

Solid Tumour Section Review

Malignant pleural mesothelioma subtypes

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Abstract

Review of histologic subtypes of mesothelioma, with associated clinical, pathologic, and molecular data.

Keywords

Mesothelioma, pleura, histology, epithelioid, sarcomatoid, biphasic, BAP1

Identity

Malignant pleural mesothelioma (MPM) is a rare but aggressive cancer associated with median survival of 7-13 months from diagnosis and limited effective treatment options (Beebe-Dimmer et al., 2016). MPM is classified by the World Health Organization into three major histologic subtypes: epithelioid, mixed/biphasic, and sarcomatoid (Galateau-Salle et al., 2016). The precise incidence of each type varies by study and sampling technique (biopsy versus surgical resection), but epithelioid is the most common, followed by biphasic and sarcomatoid respectively. Histologic subtype has significant implications for prognosis, with the poorest outcomes observed for sarcomatoid tumors.

Clinics and pathology

Etiology

Over 80% of MPM cases are associated with asbestos exposure, and therefore asbestos is the major factor implicated in MPM tumorigenesis (Broeckx and Pauwels, 2018). The mechanisms

underlying asbestos-induced mutagenesis and alterations in gene expression are varied, and include generation of reactive oxidants, induction of chronic inflammation, and direct physical interference with mitotic structures (Huang et al., 2011). Beyond asbestos exposure, known causative factors of MPM include exposure to other non-asbestos fibres, radiation exposure (such as therapeutic radiation and Thorotrast), other chronic mesothelial inflammatory conditions, and certain germline mutations particularly in BRCA1-associated protein 1 (BAP1) (Attanoos et al., 2018). However, these constitute a small percentage of cases. The majority of non-asbestos associated MPM are considered idiopathic (Attanoos et al., 2018).

Epidemiology

Approximately 3000 new patients in the United States are diagnosed with MPM every year (Beebe-Dimmer et al., 2016). The latency period between asbestos exposure and diagnosis of MPM ranges from 20-40 years. As a result, over 2/3 of MPM is diagnosed in patients over age 65. Males are affected approximately four times as commonly as females corresponding to patterns in occupational exposure. Use of asbestos has been banned in the United States since the 1970s, when the EPA's Clean Air Act (1973) banned most spray-applied asbestos products for insulation. In 1989, the EPA enacted the Asbestos Ban and Phase Out Rule which aimed to impose a complete ban on the importation, production, and sale of asbestos-containing products. However, due to the long latency period and ongoing use in the developing world, the

incidence of MPM is estimated to increase over the next several decades (Tolani et al., 2018, Cinausero et al., 2019).

Clinics

MPM does not become symptomatic until it is advanced. Symptoms include dyspnoea, chest pain, and cough. MPM has a median overall survival of 7-13 months from the time of diagnosis with 5-year survival of less than 10%, although patients who are treated with multimodality therapy have shown median survival of 13-23.9 months (Beebe-Dimmer et al., 2016, Zhuo et al., 2019, Cao et al. 2010). Longer survival is associated with female sex, younger age at diagnosis, earlier clinical stage, absent lymph node involvement, and lower comorbidity score (Van Gerwen et al., 2019). Beyond the TNM staging system, clinical factors associated with shorter survival include increased tumor volume and maximal interlobar thickness as measured on computed tomography, elevated serum lactate dehydrogenase, neutrophil-to-lymphocyte ratio >5, anemia, and malnutrition (Gill et al., 2018; Doi et al., 2019; Harris et al., 2019). Histologic subtype is one of the most significant prognostic factors, and non-epithelioid MPM is associated with shorter survival than epithelioid MPM (hazard Ratio (HR) 1.3; $p < 0.001$; Flores et al., 2008).

Pathology

Histologic subtype is defined by tumor cell morphology. Epithelioid tumors are $\geq 90\%$ epithelioid-shaped cells, sarcomatoid tumors are $\geq 90\%$ spindle-shaped cells, and biphasic tumors are a combination of the two in varying proportions. While epithelioid is consistently the most prevalent histologic subtype of MPM, the relative incidence of each subtype varies by study population and by specimen type. An estimate by Suzuki et al (2001) identified an overall prevalence of 61.5%, 22%, and 16.4% for epithelioid, biphasic, and sarcomatoid, respectively. More recently, Chirieac and colleagues (2019) compared subtypes as identified by biopsy versus surgical resection and found 80.6% concordance. Sarcomatoid histology on biopsy was found to have the highest correlation with resection histology, followed by biphasic and epithelioid. Histologic subtype is a significant independent prognostic factor, and each subtype carries unique features. For all three subtypes, the degree of differentiation correlates with survival. Poorly differentiated tumors have a HR of 2.5 compared with well or moderately differentiated tumors (Zhuo et al., 2019).

Epithelioid - This subtype is the most common and associated with most favourable prognosis (median survival 14.4 months, Verma et al., 2018). The epithelioid subtype can exhibit a range of morphologies, including solid (the most prevalent,

44%), tubulopapillary (29%), micropapillary (13%), tubular (7%), and trabecular (2%). Most epithelioid MPM contains more than one growth pattern. The solid type in particular is associated with high-grade nuclear features as well as shorter median overall survival, while tubulopapillary and micropapillary have the longest overall survival (Krasinskas et al., 2016).

In addition to growth pattern, nuclear grade, mitotic count, and necrosis have been found to predict survival in epithelioid MPM (Rosen et al., 2018). Higher Ki67 corresponds with shorter median overall survival in epithelioid, but not in non-epithelioid MPM. Ki67 level also decreases following chemotherapy, which is consistent with the prognostic effect of treatment in this group (Ghanim et al., 2015).

Patients with epithelioid MPM were found to benefit independently from both surgery and chemotherapy (Verma et al., 2018). Poor surgical candidates with epithelioid histology and minimal pleural disease can in rare cases be observed prior to resorting to chemotherapy (Kindler et al., 2018).

Biphasic - Current WHO criteria for defining biphasic tumors require a mixture of epithelial and spindle-shaped cells, with at least 10% of cells matching each type. However, the relative proportion of each cell type within biphasic tumors has implications for clinical behaviour. An analysis by Vigneswaran and colleagues (2017) demonstrated that the amount of epithelioid differentiation in biphasic MPM is a significant predictor of survival. Similarly, Harling and colleagues (2019) demonstrated shorter survival associated with increased sarcomatoid component in biphasic tumors.

Diagnosing biphasic MPM can be challenging on the basis of morphology alone. In one review series, 17% of cases originally diagnosed as biphasic were reclassified as pure epithelioid and 12% as pure sarcomatoid. Only 23% of biphasic diagnoses were made with morphology or immunohistochemistry (IHC) alone, with the remaining 77% requiring additional IHC assessment to confirm diagnosis (Galateau-Salle et al., 2018).

Biphasic tumors are sometimes grouped with sarcomatoid as 'non-epithelioid' based on their clinical behaviour. For example, atypical mitoses are associated with decreased survival in non-epithelioid mesothelioma, but, unlike in epithelioid MPM, mitotic count, necrosis, and nuclear atypia are not associated with survival (Habougut et al., 2017). On imaging, non-epithelioid MPM is more frequently associated with calcified plaques (Escalon et al., 2018). Galateau-Salle and colleagues (2018) demonstrated the presence of a transitional phenotype was associated with significantly shorter survival compared to biphasic tumors without transitional elements and behave in a manner

prognostically similar to pure sarcomatoid tumors. PD-L1 expression has also been found to be higher in both biphasic and sarcomatoid than in epithelioid MPM (Brosseau et al., 2019).

However, there are meaningful distinctions between biphasic and pure sarcomatoid MPM. Patients with biphasic tumors have an intermediate overall survival compared to epithelioid and sarcomatoid (median 9.5 months, Verma et al., 2018). Treatment with pleurectomy/decortication, radiotherapy, or chemotherapy improves survival compared with supportive care in this group but not sarcomatoid tumors, with selective benefit of radiotherapy in tumors with higher sarcomatoid proportion (Verma et al., 2018, Harling et al., 2019).

Sarcomatoid - Additional characteristics for diagnosis of the sarcomatoid subtype, in addition to the presence of $\geq 90\%$ spindle-shaped cells, include high nuclear/cytoplasmic ratio and frank sarcomatoid features (Dacic et al., 2019). It can sometimes be histologically difficult to distinguish sarcomatoid MPM from benign conditions such as

fibrous pleuritis; Kinoshita and colleagues (2018) demonstrated that the incorporation of IHC is highly specific in distinguishing these conditions.

Sarcomatoid histology is associated with larger tumor size at diagnosis and more advanced TNM stage (Paaanen et al., 2018). Patients with sarcomatoid tumors have the lowest median overall survival of the three subtypes (median 5.3 months, Verma et al., 2018). Gross macroscopic resection does not significantly prolong survival in sarcomatoid tumors, in contrast to epithelioid and biphasic tumors (Verma et al., 2018). These patients have a diminished response to systemic chemotherapy (Kindler et al., 2018, Mansfield et al., 2014).

Recent guidelines have recommended that sarcomatoid tumors (along with biphasic) should be considered candidates for systemic therapy and should not be excluded from first-line clinical trials on the basis of histology alone (Nicholson et al., 2019).

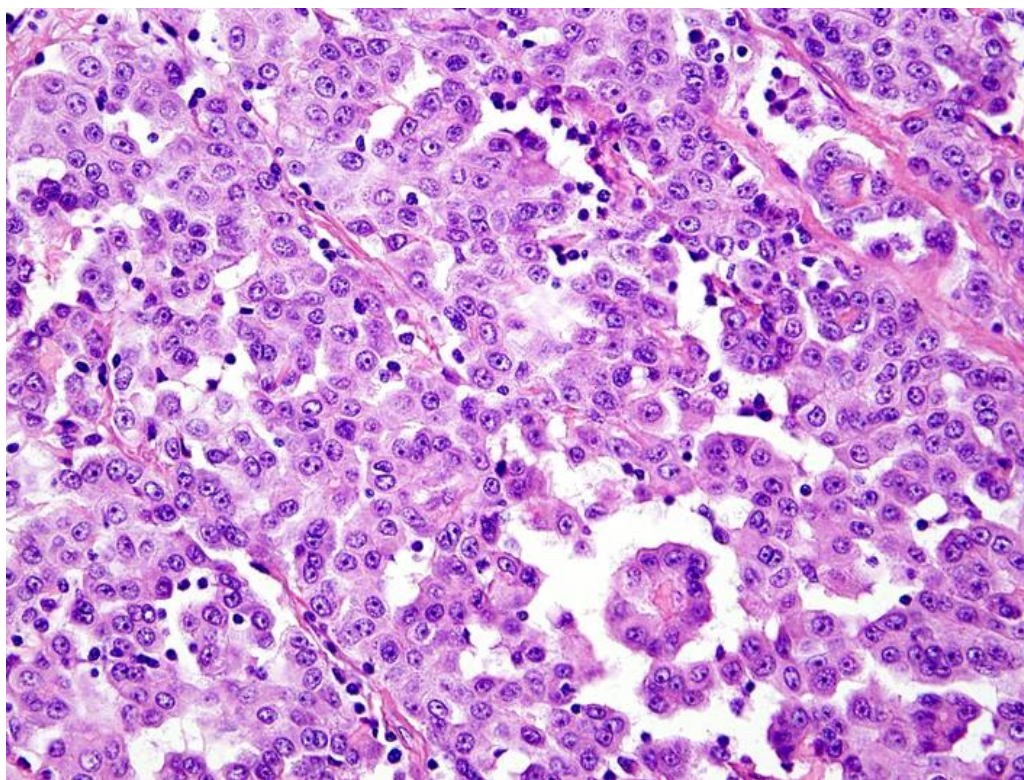


Figure 1 Malignant pleural mesothelioma, epithelioid type.

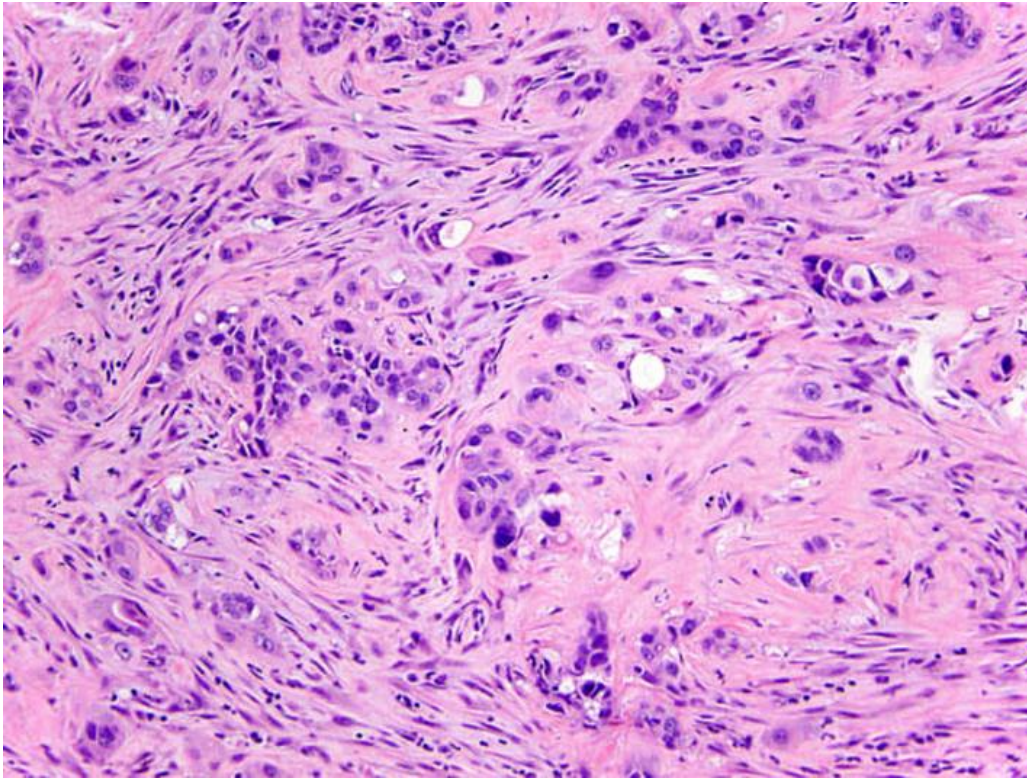


Figure 2 Malignant pleural mesothelioma, biphasic type.

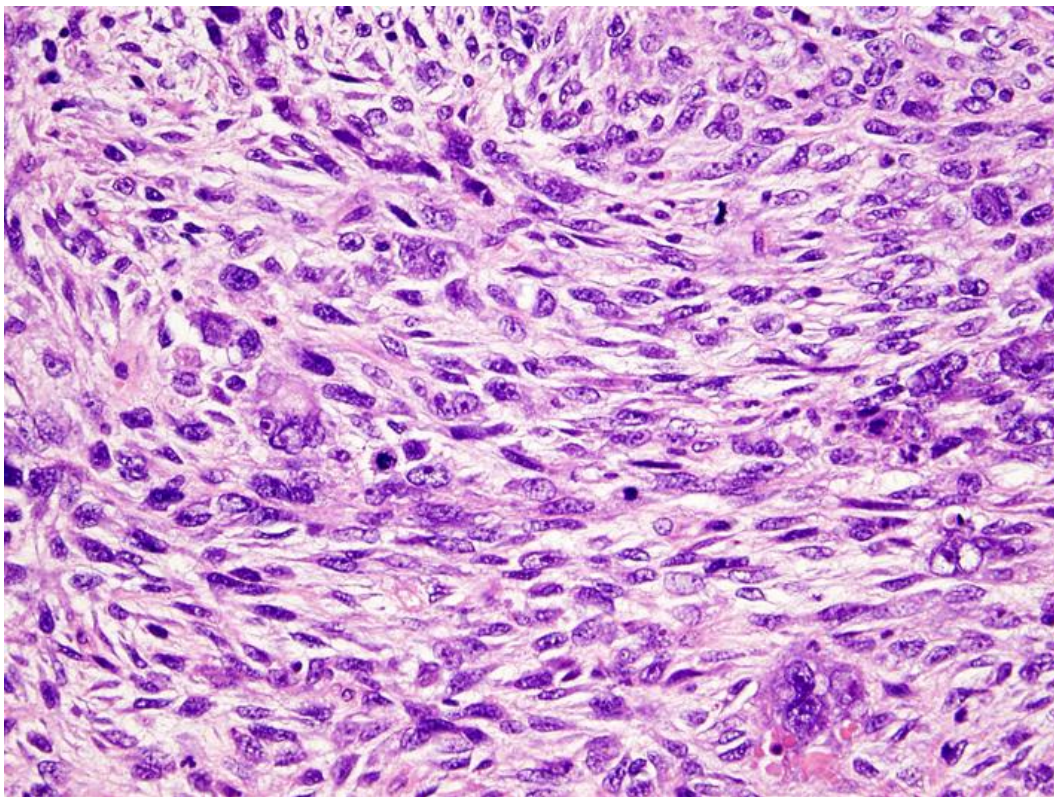


Figure 3 Malignant pleural mesothelioma, sarcomatoid type.

Treatment

Multimodal therapy is the standard approach to MPM. The majority of patients are not candidates for surgery at presentation due to advanced disease, age, or comorbidities (Sugarbaker et al., 2014). For these patients, platinum-based chemotherapy (cisplatin plus pemetrexed) is first line treatment (Cinausero et al., 2018). In patients with resectable disease, the goal of surgery is macroscopic complete resection. This can be accomplished via lung-sparing surgery (extended pleurectomy and decortication) or extrapleural pneumonectomy (Friedberg et al., 2019). Lung-sparing techniques have increased in favour due to lower morbidity and comparable outcomes. However, five-year survival following radical surgery remains low at approximately 15% (Cinausero et al., 2019). Radiation therapy also plays a role in select patients. There is some evidence that the addition of antiangiogenic agents such as bevacizumab can improve outcomes in combination with chemotherapy (Zalcman et al., 2016). Given their success in other solid tumors, targeted therapies and immunotherapeutics are being actively explored in MPM with mixed results (Cinausero et al., 2019). Overall, a review of 20,561 MPM patients in the National Cancer Database by Nelson and colleagues (2017) identified significant improvement in patient survival with surgery-based multimodality therapy compared with surgery alone, with the strongest effect seen using a combination of cancer-directed surgery, chemotherapy, and radiation therapy (HR 0.52).

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