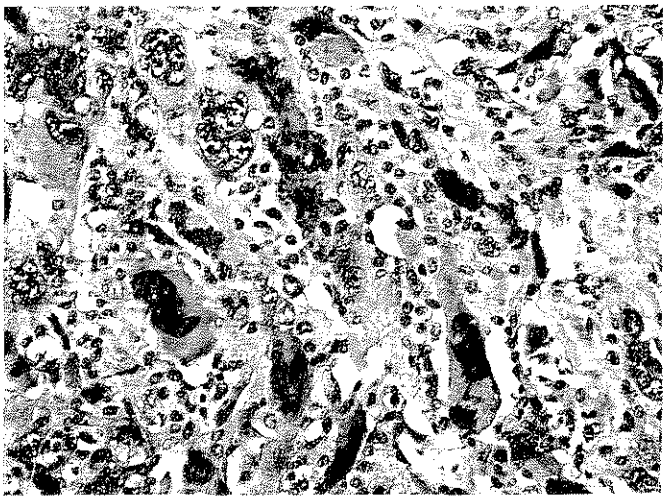

FIGURE 43.134. Pleomorphic predominantly sarcomatoid mesothelioma showing extreme nuclear atypia, pleomorphism, and hyperchromasia, with the presence of multinucleated tumor cells.

Accordingly, we believe that pleural tumors showing extreme pleomorphism should not be dismissed as large cell carcinoma or secondary sarcoma and that when they are pleura-based and have an anatomic distribution consistent with mesothelioma, they should be investigated accordingly.

The diagnosis of pleomorphic mesothelioma, whether epithelial or sarcomatoid, can be based on the following findings:

- A pleura-based tumor with an anatomic distribution that conforms to a diagnosis of mesothelioma, as revealed by imaging studies.
- A transition from the pleomorphic areas to other regions where the appearances are more characteristic of either epithelial or sarcomatoid MM.
- An immunohistochemical profile that conforms to a diagnosis of mesothelioma of either epithelial or sarcomatoid type, as opposed to secondary carcinoma or even secondary sarcoma (for example, when the neoplastic tissue shows strong positive labeling for cytokeratins throughout).
- Occasionally, ultrastructural evidence of mesothelial differentiation.

Localized Malignant Mesothelioma

In 1992, Henderson et al.[211] briefly referred to two cases of localized pleural MM, and further cases were subsequently described by Crotty et al.[838] and Allen et al.,[839] among others.[840–844] Localized pleural MM has been reported in men and women with about equal frequency, within an age range from the 40s to the 70s, although we have encountered localized and even polypoidal pleural malignant MMs in young adults of ages 20 to 30. Typically, these tumors represent localized sessile or pedunculated lesions, ranging in size from 100 mm to a few centimeters (Fig. 43.135).

As the term implies, localized pleural MMs represent circumscribed tumors with histologic, immunohistochemical, and ultrastructural features essentially identical to their diffuse malignant counterparts, and they include epithelial, biphasic, and sarcomatoid lesions. Again, the immunohistochemical profile of these lesions corresponds to that of ordinary confluent epithelial, biphasic, or sarcomatoid MMs.

Churg et al.[503] commented that localized MMs tend not to spread over the pleura, unlike conventional pleural MMs, and that they can be resected successfully in some cases, apparently with no recurrence of the tumor. However, other localized MMs can recur following surgery, and metastasize. In one of the first reports of such localized tumors, Crotty et al.[838] recorded six cases treated by surgical resection, of which three had a disease-free survival for an extended period following excision, but the other three patients sustained local recurrence of the their disease and died within 2 years of initial resection. In one case mentioned by Henderson et al.[211]—a cytokeratin-positive sarcomatoid MM histologically resembling a malignant fibrous histiocytoma, located in an interlobar fissure and treated initially by surgical resection (bilobectomy)—the gross appearances of the recurrent tumor at autopsy were characteristic of mesothelioma.

When dealing with limited biopsy tissue, recognition of localized as opposed to diffuse MM requires information beyond that obtainable from the histologic sections alone. Some diffuse MMs can present with a dominant mass lesion, accompanied by other smaller tumor nodules, so that evidence of the purely localized character of the MM is needed for diagnosis of localized MM,[503] necessitating

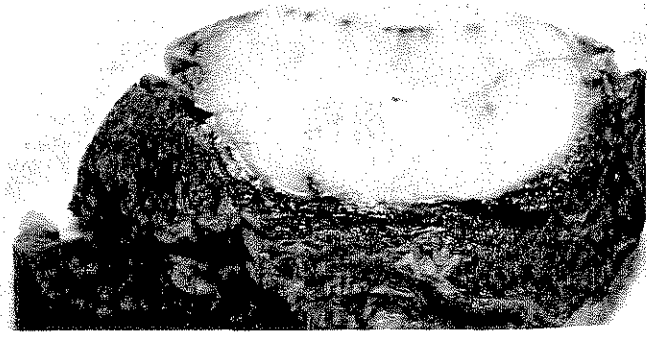

FIGURE 43.135. This localized pleural mesothelioma arose in the pleura and invaded lung parenchyma. It was diagnosed radiographically as a solitary pulmonary nodule.

integration of the histologic findings with organ-imaging studies or the gross appearances at operation.

It is sometimes claimed that the relationship between localized pleural MM and prior asbestos exposure is less well established than for diffuse pleural MMs. This may be so, perhaps explicable by the unusual gross and radiologic findings in such cases, so that an exhaustive exposure history may not be sought, and by the paucity of such localized cases reported to date; however, we have encountered such cases where there has been a clear history of antecedent asbestos exposure (including one case with childhood exposure). Therefore, on the basis of the prevailing evidence at this time, we believe that there is no compelling evidence to consider the relationship of such localized MMs to asbestos to be essentially different than for diffuse MMs.

Approach to Diagnosis/Differential Diagnosis

Our approach to the diagnosis of pleural neoplasms is to accurately classify a neoplasm according to its cytologic, histologic, immunohistochemical, and ultrastructural features. All types of specimens are potentially useful in making a specific diagnosis. In general, with respect to biopsy specimens, the larger the specimen, the more useful and potentially less difficult it is to make a specific diagnosis. Cytologic evaluation is also a potentially useful technique as described below.

The Cytology of Malignant Mesothelioma

The cytology specimens used for the investigation of a lesion suspicious of MM include effusion fluids and, less commonly, fine-needle aspiration biopsies (FNABs). As noted by some authors,[845] the difficulties that beset interpretation of effusion cytology specimens have "kept researchers and publishers in business over the last 20 years." Unfortunately, those difficulties can also lead to confusion among clinicians who may be uncertain over the interpretation of the cytopathology reports and assessment of the confidence index for a diagnosis. There are two main difficulties in pleural effusion cytology: (1) the distinction between MM and metastatic malignancy, and (2) the distinction between a reactive pleural effusion from MM. Nowadays, it is the second that is more problematic.

Numerous diagnostic criteria and ancillary investigations, such as immunohistochemical studies, electron microscopy,[846] flow cytometry,[847] atomic force microscopy,[848] and many more, have been proposed. Some techniques initially appeared to show promise in research laboratories, but that early promise was either not borne out in more extensive routine diagnostic testing, or the techniques were impractical for everyday diagnosis. There is currently no consensus concerning the optimal approach for difficult cytology specimens. There are several excellent textbooks and recent reviews on this subject[845,849–854] and it is not our aim to duplicate those comprehensive accounts. Rather, we highlight some of the problem areas and offer our approach to them (see also Mesothelioma in Chapter 45).

The main issues of importance in the cytologic diagnosis of pleural MM, as we see them, are as follows:

1. Some pathologists require the presence of invasion in a tissue specimen for a definitive diagnosis of MM, and consequently argue that a definitive diagnosis cannot be made from a cytology specimen alone.[854] Even when a combination of clinical and cytologic criteria is used, there is no consensus about the confidence index for a cytodiagnosis. Some authors believe that even distinction of MM in situ and invasive MM is possible in skilled hands.[849] However, the literature and, in particular, the criteria proposed for the diagnosis of MM in situ indicate that this specific diagnosis is almost impossible on cytology. Henderson et al.[490] recommended that invasive MM should be identified elsewhere in the same biopsy, a follow-up biopsy, or at autopsy as a requirement for the diagnosis of MM in situ. In our practice, we consider a biopsy-proven diagnosis to be optimal, but in many cases a confident diagnosis of mesothelioma can be reached from careful correlation of the cytologic findings with clinical-radiologic information, whereby the radiologic demonstration of a confluent pleura-based lesion with nodularity or other evidence of invasion can substitute for gross or histologic evidence of invasion. In particular, we require an atypical pleural mesothelial proliferation *plus* classic radiologic findings for a clear diagnosis of MM. Correlation with clinical and radiologic information can also avoid false-positive diagnosis.

These considerations also highlight the importance of clinicopathologic correlation in general; for example, if an FNAB is performed, the exact location of the biopsy (pleura-based lesion versus an intraparenchymal lung lesion impinging on pleura) must be recorded.

2. Different processing procedures can result in different appearances on the slide. It is important to be thoroughly familiar with the procedures employed in one's own laboratory.

3. Not all types of MM are equally amenable to diagnosis from effusion fluid cytology; MMs with an epithelial component (i.e., epithelial mesotheliomas and biphasic mesotheliomas) are far more likely to shed atypical and identifiable mesothelial cells into effusion fluids than sarcomatoid MMs, for which effusion fluids usually show low cellularity and a low frequency of atypical cells. It is our experience that desmoplastic sarcomatoid mesothelioma