

effusion restricted to the contralateral side is rare.⁹⁰² In contrast, with patients with breast cancer and subdiaphragmatic neoplasms (for example, stomach or ovary), there is no such predilection for the ipsilateral side.⁹⁰² It has been estimated that 50% of patients with disseminated breast cancer develop a pleural effusion during the course of their disease, on the same side as the original breast cancer in 60% of the patients, on the contralateral side in 25%, and bilaterally in about 15%.⁹⁰² In general, the interval between the diagnosis of the primary breast cancer and the subsequent development of an associated pleural effusion is about 2 years, but it can be as long as 20 years or more.⁹⁰²

The size of the pleural effusion in metastatic malignancy varies greatly. In about 75% of patients the effusion is moderate to large, within the range of about 500 to 2000 mL; in about 10% the effusions are massive (with complete opacification of the affected hemithorax); and in a further 10%, approximately, the effusions are small (less than 500 mL).⁹⁰³ About 70% of patients with a massive effusion have an underlying cancer as the basis for the effusion.⁹⁰³ Matthay et al.⁹⁰² referred to one series of 46 patients with massive pleural effusions from all causes: 31 (67%) had malignant pleural effusions, 27 as a consequence of metastatic carcinoma and one patient had a MM.

From an analysis of 500 documented cases of pleural effusion as a consequence of metastatic malignancy, Matthay et al.⁹⁰² found that the diagnostic yield from cytologic examination of pleural effusion fluid was 66%, versus 46% from pleural biopsy. Matthay et al. commented that pleural fluid cytologic examination is more sensitive for the diagnosis of metastatic cancer than pleural biopsy, and although cytology and biopsies are complementary to each other, pleural biopsy added little to cytologic examination. Matthay et al. commented further that the lower yield from pleural biopsy may represent operator technique or sampling error, the latter known to be a problem in that metastatic deposits can be widely scattered over the pleural membrane. They suggested that diagnostic yield can be increased by repeat cytology examinations and pleural biopsy. If a diagnosis is not obtained following repeat cytology examination and biopsy, thoracoscopy can be considered, and when multiple biopsies are taken at thoracoscopy, the diagnostic yield rises to about 80% to 97%.⁹⁰² Vargas and Teixeira⁹⁰⁰ commented that pleural biopsies in cases of malignant pleural effusion establish the diagnosis in about 40% to 75%, but the combination of cytologic evaluation of the effusion fluid and a needle biopsy allows a diagnosis in about 80%. Medford and Maskell⁹⁰⁶ commented that "blind" pleural biopsy increased the diagnostic yield over cytologic examination of effusion fluid by only 7% to 27%, and that at least four samples from one site are required to optimize the diagnostic return. These

authors also set forth their perception that "blind" pleural biopsy no longer has a role in the investigation of malignant pleural disease and that it should be replaced by guided biopsies under imaging control.

In general, pleural metastatic deposits are a marker of advanced disease,⁹⁰⁶ and survival of patients with pleural deposits from cancer of the lung, stomach, or ovary is usually measured in only a few months following diagnosis of the malignant pleural effusion.⁹⁰²

Although it is emphasized that lung and breast cancer and malignant lymphomas account for about 75% of malignancy-associated pleural effusions, almost any cancer with the capacity for metastasis to the lungs in particular also has the capacity for metastasis or spread to the pleura. Such unusual metastases can range from renal cell carcinomas to ependymomas arising in the central nervous system, among many others.

Pseudomesotheliomatous Tumors Affecting the Pleura Including Pseudomesotheliomatous Adenocarcinoma of Lung

By definition, pseudomesotheliomatous neoplasms affecting the pleura are characterized by diffuse infiltration of the pleura in a pattern essentially identical to, and indistinguishable from, pleural MM on gross examination or on radiologic studies, including CT scans.⁹⁰⁷ In this regard, the neoplasm characteristically takes the form of multiple nodules, plaques, or a confluent rind of tumor, with an associated pleural effusion in many instances and with frequent obliteration of the pleural cavity in the later stages of the disease, sometimes with invasion into the chest wall, diaphragm, and pericardium, as seen at autopsy.

Most pseudomesotheliomatous neoplasms affecting the pleura are thought to originate from the lung,⁹⁰⁸⁻⁹²³ but pseudomesotheliomatous metastases from carcinomas arising in other sites are well recorded, including the kidney,^{918,924-926} thyroid gland,⁴⁹⁷ larynx,⁹²⁷ stomach,⁹¹⁸ and cutaneous malignant melanoma as well as various sarcomas, including malignant phyllodes tumor.⁹²⁸

In addition, with pseudomesotheliomatous carcinomas (PMCs) of the lung, adenocarcinoma is the most frequent histologic type, but other cell types can produce pseudomesotheliomatous spread, including SCC, small cell carcinoma,⁷⁷³ large cell undifferentiated carcinoma, and carcinosarcoma.⁵³²

Pseudomesotheliomatous carcinomas of the lung were first described by Babolini and Blasi⁹²⁹ in 1956, to emphasize that the symptoms in these patients were related predominantly to involvement of the pleura with recurrent exudative effusion, often accompanied by chest pain and dyspnea. Of five cases reported by Babolini and Blasi, two appear to have represented small cell carcinoma and the other three were adenocarcinomas. About

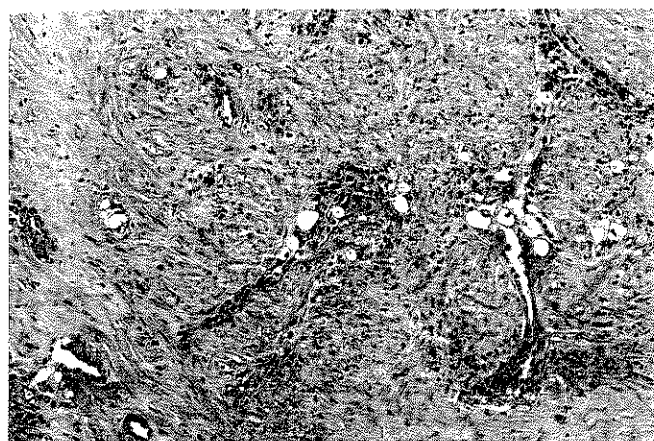


FIGURE 43.145. Pseudomesotheliomatous adenocarcinoma. Pleural biopsy from a 77-year-old man with a right pleural effusion. At thoracoscopy, the appearances were considered suggestive of a malignant mesothelioma. The neoplastic acini are embedded in a prominent fibrous stroma ("tubulo-desmoplastic adenocarcinoma").

20 years later, Harwood et al.⁹⁰⁸ reported six cases of primary lung cancer with mimicry of mesothelioma in terms of the distribution of the carcinoma within the pleura, and they introduced the term *pseudomesotheliomatous carcinoma*. In two of their six cases there were small intraparenchymal nodules in the underlying lung parenchyma and all tumors were adenocarcinomas, with bronchioloalveolar features in five. The patients were all men of ages 50 to 76 years, and they had symptoms of dyspnea on exertion, chest pain, and weight loss. Koss et al.⁹¹⁶ also reported an underlying adenocarcinoma in the lung in seven out of 14 autopsy cases. Nonetheless, in some instances, pleural pseudomesotheliomatous adenocarcinomas show no evidence of an underlying intraparenchymal tumor, probably explicable by overgrowth of a small peripheral primary lung cancer by the predominant pleural extension.

In their review, Koss et al.⁹¹⁶ reviewed 15 previously published pseudomesotheliomatous adenocarcinomas of lung and added a further 15 examples from the files of the Armed Forces Institute of Pathology (AFIP) in Washington. Ninety percent of the patients were men with a median age of 61 years, and 17% had possible to definite occupational exposure to asbestos; one patient had proven asbestosis. The prognosis for pseudomesotheliomatous adenocarcinoma was similar to that of mesothelioma: the mean survival time in this series⁹¹⁶ was 4.7 months and the longest survival was 25 months.

Although PMCs are defined entirely by the gross anatomic distribution of the neoplasm (or on radiologic examination as a surrogate for gross examination), the acinar structures in pseudomesotheliomatous adenocar-

cinoma may or may not resemble an epithelial mesothelioma; that is, these tumors may comprise simplified or isolated glands in a fibrotic stroma, with appearances characteristic of adenocarcinoma; however, in some instances they can show a complex branching and anastomosing architecture producing a histologic resemblance to epithelial mesothelioma (Figs. 43.145 and 43.146). The acini, tubules, and nests of tumor cells in PMC are characteristically surrounded by thickened and fibrotic stromal tissue (Fig. 43.145), heightening the resemblance to mesothelioma (an appearance that Hammar and Dodson⁹⁰⁷ have described as "tubulo-desmoplastic adenocarcinoma").

In the series reported by Koss et al.,⁹¹⁶ the main feature used for the diagnosis of pseudomesotheliomatous adenocarcinoma was the presence of PAS-diastase-positive mucin in gland lumina or as intracytoplasmic droplets (but "all of the AFIP surgical specimens . . . were selected on the basis of mucin-positivity within tumor cells"). The distinction between mesothelioma and pseudomesotheliomatous adenocarcinoma is usually straightforward on immunohistochemical staining, and the distinction is facilitated by use of a panel of mesothelial cell markers and generic carcinoma-related antibodies (Figs. 43.147 and 43.148), together with immunostaining for TTF-1.

A further issue that awaits clarification is whether a causal relationship between these tumors and asbestos exposure differs from other bronchopulmonary carcinomas. In our experience, a high proportion of pseudomesotheliomatous adenocarcinomas appear to have a background of occupational exposure to asbestos, but it is unclear whether this seemingly high proportion is

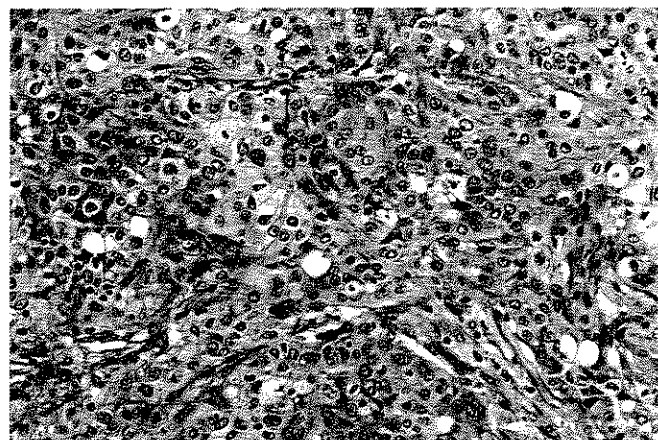


FIGURE 43.146. Pseudomesotheliomatous adenocarcinoma of pleura. This carcinoma is more cellular than the tumor illustrated in Figure 43.145, with a paucity of stromal tissue. The nuclei of the neoplastic cells are nonhyperchromatic and they show only moderate cytologic atypia. The appearances are similar to those seen in some epithelial mesotheliomas.

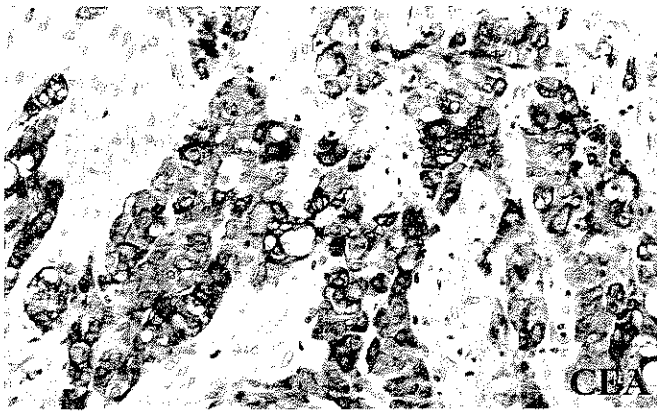


FIGURE 43.147. Pseudomesotheliomatous adenocarcinoma. (Same case as in Fig. 43.145.) The tumor shows positive staining for carcinoembryonic antigen (CEA).

explicable by (1) patterns of referral of cases for which mesothelioma is the differential diagnosis, or (2) whether the clinical and radiologic mimicry of mesotheliomas by these tumors stimulates a more detailed history concerning asbestos exposure than would be the case for conventional lung cancers (see also Chapter 27).

Spindle Cell Carcinoma and Carcinosarcoma of Lung

Although spindle cell (sarcomatoid) carcinomas of lung usually form localized intraparenchymal mass lesions, they can invade the pleura, with the potential for histologic mimicry of biphasic mesothelioma. In this regard, Mayall and Gibbs⁵³² reported two carcinosarcomas that presented as pleural tumors, with encasement of the lung



FIGURE 43.148. Pseudomesotheliomatous adenocarcinoma. Positive linear labeling of the neoplastic cells with Ber-EP4.

in a pseudomesotheliomatous fashion in one patient. No site of origin within the lung could be identified for either tumor. These authors suggested that the following findings in such tumors militate against a diagnosis of mesothelioma: (1) neutral mucin production; (2) expression of CEA; (3) squamous differentiation, although squamous differentiation can occur rarely in MMs of epithelial type; or (4) evidence of neuroendocrine differentiation.

Serosal-Surface Serous Papillary Tumors

Because serous papillary adenocarcinomas arise predominantly from the ovaries or the peritoneal mesothelium itself, mimicry of *pleural* mesothelioma is exceptional, but it can constitute a significant diagnostic problem, especially because a high proportion of serous papillary carcinomas show no evidence of CEA expression on immunohistochemistry.^{119,930-933} Even so, three patients with an underlying serous papillary adenocarcinoma of the peritoneum encountered by the authors¹¹⁹ (Figs. 43.149 and 43.150) presented with unilateral pleural effusion, apparently related to spread from the underlying peritoneal tumor (in at least one of these cases, the primary peritoneal lesion was demonstrable only on CT imaging). The diagnosis in most instances can be made on detailed immunohistochemical studies, for example, including labeling with antibodies such as Ber-EP4 (Fig. 43.150), B72.3,^{119,930,932,934} and BG8. In two cases in our files the diagnosis was established primarily by electron microscopy, which demonstrated short blunt microvilli with an antennular glycocalyx characteristic of carcinoma in one case, and by the presence of elongated branched microvilli in another case, where the microvilli lacked the sinuous and serpentine architecture characteristic of mesothelial microvilli.¹¹⁹ The resemblance of such serous

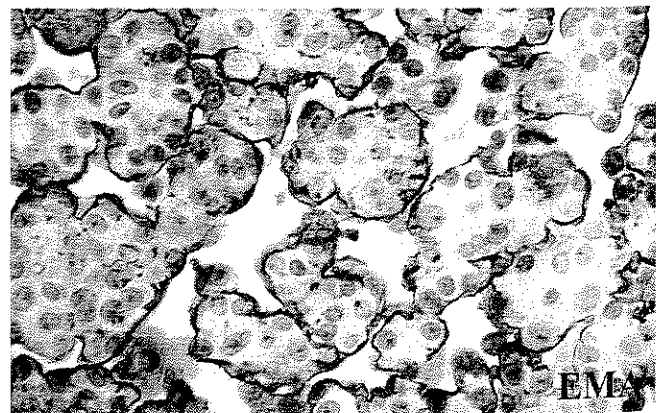


FIGURE 43.149. Pleural metastasis of a serous papillary adenocarcinoma of the peritoneum (cytology cell block section). Linear membrane-related staining for epithelial membrane antigen (EMA), essentially indistinguishable from labeling that characterizes epithelial mesotheliomas.