Letter to the Editor

The use of electron microscopy for diagnosis of malignant pleural mesothelioma

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Electron microscopy (EM) opened, since its beginnings in the early 1930s, an exciting chapter for morphological science and all its branches. In a recently published commentary by Ferlosio and Orlandi the focus is put on the role of EM in the diagnosis of malignant pleural mesothelioma (MPM) (1). In this commentary the authors raise some very important issues. Among these are the restricted uses of EM for diagnostic purposes, also the cost and technical expertise required to perform immunohistochemistry (IHC) *vs.* EM in a clinical setting, and last the challenges clinicians face in order to differentiate MPM from lung adenocarcinoma.

Regarding the first point, we very much agree with the authors that in the past few decades IHC and molecular pathology have relegated much of the need of EM as a diagnostic tool. However, as useful as these tools have been EM still remains a feasible, highly sensitive tool for the diagnosis of many different pathologies which display ultrastructure changes that must be identified in order to correctly catalogue, and therefore treat, the condition. One such example is the use of EM on skin biopsies in order to diagnose lysosomal storage diseases. In their most recent report, Alroy and Ucci summarize 19 years of experience using EM screening of more than 950 skin biopsies, and thus being able to document over 200 biochemically proven cases of lysosomal storage diseases. They conclude that EM is the most cost-effective, sensitive and efficient diagnostic tool for this condition (2). Other applications of EM for diagnostic and prognostic purposes include Alport's syndrome, thin basement membrane disease, amyloidosis and ciliary abnormalities (3).

It is generally a misconception that EM is a highly expensive and technically difficult technique to use for diagnostic purposes, especially when other, considered less expensive, alternatives exist, such as IHC and molecular pathology techniques. This is certainly the case in diagnostic protocols which require few IHC stains and a routine hematoxilin eosin slide in order to achieve a highly specific diagnosis. Previous reports have commented on the cost-effectiveness of IHC, this being one of the most widely used approaches in pathology laboratories, and results yield that this technique is cost-effective even at very low efficacies (4). However, in cases where a 10 antibody panel is required, at an estimated $50 cost per-antibody, and with a sensitivity which does not reach 100% even when used in combinations, the usefulness of the technique becomes a little less clear. Recently some authors have even considered the combined use of BAP1 IHC along with *p16* FISH in order to correctly differentiate MPM from benign mesothelial proliferation, with a sensitivity of 92.5% when combining these techniques, however, FISH is also an expensive and technically challenging method to perform in a diagnostic setting (5). Instead, EM is actually not a very expensive technique, being comparable in time and cost to

other ancillary diagnostic techniques (6).

We consider the last point to be the most important one raised: the challenge of accurately and timely diagnosing MPM. In this regard, it is important to consider the contribution as well as the limitations of the article we previously published. First, it is important to consider that the study we performed was importantly limited by number of patients, with only 25 cases of which 5 were ultimately diagnosed with MPM. It is important that results be considered carefully and not extrapolated, but rather to await a more robust sample size in order to better understand the implications of the technique and the place it might have in the MPM scenario (7). Second, we strongly agree with Ferlosio and Orlandi regarding the challenge of diagnosing MPM. Patients who are suspected cases usually present with advanced age and a compromised general wellbeing, and as such may not be ideal candidates for surgery. An EM diagnosis from cells obtained from pleural effusion would be swift, non-invasive and able to detect the ultrastructure abnormalities which are diagnostic of MPM. Unlike previous misconceptions, the material for preparation of EM samples is relatively inexpensive and most major medical centers are already equipped with EM laboratories (6).

In conclusion, EM is a highly sensitive diagnostic tool which may in some very specific cases diagnose MPM in patients who present with pleural effusion. Although molecular techniques have provided new information and further refine disease classification, EM remains an important link between the morphological information obtained from light microscopy and molecular organization. It is important to note that expert pathologists deem IHC and EM as complementary techniques, rather than competitive ones (3), and as such must be used intelligently and keeping in mind the best interest of the patient.

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Footnote

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