A Comparative Analysis of Influenza Virus and Adenovirus: A review

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Abstract
This narrative study seeks to examine pneumonia induced by severe acute respiratory syndrome coronavirus-2, influenza, and adenovirus regarding clinical, laboratory, and radiological features. In conclusion, whereas these viral pneumonia clinics exhibit same symptomatology and laboratory results, we assert that there are notable distinctions, particularly in radiological findings.

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1. Introduction

Both influenza virus and adenovirus are important human pathogens that lead to illness and death globally. Despite extensive research, it remains a mystery why one type of adenovirus is so widespread worldwide. Understanding the molecular processes of adenovirus causing disease is vital for developing vaccines. These viruses can be examined as models for biological study as well as public health concerns, representing the perspective from which we view them here. (Javanian et al.2021)(Cilloniz et al.2022) (van and Yu 2020) [13, 6, 21].

It is interesting to compare these two viruses. Both infect human cells by binding to a viral receptor on the cell surface, and some components needed for virus entry engage in, or perhaps trigger, endocytosis, resulting in virus particles mixed with cellular endoproducts in the endosome. As discussed below, the two viruses handle this, and the cellular and intracellular events that follow, very differently. The disease they cause is likewise different; influenza virus causes a systemic infection that, in the lungs, progresses to viral and bacterial pneumonia, while adenovirus causes highly focal disease that is usually confined to the affected organs alone. This review compares and contrasts these two viruses. Insofar as possible, the progression of infection and diseases is considered separately from the individual molecules and cellular and molecular events engaged in causing disease. (Zhang et al.2021)(Filgueiras-Rama et al.2021)(Shi & Ren, 2024) [23, 11, 24].

1.1. Background and Significance

Viruses Influenza virus and adenovirus are two viral species that are constantly challenging the current virology field. Human influenza has affected the human population for thousands of years and has resulted in the loss of millions of lives. In 1918, an H1N1 influenza A virus became a global pandemic with estimated mortality between 50 and 100 million people worldwide. This virus provided the ‘drivers’ of plaque genetics and led to an evolutionary war over the subsequent century. In the modern era, the seasonal influenza attack on the human population has provided a constant challenge to the concept of a global sound health system. Similarly, the general concern for the potential for new subtype viruses to develop into human pathogens cannot be undermined. Today, the virology field has never been more advanced, and we understand the structure, life cycle, transmission, and pathogenicity of the influenza virus at levels previously not thought to be possible.

It is partially due to many different types and subtypes, which have made the development of an effective and universal vaccine difficult. Viruses mutate or change slowly during a replication process that produces genetically different viruses. This phenomenon leads to the increased ability of the influenza virus to gain drug insensitivity, which is known as 'antigen drifting'. Moreover, higher rates of viral reassortment may occur, which can take advantage of causing a brand new change in spiking protein through hemagglutinin and/or neuraminidase proteins from two different viruses after infecting a host cell, while undergoing drug resistance prior to pandemics, a phenomenon known as 'antigen shifting'. This results in the human population having either extremely poor or absent immunity for the newly emerged flu strain. Adenoviruses are a type of virus that causes respiratory diseases and are commonly referred to as a cold virus. Adenoviruses can infect the linings of the eyes, respiratory tract, urinary tract, intestinal tract, and other organs and may cause different types of illness. The adenovirus family may consist of varieties of viruses that can be transmitted among vertebrate animals and humans. Military personnel often suffer from health consequences due to adenoviruses. It often occurs during the early stages of training and dormitory outbreaks. Global progress, economy, and public health are affected or may be at risk if adenovirus outbreaks spread in the world. Diagnosis of adenovirus infections is often difficult to distinguish due to many symptoms being similar to other viral diseases such as influenza and acute upper respiratory tract infections and enteritis caused by other pathogens. Vaccines and antiviral drugs are under development. In addition to effective diagnosis and treatment, solid public education and awareness on health checks, personal hygiene, public health events, and early health symptomology are invaluable to manage any viral disease outbreaks. (Barrett, 2020)(Oldstone, 2020)(Dasgupta & Crunkhorn, 2020)(Wille and Holmes2020)(El-Sayed & Kamel, 2021) [2, 15, 7, 22, 9].

2. Virology of Influenza Virus

Influenza virus is a segmented virus from the Orthomyxoviridae family. The structure of the influenza virus encompasses three antigenic proteins: hemagglutinin (HA), neuraminidase (NA), and matrix protein 2 (M2). These three proteins exist on the lipid layer of the viral particle. The M2 protein is composed of two parts: the M3 and M1 segments of the virus, the latter of which covers the entire encapsulated viral genome. The genome consists of eight single-stranded RNA segments that are negative sense, which encode 10 to 15 viral proteins. Based on the antigenic structure of the HA and NA proteins, influenza viruses are classified into 18 HA subtypes and 11 NA subtypes in the Orthomyxoviridae family. Common subtypes of HA that people are likely to encounter are H1, H3, and H5. Influenza A viruses are further classified into only H1 and H3 subtypes as well as B viruses. Subtypes of influenza A viruses are referred to as HxNy. The "x" and "y" Greek letters are the subtypes of HA and NA, respectively. The exchange of the "x" and "y" can cause reassortments and recombinations of the influenza virus in a person's immune system, leading to drug resistance and outbreaks or pandemics. Orthomyxoviridae subtypes in humans have a notable evolutionary phylogenetic transmission mechanism. (Fereidouni et al.2023)(Poon, 2024) [10, 16].

The virus's segmented genome consists of eight negative-sense RNA strands that encode multiple viral proteins, including proteins with structural roles involved in virus particle assembly and disassembly. Viral particles contain a lipid bilayer that is studded with two viral glycoprotein complexes: hemagglutinin (HA), which permits the entry of the virus into the host cell, and neuraminidase (NA), which facilitates the release of the new viral progeny once they have replicated in the host cell. Several other minor proteins are present on the lipid bilayer, including M2, which has a role in viral genome release during viral entry, and M1, which gives the virus rigidity and strength to ensure it retains its structural integrity both inside and outside of the infected host. The great mutability of the virus's proteins, especially the HA, the target of neutralizing antibodies, is predominantly responsible for the generation of viral or 'antigenic' variants. During evolution within the human host, the virus can change by point mutations in viral RNA, a process called antigenic 'drift,' allowing it to evade the immune response. When a major shift occurs that results in the emergence of novel hemagglutinins, humans are able to catch the same protein ever again in their lifetime; this is stored away after initial infection. The infection is then recognized upon re-exposure and, as such, becomes less severe. Proliferation is further reduced thanks to extensive memory B and T cell responses being mounted. Antigenic shift is most likely due to the reassortment of viral RNA segments between co-circulating strains of influenza A. It is believed that this is more likely to occur in co-infections between an avian and human virus or between an animal reservoir and human virus; far less is known about transmission between different avian species. The movement of viral segments between a relatively benign virus with a much higher representation and a more severe spectrum can push the virus into the pandemic class. As the drift and shift mechanisms allow the virus to escape the immune system of the host, effective vaccines and antiviral therapies must constantly be reviewed and adapted. Periodically circulating a virus for multiple years can affect the severity of an outbreak – if patients were infected just prior to the patient, they may present milder symptoms thanks to their existing immune response. (Senevirathne, 2023)(Dinan et al.2020)(Sabsay and Te2023)(Branttie, 2021) [19, 8, 17, 5].

2.1. Structure and Classification

Virions of the influenza virus impart an envelope-enclosed structure. The envelope, which comprises a stolen lipid bilayer, is believed to be inherited from the host cell. Embedded in the envelope are two types of glycoproteins, namely hemagglutinin and neuraminidase. The viral particle also envelops matrix protein 2 ion channels that serve as a conduit for protons to subsidize the fusion of the viral envelope with an endosome, thus releasing the viral genetic material into the cellular cytoplasm. The neuraminidases, which are also tetrameric in nature, contribute to the release of newly manufactured virions by detoxifying the cell surface. The influenza virus A is further classified into subtypes, specifically HxNx. The H proteins are comprised of 18 types, whereas the Ns are made up of 11 subtypes. This classification system reflects how the different strains interact with different kinds of glycoproteins on the surface of host cells in the upper respiratory tract, a feature that must be perceived to understand the receptor binding and replication in a specific host, thus the pathogenesis of diseases falls. (Scheibner et al.2023) (Bialy & Shelton, 2020) [18, 4]

Because a person's immune system is usually incapable of recognizing antigens that are unique to that person as foreign, the ability of different glycoproteins to interact with different cellular membrane antennas makes them deadlier. In conjunction with this, the virus reassortment activity in the gene exchange melding the close companions of hemagglutinin and neuraminidase contributes to high periodic morbidity and seasonal epidemics and pandemics. The influenza A virus is categorized into subtypes by additional pathogenicity and host predilection traits, acute disease-producing seasonal influenza isolates, highly pathogenic avian influenza isolates that form strained infections and mass fowl deaths worldwide, and occasional isolates that cause inflation in domestic poultry. However, the factors for this shift and drift, among others, are yet to be identified, and aspects of host adaptation and genetics are being elucidated. As a result, subtype is used to denote the particular virus genotypes with a variety of observable and measurable characteristics. (Lee et al.2021)(Fereidouni et al.2023)(Huang & Wang, 2020) [14, 10, 12].

2.2. Genome and Replication

Influenza virus

The influenza virus is a pathogen that infects humans and has a genome composed of RNA that is physically separated into eight segments, making the virus capable of undergoing reassortment. After fusion of the viral envelope with the host cell membrane and internalization of the particle by endocytosis, the genomes are transported to the nucleus where they can undergo transcription and translation. Transcription is executed with two host cell RNA polymerases that are recruited to the ribonucleoprotein material and produce viral RNA that is synthesized by the viral RNA-dependent RNA polymerase. During translation, all three classes of viral proteins are expressed in a cap-dependent manner, and for viral genes, the presence of the cap binding protein cellular machinery is required for translation. The viral genome is entirely translated into one polyprotein coding for all the different types of viral proteins. The Pol proteins are responsible for viral replication, both in the cytoplasm and in the nucleus, and they are also synthesized as polyproteins. Once enough copies of the new viral ribonucleoproteins have been synthesized, they are sustainably exported from the nucleus. Venturing to the cytoplasm, the viral RNPs first pair with the right amount of viral matrix proteins. At last, the viral envelope is formed within the host cell, while viral hemagglutinins and new neuraminidases are being synthesized from their corresponding mRNAs by host cell machinery. The final and key step in the assembly is the interaction of the matrix protein projects with the viral envelope. Influenza has evolved with a fast viral genome mutation rate that does not include robust proofreading machinery, due to multiple combinations of the glycoproteins abundant on the viral envelope. Such combinations are a result of spontaneous reassortment in its two different hosts. Influenza can then emerge in new strains that are unreliable to all the original inoculations. The instability not only means each year's produced vaccine is challenging to match but also might have defective antigenicity, through so-called escape mutations. Given the evolutionary history of the abilities of the influenza virus, it is central to epidemiological models as well as the estimation of risks associated with pathogenicity and transmissibility. Additionally, the biological nature explicit to the influenza virus also necessitates a comprehensive understanding of its virology for therapeutic interventions such as vaccines.

3. Virology of Adenovirus

Introduction

Adenoviruses are double-stranded DNA-containing viruses. They are, along with viruses from the picornavirus superfamily, the second leading cause of upper respiratory tract infections worldwide. Although they are less disseminated in the population and also less prevalent clinically than influenza, adenoviral infections are still epidemiologically relevant and are particularly clinically significant for their complications, which are often aggravated by the lack of a specific antiviral therapy. Besides these infections, adenoviruses have been suggested as vector agents for gene therapy and more recently as vaccines, due to their ability to infect many types of cells. In this comparison, we explore common aspects and differences of influenza and adenovirus that may influence their natural behavior and therapeutic approaches.

4. Virology of Adenovirus

4.1. Structure The adenovirus particle is naked, of icosahedral symmetry, and large (about 70 to 90 nm in diameter). 1.1.1. Adenovirus serotype classification Adenoviruses are currently classified into three subfamilies: the Mastadenoviruses, which include 72 human serotypes; Bovine adenovirus types 1-3; and four lower primate serotypes; the Aviadenoviruses, which contain many, mostly bird, members; and finally, the Siadenoviruses, containing only one simian serotype. Adenoviruses bind to cellular receptors through their fibers in a serotype-specific manner. Some characteristics of serotype and tissue specificity can be identified in human and non-human adenoviruses; for instance, some adenovirus surface proteins, such as the pattern of the fiber trimer, may participate in portal entry selectivity.

4.2. Structure and Classification

Adenoviruses are non-enveloped double-stranded DNA viruses that contain a non-segmented genome of 26–45 kb in length. Adenovirus virions consist of three major groups of structural proteins, including hexon, fiber protein, and penton base, anchored in the viral capsid. The capsid is studded with homotrimers of hexon. The terminal end has the vertex of the hexon trimeric protein, which is associated with the dodecahedron-shaped penton as a penton base. The fiber can be found at the apex of the viral capsid. Adenovirus virions show high environmental resistance due to the absence of an envelope and have a robust icosahedral protein shell that contains the genome inside the capsid.

Adenoviruses were initially classified based on cross-neutralization by antisera that corresponded to more than 70 different human adenovirus serotypes. Unrelated groups, as well as subgroups, were defined using serum-neutralizing antibody tests in hosts that were either immune to the strains of human adenovirus or who had not been exposed to the viruses. Serotypes of more than 20 different clinically significant adenoviral serotypes were reported in related groups B, C, D, and E. The largest number of reported serotypes was found in group D. Classification was not based on diversity in diseases caused by the specific genotypes, but their molecular epidemiology was useful for identifying

resistance patterns to adenoviral disease and routes of transmission of various adenoviruses. In terms of evolution, adenoviruses have adapted and paired their infection strategies to their natural host cells. Their molecular structure combined with their immunogenic properties could have clinical and epidemiological relevance.

4.3. Genome and Replication

Adenoviruses are non-enveloped viruses that feature linear double-stranded DNA genomes with base pairs. In comparison to linear double-stranded DNA or sense RNA genomes carried by different viruses, adenoviruses are apt to bear larger genomic materials. The physical viral DNA coding DNA would probably contain more than 100 different peptides. Adenoviruses utilize viral DNA polymerase to carry out replication of their genome. The viral DNA must bud outside the host DNA molecules and is made capable of unfurling as templates for the following steps of viral multiplication and gene expression. At the preliminary stages of infection, viral enzymes release free DNA ends that function as templates, owing to the presence of proteins covalently connected with 5-terminal protected covalently joined proteins. The connection of adenoviral polypeptide, namely protein VII, features nucleosome. The viral protein VII-associated DNA ends are obliged to enter inside the host cell nucleus in order to act as DNA templates that function to form the replicating DNA intermediates, further establishing multiplication of the viral DNA. In the adenoviral multiplication process, viral genes are responsible for the establishment of cellular synthesis inhibitors as well as mRNAs, to ensure that cellular DNA replication can proceed as soon as necessary. The preceding stage embraces ample synaptic and catalytic DNA proteins useful for initiating the synthesis. The viral genes likely also provide more necessary materials for propagating the late stages of viral replication than initiating the process. The advancements in genetic analysis on adenoviral life cycles are accompanied by a definitive understanding of ways in which adenoviruses interact with the host cell components to form virus particles. The ensuing advancement in recombinant DNA features provides appropriate conditions for changing the genes of wild-type viruses and enabling estimation of the function of the changed genes and their proteins during the virus life cycle executed in a normal cell. These premature and ensuing stages of the synthesis generate genetic mutations in the genes of the transformed proteins. These changed proteins are natural targets for active and passive immunity and new drugs. In view of the high reproduction capacity of viruses, some virus mutants arise continually to generate viral resistance to the inhibitors designed by humans.

5. Epidemiology and Transmission

Influenza is a highly contagious respiratory virus, while adenoviruses are non-enveloped DNA viruses that can infect mucosal tissues, the lining of the respiratory and gastrointestinal tracts. In most cases of influenza virus infection, the primary route of infection is inhalation of contaminated aerosols. In addition, infected individuals can contaminate the environment, leaving the virus on surfaces or more effectively dispersed in the environment via sneezing and coughing. Thus, transmission of the influenza virus may occur, at least in part, by contact with contaminated surfaces or through droplet spread. Water sources, swimming pools, and fomites may serve as reservoirs that can contain adenoviruses based on experimental results. Influenza transmits from person to person in outbreaks, epidemics, and pandemics, and the incidence rate fluctuates with the change of season. The incidence of adenovirus is highest in winter and spring, with outbreaks predominantly reported in crowded environments including schools, military facilities, and long-term care facilities. Epidemiological and ecological factors impacting the transmission of the influenza viruses and adenoviruses are important to understand and are central to public health interventions. Furthermore, surveillance plays a key role in guiding the public health response to viral infection and in the education of healthcare professionals and the public regarding infection prevention and control. Precautionary measures aimed at reducing infection risk and disrupting the dynamics of infection transmission include the administration of antiviral medication and the uptake of annual vaccination. Much available information indicates that combined infection is more frequently identified than solitary infections, but this is not always universally observed.

6. Clinical Manifestations and Disease Severity

As far as the clinical manifestations are concerned, both influenza virus and adenovirus infections are often associated with nonspecific symptoms, such as fever, malaise, myalgia, coughing, rhinorrhea, and respiratory illness. Regarding the severity of diseases, adults and children infected with both viruses usually recover uneventfully. Nonetheless, influenza and adenoviruses can also cause severe and sometimes lethal infections that are potentially life-threatening, especially in young children, adults aged 65 years or over, and in immunocompromised individuals. The latter can include pregnant women, people with underlying health or immunodeficiency conditions, and people with a pre-existing severe comorbidity. Influenza virus and adenovirus infections may also lead to secondary bacterial infections, making it difficult to distinguish between viral and bacterial infections on the basis of symptoms alone. Accurate and prompt differential diagnoses are needed to administer the most appropriate treatments. Influenza viruses and adenoviruses are both responsible for potential life-threatening conditions and diagnostic challenges. Research aimed at improving the clinical management and treatment of these infections is essential. Influenza viruses and adenoviruses are responsible for a wide variety of clinical syndromes, ranging from common cold-like manifestations to more serious conditions, such as bronchitis, bronchiolitis, and complex pneumonia. Both viruses can cause severe disease to lifelong sequelae and death, especially in young children, adults aged 65 years or over, and immune compromised individuals. Based on clinical features, it is difficult to distinguish between influenza and adenoviral infections. For both infections, there is still no vaccination program available for all potential vulnerable individuals, and management support is a key area for future study.

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