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60

Pulmonary Metastases of Extrapulmonary Tumors

Saul Suster

Because of its anatomical location and rich capillary bed, the lung acts as a filter for circulating malignant cells. Metastatic tumors to the lung usually present as multiple bilateral nodules, but solitary lesions are frequently encountered. In most large series, as many as 6% to 9% of solitary coin lesions have proved to be metastatic cancer to the lung.[1,2] Differentiating a primary lesion from a solitary metastatic tumor in the lung may be difficult based on morphology alone, and a multidisciplinary approach encompassing thorough clinical and radiologic evaluation, careful scrutiny of the medical history, and special pathologic diagnostic techniques is required.

The topography of lung metastases may be important in the differential diagnosis. In keeping with the preferential colonization of the terminal pulmonary circulation area by tumor cells, the peripheral subpleural portions of the lung are the initial favored sites of hematogenous metastases.[3] Age and gender distribution also provide important clues for diagnosis. Pulmonary metastases of osteosarcoma, testicular cancer, and other primitive bone and kidney tumors are predominantly seen in patients between 20 and 40 years of age, but metastases of colon and renal cell carcinoma, spindle cell sarcomas, and other common epithelial malignancies are usually observed in patients 50 to 70 years of age.

The resection of pulmonary metastases from some sarcomas and carcinomas has become a viable mode of treatment if the lungs are the only site of distant metastases. In some series, long-term tumor-free survival has been achieved after the resection of solitary lung metastases.[4] Studies from large series on resection of metastatic neoplasms to the lung have shown cumulative survival rates of up to 30% at 5 years.[5–7] The most favorable candidates for resection are patients with testicular and renal cell carcinomas and low-grade sarcomas, and the least favorable are those with melanomas and carcinomas of the colon, rectum, or cervix.[8,9]

The prognostic indicators of survival after resection include age, gender, type of primary tumor, tumor doubling time, disease-free interval, and the number of nodules seen on preoperative roentgenographic studies.[10] The most important prognostic sign appears to be the tumor doubling time as determined from the interval between the primary operation and the removal of the metastasis.[11–13] Unfavorable prognostic signs are multiple tumor nodules and lymph node involvement.[14,15]

METASTASES FROM EPITHELIAL NEOPLASMS

Spread of metastatic carcinoma to the lung may occur through a hematogenous route, through lymphatics by way of anastomoses with upper abdominal lymphatics, or by retrograde spread from involved mediastinal or hilar lymph nodes. Solitary pulmonary metastases from epithelial neoplasms pose a difficult problem for diagnosis if the exact location of the primary is unknown or no history of a primary tumor is available. The metastatic tumor in such instances may be mistaken for a lung primary lesion. Most carcinoma metastases are multiple, sharply outlined from the surrounding lung parenchyma, and rapidly growing. Metastatic neoplasms rarely adopt a pattern of growth that closely mimics a primary lung cancer. For example, some metastatic cancers to the lung may line the alveolar walls in a fashion that simulates bronchioloalveolar cell carcinoma, particularly those from the colon, breast, pancreas, stomach, and kidney.[16]

Other metastases may penetrate the wall of a major bronchus and appear as a polypoid intrabronchial mass closely resembling a primary bronchogenic tumor.[17] In some instances, massive lymphangitic spread, particularly from stomach, prostate, pancreas, or breast cancer may lead to a phenomenon called lymphangitis carcinomatosa, which is characterized by outlining of the peribronchial, septal, and pleural lymphatics by a trail of tumor tissue (Fig. 60-1). Occult hematogenous metastases with extensive obstruction of small pulmonary vessels occasionally present clinically with cor pulmonale and pulmonary hypertension of unknown origin.[18]

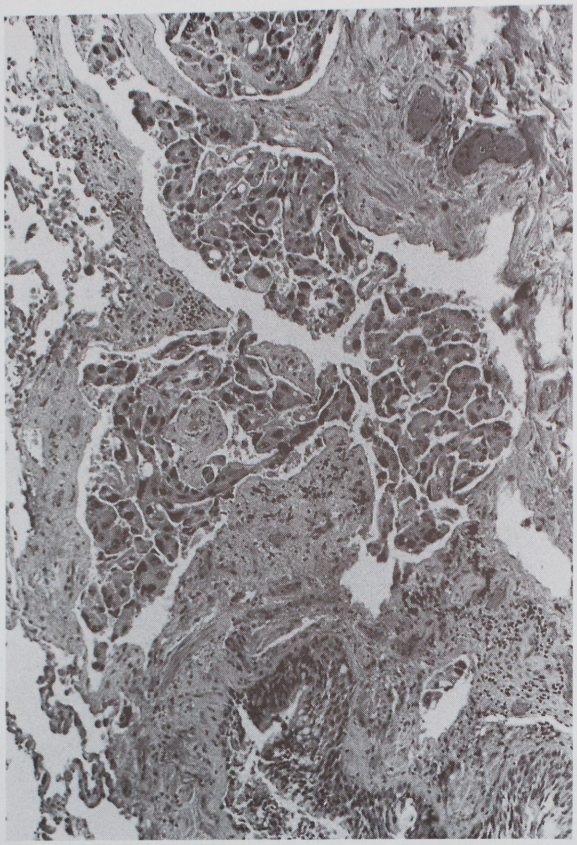

FIGURE 60-1. A metastatic carcinoma of the breast extensively involves the pulmonary lymphatics (*i.e.*, lymphangitis carcinomatosa). (H & E stain; low magnification.)

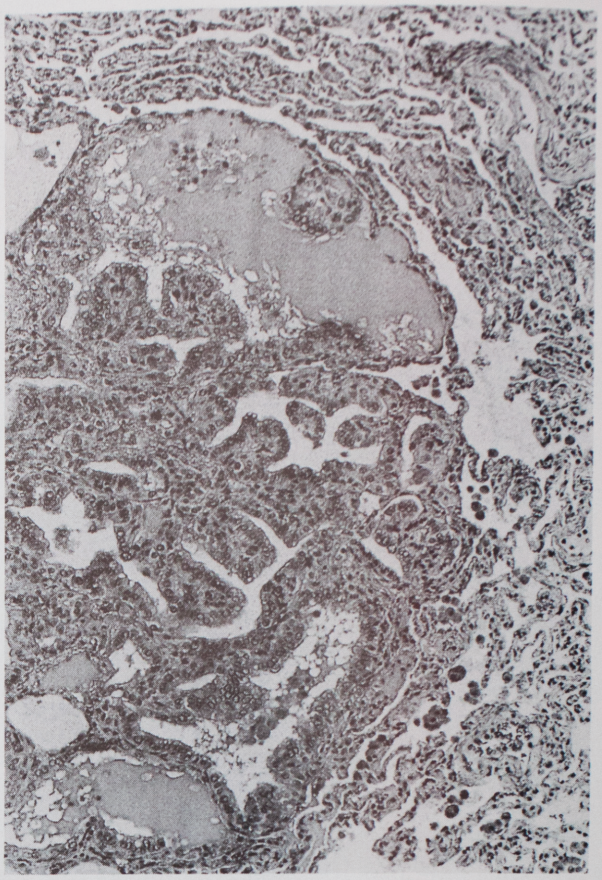

FIGURE 60-2. In this metastatic papillary carcinoma of the thyroid, notice the papillary structures and colloid material in the folliclelike structures. (H & E stain; low magnification.)

Head and Neck Cancer

Head and neck cancers metastasize initially to the lung in about 25% of patients.[19] The most common primary sites for metastases from the upper aerodigestive tract are the larynx and oral cavity.[20] The most frequent histologic types are squamous cell carcinoma and adenoid cystic carcinoma. In a study by Mazer and colleagues, the most favorable primary site was the larynx; nodal metastases at the time of initial presentation and primary tumor in the oral cavity were associated with a poor outcome, and mediastinal involvement constituted the worst prognostic indicator.[21] Salivary gland tumors may also be the source of lung metastases, particularly from adenoid cystic and acinic cell carcinomas.[22,23] A detailed clinical history is indispensable, because salivary gland tumors may metastasize after a long period of latency and can be easily mistaken for primary lung tumors of bronchial gland origin.[23]

Carcinoma of the thyroid may infrequently metastasize to the lung (Fig. 60-2). Papillary thyroid carcinoma can be confused with primary bronchogenic carcinoma with a papillary growth pattern or with sclerosing hemangioma of the lung. The differential diagnosis is aided by identification of the characteristic nuclear morphology of papillary carcinoma of the thyroid, and a more definitive diagnosis can be established in equivocal cases by demonstrating specific immunoreactivity of the tumor cells with antibodies to thyroglobulin.

Carcinoma From the Gastrointestinal Tract

Carcinomas arising in virtually any site of the gastrointestinal tract are capable of metastases to the lungs, particularly those from the stomach, pancreas and colon. Metastases from colonic carcinoma may pose a particular challenge for diagnosis, especially at the time of frozen-section analysis (Fig. 60-3). In most cases, pulmonary metastases from colorectal cancer present as disseminated disease and are not amenable to curative therapy, but some solitary metastases may be successfully treated by resection.[24–27] Differentiation of primary from metastatic adenocarcinoma may not be possible at the time of frozen section or even with the permanent sections in the absence of an adequate history. Several studies have attempted to identify distinguishing features that can separate the two, including ultrastructural and immunohistochemical findings, but the number of exceptions to these observations warrant a conservative approach.[28–30]

Moran and associates identified a type of primary lung carcinoma that is morphologically indistinguishable from mucinous (*i.e.*, colloid) carcinoma of the gastrointestinal tract and other organs.[31] Most patients in their study were initially misdiagnosed as having metastatic carcinoma of gastrointestinal tract origin, and the correct diagnosis was made after demonstration of the absence of a similar primary tumor elsewhere by thorough clinicoradiographic examinations and long-term follow-up. These cases underscore the fact that the diagnosis of metastatic adenocarcinoma to the lung originating from the gastrointestinal tract, particularly if presenting as a solitary lesion, should rest on strict clinicopathologic correlation. Pulmonary metastases may occasionally represent the initial manifestation of pancreatic carcinoma, with radiographic and clinical features indistinguishable from those of a primary lung cancer.[32]

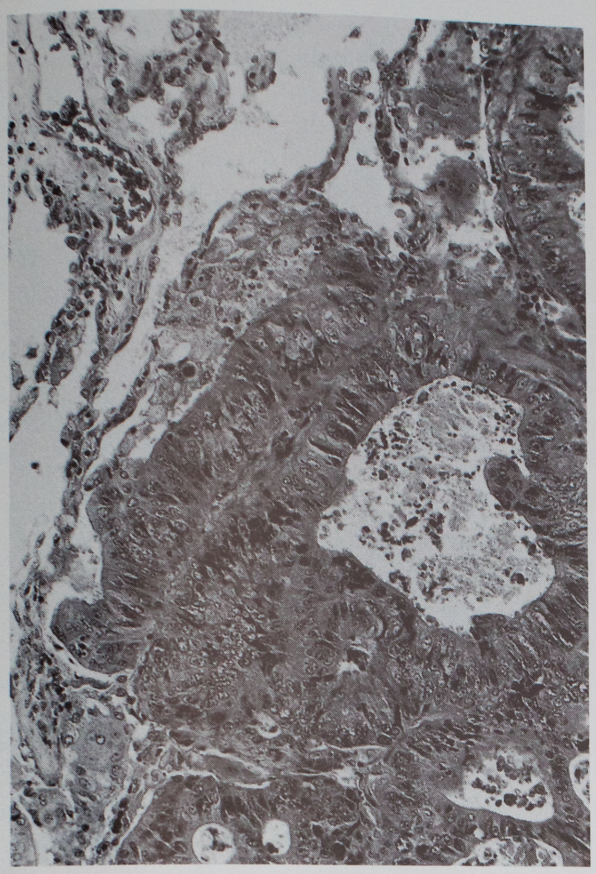

FIGURE 60-3. Metastatic adenocarcinoma of the colon. (H & E stain; low magnification.)

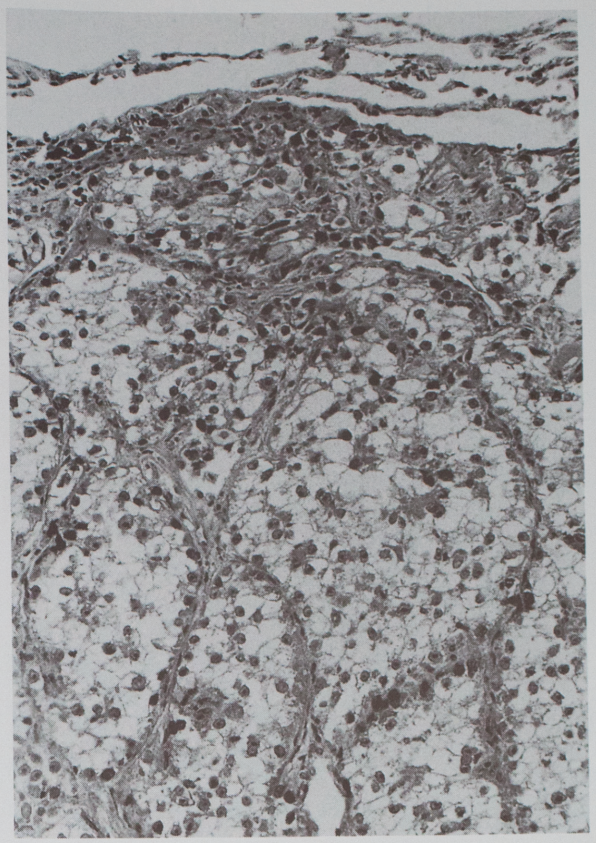

FIGURE 60-4. This metastatic renal cell carcinoma is a clear cell type of tumor. (H & E stain; low magnification.)

Genitourinary Tract Cancers

Metastases to the lungs from renal cell carcinoma are more often multiple but may present as a solitary lesion; they may precede the clinical detection of a primary tumor or develop several years (<10 years) after its resection.[33] Primary pulmonary lesions and other metastatic neoplasms that may be part of the differential diagnosis include clear cell (*i.e.*, sugar) tumor, clear cell changes in primary squamous and adenocarcinomas of the lung, large cell undifferentiated carcinoma of the lung, and metastases from clear cell carcinomas primary in the uterus, ovaries, adrenals, parathyroid, or liver. If the metastatic deposits show the classic clear cell histology, renal cell carcinoma is usually included in the differential diagnosis (Fig. 60-4). However, rare histologic variants of renal cell carcinoma, such as the granular, oncocytic, papillary, and sarcomatoid types, can introduce added difficulties in the differential diagnosis that require the use of special techniques and a thorough clinical and radiographic evaluation to arrive at the correct diagnosis.

Metastases from transitional cell carcinoma of the urinary bladder more often is a late manifestation of the disease and presents few difficulties for diagnosis because of its disseminated nature of spread and characteristic histology. Carcinomas of the urinary tract have a relatively favorable outcome after resection of pulmonary metastases, with a 5-year survival rate as high as 50%.[34] Carcinoma of the prostate, although usually presenting first with bony and regional lymph node metastases, atypically manifests first as metastases to the lungs and mediastinal lymph nodes with no obvious involvement of bone or pelvic lymph nodes.[35,36] Immunohistochemical stains for prostate specific antigen have proven useful for differentiating these tumors from a lung primary (Fig. 60-5).

Testicular cancer accounts for 7% to 10% of lung metastases in most large series.[6,7,34] Embryonal carcinoma and teratocarcinoma of the testis may metastasize as a synchronous or metachronous solitary lung nodule. There may be maturation at the metastatic site, in which the metastatic lung deposits contain only elements of mature teratoma.[37,38] Tumors of female reproductive tract are often the source of lung metastases. Uterine and cervical primaries account for the most frequent primary sites.[34,39] Infrequently, metastases from ovarian carcinoma affect only the lungs. Pulmonary metastases from choriocarcinoma, a common occurrence before chemotherapy, is rarely seen in surgical specimens. These tumors are characterized by their hemorrhagic appearance. Histologically, the demonstration of syncytiotrophoblastic-type giant cells coupled with immunoreactivity for the β-subunit of human chorionic gonadotropin can facilitate the diagnosis. Resection of pulmonary metastases from choriocarcinoma in chemotherapy-resistant patients has yielded 5-year survival rates of 50%.[40]

Other Epithelial Neoplasms

The lung infrequently is the first site of recurrence for breast cancer (Fig. 60-6).[41] Differentiation from a second primary in the lung may be impossible in some cases, particularly if a prolonged period of latency has followed resection of the primary tumor in the breast. Of 672 patients with disseminated breast cancer studied by Schlappak and colleagues, 7% presented initially with pulmonary metastases as the first manifestation of relapse.[41] In 23% of the

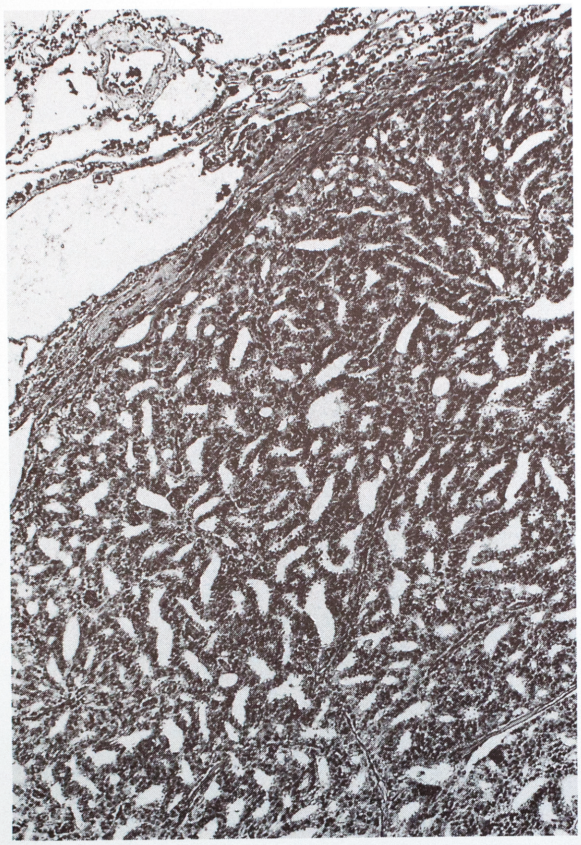

FIGURE 60-5. A metastasis from a moderately well-differentiated adenocarcinoma of the prostate has a characteristic cribriform pattern of growth. (H & E stain; low magnification.)

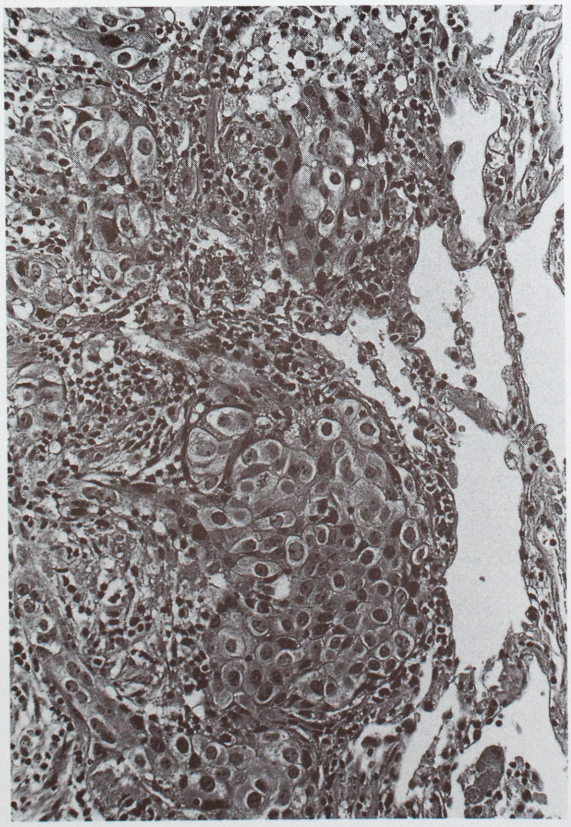

FIGURE 60-6. Metastasis to the lung from a ductal carcinoma of the breast. (H & E stain; intermediate magnification.)

patients, the lung metastases were solitary. Survival rates were the same for patients with multiple pulmonary nodules as for those with solitary nodules.

Adnexal carcinomas of the skin rarely metastasize to the lungs.[42,43] The metastases are usually slow growing and present after a long period of latency after removal of the primary lesion.[43] The lung may be a frequent site of metastases for thymomas and thymic carcinomas in children and adults.[44–46] In most cases, the histology is the same as that of the primary. Rarely, the histology of the lesion at the metastatic site differs from that of the primary tumor.[45] In patients presenting with simultaneous involvement of the anterior mediastinum and the lungs by small cell carcinoma or squamous cell carcinoma, it may be impossible to determine whether the tumor initially arose in the lung or the thymus.[46]

METASTASES FROM BONE AND SOFT TISSUE SARCOMAS

The lung is the most common site of metastases for most sarcomas of soft tissue and bone. Histologic distinction between primary and secondary tumors is not always feasible, but metastatic sarcomas considerably outnumber primary mesenchymal tumors of the lung. Establishing the diagnosis of a metastasis from a sarcoma is of importance because improved survival has been demonstrated after surgical resection of the lesions.[7,47,48] Metastases to the lung from sarcomas are usually peripherally located, although they may be central, more often multiple than solitary, and sharply circumscribed from the surrounding lung parenchyma with central areas of necrosis. Infrequently, metastatic sarcomas may present as endobronchial masses simulating primary bronchogenic carcinoma (see Chap. 56).[49]

Osteogenic Sarcoma

Although the lungs were traditionally the initial site of relapse for patients with osteogenic sarcoma, the percentage of patients with isolated pulmonary metastases appears to be decreasing, perhaps as a result of the introduction of more effective adjuvant chemotherapy.[50,51] Metastases from osteosarcoma are most often multiple and peripheral (Fig. 60-7), but they may be single and centrally located. Histologically, the lesions may show frank areas of malignancy identical to the primary tumor or may exhibit a maturation phenomenon in which extensive areas of the tumor show chondroid differentiation simulating chondrosarcoma (Fig. 60-8). A careful search must be made to identify areas containing osteoid or evidence of bone formation by the neoplastic cells.

Adult Soft Tissue Sarcomas

The lungs are the first site of metastases for adult soft tissue sarcomas. Unlike osteosarcomas, the pulmonary metastases of soft tissue sarcomas are not as amenable to resection, and they usually portend an ominous outcome. Putnam and associates reported a series of 63 patients undergoing exploration for metastatic soft tissue sarcoma to the lung, of whom 51 were found to have unresectable disease.[48] Survival usually is related to the size of the tumor burden, number of lesions, and histologic grade of the primary tumor. Because virtually all histologic types of soft tissue sarcomas may arise as a primary in the lung, it may be impossible to differentiate a primary from a metastatic lesion without sup-

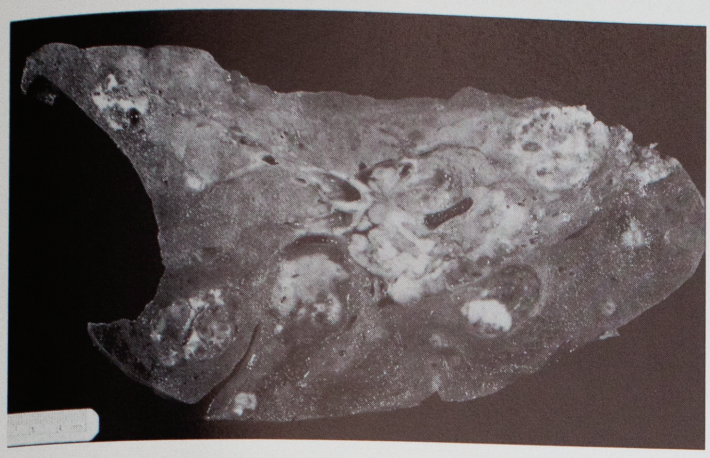

FIGURE 60-7. A sagittal section of the left lung shows multiple, hemorrhagic, and partly necrotic metastatic lesions from an osteosarcoma. (Contributed by the editor.)

porting clinical data. An important feature of metastatic sarcoma to the lung is its tendency to entrap normal respiratory epithelium at its borders, creating the illusion of a biphasic neoplasm such as a carcinosarcoma (Fig. 60-9).[52]

The histologic differential diagnosis for pulmonary metastases of sarcoma include carcinosarcoma and primary spindle cell carcinoma of the lung. Immunohistochemical techniques may aid in determining spindle cell carcinoma by demonstrating expression of keratin-intermediate filaments within the neoplastic cells to the exclusion of other markers.[53] Another potential pitfall in diagnosis is mistaking a pleural-based localized fibrous tumor (*e.g.*, fibrous mesothelioma) for an intrapulmonary mass.[54] These tumors frequently indent the pleura and present radiographically as intrapulmonary lesions. Careful gross examination is mandatory to determine the exact location. Because of their protean histologic appearances and multiplicity of growth patterns, these tumors may be easily mistaken for a variety of soft tissue sarcomas if the pathologist is unaware of its exact location and gross morphologic appearance.[53] Another peculiar phenomenon observed in pulmonary metastases from soft tissue sarcomas is a change in morphology from the original lesion; some tumors may progress to a more mature or well-differentiated phenotype, and others may revert to a more primitive phenotype, adopting a configuration reminiscent of malignant fibrous histiocytoma, regardless of the original histology of the primary (Fig. 60-10).

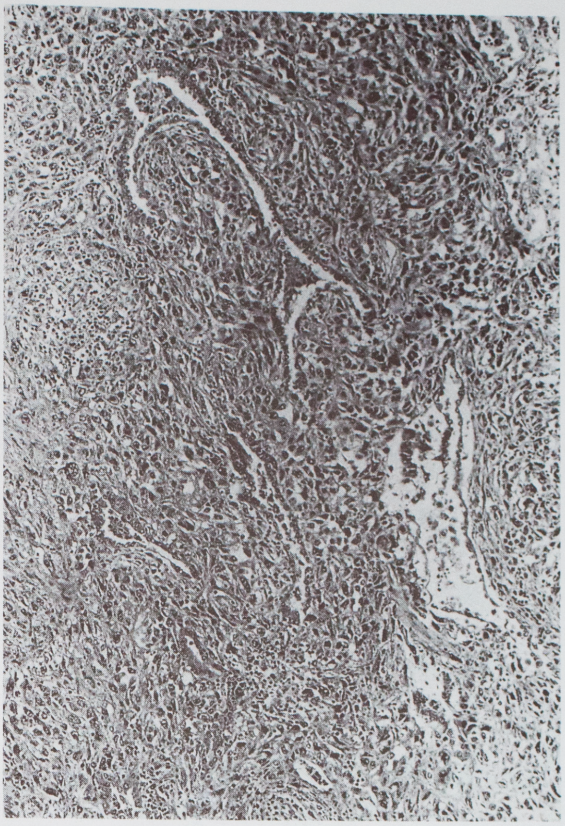

FIGURE 60-9. Glands and air spaces are entrapped at the edges of a metastasis to the lung from a malignant fibrous histiocytoma. (H & E stain; low magnification.)

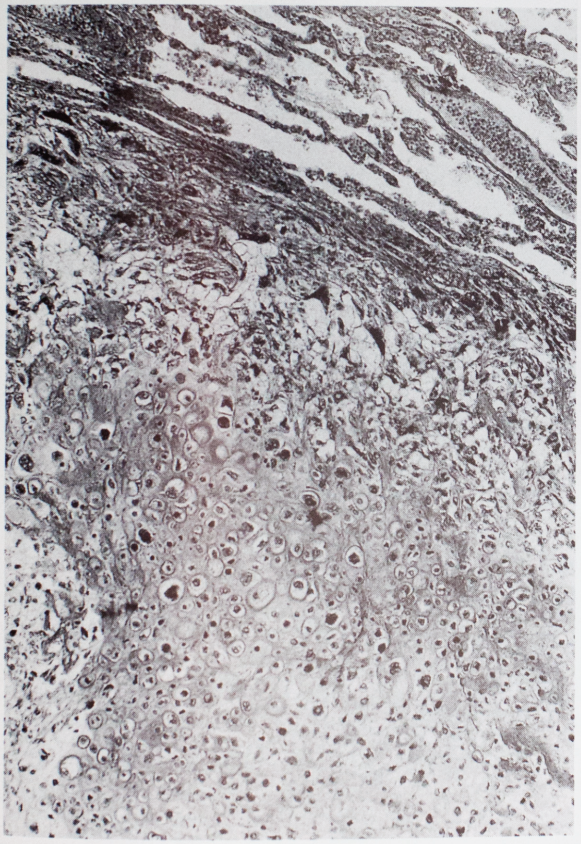

FIGURE 60-8. This metastasis from an osteosarcoma of the femur in a 16-year-old boy shows extensive cartilaginous differentiation. (H & E stain; low magnification.)

Sarcomas of the Female Reproductive Tract

Uterine leiomyosarcomas account for most metastases to the lung from sarcomas originating in the female reproductive tract. With the exception of metastases from obvious high-grade uterine leiomyosarcomas, most of these tumors metastasize after a long period of latency, and because of their benign-appearing histology, they are most frequently confused for benign primary growths of the lung or labeled as hamartomas.[52] Smooth muscle neoplasms of the lungs, particularly in postmenopausal women, should be regarded as metastatic from the genital tract until proven otherwise, and a diligent search for evidence of a previous history of uterine mass with a review of the slides from the original resection should be undertaken.

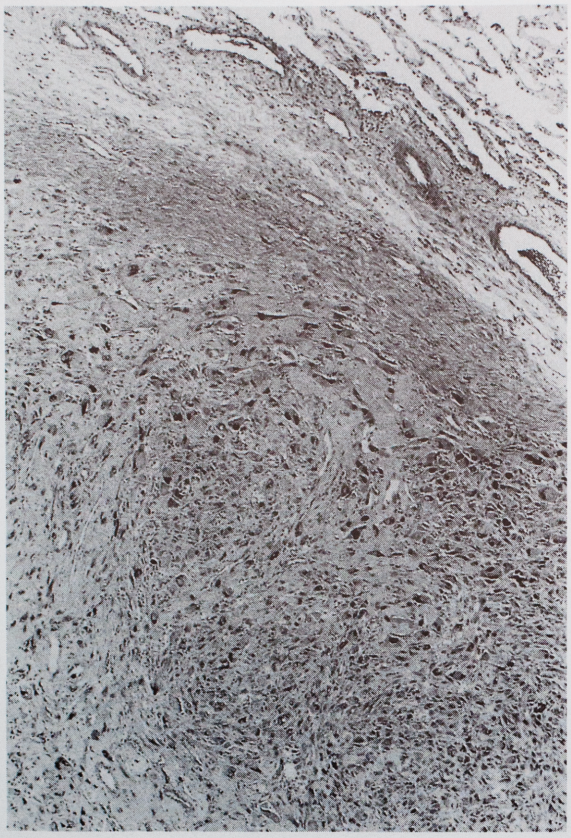

FIGURE 60-10. This pulmonary metastasis from a leiomyosarcoma of the thigh shows a bizarre morphology reminiscent of a malignant fibrous histiocytoma. (H & E stain; low magnification.)

FIGURE 60-11. Spiral arterioles are seen in a lung metastasis from an endometrial stromal sarcoma of the uterus. (H & E stain; low magnification.)

Endometrial stromal sarcoma has a propensity to metastasize to the lungs. Infrequently, a solitary lung metastasis may be the first manifestation of this tumor.[55] Metastases from endometrial stromal sarcoma may be difficult to recognize and can be confused with other spindle cell tumors, particularly hemangiopericytoma.[56] A distinctive feature helpful in the diagnosis is the characteristic spiral arterioles interspersed among tumor cells (Fig. 60-11).

Childhood Sarcomas

The lung is a primary site of metastatic spread for many childhood malignancies such as Wilms tumor, neuroblastoma, hepatoblastoma, Ewing sarcoma, and rhabdomyosarcoma. With the exception of osteogenic sarcoma, the lung is rarely the initial or only site of metastasis for these tumors. As with germ cell tumors in adults, childhood sarcomas in metastatic sites may exhibit the phenomenon of maturation after therapy, particularly for Wilms tumor (Fig. 60-12).[57] Although surgical resection of lung metastases from childhood sarcomas has gained acceptance as a treatment modality, the rate of disease-free survival after surgery has remained discouragingly low.[58] The best results have been obtained for treating metastases from Wilms tumor and for metastases that were solitary rather than multiple.[59] In most cases, surgery is indicated only for documentation of metastatic disease, and chemotherapy remains the treatment of choice.

METASTASES FROM MALIGNANT MELANOMA

The lung is the second most frequent site of metastases from malignant melanoma. In a large autopsy series by Patel and colleagues, the lungs were involved in 71.3% of cases, second only to lymph nodes.[60] Although pulmonary involvement as the presenting manifestation of malignant melanoma is rare, some studies have shown that the lungs may be the most common initial site for systemic relapse in patients with known melanoma.[61,62] This has led to an aggressive surgical approach, with early resection of pulmonary metastases.[63] Despite such dramatic efforts, median survival time for patients undergoing resection of metastatic melanoma to the lungs remains disappointingly low.[62] When presenting with the classic appearance of clusters of atypical tumors cells with prominent nesting and abundant, dark-staining cytoplasmic melanin pigment, the histologic diagnosis will be straightforward. Problems may arise in dealing with amelanotic tumors because of the diversity of growth patterns they may assume, such as sarcomatoid, myxoid, or neuroendocrinelike, and because of the unusual cytologic features they may display, such as spindle cell, balloon cell, small cell, granular cell, signet-ring cell, or anaplastic forms (Fig. 60-13). The use of immunohistochemical stains is important in these circumstances, but care must be exercised in their interpretation, because many antibodies previously thought to be specific for melanoma cells, such as S-100 protein and HMB-45, have been found to react with a variety of other neoplasms, and many antibodies previously thought not to be expressed in melanomas, such as keratin and carcinoembryonic antigen, have been found to react with melanomas.[64–66] The use of a panel of antibodies rather than a single stain is recommended. The demonstration of premelanosomes and parallel arrays of microtubules within the endoplasmic reticulum by electron microscopy can aid in establishing a definitive diagnosis.

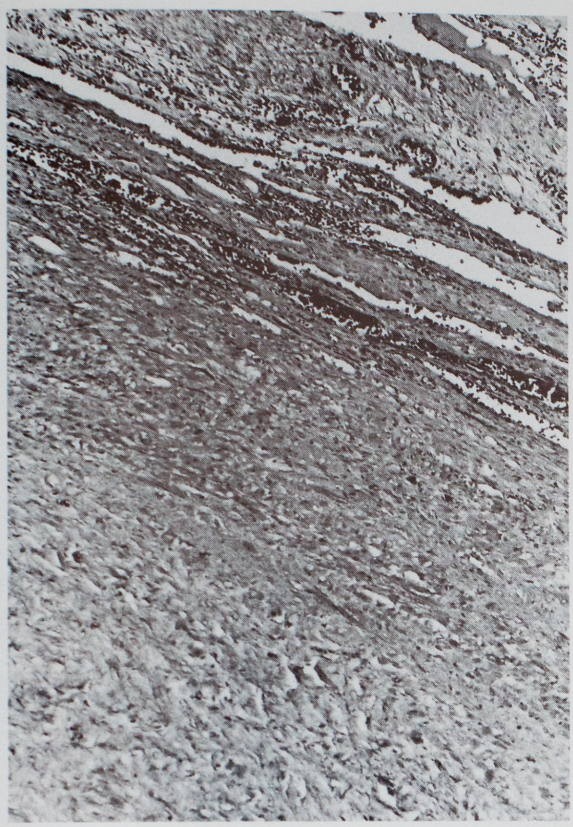

FIGURE 60-12. Metastasis to the lung from a Wilms' tumor occurred in a patient treated with irradiation and chemotherapy. Notice the absence of immature and epithelial-tubular elements and the prominence of the fibroblastic stromal component. (H & E stain; low magnification.)

METASTASES FROM BENIGN TUMORS AND PULMONARY ECTOPIAS

Secondary deposits in the lungs of tumors that are usually regarded as benign on histologic and clinical grounds are well documented, albeit rare.

Benign Metastasizing Leiomyoma

Benign metastasizing leiomyoma is a term that has been used to refer to single or multiple, cytologically bland-appearing tumors in the lung that are composed of smooth muscle (Fig. 60-14).[67,68] Another term employed for the same condition is leiomyomatous hamartoma.[69] They most often occur in the lungs of women of reproductive age or older. These lesions seem to be hormonally dependent. The lesions grew in a pregnant patient and regressed spontaneously after delivery.[67] Another report described regression of the lesions after oophorectomy.[68]

The nature of these lesions is controversial. The major issue is whether they represent leiomyomatous hamartomas or metastases. Most patients had a history of uterine surgery or were found to have multiple uterine myomas at autopsy. The prevailing opinion is that these lesions represent late metastases of low-grade, well-differentiated uterine leiomyosarcomas.[52]

Benign Metastasizing Meningioma

Benign metastasizing meningioma represents a situation in which benign-appearing metastases develop, usually after a long latency period, from an intracranial meningioma with benign, conven-

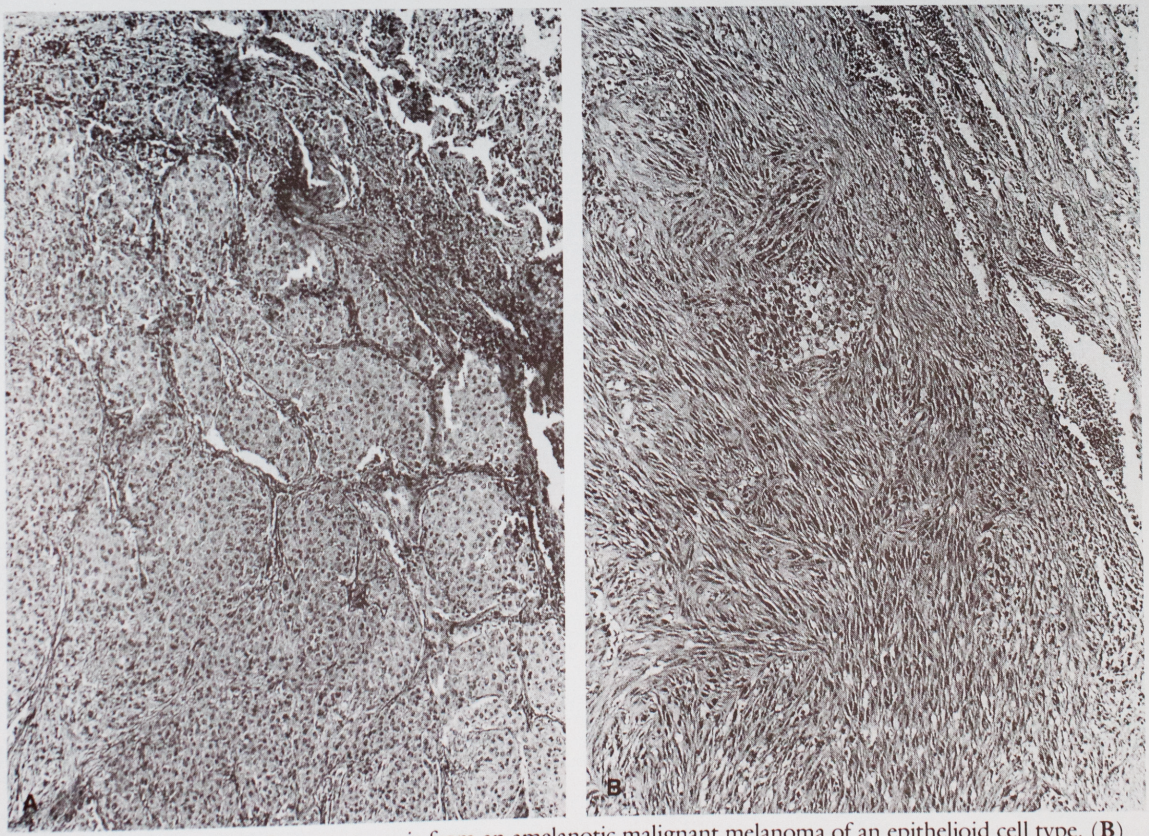

FIGURE 60-13. (**A**) Lung metastasis from an amelanotic malignant melanoma of an epithelioid cell type. (**B**) Lung metastasis from a spindle cell malignant melanoma. (H & E stains; low magnifications.)

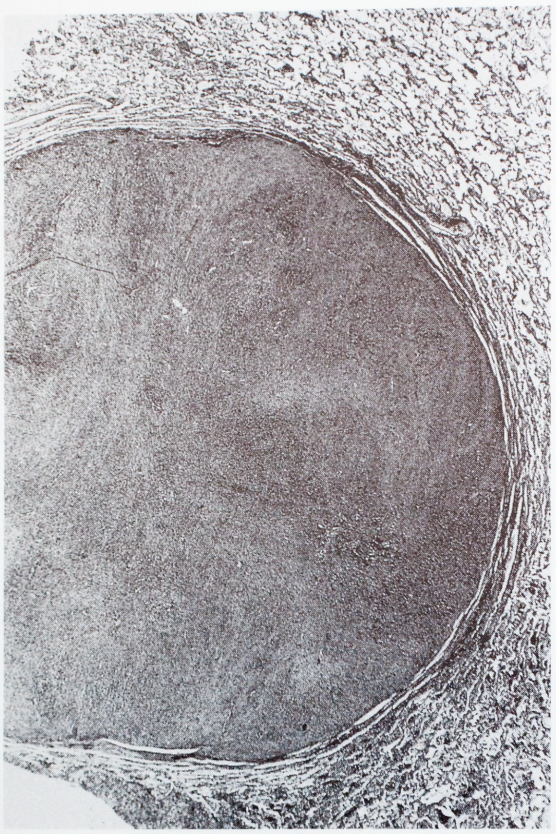

FIGURE 60-14. This benign metastasizing leiomyoma was found in a 65-year-old woman 12 years after the removal of a cellular leiomyoma. (H & E stain; low magnification.)

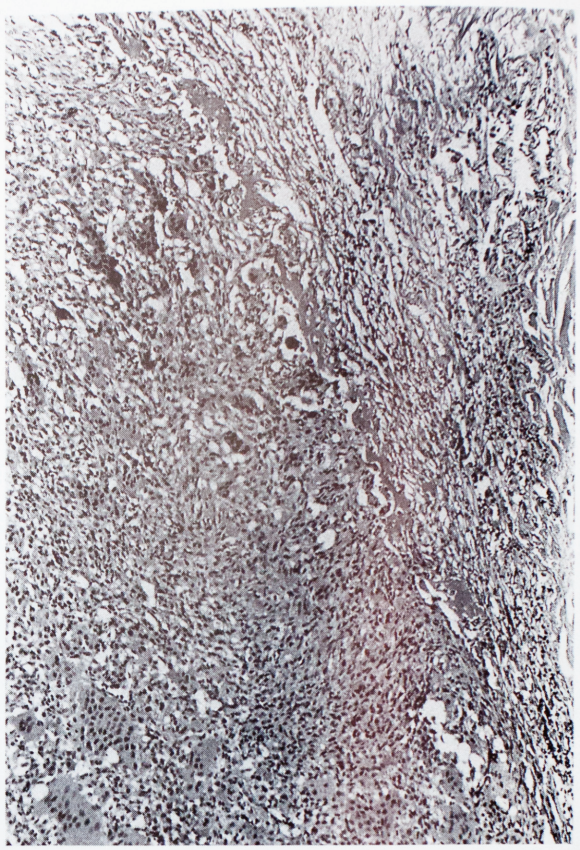

FIGURE 60-16. Metastasis to the lung from a histologically benign giant cell tumor of bone. Notice the thin rim of osteoid separating the mass from the surrounding lung parenchyma. (H & E stain; low magnification.)

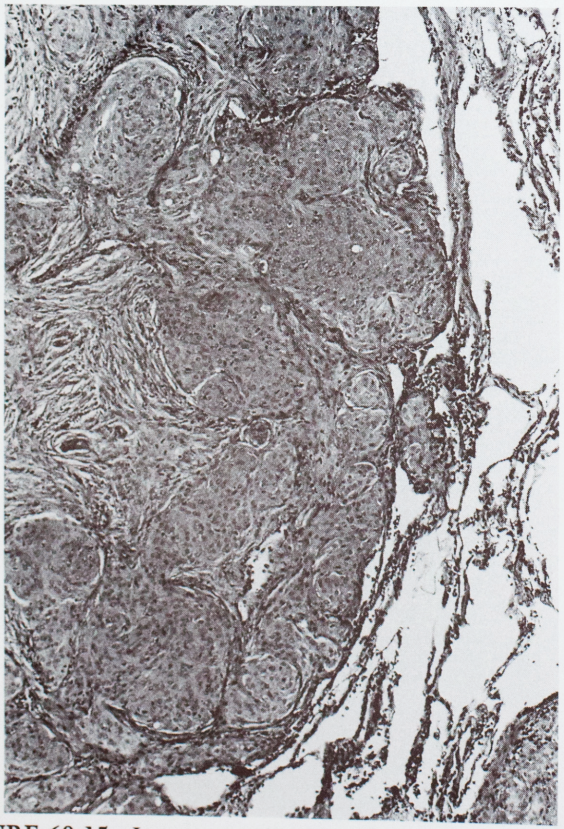

FIGURE 60-15. Lung metastasis from a meningioma. The primary lesion had been removed 16 years earlier and had an identical histologic pattern. (H & E stain; intermediate magnification.)

tional histology (Fig. 60-15).[70–72] This sometimes has been interpreted as evidence of malignant transformation in a recurrent tumor that later metastasized.[73] The main differential diagnosis for these lesions is minute pulmonary chemodectomas. Adequate history and the use of immunohistochemical stains help resolve the issue; meningiomas generally react positively with vimentin and epithelial membrane antigen and may be focally positive with keratin and S-100 protein, but they are uniformly negative for neuroendocrine markers of differentiation (see Chap. 58).[74]

Benign Giant Cell Tumor of Bone

Pulmonary metastases from giant cell tumor of the bone are a well-documented phenomenon; approximately 45 cases have been reported.[75] Histologically, the lesions are identical to nonmetastasizing, benign giant cell tumor of bone (Fig. 60-16). The clinical presentation and radiographic appearance of the primary lesion was similar in all the cases reported to that of ordinary giant cell tumor of bone. These metastatic lesions respond well to resection combined with chemotherapy and irradiation. The only patients who died of their disease were those in whom the lesions were not excised or were incompletely excised.[76–78]

Ectopias

Ectopias are rare but important in the differential diagnosis of metastatic lesions. A rare case of bilateral, multifocal brain heterotropia in the lungs of a newborn baby girl giving rise to symptoms of respiratory distress was reported.[79] Examples of pulmonary

endometriosis and benign pulmonary implants from hydatidiform mole have also been documented.[80–82] The ability of these tissues to survive and become implanted in the lung after hematogenous spread should not be confused with malignant metastatic spread from other tumors.[83]

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