Commentary

The use of electron microscopy for the diagnosis of malignant pleural mesothelioma

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Transmission electron microscopy (TEM) gave a great impulse to medical research. After its introduction for biological studies in 1931, several microscopic details from observation of animal and tumor cells by TEM were published starting from 1953. Atlas of diagnostic electron microscopy were successively published (1). TEM represented a useful adjuvant method for careful investigation of subcellular or fine modifications accompanying various pathological conditions, including inflammatory/degenerative (2), genetic (3,4) and neoplastic diseases (5-7). Moreover, in conjunction with its younger derivative scanning electron microscopy, TEM represents a useful research method for careful investigation of subcellular space. The introduction of immunohistochemistry and, successively, of molecular pathology in conjunction of routinary examination by light microscopy, restricted the use of TEM for diagnostic purposes. In addition, techniques for TEM preparation are relatively expensive and require longer time and well preserved and fixed tissues and cells for an adequate identification of diagnostic ultrastructural changes. Histologically, three types of malignant pleural mesothelioma (MPM) are classically recognized: the epithelioid, sarcomatoid and biphasic types (8). The diagnosis of MPM is generally based on the microscopic examination and the assessment of a panel of around ten immunohistochemical markers. However, in some cases immunohistochemical findings are not conclusive. International guidelines still consider TEM as a useful adjuvant diagnostic tool for diagnosis of MPM (9). The most characteristic ultrastructural features of MPM were obtained from examination of bioptic tumor tissue samples. The diagnosis of MPM is challenging and requires a panel of immunohistochemical markers or electron microscopy to specifically differentiate MPM from lung adenocarcinomas. As for immunohistochemical investigation, there is no a single diagnostic feature, but rather a combination of several ultrastructural features (10). The finding of very long thin apical microvilli and the absence of glycocalyx help to distinguish epithelioid MPM form primary or metastatic lung adenocarcinoma, since the latter display short microvilli that usually have a glycocalyx (9-11). Perinuclear tonofilament bundles, the presence of basal lamina and long desmosomes are characteristic of adenocarcinoma and not documented in MPM (9-11). Paraffin block and formalin fixation may be satisfactory, since microvilli and tonofilament bundles are enough preserves in formalin-fixed samples, but unfortunately this is not the rule. Moreover, sarcomatous MPM in the majority of cases do not show specific ultrastructural features, and in general poorly differentiated tumors lacking immunohistochemical markers lack specific features at TEM as well (10).

Recently, Domínguez-Malagón *et al.* (12) focused on the diagnostic efficacy of electron microscopy and pleural effusion cytology for the distinction of MPM and lung adenocarcinoma. The Authors highlight that, in many cases, the first diagnostic approach to MPM is performed on pleural effusion; moreover, in some patients, evaluation of pleural effusion is the only available sample for diagnosis. In their paper, Domínguez-Malagón *et al.* compared 25 pleural effusion samples collected from patients with a following bioptic histological and immunohistochemical diagnosis

of MPM (n=5) or adenocarcinoma (n=20). Of the examined fluid samples, only 60% and 55% of MPM and adenocarcinomas cases, respectively, contained cells for diagnosis. In remaining two of five samples (40%), TEM showed cells with "bushy" microvilli characteristic of MPM, and in 9 of 20 cases of lung adenocarcinomas (45%), cells with short microvilli were evidenced. The Authors concluded that TEM can help to identify unequivocal morphological changes useful for the differential diagnosis of MPM or adenocarcinomas if cell content in the pleural fluid is satisfactory for the investigation itself (12). In general, it should be emphasized that international guidelines suggest to limit the diagnostic role of TEM to those cases of epithelioid MPM in which light microscopy and immunohistochemical investigation of bioptic tissues give inconclusive results (10). The work of Domínguez-Malagón *et al.* (12) suggests that pleural effusion can be a new satisfactory source of diagnostic material for TEM in those cases in which routinary diagnostic approach with biopsy after thoracotomy doesn't give adequate or diagnostic material. The main limitation of the study of Domínguez-Malagón *et al.* is the limited number of cases with adequate amount of cells for the diagnosis of epithelioid MPM. Further cases are needed to confirm and support successful TEM application with this less invasive method of cell collection for differential diagnosis between localization of epithelioid MPM and adenocarcinoma. It should be interesting also to investigate the successful TEM application for the confirmation of diagnostic features of epithelioid mesothelioma in cells collected from effusions from another origin than pleural site.

In conclusion, the diagnosis of epithelioid MPM and its distinction from lung adenocarcinomas is generally based on the microscopic examination and the assessment of an immunohistochemical panel, but in some cases immunohistochemical findings are not conclusive and TEM can represent an useful adjuvant method of diagnosis. The opportunity to obtain fresh cells from pleural effusions for an optimal fixation and preservation for ultrastructural examination can be extremely useful in those cases in which collection of bioptic tissue is difficult, unsuccessful or even impossible, or when preservation of biotic tissue integrity was impaired from problematic technical or surgical procedures for tissue collection.

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Footnote

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