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95 PULMONARY COMPLICATIONS OF ENDOCRINE DISEASES

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INTRODUCTION

Common endocrine disorders may affect the respiratory system in a variety of ways, from an increased risk of specific infections in patients with diabetes to upper airway compression in patients with goiter. There have been many studies of pulmonary physiology in patients with endocrine disorders, some of which have revealed clinically significant functional abnormalities. In other studies, however, physiologic abnormalities have not translated into clinical dysfunction, but they have helped add to our understanding of lung parenchymal growth and development, response to extrathoracic influences, and perhaps even aging. This chapter reviews the effects of various endocrine abnormalities on the pulmonary system.

DIABETES MELLITUS

The prevalence of diabetes is continuing to soar; in 2012, 29.8 million Americans, or 9.3% of the population, were diabetic.[1] The obesity epidemic appears to have largely driven the substantial increase in the prevalence of type 2 diabetes (the most common subset of diabetes mellitus) in recent decades. In addition to genetic predisposition, obesity, and other factors such as diet and inflammatory mediators, active cigarette smoking is associated with the development of insulin resistance and type 2 diabetes.[2-4] The reason for this association has yet to be elucidated, although nicotinic acetylcholine receptors are expressed on pancreatic islet cells[5] and nicotine exposure has been associated with beta cell dysfunction and increased beta cell apoptosis.[6] Although less dramatic, there has also been an increase in the incidence of type 1 diabetes mellitus in the United States and worldwide.[7,8] Type 1 diabetes results from autoimmune destruction of pancreatic beta cells in genetically susceptible patients, most likely triggered by environmental agents. The genetic basis of autoimmune type 1 diabetes has now been largely determined, and there are some shared genetic associations with known atopy-related traits.[9]

The relationship between asthma and diabetes is less clear. Asthma, diabetes, and obesity are common, complex disorders for which the prevalence among youth has increased since the 1990s. In a large observational trial,[10] the prevalence of asthma was 10% among persons younger than 20 years old with type 1 diabetes and 16.1% among youth with type 2 diabetes, and differed according to race/ethnicity. Young persons with asthma were more likely to have poorer glycemic control and higher *body mass index* (BMI) values, particularly in the group with type 1 diabetes. In the group with type 2 diabetes, more than 90% were overweight or obese, which may account for why BMI did not correlate with asthma in this group.

In terms of *chronic obstructive pulmonary disease* (COPD), the Offspring Cohort of the Framingham Heart Study[11] did not show an association between the diagnosis of diabetes and COPD, nor did diabetes seem to accelerate COPD in smokers. However, in patients hospitalized with COPD exacerbations, there is a high prevalence of comorbid diseases, including diabetes mellitus; of the patients hospitalized with COPD in a large multicenter study, 35.8% had diabetes.[12] In a large population-based cohort study[13] of more than 350,000 patients with COPD or asthma, the use of inhaled corticosteroids was associated with an increased risk of requiring initial drug therapy for diabetes and an increased risk of requiring insulin in patients previously treated with oral antidiabetics over the 5-year observation period, with the caveat that diabetes mellitus prevalence increases with age. While a mainstay of treatment of asthma, inhaled corticosteroids are recommended in COPD patients for those who have more severe disease or who have frequent exacerbations[14] and should not be prescribed unless warranted.

As for pulmonary function findings, a meta-analysis[15] collectively representing the data from more than 3000 subjects with no prior pulmonary disease found that the presence of diabetes was associated with a mild to modest impairment in pulmonary function (Table 95-1). The pattern was restrictive with a mild decrease in diffusing capacity for carbon monoxide and was irrespective of BMI, smoking, diabetes duration, and HbA1c levels. In subanalyses, the association seemed to be more pronounced in type 2 diabetes than in type 1 diabetes. These mild functional abnormalities—generally well within 80% of the reference value[16]—have been ascribed to premature aging of the lungs in a fashion similar to nonenzymatic protein glycosylation and microangiopathic changes that develop in many affected organs in patients with diabetes.[17] In summary, diabetes mellitus (in the absence of cystic fibrosis) may cause a mild decline in pulmonary function measurements, but does not appear to cause clinically significant pulmonary impairment, and routine pulmonary function testing in patients with diabetes is not warranted.

Compared with patients with cystic fibrosis alone, patients with cystic fibrosis–related diabetes had a higher rate of pulmonary infection with multiple antibiotic-resistant

Table 95-1 Pulmonary Complications of Diabetes Mellitus

Restrictive pattern on pulmonary function tests (mild)
Left ventricular dysfunction
Pleural effusions
Obstructive sleep apnea
Infections
Poor outcome from community-acquired pneumonia
Infections *Legionella* pneumonia Increased risk of aspiration pneumonia Zygomycetes (mucormycosis) Tuberculosis

Pseudomonas aeruginosa[18] and a higher rate of treatment failure.[19] Whether cystic fibrosis–related diabetes is associated with a higher rate of decline in pulmonary function compared with cystic fibrosis subjects without diabetes is unclear, because study outcomes have been mixed.[20,21]

Cardiovascular and end-organ dysfunction develop in many patients with diabetes because of its chronic metabolic derangements. Cardiovascular factors appear to contribute more than pulmonary factors to impaired physical performance in patients with diabetes. In addition to the increased risk for cardiovascular events in patients with diabetes, there is an increased frequency of heart failure not explained by hypertension or coronary artery disease.[22] Left ventricular systolic and diastolic dysfunction with exercise appears to be more common in patients with insulin-dependent diabetes than in those without diabetes.[23] In addition, when compared with patients with similar degrees of left ventricular dysfunction, exercise limitation and pleural effusions are more common in patients with diabetes.[24]

Active cigarette smoking is a risk factor for the development of type 2 diabetes.[25] Smoking cessation has important health benefits in terms of risk reduction for a wide variety of complications, including cardiovascular events. However, weight gain is common with smoking cessation, typically 4 to 5 kg in the first year after cessation.[26,27] In a large prospective multisite cohort study[28] of subjects who did not have diabetes at baseline, subjects who newly quit smoking had more significant increases in weight, waist circumference, and fasting glucose levels and a higher risk for development of type 2 diabetes than did persons who never smoked. These metabolic changes were more common in older men with heavy smoking habits before quitting; the increased risk for diabetes peaked within 3 years after quitting. Despite weight gain with smoking cessation, overall cardiovascular events decreased in patients who quit smoking.[29] In summary, both active smoking and the post-cessation period are associated with an increased risk for type 2 diabetes. Targeting the immediate post-quit period with more aggressive weight management and lifestyle changes in higher risk patients may be warranted.

Acute respiratory distress syndrome (ARDS) has been reported as a complication of diabetic ketoacidosis.[30] But diabetes mellitus—excluding diabetic ketoacidosis—is not associated with increased risk for development of ARDS compared to patients without diabetes, and it may even be protective.[31,32] Diabetes has been associated with a higher risk for development of idiopathic pulmonary fibrosis.[33,34]

Newborn babies of diabetic mothers are at increased risk for macrosomia and preterm delivery[35,36]; infants born to mothers with poor self-care are at greatest risk.[36] However, with good maternal metabolic control and accurate estimations of gestational age, most pregnant women with diabetes can deliver at or near term without associated respiratory distress syndrome.[37,38]

Obesity is a risk factor for both type 2 diabetes mellitus and for obstructive sleep apnea. (See Chapter 88 for a full discussion of obstructive sleep apnea.) The prevalence of obstructive sleep apnea in patients with type 2 diabetes has been reported as 23% to 36%, and in patients with BMI greater than 35 kg/m^2, prevalence has been reported to be as high as 70%.[39,40] Higher apnea-hypopnea indexes in diabetic patients with obstructive sleep apnea are associated with poorer glucose control.[41] In addition, obstructive sleep apnea may impose a stress that increases sympathetic neural output during sleep, which in turn contributes to insulin resistance[42]; moreover, oxygen desaturation is specifically associated with insulin resistance in severely obese patients.[43] In patients with diabetes, obstructive sleep apnea may increase the risk for diabetic peripheral neuropathy, perhaps due to increased oxidative stress and impaired microvascular regulation.[44] Continuous positive airway pressure therapy in diabetic patients with obstructive sleep apnea may not improve metabolic control unless there is also weight loss, at least in short-term follow-up.[45]

Patients with diabetes are at increased risk for upper and lower airway infections, and are particularly predisposed to infection with Zygomycetes (mucormycosis), a group of infections caused by fungi in the *Mucor, Rhizopus,* and *Cunninghamella* genera. Angioinvasion is a hallmark of infections with mucormycosis. These ubiquitous saprophytic fungi are found in soil and decaying vegetation; infection is caused by inhalation of spores, hence the predilection for paranasal sinus and lung disease. Infection typically develops during or after an episode of diabetic ketoacidosis, perhaps because the fungi have an enzyme, ketone reductase, which favors growth in an acidic, hyperglycemic environment. Most patients have some underlying predisposition, of which diabetes mellitus is the most significant.[46] Five infectious manifestations have been described: rhinocerebral, pulmonary, disseminated, cutaneous, and gastrointestinal. Rhinocerebral infection is the most common form, especially in patients with diabetes. Presentation includes sudden periorbital or paranasal swelling and pain, bloody nasal discharge, and black necrotic nasal mucosa. *Computed tomography* (CT) findings are mostly nonspecific, but can include an air crescent sign (rim of air between necrotic lung and surrounding parenchyma) as well as the halo sign (rim of surrounding ground-glass opacities around dense consolidation).[47] Treatment requires control of the diabetes, antifungal therapy, and often aggressive surgical debridement. Mortality remains high, especially in patients with intracranial involvement.[48]

Pulmonary mucormycosis mimics invasive aspergillosis and is found mostly in patients with diabetes, hematologic malignancy, or organ transplantation or in patients on glucocorticoid or deferoxamine therapy. Inhaled mold spores

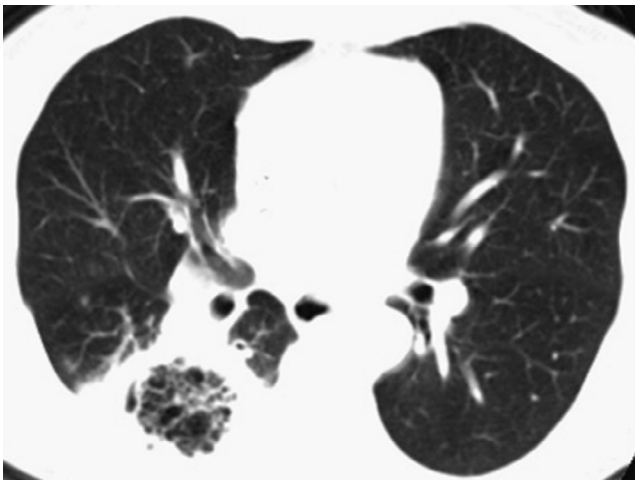

Figure 95-1 Mucormycosis. Radiograph showing pulmonary infarction of the right lower lobe in a diabetic patient with pulmonary mucormycosis.

penetrate bronchiole walls, invade arterioles, and cause thrombosis and ischemia (Fig. 95-1). Nonspecific cough, fever, and pleuritic chest pain develop. Hemoptysis may develop in one fourth of cases and can be massive.[49] The most common chest radiographic pattern is consolidation; cavitation is seen in about one third of patients,[50] and adenopathy and pleural effusions may also be present but are less common. Patients with diabetes appear to have a predilection for endobronchial disease; however, sputum culture appears to have a very low yield for diagnosis. For specimens obtained at bronchoscopy, histopathologic examination appears to be more sensitive than fungal cultures. Treatment requires antifungal therapy (see Chapter 38) and, if localized, surgical resection. Bronchial stenosis is a potential sequela.

Diabetes mellitus is an independent risk factor for drug-sensitive[51-55] and multidrug-resistant tuberculosis.[38] A review of 13 observational studies revealed that diabetes mellitus was associated with an increased risk for tuberculosis (relative risk, 3.11; 95% CI 2.27-4.26),[53] an association that is supported by studies of diabetic children in South Africa and adults in Brazil.[55] Patients with tuberculosis and diabetes tended to be older, were more likely to yield positive smears for acid-fast bacilli, and had a higher mortality than patients with tuberculosis without diabetes.[55] The radiographic location of tuberculosis in diabetes (i.e., upper or lower lobe predilection) depends on the case series; patients with diabetes and tuberculosis appear to have a higher rate of cavitation.[52,56] Treatment of latent tuberculosis in patients with diabetes with either a positive purified protein derivative skin test of greater than 10 mm of induration[57] or a positive interferon-gamma release assay is currently recommended.

Bacterial pneumonia may or may not be more frequent in patients with diabetes. In a study of more than 4000 elderly inhabitants in one township, diabetes mellitus was not an independent risk factor for community-acquired pneumonia.[58] Study findings are mixed as to whether diabetes portends a poorer outcome in persons in whom pneumonia develops.[59-61] Diabetes does not appear to be an independent risk factor for either health care–associated pneumonia or ventilator-associated pneumonia.[62] Given the demonstrated efficacy of pneumococcal vaccine and the increasing prevalence of penicillin resistance in pneumococcal strains, pneumococcal vaccination is recommended for virtually all people with diabetes. Diabetes appears to be a risk factor for *Legionella* pneumonia[63] and is associated with high mortality in infected persons.[64] Pharyngeal dysfunction and diabetic gastroparesis in persons with diabetes may predispose them to aspiration pneumonia.[65] Diabetes is a risk factor for chronic oral infections of caries and periodontitis, which also may contribute to the increased risk for aspiration pneumonia.[66] There is an increased incidence of bacterial pneumonia and associated mortality in patients with diabetes during seasonal influenza outbreaks.[67] Consistent with the recommendations of the Advisory Committee on Immunization Practices, influenza vaccination is recommended for patients with diabetes who are older than 6 months of age.[68] Regarding preventive practices in patients with known diabetes, approximately 60% have obtained annual influenza vaccines, whereas just 49% have met goals of pneumococcal vaccination.[69] As for other pathogens, preexisting diabetes has been associated with a higher mortality in patients with severe acute respiratory syndrome.[70]

THYROID DISORDERS

The incidence of multinodular goiter is declining in the United States due to the routine use of iodized salt; nevertheless, neglected goiters are still detected. Because of the thyroid's ability to expand easily in the anterior space, bound only by skin, thin muscle, and connective tissue, even large goiters may not cause tracheal impingement. However, some goiters can cause dyspnea, stridor, wheezing, hoarseness, and cough via tracheal deviation—typically if there is unilateral or unequal lobe enlargement—and airway compression.[71-73] (Video 95-1). Compression or concentric narrowing of the trachea is more common if the goiter extends posteriorly to the trachea (Fig. 95-2). Although goiters typically grow slowly, occasionally patients present with acute respiratory distress requiring urgent intubation or semiurgent surgery.

Some goiters are substernal and/or intrathoracic. There is variability of the definition of "intrathoracic goiter"; most experts concur that some portion of the goiter is permanently retrosternal (below the sternal notch), even when the neck is retroflexed.[74] Bulky and/or substernal goiters may cause orthopnea because of airflow limitation in the supine position. In these patients, flow-volume loops in the recumbent position may demonstrate upper airway obstruction not apparent in upright testing.[73] CT scanning and magnetic resonance imaging generally are the most useful diagnostic imaging studies and can estimate the degree of tracheal compression.[75]

Of particular note, CT scanning with iodinated contrast media should generally be avoided because it precludes thyroid nuclear imaging for several weeks and can trigger hyperthyroidism. Surgical resection of substernal goiters is recommended and usually relieves compressive symptoms.[71,76] Postoperative tracheomalacia appears to be rare.[71]

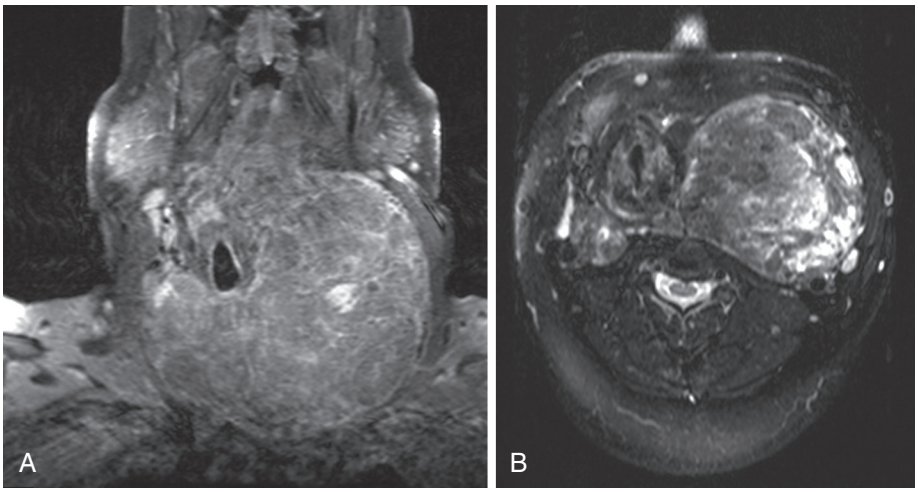

Figure 95-2 Thyroid goiter. Magnetic resonance images show a massive goiter in a 55-year-old man who presented with a change in his voice and increased shortness of breath. Endotracheal intubation required flexible bronchoscopy, followed by uneventful resection of a 900-g multinodular goiter. Coronal **(A)** and axial **(B)** gadolinium-enhanced images of the neck reveal tracheal deviation and compression.

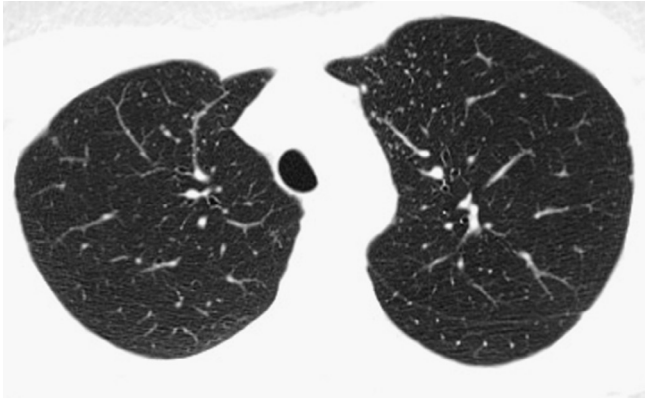

Figure 95-3 Metastatic thyroid cancer. Computed tomography scan of a patient showing metastatic thyroid cancer with micrometastases. (Courtesy Michael B. Gotway, MD.)

Iodine-131 is an alternative therapy for some patients with large goiters including those with intrathoracic extension who are not surgical candidates because of comorbid illnesses.[77,78] For patients with baseline tracheal compression, there is often some temporary goiter enlargement from edema and additional airway compromise in the week following ^{131}I treatment. Even so, with glucocorticoid prophylaxis, most patients do well and have subsequent goiter shrinkage.[79] Alternatively, bronchoscopic insertion of tracheal stents can relieve large airway obstruction from compressive benign or malignant nonoperable thyroid disease.[80] Large, multinodular goiters with retrolaryngopharyngeal extension can also cause obstructive sleep apnea, which can resolve after total thyroidectomy.[81,82]

Thyroid carcinoma accounts for 1% of all new malignancies; the most common is papillary thyroid carcinoma. Of these, 10% to15% will develop metastases, the vast majority of which are within the thoracic cavity. A miliary pattern of metastases can be seen, as well as larger nodules, and even localized pulmonary opacities[83] (Fig. 95-3 and Video 95-2). Depending on the lung burden of cancer, dyspnea may be present. Thyroid cancer can also directly invade the trachea. In patients who are otherwise good surgical candidates, resection with tracheal reconstruction has been successful.[84]

Smoking is a risk factor for hyperthyroidism, including Graves disease, toxic nodular goiter, and autoimmune hypothyroidism (Hashimoto thyroiditis), especially in women.[85-87] Smoking increases the risk of Graves ophthalmopathy beyond the risk associated with hyperthyroidism alone.

HYPERTHYROIDISM

Many patients with hyperthyroidism complain of both resting and exertional dyspnea. Congestive heart failure likely explains some of these complaints[88] and is the presenting feature in 6% of patients with newly diagnosed hyperthyroidism.[89] Some hyperthyroid patients have decreased vital capacity,[90] decreased respiratory muscle strength,[89-93] and elevated resting minute ventilation (perhaps due to increased central ventilatory drive) that becomes excessive with exercise.[92] With treatment, vital capacity and respiratory muscle strength improve,[90] although some patients have persistent dyspnea.[91]

Patients with coincident asthma and thyrotoxicosis may have worsening asthma control if β-blocker agents are used to control manifestations of hyperthyroidism. There may be an association between atopic disease, asthma, and Graves disease.[94] Approximately 30% of patients with hyperthyroid Graves disease have an elevation in serum *immunoglobulin E* (IgE) levels, and those with elevated serum IgE are more likely to have a personal or family history of atopy.[95]

Several reports have suggested a link between hyperthyroidism, especially Graves disease, and pulmonary hypertension in which the pulmonary artery pressures can improve and even normalize with treatment of the hyperthyroidism.[96-98] The explanation for this association is not clear, but may be due to a generalized autoimmune state, a direct influence of thyroid hormone on pulmonary vasculature, changes in metabolism of pulmonary vasculature vasodilators/vasoconstrictors, decreased surfactant production and function, or excess cardiovascular

stimulation by the sympathoadrenal system. Treatment of the hyperthyroidism is important to relieve the additional burden of cardiovascular stress on the pulmonary vascular system.[97] Rarely, mothers with hyperthyroidism from Graves disease deliver infants with hyperthyroidism via placental passage of maternal thyrotropin receptor-stimulating antibodies. In addition to a variety of infant metabolic and developmental problems, neonatal Graves disease has been associated with persistent pulmonary hypertension in newborns.[99] Interestingly, there may also be an increased prevalence of hypothyroidism in patients with primary pulmonary hypertension.[100]

Furthermore, several reports of an increased presence of antinuclear cytoplasmic antibodies and even granulomatosis with polyangiitis (Wegener granulomatosis) have been documented in patients with Graves disease treated with propylthiouracil.[101] Propylthiouracil-induced nonspecific interstitial pneumonia[102] and alveolar hemorrhage[103] have also been reported.

HYPOTHYROIDISM

Hypothyroidism has been associated with dyspnea on exertion, alveolar hypoventilation, respiratory failure, obstructive and central sleep apnea, and pleural effusions. Lung volumes are generally normal or mildly decreased in mixed populations of obese and nonobese hypothyroid patients.[104,105] Lung volumes typically, although not uniformly, improve with thyroid replacement and/or weight loss. A reduced diffusing capacity for carbon monoxide can be seen in some hypothyroid, nonobese patients with normal lung volumes and arterial blood gases that improve to near-normal after replacement therapy.[105] Hypothyroidism is associated with overall respiratory muscle weakness as measured by maximal inspiratory and expiratory pressures, and the degree of impairment is linearly related to the degree of pretreatment hypothyroidism.[106] Diaphragmatic muscle weakness in both obese and nonobese hypothyroid patients may range from mild impairment, which limits exercise tolerance, to severe dysfunction, with marked resting dyspnea and chronic hypercarbia.[104] Thyroid replacement therapy can improve respiratory muscle strength. Some nonobese and obese hypothyroid patients have a markedly blunted ventilatory response to hypoxia and hypercapnia,[105,107] which improves often within weeks of initiation of thyroid hormone replacement. This improvement is not associated with changes in spirometric function or maximal voluntary ventilation, thus suggesting a central cause for the abnormal ventilatory response. Hypothyroidism can cause respiratory failure that may require prolonged mechanical ventilation.[107]

Although up to 25% of patients with hypothyroidism have radiographic evidence of a pleural effusion, most patients also have underlying congestive heart failure (Table 95-2).[108] A small percentage of hypothyroid patients do not have another disease process that would explain the effusion. In these patients, the hypothyroid-related effusions tend to be small, less than one third of the pleural space; unilateral or bilateral; serous or serosanguineous; and transudates or exudates, although generally noninflammatory.[108] Hypothyroid-related effusions typically resolve with treatment of the hypothyroidism.[108]

Table 95-2 Etiologies of Pleural Effusions in Hypothyroid Patients (n = 28)

Etiology	No.	
Nonhypothyroid-associated pleural effusions	22	
Pneumonia		7
Congestive heart failure		7
Malignancy		4
Atelectasis		2
Pancreatitis		1
Cirrhosis with ascites		1
Hypothyroid pleural effusion	5	
Hypothyroid-associated effusion due to pericardial involvement	1	

Modified from Gottehrer A, Roa J, Stanford GG, et al: Hypothyroidism and pleural effusions. *Chest* 98:1130–1132, 1990.

Hypothyroidism can predispose patients to sleep apnea,[109,110] possibly from narrowing of the upper airway from mucopolysaccharide and protein deposition in the tongue and oropharynx,[111] from abnormalities in ventilatory control, and/or from weight gain. Hypothyroidism can contribute to the neurocognitive impairment found in patients with sleep apnea.[112] In one case series, only 3.1% of patients with obstructive sleep apnea were found to have hypothyroidism[110]; in contrast, 25% of newly diagnosed hypothyroid patients were found to have obstructive sleep apnea. Age and body weight were the best predictors of associated obstructive sleep apnea.[110] Hypothyroid patients with obstructive sleep apnea have blunted ventilatory responses to both hypoxia and hypercapnia. Some studies have shown improvement in sleep respiratory disturbance index and awake ventilatory response to hypoxia and hypercapnia with thyroid replacement[110,113]; in other studies, however, investigators found less than full improvement or no improvement in sleep apnea with thyroid replacement.[114,115] Central sleep apnea can also detected in hypothyroid patients, and the blunted ventilatory response to hypoxia may improve with thyroid replacement.[114]

Thyroid hormones play an important role in the growth and development of the lung and in the maturation of the lung's surfactant system.[116,117] Transient hypothyroxinemia is common in premature infants, as is respiratory distress syndrome. However, the administration of maternal antenatal thyrotropin-releasing hormone, which increases fetal thyroid hormone levels, did not decrease the frequency or severity of respiratory distress syndrome in premature babies in a large multicenter trial.[118] Treatment of premature infants with thyroxine also did not decrease the incidence of respiratory distress syndrome, the use of surfactant therapy, or the overall developmental outcome at 24 months.[119]

The "brain-thyroid-lung syndrome"[120-122] is a rare form of neonatal progressive respiratory failure characterized by chorea or cerebral dysgenesis, congenital hypothyroidism, and respiratory disease. It is related to defects of the *NKX2-1* gene encoding thyroid transcription factor-1, which appears to be critical for central nervous system, thyroid, and lung development and function. In the lung, thyroid transcription factor-1 deficiency syndrome leads to a disturbance of surfactant protein-A production, resulting in

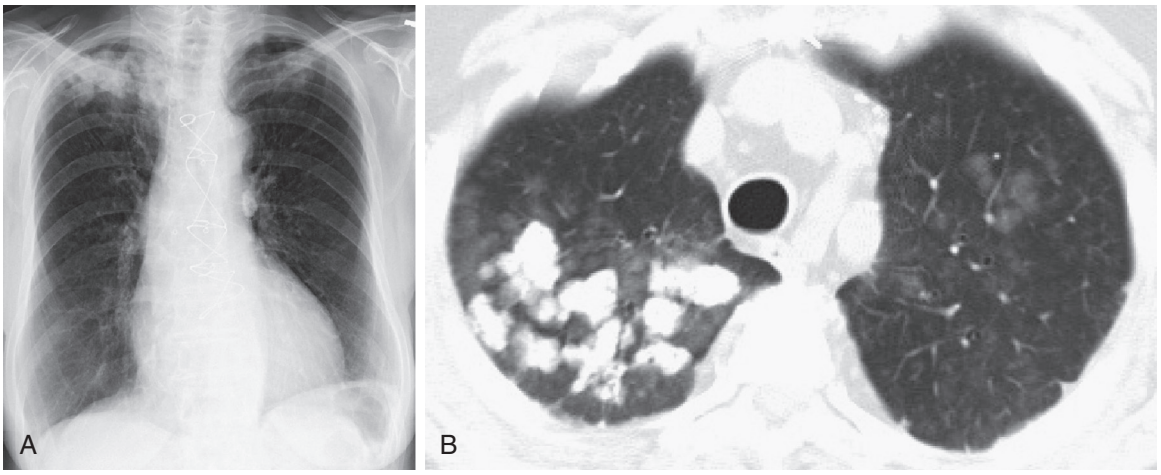

Figure 95-4 Metastatic calcification. Frontal chest radiograph **(A)** and corresponding axial chest CT scan **(B)** show the apical predilection of metastatic pulmonary calcification that can be seen in hyperparathyroidism.

spectrum of disease from mild to progressive and fatal respiratory failure.

PARATHYROID DISEASES

Hyperparathyroidism, typically secondary hyperparathyroidism in patients with end-stage renal disease, can cause diffuse metastatic calcification in the lungs. Metastatic calcification is the deposition of calcium salts in previously normal tissue; in contrast, dystrophic calcification is the calcification of diseased or abnormal tissue, as in granulomatous processes. Despite dietary phosphate restriction, administration of phosphate binders, and hemodialysis, patients with renal failure are at risk for metastatic calcification, especially when the calcium-phosphorus concentration product increases above 70 mg^2/dL^2. Calcium salts tend to precipitate in alkaline conditions. Indeed, metastatic calcification has a predilection for the apical portions of the lungs (Fig. 95-4), the stomach, and the kidneys—all tissues with relative alkalinity, because of either carbon dioxide removal or hydrogen ion excretion. Due to the higher ventilation-perfusion ratio and lower carbon dioxide concentration at the lung apex, it is estimated that the pH at the apex is 7.5 compared to a pH of 7.3 at the base.[123,124] Other common sites of deposition include soft tissues and the skin. Pulmonary metastatic calcific nodules may deposit predominantly in the alveolar septa and are associated with varying degrees of fibrosis and septal thickening. This phenomenon appears to be common; from 60% to 80% of dialysis patients on long-term therapy have autopsy or scintigraphic evidence of pulmonary metastatic calcification.[125]

Most patients with end-stage renal disease and metastatic pulmonary calcification are asymptomatic and have normal chest radiographs and pulmonary function. However, patients with heavy deposition of calcific nodules may complain of dyspnea and nonproductive cough, and can rarely progress to respiratory failure.[126] Radiographically, patients with more extensive calcification typically have numerous nodules about 3 to 10 mm in size that are better visualized on CT scans than on plain chest radiographs (Fig. 95-5).[127]

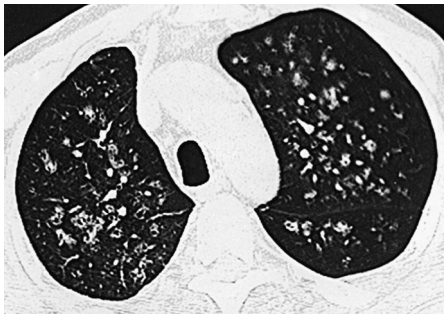

Figure 95-5 Metastatic calcification in the lungs secondary to chronic renal failure. A 59-year-old man with end-stage renal disease for 5 years complained of chronic progressive shortness of breath. The serum calcium level was 9.9 mg/dL (normal range, 8.5 to 10.5 mg/dL) and the parathyroid hormone level was 271 pg/mL (normal for the laboratory, 11 to 54 pg/mL). High-resolution computed tomography revealed numerous nodular ground-glass densities in a peribronchial pattern, most prominently in the upper lobes. (Courtesy Marcia McCowin, MD.)

In addition to the nodular densities, patchy consolidation and ground-glass attenuation may be seen. The calcific nature of the nodules may not be apparent on plain radiographic or even CT images, perhaps due to the small size of the calcium deposits. However, radionuclide bone scans usually reveal intense uptake in the lungs and other affected organs (Fig. 95-6).[125] Pulmonary function tests in patients with extensive metastatic calcification may show ventilatory restriction with hypoxemia and low diffusing capacity for carbon monoxide.[123] Parathyroidectomy or treatment with vitamin D analogues can decrease the calcium-phosphorus double product, reverse bone scan abnormalities and organ deposition, and presumably improve pulmonary function.

Hyperparathyroidism is also associated with calcification in pulmonary arterial and bronchial walls. Of note, about one third of patients with end-stage renal disease on long-term hemodialysis via arteriovenous access have pulmonary hypertension,[128,129] but pulmonary hypertension does not seem to correlate with the presence or severity of pulmonary artery calcification or parathyroid hormone levels.[128,130]

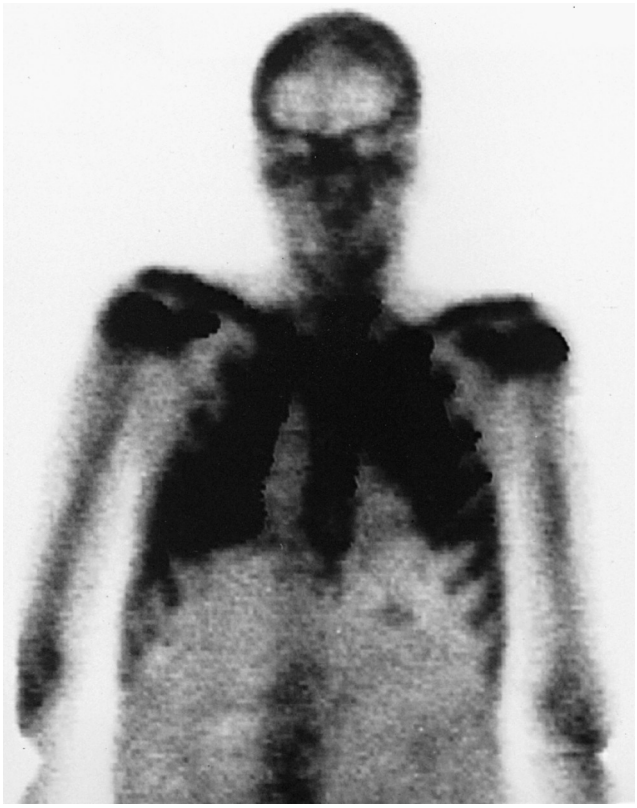

Figure 95-6 Metastatic calcification in the lungs caused by chronic renal failure. This is the same patient as in Figure 95-5. Whole-body bone imaging with technetium-99m-diphosphonate revealed diffuse soft tissue avidity in both lungs.

Rarely, enlarged mediastinal parathyroid cysts can cause tracheal compression with stridor or vocal cord impingement and hoarseness, or both. Surgical excision is the treatment of choice.[131]

Hyperparathyroidism is frequently associated with muscle weakness and fatigue. Respiratory muscle function can be affected as well, and post-parathyroidectomy improvement in forced vital capacity and forced expiratory volume in 1 second values correlates with preoperative serum calcium and preoperative parathyroid hormone values.[132]

Vitamin D deficiency and metabolic bone disease from a variety of causes can affect skeletal muscle strength and bone integrity and, in turn, may impair pulmonary function. Unrelated to skeletal effects, vitamin D deficiency has been associated with increased severity of asthma[133] and increased risk for asthma exacerbations in children.[134,135] Vitamin D deficiency has been associated with impaired pulmonary function in adults[136,137] and a more rapid decline in pulmonary function in smokers.[138] Vitamin D deficiency has not been associated with COPD exacerbations,[139] and supplementation with high-dose vitamin D does not reduce future COPD exacerbations.[140] Hypophosphatasia from mutations in the gene for the tissue-nonspecific isozyme of alkaline phosphatase can lead to rickets or osteomalacia. Fatal respiratory insufficiency due to progressive chest deformity can develop in severely affected babies. Enzyme replacement therapy is associated with improved findings on skeletal radiographs and improved pulmonary and physical function in affected children.[141]

ADRENAL DISEASES

Endogenous Cushing syndrome (i.e., not from glucocorticoid administration) may be caused by pituitary Cushing disease, adrenal neoplasia, or ectopic adrenocorticotropic hormone production from small-cell lung cancer or from carcinoids arising from a variety of organs, especially the lung, including the variation of pulmonary carcinoid tumorlets.[142-144] Cortisol levels tend to be much higher with ectopic adrenocorticotropic hormone production and adrenal neoplasia than with pituitary Cushing disease and pose a greater risk for infection. Hypercortisolism particularly predisposes patients to mucocutaneous fungal infections and opportunistic pulmonary infections. The most common pulmonary infections are caused by *Cryptococcus, Aspergillus, Nocardia, Pneumocystis,* and *Mycobacterium tuberculosis.*[145-148] *Pneumocystis jirovecii* pneumonia tends to develop in patients with especially high morning cortisol levels.[103] Correction of hypercortisolism is an important adjunct to antimicrobial therapy. Cushing syndrome is also associated with a hypercoagulable state and an increase in clinically significant thromboembolic events.[149,150] Even in patients without baseline hypercortisolism, cortisol levels increase in stress and extremely elevated cortisol levels at presentation appear to be independent predictors of worse outcomes in community-acquired pneumonia.[151,152]

Adrenal insufficiency may be due to either primary adrenal failure (Addison disease) or secondary adrenal insufficiency. Secondary adrenal insufficiency is most commonly iatrogenic as a result of the withdrawal of exogenous glucocorticoid therapy, or results directly from disease of the hypothalamic-pituitary axis. In industrialized countries, 70% to 80% of cases of Addison disease are autoimmune in origin; in contrast, in resource-poor countries, tuberculosis remains the most common cause.[153,154] CT scanning is sometimes helpful in determining the cause of Addison disease, because tuberculosis and histoplasmosis may cause adrenal calcification.[155] Adrenal insufficiency via hypothalamic-pituitary axis dysfunction may be seen in stressed, very-low-birth-weight infants and may render them more susceptible to bronchopulmonary dysplasia.[156]

ACROMEGALY

Acromegaly is a disorder of excess growth hormone secretion in adults, most commonly from a benign pituitary adenoma. Rarely, bronchial carcinoid or small-cell lung cancer can produce excess growth hormone–releasing factor, which stimulates excess growth hormone secretion. Clinically, acromegaly is characterized by excessive bone growth, soft tissue hypertrophy, and coarsening of facial features. These changes appear to be due to high levels of growth hormone and *insulin-like growth factor I* (IGF-I), which is secreted in response to growth hormone; the net effect is an increase in somatic growth and metabolic disturbances. Mortality in acromegaly is increased primarily

from cardiovascular disease,[157] although control of acromegaly can lead to a significant decrease in coronary heart disease risk factors, especially in patients whose IGF-I levels are normalized.[158]

Patients with acromegaly can develop macroglossia, nasal polyps, oropharyngeal airway narrowing, and vocal cord restriction and edema. In addition, coincidental goiter is not uncommon and can contribute to upper airway narrowing.[157,159] Respiratory manifestations of acromegaly include sleep apnea, extrathoracic airway obstruction, vocal cord dysfunction, and difficult intubation.[157,159] The prevalence of sleep apnea has been reported as between 20% and 60%.[160-162] Increased rates of obstructive sleep apnea may be due to a narrowed upper airway from osseous enlargement, hypertrophy of tissues in the oropharynx, inspiratory collapse of the hypopharynx, and macroglossia. The circumference of the neck and fingers, but not BMI, are predictive of the development of sleep apnea in acromegaly.[162] Obstructive sleep apnea may improve with treatment of acromegaly with pituitary ablation[163] or somatostatin analogues, but is highly variable.[160,161,164,165] Persistence of obstructive sleep apnea after treatment may be due to irreversible upper airway remodeling. Central sleep apnea is also common. Patients with central sleep apnea and acromegaly have higher growth hormone and IGF-I levels and higher ventilatory responses to carbon dioxide than acromegalic patients with obstructive sleep apnea.[166] Central sleep apnea in these patients may therefore be due to altered ventilatory control.

Total lung capacity and vital capacity are typically increased in patients with acromegaly compared with controls,[167-172] and appear to correlate with both the duration of acromegaly and in level of IGF-I.[169,173] Possible causes for the increased lung volumes in these patients include hypertrophy or enlargement of individual alveoli, or an increase in the number of alveoli.[167,170,171] Diffusing capacity for carbon monoxide may be within normal limits[167,170] or elevated.[168] Changes in vertebrae and rib morphology contribute to the barrel chest of patients with acromegaly. In addition, with acromegaly, there is a decrease in respiratory muscle force that may contribute to increased dyspnea and fatigue with exercise.[172]

Evidence of a variable extrathoracic airway obstruction on flow-volume loops is seen in 30% to 50% of patients with acromegaly.[169] As noted, intubation may be more difficult in patients with acromegaly because of vocal cord fixation, vocal cord edema, prolapse of an enlarged tongue, and soft tissue thickening of the oropharynx.[174] Preoperative treatment of patients with somatostatin analogues may decrease soft tissue swelling and enable easier intubation.[165]

Key Points

- Diabetes mellitus, by far the most common endocrine disorder, is associated with sleep apnea and predisposes to certain bacterial, fungal, and mycobacterial respiratory infections. Cigarette smoking is a risk factor for type 2 diabetes. Patients with diabetes should receive pneumococcal and influenza vaccinations and, because of an increased risk for progression to active tuberculosis, should receive treatment for latent tuberculosis infection if they have a tuberculin skin test greater than 10 mm or a positive interferon-gamma release assay.
- Thyroid enlargement may cause upper airway compression. Patients with hyperthyroidism may have dyspnea worsened by decreases in vital capacity and respiratory muscle strength. More commonly, patients with hypothyroidism suffer from dyspnea, alveolar hypoventilation, pleural effusion, and, sometimes, respiratory failure.
- Secondary hyperparathyroidism from end-stage renal disease often causes diffuse metastatic pulmonary calcification, which frequently is asymptomatic.
- Endogenous Cushing syndrome predisposes to a variety of opportunistic infections, whereas acromegaly from excess growth hormone is associated with a high prevalence of sleep apnea, and may lead to upper airway structural disorders.

Complete reference list available at *ExpertConsult*.

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