments.

Pathological diagnosis based on biopsy specimen

There are two categories for differentiation of an epithelioid mesothelioma; benign or malignant cells. The former is a result of mesothelial cell proliferation, while the latter is from malignant epithelial neoplasm, one type of which is a metastatic carcinoma arising from a site other than the pleura.

For cases of benign mesothelial proliferation, it is important to differentiate a malignant mesothelioma from reactive mesothelial proliferation. Immunohistochemistry findings showing loss of BAP-1 expression, as well as homozygous deletion of CDKN2A (9p21; encoding p16) by FISH and/or cytoplasmic loss of MTAP expression by immunohistochemistry that identify CDKN2A homozygous deletion can distinguish a mesothelioma from benign proliferation [20]. Loss of BAP1 nuclear expression is more commonly seen in an epithelioid mesothelioma, whereas homozygous deletion in the region of 9q21 is seen in more than 80% of sarcomatoid mesothelioma cases [21]. Results of immunohistochemistry showing a high expression of EZH2 may also be useful [22]. While these methods can assist in distinguishing mesothelioma from benign mesothelial proliferation, they are not appropriate for distinguishing mesothelioma from other types of malignant tumors.

Regarding differentiation from a malignant neoplasm, in epithelioid mesothelioma cases, a biopsy specimen including a sufficient number of neoplastic cells can be helpful for pathological diagnosis using an immunohistochemical method. However, a definitive diagnosis is occasionally difficult when a sarcomatoid mesothelioma contains a desmoplastic mesothelioma. This is because a desmoplastic mesothelioma shows hypocellular areas and/or neoplastic cells with slight atypia, while the sarcomatoid features of a sarcomatoid mesothelioma are similar those of a sarcomatoid carcinoma or sarcoma, with immunohistochemical markers that are not specific. Occasionally, molecular testing can be helpful, because sarcomatoid carcinomas of the lung are frequently associated with a MET exon 14 splice-site mutation [23]. A solitary fibrous tumor shows NAB2-Signal Transducer and Activator of Transcription 6 (STAT6) gene fusion and Nuclear Factor IX (NFIX), as well as mapping to 19q13.2 and STAT6, and also to 12q13.3 [24]. A biphasic mesothelioma has both epithelioid and sarcomatoid elements. In definitive resection specimens, by consensus, more than 10% of each element must be present. However, any tumor can be diagnosed as a biphasic mesothelioma regardless of the percentage of each component in small biopsy specimens. In addition, a biphasic mesothelioma must be differentiated from tumors showing a biphasic element, such as pulmonary carcinosarcoma and synovial sarcoma. Differential diagnosis of a pulmonary carcinosarcoma is relatively easy, because of the variable expressions of adenocarcinoma-related

markers, such as napsin A, TTF-1, or p40, depending on the direction of differentiation, and this tumor is usually more prominent in a non-small cell carcinoma component, if that is present [25]. Most synovial sarcomas express Epithelial Membrane Antigen (EMA) and/or cytokeratin [26]. TLE1 staining is a characteristic, though not specific [27], while expression of calretinin is common. These antibodies are specific against a mesothelioma. However, molecularly, a synovial sarcoma indicates SS18-SSX fusion testing, and such molecular change is helpful to discriminate between mesothelioma and synovial sarcoma [28].

An ultra structural examination is useful for definite diagnosis of epithelioid tumors, which have long microvilli, while that is less useful for a sarcomatoid mesothelioma because of its non-specific ultra-structural features.

Finally, when immunohistochemical and/or molecular results are not definitive, the final diagnosis may be dependent on clinical and radiological correlations, as diffuse pleural thickening would favor a mesothelioma and a localized mass a carcinoma.

Prognosis

Although malignant mesothelioma cases have an extremely poor prognosis, recent studies have shown similar survival for patients with epithelioid mesothelioma with pleomorphic features as seen in those with a sarcomatoid mesothelioma [4].

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