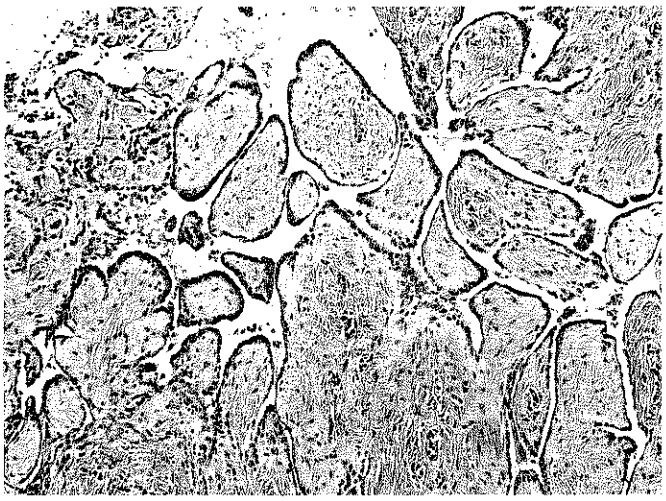

FIGURE 43.91. Well-differentiated papillary mesothelioma (WDPM) of the peritoneum, discovered incidentally at laparotomy carried out for other reasons; this lesion comprised this pattern of tissue entirely and was noninvasive in character.

FIGURE 43.92. Pleural mesothelioma with areas of WDPM. Multilayering of the mesothelium covering some of the WDPM formations.

not require radical surgery or chemotherapy,[762] but instead should simply be observed by way of clinical follow-up.

- Multifocal pleural tumors with features of WDPM (Figs. 43.92 and 43.93), when associated with pleural effusion or pleural thickening, frequently pursue a progressive clinical course even when they are only minimally and superficially invasive, with significant morbidity and mortality[770]; however, evidence indicates that the WDPM appearances are associated with a more indolent course than pleural MM, with longer survivals in most cases.
- When areas of WDPM are admixed with other areas of invasive mesothelioma, where the appearances would allow a diagnosis of conventional MM in the absence of the WDPM-like foci, we diagnose such lesions as a pleural MM with WDPM-like areas. The WDPM-like tissue may point to a more indolent clinical course than ordinary pleural MMs. In this regard, the natural history of WDPM in terms of survival times seems to be related directly to the proportion of the WDPM-like tissue, and inversely to the extent of the lesion(s) and their invasiveness.

## Noninvasive Atypical Mesothelial Proliferations: The Concept of Mesothelioma In Situ and Discrimination Between Early-Stage Mesothelioma and Reactive Mesothelial Hyperplasia

In the 1980s Bolen et al.[536,771] proposed a multipotential subserosal fibroblastoid cell as the stem cell for mesothelial healing and regeneration, and as the progenitor cell for mesothelioma development, and proposed that an origin of mesothelioma from such subserosal cells could account for the bidirectional differentiation characteristic of biphasic mesotheliomas. As an alternative model,

FIGURE 43.93. Pleural mesothelioma with WDPM-like areas. (Same case as in Fig. 43.92.) The apparent invasion in the lower part of this field is explicable in part by an en face appearance resulting from a tangential plane of section, but not entirely so, taking into account the extent of the epithelial-type tumor within the submesothelial fibrous tissue. En profile infiltration into the pleural fibrous tissue is also evident, where there is no suggestion of an oblique plane of section (arrows), and there were multiple other areas of undoubted invasion into the pleural fibrous layer.

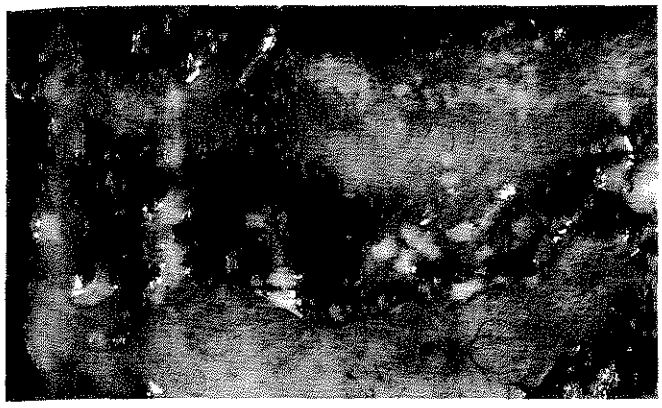

FIGURE 43.94. Pleurectomy specimen from a patient who presented with a massive pleural effusion. No distinctive abnormality was seen at thoracoscopy, but multiple random biopsies revealed an extensive atypical mesothelial proliferation, in situ in most areas of the biopsies, but with small foci of invasion. A pleurectomy was subsequently carried out, and in the surgical specimen, small foci of white invasive tumor were found, some of which extended into subpleural adipose tissue. The entire pleurectomy specimen was examined as a series of Swiss roll sections, and the areas devoid of invasive mesothelioma were seen to show extensive in situ mesothelial atypia.

Whitaker et al.[489] advanced the concept of mesothelioma in situ, based in part on experimental models of mesothelial healing following injury that did not disrupt the submesothelial basal lamina,[492,493,495] and on their observation of a number of cases of apparently early-stage MM of epithelial type, where mesothelial atypia appeared to be predominantly in situ, in the absence of any radiologic or gross anatomic evidence of pleural thickening or nodularity. This being so, Whitaker's group[489,679] suggested that mesothelioma in situ could be defined as the replacement of benign surface mesothelium by mesothelial cells with markers of malignancy. The problem was to define an acceptable and consistently reproducible marker of neoplastic change. Accordingly, they described 22 cases of pleural disease characterized by atypical and predominantly in situ mesothelial proliferation.[489] The cases had presented in conventional fashion with a pleural effusion with either no identifiable pleural tumor or only tiny nodules at thoracoscopy (Fig. 43.94), and the diagnosis in a number of cases was established by existing cytologic criteria. Whitaker et al.[489] suggested that the markers for MM in situ in pleural biopsies included the following[119,490]:

- *Absence of background inflammation* as a potential drive for reactive mesothelial hyperplasia (to which one could add the clinical absence of any underlying cause or association for pleural inflammation and reactive mesothelial proliferation).
- *An abnormal architecture of the mesothelium at the surface of the affected pleural tissue.* The architectural abnormalities included noninvasive, linear, papillary and tubulopapillary patterns, sometimes with a complex exophytic architecture (Fig. 43.95). Whitaker's group[679] emphasized that a prominent papillary pattern of mesothelial proliferation in pleural biopsies is a disturbing feature, not usually seen with reactive mesothelial hyperplasias (although this observation does not apply to mesothelial proliferations affecting the peritoneum and in relation to the omentum in particular).
- Substantial cytologic atypia (Fig. 43.95B), but Whitaker's group also considered that other cases might occur where there is substantially less cytologic atypia, so that such cases would be diagnosable (if at all) only by ancillary techniques. Among these techniques they included strong linear labeling for EMA or areas occupied by silver labeling of nucleolar organizing regions (AgNORs), in excess of the areas found in proven benign reactive mesothelial proliferations.
- In relation to labeling for EMA, Whitaker et al.[489] found that 17 of 22 cases showed thick linear labeling

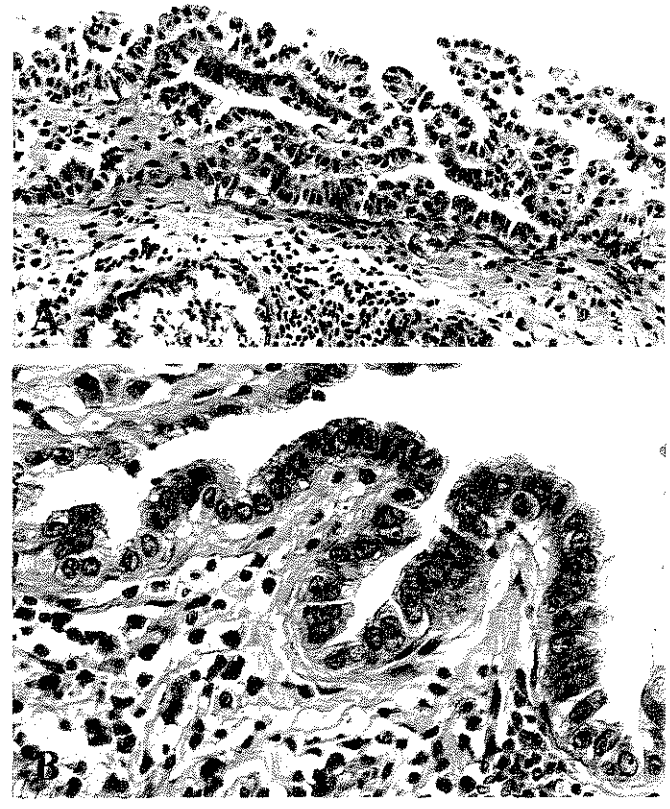

FIGURE 43.95. **(A)** Atypical mesothelial proliferation seen in a pleural biopsy, with an exophytic papillary architecture at the surface. **(B)** Same pleural biopsy illustrating the mesothelial atypia at higher magnification.

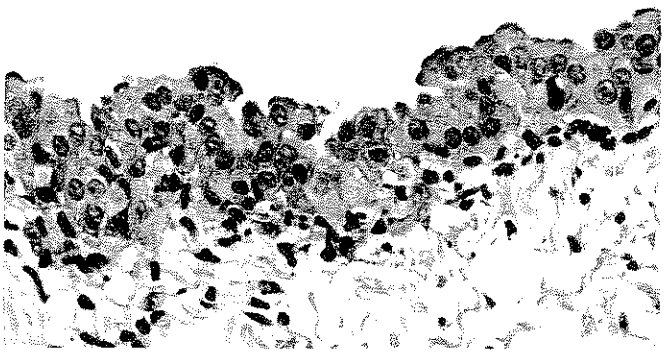

FIGURE 43.96. Example of benign reactive mesothelial proliferation in a pleural biopsy taken from a patient with proven lung cancer. Compare with Figure 43.95B.

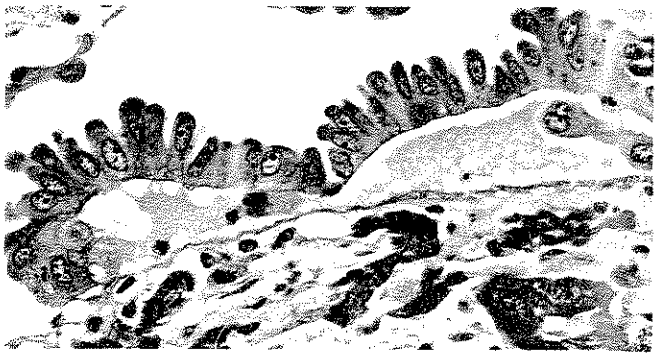

FIGURE 43.98. Prominent reactive mesothelial atypia in a case of organizing fibrinous pericarditis. Fibrinous exudate is evident in the lower half of this field.

of the mesothelial cells for EMA, whereas proven benign reactive mesothelial proliferations usually showed no significant labeling or only patchy weak labeling, as studied in the same laboratory.[119] (On the other hand, we emphasize that in tissue biopsies, a substantial proportion of cases of invasive mesothelioma may show no detectable immunohistochemical labeling for EMA.) Saad et al.[671] investigated EMA expression in 20 cases of reactive mesothelial proliferation (RMP) versus 20 cases of MM, using antibodies based on the Mc5 and E29 clones. For the Mc5 clone, there was positive staining in 14/20 cases of MM (70%) and 12/20 cases of RMP (60%); for the E29 clone, the corresponding results were 15/20 for MM (75%) and 0/20 for RMP. For the E29 clone, the sensitivity and specificity for MM were 75% and 100%, respectively. The authors concluded that EMA antibodies based on the E29 clone are a reliable discriminator between RMP and MM. Simon et al.[402] also commented on this pattern of EMA labeling as a discriminator between benign RMPs and areas of seemingly in situ MM.

Nonetheless, because it is known that there is overlap in the degree of cytologic atypia between benign reactive mesothelial proliferations (Figs. 43.96 to 43.98) versus mesothelioma[37,490,503,513] (Fig. 43.95), Whitaker et al.[489] and Henderson et al.[119] emphasized that the only consistently reliable marker for mesothelioma as opposed to RMP is the presence of acceptable neoplastic invasion in the same biopsy, or a different biopsy taken at a different time, or at autopsy (Figs. 43.99 to 43.103). Accordingly, Henderson et al. commented in 1997:

> We caution against rash or premature diagnosis of mesothelioma in situ from conventional light microscopy examination of

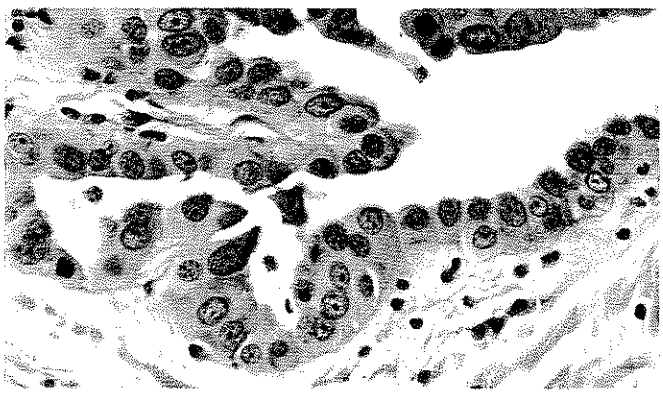

FIGURE 43.97. Extreme reactive mesothelial atypia as seen in the visceral and parietal layers of the pleura, in an apical wedge resection specimen of lung and in the pleura, from a man in his 20s, with a history or recurrent pneumothoraces on the same side.

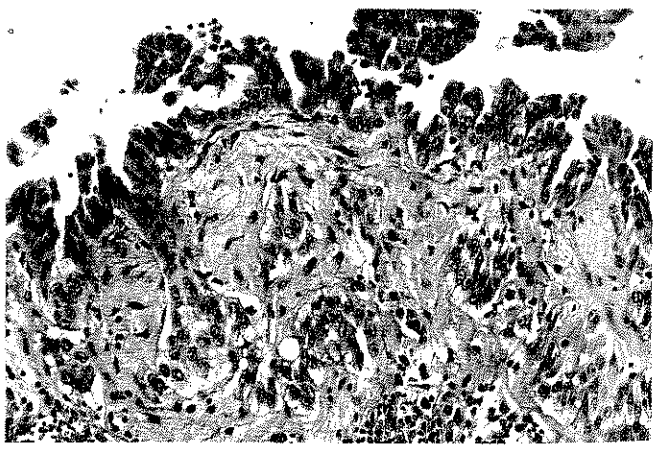

FIGURE 43.99. Different area of the same biopsy shown in Figure 43.95. Foci of infiltration into the submesothelial fibrous tissue are evident, so that the findings overall were interpreted as those of an exophytic-papillary mesothelioma in situ with multiple foci of superficially invasive mesothelioma.

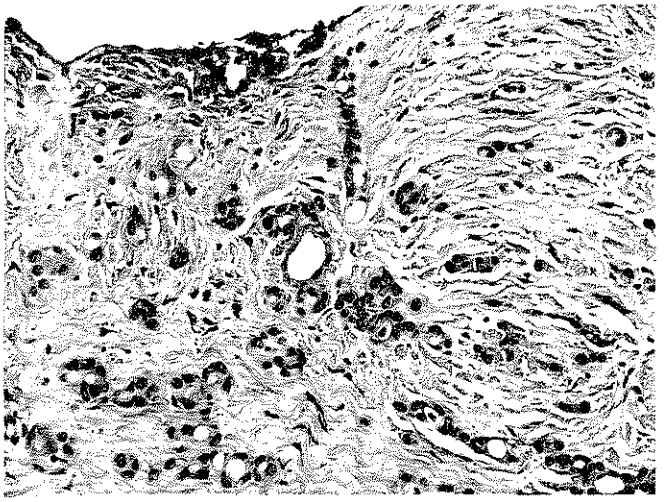

FIGURE 43.100. Early-stage invasive mesothelioma of epithelial type, with infiltration of the submesothelial fibrous tissue, in a pattern that is inconsistent with benign mesothelial entrapment as part of a fibroinflammatory process. In addition, this biopsy showed no evidence of exudative inflammation. There is only minor cytological atypia.

biopsy tissue, taking into account that there is overlap in the cytologic abnormalities that occur in reactive mesothelial hyperplasias versus mesothelioma. However, [findings suggestive of a component of mesothelioma in situ] (especially in conjunction with effusion fluid cytology) may delineate "at risk" patients with "early" stage disease who require further investigation and follow-up. Because of the minimal and perhaps predominantly in situ tumor burden, the mesotheliomas may also be amenable to new modalities of therapy, and some of our "in situ" patients have had prolonged survivals.

Henderson *et al.*[119,490] also emphasized that in all of their cases,[489,679] biopsy or autopsy examination did

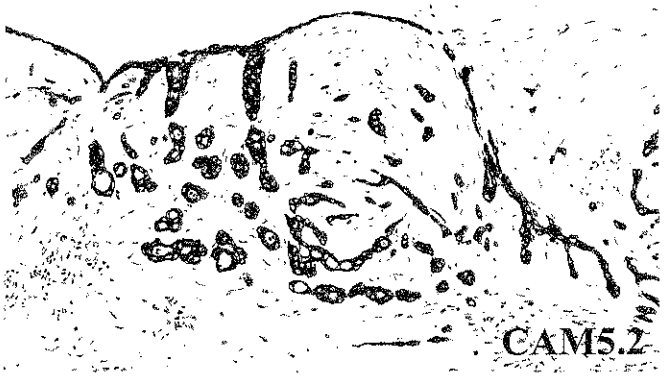


FIGURE 43.101. Same biopsy as illustrated in Figure 43.100, immunostained for low molecular weight cytokeratin (CAM5.2), illustrating the pattern of infiltration into the pleural fibrous layer.


FIGURE 43.102. **(A,B)** Early-stage invasive malignant mesothelioma of epithelial type. Both of these figures are from the same case. The parietal pleural biopsy showed multiple foci of infiltration into the fibrous layer of the pleura, in the absence of exudative inflammation, with only equivocal and focal extension of a few mesothelial cells into the subjacent fat. The pattern of infiltration into the fibrous layer, with near-filling by linear and compressed tubular aggregates of mesothelial cells **(B)** is inconsistent with benign entrapment.

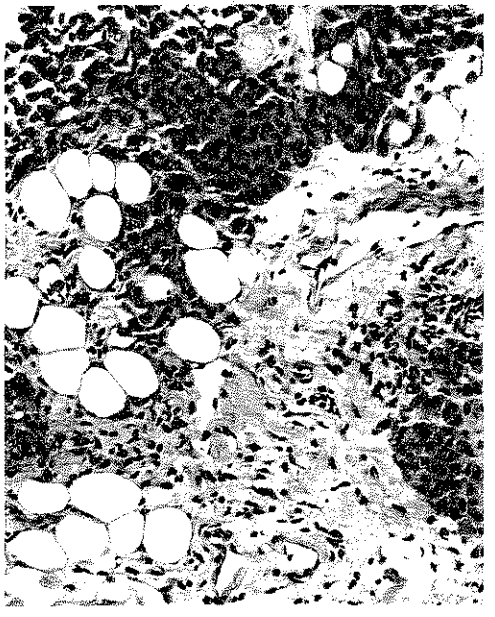

FIGURE 43.103. Area of invasion into subpleural adipose tissue, as a marker of malignancy for this mesothelial proliferation. The proliferation was noninvasive elsewhere in the biopsy.

confirm the development of invasive mesothelioma, but one patient was still alive at the time of writing[119] (with only a short period of follow-up). (Subsequently, Churg et al.[503] commented that in one instance in which Whitaker et al.[489] and Henderson et al.[119,679] "made a diagnosis of mesothelioma in situ without the presence of invasive tumor, the lesion appeared to have been benign on follow-up.")

Churg et al.[503] suggest that the term *mesothelioma in situ* not be used, and instead noninvasive atypical mesothelial proliferations should be designated as either "atypical mesothelial hyperplasia" or "atypical mesothelial proliferation" (the latter being favored by the International Mesothelioma Panel[37]). We have no argument with the term *atypical mesothelial proliferation* for entirely noninvasive atypical mesothelial lesions, but we would discourage use of the term *atypical mesothelial hyperplasia*, because by definition the word *hyperplasia* indicates a benign process, whereas the reactive versus neoplastic status for such lesions is indeterminate.

As a further point, we would emphasize that complex exophytic mesothelial proliferations, such as illustrated by Churg et al.[503] in their Fig. 4.23A,B, are not patterns usually or typically encountered with benign inflammation-induced mesothelial proliferations. Such appearances (Fig. 43.95A) raise a suspicion of MM where the invasive component (if present) has not been sampled by the biopsy. Such lesions should not be dismissed as benign; they are an indicator for close follow-up and further cytologic or biopsy investigation, as indicated by Churg et al. In other words, noninvasive atypical mesothelial proliferation in biopsy tissue does not correspond to a treatable disorder, but instead is a requirement for follow-up or further investigation.

It is sometimes stated that there is no proof that in situ mesothelial atypia in association with areas of invasive mesothelioma represents the same lesion.[503] However, Simon et al.[402] did report a single case of mesothelioma in situ in association with focal early-stage invasive mesothelioma. They investigated the lesion by laser microdissection and comparative genomic hybridization and found similar chromosomal alterations in both the areas of in situ mesothelial atypia and in the foci of early invasive mesothelioma. Accordingly, in the areas of mesothelioma in situ they recorded losses at 3p, 5q, 6q, 8p, 9p, 15q, 22q, and Y, with a gain on 7q; in the area of early invasive mesothelioma there were losses at 3p, 5pq, 6q, 8p, 9p, 15q, and 22q with no gain. In contrast, the advanced mesothelioma showed losses at 1p, 4pq, 6q, 9p, 13q, 14q, and 22q, with gains at 1q, 7pq, and 15q.

We still consider mesothelioma in situ to be a useful concept concerning the development of MM. In addition, by refocusing attention on the mesothelium itself as the target for neoplastic transformation, this concept points to the potential for diagnosis of noninvasive mesotheliomas, with the promise of more effective therapy in the future. We continue to believe that the term *mesothelioma in situ* represents a valid retrospective diagnosis in cases where at least early-stage invasive mesothelioma has been demonstrated.

As discussed above and illustrated in Figures 43.95B to 43.98, there can be substantial overlap in the degree of cytologic atypia encountered in proven atypical reactive mesothelial hyperplasias, versus proven invasive MMs of epithelial type. Although thick linear membrane-related labeling for EMA (using antibodies based upon the E29 clone) may sway the probability index toward a diagnosis of early-stage mesothelioma, this finding cannot be considered decisive or definitive, and at present there is no universally accepted immunohistologic or molecular marker for consistent discrimination between reactive mesothelial hyperplasia versus MM. This being so, histologic assessment of invasion is crucial to the diagnosis of MM and its discrimination from an atypical reactive mesothelial proliferation, in everyday diagnostic practice. We have found the following guidelines and caveats to be useful in the approach to differential diagnosis of mesothelial lesions where the discrimination between mesothelioma and hyperplasia is problematic:

- It is useful to correlate the histologic appearances with the findings on pleural effusion fluid cytology and with any abnormalities revealed by imaging studies, such as chest radiographs or CT scans. In this regard, the radiologic investigations can be regarded as a surrogate for gross anatomic findings. For example, radiologic demonstration of a confluent and nodular pleural lesion with encasement of the lung and contraction of the affected hemithorax together with an effusion (in which a florid atypical papillary mesothelial proliferation was found) can effectively substitute for the histologic detection of invasion, at a high order of confidence.
- Neoplastic invasion of subpleural adipose tissue (Fig. 43.103) or deeper structures by epithelioid cells that show a mesothelial phenotype on immunohistochemistry or by spindle-shaped fibroblastoid cells that express cytokeratins represents a decisive indicator of malignancy, for either epithelial mesothelioma or sarcomatoid mesothelioma respectively.
- Even so, mesothelioma remains diagnosable even when there is no infiltration into subpleural tissues such as fat, provided that the pattern of invasion within more superficial tissues, namely the pleural fibrous layer, is characteristic or diagnostic of neoplastic invasion (Figs. 43.99 to 43.102) as opposed to artifact or benign entrapment of mesothelial cells as part of an organizing fibroinflammatory process (see below).

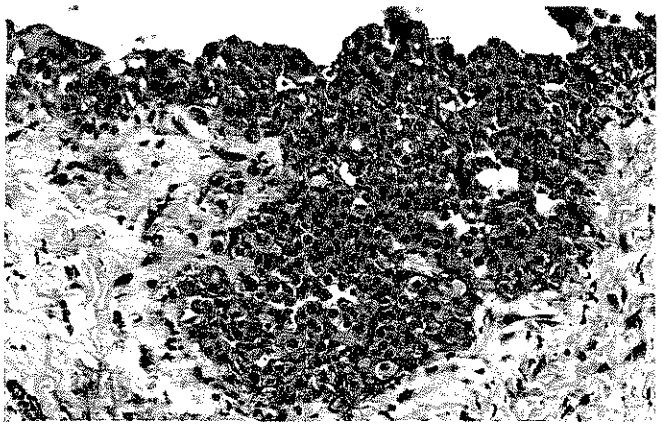

FIGURE 43.104. Pseudo-invasion in a case of benign reactive mesothelial hyperplasia, resulting from folding of the pleural membrane. (Same case as in Fig. 43.96.)

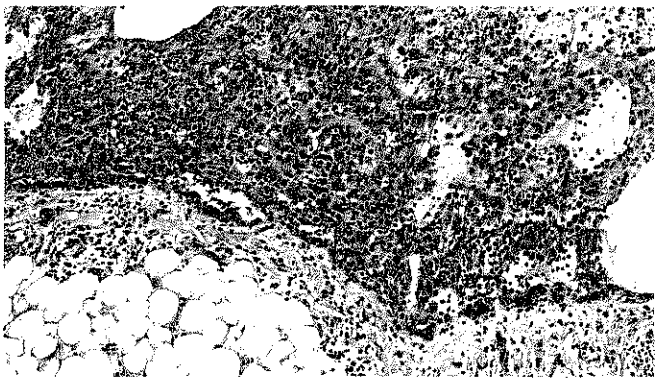

FIGURE 43.105. Prominent benign reactive mesothelial hyperplasia in a patient with proven tuberculous pleuritis. It is evident that the mesothelial proliferation is entirely noninvasive in character, and admixed with numerous inflammatory cells.

- We take great care to ensure that pleural biopsies are orientated correctly when subject to histologic sectioning, so that the tissue is embedded on edge, resulting in *en profile* as opposed to *en face* sections, because the latter can create problems concerning interpretation over what is, and what is not, acceptable evidence of invasion. When sufficient pleural membrane is available, we find it useful to prepare a *Swiss roll* from the biopsy and to fix the pleural tissue after the Swiss roll has been prepared, then taking a series of transverse sections, to facilitate correct orientation of the pleural membrane.
- It is necessary to discriminate between pseudo-invasion, for example, resulting from an *en face* plane of section through the biopsy or from folding of the pleural membrane (Fig. 43.104) versus genuine neoplastic infiltration of the submesothelial tissue. When there is doubt over whether the process represents pseudo-invasion versus genuine neoplastic invasion, we dismiss the appearances as inconclusive.
- Although most inflammation-driven reactive mesothelial hyperplasias are noninvasive (Fig. 43.105), some organizing serosal inflammatory reactions, especially in the pericardium in our experience, can result in the burying of hyperplastic mesothelial cells within the organizing and proliferative fibrous tissue, so that this well-recognized pattern of benign mesothelial entrapment requires distinction from genuine invasion (cf. Figs. 43.99 to 43.102 with Figs. 43.106 and 43.107). The presence of a florid fibrinous or neutrophilic inflammatory reaction should alert one to the likelihood of benign entrapment, but the authors have encountered cases of proven invasive mesothelioma with prominent associated inflammatory exudate. In such organizing inflammatory processes, the entrapment appears to be the result of burying of the site where the mesothelium is normally located, by a layer of inflammatory exudate that extends across the surface of the membrane, with subsequent organization. This process of entrapment of mesothelium is sometimes designated as mesothelial sequestration, but in many instances the lowermost level of the entrapped mesothelium seems actually to be situated at its original level. Instead, it is the surface of the pleura that has moved inward, into the lumen of

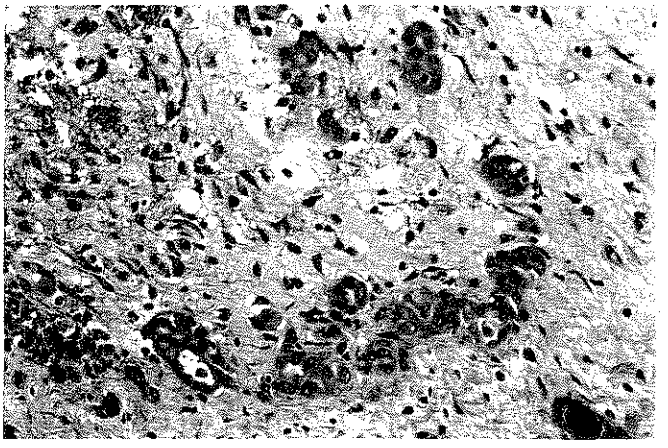

FIGURE 43.106. Benign mesothelial entrapment in a case of constrictive pericarditis, in a young man. Islands and tubules formed by mesothelial cells are evident within the fibrous tissue. There was prominent fibrinous inflammatory exudate near the surface of the pericardium (near the top left hand corner). In addition, the proliferative mesothelial cells in this biopsy showed scattered intracytoplasmic mucin-like droplets, stainable by the PAS-diastase stain. Follow-up for a period of over 5 years was entirely benign.

the pleura (or pericardium), a process that we sometimes liken to the shrinking of the Aral Sea and that we designate as the *Aral Sea effect.* In other words, ships marooned by the shrinkage of the Aral Sea have not moved into the surrounding desert, but rather the shoreline has moved away from the ships. In this regard, we find immunohistochemical staining for cytokeratins (or calretinin) to be of value, because it delineates a clear boundary between the zone of the proliferative and entrapped mesothelial cells, versus the deeper tissues, as shown in Figure 43.107.

- Therefore, neoplastic invasion remains the linchpin for diagnosis of early-stage mesotheliomas of epithelial type. When there is any doubt over whether genuine invasion is present or not, we prefer to err on the side of underdiagnosis of mesothelioma as opposed to inappropriate overdiagnosis. We base this approach on the principle that if the lesion is mesothelioma, it will declare itself as such soon enough, whereas inappropriate overdiagnosis of mesothelioma can lead to erroneous cytotoxic chemotherapy or even radical surgery, together with the anguish that a diagnosis of mesothelioma usually entails.
- Even when invasion cannot be found in a biopsy sample, there are several findings in combination that are suspicious of mesothelioma, although nondiagnostic by themselves. They include the extent of the mesothelial proliferation, the presence of a complex exophytic or papillary architecture at the surface of the pleura (in the absence of exudative inflammation), prominent cytologic atypia, focal necrosis within sheets of proliferative mesothelial cells in the pleura (Fig. 43.108), prominent intracytoplasmic vacuoles devoid of mucin-like content, and strong thick linear labeling for EMA (using antibodies based on the E29 clone). The presence of two or three or more such features is an indication for clinical follow-up or further investigation, to clarify the hyperplastic versus neoplastic properties of the mesothelial proliferation.

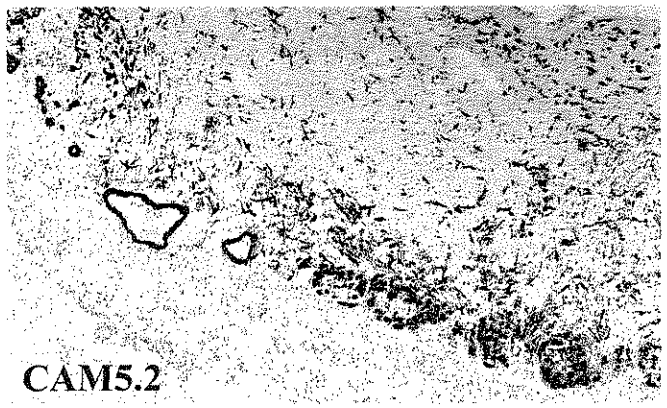


FIGURE 43.107. Same biopsy as illustrated in Figure 43.106, immunostained for low molecular weight cytokeratin (CAM5.2). Note the reasonably clear demarcation or boundary zone between the entrapped mesothelial cells and the deeper tissues, the appearances being unlike those of neoplastic invasion by a malignant mesothelioma, where the deep boundary of the lesion is less sharply demarcated and is infiltrative in character.

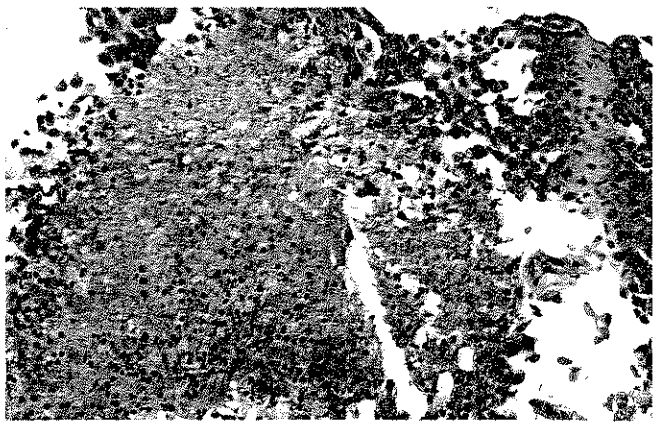

FIGURE 43.108. Focal tumor necrosis in an atypical mesothelial proliferation, as one indicator of malignant mesothelioma. Neoplastic invasion into subpleural adipose tissue was found in a different area of the same biopsy.

## Small Cell Mesothelioma

In 1992, Mayall and Gibbs[772] drew attention to a small cell variant of MM, likely to be confused with small cell carcinoma of lung. In this regard, it is also worth emphasizing that Falconieri et al.[773] reported four cases of small cell carcinoma of lung with spread into the pleura, simulating pleural MM.

It is notable that most of the cases reported by Mayall and Gibbs[772] represented autopsy cases, with the potential for the small cell features being explicable at least in part by postmortem artifact. Krismann et al.[774] have expressed doubt about the existence of small cell mesothelioma, because the German Mesothelioma Registry, which contained more than 6000 mesothelioma cases as of 2004, did not contain a single example of small cell mesothelioma. Nonetheless, we have encountered extremely rare cases of mesothelioma with a small cell pattern (fewer than even lymphohistiocytoid mesothelioma). The following findings aid distinction of this form of mesothelioma from small cell carcinoma infiltrating pleura:

- In the cases of small cell mesothelioma the we have encountered, the tumor showed a transition from the