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Viral, Mycoplasmal, Rickettsial, and Chlamydial Infections

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VIRAL INFECTIONS

Great advances have been made in the diagnosis, treatment, and prevention of viral infections, but viral pneumonias remain a potentially lethal complication for immunocompromised patients, transplant recipients, and others receiving immunosuppressive therapy. In healthy individuals and in hospitalized patients, viral infections of the lower respiratory tract produce significant morbidity and mortality. Although the diagnosis of viral pneumonia is usually based on clinical grounds, microbiologic cultures, serologic tests, and biopsies of lung tissue are often needed. The pathologist frequently plays a crucial role in the management of patients with viral infections of the lower respiratory tract.

Cytomegalovirus Pneumonia

Cytomegalovirus (CMV) is the most common viral pathogen affecting immunocompromised patients and transplant recipients.[1] The risks are related to the type of transplanted organ, to the degree of immunosuppression, and to serologic evidence of prior CMV infection.[2] Among transplant recipients, the infection rate is highest for bone marrow transplants; intermediate for heart, heart-lung, and liver transplants; and lowest for renal transplants.[1,3] Most clinically significant CMV infections occur 1 to 4 months after organ transplantation.

CMV infection in bone marrow transplant recipients is associated with a high fatality rate. An interstitial pneumonia attributed to CMV develops in 16% to 20% of allogenic marrow recipients.[4] Acute graft-*versus*-host disease predisposes these patients for developing CMV pneumonitis.[4,5] CMV pulmonary infection is uncommon in syngenetic or autologous bone marrow transplant recipients.[4,5] In recipients of solid organs, the CMV-seronegative recipient who is given blood products or organs from CMV-seropositive donors is particularly at risk for severe CMV infection.[6,7] Reactivated infection occurring in patients with previous exposure to CMV may or may not be associated with symptomatic disease.

Other immunocompromised patients, such as those with solid tumors, lymphoproliferative disorders, or rheumatologic diseases on steroid therapy, may rarely develop CMV pneumonitis.[8] An intrauterine or neonatal CMV infection in premature infants is associated with high rates of mortality and morbidity.[8] CMV is commonly isolated from respiratory tract secretions and tissues of patients infected with human immunodeficiency virus (HIV), and it is frequently associated with *Pneumocystis carinii* and other opportunistic pulmonary pathogens (see Chap. 45).[9,10] Pulmonary CMV infection in the immunocompromised patient typically leads to interstitial pneumonitis. The presentation may be insidious or abrupt. Initial symptoms include nonproductive cough, tachypnea, dyspnea, and fever. Disseminated infection frequently leads to hepatitis, hemorrhagic enteritis, or retinitis.[11] Laboratory studies indicate leukopenia with atypical lymphocytes, and the results of liver function tests are elevated. The chest radiograph typically reveals bilateral interstitial or reticulonodular infiltrates, but it sometimes reveals nodules or patchy consolidation. Consolidation suggests a superimposed fungal or bacterial infection.

Several morphologic patterns of pulmonary injury seen in CMV infection may correlate with the clinical presentation. In most cases, there is an associated interstitial pneumonitis with neutrophilic inflammation, extensive necrosis, and hemorrhage

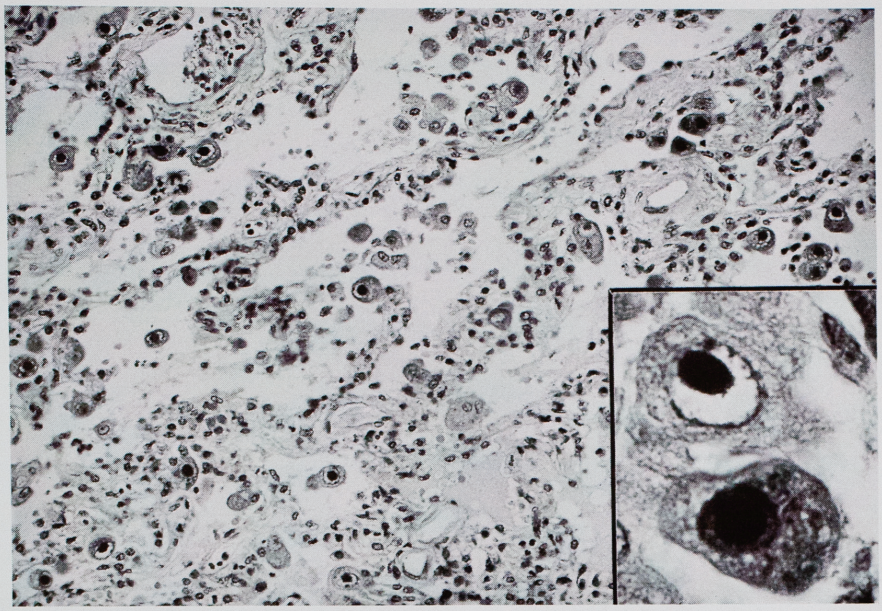

FIGURE 42-1. In cytomegalovirus pneumonitis, there are numerous, enlarged alveolar lining cells with prominent intranuclear inclusions and an associated lymphocytic septal infiltrate. (H & E stain; intermediate magnification.) Two cells have intranuclear and intracytoplasmic inclusions (*inset*). (H & E stain; oil immersion.)

(Fig. 42-1). Hyaline membranes and other features of diffuse alveolar damage may be found.[1] The viral inclusions may be located in alveolar pneumocytes, interstitial cells, endothelial cells, or macrophages (Fig. 42-2; see Fig. 42-1). Some viral inclusion-bearing cells may exist without a significant inflammatory response. The CMV-infected cells are 25 to 40 μm in diameter, and each cell characteristically has an enlarged nucleus with a single prominent, eccentric, eosinophilic inclusion. These Feulgen-positive Cowdry type A intranuclear inclusions are surrounded by a clear halo when fully developed and resemble owl eyes. Basophilic granular viral inclusions may be detected in the cytoplasm by hematoxylin and eosin and periodic acid-Schiff (PAS) or methenamine-silver stains. The diagnosis of CMV pneumonitis often requires careful searching, because the infected cells may be sparsely distributed and associated with a minimal or no inflammatory reaction. An immunoperoxidase stain or *in situ* hybridization for CMV increases the diagnostic yield.[12,13] The shell-vial centrifugation culture technique can more rapidly diagnose CMV.[14] CMV can be detected in bronchoalveolar lavage (BAL) fluid within 1 day, and the method has a sensitivity and specificity approaching that of conventional viral culture.

Herpes Simplex Virus

Herpes simplex virus (HSV) is an uncommon lower respiratory tract pathogen. In immunocompromised patients, the risk factors for HSV infection are not as well defined as for other viruses. However, as with CMV, patients with severe burns, alcoholism, acquired immunodeficiency syndrome (AIDS), or solid or hematopoietic malignancy and organ transplant recipients are at increased risk for developing HSV tracheobronchitis and pneumonia.[15,16] Infants born to mothers with active genital HSV infection may also develop pneumonia. Rare examples of HSV tracheobronchitis have been described in immunocompetent or elderly adult patients.[17]

HSV 1 and HSV 2 have been associated with lower respira-

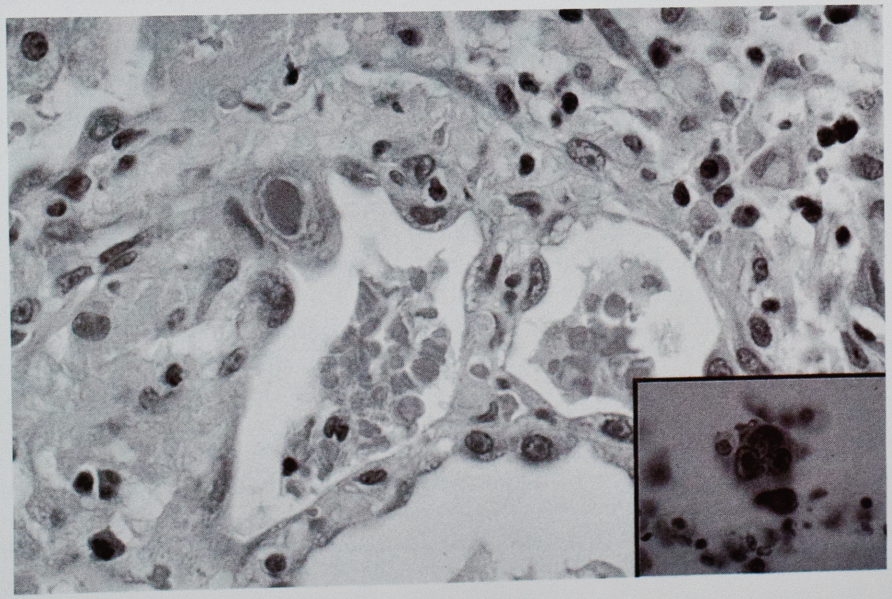

FIGURE 42-2. In cytomegalovirus (CMV) pneumonitis, a CMV inclusion-bearing cell is identified within the vascular endothelium (H & E stain; high magnification.) Identification is achieved with immunostaining of the virus, and high magnification (*inset*). (Courtesy of P. Angritt, M.D., Washington, DC.)

tory tract infection, but HSV 1 has been more frequently identified in viral cultures. A focal bronchopulmonary infection typically is observed in patients with severe burns, but disseminated diffuse pulmonary HSV infection occurs in other immunosuppressed patients.[15,16] The diffuse pattern has been associated with hematogenous spread of HSV to the lungs.[15]

In patients with HSV lower respiratory tract infection, the typical labial herpes cold sores may precede or coincide with active pulmonary disease. Acute bronchospasm may signify herpetic tracheobronchitis, and endoscopic or bronchoscopic examination may reveal ulceration of the tracheobronchial or esophageal mucosa.[3] The nonspecific clinical findings that suggest HSV pneumonia include dyspnea, cough, fever, chills, diaphoresis, chest pain, and leukocytosis. Some persons with HSV pneumonia develop adult respiratory distress syndrome with profound hypoxemia.[18,18a]

Necrotizing tracheobronchitis and pneumonia are the dominant patterns of tissue injury seen in HSV lower respiratory tract infections.[19] Necrotizing tracheobronchitis is characterized by extensive mucosal ulceration and pseudomembrane formation. Bronchial narrowing and total airway obstruction have been attributed to chronic, long-standing mucosal inflammation.

Microscopically, the ulcerated tracheal or bronchial mucosa is covered by a thick fibrinopurulent exudate containing degenerating neutrophils, nuclear debris, and necrotic material (Fig. 42-3). Within the lungs, a patchy, nodular necrotizing bronchopneumonia may be the result of contiguous spread from the airways. Elements of diffuse alveolar damage with hyaline membrane formation and alveolar hemorrhage may be observed.

The viral inclusions of HSV may be identified in tracheobronchial ulcers, in submucosal glands, or at the periphery of necrotic parenchymal pulmonary lesions.[19] The viral inclusions occur early in the clinical course of infection and may be easily overlooked.[19] The typical HSV inclusions show ground-glass nuclear chromatin, eosinophilic Cowdry type A intranuclear inclusions, and multinucleation. However, identification of HSV viral inclusions in lung tissue may be difficult, because multinucleation is less commonly seen in lung than in mucocutaneous lesions and the nuclear inclusions resemble those of CMV. The morphologic features that favor HSV include nonenlarged cells, red intranuclear inclusions, and the absence of cytoplasmic inclusions (see Chap. 45; see Fig. 45-5). Rarely, CMV and HSV coexist in the same specimens.[20] Immunoperoxidase or immunofluorescent techniques should be used to identify HSV in tissues or cytologic specimens (see Fig. 42-3, *insets*).[21]

The diagnosis of HSV infection in immunosuppressed patients can be suggested on clinical grounds, but definitive proof of HSV lower respiratory tract infection requires a biopsy with tissue cultures or immunohistologic or immunofluorescent studies.[8,15] Examination of BAL and other respiratory tract secretions can only suggest the possibility of HSV lower respiratory tract infection. HSV may be in BAL specimens because of asymptomatic viral shedding or contamination from an upper respiratory tract or oral infection, rather than representing active lower respiratory tract disease.

Varicella-Zoster Virus

Varicella-zoster virus (VZV) is a herpesvirus that causes chicken pox (*i.e.*, varicella). Zoster or shingles refers to the reactivated neurocutaneous infection that occurs in debilitated or immunocompromised adults. Healthy adults with varicella infection are at increased risk for VZV pneumonia, but the greatest risk for VZV pneumonia is among immunocompromised adults and pediatric patients with lymphoma, Hodgkin disease, and other hematologic disorders and among transplant recipients.[22–24]

The characteristic papulovesicular rash of chicken pox usually precedes or accompanies pulmonary involvement.[25] Patients frequently present with cough, dyspnea, hemoptysis, and various degrees of respiratory distress.[22] A sharp chest pain signifies pleural vesicles. Chest radiographs of patients with acute VZV pneumonia demonstrate interstitial or nodular patterns. Resolved pulmonary infection may show multiple fibrocalcific nodules.[25]

The lungs at autopsy are heavy and congested with multiple foci of hemorrhage and necrosis. Vesicles may form on the visceral pleura and on tracheobronchial mucosa (Color Fig. 42-1).[26] Microscopically, a focally hemorrhagic and necrotizing pneumonia is

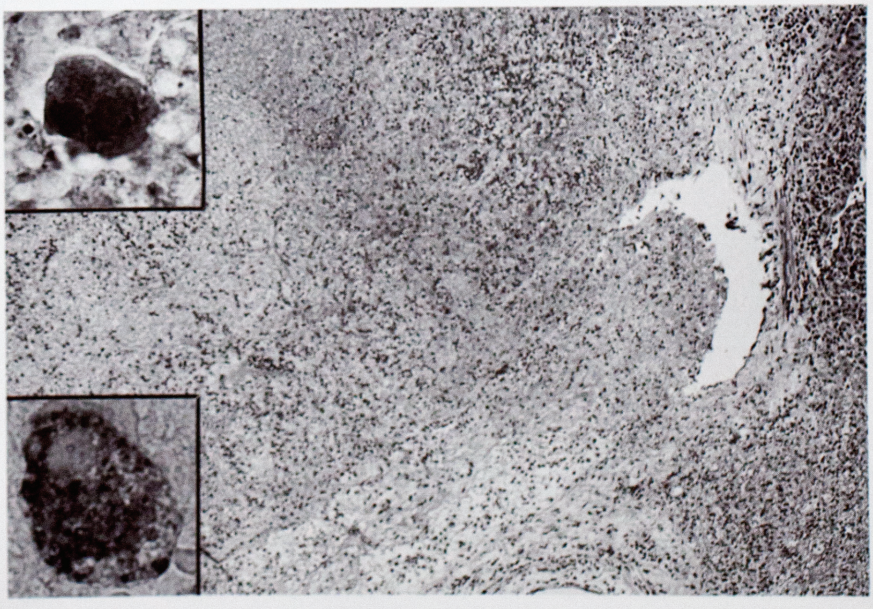

FIGURE 42-3. Herpesvirus (HSV) infection can cause an extensive necrotizing pneumonia. (H & E stain; low magnification.) An eosinophilic, multinucleated cell lies within necrotic debris (*top inset*). (H & E stain; oil immersion.) Positive immunoreactivity for HSV (*bottom inset*). (Immunoperoxidase stain; oil immersion.)

accompanied by diffuse alveolar damage.[24,25] Extremely rare multinucleated cells with eosinophilic Cowdry type A inclusions resemble those seen in HSV infection. These inclusions may be identified in alveolar macrophages and alveolar or bronchiolar lining cells at the periphery of necrotic foci.[22] The airways may demonstrate necrotizing bronchitis and bronchiolitis. Giant cells similar to those seen in measles virus pneumonia were reported by Saito and colleagues in a premature infant.[27]

The diagnosis of VZV pneumonia is usually made on clinical grounds for symptomatic patients who manifest the typical viral exanthem and with radiographic evidence of a pulmonary process. The viral inclusions may be readily seen on Tzanck preparation of skin; viral infected cells are exceptionally rare in pleural or BAL fluids. Definitive identification of VZV requires viral cultures or immunofluorescent techniques because the viral inclusions morphologically resemble those of HSV.

Adenovirus

Adenoviruses can cause upper and lower respiratory tract infections in patients of all ages, ethnicity, and immunocompetency. Epidemics of adenovirus-related respiratory disease have occurred throughout the world. At least 41 serotypes of adenovirus have been associated with specific infections.[8,28] In young children, adenovirus types 1, 2, 3, 5, and 7 cause pharyngotonsillitis, otitis, and keratoconjunctivitis. Infection with adenovirus types 3, 4, 7, or 21 leads to lower respiratory tract disease, including bronchitis, bronchiolitis, and pneumonia.

In military recruits and otherwise healthy adults, adenovirus pneumonia is usually self-limited and rarely fatal. Patients typically present with a febrile upper respiratory tract illness and few pulmonary findings. However, severe, life-threatening pulmonary infections may develop in neonates, young children, and transplant recipients.[3,29,30] The mortality rate approaches 60% in symptomatic immunocompromised patients.[31] The late sequelae of adenovirus infection acquired in childhood include bronchiectasis, bronchiolitis obliterans, pulmonary fibrosis, and lobar collapse.[32–34]

In an autopsy series of patients with fatal cases of adenovirus infection, Becroft identified severe necrotizing bronchitis, bronchiolitis, and pneumonia.[34] On microscopic examination, the airways demonstrated extensive mucosal ulcerations with destruction of bronchial glands (Fig. 42-4). Eosinophilic PAS-positive material lined the denuded mucosal surface, and necrotic debris filled the bronchiolar lumen. Hyaline membranes and other features of diffuse alveolar damage were seen in the adjacent pulmonary parenchyma.

Two viral inclusion-bearing cells are found within bronchiolar or alveolar epithelium in adenovirus pneumonia.[34,35] One type contains an eosinophilic, Feulgen-negative inclusion surrounded by a perinuclear halo (Color Fig. 42-2). The other type, called a smudge cell, contains an enlarged, basophilic, Feulgen-positive inclusion without a perinuclear halo.[35] In immunocompromised patients, these viral inclusions may be absent or be mistaken for CMV.[36]

Influenza Virus

Influenza virus is a highly contagious cause of epidemic respiratory tract infections worldwide. Most patients completely recover from influenza virus infection, but lower respiratory tract disease remains the most serious complication.[37] During the 1918 influenza pandemic, more than 20 million deaths were attributed to influenza pneumonia and related complications.[38] The 1957 Asian and 1968 Hong Kong influenza epidemics similarly produced high rates of morbidity and mortality.[39] In nonendemic years, influenza virus infection is responsible for many hospitalizations and between 10,000 and 20,000 deaths annually.[37]

Of the three types of influenza virus, influenza virus A and B are associated with epidemic respiratory tract infection; influenza virus C causes mild disease.[37] Although the entire population is susceptible to influenza virus infection, severe infection occurs in very young or elderly patients and in patients with underlying cardiovascular and pulmonary diseases.[37] Young children who survive influenza pneumonia may develop interstitial pneumonitis, fibrosis, or bronchiolitis obliterans later in life.[40] Persons who are immunocompromised, hospitalized, or reside in nursing homes are more likely to develop influenza pneumonia than other

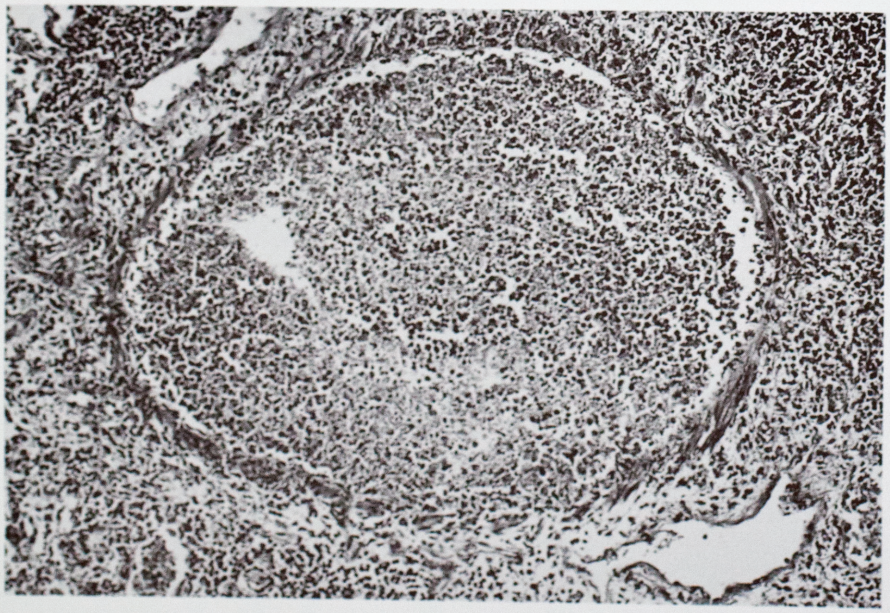

FIGURE 42-4. In adenovirus necrotizing bronchiolitis, there is sloughing of bronchiolar mucosa, and the lumen is filled with necrotic debris. An extensive acute and chronic inflammatory cell infiltrate extends beyond the bronchiolar wall into adjacent lung parenchyma. (H & E stain; low magnification; courtesy of D. Schwartz, M.D., Atlanta, GA.)

populations. Fatal influenza pneumonia has occurred in patients without identifiable predisposing risk factors.[41]

In a healthy adult, uncomplicated influenza virus infection leads to the classic presentation of flu-type symptoms, a benign clinical course, and complete recovery. However, in patients at risk for severe infection, complicated influenza virus infection leads to tracheobronchitis and pneumonia. The clinical presentation and the pattern of lower respiratory tract disease is highly variable. A diffuse, primary viral pneumonia in a debilitated patient may be fatal (Color Fig. 42-3) but not so in patients who develop localized pneumonia. Viral pneumonia is often followed by a superinfection with bacterial or fungal organisms.[37]

Most cases of influenza pneumonia are diagnosed on clinical grounds and rarely require tissue biopsy. A hemorrhagic or necrotizing bronchiolitis has been described in antemortem and postmortem lung specimens.[39,41] Several histologic patterns of pulmonary injury have been reported, but the changes could have been caused by viral pneumonia, combined viral and bacterial pneumonia, or bacterial pneumonia after viral pneumonia.

In patients with acute necrotizing tracheobronchitis, the earliest histologic changes are necrosis of the ciliated and goblet cells, followed by mucosal desquamation.[38] Intraepithelial viral inclusions are not apparent using light microscopy, but intranuclear fibrillary inclusions have been identified ultrastructurally.[42] Regenerative changes, including epithelial hyperplasia and squamous metaplasia, have been described after the second week, and bronchiolitis obliterans has occurred in later stages.[39] In the pulmonary parenchyma, various stages of diffuse alveolar damage with prominent hyaline membranes characterize pure influenza pneumonia.[39,41] Foci of pulmonary congestion and thrombosis also may be apparent. These histologic changes have been described in rapidly fatal cases of pneumonia uncomplicated by bacterial superinfections. Another morphologic pattern of injury is that of a hemorrhagic or necrotizing pneumonia in which the viral infection leads to damage to endothelial cells, destruction of alveolar lining, and dilatation of alveolar septal capillaries. A suppurative bronchopneumonia has been seen in patients with mixed or superimposed bacterial or fungal pneumonia.[39]

Measles Virus

Measles (*i.e.*, rubeola) is a highly contagious but usually self-limited childhood infection that seldom causes significant pulmonary complications. The overall incidence of measles has decreased since the introduction of viral immunization in the 1960s. However, nonimmunized or immunodeficient patients are at increased risk for developing measles pneumonia. Most fatal cases have occurred in immunodeficient children with impaired T-cell–mediated immunity.[43,44]

In immunocompetent adults, measles pneumonia is seldom fatal, but it may be associated with significant morbidity. Outbreaks of measles pneumonia have occurred among nonimmunized, otherwise healthy military recruits.[45] Immunocompetent adults with measles pneumonia usually present with a generalized maculopapular rash, high fever, rales, and hypoxemia. The clinical course is sometimes complicated by a secondary bacterial pneumonia. The characteristic skin rash of measles may be lacking in immunodeficient patients.[43,44]

In patients with fatal cases, the lungs at postmortem examination demonstrate diffuse consolidation with focal hemorrhage and necrotizing tracheobronchitis. Measles pneumonia is typically manifested by a giant cell pneumonia with diffuse alveolar damage.[46,47] Numerous multinucleated giant cells with prominent eosinophilic intranuclear and intracytoplasmic viral inclusions are identified in alveolar epithelium and septa (Color Fig. 42-4).[47a] Involvement of the airways leads to squamous metaplasia in the terminal bronchioles and alveolar ducts.[46] The microscopic findings may include vascular thrombosis and superimposed bacterial pneumonia.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infection in infants and young children.[48–50] In the community, infection with RSV typically occurs in the late autumn and winter months. During RSV outbreaks, other hospitalized pediatric patients are at risk for nosocomial RSV infection.[51] Among adults, RSV has been recognized as an important pathogen in immunocompromised, institutionalized, elderly, or other debilitated patients.[49,52]

In pediatric patients, RSV principally causes bronchiolitis and pneumonia, but it can also cause croup and tracheobronchitis.[50] Immunocompromised adult patients with RSV infection often present with fever, cough, rhinorrhea, and otalgia.[52] Various degrees of respiratory distress may be evident. Chest radiographs show bilateral interstitial or lobar infiltrates and pleural effusions.

Lung biopsy specimens demonstrate various patterns of tissue damage.[53] In the early stages of acute bronchiolitis, polypoid tufts of residual bronchiolar epithelium result from mucosal regeneration and sloughing (Fig. 42-5). Rare cytoplasmic viral inclusions within the degenerating bronchiolar epithelium are associated with necrotic cellular debris and mucus. In RSV pneumonia, an extensive intraalveolar or interstitial lymphocytic infiltrate accompanies necrotizing bronchiolitis and bronchitis. Intracytoplasmic viral inclusions may be exceedingly difficult to identify. Rarely, RSV pneumonia produces diffuse alveolar damage with multinucleated giant cells that resembles measles pneumonia (Fig. 42-6).[52,54]

Parainfluenza Virus

Parainfluenza is second to RSV in causing respiratory illness within the pediatric patient population.[49] In infants and young children, parainfluenza virus 1 and 2 are responsible for laryngotracheobronchitis (*i.e.*, croup) and bronchiolitis.[50] In severely immunocompromised infants, fatal pneumonia has been associated with parainfluenza type 3.[50,55] In older children and adults, parainfluenza pneumonia is extremely uncommon, but rare cases of pneumonia and bronchiolitis obliterans organizing pneumonia have been reported.[56–58] In lung tissues, parainfluenza infection leads to diffuse alveolar damage with hyaline membrane formation and interstitial inflammation.[57,59] Unlike other viral pulmonary infections, viral inclusions are usually not found in parainfluenza pneumonia, but giant cells similar to those seen in measles pneumonia have been described in some patients.[55,57,59]

Epstein-Barr Virus

Epstein-Barr virus (EBV) is the causative agent of infectious mononucleosis, a self-limited, febrile illness with pharyngitis and lymphocytosis. In exceptional cases, radiographic or clinical evi-

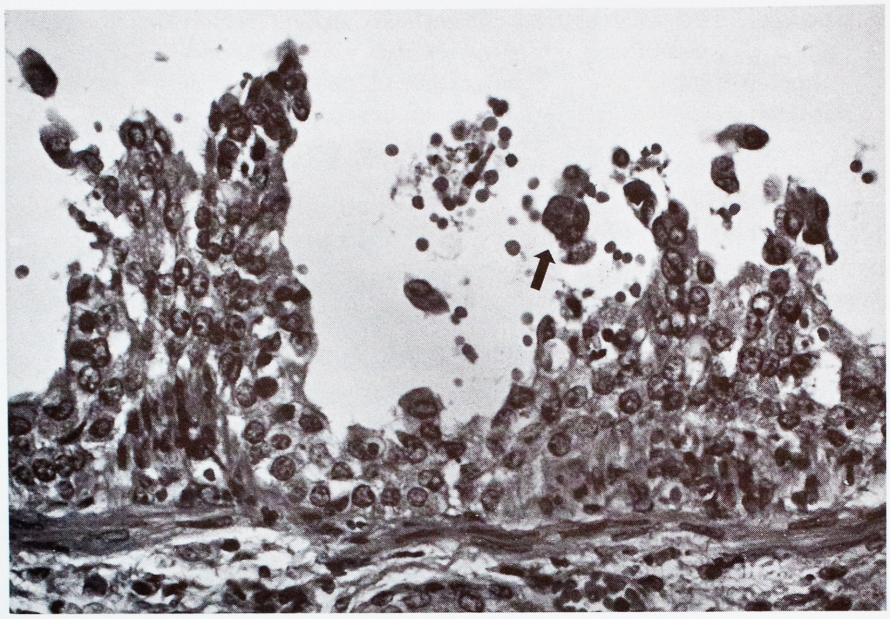

FIGURE 42-5. In respiratory syncytial virus bronchiolitis, mucosal hyperplasia and sloughing leads to polypoid epithelial formations. A multinucleated inclusion-bearing cell lies at the apex of a polypoid tuft (*arrow*). (H & E stain; high magnification; courtesy of C. Abramowsky, M.D., Atlanta, GA.)

dence of a pulmonary infection has followed an infectious mononucleosislike illness.[60–62] Schooley and colleagues described two patients with serologic evidence of recent EBV-related infection who developed a febrile illness with interstitial pneumonitis that responded to acyclovir therapy.[62]

In transplant recipients, a spectrum of posttransplant lymphoproliferative disorders has been strongly linked with EBV.[3,63,64] Pulmonary involvement, although uncommon, is characterized by bilateral interstitial infiltrates. Open lung biopsies reveal a polyclonal lymphoplasmacytic interstitial infiltrate that morphologically resembles malignant lymphoma. Discontinuation of immunosuppressive therapy has sometimes resolved the pulmonary infiltrates.

As an oncogenic virus, EBV is strongly linked to nasopharyngeal carcinoma and non-Hodgkin lymphoma.[65] EBV has been related to a poorly differentiated lung carcinoma in Asian patients that morphologically resembles the lymphoepithelioma variant of nasopharyngeal carcinoma.[66,67] In one patient, there was serologic evidence of previous EBV infection; EBV DNA was detected in the tumor by *in situ* hybridization.[67]

Human Immunodeficiency Virus

HIV is the causative agent of AIDS. Pulmonary processes in this important group of patients are described in Chapter 45.

MYCOPLASMAL INFECTIONS

Mycoplasma pneumoniae is a significant cause of respiratory tract infections in the general population and accounts for 30% to 50% of community acquired pneumonias.[68–70] Most cases of mycoplasma pneumonia occur in otherwise healthy children and young adults, but outbreaks have been reported in schools, universities, and military camps.[70,71] Infection is uncommon in elderly and immunocompromised persons.

Mycoplasma pulmonary infection leads to an atypical pneumonia that is characterized by pulmonary infiltrates, a normal leukocyte count, and absence of a bacterial pathogen.[68] The clinical presentation often evolves from an upper respiratory tract

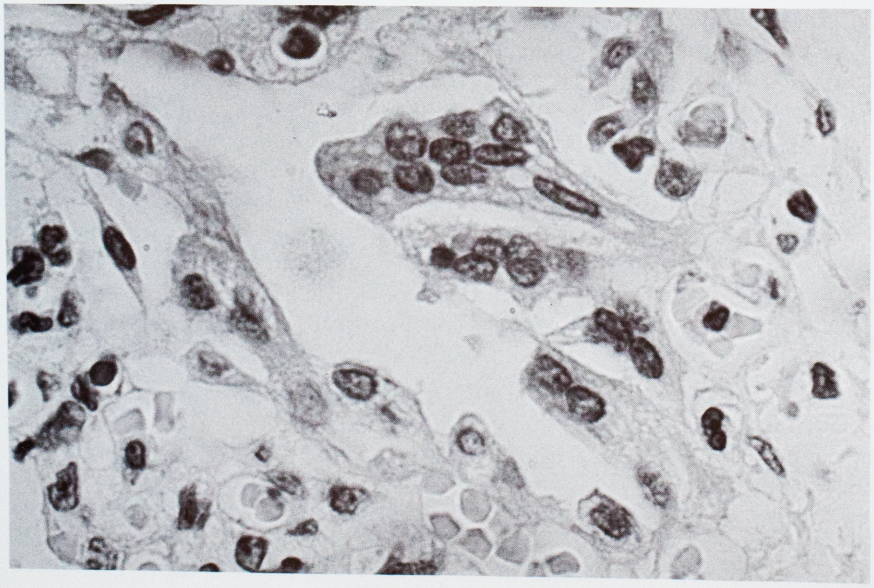

FIGURE 42-6. In respiratory syncytial virus pneumonia, multinucleated syncytial giant cells line the alveolar epithelium. Rare eosinophilic inclusions are seen within the cytoplasm. (H & E stain; high magnification; courtesy of C. Abramowsky, M.D., Atlanta, GA.)

infection (*e.g.*, pharyngitis, otitis) to a lower respiratory infection (*e.g.*, tracheobronchitis, bronchiolitis, pneumonia).[69] Most cases of mycoplasma pneumonia are mild and self-limited and end with complete recovery. The intrathoracic manifestations of mycoplasma pneumonia include bronchiolitis obliterans, bronchiectasis, interstitial fibrosis, abscess, pleuritis, Stevens-Johnson syndrome, and adult respiratory distress syndrome.[70–74] Some patients develop extrapulmonary involvement of the central nervous system, skin, and the gastrointestinal, hematologic, and musculoskeletal systems.[75,76]

Few antemortem pathologic studies of *M. pneumoniae* pneumonia have been published because the diagnosis is primarily based on clinical grounds. The histopathologic features of mycoplasma pneumonia are nonspecific and overlap with other infectious processes. In an open lung biopsy study of mycoplasma pneumonia, Rollins and associates found acute and chronic bronchiolitis and peribronchiolitis.[77] Most of their patients showed a prominent neutrophilic exudate within bronchioles, metaplastic bronchiolar cells, and extensive lymphoplasmacytic inflammation in the bronchiolar wall (Fig. 42-7). The adjacent lung tissues showed peribronchiolar septal widening and type 2 pneumocyte hyperplasia. Autopsy studies of fulminant mycoplasma pneumonia have shown necrotizing tracheobronchitis, interstitial pneumonitis, and diffuse alveolar damage in addition to the previously described histologic features.[76–78]

RICKETTSIAL INFECTIONS

Rickettsiae is a family of bacteria that are obligate intracellular parasites maintained in nature through a cycle involving mammalian reservoirs and insect vectors. Rickettsioses in humans include a variety of illnesses characterized by the triad of fever, headache, and rash, except for acute Q fever, for which a rash is uncommon. In the United States, there are several endemic rickettsial infections: Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsii*; Q fever, caused by *Coxiella burnetii*; flea-borne murine typhus, caused by *Rickettsia typhi*; rickettsial pox, caused by *Rickettsia akari*; and epidemic louse-borne typhus, caused by *Rickettsia prowazekii*. RMSF and Q fever are discussed in this section, because they have the best-defined pulmonary involvement in man.

Rocky Mountain Spotted Fever

R. rickettsii, the etiologic agent of RMSF, is the most prevalent and severe rickettsiosis endemic in the United States. In 1990, approximately 650 cases of RMSF were reported to the Centers for Disease Control. The states with the highest incidence of case reports were Oklahoma, North Carolina, and South Carolina. Most cases occur between May and September, and the highest incidence of infection is among children 5 to 9 years of age. *R. rickettsia* are maintained in nature through transovarian transmission in several species of ticks, which serve as its natural host or reservoir. The classic triad of fever, rash, and a history of a tick bite may be identified in only 3% of patients within the first 3 days of illness.[79] RMSF should be considered for any person who develops fever during the spring and summer and who has been in a RMSF endemic area, even though there is no rash or history of tick exposure.

Pulmonary manifestations, including pneumonitis or pneumonia, have been reported in 2% to 17% of patients with RMSF before treatment. Donohue and colleagues reported lower respiratory tract involvement in 42% of patients hospitalized with RMSF.[80]

Pathologic studies of lower respiratory tract involvement in 25 patients with fatal cases of RMSF (*i.e.*, 20 children and 5 adults) have strongly suggested rickettsial involvement of the pulmonary microcirculation.[81–83] The histologic examination reveals a hemorrhagic pneumonitis with diffuse chronic interstitial inflammation, a mononuclear vasculitis in the walls of arterioles or venules, and intraalveolar edema (Fig. 42-8). The pathophysiologic sequelae of this direct endothelial damage include vasculitis and increased vascular permeability, which may contribute to the development of adult respiratory distress syndrome and noncardiogenic pulmonary edema frequently observed in patients with fatal and near-fatal cases.

The principal test for confirmation of RMSF uses antigens of

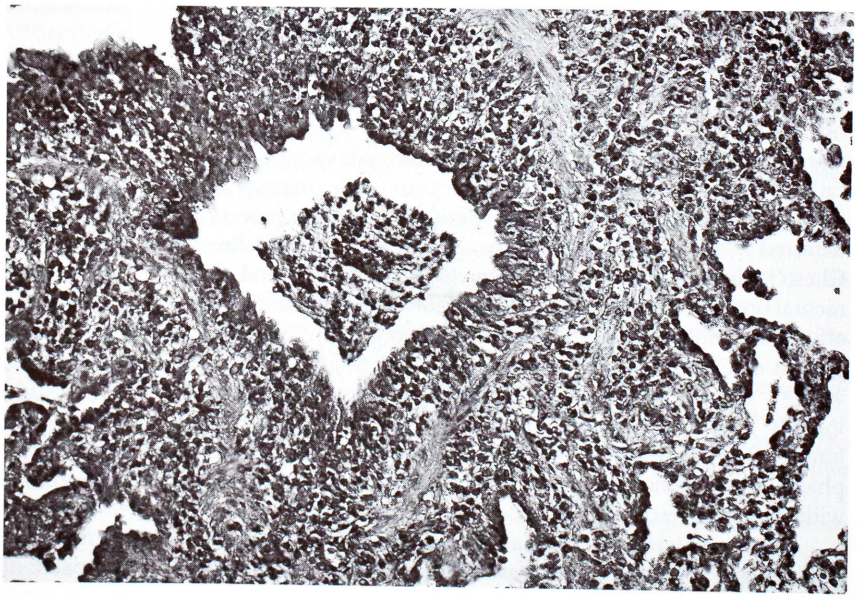

FIGURE 42-7. *Mycoplasma pneumoniae* bronchiolitis and peribronchiolitis extend into adjacent alveolar tissue. The bronchiolar lumen contains sloughed epithelium admixed with inflammatory cells. (H & E stain; low magnification; courtesy of T. Colby, M.D., Rochester, MN.)

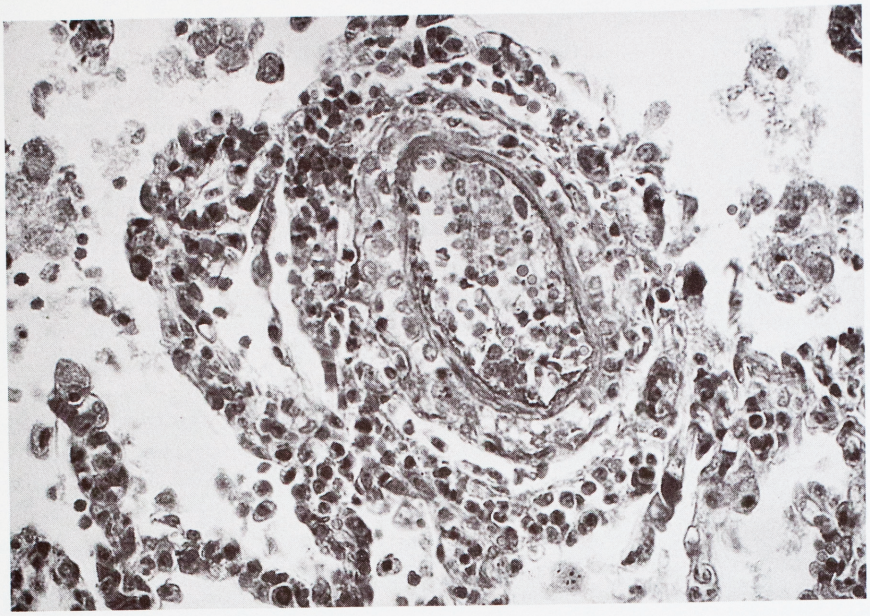

FIGURE 42-8. *Rickettsia rickettsiae* pneumonia is characterized by interstitial pneumonitis and vasculitis. (H & E stain; intermediate magnification; courtesy of C. Abramowsky, M.D., Atlanta, GA.)

the rickettsia.[84] Direct immunofluorescent antibody stains of paraffin-embedded sections can be performed for lung and skin biopsies. This method is not 100% sensitive and may be potentially hazardous if performed on frozen sections. Detection of *R. rickettsia* DNA in clinical specimens using polymerase chain reaction technology has been developed and may prove useful.[85]

Q Fever

Q fever is a febrile illness caused by the widely distributed rickettsial organism *C. burnetii*. First described in 1937 by Derrick among abattoir workers in Australia, Q fever is primarily an occupational disease affecting those with direct contact with infected animals.[86,87] Cattle, sheep, goats, and ticks are the most common animal reservoirs of the organisms. Airborne transmission of *C. burnetii* is facilitated by its ability to survive for long periods outside of a host and by its extreme infectivity; a single organism can initiate infection.

The most common presentation of Q fever infection is that of a self-limited, febrile illness characterized by severe retrobulbar headache, high spiking fevers (39°C) with rigors, general malaise, and myalgia, sometimes complicated with pneumonia and hepatitis. Although Q fever is regarded primarily as a respiratory disease, the incidence of pulmonary involvement varies dramatically.[88] The pneumonia in Q fever most commonly presents as an atypical pneumonia, but it may be a rapidly progressive process or detected as an incidental finding in a patient with a febrile illness. Chest radiographic abnormalities include multiple, round, segmental opacities; linear or partial lobar consolidation; and pleural effusions. Unlike RMSF and typhus group organisms, the pathogenesis of Q fever does not involve vasculitis. Studies of animals with *C. burnetii* infections have shown the organism to reside initially within the phagolysosomes of susceptible cells in the lungs.[89] The inflammatory response is transformed into a macrophage- and lymphocyte-predominated pneumonia that subsides with complete resolution of the disease.

Because Q fever pneumonia is rarely fatal, information about its histologic appearance in humans is limited. Whittick first demonstrated rickettsial-like organisms at autopsy in the lung of a patient with a fatal case of Q fever in 1950.[90] Urso described the anatomic findings in another patient with a fatal case that clinically resembled bacterial lobar pneumonia.[91] The histologic features were those of a severe, focally necrotizing, and hemorrhagic pneumonia, necrotizing bronchitis, and bronchiolitis. Peirce and associates described a patient with fulminant Q fever pneumonia that was established by transbronchial biopsy and serology.[92] Numerous alveolar macrophages contained intracytoplasmic coccobacillary bodies. Janigan and Marrie described a pulmonary inflammatory pseudotumor related to Q fever pneumonia. Immunochemistry and electron microscopy revealed *C. burnetii* organisms within the resected specimen.[93]

Because of the hazards associated with cultivation of *C. burnetii*, tests for antibodies to *C. burnetii* are recommended for confirmation of the diagnosis. A fourfold rise in the titer between the acute and convalescent samples is considered diagnostic. Most acute Q fever infections resolve without treatment.

CHLAMYDIAL INFECTIONS

The Chlamydiaceae are a genetically diverse group of bacteria with a unique dimorphic intracellular development cycle. They are obligate intracellular parasites that depend on the host cell for adenosine triphosphate metabolites. Like the rickettsiae, chlamydial organisms replicate in the cytoplasm of infected host cells. Infection of the host begins with an elementary body, a sporelike particle adapted to an extracellular environment. After fusion with a primary lysosome of the parasitized cell, the elementary body converts to a metabolically active, noninfectious reticulate body, which is adapted to the intracellular environment. The reticulate body replicates by binary fission and releases more infectious elementary bodies by lysis of the host cell or extrusion of the inclusions.

Three species of *Chlamydia* have been recognized: *Chlamydia trachomatis, Chlamydia psittaci*, and *Chlamydia pneumoniae*. Each is capable of producing pulmonary disease in man.

Chlamydia trachomatis

C. trachomatis is recognized as a cause of urogenital and conjunctival disease (Color Fig. 42-5), and it is an etiologic agent of pneumonia in infants and immunocompromised adults. The clinical presentation of *C. trachomatis* pneumonitis is characterized by a progressive, staccato cough in a febrile 4- to 8-week-old infant.[94] Eosinophilia and elevated serum IgG and IgM levels are common. Infants acquire infection during passage through the birth canal of a mother with a *C. trachomatis* genital infection. The incidence of chlamydial pneumonitis among infants born to infected mothers may be as high as 16%.[95] Because most cases of *C. trachomatis* pneumonitis can be diagnosed clinically and are not life threatening, there have been few detailed reports of the pulmonary histopathology, which is characterized by a nonspecific interstitial pneumonitis that is often associated with a necrotizing bronchiolitis.[96,97]

Chlamydia psittaci

C. psittaci is the etiologic agent of psittacosis (*i.e.*, parrot fever), an endemic disease of birds that is transmissible to humans. Humans are initially infected by inhaling the air of infected birds; person-to-person transmission is rare. Psittacosis produces a systemic illness predominantly involving the lungs. After an incubation period of 1 to 2 weeks, patients often present with an acute febrile illness characterized by high fevers, persistent cough, and headaches.[98] Most patients report close contact with birds or commercial poultry.

The histopathologic features of psittacosis involvement of the lung were defined in autopsies of infected patients before the availability of tetracyclines. Lillie[99] and Binford[100] summarized the pulmonary inflammatory process in patients with fatal cases. Early in the course of the disease, the intraalveolar exudate contains fibrin, polymorphonuclear cells, and epithelial cells, but there is no interstitial inflammation. Later, a chronic lymphocytic inflammatory response occurs in the alveolar and interstitial spaces.

The diagnosis of psittacosis is made by serologic studies, because isolation of the organism in the clinical laboratory is hazardous. The serologic methods rely on detecting genus-specific antibody that may result from an infection with *C. trachomatis, C. psittaci*, or the TWAR strain of *C. pneumoniae*.[101] Van Berkel and colleagues demonstrated *C. psittaci* antigens in lung tissue by using a rabbit antiserum against *C. psittaci* and an indirect immunofluorescent technique.[102]

Chlamydia pneumoniae, *TWAR Strain*

C. pneumoniae has been established as a new species on the basis of DNA, immunologic, and ultrastructural studies.[103] Only one serovar or strain (*i.e.*, TWAR) has been identified. It was first isolated in 1965 from the eye of a Taiwanese child and, in 1983, from a college student with pharyngitis. Because isolation of *C. pneumoniae* is hazardous, the development of a TWAR-specific monoclonal antibody microimmunofluorescent test has played a key role in defining the epidemiology of this disease.[104] The test can differentiate between IgM and IgG serum fractions; the former is usually lost 2 to 6 months after infection, but IgG antibody persists.

The seroprevalence rates are low in children, and they increase with age. Several studies have correlated TWAR with acute respiratory disease, including pneumonia, bronchitis, pharyngitis, and sinusitis. During a 5-year period at the University of Washington Student Health Center, *C. pneumoniae* infection was diagnosed in 22 students, representing almost 10% of all diagnosed pneumonias and 20% of radiographically proven pneumonias. Two studies of community-acquired pneumonia in Canada and Pittsburgh demonstrated TWAR antibodies in 6% of 660 patients, making TWAR the third or fourth most commonly recognized cause of pneumonia in these studies.[105,106]

Pathologic studies of uncomplicated TWAR pneumonia are limited because the illness usually is not fatal. Chlamydial-like intracytoplasmic elementary bodies were reported in an open lung biopsy specimen from a patient with a convalescent titer positive for the TWAR antibody.[107] This patient presented with an indolent, multinodular, necrotizing pneumonia 3 months after the institution of cyclophosphamide therapy for Wegener granulomatosis. Microscopic examination of lung biopsy specimens showed a nodular organizing pneumonia and bronchiolitis.

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