Mesothelial Proliferations

An Increasing Morphologic Spectrum

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During the past 2 decades, a great deal has been written about the epidemiology, clinical features, and pathologic characteristics of malignant mesotheliomas (MMs), as well as the multiple other neoplasms with which they may be confused. This is, in part, because throughout the 1970s and 1980s, the incidence of MMs demonstrated an alarming increase. Fortunately, this trend has now reached a plateau; however, MM continues to represent an important tumor entity to recognize accurately because of the grave prognostic import this diagnosis carries.

In this issue of the Journal, Khalidi et al describe 3 cases of a rare mesothelioma variant, namely, so-called lymphohistiocytoid (lymphoma-like) MM. This lesion was reported for the first time in 1988 by Henderson and colleagues, after a survey of cases entered in the Australian Mesothelioma Surveillance Program. As they and Khalidi and colleagues documented, the resemblance between lymphohistiocytoid MM and malignant hematopoietic lesions of the pleura can be striking. Because of the large number of lymphocytes and plasma cells in these tumors and the wide dispersion of the malignant keratin-positive epithelioid cells, another potential diagnostic trap would be to consider them “inflammatory pseudotumors.” As such, lymphohistiocytoid MM is, perhaps, yet another neoplasm that may assume a “lymphoepithelioma-like” image, reinforcing the notion that the latter appearance is a pattern rather than a singular clinicopathologic entity.

Like many other groups of neoplasms, mesothelial tumors have undergone considerable nosologic revisionism during the past 25 years. The lesion formerly known as “benign fibrous mesothelioma” is now known to represent solitary fibrous tumor of the pleura, which is an entirely unrelated proliferation at the cellular and epidemiologic levels. Similarly, adenomatoid tumor is now known to be a benign neoplasm with definite mesothelial differentiation, instead of an endothelial lesion as originally thought. “Multicystic” mesothelioma and “well-differentiated papillary mesothelioma” continue to be the subjects of some debate regarding their status as benign or “borderline” mesothelial neoplasms vs complex mesothelial hyperplasias. Based on the information now extant, we prefer the latter of those interpretations, and there is little doubt that the clinical outcome for patients with those 2 forms of mesothelial proliferation is extremely favorable in the vast majority of cases.

In turning attention to overtly malignant mesothelial tumors, a surprising variety of patterns has emerged, aside from lymphohistiocytoid mesothelioma, to expand the traditional categoric outline that simply included “epithelioid,” “biphasic,” and “sarcomatoid” mesotheliomas. The epithelioid subgroup now has been expanded to include mesothelial malignant neoplasms that have a wholly clear cell, oncocyto id or granular-cell, tubulopapillary, large polygonal cell, polyhedral stromal mucin-producing, “medullary” epithelioid, or even small-cell appearance. The differential diagnostic potentialities raised by such images are numerous, including metastatic non–small cell carcinomas of various primary origins, metastatic melanoma, pleural sarcomas with an epithelioid or small round cell appearance, and even metastatic small cell neuroendocrine carcinoma. In reference to biphasic MM, primary synovial sarcoma of the pleura now has been well-characterized as an important diagnostic alternative. Indeed, in the absence of data showing the characteristic t(X;18) chromosomal translocation of synovial sarcoma, which is associated with production of SYT-SSX fusion transcripts, its separation...
from MM can be extremely challenging. This is so because the immunophenotypes of the 2 tumors are largely overlapping. Monophasic sarcomatoid mesothelioma potentially simulates a range of spindle-cell sarcoma morphotypes that may affect the pleura, again including monophasic synovial sarcoma, but also fibrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, chondrosarcoma, osteosarcoma, leiomyosarcoma, and malignant peripheral nerve sheath tumor.

This information brings one to consideration of adjunctive pathologic studies in the objectification of the diagnosis of MM. In regard to this important topic, it should be remembered that there are definite roles for a number of laboratory analyses, including histochemistry, immunohistology, electron microscopy, fluorescence in situ hybridization, the polymerase chain reaction using appropriately chosen primers, and traditional cytogenetic evaluations. Although most attention has been given in recent years to the immunohistochemical separation of epithelioid MM from metastatic adenocarcinoma, the panel of markers used for that purpose is generally not helpful in the differential diagnosis of nonepithelioid MM variants, with selected exceptions. Standard approaches to separating MM from adenocarcinoma include immunostains for keratin (“pan-keratin” or keratin 5/6), epithelial membrane antigen, thrombomodulin, HBME-1, calretinin, tumor-associated glycoprotein-72 (recognized by B72.3), carcinoembryonic antigen, CD15, Ber-EP4, BG8, and MOC-31, with expected reactivity in MM primarily including the first 5 of those determinants. Electron microscopy still is extremely useful in this particular context, inasmuch as the long, branching, “bushy” microvilli that one associates with mesothelial cells are best represented in epithelioid MM. Neither immunohistology nor electron microscopy is as helpful in the realm of biphasic or spindle-cell tumors, and an entirely different set of morphologic and immunophenotypic variables must be assessed in those lesions. For example, keratin and calretinin assume much greater value in the differential diagnosis of sarcomatoid MM because the principal interpretative alternatives are those of true sarcoma or solitary fibrous tumor, and sarcoma-like mesotheliomas may divergently express some “mesenchymal” markers, such as desmin and muscle actin isoforms. Moreover, fluorescence in situ hybridization or polymerase chain reaction may be necessary to separate such entities as synovial sarcoma (which are also reactive for keratin and calretinin) from MM with certainty. Ultrastructural analyses likewise are not very helpful in that setting, because sarcomatoid MM tends to lose the specialized features of epithelial cells when it undergoes spindle-cell transformation. To summarize, the particular pathologic assessments that are done should be tailored to the specific morphologic image associated with a mesothelioma subtype. In particular reference to lymphohistiocytoid MM, the differential diagnosis mainly concerns itself with an exclusion of non-Hodgkin lymphoma, as outlined by Khalidi and coworkers.

Is it currently critical to separate MM from malignant mimickers, vis-à-vis implications for treatment and prognosis? The answer to this question is generally “no.” Regardless of whether a given patient has MM, metastatic pleural carcinoma, or a pleural sarcoma, the patient’s outlook is equally dismal and generally refractory to all therapeutic modalities.

Why, then, do we spend so much time and effort on this exercise? It is, primarily and sadly, because of the intrusion of legal issues into the current practice of medicine. Without exaggeration, one can now expect that most patients with pleural malignant neoplasms (or their families) will find their way to an attorney and that personal injury litigation will eventuate. Because some mesotheliomas have been linked pathogenetically with exposure to aerosolized amphibole asbestos fibers, and metastatic carcinomas and pleural sarcomas have not, the grounds for certification of liability have been established for monetary settlements if scientific evidence can be provided of excess tissue asbestos burdens in any given case. Regardless of that fact, we should still aspire to provide the most accurate diagnosis possible in cases of pleural neoplasia. It is entirely possible that future treatment modalities will differentially benefit 1 or more lesions in this group. Better recognition of the lymphohistiocytoid variant of MM, along with its other histologic forms, furthers that goal.

Table 1

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<thead>
<tr>
<th>Benign</th>
<th>Hyperplastic vs benign neoplastic vs “borderline” neoplastic</th>
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</thead>
<tbody>
<tr>
<td>Adenomatoid tumor</td>
<td>Multicystic mesothelioma</td>
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<tr>
<td>Localized or diffuse “well-differentiated papillary mesothelioma”</td>
<td>Overtly malignant</td>
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<tr>
<td>Localized or diffuse epithelioid mesothelioma</td>
<td>Hyperplastic vs benign neoplastic vs “borderline” neoplastic</td>
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<tr>
<td>Large polygonal-cell type</td>
<td>Multicystic mesothelioma</td>
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<tr>
<td>Tubulopapillary type</td>
<td>Overtly malignant</td>
</tr>
<tr>
<td>Mucin-containing polyhedral-cell type</td>
<td>Localized or diffuse epithelioid mesothelioma</td>
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<tr>
<td>Small cell type</td>
<td>Large polygonal-cell type</td>
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<tr>
<td>Clear cell type</td>
<td>Oncocytoid or granular-cell types</td>
</tr>
<tr>
<td>Oncocytoid variant of MM, along with its other histologic forms, furthers that goal.</td>
<td>Clear cell type</td>
</tr>
<tr>
<td>Fibrosarcoma or malignant fibrous histiocytoma-like</td>
<td>Oncocytoid or granular-cell types</td>
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<tr>
<td>With divergent differentiation (eg, osteochondroid, myogenous)</td>
<td>Desmoplastic</td>
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<tr>
<td>Lymphohistiocytoid lymphoma-like</td>
<td>Localized or diffuse biphasic mesothelioma</td>
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References


