

TABLE 107-5 CLINICAL FINDINGS SUGGESTIVE OF METASTATIC DISEASE

Symptoms elicited in history	<ul style="list-style-type: none"> • Constitutional: weight loss >10 lb • Musculoskeletal: focal skeletal pain • Neurologic: headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical examination	<ul style="list-style-type: none"> • Lymphadenopathy (>1 cm) • Hoarseness, superior vena cava syndrome • Bone tenderness • Hepatomegaly (>13 cm span) • Focal neurologic signs, papilledema • Soft-tissue mass
Routine laboratory tests	<ul style="list-style-type: none"> • Hematocrit, <40% in men; <35% in women • Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

Abbreviations: GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase.

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distribution of the arm, often with radiologic destruction of the first and second ribs. Often Horner's syndrome and Pancoast syndrome coexist. Other problems of regional spread include superior vena cava syndrome from vascular obstruction; pericardial and cardiac extension with resultant tamponade, arrhythmia, or cardiac failure; lymphatic obstruction with resultant pleural effusion; and lymphangitic spread through the lungs with hypoxemia and dyspnea. In addition, lung cancer can spread transbronchially, producing tumor growth along multiple alveolar surfaces with impairment of gas exchange, respiratory insufficiency, dyspnea, hypoxemia, and sputum production. Constitutional symptoms may include anorexia, weight loss, weakness, fever, and night sweats. Apart from the brevity of symptom duration, these parameters fail to clearly distinguish SCLC from NSCLC or even from neoplasms metastatic to lungs.

Extrathoracic metastatic disease is found at autopsy in more than 50% of patients with squamous carcinoma, 80% of patients with adenocarcinoma and large-cell carcinoma, and greater than 95% of patients with SCLC. Approximately one-third of patients present with symptoms as a result of distant metastases. Lung cancer metastases may occur in virtually every organ system, and the site of metastatic involvement largely determines other symptoms. Patients with brain metastases may present with headache, nausea and vomiting, seizures, or neurologic deficits. Patients with bone metastases may present with pain, pathologic fractures, or cord compression. The latter may also occur with epidural metastases. Individuals with bone marrow invasion may present with cytopenias or leukoerythroblastosis. Those with liver metastases may present with hepatomegaly, right upper quadrant pain, fever, anorexia, and weight loss. Liver dysfunction and biliary obstructions are rare. Adrenal metastases are common but rarely cause pain or adrenal insufficiency unless they are large.

Paraneoplastic syndromes are common in patients with lung cancer, especially those with SCLC, and may be the presenting finding or the first sign of recurrence. In addition, paraneoplastic syndromes may mimic metastatic disease and, unless detected, lead to inappropriate palliative rather than curative treatment. Often the paraneoplastic syndrome may be relieved with successful treatment of the tumor. In some cases, the pathophysiology of the paraneoplastic syndrome is known, particularly when a hormone with biological activity is secreted by a tumor. However, in many cases, the pathophysiology is unknown. Systemic symptoms of anorexia, cachexia, weight loss (seen in 30% of patients), fever, and suppressed immunity are paraneoplastic syndromes of unknown etiology or at least not well defined. Weight loss greater than 10% of total body weight is considered a bad prognostic sign. Endocrine syndromes are seen in 12% of patients; hypercalcemia resulting from ectopic production of parathyroid hormone (PTH), or more commonly, PTH-related peptide, is the most common life-threatening metabolic complication of malignancy, primarily occurring with squamous cell carcinomas of the lung. Clinical symptoms

include nausea, vomiting, abdominal pain, constipation, polyuria, thirst, and altered mental status.

Hyponatremia may be caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) or possibly atrial natriuretic peptide (ANP). SIADH resolves within 1-4 weeks of initiating chemotherapy in the vast majority of cases. During this period, serum sodium can usually be managed and maintained above 128 mEq/L via fluid restriction. Demeclocycline can be a useful adjunctive measure when fluid restriction alone is insufficient. Vasopressin receptor antagonists like tolvaptan also have been used in the management of SIADH. However, there are significant limitations to the use of tolvaptan including liver injury and overly rapid correction of the hyponatremia, which can lead to irreversible neurologic injury. Likewise, the cost of tolvaptan may be prohibitive (as high as \$300 per tablet in some areas). Of note, patients with ectopic ANP may have worsening hyponatremia if sodium intake is not concomitantly increased. Accordingly, if hyponatremia fails to improve or worsens after 3-4 days of adequate fluid restriction, plasma levels of ANP should be measured to determine the causative syndrome.

Ectopic secretion of ACTH by SCLC and pulmonary carcinoids usually results in additional electrolyte disturbances, especially hypokalemia, rather than the changes in body habitus that occur in Cushing's syndrome from a pituitary adenoma. Treatment with standard medications, such as metyrapone and ketoconazole, is largely ineffective due to extremely high cortisol levels. The most effective strategy for management of the Cushing's syndrome is effective treatment of the underlying SCLC. Bilateral adrenalectomy may be considered in extreme cases.

Skeletal-connective tissue syndromes include clubbing in 30% of cases (usually NSCLCs) and hypertrophic primary osteoarthropathy in 1-10% of cases (usually adenocarcinomas). Patients may develop periostitis, causing pain, tenderness, and swelling over the affected bones and a positive bone scan. Neurologic-myopathic syndromes are seen in only 1% of patients but are dramatic and include the myasthenic Eaton-Lambert syndrome and retinal blindness with SCLC, whereas peripheral neuropathies, subacute cerebellar degeneration, cortical degeneration, and polymyositis are seen with all lung cancer types. Many of these are caused by autoimmune responses such as the development of anti-voltage-gated calcium channel antibodies in Eaton-Lambert syndrome. Patients with this disorder present with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely, cranial nerve symptoms or involvement of the bulbar or respiratory muscles. Depressed deep tendon reflexes are frequently present. In contrast to patients with myasthenia gravis, strength improves with serial effort. Some patients who respond to chemotherapy will have resolution of the neurologic abnormalities. Thus, chemotherapy is the initial treatment of choice. Paraneoplastic encephalomyelitis and sensory neuropathies, cerebellar degeneration, limbic encephalitis, and brainstem encephalitis occur in SCLC in association with a variety of antineuronal antibodies such as anti-Hu, anti-CRMP5, and ANNA-3. Paraneoplastic cerebellar degeneration may be associated with anti-Hu, anti-Yo, or P/Q calcium channel autoantibodies. Coagulation or thrombotic or other hematologic manifestations occur in 1-8% of patients and include migratory venous thrombophlebitis (Trousseau's syndrome), nonbacterial thrombotic (marantic) endocarditis with arterial emboli, and disseminated intravascular coagulation with hemorrhage, anemia, granulocytosis, and leukoerythroblastosis. Thrombotic disease complicating cancer is usually a poor prognostic sign. Cutaneous manifestations such as dermatomyositis and acanthosis nigricans are uncommon (1%), as are the renal manifestations of nephrotic syndrome and glomerulonephritis ($\leq 1\%$).

DIAGNOSING LUNG CANCER

Tissue sampling is required to confirm a diagnosis in all patients with suspected lung cancer. In patients with suspected metastatic disease, a biopsy of the most distant site of disease is preferred for tissue confirmation. Given the greater emphasis placed on molecular testing for NSCLC patients, a core biopsy is preferred to ensure adequate