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Pulmonary Manifestations of Systemic Diseases



Editor-in-Chief
Surinder K Jindal

Guest Editor
Shankar S Patil

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Pulmonary Manifestations of Systemic Diseases

Shankar S Patil MD FRCP FAMS DSc (Gul) Dsc (NTR) DSc (RGUHS)

Academy of Respiratory Medicine
Education Advisor, Asian Heart Institute
Mumbai 400 051, Maharashtra, India

ABSTRACT

The entire cardiac output reaches the lungs for exchange of gases—absorption of oxygen and elimination of carbon dioxide—through its surface. Through hematogenous route, many infectious and noninfectious disorders may affect the lungs. Noninfectious conditions, such as granulomas, collagen vascular disease, and parasitic diseases may affect the lungs as a part of systemic manifestations. Similarly, diseases affecting the alimentary tract, cardiovascular system, central nervous system, and renal system may affect the lungs. Medications used in the treatment of many ailments may cause untoward effects in the lungs. Pulmonary symptoms have to be evaluated in the background of systemic diseases with imaging studies and immunological tests. Appropriate treatment has to be initiated.

INTRODUCTION

The respiratory system is essentially concerned with exchange of gases between the inspired air and blood in the alveolar capillaries. It provides an enormous surface in a small volume for transfer of gases through which blood gets rid of carbon dioxide and absorbs oxygen, while doing so, the pressures of oxygen and carbon dioxide are maintained in the arterial blood at 100 mmHg and 40 mmHg respectively, while breathing ambient air at sea level. In addition, the structure and function of the lungs helps in the filtration of blood flowing to the systemic circulation, and metabolism of metabolically active peptides in the circulation.

The lungs have dual arterial blood supply from pulmonary and bronchial arteries and dual venous drainage. Pulmonary circulation receives the entire

Email: psshankar@hotmail.com

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cardiac output while the bronchial circulation receives only about 1–3%. There is wide anastomosis between pulmonary and bronchial circulation within the lung. Pulmonary vasculature is a low-pressure circulation facilitating exchange of respiratory gases.

The infectious diseases often present with systemic manifestations and lungs may also be involved. A number of noninfectious systemic disorders involve lungs as a part of the total clinical picture. Such conditions include granulomatous diseases (sarcoidosis), connective tissue disorders [rheumatoid arthritis, systemic lupus erythematosus (SLE), and systemic sclerosis (SSc)], vasculitis [Wegener's granulomatosis now classed granulomatosis with polyangiitis (GPA), Churg-Strauss syndrome, and Goodpasture's syndrome], and other rare diseases include tuberous sclerosis, lymphangioleiomyomatosis (LAM), and lymphoma. Pulmonary manifestations are encountered in diseases of alimentary tract (gastroesophageal reflux disease, ulcerative colitis), liver and pancreatic disorders, endocrine diseases (thyroid disorders, diabetes mellitus, obesity), renal failure, cardiac failure, or neurological diseases.

Pulmonary involvement in systemic disorders may occur as a manifestation of underlying pathological process or it may occur as a complication of the underlying disease process. Sometimes, the pulmonary manifestations may arise as result of treatment. Pulmonary manifestations in the background of systemic diseases should be evaluated in a systematic fashion. Imaging studies especially high-resolution computed tomography (HRCT) help in the diagnosis, assessment of disease severity and activity, and evaluation of response to the treatment. Some of the important systemic disorders that produce pulmonary failures are considered here (detailed manifestations are available in individual articles by different authors in this very issue).

DRUG-INDUCED LUNG DISEASES

The administration of certain drugs is associated with pulmonary damage. The number of drugs causing lung injury is increasing every year. There are over 40 commonly used therapeutic agents which are reported to produce pulmonary damage. They may produce untoward effects on the lungs either directly or indirectly. The direct effects occur by toxic or immunologic mechanisms.

Drugs which produce indirect effects include sedatives in patients with chronic obstructive pulmonary disease causing respiratory failure, anticoagulants causing hemoptysis, muscle relaxants paralyzing the respiratory muscles, immunosuppressive agents resulting in infections, and oral contraceptives with high-estrogen content resulting in pulmonary thromboembolism.

The direct adverse effects of drugs in therapeutic doses may be felt on the airways, alveoli, and pleural surface. The drugs are classified as cytotoxic and noncytotoxic agents.

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Mechanism of Pulmonary Damage

The lungs are constantly exposed to a variety of insults and the homeostatic mechanisms are able to maintain a balance between damaging inflammatory reactions and protective detoxification mechanisms.[1] A variety of therapeutic agents may affect these mechanisms to result in pulmonary damage.

Lung Homeostatic Mechanism

Certain cytotoxic drugs may cause pulmonary damage by bringing about an alteration in the normal balance between oxidants and antioxidants. Bleomycin and cyclophosphamide are able to generate reactive oxygen species (oxidants).[2,3] These are able to cause tissue damage unless neutralized by antioxidants, such as superoxide desmutase, catalase, glutathione peroxidase, ceruloplasmin, and alpha-tocopherol. Carmustine and cyclophosphamide reduce glutathione reductase, the enzyme needed for regeneration of the glutathione, and alter the body antioxidant defenses.[4] Nitrofurantoin appears to exert its toxic effects by producing reactive oxygen species.[5]

Immunologic System

Lung is constantly exposed to substances that can activate the immunologic system. Alveolar macrophages and lymphocytes release mediators that attract and activate other inflammatory cells, such as polymorphonuclear leukocytes, eosinophils, and monocytes. These cells release cytotoxic mediators.

The mediators bring about an immune tolerance, avoid over-reactions to the substances exposed, and prevent tissue damage. The balance may be broken by cytotoxic drugs. Bleomycin and methotrexate may cause hypersensitivity reactions either through recognition of the drug as a foreign agent or through alteration in the normal immune balance.[6,7]

Gold salts and nitrofurantoin cause activation and sequestration of lymphocytes in the lung and produce pulmonary damage.[8,9] Amiodarone has also shown to produce pulmonary damage through immune mechanisms. Its administration is associated with reduction in normal helper/suppressor T cell ratio.[10] Pulmonary leukocyte sequestration is also noted in patients receiving beta-sympathomimetics (terbutaline), and opiates (heroin).[11,12] They lead to activation of serum complement and development of noncardiogenic pulmonary edema. Amphotericin B injures polymorphonuclear leukocytes to cause acute pulmonary damage.[13]

Aspirin inhibits cyclooxygenase pathway of arachidonic acid metabolism and increases production of leukotrienes to result in an increased vascular permeability.[14]

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Matrix Repair System

Collagen deposition helps restrict the damaging processes and repair the damaged tissue. Bleomycin may stimulate the rate of proliferation of fibroblasts resulting in an excess deposition of collagen to cause severe pulmonary disability.[15] Penicillamine and gold thiosulfate affect the balance between collagenosis and collagenolysis.[16,17]

Proteolytic System

Polymorphonuclear leukocytes and alveolar macrophages produce proteolytic enzymes, particularly elastase. These proteolytic enzymes are inactivated by antiprotease enzymes, such as alpha-1 protease inhibitor. Reactive oxygen radicals released by cytotoxic drugs, such as bleomycin and cyclophosphamide may inactivate the antiprotease enzyme and bring about an increased activity of proteolytic enzymes.[1] Colchicine stimulates protease release from macrophages.[18]

Neurological System

Central neurological mechanisms play an important role in controlling pulmonary capillary permeability. Opiates, major tranquilizers, salicylates and methotrexate can cause pulmonary edema through their effect on medulla and hypothalamus.[19]

PULMONARY MANIFESTATIONS OF RHEUMATOID ARTHRITIS

The pleuropulmonary complications associated with rheumatoid arthritis are noted frequently. The different elements of the respiratory system are affected either separately or together. They include pleurisy with or without effusion, necrobiotic intrapulmonary nodules, and fibrosing alveolitis (Table 1).

Pulmonary manifestations are encountered more commonly in men than women. They may be noted along with lesions of rheumatoid arthritis either before or after the appearance of arthritic manifestations. There is no correlation between the severity of arthritis and lung disease. The presence of circulating rheumatoid

Table 1: Pleuropulmonary Complications of Rheumatoid Arthritis

- Pleural disease
- Interstitial lung disease
- Necrobiotic nodule
- Bronchiolitis obliterans
- Small airway disease
- Rheumatoid laryngitis
- Pulmonary infections

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factor is helpful in the diagnosis. However, the pleuropulmonary complications are more likely to occur in patients with more severe chronic articular disease with high titers of rheumatoid factor.[20]

LUNGS IN SYSTEMIC SCLEROSIS

Systemic sclerosis is a generalized disorder of connective tissues characterized by widespread thickening and fibrosis of the skin due to accumulation of excess collagen and proteoglycans, obliterative lesions of arterioles and capillaries, and disturbances of function of various internal organs due to fibrosis notably the lungs, kidneys, gastrointestinal tract, heart, and skeletal muscles.[21]

Systemic sclerosis shows marked heterogeneity in extent, progression, and internal organ involvement. Pulmonary involvement is more common in patients with SSc than in other collagen vascular diseases. The lungs are involved in more than 70% of cases.[22] Often it remains asymptomatic and the abnormality is evident on pulmonary function tests or chest radiography. The pulmonary complication may be either interstitial or vascular disease. Secondary complications are aspiration pneumonia and lung cancer (Table 2). The condition is noted in the age group between 30 and 50 years and is more common in women.

LUNGS IN SYSTEMIC VASCULITIS

Systemic vasculitis may affect upper airways, bronchial tree, pulmonary interstitium, and pulmonary vasculature. These disorders develop in the background of destructive inflammation of blood vessels.

Table 2: Pulmonary Manifestations of Systemic Sclerosis

- Interstitial lung diseases
  - Usual interstitial pneumonia
  - Honeycomb lungs
  - Lymphocytic interstitial pneumonia
  - Cellular interstitial pneumonia
  - Organizing pneumonia
  - Diffuse alveolar hemorrhage
- Pulmonary hypertension
- Aspiration pneumonia
- Bronchiolitis obliterans
- Relapsing organizing pneumonia
- Pleural disease
- Lung malignancy

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Table 3: Small, Medium, and Large-Vessel Vasculitides in the Lung

Small to medium vessel vasculitis in the respiratory tract[23]

- Granulomatosis with polyangiitis
  - Tracheobronchial tree (dyspnea, wheezing, stridor)
- Allergic granulomatosis with polyangiitis
- Microscopic polyangiitis

Large vessel vasculitis

- Takayasu's arteritis or granulomatous arteritis[24]
  - Concomitant involvement of aorta dyspnea, chest pain, hemoptysis
- Behcet's disease[25]
  - Arterial aneurysms
  - Arterial thrombosis
  - Pulmonary infarction
  - Recurrent pneumonia
  - Bronchiolitis obliterans organizing pneumonia
  - Pleurisy

Pulmonary vasculature develops in close association with the branching of bronchial tree to form a dense capillary network surrounding the alveoli. This is essential to offer large alveolar surface for gas exchange. Lungs through the airways have a direct contact with the external environment, and are constantly exposed to sensitizing antigens. Nature has equipped the lungs with a large number of immune cells in the interstitium and alveolar surface. Their fight may result in the development of immunological inflammation in systemic vasculitis. Immune complex-mediated vasculitis may affect small, medium, and large vessels in the lung (Table 3). Involvement of lung parenchyma may present in a localized or diffuse form (Table 4).

PARASITIC PULMONARY DISEASES

Parasitic diseases are commonly encountered in tropical and subtropical countries. Lungs, pleura and chest wall may be affected by a variety of parasites. The parasites include protozoa (*Entamoeba histolytica*, *Plasmodium falciparum*, and *Toxoplasma*

Table 4: Involvement of Lung Parenchyma

- Localized granulomatous vasculitis[26]
  - Nodules
  - Cavities
- Diffuse alveolar hemorrhage
  - Hemoptysis
  - Pulmonary infiltrates
  - Hypoxemic respiratory failure

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gondii), metazoa (roundworms, flatworms, and flukes), nemathelminthes (*Ascaris lumbricoides*, *Ancylostoma duodenale*, *Strongyloides stercoralis*, *Toxocara canis* and *catis*, *Trichinella spiralis*, *Wuchereria bancrofti*, and *Dirofilaria immitis*), and platyhelminthes, such as cestodes (*Echinococcus granulosus*) and trematodes (*Paragonimus* and *Schistosoma*).[27]

The clinical manifestations are varied. They can present features of involvement of intercostals muscles (trichinosis), diffuse parenchymal infiltrations (migratory phase of nematodes, visceral larva migrans, schistosomiasis, paragonimiasis, and toxoplasmosis, pleuropulmonary manifestations (amebiasis, hydatid disease, paragonimiasis), pulmonary hypertension (schistosomiasis) or tropical pulmonary eosinophilia.

PULMONARY-RENAL SYNDROMES

The lungs and kidneys may be involved together in a variety of condition. In infections, such as tuberculosis of *Legionella* pneumonia, kidneys may be affected in presence of a primary lung disease. A combination of pulmonary and renal diseases may be noted in sarcoidosis and SSc. In SLE, there is multisystem involvement which may include kidneys and lungs.[28]

Pulmonary-renal syndrome (PRS) consists of a group of disorders characterized by necrotizing glomerulonephritis and pulmonary hemorrhage. It includes antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), such as Wegener's granulomatosis GPA, microscopic polyangiitis (MPA), and eosinophilic GPA (Churg-Strauss syndrome). ANCA-negative vasculitis includes Henoch-Schönlein purpura, immunoglobulin nephropathy and antiglomerular basement membrane (GBM) disease (Goodpasture's syndrome), and SLE.

Thus, PRS develops in the background of several diseases with diverse pathological mechanisms. PRS is a life-threatening condition with an acute onset having a fulminant course. The manifestations may be severe renal failure with minimum pulmonary manifestations or predominant respiratory manifestations with minimal renal disease. These disorders are recognized on clinical presentation, if there is a high degree of suspicion. The treatment includes immunosuppressive agents, plasma exchange, mechanical ventilation, and dialysis.

LUNGS IN GASTROINTESTINAL DISORDERS

Lungs develop as an appendage of the upper gastrointestinal tract. The anatomic structure of the lungs makes it susceptible to aspiration of food, saliva, and vomitus during swallowing and regurgitation.

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Tracheoesophageal fistula can cause aspiration pneumonia or lung abscess. Hiatal hernia appears as a posterior mediastinal shadow with air-fluid levels. Pharyngoesophageal diverticulum appears as a superior mediastinal shadow and can lead to recurrent aspiration pneumonia and lung abscess.

Gastroesophageal reflux disease develops due to incompetence of lower esophageal sphincter, facilitates stomach contents, and corrosive acid to regurgitate up and damage mucosa of the esophagus. It can lead to a variety of pulmonary manifestations like chronic cough, bronchial asthma, pneumonia, and pulmonary fibrosis.[29]

Inflammatory bowel disease (IBD) may present with pulmonary manifestations, such as airway inflammation, lung parenchymal, and pleural involvement. Patients present with wheezing, cough, sputum, and breathlessness. Bronchiolitis obliterans organizing pneumonia and interstitial lung disease are other manifestations.[30] Pulmonary infiltrates with eosinophilia and necrobiotic nodules can also occur. Alpha-1 antitrypsin deficiency may present with emphysema or bronchiectasis.[31]

PULMONARY DISORDERS IN LIVER DISEASES

Pulmonary disorders may develop in the background of liver diseases. These manifestations are recognized quite late in the course of liver disease. Hepatopulmonary syndrome (HPS) results in hypoxemia through pulmonary microvasodilatation and ventilation-perfusion imbalance. In its advanced state, the condition results in significant intrapulmonary arteriovenous shunting.[32] The severity of HPS seems to parallel the severity of liver failure. The diagnosis of HPS is based on the presence of three criteria, such as (i) chronic liver disease, (ii) increased alveolar-arterial oxygen gradient on room air, and (iii) evidence of intrapulmonary vasodilatation.

Very rarely, thrombi formed in the branches of congested portal vein pass through portosystemic shunts and cause pulmonary hypertension. Portopulmonary hypertension (POPH) develops from vasoconstriction and remodeling in resistance vessels, and its severity and liver manifestations have no correlation.[33] Transthoracic echocardiography is recommended for screening of POPH and right heart catheterization establishes the diagnosis. Portal hypertension results in the development of ascites which may cause a restrictive pulmonary function abnormalities or pleural effusion. Translocation of ascites into the pleural space results in hepatic hydrothorax. Massive necrosis of the liver from any cause may be associated with hypoxemic respiratory failure necessitating ventilatory support.[34]

LUNGS IN PANCREATIC DISORDERS

Severe form of acute pancreatitis exhibits multiorgan/system failure, of which pulmonary complications are commonly encountered. It presents with hypoxemia,

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acute respiratory distress syndrome (ARDS), atelectasis due to decreased quantity of surfactant, and pleural effusion. Some of these manifestations are the result of the effect of noxious cytokines.[35]

Hypoxemia develops without any radiologic abnormalities in 70% of patients. Hypoxemia is caused by ventilation-perfusion imbalance. Respiratory failure is associated with hypoxemia, tachycardia, dyspnea, and cyanosis. The condition may progress to ARDS becoming refractory to supplemental oxygen. It requires endotracheal intubation and ventilatory support with positive end-expiratory pressure.[36]

Pleural effusion appears to be more common in patients with pancreatitis due to alcohol abuse than in those with pancreatitis due to gall stone pathology.[37] The fluid is exudative with high protein and lactic dehydrogenase levels. The amylase level is raised. Chronic pancreatic pleural effusion arises from an internal pancreatic pleural fistula communicating with the pleural cavity. The effusion is massive and may recur. The level of amylase in the pleural fluid is quite high.

PULMONARY MANIFESTATIONS IN GASTROINTESTINAL DISEASES

The respiratory tract and gastrointestinal system share many functional similarities. The origin of both systems remains structurally distinct and functionally integrated. However, the pathophysiologic changes in one system may be reflected in the other.[38] The direct effect of spilling of gastric contents and food material into the bronchial passages results in aspiration pneumonia.[39] Gastroesophageal reflux can be related to chronic cough, asthma, bronchiectasis, and interstitial lung disease. IBD exhibits multisystem involvement and extraintestinal manifestations reflect effects of deranged immunologic mechanism.[40] However, the involvement of lung is not commonly recognized. In long-standing cases, there is occurrence of bronchiectasis and interstitial lung diseases.

PULMONARY INVOLVEMENT IN CARDIOVASCULAR DISEASES

There is a complex interaction between respiratory and cardiovascular systems. Anatomical and functional derangements of the cardiovascular system have significant effect on different components of respiratory system.

The individuals with cardiac failure exhibit dyspnea and exercise limitation. There are coexistent mechanisms occurring in the respiratory system, such as decreased lung compliance, ventilation-perfusion mismatch, increased intrapulmonary shunt, stimulation of pulmonary stretch receptors and juxtapulmonary receptors, respiratory muscle weakness, and airway hyperresponsiveness.[41]

The patients exhibit cardiogenic pulmonary edema which develops due to an increased capillary hydrostatic pressure secondary to an elevated pulmonary

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venous pressure. The condition develops from left ventricular systolic dysfunction, left ventricular diastolic dysfunction, left ventricular outflow obstruction, left ventricular volume overload, atrial outflow obstruction, and arrhythmias.[42] The patient exhibits sudden onset of severe dyspnea, respiratory distress, tachypnea, and orthopnea. Often, patients develop pleural effusion secondary to cardiac failure, and cardiac injury. Pulmonary hypertension may be noted in cardiovascular diseases from pulmonary veno-occlusive disease and pulmonary venous hypertension (left-sided atrial, ventricular, valvular heart disease).[43]

PULMONARY MANIFESTATIONS OF NEUROMUSCULAR DISEASES

The muscles of respiration include diaphragm, chest wall muscles, the abdominal muscles, and muscles of upper airway. Diaphragm is the principle muscle of inspiration. The chest wall muscles help in inspiration. The abdominal muscles help in expiration. Acute respiratory muscle fatigue and exhaustion leads to respiratory failure. Chronic neuromuscular disease may affect major respiratory muscle groups including inspiratory, expiratory, and bulbar muscles. If the condition is not treated, it leads to hypercapnic respiratory failure, which in some is precipitated by chronic aspiration, secretions retention, and pneumonia. There is impairment of cough and swallowing mechanisms.[44]

There is a high mortality from deteriorating pulmonary functions in neuromuscular diseases, such as Duchenne muscular dystrophy and spinal muscular atrophy. There is muscle weakness, impaired mucociliary clearance, defective gas exchange at rest and during exercise, and impaired respiration control during wakefulness and sleep.[45] Patients with neuromuscular disorders exhibit ventilatory defect due to inspiratory muscle insufficiency. In the absence of ventilatory assistance, it leads to hypercapnic ventilatory failure.

Pulmonary insufficiency by causing both hypoxemia and hypercapnea may result in cardiac failure, polycythemia, and central nervous system dysfunction. Chronic pulmonary insufficiency may be associated with papilledema, mental disturbances, such as drowsiness, confusion and delirium, and coma.

SEX HORMONE RELATED PULMONARY DISORDERS

Pregnancy brings about a variety of changes in the structure and function of the body which have major pulmonary and cardiovascular consequences. A multitude of changes occurring in pulmonary anatomy and physiology may predispose to many pulmonary disorders (Table 5).

In order to deliver oxygenated blood and nutrient substances to the developing fetus, marked physiologic changes occur in the respiratory and cardiovascular

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Table 5: Changes in Thoracic Cage during Pregnancy

- Elevation of diaphragm
- Increase in chest circumference
- Increase in subcostal angle

Table 6: Pulmonary Function Tests during Pregnancy

- Normal vital capacity
- Normal total lung capacity
- Fall in FRC, RV, and ERV
- Increased tidal volume
- Normal closing volume
- Normal forced expiratory volume
- Normal lung compliance
- Decrease diffusing capacity

FRC, functional residual capacity; RV, residual volume; ERV, expiratory reserve volume.

system. Pulmonary function tests demonstrate the changes that have been induced by pregnancy (Table 6).

During pregnancy, dyspnea, acute respiratory distress, rib fracture, and venous thromboembolism may be encountered.[46]

Menstruation is a cyclic endocrinologic phenomenon. Through the ebb and flow of hormones affect primarily the female genitourinary tract, menstruation may be associated with catamenial hemoptysis, catamenial pneumothorax, or variations in the severity of bronchial asthma in some women. LAM is a rare pulmonary disorder characterized by an abnormal proliferation of smooth muscle-like cells that can lead to obstruction of airways, lymphatics, and blood vessels.[47]

Patients with pelvic mass (fibroma of ovary, thecoma, granulosa cell tumor, benign ovarian cyst, fibrosarcoma of the uterus, and endometriosis) may present with weight loss and shortness of breath. Clinical examination reveals pleural effusion and minimal ascites, a manifestation of Meigs' syndrome.[48]

CONCLUSION

Many systemic disorders involve different structures of pleuropulmonary system. The manifestations may develop acutely or insidiously. Medications used in the management of various systemic and pulmonary disorders may present with drug-induced pleuropulmonary disorders. Presence of any manifestations referable to the lungs or pleura in the background of systemic diseases should be carefully evaluated. Proper history and physical examination will reveal underlying abnormality. Imaging studies, biopsy, and pleural fluid analysis help in confirming the diagnosis.

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Declaration of conflict of interest

The author(s) hereby declare/certify that they have no financial or non-financial interest in regard to the subject matter discussed in the manuscript.

Editor's Comment

A variety of infectious and non-infectious systemic conditions can involve lungs and pleura and present manifestations referable to the respiratory system. Among non-infectious disorders, granulomatous conditions and connective tissue disorders are outstanding examples. The diseases affecting alimentary tract, cardia, endocrine system, renal system, and nervous system can present with pulmonary manifestations either acutely or insidiously. The pulmonary manifestations are either due to underlying pathological process or as a complication of underlying disorder. The pulmonary manifestations are to be evaluated by proper history, clinical examination, imaging studies, biopsy, and pleural fluid analysis.

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