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Original Article

Histopathological and immunohistochemical differentiation between benign and malignant mesothelial proliferation

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Abstract

Mesothelial proliferation is an important histopathological debate and differentiation between benign and malignant mesothelial growth is one of the challenging issues for the selection of appropriate treatment. Mesothelioma includes three histologic variants; epithelial, sarcomatous/desmoplastic and mixed. On the other hand, florid reactive hyperplasia, organizing pleuritis and entrapment of mesothelial cells are benign conditions related to mesothelium that may have many overlapping features with mesothelioma. Histological evaluation for stromal invasion or the use of immunohistochemical stains are essential to identify benign from malignant mesothelial proliferation as cytologic atypia is often not helpful because benign processes are commonly atypical and mesotheliomas are often monotonous. Recently, two new markers are used to distinguish reactive versus malignant mesothelium; BAP1 and methylthioadenosine phosphorylase (MTAP). Several causes may induce benign mesothelial proliferation include: infections, reaction to certain drugs, collagen vascular disease or a result of surgery, trauma, or physical injury. Unfortunately, mesothelial hyperplasia may be associated with a bronchogenic carcinoma in the lung. So tight correlation of clinical, histological and radiological investigation is essential in dealing with pleural abnormality. The present review aims to remove the ambiguity and clarify the histologic features of reactive mesothelial proliferation versus malignant mesothelioma and to detect the valuable immunohisochemical (IHC) markers for this differentiation

Keywords: Pleura, mesothelioma, mesothelial proliferation/hyperplasia, methylthioadenosine phosphorylase (MTAP), BRCA-1 associated protein 1 (BAP1).

Abbreviations: **MTAP**; methylthioadenosine phosphorylase, **BAP1**; BRCA-1 associated protein 1, **IHC**; immunohisochemistry

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Introduction

Mesothelium is a membrane that lines body serous cavities (pleural, peritoneal and pericardial) and internal organs. It is formed of monolayer mesothelial cells which have epithelial characteristics; surface microvilli, apical/basal polarity, cytokeratins and junctional complexes. Embryologically, they are derived from mesoderm with mesenchymal features.[1] Proliferation of mesothelial cells occur in benign and malignant conditions and differentiation between them is very important for treatment.[2] Mesothelioma is an aggressive and uncommon malignant neoplasm associated with occupational exposure to asbestos after long incubation period.[3] In addition germline mutation in BRCA-1 associated protein 1 (BAP1) and radiotherapy may play a role in development of mesothelioma.[4] The incidence and mortality rates are higher in males than females and most cases are diagnosed at older age due to long latent period between exposure to asbestos and development of mesothelioma.[5] There are multiple challenging issues facing the pathologist on histological analysis of the pleura; [1] separation of the epithelioid type of mesothelioma from the florid reactive hyperplasia of the mesothelium, [2] invasion of the stroma versus entrapment of the mesothelium and [3] organizing pleuritis versus desmoplastic mesothelioma.[6]

Reactive mesothelial hyperplasia versus epithelioid mesothelioma

Hyperplasia of mesothelium occurs in response to infection, collagen diseases, pulmonary infarction and pneumothorax, which may be florid and mimic neoplastic proliferation of mesothelium. Accurate diagnosis needs appropriate interpretation of clinical, radiological, surgical and pathological data. Mesothelioma is clinically suspected with circumferential and nodular pleural thickening on computed tomography.[6] Histopathological differentiation between reactive and malignant proliferation of mesothelial cells depends on appropriate morphology and IHC evaluation, and the histological features are summarized in table 1.[1,2] The most important indicator of malignancy is the stromal invasion, which is demonstrated by immunostains like pancytokeratin or calretinin.[7] Recently, two new markers are used to distinguish reactive versus malignant mesothelium; BAP1 and methylthioadenosine phosphorylase (MTAP). Loss of BAP1 and MTAP is observed in mesothelioma **Figure 1**.[6] These markers have low sensitivity when used individually, so best results are obtained with combination of both.[8] However, BAP1 is preserved in sarcomatous and desmoplastic mesothelioma.[2]

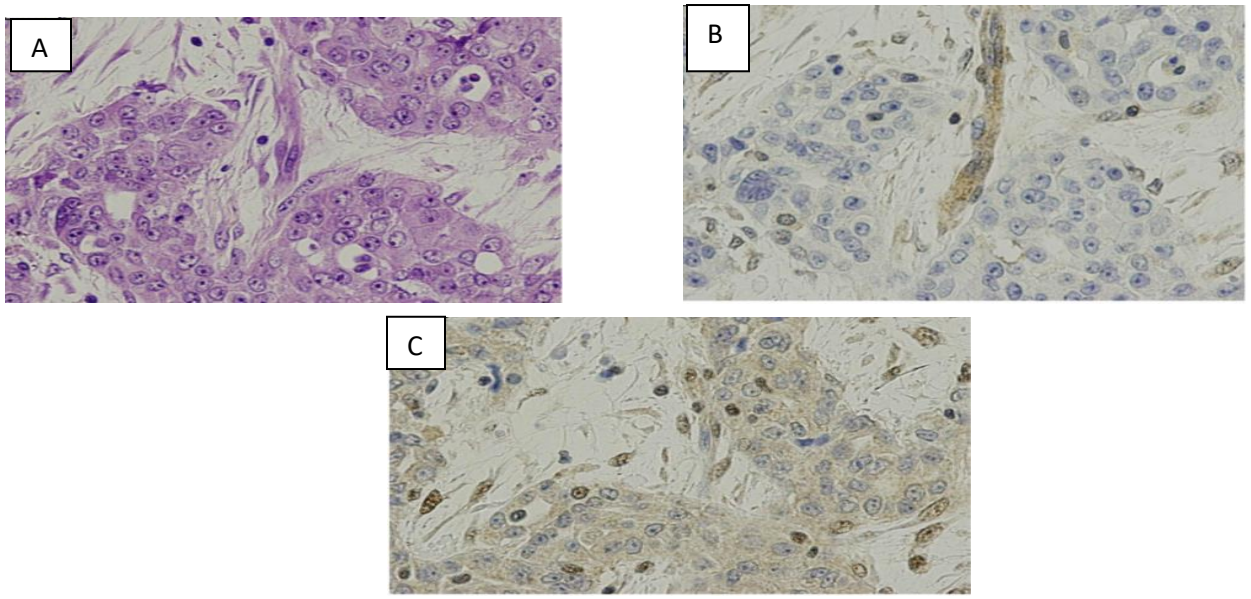

Figure. 1. (A): Epithelioid mesothelioma by H&E staining (x400), (B): loss of MTAP IHC in mesothelial cells (cytoplasmic/nuclear staining) (x400), (C) loss of BAP1 IHC in mesothelial cells (nuclear staining) (x400) [6].

Table 1: Histological difference between mesothelium proliferation and mesothelioma

	Mesothelial Hyperplasia	Mesothelioma
Stromal invasion	Absence of stromal invasion (beware of entrapment and en face cuts)	Stromal invasion usually apparent (highlight with pancytokeratin staining)
Cellularity	Cellularity may be prominent but is confined to the mesothelial surface/pleural space and is not in the stroma	Dense cellularity, including cells surrounded by stroma
Architecture	Simple papillae; single cell layers	Complex papillae; tubules and cellular stratification
Stroma	Loose sheets of cells without stroma	Cells surrounded by stroma (‘‘bulky tumor’’ may involve the mesothelial space without obvious invasion)
Necrosis	Rare	Present (occasionally)
Inflammation	Common	Usually, minimal
Growth pattern	Uniform growth (highlighted with cytokeratin staining)	Expansile nodules; disorganized growth (highlighted on cytokeratin staining)

The following features are not useful in differentiation between benign and malignant mesothelial proliferations: - Mitotic activity Mild to moderate cytologic atypia

Invasion of the stroma versus entrapment of mesothelium

Mesothelium entrapment is a common finding in the inflammatory reaction, so diagnosis of mesothelioma within active inflammatory processes must be done with caution. When layers of proliferated mesothelial cells are arranged parallel to the pleural surface or deep in the pleura, they are considered benign and represent the original pleural surface which is buried by organized product of inflammation and effusion **Figure 2**. But distribution of mesothelial cells from pleural surface to the junction with fat is considered malignant and usage of pancytokertin stains is useful. [6]

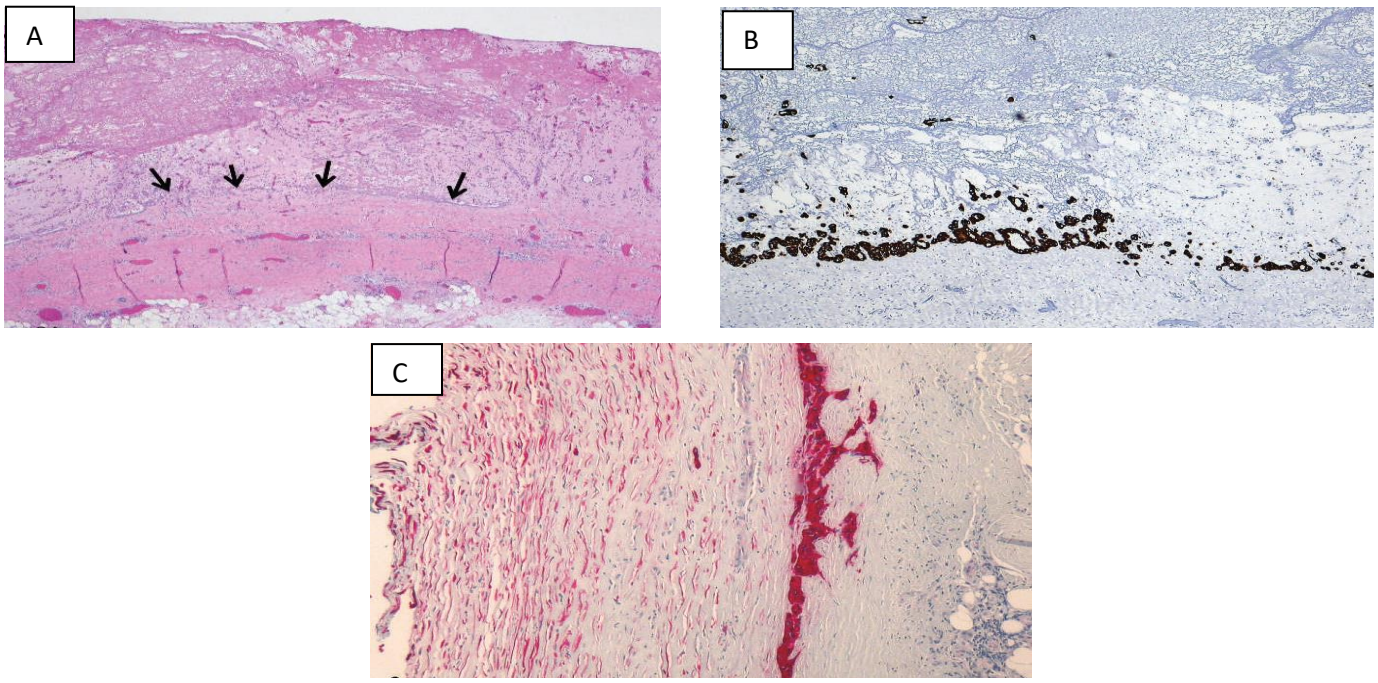

Figure 2. A: There is a linear array of individual mesothelial cells and simple glands (arrows) at the junction of denser fibrous tissue and looser organizing connective tissue/fibrin by H&E staining (x40). B: Pankeratin stain highlights the linear array. This appearance is seen in benign organizing effusions (x40), and the linear array probably represents the original surface line of the mesothelial layer. C: The lumen is to the left. This type of layering represents repeated effusions with proliferation of surface mesothelial cells and subsequent organization. The darker-staining mesothelial cells to the right probably represent the original lining layer, the sharp circuHF`2Qmscription (lack of invasion) of the process, another sign that one is dealing with a benign process (pankeratin, x40). [6]

Organizing pleuritis versus desmoplastic mesothelioma

The diagnosis of desmoplastic mesothelioma is very challenging due to paucicellularity and scar like appearance mimicking organizing pleuritis. Some histologic features suggest the diagnosis of desmoplastic mesothelioma as; expansile stromal nodule or short storiform pattern but these are not specific **figure 3** .[6] The most reliable sign of malignancy is stromal fat and lung which can be detected by pancytokeratin. [9] One of the important issues is to differentaite between fake fat which represent traction artifact in a fibrotic stroma from true fat cells, which can be made by S100. In old organizing pleuritis may include fatlike spaces parallel to pleural surface with positive pancytokeratin to cells surrounding these fake fat with false diagnosis of mesothelioma .[10] The growth pattern of desmoplastic mesothelioma is downward with invasion of true stromal fat but not parallel to pleural surface. **Table 2** summarize the features differentaing desmoplastic mesothelioma and organizing pleuritis .[2,9]

Table 2: Histological difference between organizing pleuritis and desmoplastic mesothelioma

	Organizing pleuritis	**Desmoplastic mesothelioma**
Stroma pattern	Storiform pattern not prominent	Storiform pattern often prominent
Stromal invasion	Absence of stromal invasion	Stromal invasion present (highlight with pancytokeratin staining)
Necrosis	Necrosis, if present, is at the surface epithelioid mesothelial cells (where there is often associated acute inflammation)	Bland necrosis of paucicellular, collagenized tissue
Pattern of growth	Uniform thickness of the process	Disorganized growth, with uneven thickness, expansile nodules, and abrupt changes in cellularity
Cellularity	Hypercellularity at the surface with maturation and decreased cellularity deep (so-called zonation)	Lack of maturation from the surface to the depths of the process
Vascularity	Perpendicularly oriented vessels	Paucity of vessels, without orientation
Stromal expansion	No nodular stromal expansions	Nodular stromal expansions

The following features are not useful in differentiation between organizing pleuritis and desmoplastic mesothelioma: - Cellularity
- Atypia (unless severe)
- Mitotic activity unless numerous atypical mitotic figures

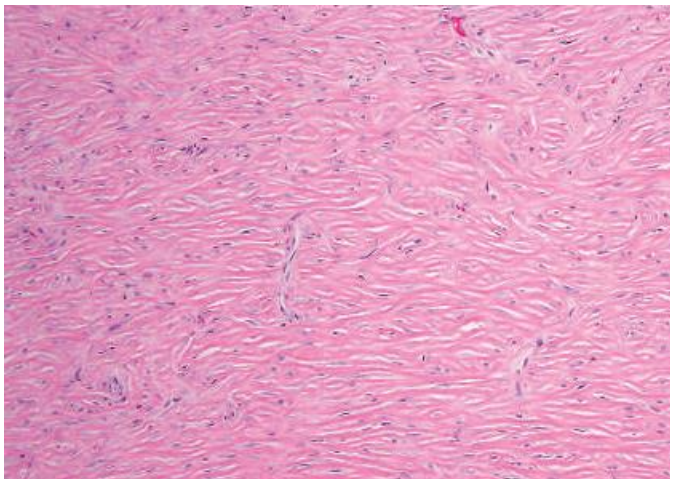

Figure. 3. A case of desmoplastic mesothelioma showing short storiform pattern with ropey collagen, but this finding can be seen in organizing pleuritis (hematoxylin-eosin, x200) [6].

Conclusion

Mesothelioma is an uncommon malignant tumor and sometimes its diagnosis is challenging. Careful histopathologic evaluation for invasion and immunohistochemical staining to confirm invasion of fat or to exclude lung adenocarcinoma and metastasis, are very helpful. Taking into consideration the clinical features and description of the pleura on imaging and pleuroscopy.

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