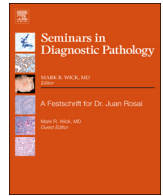




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Histopathology of viral infections of the lung



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Introduction

Lower respiratory viral infections are a significant source of morbidity and mortality worldwide, causing an estimated 3.9 million deaths each year.¹ In particular, viruses cause up to 50%

of community-acquired pneumonia (CAP) in children and adults, and predispose patients to secondary bacterial pneumonia.^{1,2} Those at risk for more severe disease include the very young, very old, immunocompromised, and patients with pre-existing respiratory conditions.

Patients with viral pneumonia commonly present with fever, cough, headache, and myalgia. Compared to patients with bacterial or mixed bacterial-viral pneumonia, patients with pure viral

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pneumonia are less likely to have a productive cough with expectoration.³ Other clinical and radiologic parameters including routine laboratory values and chest radiograph findings are similar between viral and bacterial CAP.³

Overall, the most common causes of viral pneumonia are influenza A virus, influenza B virus, respiratory syncytial virus (RSV), adenovirus and parainfluenza virus.^{3,4} With the increased use of nucleic acid amplification testing (NAAT), other viruses including metapneumovirus, rhinovirus and coronaviruses have been identified.⁵ In the immunocompromised or debilitated host, additional viruses such as cytomegalovirus (CMV), herpes simplex virus (HSV), varicella zoster virus (VZV) are important causes of pneumonia. CMV is the most common cause of viral pneumonia in the immunocompromised host and prophylactic antiviral therapy is commonly administered in patients who are at risk for reactivation.⁶ RSV is also an important cause of morbidity and mortality in immunosuppressed patients.⁷ Finally, some vaccine-preventable diseases such as measles pneumonia have increased in prevalence due to low vaccination rates in some populations and increased international travel.⁸

Laboratory diagnosis of viral pneumonia is usually accomplished through routine testing in the microbiology laboratory using cell culture, antigen detection methods, and increasingly, NAATs such as polymerase chain reaction (PCR).⁴ Despite the widespread availability of these testing options, viral infections are not always suspected initially and pathologists may therefore play an important role in confirming the presence of infection in histologic and cytologic specimens. In particular, pathologists play an important role in diagnosis of viral respiratory infections at autopsy.⁷

General pathologic features

General tissue responses to viral infections of the lung include interstitial inflammation, diffuse alveolar damage (DAD) and necrotizing bronchitis/bronchiolitis (Table 1).^{7,9} DAD is commonly seen with many respiratory virus infections, and may be observed in the acute, or more commonly, late (organizing) stages. Acute DAD is characterized by intra-alveolar edema (Fig. 1) followed by fibrin deposition and formation of hyaline membranes lining the alveolar walls (Fig. 2). In the organizing stage, type II pneumocyte proliferation, granulation tissue, and eventually collagen deposition are seen (Fig. 3). In addition to DAD, influenza virus, parainfluenza virus, human metapneumovirus, and RSV are commonly associated with interstitial pneumonia characterized by leukocytic infiltration of the alveolar septa¹⁰ (Fig. 4) while the members of the Herpesviridae (CMV, HSV, VZV) and Adenoviridae (Adenovirus) are associated with necrotizing bronchiolitis. Some viruses such as CMV, HSV, VZV and adenovirus also produce characteristic aggregates of nucleoproteins and virions called *inclusions* as they proliferate within cells (Fig. 5).⁹ The location (i.e. intranuclear, intracytoplasmic) and characteristics of these inclusions allow for detection and presumptive identification of the etiologic virus (Table 1).^{7,9} Intranuclear inclusions surrounded a clear halo and margined peripheral chromatin are commonly referred to as “Cowdry A” type inclusions and are characteristic of CMV infection (Fig. 5). However, the halo is a non-specific artifact of formalin or ethanol fixation and may be seen with the intranuclear inclusions of other viruses as well. Another cytologic change observed with some viruses (e.g. RSV, parainfluenza, human metapneumovirus, measles) is fusion of infected cells and creation of characteristic multinucleated giant cells (MNGCs).⁹ Multinucleated giant cells may also be seen with HSV and VZV infection, but this occurs primarily in stratified squamous epithelium.⁷

Given the potential overlap of morphologic features, immunohistochemical (IHC) or *in situ* hybridization (ISH) stains are commonly used to confirm the identity of the suspected virus when

inclusions are seen. These stains are also useful for identifying respiratory viruses that do not produce characteristic cytopathic features such as influenza A and B viruses. While some IHC stains are commercially available (e.g. HSV, VZV, CMV, adenovirus), others are available only through specialized research centers and public health laboratories such as the Centers for Disease Control and Prevention (CDC). PCR may also be performed on fresh or formalin-fixed paraffin-embedded (FFPE) tissue sections, although commercial availability of this testing is limited.

Influenza viruses

Etiology, epidemiology and clinical presentation

Influenza viruses are RNA viruses with segmented genomes in the family Orthomyxoviridae.¹⁰ While there are 4 types of influenza viruses (A-D), influenza A and B viruses are most commonly associated with human disease, and influenza A virus generally causes the greatest morbidity and mortality.¹⁰ Influenza A viruses are further classified based on the characterization of their hemagglutinin (H) and neuraminidase (N) surface glycoproteins; while there are 18 hemagglutinin subtypes and 11 neuraminidase subtypes, only a limited number have established stable lineages in humans during the past century.¹¹ Of these, the 1918 H1N1 pandemic was the most lethal in recorded history.¹⁰ Currently, the influenza A viruses circulating worldwide are H1N1 (2009) and H3N2, both of which are included in annual vaccine formulations along with the currently circulating influenza B strain.¹¹ Less commonly, humans can become infected with avian influenza viruses, including the highly pathogenic Asian avian influenza A (H5N1) virus.¹¹ Influenza viruses are a common cause of community-acquired pneumonia, particularly during winter months, and have been detected in 14–64% of patients hospitalized for pneumonia.^{3,12–14} The severity of disease varies each year with the circulating strains and vaccine effectiveness. In general, influenza is estimated to cause 200,000 hospitalizations and 36,000 deaths.¹⁰ Treatment is largely supportive, although antivirals such as oseltamivir may be useful if administered early in infection.¹⁵ Given that the clinical and pathologic features of influenza A and influenza B infection are indistinguishable,¹⁵ they are discussed together in this section.

Pathologic features

The gross pathology findings reported in the literature are derived primarily from autopsy studies and are therefore highly skewed towards fatal cases. Features that were noted in fatalities during the 2009 H1N1 pandemic included heavy congested lungs with subpleural hemorrhages, hemorrhagic and edematous tracheal/bronchial mucosa, and diffuse hemorrhagic consolidation on cut surfaces.^{7,15} Hemorrhagic pleural effusions have also been reported.⁷ Lungs with bacterial co-infections commonly contain purulent material within large airways and parenchymal abscess formation.¹⁵ Microscopically, findings of primary influenza include necrotizing bronchitis and bronchiolitis, focal necrosis of the submucosal tracheal and bronchial glands, and prominent hemorrhage, congestion, and lymphoplasmacytic infiltrates in the bronchial lamina propria.¹⁵ The surface tracheal and bronchial epithelium is commonly eroded, but the basal epithelium and basement membrane are commonly preserved.¹⁵ Although pathologic changes are most commonly found in the airways, some influenza A virus subtypes (e.g. H5N1, 2009 H1N1) have a predilection for the lung parenchyma, and may cause interstitial pneumonia, intra-alveolar hemorrhage, and diffuse alveolar damage (Figs. 1, 4).¹⁰ Secondary bacterial infection is common with influenza viral pneumonia and may obscure the histopathologic changes of viral pneumonia.¹⁰ Unlike many other respiratory viruses causing pneumonia, no viral inclusions are seen by light microscopy

Table 1
Cytopathologic features of common viruses infecting the lower respiratory tract.

Virus	Characteristics of inclusions		Histologic patterns	Comments
	Intracytoplasmic	Intranuclear		
Adenovirus	None	Smudgy, amphophilic to basophilic; occasional Cowdry A, condensed peripheral chromatin	Necrotizing bronchitis and bronchiolitis, bronchocentric parenchymal necrosis with hemorrhage, diffuse alveolar damage	Moderate nuclear enlargement of infected cells
Cytomegalovirus (CMV)	Eosinophilic to basophilic, variably-sized; may be surrounded by a halo and mimic intracellular yeasts	Prominent, amphophilic to basophilic; Cowdry A classic	Interstitial pneumonia, diffuse alveolar damage, necrotizing tracheobronchitis	Nuclear and cytoplasmic enlargement of infected cells
Herpes simplex virus (HSV)	None	Ground glass chromatin with prominent margination, occasional Cowdry A	Necrotizing bronchitis and bronchiolitis, bronchocentric parenchyma necrosis with hemorrhage, diffuse alveolar damage	Infection of single or multinucleated cells, latter with nuclear molding ^a ; accompanying tracheitis, esophagitis, and other visceral involvement common.
Influenza A and B viruses	None	None	Necrotizing bronchitis and bronchiolitis, focal necrosis of submucosal tracheal/bronchial glands, interstitial pneumonia, diffuse alveolar damage	Secondary bacterial pneumonia common.
Measles virus	Eosinophilic, variably-sized, may be multiple	Eosinophilic, ground glass chromatin, occasional Cowdry A	Interstitial pneumonia, diffuse alveolar damage	Multinucleated giant cells common, nuclei not molded ^{b,c}
Human metapneumovirus	None		Interstitial pneumonia, diffuse alveolar damage	Multinucleated giant cells, nuclei not molded
Parainfluenza virus	Eosinophilic	None	Interstitial pneumonia, diffuse alveolar damage	Multinucleated giant cells common, nuclei not molded ^c
Respiratory syncytial virus (RSV)	Eosinophilic, irregular, variably-sized, globular, surrounded by halo	None	Necrotizing bronchiolitis, sloughing of bronchial epithelium with obstruction, interstitial pneumonia, diffuse alveolar damage	Multinucleated giant cells common, nuclei not molded ^c Secondary bacterial pneumonia common.
Varicella zoster virus (VZV)	None	Ground glass chromatin with prominent margination, occasional Cowdry A	Bronchial and tracheal ulceration, necrotizing bronchiolitis, bronchocentric parenchyma necrosis with hemorrhage, diffuse alveolar damage	Singly-infected cells ^a ; multinucleation in stratified squamous epithelium with nuclear molding

^a Inclusions of VZV and HSV are indistinguishable; multinucleated cells are uncommon outside of stratified squamous epithelium (HSV > VZV).

^b Different than the measles virus Warthin-Finkeldey multinucleated giant cells found in reticuloendothelial tissues that do not contain inclusions.

^c Multinucleated giant cells with inclusions that are seen with RSV, measles virus and human metapneumovirus infection are difficult to distinguish.

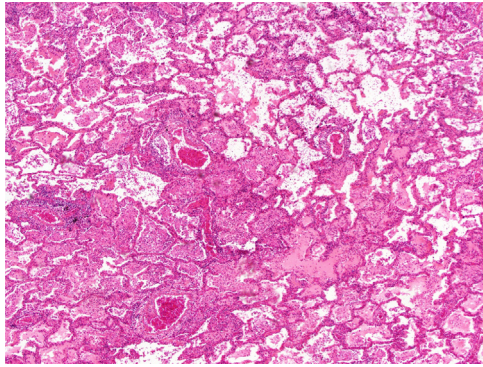


Fig. 1. Low power (40 × total magnification) H&E-stained section of lung from a fatal case of influenza A pneumonia in which diffuse intra-alveolar edema and inflammation are observed. No viral inclusions are formed with influenza A and B virus infections.

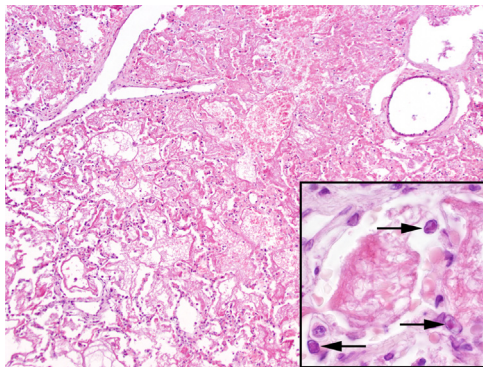


Fig. 2. Diffuse alveolar damage with intra-alveolar fibrin deposition and early hyaline membrane formation due to Varicella zoster virus infection (H&E, 100 ×; inset 400 ×). Intranuclear viral inclusions are seen on high magnification (arrows). Infection with herpes simplex viruses has a similar appearance.

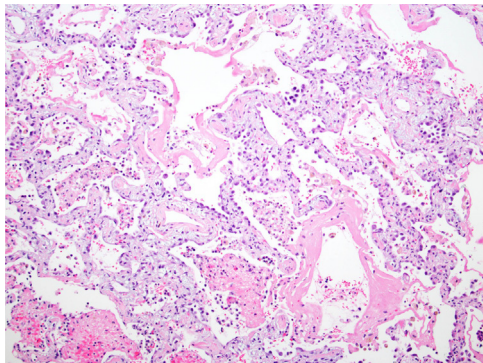


Fig. 3. Acute and organizing diffuse alveolar damage characterized by the presence of both hyaline membranes and septal thickening due to proliferating fibroblasts, typically in a myxoid background with prominent reactive type II pneumocytes (H&E, 100 ×).

with influenza A infection. Influenza virus IHC stains are available through the CDC Infectious Disease Pathology branch.

Respiratory Syncytial Virus (RSV)

Etiology, epidemiology and clinical presentation

RSV is an RNA virus in the Paramyxoviridae family.⁷ RSV is a common cause of recurrent respiratory infection in both children and adults and is the leading cause of bronchiolitis in the first year

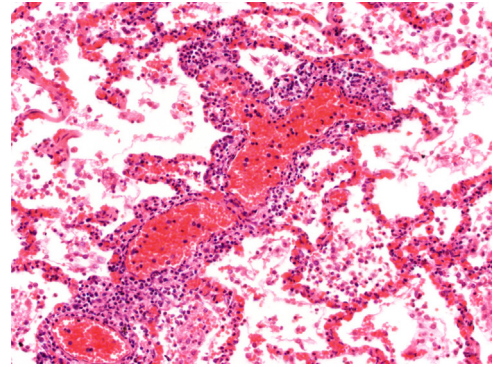


Fig. 4. Early influenza A pneumonia showing hyperemic alveolar septa with focal leukocytic infiltration (H&E, 200 ×).

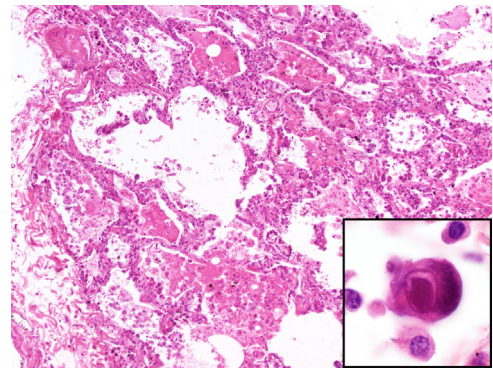


Fig. 5. Cytomegalovirus pneumonia in a patient with Acquired Immune Deficiency Syndrome with necrotizing bronchocentric alveolitis (H&E 100 ×). Occasional enlarged cells with characteristic intranuclear Cowdry A type inclusions and smaller intracytoplasmic inclusions were observed (inset, 1000 ×).

of life.¹⁶ The CDC estimates that RSV infection is responsible for 2.1 million outpatient visits and 57,527 hospitalizations among children < 5 years of age in the United States each year.¹⁶ In immunocompetent adults, RSV is responsible for an estimated 7–10% of all viral infections and 2–5% of community-acquired pneumonia cases; fortunately, most illnesses are mild and RSV pneumonia is seldom fatal.^{7,16,17} Adults at risk of severe disease include immunocompromised hosts, the elderly, and those with pre-existing cardiac and pulmonary diseases.^{16,17} According to the CDC, there are 177,000 hospitalizations each year among adults > 65 years of age, and 14,000 deaths.¹⁶ Most infections occur during the winter months, similar to influenza.¹⁶ Symptoms of RSV pneumonia are comparable to those of other viral pneumonias, and include fever, cough and chest pain. Ribavirin may be used for individuals with severe disease.¹⁵

Pathologic features

Lungs in cases of RSV pneumonia are usually heavy and congested, with scattered nodular consolidations and areas of hyperexpansion.¹⁵ Thick exudates may be extruded from bronchi and bronchioles on cut section. The primary microscopic findings include necrotizing bronchitis and bronchiolitis, interstitial pneumonia, and DAD.⁷ Bronchial and bronchiolar epithelial sloughing may be prominent, particularly in fatal cases, resulting in extensive airway plugging (Fig. 6).^{15,18} An autopsy study of untreated RSV-related deaths found that most bronchiolar inflammation was within the submucosal layer, accompanied by occasional large hyperplastic lymphoid aggregates.¹⁸ Unlike influenza, multinucleated giant cells are frequently seen within alveoli, and less

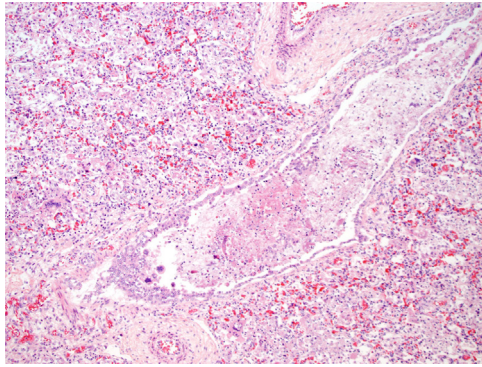


Fig. 6. Fatal case of respiratory syncytial virus infection (H&E, 40 ×). Note the prominent bronchial plug containing sloughed epithelium, serum proteins, and macrophages. Multinucleated giant cells can be seen within the bronchial epithelium and neighboring alveoli.

commonly, in bronchioles, and may contain large globular eosinophilic viral inclusions (Fig. 7).^{7,15}

Human parainfluenza virus

Etiology, epidemiology and clinical presentation

Human parainfluenza viruses (HPIVs) are RNA viruses within Paramyxoviridae family. Of the 4 HPIV serotypes, HPIV-3 is most likely to cause lower respiratory disease.¹⁵ HPIV is the second most common cause of lower respiratory virus infection in young children after RSV¹⁵ and accounts for 10–50% of viruses found in adults with viral pneumonia.^{3,12,14} The most common symptoms of infection include rhinorrhea and cough, while manifestations of lower respiratory tract disease include bronchitis, bronchiolitis, and pneumonia.^{7,15} Repeat lower respiratory infections can occur, particularly among the immunocompromised and elderly.^{7,15} HPIV infection is rarely fatal, unless the patient is immunocompromised or has pre-existing respiratory disease.¹⁵ Aerosolized ribavirin therapy may be used for immunocompromised patients with severe illness.¹⁵

Pathologic features

In fatal cases, lungs are heavy and congested and may be grossly hemorrhagic.¹⁵ The primary histopathologic features are interstitial pneumonia and DAD.¹⁵ Like RSV infection, MNGCs with cytoplasmic inclusions may be seen within alveoli (Fig. 8). Given the overlapping features with pneumonia due to RSV and other viruses forming MNGCs with inclusions (i.e. measles virus, human metapneumovirus),

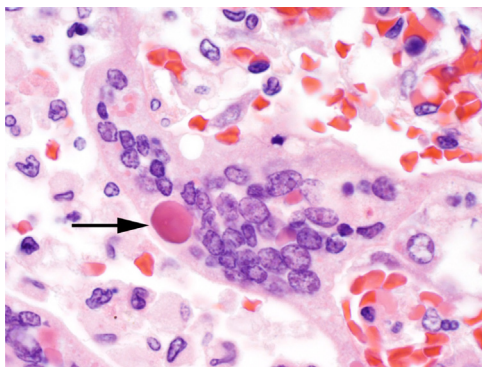


Fig. 7. Multinucleated giant cell (MNGC) of respiratory syncytial virus infection demonstrating a large intracytoplasmic inclusion (arrow); (H&E, 1000 ×). MNGCs are more commonly seen within alveoli than within bronchioles.

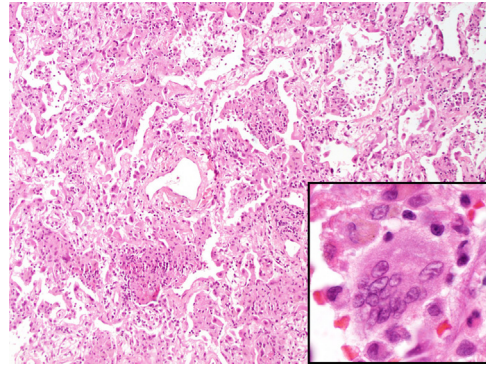


Fig. 8. Fatal case of parainfluenza virus infection demonstrating organizing DAD and intraalveolar exudates (H&E, 100 ×). Occasional multinucleated giant cells (MNGCs) are seen within alveoli (inset, 400 ×). Intracytoplasmic inclusions may be present within MNGCs but were not seen in this case.

IHC and PCR are useful for confirming the cause of infection.¹⁵ These tests may be available through the CDC following consultation. In poorly-preserved tissues, the MNGCs may also resemble those caused by HSV and VZV. Virus-specific IHC is useful for differentiating these viral causes of lower respiratory disease.

Adenovirus

Etiology, epidemiology and clinical presentation

Adenoviruses are a diverse group of DNA viruses with many described serotypes and genotypes.¹⁵ Given this diversity, it is unsurprising that they cause a broad spectrum of infections in the throat, lungs, eyes, bladder, intestine, brain, liver and heart. In particular, serotypes 3 and 7 are especially pathogenic and may cause disseminated and fatal disease in previously healthy individuals.¹⁵ Adenoviruses are estimated to cause up to 10% of all pneumonias in infants and young children, with most cases occurring between the ages of 6 months and 5 years of age.¹⁵ Adenovirus pneumonia in neonates is rare but associated with high morbidity and mortality.^{7,15} In adults and adolescents, adenovirus is estimated to cause 5% of community-acquired pneumonia.⁷ Periodic outbreaks are also commonly reported among military recruits. Adenovirus pneumonia presents with manifestations similar to other viral causes of pneumonia, with fever, cough, dizziness and chest pain. Rhinorrhea is less common compared with upper respiratory adenovirus infections.⁷ A monocytosis may be observed on peripheral blood counts.⁷ The mortality rates of adenovirus pneumonia are approximately 15% and 60% in immunocompetent and immunocompromised individuals respectively.¹⁵ Treatment consists of supportive measures only.¹⁵

Pathologic features

On autopsy, the lungs from patients with adenovirus pneumonia are heavy and congested, and necrotic foci may be seen as firm tan-yellow nodules on cut surfaces.¹⁵ The bronchi are commonly congested and hemorrhagic, and filled with mucoid or purulent exudates.¹⁵ Fatal cases show necrotizing bronchitis and bronchiolitis with surface epithelial denudation.^{7,15} As with influenza virus infection, bronchial glands may show focal necrosis and inflammation.¹⁵ Airways are commonly occluded with mixed inflammatory cells, cellular debris and sloughed epithelium.¹⁵ Parenchymal involvement occurs as infection progresses, resulting in interstitial pneumonia and DAD with numerous neutrophils.^{7,15} Intranuclear inclusions are commonly seen within respiratory epithelial cells and alveolar pneumocytes (Table 1). Early inclusions

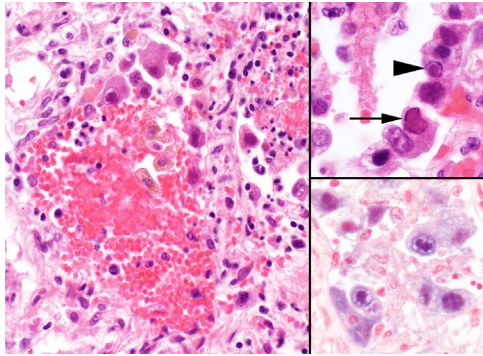


Fig. 9. Adenovirus pneumonia showing intra-alveolar hemorrhage, necrosis, and pneumocytes with large basophilic intranuclear inclusions (H&E, 400 \times). On higher magnification, the inclusions are seen to fill the nucleus and blur with the peripheral condensed chromatin (arrow, inset, upper right, 1000 \times). Smaller intranuclear inclusions with a peripheral halo (i.e. Cowdry A) are also seen (arrowhead). Infected cells are highlighted using a commercially-available *in situ* hybridization stain (inset, lower right, 1000 \times).

are small and surrounded by a narrow clearing and peripheral rim of condensed chromatin (Cowdry A type), while later inclusions are larger and blur with the marginal chromatin giving the characteristic “smudgy” appearance (Fig. 9).^{9,15} IHC and ISH stains are commercially available and useful for differentiating adenovirus intranuclear inclusions from single-cell inclusions of HSV and VZV.

Cytomegalovirus (CMV)

Etiology, epidemiology and clinical presentation

CMV is a ubiquitous DNA virus in Herpesviridae family. Most individuals become infected with CMV in childhood, although infection can occur in all age groups. While most infections are asymptomatic, there is a broad spectrum of manifestations including mild mononucleosis-like illness to disseminated multi-organ disease.¹⁹ As with other herpes viruses, CMV establishes latency and may subsequently reactivate if the host becomes immunocompromised.¹⁹ CMV pneumonia is rare in immunocompetent individuals but is an important source of morbidity and mortality in immunocompromised populations, including patients with AIDS, transplant recipients and hospitalized ventilator-dependent patients.^{7,19} Given the severity of illness, prophylactic antiviral therapy with valganciclovir or ganciclovir is routinely administered to at-risk groups such as solid organ transplant recipients who are CMV seronegative and receive an organ from a CMV seropositive donor.^{6,7} Mild disease usually resolves spontaneously and does not require treatment, whereas severe disease is potentially life-threatening and is treated with valganciclovir or ganciclovir.¹⁹

Pathologic features

Grossly, lungs may be heavy and consolidated, particularly in the setting of DAD and interstitial pneumonia.^{7,20} Miliary patterns of involvement have also been described, with the presence of multiple firm nodular lesions measuring up to 4 mm in diameter.²⁰ Microscopically, nodular lesions consisted of well-delineated foci of alveolar fibrin deposition, hemorrhage, and neutrophilic infiltrate.²⁰ Enlarged cells with characteristic CMV inclusions are observed in epithelial cells, endothelial cells, and/or alveolar macrophages (Table 1, Fig. 5). Unlike most other viruses involving the lung, CMV-infected cells have both intracytoplasmic and intranuclear inclusions. The intranuclear inclusion is large and commonly surrounded by a halo and a prominent rim of marginated host chromatin, providing

the classic “owl’s eye” appearance (Cowdry type A inclusion). The intracytoplasmic inclusions are smaller, variable in size, and may be indistinct or well-defined. Interestingly, intracytoplasmic inclusions stain faintly with PAS and GMS, and thus may be mistaken for intracellular yeasts. The intranuclear inclusion is PAS and GMS negative. CMV IHC is useful for detecting infected cells, but may also be positive in occasional cells in patients with CMV viremia without lung disease.²¹

Herpes simplex virus (HSV-1 and HSV-2)

Etiology, epidemiology and clinical presentation

HSV-1 and HSV-2 are two closely-related DNA viruses in the Herpesviridae family. Both have a worldwide distribution and are transmitted through close personal contact with an infected individual. In the United States, more than 50% of adults are estimated to be infected with HSV-1 and 20% with HSV-2.¹⁹ Immunocompetent individuals typically experience vesicular lesions involving the skin, mouth or genital tract, while neonates and immunocompromised patients are at increased risk for multi-organ life-threatening infection.^{7,19} HSV infection has also been detected in 13.4% of patients with bacterial ventilator-associated pneumonia and was associated with worse outcomes,²² although detection in tracheal aspirates or bronchoalveolar lavage fluids may represent viral shedding from the upper respiratory tract without lung involvement.²³ Both HSV-1 and HSV-2 may involve the lung.²⁴ Symptoms include fever, productive cough, and dyspnea, and high leukocytosis is typically noted on peripheral blood counts.⁷ HSV pneumonia is associated with high morbidity and mortality, despite treatment with acyclovir.⁷

Pathologic features

Grossly, lungs are heavy, congested and may demonstrate well-demarcated tan-yellow necrotic foci, measuring 0.5–3 mm in diameter, with a hyperemic rim.^{19,24} Microscopically, bronchial and bronchiolar-centered parenchymal necrosis, interstitial pneumonia and DAD are frequent findings.^{7,24} Concomitant herpetic esophagitis, tracheitis, and involvement of other viscera are common.²⁴ Infected cells with intranuclear inclusions are most commonly seen at the edge of the necrotic lesions and are essentially identical to those of varicella zoster virus (see below, Table 1, Fig. 2); inclusions may be large and have a glassy appearance or be surrounded by a halo and peripheral rim of marginated host chromatin (Cowdry type A). Inclusions are most commonly seen in single cells; multinucleated giant cells are rare and usually found in stratified squamous epithelium.¹⁹ When present, the nuclei of multinucleated giant cells infected with HSV are classically molded and exhibit marginated chromatin.¹⁹ Commercially-available IHC and ISH stains may be helpful for identifying HSV-infected cells.⁷

Varicella zoster virus

Etiology, epidemiology and clinical presentation

VZV is a member of the Herpesviridae closely related to HSV-1 and HSV-2.¹⁹ Primary infection usually occurs during childhood and results in a self-limited exanthematous syndrome called chickenpox. Although rare, complications include hepatitis, pneumonia, and central nervous system involvement.¹⁹ Pneumonia is the most common complication of primary VZV infection in adults and is associated with mortality rates of up to 50% in immunocompromised individuals and pregnant women.²⁵ Bacterial superinfection is common. Fortunately, VZV infection rates have dropped significantly

since the introduction of universal childhood vaccination in 1995.^{7,19} Patients with varicella pneumonia typically present with fever, tachypnea, cough, and dyspnea within 6 days of the primary vesicular eruption.²⁵ Hemoptysis and pleuritic chest pain may also be present.²⁵ The presence of deep tracheal/bronchial ulcerations may portend a worse prognosis.²⁵ Patients are treated with acyclovir.¹⁹

Pathologic features

Grossly, the lungs are heavy and congested, and soft yellow-tan necrotic lesions with a hemorrhagic rim, similar to those seen with HSV, may be present on the visceral pleura and cut surfaces. Microscopically, the findings are indistinguishable from those of HSV infection, with necrotizing bronchitis and bronchiolitis, broncho-centric parenchymal necrosis with hemorrhage, DAD, and intranuclear viral inclusions (Fig. 2).⁷

Other viral pneumonias

Several other viruses may cause pneumonia, including corona viruses, human metapneumovirus, rhinovirus and measles. The main diagnostic points are discussed briefly below.

Severe Acute Respiratory Syndrome (SARS) Coronavirus (SARS-CoV)

SARS-CoV first emerged in November 2002 in the Guangdong province of China and quickly swept throughout 26 countries over the following year, causing an estimated 8000 cases.²⁶ Since then, only rare naturally-occurring cases have been reported in China through animal-to-human transmission.²⁶ Infected patients present with influenza-like symptoms which may quickly evolve to respiratory distress requiring ventilatory support.²⁶ Fatal cases revealed DAD in the exudative or organizing phase.²⁷ Multinucleated giant cells were seen within alveoli, but no viral inclusions were observed.²⁷

Human metapneumovirus (HMPV)

HMPV is a member of the Paramyxoviridae along with RSV and measles. It was first detected in 2001 and has since been recognized as an important cause of upper and lower respiratory disease in all ages, especially among young children, immunocompromised patients and the elderly.^{14,28} Infection occurs early in life and reinfection is common. Children most commonly present with cough, fever and rhinorrhea, but may also develop croup, asthma exacerbation, bronchiolitis and pneumonia.²⁸ Signs and symptoms of infection overlap significantly with those of other respiratory infections including RSV. Disease may be severe in immunocompromised individuals including stem cell transplant recipients and patients being treated for malignancy, with reports of pneumonia and rare fatalities.²⁸ HMPV has been detected in up to 25% of cases of community-acquired viral pneumonia¹⁴ and is an important cause of hospitalization in adults over the age of 65.²⁸ Treatment is mainly supportive, although ribavirin may be used in severely ill patients.²⁹

There are only rare published reports of cytologic and histologic features of HMPV pneumonia. Bronchoalveolar lavage performed on 6 children with HMPV infection demonstrated eosinophilic inclusions within the cytoplasm of histiocytes, epithelial cells and multinucleated giant cells, whereas biopsies showed chronic bronchiolar inflammation.³⁰

Rhinovirus

Rhinovirus is one of the causes of the “common cold” and is frequently detected in concert with RSV and parainfluenza virus in

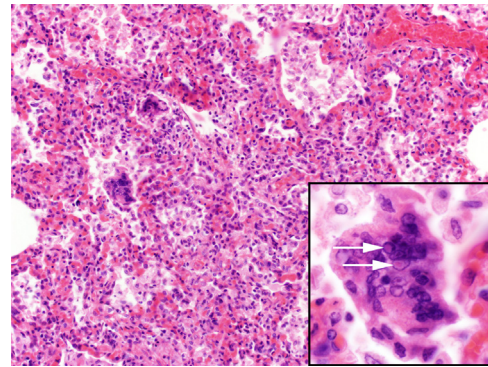


Fig. 10. Measles pneumonitis with interstitial pneumonia and readily visible multinucleated giant cells (H&E, 200 ×). Both intranuclear inclusions (arrows) and faint intracytoplasmic inclusions were seen (inset, 1000 ×).

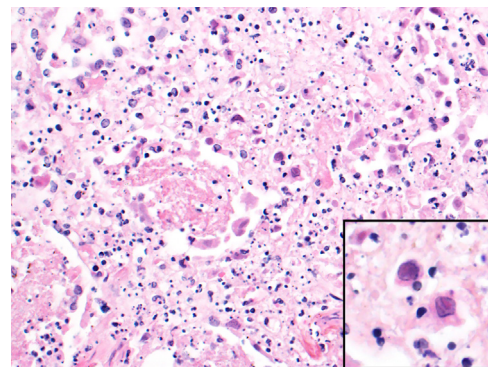


Fig. 11. Herpes simplex virus type 2 (HSV-2) pneumonia with acute necrotizing alveolitis (H&E, 400x). Characteristic intranuclear Cowdry A type inclusions are observed (inset, 600x). This histopathologic appearance is indistinguishable from pneumonia due to varicella zoster virus.

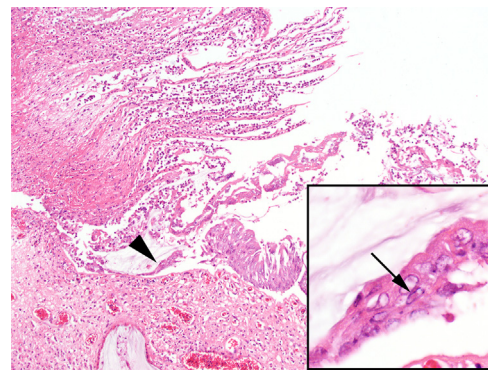


Fig. 12. Tracheal infection with varicella zoster virus (VZV) demonstrating an ulcer with acute inflammatory exudate and hyperplastic glandular mucosa with focal squamous metaplasia (H&E, 100x). Viral inclusions are seen primarily in the basal epidermis (arrow head). On higher magnification (inset, 400x), characteristic intranuclear Cowdry A type inclusions are observed (arrow).

patients with bronchiolitis or pneumonia.^{7,14} The histologic features of rhinovirus-associated pneumonia have not yet been reported.

Measles virus

Measles, also known as rubeola, is caused by measles virus, an RNA virus in the family Paramyxoviridae.³¹ Prior to licensure of the live measles vaccine in 1963, this virus was almost as important as influenza A virus as a cause of life-threatening pneumonia. In the mid 1900's, the CDC estimates that there were 3–4 million infections and more than 500 measles-related deaths in the United States each

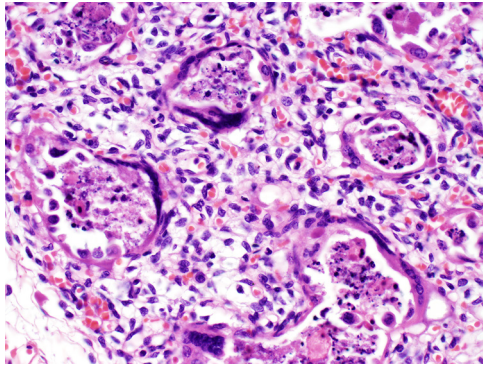


Fig. 13. Measles giant cell pneumonitis (“Hecht pneumonia”) with multinucleated giant cells partially encircling alveolar septa. The alveoli contain necrotic sloughed alveolar cells and inflammatory cells. Note the marked thickening of the alveolar septa. The majority of giant cells in this case did not contain identifiable inclusions.

year.³¹ Unfortunately, there have been a number of outbreaks in recent years among unvaccinated populations and therefore pathologists should be familiar with the primary histologic features of infection.³¹ The hallmark of infection of the lower respiratory tract is giant cell pneumonitis, characterized by multinucleated giant cells that may contain intracytoplasmic and intranuclear inclusions (Table 1, Fig. 10).³² Of note, the MNGCs found in the lung are different than Warthin-Finkeldey giant cells which are found in reticuloendothelial tissues and don't have inclusions.⁷ Other findings include interstitial pneumonia and DAD.⁷

Conclusions

Although infrequently the cause of a serious lung infection in adults, viruses are common causes of pneumonia in the children and immunocompromised patients. In tissue biopsy, the histologic response is similar across viruses resulting mostly in various stage of DAD or an interstitial pneumonia with mixed acute and chronic inflammatory infiltrate. Necrotizing bronchiolitis is common and often the clue to search for viral cytopathic changes when present in the backdrop of DAD. Several viruses have characteristic features allowing for their specific identification. However, some features such as multinucleation and Cowdry A inclusions are shared by various viruses and therefore immunohistochemistry and in situ hybridization stains are necessary for the identification of the specific virus. Furthermore, many viruses do not cause cytopathic changes and their presence requires high degree of suspicion with confirmation using other methods including conventional microbiology tests. When reporting our findings, we typically first state the morphologic findings followed by either a definitive diagnosis of a virus, as defined by the cytopathic changes and/or ancillary studies or if not definitive, the cytopathic findings and the most likely associated virus. An example of report could read as “Acute necrotizing bronchiolitis and organizing diffuse alveolar damage. Herpes simplex viral inclusions identified, confirmed with immunohistochemical study”.

Addendum with additional images from Viral Infections of the Lung

Figs. 11–13

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