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Metastatic Lung Cancer

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Lung cancer may spread by direct extension into the pleura and adjacent structures through the bronchial tree (*i.e.*, tubular spread), and through the blood vessels and lymphatics. Tubular spread gives rise to intrapulmonary secondary deposits; local invasion results in extension into the mediastinum and pleura with subsequent spread to the chest wall and diaphragm. Distant metastases most commonly manifest initially as deposits in hilar and mediastinal lymph nodes, but spread to lymph nodes in the abdomen and cervical region is also common. In addition to lymphatic metastases, lung cancer spreads by hematogenous routes as the result of local invasion of pulmonary veins.[1]

After the tumor has entered the veins, lung cancer has the potential to spread to virtually every organ in the body through the systemic circulation, but there are peculiarities in its metastatic pattern. In a large autopsy series, Onuigbo found that distant metastases from lung cancer were often not widespread, that they appeared to involve selectively certain organs, that they were asymmetric and often confined to one side in paired organs, and that they showed little correlation with the blood supply.[2] All of these features were at odds with the expected pattern of dissemination of cancer cells circulating in the bloodstream. He concluded that lung cancer cells did not have a great capacity to survive in the bloodstream and successfully implant in other organs and that distant lung metastases most often were the result of retrograde lymphatic spread of involved abdominal nodes.[2]

Later investigators proposed that selective routes of hematogenous or lymphogenous metastases may be related to the existence of heterogenous tumor cell populations within the same neoplasm having different metastatic potentials.[3] A study by Nomori and colleagues of metastatic lung carcinoma showed that tumor cells from hematogenous metastases had a higher nuclear DNA content by cytofluorometric analysis than the cells derived from lymphatic metastases.[4] The investigators postulated that blood-borne metastatic tumor cells from lung cancer in the brain and liver were derived from a discrete, more malignant tumor cell subpopulation within the primary tumor.

Generalizations about metastatic routes of spread in lung cancer may be overstated, because separation of metastases into lymphogenous and hematogenous is rather arbitrary because of the intimate association that exists between the blood and lymph systems and the numerous connections between the two through venolymphatic anastomoses or by way of the thoracic duct.[5] Distribution of metastases in lung cancer may be subject to the influence of the properties of the tumor cells and of individual host immune factors in different organs.[6]

The first symptoms of intrathoracic spread of lung cancer include hoarseness due to involvement of the recurrent laryngeal nerve; pleuritis with or without effusion; unilateral paralysis of the diaphragm due to involvement of the phrenic nerve; dysphagia due to esophageal involvement; Horner syndrome due to involvement of the cervical thoracic nerves; and superior vena cava syndrome due to entrapment of the vessel by tumor. Pancoast tumor is cancer arising in the apex of the lung or the superior sulcus. These tumors show a propensity for early invasion of surrounding structures, including pleura, chest wall, and the tracheal and cervical sympathetic plexus. Extension to these neural structures can result in the Horner syndrome (*e.g.*, enophthalmos, ptosis, miosis, anhidrosis on the same side of the lesion). Such tumors are often unresectable at the time of presentation. Symptoms of extrathoracic spread depend on the sites of metastases. The most commonly involved extrathoracic sites are the brain, liver, adrenals, and bone. A diagnostically helpful but infrequent clinical sign of extrathoracic spread of lung cancer is the Virchow node, which represents essentially the selective invasion of a supraclavicular lymph node in the absence of general lymph node metastases in the neck, a phenomenon believed to result from dissemination through the thoracic duct.[7]

PATTERNS OF SPREAD IN RELATION TO HISTOLOGIC TYPE

Table 59-1 shows the distribution by organ site of metastases of lung cancer from a large autopsy series.[8] In this series of 662 autopsied cases, the incidence of metastases for squamous cell carcinoma was 94%; adenocarcinoma, 96.4%; large cell carci-

TABLE 59-1
Patterns of Metastatic Spread of Lung Cancer According to Histologic Type in an Autopsy Series of 662 Patients

Site	Percentage of Total	Histologic type (%)			
		SQUAMOUS	SMALL CELL	ADENOCARCINOMA	LARGE CELL
Regional nodes	89.1	83.3	95.7	91.0	89.4
Brain	44.7	35.9	50.0	46.8	49.2
Distant nodes	44.6	29.2	62.0	47.9	44.7
Liver	44.1	37.1	61.7	42.4	33.3
Adrenal	33.7	20.0	44.4	41.2	35.5
Bone	29.5	25.6	35.0	43.7	24.5
Pleura	24.3	23.6	22.7	29.9	18.1
Kidney	23.6	23.0	24.7	25.5	19.4
Pericardium	17.5	15.0	20.3	18.6	17.0
Chest wall	15.6	15.9	12.3	18.0	13.8
Esophagus	13.1	13.7	17.8	10.2	8.5
Pancreas	13.2	4.8	30.2	9.7	8.6
Peritoneum	10.7	6.0	12.9	12.6	14.9
Diaphragm	7.6	4.3	5.5	10.8	12.8
Thyroid	6.6	4.3	9.8	7.2	5.3
Skin	3.2	1.3	3.8	6.0	2.1

Adapted from Auerbach O, Garfinkel L, Parks, VR. Histologic type of lung carcinoma in relation to smoking habits, years of diagnosis and sites of metastases. Chest 1975;67:382.

noma, 96.8%; and small cell carcinoma, 99.4%. Although local spread was more or less uniform for all four histologic types, noticeable differences were seen in their pattern of distal spread; squamous cell carcinoma had a lower rate of metastasis to distant lymph nodes, brain, liver, adrenals, and bone than small cell carcinoma.

In a study by Matthews and associates of 202 autopsied patients who died within a month of resection of their lung cancers, distant metastases were found in 17% of patients with squamous cell carcinoma and in 63% of those with small cell carcinoma, underscoring the ability of small cell carcinoma to metastasize earlier.[9] Another factor that may influence the spread of lung cancer is the degree of differentiation of a tumor. Although approximately one half of well-differentiated squamous carcinomas in one study did not progress beyond local spread, poorly differentiated squamous carcinomas disseminated widely to distant sites (see Chap. 48).[10]

Poorly differentiated adenocarcinomas behaved more aggressively than the well-differentiated forms, although the differences were not as striking as for squamous cell cancer (see Chap. 47). No clinically significant differences have been demonstrated among the various histologic subtypes of small cell carcinoma of the lung (see Chap. 49).[11] In the study by Auerbach and colleagues, the most frequent sites of extrathoracic spread for bronchogenic carcinoma in descending order of frequency were brain, distant lymph nodes, liver, adrenals, and bone.[8] Skin metastases and metastases to supraclavicular lymph nodes (*i.e.*, Virchow node) were extremely uncommon.

Carcinoid tumors of bronchial origin metastasize in about 10% of the cases studied.[12] Metastases are most often to hilar lymph nodes, although distant metastases, particularly to bone and liver, may also occur. Metastatic carcinoids to the liver are associated with the development of a clinical carcinoid syndrome. Spindle cell carcinoids are associated with a rate of metastatic spread similar to that of conventional carcinoids.[13] Atypical carcinoids are associated with a much higher rate of metastases. In a study of 23 patients with atypical carcinoids at the Mayo Clinic, 70% developed metastases to regional lymph nodes or distant bones and viscera (see Chap. 51).[14]

Bronchoalveolar carcinoma is unique among lung cancers for showing the highest rate of spread to the contralateral lung, although it has not been conclusively demonstrated whether this represents metastasis, a second primary, or a field-effect phenomenon whereby the entire lung parenchyma is subject to an increased predisposition to the development of this particular type of malignancy (see Chap. 47).[15] Less common primary tumors of the lung that frequently metastasize include carcinosarcoma and pulmonary blastoma. Carcinosarcomas most often metastasize to hilar lymph nodes, but they may also spread distally to bone.[16] Pulmonary blastomas most frequently metastasize to mediastinal lymph nodes and brain, but they may also spread to organs beneath the diaphragm.[17] Metastases at initial presentation correlate with a poor prognosis (see Chap. 54).

PATTERNS OF METASTASIS AND HISTOLOGIC APPEARANCES BY ORGAN SYSTEMS

The histologic appearance of metastatic lung cancer can depend on the organs involved.

Metastases to Lymph Nodes

The regional lymph nodes are the initial site of metastases in most patients with bronchogenic carcinoma. In general, tumors first spread to the ipsilateral hilar nodes and then go to the corresponding peritracheal nodes. Tumors from the left lung also cross the midline to involve right-sided lymph nodes. Tumors located in the lower lobes may spread to periesophageal and paraphrenic lymph nodes. Tumors located in the apices of the upper lobes may involve by direct lymphatic extension the supraclavicular and axillary node groups. Tumors located in the lower lobes may spread to celiac and abdominal paraaortic lymph nodes through direct lymphatic connections.

Lymph node mapping of lung cancer spread has been useful for staging and determining prognosis. Naruke and associates found that the survival rate for patients with subcarinal lymph node metastases was lower than for those without metastases to the subcarinal region, particularly in patients with carcinoma of the left lung in whom the presence of subcarinal lymph nodal involvement was associated with contralateral mediastinal node metastases (see Chap. 46).[18] In a study by Martini and colleagues, survival rates were worse for patients with N2 nodal involvement in the inferior mediastinum compared with those without lymph node involvement at that level.[19] Maggi and associates found that metastatic involvement of upper and lower subcarinal mediastinal lymph nodes was associated with a worse prognosis compared with involvement of one compartment only.[20] These researchers also found sparing of pulmonary and hilar nodes with involvement of more distal nodes by metastases in a significant number of patients, underscoring the importance of mediastinal lymphadenectomy for proper staging of lung cancer.

The histopathologic identification of lymph nodal metastases from lung cancer is simple and straightforward if the existence of the primary tumor is well documented. Problems may arise in evaluating a lymph node metastasis from an unknown primary. Although rare, cervical, axillary, and inguinal node metastases of an unknown primary have been the initial clinical manifestations of occult lung cancers.[21–24] As with metastases from other organs, the subcapsular sinuses are the initial site of involvement; the tumor subsequently involves the medullary sinuses and eventually replaces the entire lymph nodal tissue (Fig. 59-1).

It may not be possible to determine the primary origin in the lung from the histology of the tumor in the lymph node, particularly for adenocarcinoma or squamous cell carcinoma, although in some cases, the histology of the lesion is highly suggestive of a lung primary, such as small cell carcinoma or large cell undifferentiated carcinoma. Although tumors with a virtually indistinguishable morphology to that of oat cell carcinoma of the lung have been shown to arise in many organs, the presence of metastatic deposits in lymph nodes most likely corresponds to a lung primary. Anaplastic large cell carcinoma of the lung, although a much rarer tumor, also displays a distinctive histology (*i.e.*, sheets of bizarre, atypical cells admixed with abundant neutrophilic inflammatory infiltrate) that is shared by few other tumors (Fig. 59-2). The differential diagnosis in such instances includes anaplastic carcinoma of the urinary bladder and a metastasis of inflammatory malignant fibrous histiocytoma. The differential diagnosis may be narrowed in the latter instance by the use of immunohistochemical stains (see Chap. 50).

Metastases to the Central Nervous System

Brain metastases are the most frequent site of extrathoracic spread of lung cancer.[8,25,26] Cerebral metastases are found at the time of diagnosis in as many as 30% of patients with lung cancer, and this figure increases significantly in autopsy series.[25–29] The incidence of cerebral metastases depends on the histologic type. Adenocarcinomas and undifferentiated small and large cell carcinomas metastasize more frequently to the brain than squamous cell carcinoma.[25,27,30] Brain metastases from lung cancer are most often multiple, but solitary metastases do occur and have been particularly frequent when the primary carcinoma is peripherally located.[31] In some series, solitary metastases to the brain have been found in as many as 30% to 45% of patients with lung carcinoma.[26,27] Cerebral metastases may be the presenting symptom

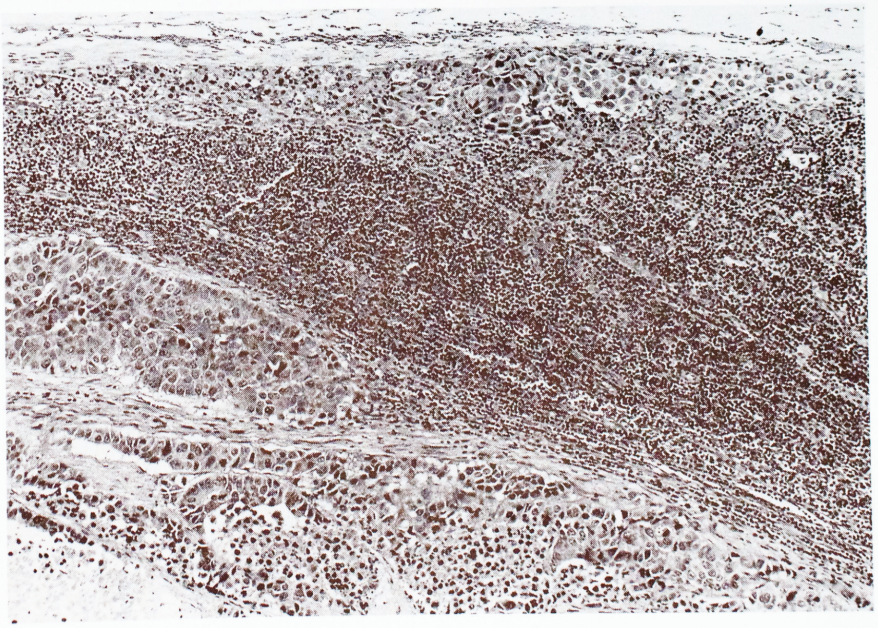

FIGURE 59-1. This cervical lymph node metastasis from an adenocarcinoma of the lung shows subcapsular involvement by tumor cells. (H & E stain; low magnification.)

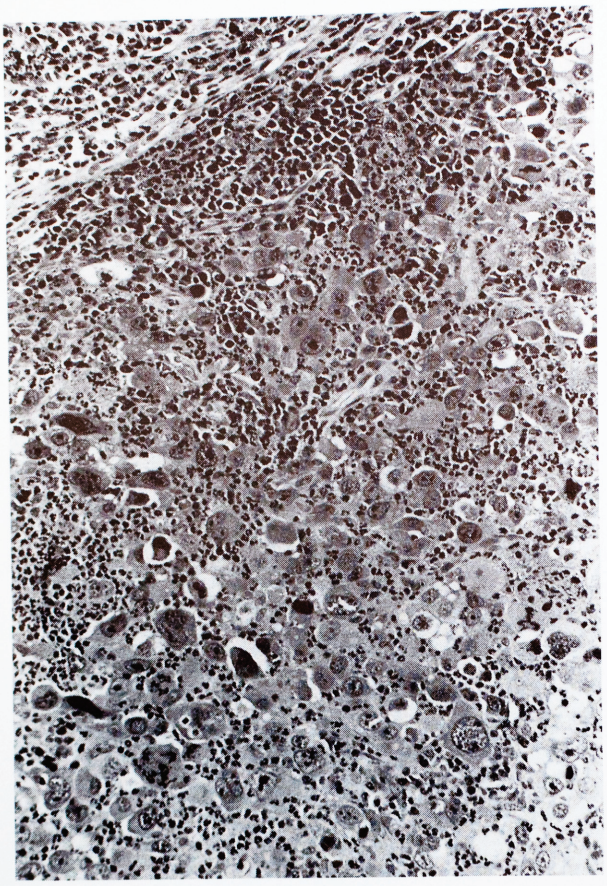

FIGURE 59-2. This lymph node metastasis from large cell undifferentiated carcinoma of the lung shows prominent polymorphonuclear leukocytic infiltrate admixed with bizarre tumor cells. (H & E stain; low magnification.)

of bronchogenic carcinoma.[32] Brain metastases in patients with lung cancer have been associated with a poor prognosis.[33,34] However, improved median survival has been observed for patients treated by neurosurgical resection of the metastases compared with patients treated with adjuvant therapy only.[35,36]

Lung cancer can spread to the meninges, most often in the form of meningeal carcinomatosis.[37,38] In more than 70% of cases in one large series, the involvement was diffuse, usually including intracranial and intraspinal meninges down to the cauda equina.[38] Meningeal carcinomatosis is frequently a manifestation of advanced disease with an ominous prognosis.

The histologic appearance of metastatic lung cancer to the brain usually mirrors that of the primary tumor, although cases have been described in which different histologic types were observed in the brain metastasis and the lung primary (Fig. 59-3).[39] In general, metastases from lung cancer are easily differentiated from primary brain tumors. In certain instances, such as undifferentiated large cell carcinoma, differentiation from glioblastoma multiforme may be difficult to establish in the absence of a history of lung primary. Metastases from small cell carcinoma appear to have a predilection for the cerebellum (Fig. 59-4). The presence of rosette formations in cerebellar metastases of oat cell carcinoma may lead to confusion with medulloblastoma. Metastatic small cell carcinoma to the brain may occasionally induce a prominent gliovascular proliferation similar to that seen in astrocytic neoplasms, raising the possibility of small cell glioblastoma multiforme in the differential diagnosis (Fig. 59-5).

Metastases to Bone and Bone Marrow

Lung cancer is the most frequent source of metastases to bone; it accounted for approximately 44% of all metastatic tumors to bone in a large autopsy series.[44] Although bone metastases from lung cancer are predominantly lytic, osteoblastic metastases may occur.[40,41] Bone metastases from bronchial carcinoids are characteristically osteoblastic.[42,43] The distribution of metastases from lung cancer to bone seems to favor the bones of the trunk and skull, which account for the bulk of hematopoietic marrow deposits in the body. In a study of 44 patients with bone metastases from lung cancer, most lesions were located in the axial skeleton, including the spine (21%), ribs or sternum (20%), pelvis (19%), and skull (13%).[44] Metastases to the extremities (*e.g.*, femur, humerus, distal extremities) accounted for less than 20% of the total. The most common presenting symptom of metastatic lung cancer to bone is pain, and the first symptom may be a pathologic fracture. Metastases may also mimic primary bone tumors or other nonneoplastic diseases of bone; for example, a metastasis to the vertebra may simulate the signs and symptoms of a herniated disc.[45]

Bone metastases from carcinoma of the lung are easy to identify by conventional microscopy. Only rarely does it become difficult to differentiate them from a primary bone tumor. Metastases that elicit a florid osteoblastic response may be mistaken for primary osteogenic sarcoma.

Metastatic lung cancer rarely may induce a florid stromal reaction with marked osteoclastic proliferation resembling giant cell tumor of bone (Fig. 59-6). The metastatic cancer cells may be few and widely scattered and obscured by the stromal proliferation; the use of immunohistochemical stains for keratin and other epithelial markers can highlight the small islands of tumor cells embedded in the stroma. In most instances, the clinical setting (*e.g.*, age of the patient, location of the lesion, radiographic appearance) and a thorough review of the patient's history can provide information sufficient to establish the metastatic nature of the lesion.

Distant bone metastases from small cell carcinoma of the lung may occasionally display a different histology from that of the primary, with the emergence of an undifferentiated large cell component admixed with the small cell elements (Fig. 59-7). Occasionally, a metastasis to bone may be the first manifestation of occult lung cancer; microscopic differentiation from a primary tumor of bone is essential for planning management.

Examination of bone marrow aspirates and trephine biopsy specimens is a sensitive way to demonstrate hematogenous dissemination of lung cancer, particularly from small cell carcinoma.[46] Bone marrow involvement in small cell cancer of the lung is a negative prognostic factor.[47] The use of specific monoclonal antibodies associated with neuroendocrine tissues has been proposed as a means of increasing the yield of detection of micrometastases from small cell carcinoma in the bone marrow.[48] Metastatic small cell carcinoma to the bone marrow characteristically displays relatively small nuclei, often somewhat elongated, with relatively little stroma separating the tumor cells (Fig. 59-8).[49]

Metastases to the Liver

The liver is the third most frequent distant site of spread for lung cancer.[8] Metastases from lung cancer represent the most frequent type of metastatic tumor to the liver.[50] Metastases from lung

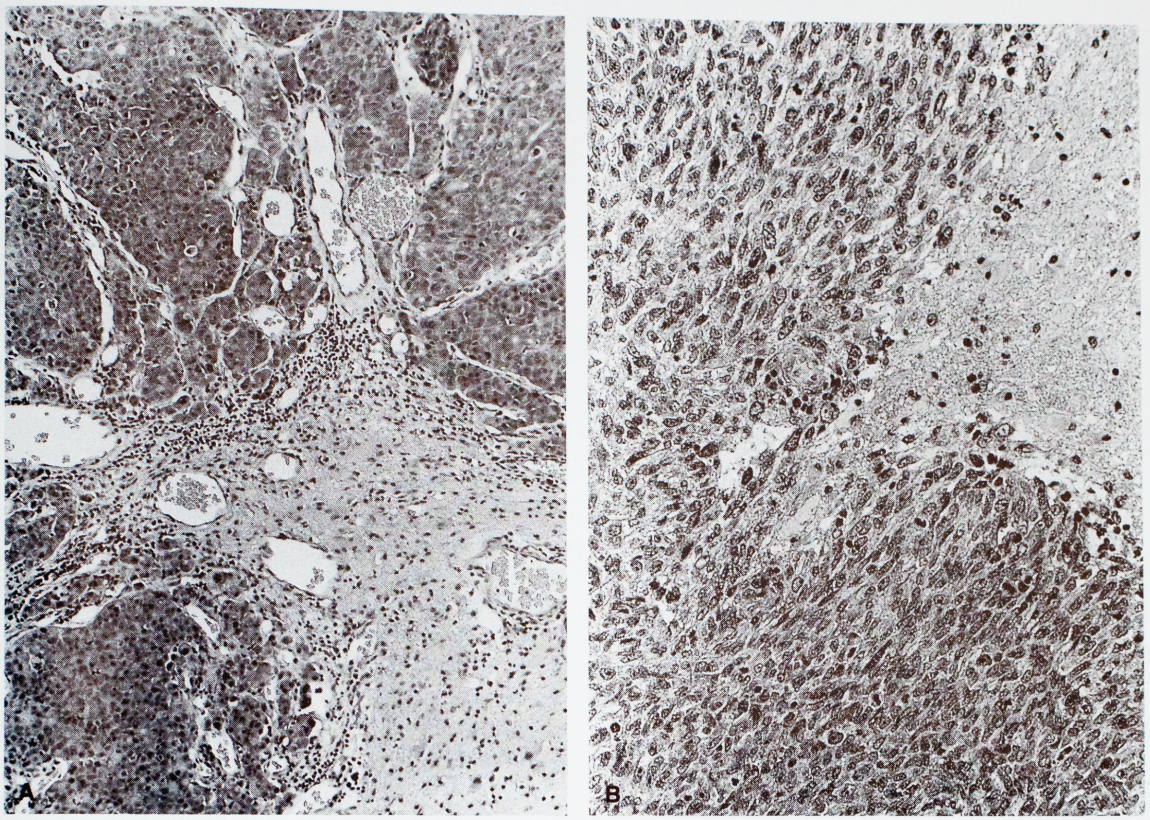

FIGURE 59-3. (**A**) In a cerebral metastasis from a well-differentiated adenocarcinoma of the lung, the tumor deposits show a poorly differentiated morphology compared with that of the primary tumor (H & E stain; low magnification.) (**B**) In a cerebral metastasis from a poorly differentiated squamous cell carcinoma of the lung, there is a prominent spindle cell pattern of growth not found in the primary tumor. The diagnosis was supported by demonstration of immunoreactivity for keratin intermediate filaments in the tumor cells. (H & E stain; intermediate magnification.)

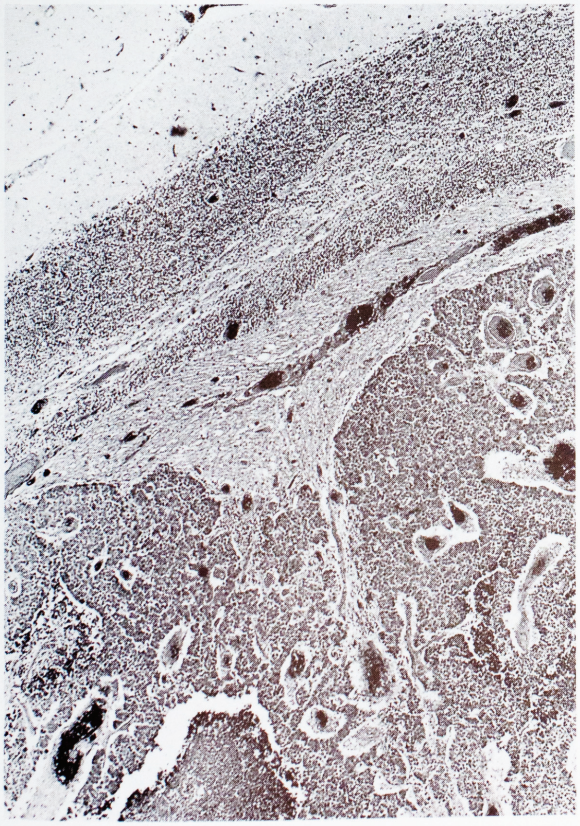

FIGURE 59-4. Cerebellar metastasis from a small cell carcinoma of the lung. (H & E stain; low magnification.)

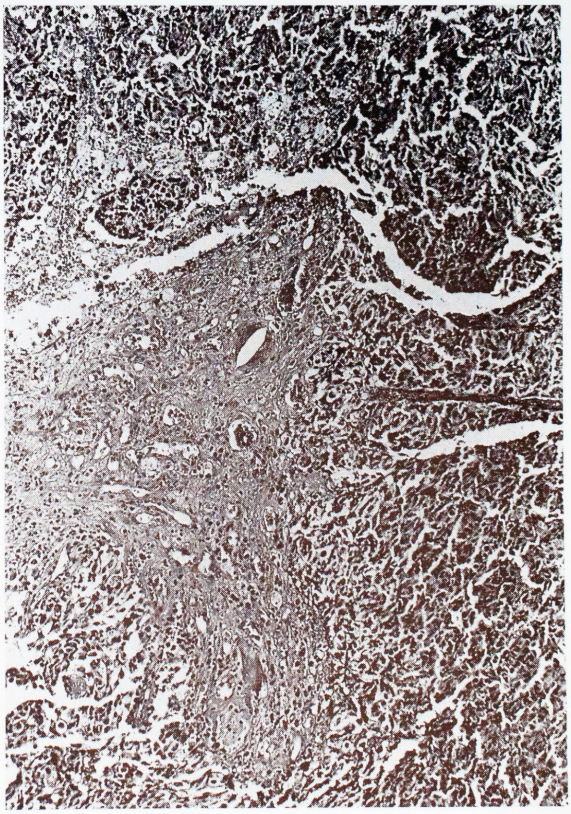

FIGURE 59-5. In this small cell carcinoma of the lung that metastasized to the brain, there is prominent gliovascular proliferation (*center*). (H & E stain; low magnification.)

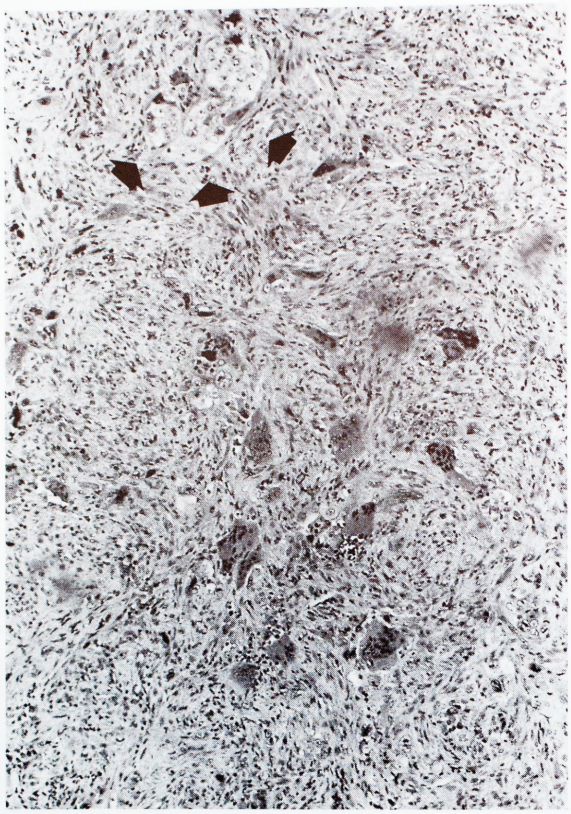

FIGURE 59-6. An adenocarcinoma of the lung that metastasized to a vertebra shows a prominent osteoclastic reaction; a small cluster of tumor cells are present (*arrows*). The tumor was initially mistaken for a giant cell tumor of bone. (H & E stain; low magnification.)

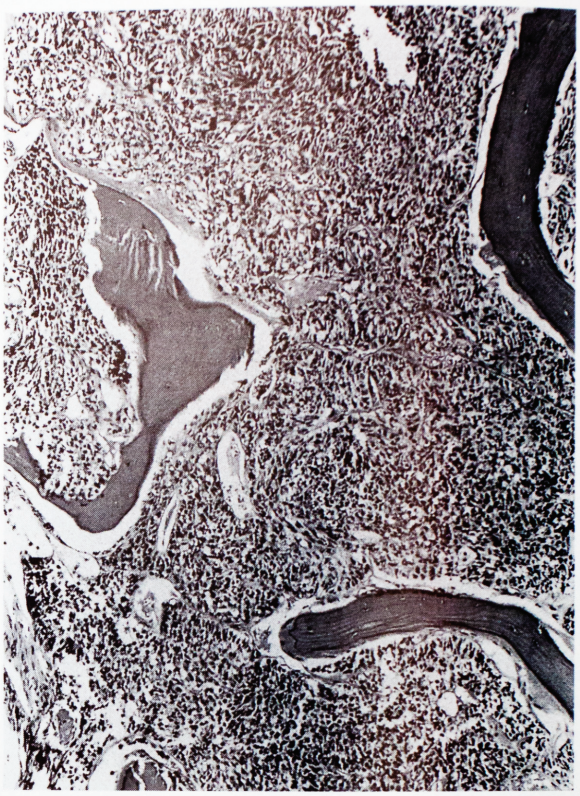

FIGURE 59-8. A Jamshidi needle biopsy specimen of the iliac crest shows bone marrow replacement by a metastatic small cell carcinoma of the lung. (H & E stain; low magnification.)

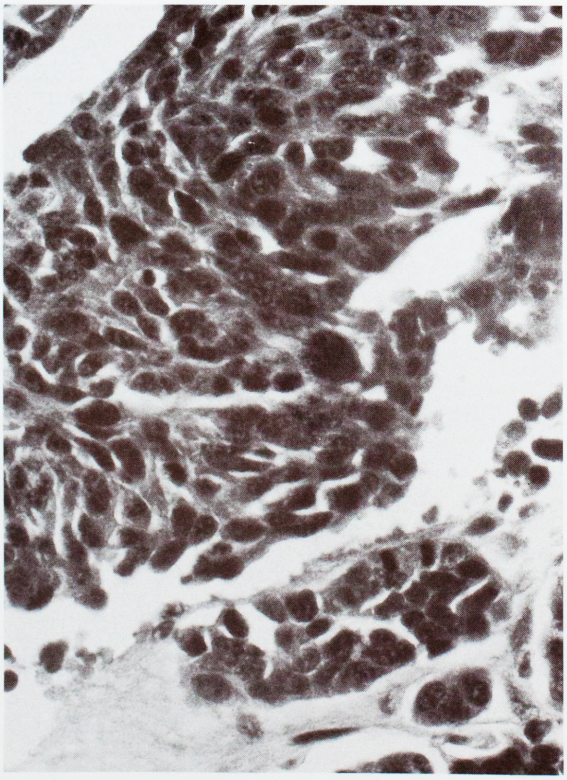

FIGURE 59-7. In this metastasis to a vertebra from a small cell carcinoma of the lung, notice the larger anaplastic cells admixed with a smaller cell component. These cells were not found in the primary lesion. (H & E stain; high magnification.)

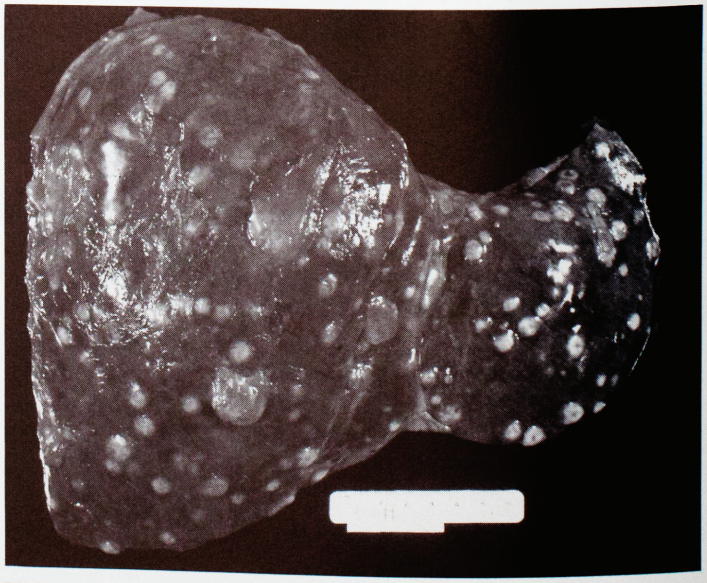

FIGURE 59-9. In an adenocarcinoma of the lung that metastasized to the liver, the external surface is extensively involved by multiple nodules. Notice the central umbilication of the nodules.

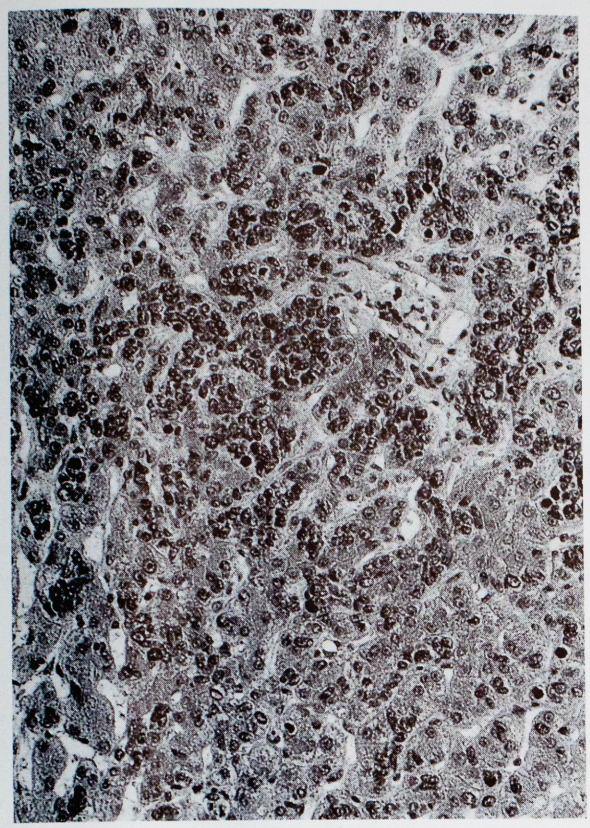

FIGURE 59-10. The metastasis to the liver from a small cell carcinoma of the lung shows distinctive sinusoidal infiltration by the tumor cells. (H & E stain; intermediate magnification.)

cancer most commonly reach the liver through the portal circulation or the hepatic artery.

Grossly, bronchogenic carcinoma may grow as a solitary, uniformly nodular, expandible mass, but it is most often multifocal and diffusely infiltrates the hepatic parenchyma (Fig. 59-9). The nodules located on the surface are characteristically umbilicated, a feature that may be of importance in differentiating them from primary liver cell carcinoma or cholangiocarcinoma.

The involvement of the organ is sometimes in the form of miliary spread, with numerous small nodules diffusely scattered throughout all lobes of the liver; this situation is particularly associated with metastases from small cell carcinoma.[51] Metastatic bronchogenic carcinoma in the liver usually resembles histologically the primary lesion and is readily identified as a metastasis (Fig. 59-10). Occasionally, metastatic small cell carcinoma grows by infiltrating through the sinusoids, superficially resembling hepatocellular carcinoma.

Hepatic metastases from bronchial carcinoids are easily differentiated from oat cell carcinoma by the lack of anaplasia and the preservation of the organoid or neuroendocrine pattern of growth of the primary tumor (Fig. 59-11). In some instances, resection of hepatic metastases from carcinoma has been beneficial, particularly if the lesions are isolated, fewer than three, and equal to or smaller than 5 cm in diameter.[52]

Metastases to the Adrenals and Other Organs

Adrenal metastases are a distinctive feature of lung cancer. In a large autopsy series by Karolyi, 25.3% of patients with lung cancer had adrenal metastases.[53] Of these, 25.9% of cases were ipsilateral, 16.3% were contralateral, and 57.8% were bilateral. The high incidence of unilateral adrenal metastases from lung cancer was also observed in the study by Onuigbo.[2]

In early tumor progression, a striking difference could be seen between metastases to the two sides, but this difference steadily decreased to equal proportions in patients autopsied at more advanced stages of the process.[53] As a result of these observations, it was proposed that adrenal metastases from early-stage lung cancer probably develop by lymphogenous dissemination, but in later stages, they develop mainly through hematogenous routes.

Pleural metastasis from lung cancer was the most frequent source of pleural carcinomatosis and accounted for 33% of the patients in one study.[54] The chief clinical presentation included pleural effusion, dyspnea, cough, and chest pain; however, a few patients were completely asymptomatic. Pleural involvement by metastatic carcinoma of the lung is an indication of advanced disease and portends a poor prognosis. Bilateral pleural involve-

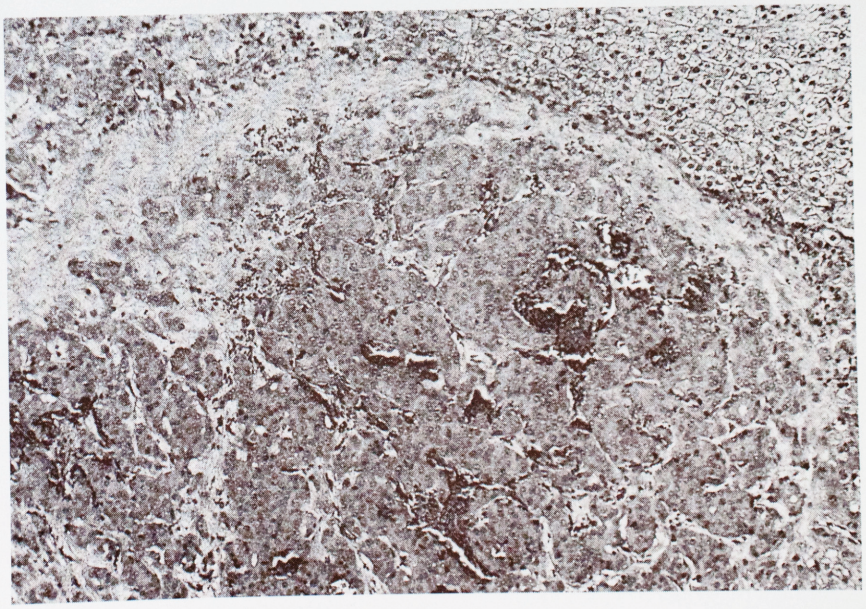

FIGURE 59-11. In this metastasis to the liver form bronchial carcinoid tumor, notice the sharp circumscription from the surrounding parenchyma and preservation of the neuroendocrine growth pattern. (H & E stain; low magnification.)

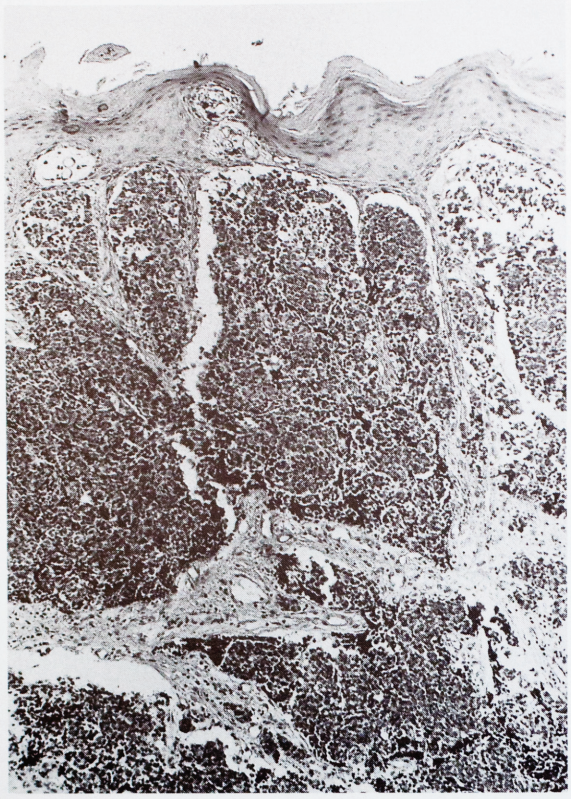

FIGURE 59-12. Metastasis to the skin from a small cell carcinoma of the lung. (H & E stain; low magnification.)

ment by carcinoma of the lung appears to be related to the presence of hepatic metastases, and it is usually accompanied by involvement of the lung parenchyma on the contralateral side.[55] A rare manifestation of metastatic lung cancer is acute abdomen due to perforation of the appendix or small bowel by metastatic carcinoma.[56,57] Metastasis to the small bowel is a poor prognostic sign, occurring late in the course of lung cancer; surgery is indicated for palliation of symptoms of obstruction or perforation.

Breast metastases from lung cancer were found in 6 of 51 cases of metastatic cancer to the breast studied in one series and accounted for the most common malignant epithelial tumor to metastasize to this organ.[58] In all six cases, the breast metastasis was the initial presenting sign of an occult carcinoma of the lung (*i.e.*, five oat cell carcinomas, one bronchoalveolar carcinoma). Cerebral, skeletal, and other distant metastases occurred soon after the appearance of the mammary metastasis. Although rare, the lung is the most frequent primary source of metastases to the thyroid gland. In a study from the Mayo Clinic, of 467 patients dying of disseminated cancer, autopsy revealed metastases to the thyroid in 18 patients, of whom four had primary tumors in the lung.[59] Similarly, metastases to the testis, a rare occurrence, has been most frequently associated with lung cancer.[60] Another rare manifestation of metastatic carcinoma of the lung is hematogenous metastasis to the limbs presenting as painful soft tissue masses in the proximal skeletal muscles.[61] Local irradiation is indicated for palliation of swelling and pain.

Metastases from lung cancer to the skin are rare; small cell carcinoma is the histologic type most frequently associated with this pattern.[8] In the absence of a history of lung cancer, metastases from small cell carcinoma of the lung to the skin may be impossible to differentiate from the trabecular carcinoma of the skin described by Toker and known as Merkel cell carcinoma or primary neuroendocrine carcinoma of the skin; the two entities share identical histologic, immunohistochemical, and ultrastructural features (Fig. 59-12).[62–64] Thorough clinicoradiographic studies are indicated to rule out a metastasis from an occult primary in the lung, although it must be kept in mind that a primary neuroendocrine carcinoma of the skin is much more common than cutaneous metastases from occult small cell carcinoma of the lung.

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