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NEW INSIGHTS IN DIAGNOSIS AND CLASSIFICATION OF MESOTHELIOMA

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ABSTRACT Mesothelioma is a rare malignant tumor that arises from the cells lining the body cavities. The diagnosis of mesothelioma can be challenging especially on small biopsy specimens. New guidelines are available for the diagnosis and classification of mesothelioma. This article will focus particularly on the advancements that have been made over the recent years including the histologic classification of mesothelioma, the indispensable integrity of morphology and ancillary techniques in the diagnosis of mesothelioma and recognition of its various prognostic factors and newer entities such as Mesothelioma-in -situ (MIS).

KEYWORDS : Mesothelioma, BAP1 (BRCA associated Peptide 1), histomorphology, ancillary tests.

INTRODUCTION

Mesothelioma is a rare neoplasm that arises from the cells lining the body cavities. Mesothelioma most commonly arises from the pleura (85%). 14% arises from the peritoneum. Remaining 1% originate from the pericardium or tunica vaginalis of the testis.[1]

Mesotheliomas often need to be distinguished from other pleural-based malignancies. Clinical context and radiographic imaging should be considered when forming a differential diagnosis. The common clinical symptoms of mesothelioma are shortness of breath, nausea, anorexia, weight loss, chest pain, abdominal pain, pleural effusion, etc. [2,3] Laboratory findings include elevated levels of hyaluronan, CA-125, AFP, CEA, Mesothelin, SMRP (Soluble Mesothelin Related Peptide). [1]

Mesothelioma is strongly associated with asbestos exposure. Crocidolite is most strongly linked to the development of malignant mesothelioma.[2] According to World Health Organization (WHO), four different molecular clusters are recognised that affects the degree of epithelial-mesenchymal transition (EMT) in mesothelioma. These clusters include high EMT score, low mRNA expression of mesothelin, a higher score for the T helper 2 cell signature, and homozygous deletions for CDKN2A. [3]

Diagnosis of mesothelioma remains challenging especially in small biopsies. The gold standard for the confirmation of the diagnosis of malignant mesothelioma is tissue invasion, which may not be possible for detection on small biopsies. [1] Diagnosis can be achieved with the use of ancillary testing/IHCs - BAP1 and MTAP or FISH (Fluorescence in Situ Hybridization) for CDKN2A. [1]

PATHOGENESIS

Mesothelioma have a complex pathogenesis. Common mechanisms that revolve around mesothelioma include chronic inflammation, deregulation of cell death and genetic abnormalities. Mesothelioma is linked with asbestos exposure. Inhaled asbestos fibers get lodged in the pleural/peritoneal space. Macrophages present in these areas try to phagocytose the asbestos fibers and while doing so these macrophages release a lot of reactive oxygen species and reactive nitrogen species promoting genotoxic effect. Repeated DNA damage thus caused leads to accumulation of oncogenic mutations in mesothelial cells which subsequently leads to development of mesothelioma. [1,4,6,7]

Frequently mutated genes according to comprehensive genomic analysis include BAP1, NF2, TP53, etc. In patients with germline mutations of BAP1, exposure to even small amounts of asbestos increases risk of mesothelioma. BAP1 is a tumor suppressor gene located on chromosome 3p21.1. BAP1 produces a deubiquitinase enzyme that controls a range of physiological processes including apoptosis, DNA repair, growth inhibition and cellular advancement. Mechanisms of BAP1 inactivation include point mutations, copy number loss, inactivating structural rearrangements, minute chromosomal deletions or germline BAP1 alterations. [1,5,6,8]

BAP1 IHC, a surrogate for BAP1 genomic status, is used as a diagnostic marker for mesothelioma. Reactive mesothelial proliferations have intact BAP1 nuclear staining. Complete absence of nuclear expression or presence of cytoplasmic staining is considered as loss of BAP1 expression. Aberrant BAP1 protein expression which is defined as absence of nuclear BAP1 staining, is present in ~50-70% of epithelioid mesothelioma.[1,6,8]

Homozygous loss of CDKN2A is seen in 67 to 83% of epithelioid and biphasic mesotheliomas and in ~100% of sarcomatoid mesotheliomas. MTAP is frequently codeleted with CDKN2A. MTAP is located near CDKN2A. NF2 deletions and losses occur in about 30-40%. PDL1 is expressed in approximately 30% of epithelioid mesotheliomas, which in part may explain lack of response to anti-PDL1 therapy. [1,6]

ANCILLARY TESTING IN MESOTHELIOMA

The judicious application and interpretation of immunohistochemical staining in the light of clinical and radiographic settings can help with the differential diagnosis. Markers that have been proposed as indicators for mesothelial differentiation include WT-1, D2-40 (podoplanin), calretinin, and cytokeratin 5/6. Other mesothelial markers are mesothelin, HBME-1, thrombomodulin. Pancytokeratins (AE1/AE3, CAM 5.2, OSCAR) are often expressed by both carcinoma and mesothelioma. Markers such as CEA, B72.3, MOC-31 and Ber-EP4 are more often positive in carcinomas than mesotheliomas. These markers can be expressed, even strongly, in mesothelial lesions. Claudin-4, an antibody which is directed against epithelial tight junctions has recently emerged as the best marker to differentiate carcinoma from mesothelioma. According to WHO, for confirmation of mesothelioma, it is recommended to demonstrate reactivity for two mesothelial markers (CK5/6, calretinin, WT-1, and/or D2-40) and negativity for two carcinoma markers (claudin 4, MOC-31, Ber-EP4, etc).[1,3]

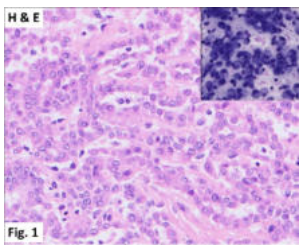

Figure 1: Photomicrograph (H and E, 40X) showing epithelioid mesothelioma characterized by a proliferation of tumor cells arranged in tubulopapillary pattern. Individual tumor cells have round to ovoid nuclei with vesicular nuclei, prominent nucleoli and abundant amount of eosinophilic cytoplasm (inset-cytology).

HISTOLOGIC SUBTYPES OF MESOTHELIOMA

EPITHELIOID MESOTHELIOMA

Epithelioid mesothelioma constitutes the majority (approximately 55%) of mesothelioma. Epithelioid mesothelioma may exhibit various architectural patterns including tubulopapillary, trabecular, adenomatoid, microcystic, solid, and micropapillary. Rhabdoid, deciduoid, small cell, clear cell, signet ring, lymphohistiocytoid, and pleomorphic cytologic morphologies have been described in epithelioid mesothelioma. A subset may also show myxoid stroma. Epithelioid mesothelioma with abundant myxoid stromal change is prognostically more favourable while the presence of micropapillary pattern, pleomorphic features and/or solid pattern strongly portend a worse prognosis. The presence of solid (≥ 50%), pleomorphic, and rhabdoid features in a diffuse epithelioid mesothelioma predicts poor

prognosis, whereas lymphohistiocytoid features and myxoid stroma (≥ 50%) are associated with better prognosis. A histological grading system has been proposed for epithelioid mesothelioma that incorporates nuclear atypia and a high mitotic count. A high nuclear grade is an independent poor prognostic factor. [1,6]

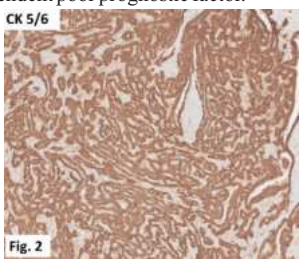

Figure 2 (10X): On IHC, tumor cells were positive for CK5/6, CK7 (not shown) while negative for WT1, TTF1, Claudin and p16. Bap1 immunoexpression was lost.

SARCOMATOID MESOTHELIOMA

Sarcomatoid mesothelioma is rare, comprising 7-22% of all cases of mesothelioma. Sarcomatoid mesothelioma resembles sarcoma and is characterized by haphazard proliferation of spindled mesothelial tumor cells. [1,6] Similar to epithelioid mesothelioma, specific cellular features are applied in sarcomatoid mesothelioma which include pleomorphic, lymphohistiocytoid, or transitional morphology. Lymphohistiocytoid type is associated with a more favorable prognosis. [1,6]

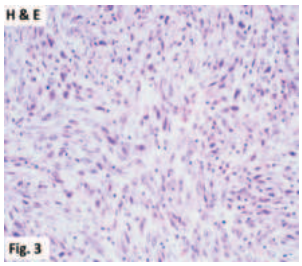

Figure 3: Photomicrograph (H and E, 40X) showing sarcomatoid mesothelioma characterized by malignant spindle-shaped cells arranged in haphazard fascicles.

BIPHASIC MESOTHELIOMA

Mesotheliomas in which both epithelioid and sarcomatoid morphology are present are classified as biphasic mesothelioma. Biphasic mesothelioma contributes approximately to 20% of all mesotheliomas. According to WHO, at least 10% of each component (epithelioid and sarcomatoid) is required for diagnosis of biphasic mesothelioma. According to recent classification schemes, in small biopsies, any amount of epithelioid and sarcomatoid mesothelioma should be classified as biphasic. Biphasic mesothelioma has a prognosis that lies in between epithelioid and sarcomatoid mesothelioma. [1,3,6]

HISTOLOGIC GRADING

Histologic aka nuclear grading system incorporates nuclear atypia and mitotic count. Nuclear grade is calculated as sum of nuclear atypia and mitotic count. Nuclear atypia is scored as 1, 2 and 3. Score 1 for mild cytologic atypia with occasional small nucleoli; score 2 for increased cytologic atypia with moderate pleomorphism and occasional nucleoli; score 3 for marked cytologic atypia with enlarged and highly pleomorphic nuclei and prominent nucleoli. Mitotic count is scored as 1 (0 to 1 mitotic figures/2mm2), 2 (2 to 4 mitotic figures/2mm2) and 3 (≥ 5 mitotic figures/2mm2). The nuclear atypia and mitotic count scores are added together and the sum of nuclear atypia and mitotic count yields a three-tier nuclear grade; nuclear grade 1 (sum = 2-3), nuclear grade 2 (sum = 4-5), and nuclear grade 3 (sum = 6). In WHO and CAP synoptic reporting for mesothelioma, a combination of the three-tiered system with the addition of necrosis is used. This yields a two-tiered system (i.e. low grade and high grade) according to which mesothelioma is designated as low grade if nuclear grade is 1 or nuclear grade is 2 without necrosis and designated as a high grade if nuclear grade is 2 with necrosis or nuclear grade is 3. Nuclear grading has been applied in epithelioid mesothelioma in both biopsy or resection specimens. [3] However, there is no consensus on the need to grade sarcomatoid or biphasic mesotheliomas as tumors with sarcomatoid morphology behave aggressively. [1,6]

MESOTHELIOMA-IN-SITU (MIS)

MIS is defined as the proliferation of mesothelial cells, either as a monolayer or small papillary growth, without invasion of the underlying tissue. The concept of MIS was controversial as it could not be proven definitively as a malignant precursor. However, in recent years, loss of BAP1 in patients with pleural effusion or detection of homozygous deletion of CDKN2A by FISH in proliferating mesothelial cells, has shown that signatures of malignancy can be detected in mesothelial cells even before the development of malignant mesothelioma. [1,6]

PERITONEAL MESOTHELIOMA

Peritoneal mesothelioma and pleural mesothelioma share same risk factor i.e. asbestos exposure but harbors distinct gene expression profiles. [1,6] Peritoneal mesothelioma accounts to ~10%-15% of all mesotheliomas. Peritoneal mesotheliomas are more frequent in women and younger age groups as compared to pleural mesothelioma. Peritoneal malignancies can originate from the ovaries, fallopian tubes, stomach, pancreas, colon, and kidney. Peritoneal mesothelioma is classified into the same histologic subtypes as pleural mesothelioma (epithelioid, biphasic, and sarcomatoid). According to studies that have been conducted in recent years, peritoneal mesotheliomas is found to have a better prognosis than pleural mesotheliomas. [1,6]

CONCLUSION

Mesothelioma is a rare primary tumour of the serosal lining cells. All mesotheliomas are clinically aggressive. Recently, there have been advancements in the field of mesothelioma. The use of ancillary tests has enhanced the ability to diagnose mesothelioma on small biopsies and in cytological fluids. Three main histological subtypes have been described. Median survival is 19, 13, and 8 months in patients with epithelioid, biphasic, and sarcomatoid tumours, respectively. [1, 3, 6] Younger age, epithelioid histo-type and early TNM staging are associated with better prognosis. The various prognostic factors that have been recognized are now recommended for inclusion in the reporting of routine mesothelioma specimens. The emergence of mesothelioma-in-situ as a distinct entity has enabled the clinicians to intervene earlier in the disease.

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