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Original Research

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Emergence of Community-Acquired Adenovirus Type 55 as a Cause of Community-Onset Pneumonia

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Background: **Since 2008, severe cases of emerging human adenovirus (HAdV) type 55 (HAdV-55) were reported sporadically in China. But no comparative studies had been conducted to discern the differences in epidemiologic and clinical abnormalities between HAdV-55 and other types (HAdV-7, HAdV-3, HAdV-14, HAdV-50, and HAdV-C).**

Methods: **A multicenter surveillance study for adult and adolescent community-acquired pneumonia (CAP) was conducted prospectively in Beijing and Yan Tai between November 2010 and April 2012. A standardized data form was used to record clinical information. The viral DNA extracted from the clinical samples or adenovirus viral isolates was sequenced.**

Results: **Among 969 cases, 48 (5%) were identified as adenovirus pneumonia. Six branches were clustered: HAdV-55 in 21, HAdV-7 in 11, HAdV-3 in nine, HAdV-14 in four, HAdV-50 in two, and HAdV-C in one. Most HAdV-55 cases were identified during February and March. All the hypervariable regions of the hexon genes of the 21 HAdV-55 strains were completely identical. Patients who had HAdV-55 were about 10 years older ($P = .027$) and had higher pneumonia severity index scores ($P = .030$) compared with those with other types (HAdV-7, HAdV-3, HAdV-14, HAdV-50, and HAdV-C). Systemic BP was also higher among patients in the HAdV-55 group ($P = .006$). Unilateral or bilateral consolidations were the most common radiologic findings in both patients with HAdV-55 and those with other types (57.9% vs 36%). More than one-half of the patients were admitted to hospital; oxygen therapy was given to 29.2% of the 48 patients, and two needed mechanical ventilation.**

Conclusions: **HAdV-55 has established itself as a major pneumonia pathogen in the Chinese population, and further surveillance and monitoring of this agent as a cause of CAP is warranted.**

CHEST 2014; 145(1):79–86

Abbreviations: BNACAP = Beijing Network for Adult Community-Acquired Pneumonia; CAP = community-acquired pneumonia; CPE = cytopathic effect; HAdV = human adenovirus; PCR = polymerase chain reaction; PSI = pneumonia severity index

Community-acquired pneumonia (CAP) refers to pneumonia acquired outside of hospital or long-term care facilities. The overall annual incidence of CAP ranges from five to 20 per 1,000 adults.[1] Many microbial pathogens can cause CAP, and the role of viruses may have been underestimated thus far because of a lack of appropriate diagnostic methods.[2-3] Modern molecular techniques have revealed that respiratory viruses account for about 22% of adult CAP cases.[4-10] The most common viruses are influenza, parainfluenza, respiratory syncytial virus, metapneumovirus, and adenovirus.

We previously reported 18 sporadic CAP cases caused by human adenovirus (HAdV) from our single center between August 2008 and April 2011. Polymerase chain reaction (PCR) analysis using type-specific primers targeting the hexon gene revealed that they all belonged to species B (HAdV-11, HAdV-7, HAdV-3, and HAdV-14),[11] and HAdV-11 accounted for 58.8% (10 of 17) of them. However, further genome sequence analysis proved that these 10 HAdV-11 strains were actually HAdV type 55 (HAdV-55). HAdV-55, an intertypic recombinant described originally as genome type 11a, was identified from an outbreak of acute

respiratory tract infection in Shanxi Province, China, in 2006.[12] It exhibited a neutralizing antigen epitope of HAdV-11 and the pathogenic properties of HAdV-14.[13-14] The whole-genome sequencing analysis showed that HAdV-55 had an HAdV-14 chassis with a partial HAdV-11 in the hexon gene.[15-16] For this reason, it was renamed HAdV-55.[13]

Our previous case series[11] indicated that HAdV-55 apparently emerged in Beijing.[12] Adenovirus 14 is an emerging agent of concern that has been causing outbreaks of pneumonia not just in China, but worldwide. Adenovirus 55, which is related to adenovirus 14, is now also emerging as an agent of concern. We investigated whether HAdV-55 has a different clinical profile from the profiles of other adenovirus types circulating in China.

Materials and Methods

Beijing Network for Adult CAP

The Beijing Network for Adult Community-Acquired Pneumonia (BNACAP), which consists of 11 general hospitals from nine different districts in Beijing and one teaching hospital in Yan Tai, is a clinic-based, multicenter, prospective surveillance system for adults and adolescents with CAP. Yan Tai is a city by the sea in Shan Dong Province, located about 770 km southeast of Beijing. The institutional review board of Beijing Chao-Yang Hospital approved the study (project approval number 10-KE-49). All patients gave their written informed consent.

Study Population

Between November 2010 and April 2012, all adolescent and adult patients (aged 14 years or older) from 12 general hospitals who met the inclusion criteria of CAP were prospectively enrolled during daytime 7 days a week.[3] Patients with HIV infection or neutropenia, those receiving immunosuppressive chemotherapy or prednisone steroids equivalent to 15 mg/d for 30 days, pregnant or breast-feeding women, and those with known or suspected active TB were excluded.

Clinical Data Collection

Clinical information collected by investigators with a standardized data form included the following: age, sex, comorbidities, smoking history, vaccination against influenza and *Streptococcus pneumoniae* in the past year, symptoms (fever, cough, sputum, dyspnea, chest pain), GI symptoms (nausea, vomiting, diarrhea, and abdominal pain), and neurologic symptoms (headache, dizziness). Clinical signs (body temperature, heart rate, respiratory frequency, BP, and crackles) and treatments (antibiotics, antiviral therapy, or oxygen use) were also recorded. The pneumonia severity index (PSI) was used to assess the severity of illness on the day of enrollment.[17]

Symptoms and signs of all patients were followed up, either during their hospitalization or after discharge, until all symptoms disappeared. For outpatients, the same information was gathered. All the information collected from the patients was input into a computerized database.

Microbiologic Diagnostic Tests Undertaken

The nasal or throat swab specimens collected by the attending physicians were collected in 2-mL viral transport media, transported at 2°C to 8°C, and preserved at −80°C. The viral RNA was extracted from the clinical samples using a QIAamp RNA mini kit (QIAGEN). Following this, a commercially available Seeplex RV 15 ACE Detection kit (Seegene Inc), a multiplex, one-step, reverse transcriptase PCR, was used to screen for 15 different viruses as the cause of the respiratory illness. The kit included assays for adenovirus, influenza A and B viruses, human metapneumovirus, rhinovirus, respiratory syncytial virus (groups A and B), coronavirus (229E, NL63, OC43, and HKU1), parainfluenza virus (type 1, 2, 3, 4), bocavirus, and enterovirus.

Blood cultures were performed for patients presenting with chills and shivering. If pleural fluid and sputum samples were available, Gram stain and culture were performed. Urinary antigen tests for *Legionella pneumophila* and *S pneumoniae* (Binax) were also performed on all urine specimens. Acute sera (1-3 days after onset) and convalescent sera (2-4 weeks after onset) were collected for testing of the antibody for HAdV or other respiratory viruses.

Criteria for Viral Pneumonia

Viral pneumonia was diagnosed based on one of the following criteria: (1) the presence of HAdV or other respiratory viruses detected in sputum or throat swab samples by molecular methods or (2) seroconversion, defined as a fourfold or greater increase in titers of antibodies to HAdV or other respiratory viruses.

Cell Culture and Virus Isolation

Nasal or throat swab specimens were inoculated onto Hep-2 cells and cultured in a maintenance medium for detection of a

Manuscript received May 19, 2013; revision accepted August 1, 2013.
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Funding/Support: This work was supported by the Beijing Science and Technology Project [Grant D101100049810002], the National Natural Science Foundation of China [Grants 81070005/H0104, 81030032/H19, and 81271840], China's Key Technologies Research and Development Program of the National Ministry of Science [Grants 2013ZX10004-202 and 2012ZX10004201-003], and the Program for New Century Excellent Talents in University [Grant NCET-09-0006].
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DOI: 10.1378/chest.13-1186