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REVIEW ARTICLE

Pleural neoplastic pathology

Georgia Karpathiou [a,*], **Dimitrios Stefanou** [a], **Marios E. Froudarakis** [b]

[a] *Department of Pathology, Medical School University of Ioannina Greece*
[b] *Department of Pneumonology, Medical School Democritus University of Thrace, Greece*

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Summary
Background/Purpose: Malignant pleural effusion is a frequent situation in pulmonary medicine. However, it is sometimes difficult to recognize the underlying etiology. The aim of this review is to provide the key characteristics of primary and metastatic pleural neoplasms.
Methods: A review of the recent literature regarding pleural neoplasia is provided.
Results: Malignant pleural mesothelioma (MPM) is the commonest primary pleural epithelial tumor showing remarkable histological heterogeneity often with prognostic significance. Various genetic alterations like changes in *INK4* locus, *NF2*, *BAP1* but also epigenetic changes are present in MPM. It should be distinguished from atypical mesothelial hyperplasia, mainly through morphological and clinical criteria, and from other rare primary and metastatic tumors, for which immunohistochemistry is rather important. Solitary fibrous tumor, the commonest primary pleural mesenchymal tumor is characterized by STAT6 overexpression. Other primary tumors, like adenomatoid tumor, well-differentiated papillary mesothelioma, synovial sarcoma, vascular tumors, various other sarcomas, thymic tumors and tumors of uncertain histogenesis are rarely encountered in the pleura. In contrast, metastatic disease is the commonest neoplasia of the pleura, and especially lung, breast and lymphoid malignancies.
Conclusion: The basic pathological, immunohistochemical and molecular characteristics of these entities are provided in the current review, along with their differential diagnosis.

Contents

* Corresponding author. Current address: Department of Pathology, University Hospital of Saint-Etienne, North Hospital, 42055 Saint-Etienne Cedex 2, France.
E-mail address: gakarpath@yahoo.gr (G. Karpathiou).

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Introduction

Pleural effusion may be caused by a variety of stimuli; infections, neoplasms, trauma, drugs, collagen vascular disease, iatrogenic, or it can be "idiopathic" when no evident cause is available [1]. Malignant pleural effusions are a common medical problem in patients with cancer [1,2]. It occurs usually in patients with advanced neoplastic disease and it is associated with reduced life expectancy [3,4]. Breast and lung cancer are responsible for approximately 75% of the malignant pleural effusions [5]. In order to have adequate tissue samples to establish a histological diagnosis, patients presenting with a suspected malignant pleural effusion but unknown primary tumor should undergo thoracoscopy [1]. Indeed in such "treatment-naïve" patients, histology of the primary tumor, and patient's performance status are important parameters predicting survival [6]. However, histological evaluation of the pleura might be difficult, especially the differential diagnosis of mesothelioma from metastatic disease or reactive pleuritis. Furthermore, novel molecular biological markers are under intense investigation to better understand pleural carcinogenesis [2]. The current review aims to provide basic knowledge of pleural pathology.

Primary pleural tumors

Primary tumors of the pleura are relatively rare. Of these the most common are malignant pleural mesothelioma (MPM), representing a malignant epithelial neoplasm, and solitary fibrous tumor (SFT), a mesenchymal tumor. Other primary pleural tumors, like well-differentiated papillary mesothelioma, synovial sarcoma, angiosarcoma, epithelioid hemangioendothelioma and adenomatoid tumor are extremely rare.

Malignant pleural mesothelioma (MPM)

Malignant pleural mesothelioma (MPM) is a highly aggressive neoplasm, with a median overall survival for the epithelioid type of 16 months, a 2-year overall survival of 34% and a 5-year overall survival of 11% [7,8]. Approximately 2.000 cases of MPM occur every year in the USA [9] and one per million of general population in France, a number rising at 50 to 100 for asbestos-exposed population [10]. It is therefore a rare neoplasm. Almost eighty seven percent (87.3%) of male cases and 64.8% of female cases are attributable to asbestos and they typically show a long latency period of few decades [7,11]. Asbestos fibers that reach the pleura after inhalation interact with mesothelial cells and inflammatory cells initiating prolonged tissue damage, repair and inflammation, which finally lead to carcinogenesis of MPM via unknown mechanisms [12]. These possibly include reactive oxygen species generated due to asbestos fibers leading to DNA damage and strand breaks, physical interference of asbestos fibers after being engulfed by mesothelial cells, with the mitotic machinery, resulting in chromosomal structural abnormalities and aneuploidy of mesothelial cells, accumulation of carcinogens on the surface of asbestos fibers, absorption by the fibers of important cellular proteins, the deficiency of which may be harmful, and the release of cytokines and growth factors by mesothelial cells and macrophages inducing inflammation and tumor promotion [12].

Asbestos exposure is also associated with pleural plaques, a usually incidental asymptomatic finding. These are composed of avascular layered collagen (Fig. 1) and they develop in 20.4% of the asbestos-exposed subjects, possibly as a local pleural response to accumulation of asbestos fibers, which translocate to pleural spaces and cause pleural fibrosis [13]. It is important to obtain several and large biopsies from pleural tissue neighboring the plaques in order to exclude or confirm histologically a diagnosis of MPM, as suggested by Boutin [14].

Despite this well-established relationship with asbestos exposure, only 17 pleural malignant mesotheliomas were diagnosed in a 7-year follow up of 5287 asbestos-exposed subjects [13], implying individual susceptibility to asbestos. In fact, the molecular changes found in MPM vary considerably between different patients including alterations in a given gene and combined genetic and epigenetic alterations, consistent with molecular variations [15].

Grossly, it shows a diffuse growth over parietal and visceral pleura, including the fissures, while in late stages it invades the lung, the mediastinum, the diaphragm and the

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