Clinical Presentation of Lung Cancer

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9

Contents

9.1 Introduction

Lung cancer is usually recognized late in its natural history. Late recognition, which is the case in 80% of newly diagnosed patients with lung cancer, relates to disseminated and unresectable disease at presentation. Actually, despite major advances in biomedical technology the 5-year mortality rate from the day of its presentation approximates 87–90% [1–3]. The clinical presentation of lung cancer usually relates to the development of a new, or worsening of a preexisting clinical symptom or sign and, less frequently, to an abnormal chest roentgenographic shadow in an asymptomatic patient. Indeed, more than 90% of patients with lung cancer are symptomatic at presentation. Lung cancer symptoms are multiple and variable and can be the result of: (1) the local growth of the primary tumor, (2) its extension to the adjacent intrathoracic structures, (3) distant metastases, (4) nonspecific systemic effects, and (5) the immunologic response or the ectopic production of peptide proteins (hormones) by the same lung cancer or its metastases (paraneoplastic syndromes) [4, 5].

9.2 Symptoms and Signs due to Local Growth (Bronchopulmonary) of the Primary Tumor

Cough, hemoptysis, dyspnea, and chest discomfort are common presenting symptoms in patients with lung cancer [6]. Cough is by far the most common local manifestation of lung cancer and is usually mildly productive or even dry. In some patients it may present as paroxysmal, while in a minority, those affected by a secretory bronchoalveolar carcinoma may be associated with bronchorrhea. Most patients with lung cancer also present with a chronic productive cough due to chronic bronchitis, and in these patients the initial manifestation of lung cancer development is a change in the character of cough or the appearance of blood-tinged sputum. Hemoptysis is a common presenting symptom, but is rarely severe. It is

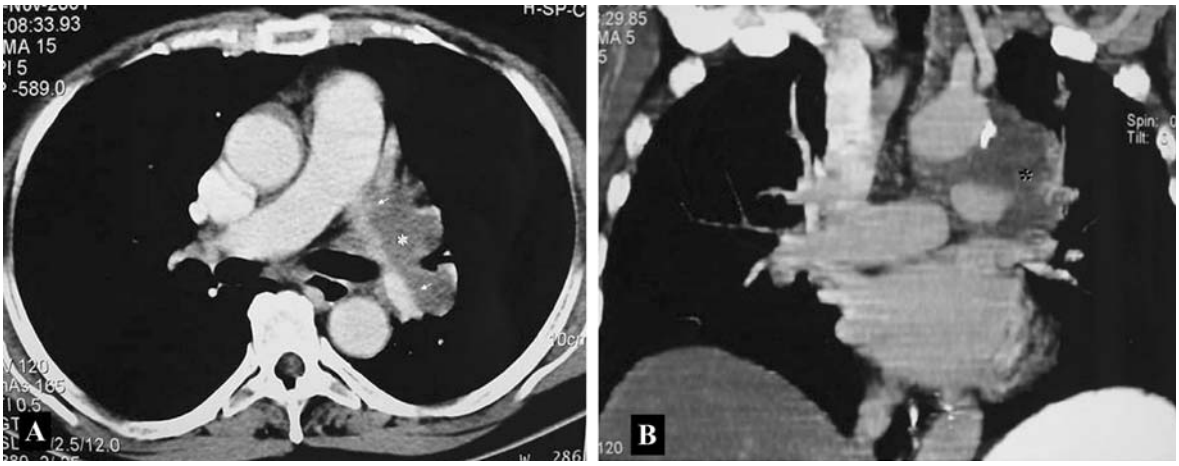

Fig. 9.1. A A contrast-enhanced spiral computed tomography (CT) scan showing the infiltration of the left pulmonary artery (*arrows*) by a central bronchogenic neoplasm (*asterisk*). **B** The coronary reconstruction film reveals better the encircling infiltration of the left pulmonary artery (*asterisk*). Reproduced courtesy of Dr. K. Malagari

an important sentinel sign in smokers and, if related to the development of lung cancer is usually associated with an abnormal chest roentgenogram. However, in the case of a normal chest roentgenogram, further diagnostic examinations are mandatory in the high-risk patient, including chest computed tomography (CT), bronchoscopy, and repetitive sputum cytology and close observation for several months [7]. In some patients the local development of lung cancer may lead to large mediastinal vessel invasion, including the pulmonary artery, its divisions, and others (Fig. 9.1 A and B). More frequently the local bronchial development of lung cancer leads to obstructive pneumonia. Many cases of obstructive pneumonia are sterile and the inflammatory reaction that leads to parenchymal consolidation is presumably due to retained secretions. However, the occurrence of fever is usually the result of a secondary infection and should be adequately treated. Pneumonia in high-risk patients, especially if it reoccurs, should be observed with suspicion for occult carcinoma and further diagnostic examinations should be requested. A local wheeze is a sign of localized bronchial stenosis and may be associated with unilateral hyperinflation in the chest roentgenogram obtained at full expiration. In such cases, further diagnostic examination is necessary to unmask the cancer. A recent appearance of dyspnea on exertion or even at rest may be related to the central (trachea or main bronchi) development of lung caner and in this case is commonly associated with wheeze. An ill-defined chest discomfort is not uncommonly associated with the development of lung cancer. Finally, in few cases the development of lung cancer heralds itself by the reactivation of old tuberculosis leading at the same time to diagnostic confusion and delay [8].

The local growth and the intrathoracic extension of the non-small-cell primary lung cancer according to the staging system developed by the American Joint commission on cancer classifies as follows [3, 9]: T (tumor) 1, tumor less than 3 cm in size, surrounded by lung or pleura; no tumor more proximal than the lobe bronchus; T2, tumor of more than 3 cm, involving the main bronchus at a distance greater than 2 cm from the carina, invading pleura, atelectasis or pneumonia extending to the hilum but not the entire lung; T3, tumor invading the chest wall, diaphragm, mediastinal pleura, pericardium, main bronchus at a distance of less than 2 cm from the carina, atelectasis or pneumonia of the entire lung; T4, tumor that invades the mediastinum, the heart, the great vessels, the trachea, the esophagus, the vertebral body, the carina (including separate tumor nodules), and malignant pleural effusion.

9.3 Symptoms and Signs due to the Intrathoracic Extension of the Primary Tumor

Intrathoracic extension of lung cancer, either directly by compression or invasion or via the lymphatics, produces a variety of symptoms and signs including the following characteristic syndromes.

9.3.1 Superior Pulmonary Sulcus Tumor, Pancoast Syndrome, and Horner's Syndrome

According to Pancoast's classic description, a lung cancer "at a definitive location at the thoracic inlet produces constant and characteristic phenomena of pain in the eight cervical and first and second thoracic trunk distribution, and Horner's syndrome" [10]. Pancoast tu-

Table 9.1. Common and rare conditions causing Pancoast's syndrome

Neoplasms	Infections	Miscellaneous
Lung cancer	*Staphylococcus aureus*, *Pseudomonas aeruginosa*	Cervical rib syndrome
Adenoid cystic carcinoma	Nocardiosis, Actinomycosis	Amyloidoma
Hemangiopericytoma	Tuberculosis	Thyroid cyst
Mesothelioma	*Pasteurella multocida*	Sympathetic dystrophy
Plasmocytoma	Hydatid cyst	
Lymphomatoid granulomatosis	Mucormycosis, Aspergilloma, *Cryptococcus neformans*	
Lymphoma non-Hodgkin	Mycotic aneurism	
Thyroid carcinoma		
Metastatic neoplasms		

mor is quite consistantly a lung cancer (other malignancies as well as inflammatory and infectious diseases are rare etiologic conditions; Table 9.1) [11] that develops peripherally at the apex of the upper lobes, at or near the superior pulmonary sulcus, and more commonly is a low-grade epidermoid bronchogenic carcinoma that grows slowly and metastasizes late (Fig. 9.2 A–C) [12]. Constrained by the narrow confines of the thoracic inlet, the developing carcinoma invades the lymphatics of the endothoracic fascia and involves by direct extension one or more of the following structures: the lower roots of the brachial plexus, the intercostals nerves, the stellate ganglion, the sympathetic chain, and the adjacent ribs and vertebrae. It's initial clinical presentation is pain localized to the shoulder and the vertebral border of the scapula; later the pain extends

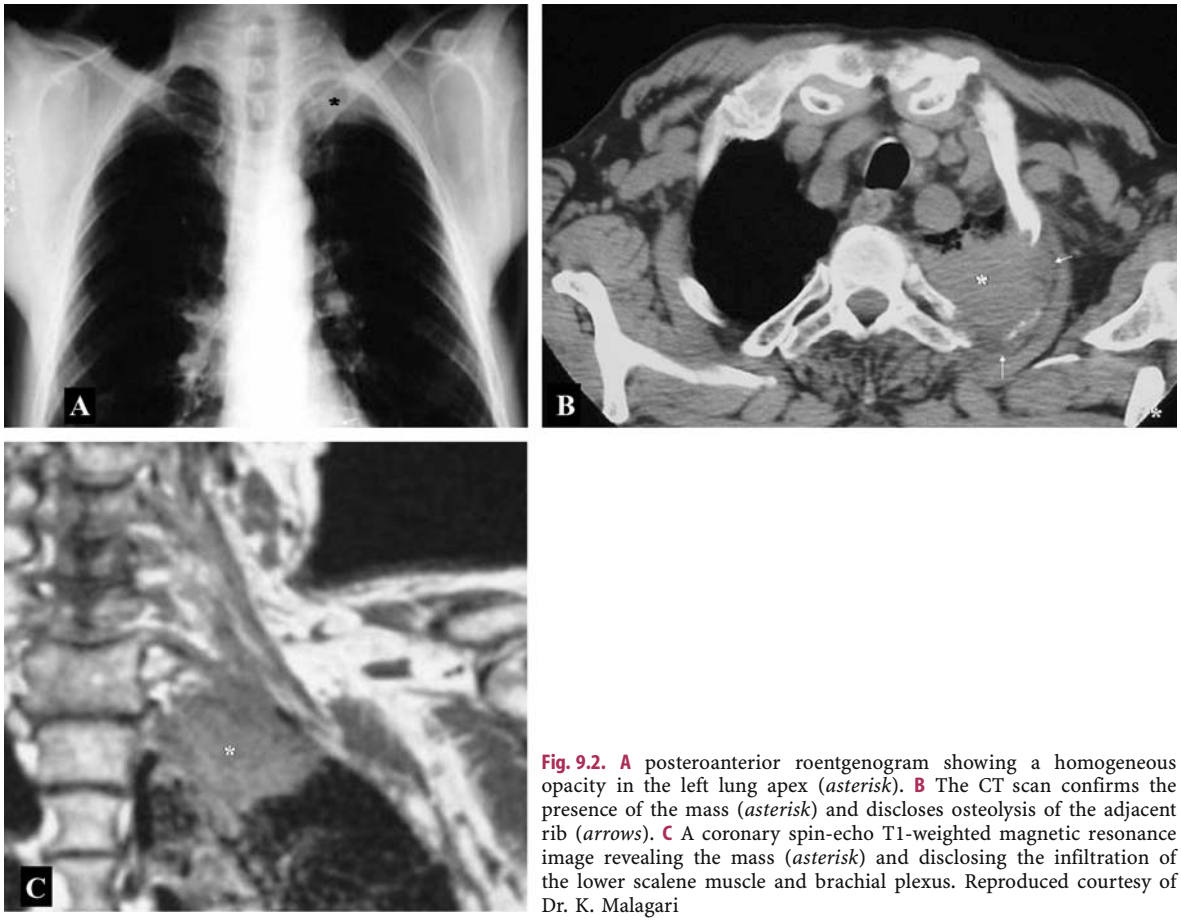

Fig. 9.2. **A** posteroanterior roentgenogram showing a homogeneous opacity in the left lung apex (*asterisk*). **B** The CT scan confirms the presence of the mass (*asterisk*) and discloses osteolysis of the adjacent rib (*arrows*). **C** A coronary spin-echo T1-weighted magnetic resonance image revealing the mass (*asterisk*) and disclosing the infiltration of the lower scalene muscle and brachial plexus. Reproduced courtesy of Dr. K. Malagari

down the arm toward the elbow, along the distribution of the ulnar nerve (T1 nerve root involvement) and subsequently to the ulnar surface of the forearm and the small ring fingers of the hand (C8 dermatome distribution). Weakness and atrophy of the muscles of the hand supervenes, as well as the loss of the triceps reflex. When the lung cancer invades the sympathetic chain and the stellate ganglion, Horner's syndrome (enophthalmos, pupillary constriction, palpebral ptosis, and anhidrosis) develops on the ipsilateral side of the face. Adjacent bone involvement increases the severity of pain. Furthermore, the invasion of the spinal canal and spinal cord leads to the signs and symptoms of spinal-cord compression syndrome. Infrequent manifestations include supraclavicular adenopathy, superior vena cava syndrome, and involvement of the phrenic or laryngeal nerves [11]. The vast majority of superior sulcus tumors are due to non-small-cell lung cancer and can be staged as T3N0M0 (stage IIB) or higher. T3 refers to the direct invasion of the chest wall and T4 to the direct invasion of the mediastinum, the great vessels, the esophagus, the trachea, the vertebral body, or the heart [13]. In a series reported from the MD Anderson Cancer Center at the University of Texas, 25% of patients with superior sulcus tumors were stage IIB (T3N0M0), 22% were stage IIIA (T1-3N2), and 53% stage IIIB (T4 or N3) [14]. Pretreatment evaluation in patients with Pancoast's lung cancer should include: (1) history and physical examination, (2) blood count and serum chemistries, (3) pulmonary function tests, (4) CT scan of the chest and the upper abdomen, (5) magnetic resonance imaging (MRI) in the case of brachial plexus symptomatology in order to assess local vessel involvement and determine resectability, (6) surgical assessment of the mediastinum (mediastinoscopy), or alternatively, via fluorodeoxyglucose-positron emission tomography (PET) scan, (7) CT scan or MRI of the head, and eventually (8) whole-body PET scan to rule out distant metastasis [13, 15]. A combined-(tri)-modality therapeutic approach (chemotherapy, radiotherapy, and after restaging, surgical resection provided an experienced surgeon is available) should be attempted in patients with locally extensive disease.

9.3.2 Superior Vena Cava Syndrome

The superior vena cava is a 6- to 8-cm long, thin-walled, low-pressure vessel that drains venous blood from the head, neck, upper extremities, and upper thorax to the heart. It extends from the junction of the right and left innominate veins to the right atrium. It is located in the middle mediastinum and is surrounded by the sternum, trachea, right bronchus, aorta, pulmonary artery, and the perihilar and paratracheal nodes. Several space-occupying lesions developing in the middle mediastinum may compress or invade the vessel, leading to blood flow reduction or complete obstruction. In such conditions, intravascular thrombosis quite constantly coexists. Superior vena cava syndrome is the clinical syndrome resulting from the homonymous vessel obstruction or the severe reduction of venous return from the head, neck, and upper extremities [16]. Clinically, it presents with head, facial, neck, upper thorax, and upper extremity edema and venous distension, headache, cyanosis, and the formation of an extensive collateral circulation. Bending forward or lying down

Table 9.2. Common and rare conditions causing superior vena cava syndrome

Neoplasms	Infections	Vascular conditions	Miscellaneous
Lung Cancer	Histoplasmosis	Thromboembolism	Fibrosing mediastinitis
Lymphomas, non-Hodgkin, Hodgkin	Tuberculosis	Catheter-related: e.g., pacemakers, defibrillators	Encapsulated pleural effusion
Plasmocytomas	Syphilis	Pericarditis	Biermer's disease
Metastatic cancers	Actinomycosis	Budd-Chiari syndrome	Hirschprung's disease
Sarcomas	Nocardia species	Aortic aneurism	Mediterranean fever
Castleman's disease	Aspergillosis	Arterial-venous fistulas	Retrosternal goiter
Teratoma, amartoma	Zygomycosis	Vasculitis	Sarcoidosis
Dermoid cyst	HIV infection	Hyperhomocysteinemia	Cystic fibrosis
Cystic hygroma	*Klebsiella pneumoniae*	Right subclavian aneurism	Postsurgery
Thymoma	Hydatid cyst	Innominate artery aneurism	Mustard operation
Thyroid carcinoma		Behcet's disease	
Atrial myxoma		Leukocytoclastic vasculitis	
Paraganglioma		Heparin-induced thrombosis	
Choriocarcinoma		Thoracic outlet syndrome	
Melanoma			
Lymphangioma			
Neurogenic tumor			
Lymphocytic leukemia			
Esophageal melanotic-Schwannoma			

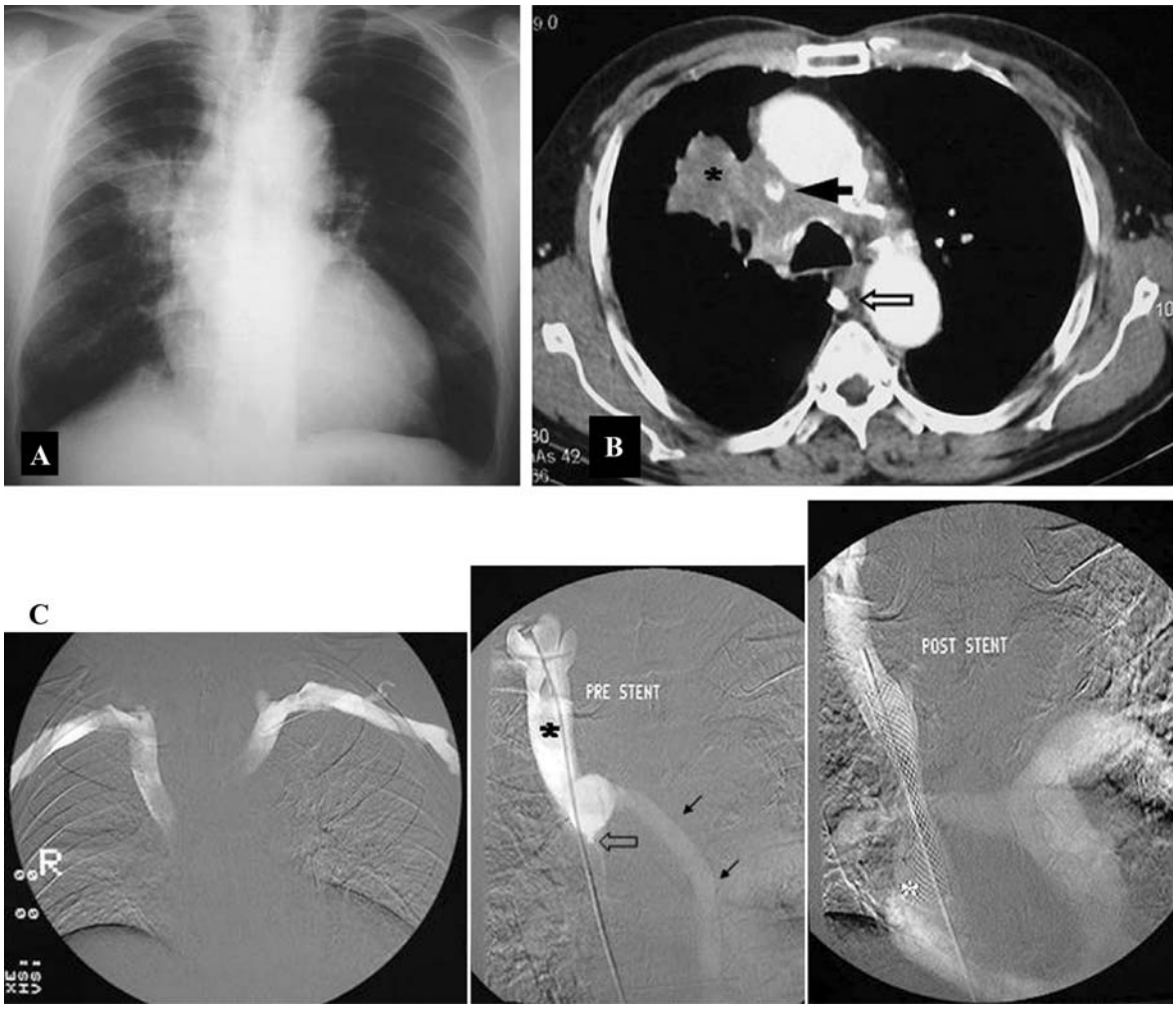

Fig. 9.3. **A** A posteroanterior chest roentgenogram showing an opacity of the right upper lobe with extensive basis in the mediastinum. **B** The contrast-enhanced spiral CT scan reveals a soft-tissue mass in the right upper lobe (*asterisk*) that circumscribes and compresses the superior vena cava (*arrow*). Also evident is the azygos dilation that is eventually related to the development of a collateral circulation (*open arrow*). **C** Sequential venous angiograms before (*left*), during (*middle*, *PRE STENT*), and after the placement of a stent (*right*, *POST STENT*). A subclavian venogram (*left*) reveals the complete obstruction of the superior vena cava (it is evident only in the lower course of the brachiocefalic veins). In the next image (*middle*) a balloon-tipped catheter has been introduced through the lower vena cava, the right atrium and the obstructive portion of the superior vena cava in the right brachiocefalic vein (*asterisk*). The concentric obstruction of the superior vena cava is clearly evident (*open arrow*). Also evident is reverse flow in the azygos vein (*arrows*). In the next image (*right*) the patient underwent balloon dilatation of the superior vena cava stenosis followed by placement of a metallic mesh stent. The stent is positioned in the brachiocefalic vein and superior vena cava. The restoration of normal flow in the superior vena cava and opacification of the right atrium are clearly seen (*asterisk*), as is that of the central pulmonary arteries. Reverse flow is no longer evident in the azygos vein. The patient experienced marked symptomatic relief following endovascular therapy. Reproduced courtesy of Dr. K. Malagari

aggravates symptoms and signs. Laryngeal edema and, in severe cases, stupor and coma may ensue. Lung cancer is by far the most common cause of the syndrome (70%), although several other conditions have been described in its etiology (Table 9.2). Because of the localization of the causative process in the mediastinum, superior vena cava syndrome may coexist with other mediastinal syndromes such as dysphagia, vocal hoarseness, and dyspnea due to large airways obstruction.

The severity of superior vena cava syndrome depends upon the rapidity of occlusion and collateral vessel development; the more acute the occlusion, the more severe the syndrome. Collateral venous return to the heart, in the case of obstruction, occurs through four principal pathways: (1) the azygous venous system, which include the azygous vein, the hemiazygous vein, and the connecting intercostal veins, (2) the internal mammary venous system plus the tributaries and the

secondary communications to the superior and inferior epigastric veins, and (3) and (4) the long thoracic venous system with its connections to the femoral and vertebral veins, respectively. In the absence of tracheal compression and airway compromise, superior vena cava syndrome is rarely an oncologic emergency [17]. In the majority of cases there is enough time to obtain an etiological diagnosis and decide upon adequate and specific management. Chemotherapy and radiotherapy are effective in relieving symptoms in lung-cancer-related superior vena cava syndrome. The insertion of stents may provide a more rapid relief from symptoms (Fig. 9.3 A–C) [18].

9.3.3 Recurrent Laryngeal and Phrenic Nerve Palsy

Compression, entrapment, or invasion of the recurrent laryngeal nerve by the primary cancer or its nodal metastases around the aortic arc, leads to hoarseness. Hoarseness is an uncommon sign at presentation and appears late in the natural history of the disease. Recurrent laryngeal nerve palsy predisposes to lung aspiration and is associated with ineffective ability to cough and expectorate. Rarely, recurrent laryngeal nerve palsy manifests with dysphagia both for solid and liquid foods, since this nerve contributes to the innervation of the cricoid muscles and the proximal esophagus.

Neoplastic involvement can also affect the phrenic nerve, leading to hemidiaphragmatic paresis or paralysis. Clinically, phrenic nerve palsy may be asymptomatic in patients with good respiratory reserve, or may manifest with dyspnea on exertion or even at rest in the respiratory-compromised patient. Chest roentgenogram shows hemidiaphragmatic elevation, while fluoroscopy or ultrasound examination during the sniff maneuver unequivocally poses the diagnosis by disclosing the paradoxical movement of the involved hemidiaphragm.

9.3.4 Chest Wall Invasion

Chest wall invasion refers to the direct involvement by the lung cancer in the rib cage, the vertebral bodies, the diaphragm, and the structures that form the anatomical limits of the superior pulmonary sulcus. Rib-cage and vertebral-body invasion leads to pain in the involved area that is usually dull, intermittent, and aching, lasting from minutes to hours. The invasion of the central dome of the diaphragm manifests with pain in the ipsilateral shoulder. Superior pulmonary sulcus carcinoma leads to the characteristic Pancoast's syndrome, as mentioned above. Limited and circumscribed chest wall invasion belongs to the T3 category, which also includes invasion of the mediastinal pleura or the parietal pericardium and is considered resectable by current surgical techniques (vertebral body invasion is considered T4 category).

9.3.5 Pleural Involvement

Lung cancer is the leading cause of malignant pleural effusion [19]. A pleural effusion is observed in 15% of patients at their first evaluation. However, during the course of the disease at least 50% of patients with disseminated disease will develop a pleural effusion. The mechanisms by which a lung cancer leads to pleural effusion are several and may be distinguished directly and indirectly [20]. Direct mechanisms include: (1) the pleural metastatic involvement that induces an increased pleural permeability, (2) the pleural metastatic involvement that induces obstruction of the lymphatic vessels and decreased pleural fluid drainage, (3) the mediastinal lymph node involvement that also leads to decrease pleural lymphatic drainage, (4) the thoracic duct interruption that leads to chylothorax, (5) the large bronchi obstruction that leads to atelectasis and decreases the intrapleural pressure, thus increasing fluid formation, and finally (6) the pericardial effusion that may increase hydrostatic pressures in both the systemic and pulmonary circulation. Indirect mechanisms of pleural effusion formation in lung cancer patients include: (1) hypoproteinemia, (2) postobstructive pneumonitis, (3) pulmonary embolism, and (4) postradiation therapy. When symptomatic, pleural involvement manifests itself with dyspnea, pain, and cough. In patients with lung cancer, pleural effusion is an exudate, and in the large majority of cases indicates that the patient is not curable with surgery [20]. In cytology-negative pleural effusions, a thoracoscopy and a CT scan of the chest to evaluate the mediastinal nodes are necessary to consider operability. Occasionally, pleural involvement in lung cancer may manifest with spontaneous pneumothorax.

9.3.6 Heart Involvement

The mechanisms by which lung cancer leads to pericardium and heart involvement are several and include: (1) retrograde lymphatic migration of tumor cells, (2) hematogenous dissemination, and (3) direct tumor invasion. The pericardial neoplastic involvement usually presents as pericardial effusion, cardiac tamponade, or constrictive pericarditis [21]. Malignant pericardial effusion is often asymptomatic and discovered by imaging or at autopsy. When clinically evident, it most commonly manifests with the onset of an arrhythmia (sinus tachycardia or atrial fibrillation) and enlargement of the cardiac shadow in the chest roentgenogram, or with

signs of congestive heart failure or tamponade. Unlike pericardial neoplastic involvement, myocardial neoplastic involvement is more frequently silent and discovered only at autopsy or, less often, during surgery. Echocardiography is the primary imaging tool used to establish the presence of a pericardial effusion. It is also useful to quantify the volume of the neoplastic effusion and to evaluate its hemodynamic effects, particularly the presence of tamponade or constrictive pericarditis. Malignant pericardial effusion with mild hemodynamic compromise may be treated conservatively with careful monitoring, repeated echocardiography, fluid administration, and in the presence of a definitive histological diagnosis, specific therapy aimed at the underlying malignancy [22]. Cardiac tamponade and overt hemodynamic compromise requires removal of the fluid by percutaneous catheter pericardiocentesis [23, 24]. When the malignant pericardial effusion does not respond, substernal pericardiostomy or surgical-limited or radical pericardiectomy may be attempted [23].

9.3.7 Esophageal Involvement

Esophageal displacement and deformity is common in patients with lung cancer and may be related to the primary tumor or, more commonly, to its nodal metastases. However, displacement and deformity are not enough to lead to obstructive symptoms and clinically evident dysphagia. Esophageal invasion by the primary tumor, which more commonly occurs when this develops in the left main stem bronchus, is more likely to lead to obstruction, thus manifesting with dysphagia. In rare cases, a bronchoesophageal fistula may develop and manifests with cough upon swallowing or aspiration.

The American Joint Commission on Cancer staging system classifies the nodal involvement of the non-small-cell primary lung cancer as follows [3, 9]: N (node) 1, involvement of the ipsilateral peribronchial or hilar nodes and intrapulmonary nodes by direct extension; N2, involvement of ipsilateral mediastinal or subcarinal nodes; N3, involvement of contralateral lung nodes or any supraclavicular node.

9.4 Symptoms and Signs due to Distant Extrathoracic Spread of the Primary Tumor

Widespread hematogenous dissemination occurs early in lung cancer patients. Metastases may involve any organ or system [25], and are present in approximately one-third of these patients at presentation. Small-cell and poorly differentiated carcinomas present with a higher tendency to metastasize, followed by the adenocarcinomas, large-cell carcinomas, and squamous cell carcinomas. The most common sites of distant metastases are: (1) the brain, where metastases may manifest with symptoms and signs of increased intracranial pressure and/or neurologic deficits, (2) the bones, where symptoms include pain and pathological fractures, (3) the liver, where metastases may manifest with fever, biochemical abnormalities, pain, and general symptoms such as anorexia, weakness, and weight loss, (4) the spinal bones and the relative epidural tissues, where metastases manifest with spinal cord compression syndromes, and (5) the adrenal glands, which are clinically silent.

The distal metastases of the non-small-cell primary lung cancer according to the staging system developed by the American Joint commission on cancer are classified as stage IV disease [3, 9].

Summarizing the case for the non-small-cell lung cancer, the current classification states as: (1) local disease, IA if T1N0M0, IB if T2N0M0, and IIA if T1N1M0, (2) locally advanced disease, IIB, if T2, N1,M0 or T3N0M0, IIIA if T1N2M0, or T2N2M0, or T3N1M0, or T3N2M0 and IIIB if any TN3M0, and (3) advanced disease, IIIB if T4 any NM0, and IV if any T any NM1 [3, 9].

9.4.1 Nonspecific Systemic Effects Related to Lung Cancer

Systemic symptoms such as anorexia leading to weight loss and cachexia, and generalized malaise occur in at least 20% of patients with advanced disease and contribute considerably to poor performance status [26]. Tumor necrosis factor-α and related cytokines have been considered to be involved in the pathogenesis of this generalized tissue-wasting syndrome.

9.4.2 Paraneoplastic Endocrine Syndromes Associated with the Lung Cancer

A paraneoplastic syndrome is the constellation of symptoms and signs that appear in patients with malignancy unrelated to the local effects of the primary tumor or its metastases [5]. The pathogenetic mechanisms by which these syndromes occur are several and include the ectopic production of peptide proteins with hormonal activity, immunologic mechanisms, and other incompletely understood mechanisms. Paraneoplastic syndromes may affect virtually every organ system of the body, and in some cases herald the appearance or the recurrence of a cancer.

9.4.3 Ectopic Cushing's syndrome

A proportion estimated between 10 and 30% of Cushing's syndrome cases are caused by the ectopic production of adrenocorticotropic hormone (ACTH) by several neoplasms, and among them most commonly by lung cancer [5]. The normal human lung produces small amounts of the parent compound pro-opiomelanocortin (pro-OMCT), which is cleaved into several molecules including pro-ACTH and ACTH [27]. In the setting of the lung malignancy, most commonly in small-cell carcinoma or in carcinoid tumor, overexpression of the gene responsible for the production of the pro-OMCT may lead to clinically active levels of ACTH and the expression of the related syndromes. Clinically, ectopic Cushing's syndrome differs from the classic clinical expression of Cushing's disease (probably because of the presence of an aggressive malignancy) and manifests mainly with weight loss, peripheral edema, proximal myopathy, and moon face. Drowsiness, confusion, depression, and frank psychosis may also occur. Hypokalemia, alkalosis, and hyperglycemia are the most common biochemical abnormalities observed. Diagnostic validity for an ectopic Cushing's syndrome present the finding of elevated 24-h urinary free-cortisol levels, an elevated plasma cortisol level, and an elevated plasma ACTH that does not decrease after a high-dose dexamethasone suppression test, in the presence of malignancy. Ectopic Cushing's syndrome has been associated with decreased survival in lung cancer patients [28], decreased chemoresponsiveness, and an increase in chemotherapy-related complications including severe opportunistic infections [5]. Effective treatment of the underlying tumor may contribute to improvement of the clinical picture for these patients. If this is not feasible and the patients experience significant clinical effects or deterioration, steroid-synthesis inhibitors, such as aminoglutetimide, mitotane, metyrapone, and ketoconazole, or ACTH-production suppressors, such as the somatostatin analogue octreotide, may offer some benefit. Bilateral adrenalectomy has also been attempted in severe cases.

9.4.4 Syndrome of Inappropriate Antidiuretic Hormone

The antidiuretic hormone (ADH) that is produced in the hypothalamus and secreted by the posterior pituitary gland is involved in the maintenance of extracellular fluid homeostasis. The ectopic secretion of clinically significant levels of ADH by lung cancer (most commonly small-cell carcinoma) manifests with hyponatremia and "inappropriate" natriuresis. When severe enough, it presents clinically with mental status changes, confusion, lethargy, seizures, and coma [5, 29]. The syndrome of inappropriate ADH is diagnosed when hyponatremia and decreased plasma osmolality coexist with "inappropriate" urine osmolality, in the presence of continued urinary sodium excretion. The syndrome resolves with chemotherapy for small-cell lung cancer and reappears when the cancer reoccurs. Specific measures for the treatment of severe hyponatremia include fluid restriction and the administration of demeclocycline, a drug that interferes with the activity of ADH at the renal collecting duct. In the case of severe symptomatic hyponatremia the administration of hypertonic saline and furosemide may become necessary. The rapid correction of hyponatremia should be obviated since this may lead to central pontine myelinolysis.

9.4.5 Hypercalcemia

Hypercalcemia occurs in approximately 1% of patients with lung cancer at presentation, but may affect up to 40% of patients at some point in their clinical course [5]. Hypercalcemia is due to either osteolytic bone destruction or ectopic hormone production. Hormonal hypercalcemia is the most common paraneoplastic syndrome in lung cancer patients (mainly squamous cell) and is related to the ectopic production of parathyroid hormone-related peptide (PTHrP) by the tumor. PTHrP is a 141-amino-acid protein that has parathyroid-hormone-like action that is mediated through its N-terminal sequences, which show some limited sequence homology with the hormone. The clinical picture of the syndrome includes neurological and gastrointestinal manifestations as well as dehydration. Fatigue, irritability, confusion, headache, drowsiness, lethargy, and coma may simulate cerebral metastases. Abdominal pain, anorexia, nausea, and vomiting are related to the gastrointestinal effects of the ectopic hormone. Occasionally, renal tubular damage due to hypercalcemia may lead to hypokalemic alkalosis. The rapid onset as well as the absence of nephrocalcinosis and ectopic soft-tissue calcifications may help to distinguish this disorder from primary hyperparathyroidism. Treatment of cancer-related hypercalcemia is mandatory, regardless of symptoms, when serum calcium is above 3.5 mmol/l (14 mg/dl) and includes vigorous intravenous hydration with normal saline and after with volume repletion loop diuretics. Biphosphonates (pamidronate), which act by reducing osteoclastic bone resorption, is the most effective specific treatment. Alternative drugs include gallium nitrate, calcitonin, and plicamycin. Radical lung cancer resection may resolve hypercalcemia in some patients.

9.4.6 Carcinoid Syndrome

Carcinoid syndrome was first described 44 years ago [30] and since then several cases have been described, mainly in patients with small-cell or undifferentiated lung carcinoma. The neoplasm secretes either 5-hy-

droxytryptamine or 5-hydroxytryptophan, and high levels of 5-hydroxyindoleacetic acid can be detected in the urine. The syndrome is characterized clinically by episodes of explosive diarrhea, cutaneous flushing, tachycardia, anorexia, and weight loss. The expression of this syndrome coexists with the presence of multiple liver metastases, as is the case with the gastrointestinal and pulmonary carcinoid tumors.

9.4.7 Miscellaneous

Secretion of human chorionic gonadotropin accompanied with relative clinical signs and symptoms is rare in lung cancer patients and occurs mainly in large-cell carcinoma. Affected men present with gynecomastia, testicular atrophy, and a high-pitched voice. Calcitonin production is common in patients with lung cancer. It usually remains an asymptomatic biochemical abnormality.

9.4.8 Paraneoplastic Neurologic Syndromes

Paraneoplastic neurologic syndromes may affect any component of the nervous system from the central nervous system to the striated muscles and present with an extensive list of clinical syndromes. These syndromes may develop well before lung cancer is clinically and roentgenologically evident, and may present an independent clinical course from the primary disease. Most of the paraneoplastic neurological syndromes associated with lung cancer appear to share a common autoimmune pathogenetic mechanism related to the fact that lung cancer and the nervous system have common antigens and may become the target of autoantibodies [31]. In recent years several autoantibodies have been identified in patients with neurologic paraneoplastic syndromes recognizing nuclear and cytoplasmic antigens of neurons in the brain, spinal cord, and ganglia. The association between paraneoplastic neurologic syndrome and a specific antinuclear autoantibody, type-1 antineuronal nuclear antibody (ANNA-1, or anti-Hu) has been described in subacute sensory peripheral neuropathy and paraneoplastic encephalomyelitis. Autoantibodies against retinal antigens have been associated with cancer-associated retinopathy and autoantibodies against P/Q-type voltage-gated calcium channels have been associated with Lambert-Eaton myasthenic syndrome. Small-cell lung cancer is the most common type of lung cancer associated with these syndromes. After studying autoimmune-mediated paraneoplastic neurologic syndromes, it soon became evident that neither removal of the autoantibodies (e.g., by plasma exchange) nor suppression of the inflammation with specific cytotoxic drugs affected the clinical course of this neurological disorder. This might be related to the fact that damage is rapid and irreparable, or that autoantibodies are produced locally in the neural tissue and not removed by plasma exchange.

9.4.9 Paraneoplastic Encephalomyelitis and the Anti-Hu Antibody Syndrome

Encephalomyelitis may involve several areas of the nervous system, producing several neurological syndromes such as: (1) paraneoplastic limbic encephalitis due to involvement of the limbic region, presenting with mood and behavior changes, memory loss progressing to dementia, and seizures, (2) paraneoplastic cerebellar degeneration due to the involvement of the cerebellum, presenting with ataxia, nystagmus, dysarthria, and diplopia, and ends by limiting the ability of the patient to ambulate, (3) autonomic neuropathy due to the involvement of the autonomic nervous system, presenting with symptoms of autonomic dysfunction such as orthostatic hypotension, neurogenic bladder, and intestinal pseudo-obstruction (Ogilvies's syndrome), and (4) opsoclonus-myoclonus paraneoplastic syndrome. Anti-Hu antibody syndrome is known as the encephalomyelitis and sensory neuropathy syndrome associated with the type-1 antineuronal nuclear autoantibody ANNA-type1 or anti-Hu.

9.4.10 Cancer-Associated Retinopathy

Cancer-associated retinopathy is rare and presents with rapid vision loss, night blindness, color loss, and central or ring scotomas. It is associated with autoantibodies against several retinal proteins.

9.4.11 Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome is the most common and the better-studied neurologic paraneoplastic syndrome, with a prevalence of 3% in patients with small-cell lung cancer. This syndrome is mainly characterized clinically by proximal muscle weakness that is more prevalent in the lower extremities, fatigue, and depression of the deep tendon reflexes. Lambert-Eaton myasthenic syndrome is associated with autoantibodies against P/Q-type voltage-gated calcium channels. A transient increase in strength with repetitive action, lack of palpebral muscle involvement, and failure to improve with the administration of anticholinesterases help in the differential diagnosis from myasthenia gravis.

9.4.12 Cutaneous Paraneoplastic Manifestations

Lung cancer is occasionally associated with a variety of cutaneous paraneoplastic manifestations including: (1) acquired hypertrichosis lanuginosa, an excess growth of fine lanugo hair on the hair-bearing surfaces of the body, (2) Bazex's disease, an erythematous hyperkeratosis with scales and pruritus on the palms and soles, (3) erythema gyratus repens, consisting of a marbled erythematous swirling and a thin covering of scale over the trunk, axilla, and groin, (4) Leser-Trelat syndrome, which is characterized by the sudden appearance of a large crop of hyperpigmented seborrhoeic keratoses, (5) acanthosis nigricans, a bilaterally symmetric hyperkeratosis and hyperpigmentation of the skin that mainly involves the flexural and intertriginous areas, and several other, less commonly occurring manifestations [2, 4, 32]. Cutaneous paraneoplastic manifestations may coincide, follow, or antedate the diagnosis of lung cancer, or herald its recurrence. Since they may be the presenting sign of an occult carcinoma, recognition of their features is of paramount importance for early detection, although their presence is often associated with a poor prognosis.

9.4.13 Coagulopathies and Hematologic Manifestations

Several hematologic manifestations may occur during the natural history of lung cancer, including: (1) normochromic, normocytic or hypochromic, microcytic anemia, (2) neutrophilic leukocytosis and lymphocytopenia, (3) leukemoid reactions, (4) peripheral eosinophilia either associated or not with eosinophilic pulmonary infiltrates (eosinophilic pneumonia), (5) thrombocytosis, (6) thrombocytopenia and purpura, and (7) hemolytic anemia associated with disseminated intravascular coagulation.

Migratory thrombophlebitis (Trousseau's sign) and thromboembolic disease have been well documented in patients with lung cancer [33]. Thrombophlebitis is typically migratory, may involve any vessel including unusual sites, and tends to be resistant to anticoagulant treatment. Occasionally, thrombophlebitis, either with or without pulmonary embolism, constitutes the first manifestation of an occult lung carcinoma.

Thrombotic nonbacterial (marantic) endocarditis is a rare and late manifestation in lung cancer. It involves mainly the valves of the left side of the heart and presents with emboli to the brain or other organs.

9.4.14 Paraneoplastic Rheumatic Syndromes

Lung cancer is occasionally associated with a variety of rheumatological syndromes, including dermatomyositis/polymyositis, vasculitis, and carcinoma polyarthritis [34, 35]. Paraneoplastic rheumatic syndromes may coincide, follow, or antedate the diagnosis of lung cancer, or herald its recurrence [36].

9.4.15 Renal Manifestations

Both glomerulonephritis and nephrotic syndromes have occasionally been associated with lung cancer and are recognized as paraneoplastic syndromes.

9.4.16 Pierre Marie-Bamberger syndrome (Secondary Hypertrophic Osteoarthropathy)

Hypertrophic osteoarthropathy is characterized by the coexistence of finger clubbing, subperiosteal new bone formation, mainly along the long bones of the extremities, and arthritis. Finger clubbing can occur as an isolated manifestation in lung cancer patients. Hypertrophic osteoarthropathy is one of the most commonly occurring paraneoplastic syndromes in lung cancer and is usually observed in squamous cell and adenocarcinomas, while it is extremely rare in the small-cell carcinoma. Finger clubbing is related to the local vascular neoformation in the nail bed and the volar pad of the distal phalanx of the digits. The pathogenesis of hypertrophic pulmonary osteoarthropathy is associated with the presence of megakaryocytes and platelet clumps that find access at the distal arterial (digital) circulation through right to left shunting within the pulmonary circulation. Localized neovascular formation and proliferation is associated with platelet-induced endothelial activation and the production in the local circulation of growth factors such as platelet-derived growth factor and others [37, 38]. Joint manifestations vary from arthralgia to painful arthritis involving the knees, ankles, and wrists. Isolated clubbing is usually asymptomatic and is often first noted by the physician. In order to effectively identify clubbing, a value of the digital profile angle greater than 180° and a phalangeal depth ratio greater than 1 are necessary [39]. Roentgenologic findings include periosteal thickening of the long bones, soft-tissue swelling, and high radioactive tracer uptake along the involved bones (Fig. 9.4). The bony alterations at the distal phalanxes and on the periostium of the long bones of the extremities may remain indelible several centuries after the death of the individual [40].

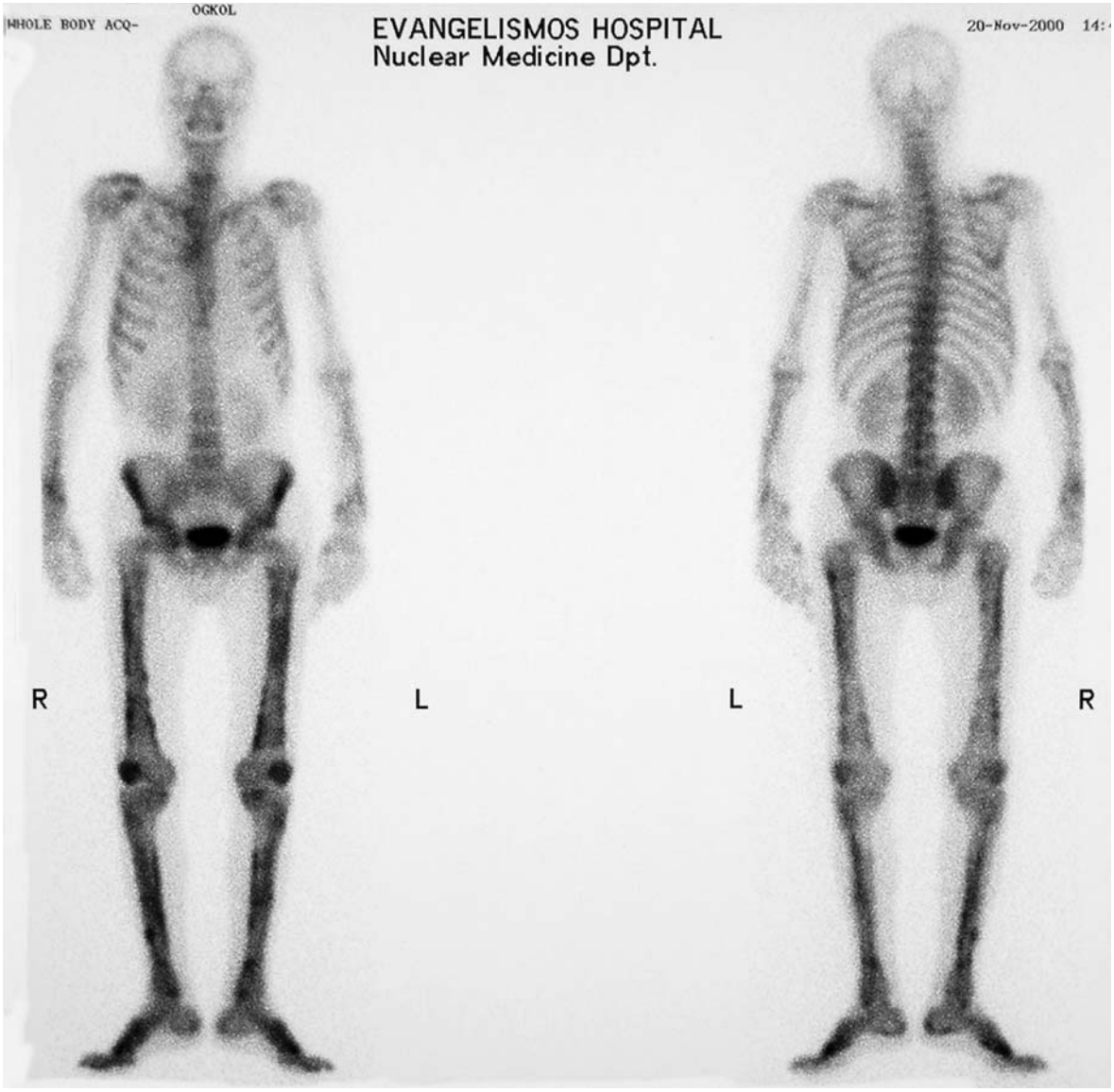

Fig. 9.4. Pierre Marie-Bamberger syndrome (secondary hypertrophic osteoarthropathy) in a patient with squamous lung cancer. The high uptake of radioactive tracer is clearly seen along the long bones of the extremities and the pelvis. *R* Right side, *L* left side. Reproduced courtesy of Dr. Ph. Rondogianni

Key Points

- Lung cancer is usually recognized late in its natural history. Late recognition relates to disseminated and unresectable disease at presentation.
- The clinical presentation of lung cancer usually relates to the development of a new, or worsening of a preexisting clinical symptom or sign and, less frequently, to an abnormal chest roentgenographic shadow in an asymptomatic patient.
- Lung cancer symptoms are multiple and variable and can be the result of the local growth of the primary tumor, its extension to the adjacent intrathoracic structures, or its distant metastases.
- Nonspecific systemic effects, and symptoms due to an immunologic response to or ectopic production of peptide proteins (hormones) by the same lung cancer or its metastases (paraneoplastic syndromes) may be present.
- Paraneoplastic syndromes may coincide, follow, or antedate the diagnosis of lung cancer, or herald its recurrence.

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