

Early diagnosis of viral pneumonia

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Sharma MV. Early diagnosis of viral pneumonia. *J Pulmon.* 2019;3(1):1-3.

An accurate and etiologic diagnosis of viral pneumonia is important as viral pneumonia is contagious and early initiation of antiviral therapy may reduce morbidity, mortality, and spread of infection to others. Proper history, clinical examination, and appropriate evaluation will help in early diagnosis of viral pneumonia. History of upper respiratory symptoms with a fever which precedes dry cough and rapidly progressive breathlessness by 2-5 days is typical of viral pneumonia. History of contact and outbreak in the community with seasonal changes in incidence are additional clinical clues. Pleuritic chest pain, high-grade fever, and chills are unusual. Symptoms are usually out of proportion to physical findings. Tachypnea, hypoxia, and tachycardia are predominant signs. Clinical signs of consolidation are unusual. Severe cases may have respiratory failure, multi-organ failure. A chest X-ray may be normal in early cases, may show patchy areas of unilateral or bilateral bronchopneumonia. Lobar consolidation, cavity, and pleural effusion are unusual. HRCT may show patchy, unilateral, or bilateral consolidation, ground-glass opacities or centrilobular nodules which are usually poorly defined and/or reticular shadows. Investigations in suspected viral pneumonia include viral culture, cytologic evaluation, rapid antigen detection, and gene amplification. Rapid antigen detection kits are now available which provides results within hours. Hence this is useful in the emergency department for early diagnosis. Bronchiolar lavage may be done when other investigations are inconclusive to obtain material for cytopathologic and microbiologic evaluation. Rarely lung biopsy may be needed to make a diagnosis when all the other less invasive evaluations fail to establish a definitive diagnosis. Histologic findings include diffuse alveolar damage with intra-alveolar hemorrhage, interstitial lymphocytic infiltration, interstitial edema, fibrin deposition, type 2 granular pneumocyte hyperplasia, and hyaline membrane.

BACKGROUND

Viruses rank as the second common etiologic agent for community-acquired pneumonia ranging from 13%-50% causative agent for pneumonia and 8%-27% of causative agent for mixed bacterial-viral infections¹. Viral pneumonia is a mild and self-limiting illness in the majority. But in some cases, it can be a life-threatening disease. The incidence of viral pneumonia is steadily on the rise during the past two decades. This is due to the increase in the susceptible population and also improved diagnostic techniques (1). The most frequent causative organisms for viral pneumonia in children and immunocompetent adults are influenza virus, adenovirus, Respiratory Syncytial Virus (RSV) and Para-Influenza Virus (PIV). Other viruses include rhinovirus, coronavirus and human metapneumovirus.

Viruses can also lead to nosocomial pneumonia in up to 22.4% of cases (2). Adenovirus, influenza virus, para influenza virus, measles virus, rhinovirus, respiratory syncytial virus, and varicella zoster virus are easily transmitted during the hospital stay and can cause nosocomial pneumonia. Adenovirus,

influenza virus, respiratory syncytial virus and para influenza virus together account for 70% of nosocomial cases of pneumonia due to viruses (2).

During influenza outbreaks, Influenza virus types A and B account for more than 50% of viral pneumonia in adults. The impact of influenza virus infection and its complications are high in elderly and are highest in persons with underlying chronic illnesses. One study reported up to 63% of the 300,000 influenza-related hospitalizations and 85% of 36,000 influenza-related deaths occurred in patients aged 65 years or older even though this age group constitutes only about 10% of the general population (3).

Most of the viruses which cause pneumonia usually infect children and lead to a mild self-limiting illness. Healthy adults also usually develop mild disease with a viral infection. Viral pneumonia during pregnancy has more serious clinical evolution. Elderly persons and immunosuppressed persons develop severe viral pneumonia. Morbidity and mortality due to viral pneumonia are highest in elderly patients and in immunosuppressed persons (3). The exception to this was observed in the 2009-2010 H1N1 influenza pandemic, where severe infection and complications were more common in 5-59 years age group. The cause for this may be due to a lack of previous exposure to H1N1.

An accurate and early etiologic diagnosis of viral pneumonia is important as viral pneumonia is contagious and early initiation of specific antiviral agents may reduce morbidity, mortality, and spread of infection to others (1). Even with all the currently available investigations, a definite causative microorganism may not be identified in up to 50%-80% of patients with suspected pneumonia.

Clinical characteristics of different viral cases of pneumonia often overlap with each other and also with bacterial pneumonia. Frequently viral pneumonia is complicated by superadded bacterial pneumonia making clinical diagnosis difficult or impossible (4). However, a proper history, clinical examination, and appropriate investigations will help to establish the causative organism in pneumonia.

Viral pneumonia usually starts with a viral upper respiratory infection. This viral upper respiratory tract infection leads to the waning of humoral, cellular and innate immune responses leading to reduced clearance of the virus from the respiratory tract. This results in the spread of the virus to the lower respiratory tract and increased inflammation in the lower airways and lungs (3). Respiratory muscle strength in elderly persons is usually reduced due to debility and age-related changes in skeletal muscles. In addition, these patients have impaired mucociliary clearance. With age incidence of diabetes and other chronic diseases which reduce immunity also increases. These may be the reason why viral pneumonia is more severe in the elderly (3).

Most of viral pneumonia typically occurs during specific seasons of a year, amongst closed populations or in populations with cardiopulmonary, chronic systemic illness or immunosuppressant disease. Viral respiratory infection usually starts with upper respiratory tract symptoms with rhinitis,

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Received: March 17, 2019, Accepted: March 26, 2019, Published: March 30, 2019



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sore throat, dry cough, fever, headache, malaise, and myalgia. After 3-5 days patients develop a non-productive cough and progressive breathlessness, which is the hallmark of viral pneumonia. In early stages and in mild disease, exertional dyspnea may be the sole symptom of viral pneumonia. Breathlessness is usually progressed very rapidly within hours in the majority. In patients with underlying cardiac illness, this rapidly progressive breathlessness may be mistaken for a cardiac event. Pleuritic chest pain, rigor, and chills are unusual in viral pneumonia. Elderly persons and immunocompromised patients may present with low-grade fever, generalized weakness and alteration in mental status without any other symptoms (3). During outbreaks with the respiratory viruses in the community, a history of contact with a case along with the typical symptoms suggests the diagnosis of viral pneumonia (4).

Influenza virus infection usually presents with sudden onset of fever with or without chills, body ache, arthralgia, nonproductive cough, sore pain, and watery nasal discharge. When there is an outbreak of influenza in the community, these symptoms with a history of contact is highly suggestive of influenza virus infection (1). The incubation period in influenza is 1-2 days and symptoms usually last around 3-5 days. Influenza virus infection occurs in epidemics and pandemics, usually during winter and early spring (5).

Symptoms of H1N1 influenza are similar to seasonal influenza. Fever and cough are the most common symptoms in H1N1 influenza. Dyspnea (54%), fatigue/weakness (40%), chills (37%), myalgia (36%), rhinorrhea (36%), sore throat (31%), headache (31%), vomiting (29%), wheezing (24%), and diarrhoea (24%) are the most common other symptoms (6).

Avian influenza (H5N1) infection can manifest with pain abdomen, diarrhea, and vomiting in addition to upper respiratory symptoms (6). It may be mistaken for gastroenteritis. Non-productive cough, dyspnea, tachypnea, and chest pain indicate progression of the disease to pneumonia. In severe avian influenza cases, encephalitis/encephalopathy, renal failure, cardiac failure, hepatic failure, multiorgan failure, and disseminated intravascular coagulation can occur (6).

Mixed viral and bacterial pneumonia occur due to bacterial infection on the top of viral infection. This is common and manifest as a gradual progression of the symptoms or as a transient improvement in the symptoms followed by a sudden worsening of respiratory symptoms with high-grade fever with chills, productive cough, purulent sputum, worsening breathlessness, and pleuritic chest pain.

In viral pneumonia, symptoms are usually out of proportion to physical signs. In the early course of the disease and in very mild illness physical examination may be normal. Most common and early physical findings in patients with viral pneumonia include tachypnea, hypoxia, and tachycardia. Presence of skin rashes, fewer or normal respiratory findings except tachypnea and hypoxia, multilobar involvement with bilateral physical findings all favor diagnosis of viral pneumonia (1). Some patients may have only mild low-grade intermittent fever, whereas other patients with severe illness may have respiratory and/or multi-organ failure. Signs of lobar consolidation, pleural rub, and pleural effusion are unusual in viral pneumonia (1).

Influenza pneumonia can be primary influenza pneumonia, secondary bacterial pneumonia and mixed viral and bacterial pneumonia (1). Symptoms in primary influenza pneumonia are non-productive cough, throat pain, headache, body ache and malaise followed by progressive dyspnea. Primary viral pneumonia is the least common and the most severe form of pulmonary complication in influenza virus infection (7).

Relapse of fever which is usually high grade with rigors, cough with purulent sputum, pleuritic chest pain, and progressive dyspnea after a brief period of initial improvement indicates secondary bacterial pneumonia (7). Most common pathogens include *Streptococcus pneumoniae* (48%), *Staphylococcus aureus*, *Haemophilus influenzae*, and Gram-negative pathogens (7).

In elderly persons, upper respiratory symptoms in viral infections are less frequent. One study demonstrated that the triad of cough, fever, and acute onset of respiratory symptoms had only a 30% positive predictive value in elderly when compared to 78% in young adults (3). Fever which may be low grade or high grade and changes in the mental status may be the only

symptoms of influenza pneumonia in an elderly patient with chronic cognitive impairment. Gastrointestinal symptoms and body ache are more common in influenza than in respiratory syncytial virus infection.

The radiographic manifestations in viral pneumonia depend on the patient's pre-existing or co-existing lung diseases, the severity of illness, presence or absence of bacterial co-infection, cardiac disease and immunologic status. Many pathogens can have overlapping radiographic features. Radiological features help in the differential diagnosis, assessing the evolution of the disease and pulmonary complications.

A chest X-ray may be normal in early cases of viral pneumonia. Later bilateral lung involvement with patchy bronchopneumonia with interstitial shadows may be seen. Lobar consolidation, cavity formation, and pleural effusion are unusual (8).

High resolution computed tomography scan of the thorax may show patchy, unilateral, or bilateral consolidation and ground-glass opacity or ill-defined centrilobular nodules. In one study centrilobular nodules were found in 64% of patients with atypical pneumonia and 77% with viral pneumonia, as compared to 11%-17% of those with bacterial pneumonia (9). Centrilobular nodules in viral pneumonia are associated with a background of diffuse ground-glass attenuation and/or reticulation. This usually occurs in severe cases due to alveolar hemorrhage. Focal or diffuse areas of airspace consolidation may be seen in viral pneumonia.

Virologic tests are the mainstay of definitive etiological diagnosis in suspected cases of viral pneumonia. Investigations in suspected viral pneumonia include viral culture, cytologic evaluation, rapid antigen detection, and gene amplification. Rapid antigen detection kits are now available which will provide results within hours, making them useful in the emergency department. Sensitivity and specificity of these kits is 80% to 95%. Viral culture is the gold standard for diagnosis of viral pathogens. Viral culture takes a long time. Hence faster methods for diagnosis have been introduced. Viral-antigen detection is a new test, but the results are less sensitive and less specific than viral culture. Other tests in viral pneumonia include amplification of viral nucleic material such as hybridization techniques, Polymerase Chain Reaction (PCR) and serological tests to detect an increase in specific serum antibodies.

Recent PCR-based tests with single, multiplex and real-time readings have sensitivity better than that of cultures. Reverse-transcriptase (RT) PCR and nested PCR are the most sensitive methods. These tests increase the detection rate of respiratory viruses in adults with hematologic cancers and pneumonia from 19% to 35%. Contamination of the specimens can lead to false positive PCR results. Immunocompromised patients, who shed the virus for long periods, the diagnosis by PCR can be of little clinical significance. This is overcome by using quantitative PCR, which will show the level of viral load. Quantitative PCR can help in differentiating active infection from contamination.

Viral infections can be diagnosed by paired acute/convalescent serologies measured by complement fixation or enzyme immunoassay (1). A four-fold rise in titers is the required diagnosis. This test requires blood to be drawn in the convalescent phase of the illness. Hence it may not be useful in the acute stage of the illness unless sufficient time has elapsed so that the convalescent period is over. In the acute phase of the disease first, high titer may suggest the diagnosis. Positive serologies are useful for confirming the diagnosis of viral infection.

Bronchoscopy and Bronchiolar lavage may be done to obtain material for cytopathologic analysis and microbiologic studies when other investigations are inconclusive. Rarely lung biopsy may be required to make a diagnosis, especially in the immunocompromised patient when all other investigations are non-informative. Histologic findings include diffuse alveolar damage consisting of intra-alveolar hemorrhage, interstitial lymphocyte infiltration, edema, fibrin deposition, type 2 pneumocyte hyperplasia and formation of the hyaline membrane (10).

CONCLUSION

History of preceding upper respiratory symptoms with fever, malaise and body ache, followed by dry cough and rapidly progressive breathlessness,

contact with a case, fewer physical findings except for tachypnea hypoxia and tachycardia, patchy areas of consolidation are the clues for suspecting viral pneumonia. Rapid antigen detection kits are useful for early diagnosis. Viral nucleic material amplification, such as hybridizations, various Polymerase Chain Reactions (PCRs) and serologic tests can be used to follow the increase in specific serum antibodies and for diagnosis.

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