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Prognostic factors in malignant pleural mesothelioma

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Summary Malignant pleural mesothelioma (MPM) is a clinically aggressive tumor originating from mesothelial cells, which line the serosal cavities. Recent years have seen extensive research aimed at identifying new therapeutic targets, predictive markers and prognostic factors in this disease. These include both serum and tissue markers, and are related to multiple cellular pathways which affect cell survival, proliferation, apoptosis, angiogenesis, interaction with the immune response and DNA repair. Several of these molecules may become relevant for pathologists as part of the effort to select patient sub-populations for targeted therapy in the future. This review summarizes current data in this area and discusses their potential clinical relevance.

1. Introduction

Malignant mesothelioma (MM), primary cancer of the serosal cavities, has its origin in the mesothelial cells lining the pleural, peritoneal and the pericardial cavities, as well as the tunica vaginalis. The pleural cavity is the most common site of origin of this tumor. Malignant pleural mesothelioma (MPM) may have epithelioid, sarcomatoid or biphasic morphology (Fig.), and the conditions which enter the differential diagnosis are unique to each of these entities. The main differential diagnosis for epithelioid mesothelioma, the most common morphological variant, is metastatic carcinoma, particularly adenocarcinoma, and the most widely used ancillary method in this context is immunohistochemistry (IHC). A wide array of antibodies is presently available for this purpose, including general carcinoma and mesothelioma markers, as well as carcinoma markers which are more organ-specific (reviewed by Ordóñez [1]). Additional methods, including electron microscopy, measurement of soluble molecules in the serum and/or effusion specimen and fluorescent in situ hybridization (FISH) may be employed, depending on laboratory expertise, and assessment of the cytology specimen may be informative of mesothelioma of the epithelioid type [2,3].

MPM is one of the most clinically aggressive malignancies, with the majority of patients succumbing to their disease within 2 years of diagnosis. The combination of surgery with chemotherapy, and the optimization of the latter, has in recent years led to some improvement in the survival and life quality of MPM patients, whereas targeted therapy has to date failed to have major clinical impact in this disease [4]. Despite this improvement, long-term survival is rare in MPM, making it difficult to identify biological factors which may clearly differentiate between patients with poor and improved progression-free or overall survival (PFS; OS). Another limiting factor is the difficulty to outperform clinicopathologic factors shown to have predictive or prognostic role in MPM in different clinical models. The most important of these parameters is the histological subtype of the tumor, with sarcomatoid and biphasic MPM being associated with significantly worse outcome than epithelioid MPM. Other parameters reported to be associated

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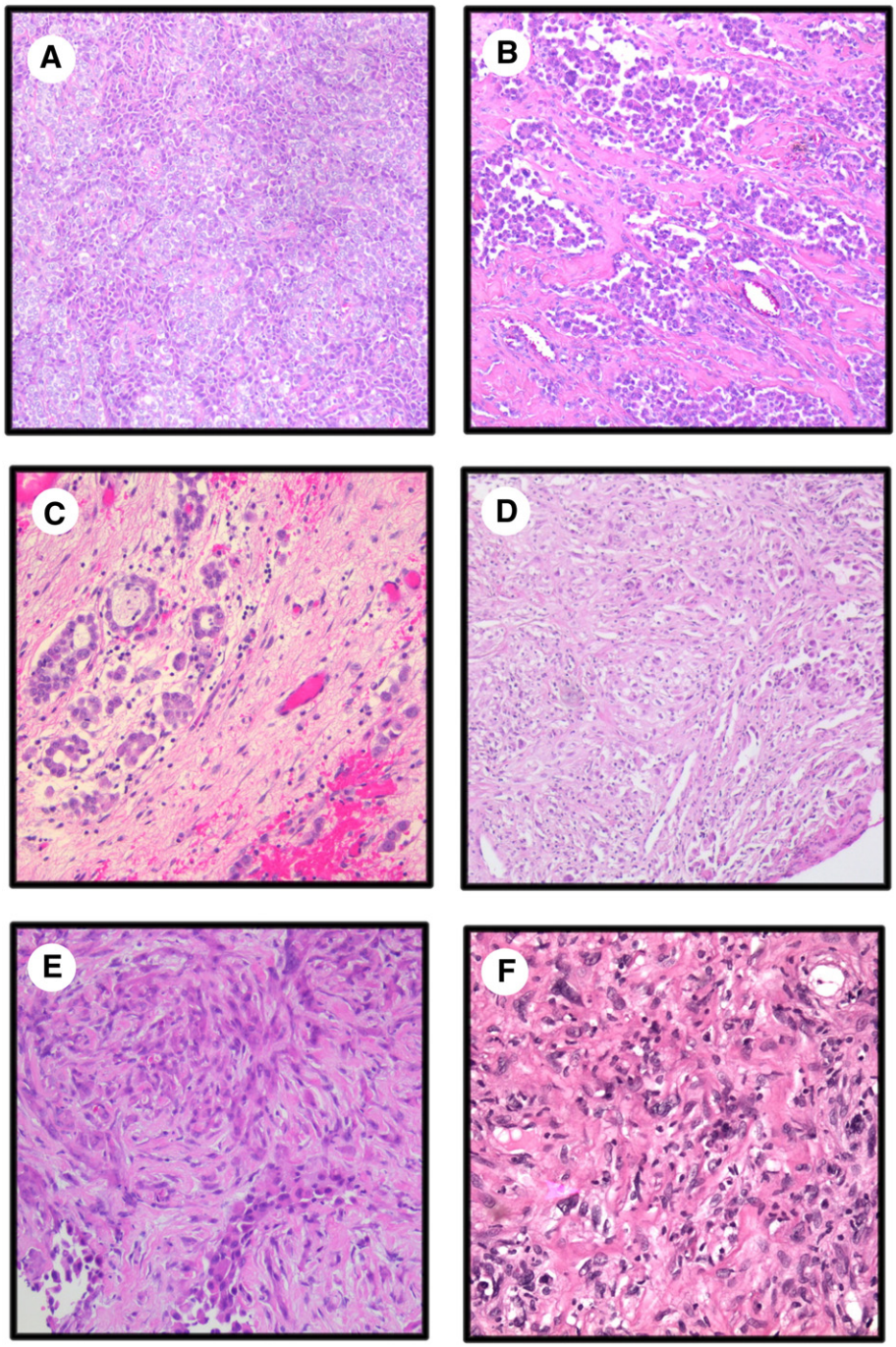

Fig. The morphology of malignant pleural mesothelioma. Examples of epithelioid (A-C), biphasic (D-E) and sarcomatoid (F) malignant pleural mesothelioma, H&E stain.

with adverse outcome in different scoring systems include male gender, poor performance status, disease stage, high serum lactate dehydrogenase (LDH) level, anemia and leukocytosis (reviewed by Campbell and Kindler [4]). Analysis of a large MPM series recently showed that in patients who underwent pathologic staging (n = 550), advanced TNM stage, non-epithelioid histology, age ≥50 years, male gender, non-curative surgery, absence of adjuvant therapy, platelet counts ≥400 000 and white blood cell counts ≥15.5 were significantly related to poor survival [5]. Nuclear grade was reported to be a strong independent prognostic marker in epithelioid MM [6], whereas serum c-reactive protein (CRP) was an independent prognostic marker of OS in three studies [7–9], in the latter of which it additionally predicted response to multimodality therapy [9]. Low pleural fluid glucose levels were another independent prognosticator of poor OS in the study by Tanrikulu et al [7], whereas low albumin and high fibrinogen