Human Adenovirus Type 7 Infection Associated with Severe and Fatal Acute Lower Respiratory Illness and Nosocomial Transmission

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A 23-year-old male died of severe pneumonia and respiratory failure in a tertiary hospital in Beijing, and 4 out of 55 close contacts developed fever. Molecular analysis confirmed human adenovirus type 7 (HAdV7) as the causative agent. We highlight the importance of early diagnosis and treatment and proper transmission control of HAdV7.

CASE REPORT

H uman adenovirus type 7 (HAdV7) infection is associated with acute respiratory disease syndrome, pharyngocconjunctival fever, pneumonia, and central nervous system disease (1–4). According to the last global survey, approximately one-fifth of all HAdV infections reported to the World Health Organization (WHO) were attributed to HAdV7 (5). HAdV7 outbreaks generally occur in settings with close living conditions, such as military barracks, hospital wards, and chronic care facilities (1, 6–8). In hospitals, HAdV has emerged as a nosocomial pathogen, and nosocomial outbreaks caused by HAdV7 with fatal cases have been reported worldwide (8–10). Although some prevention measurements have been carried out to control nosocomial transmission, questions regarding the efficacy of these programs persist, and the contribution of HAdV7 (and adenoviruses in general) to nosocomial infection is likely to be underestimated. Here, we report a case of HAdV7 infection associated with severe pneumonia and fatal acute lower respiratory disease and nosocomial transmission.

The index case, a 23-year-old male in Wuhan City, Hubei Province, China, presented with a fever of approximately 39°C on 18 January 2014, but discontinuous treatment did not alleviate his symptoms. On 26 January, he was admitted to the emergency department of a tertiary hospital in Beijing. A routine blood test showed high neutrophil levels (71.4%) and elevated plasma C reactive protein (19 mg/ml), and chest radiographs revealed an increase of right lung markings. However, the use of cefoxitin suggested that all isolates were derived from a common ancestor (HAdV_7_309-1B from the index case). To assess the genetic relationships of different virus serotypes and determine their origin,

Received 6 September 2014 Returned for modification 1 October 2014 Accepted 8 December 2014


Editor: Y.-W. Tang

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doi:10.1128/JCM.02517-14
phylogenetic analysis of the partial sequences was performed (Fig. 2A and B). Strain HAdV_7_309-1B displayed one substitution at position 1228 of the hexon gene, which was a silent mutation. The strains identified in this report are closely related to the predominant HAdV7 isolates reported in China in recent years (12).

As shown by the case described above, early identification and treatment of adenovirus infection is vital. Initially, the index case only presented with mild acute respiratory symptoms. However, without prompt treatment, the viral load may increase by replication in human lungs, leading to severe pneumonia (13, 14). There are no approved antiviral agents with proven efficacy for the treatment of severe pneumonia caused by HAdV (15). Thus, the patient’s condition deteriorated quickly even after later antiviral and hormone therapy. In contrast, the other four patients recovered well after timely antiviral treatment with ribavirin. The combined use of Chinese patent medicines (Lianhua Qingwen capsule and Radix Isatidis) that have antiviral curative effects may also have played a role.

Nosocomial control of HAdV7 transmission is another challenge faced by health care centers. HAdV7 transmission generally occurs through respiratory droplets and close contact, which can lead to rapid and wide-spread infection. Large community and regional outbreaks of acute respiratory disease with an increased incidence of severe and fatal outcomes caused by HAdV7 have been described in Europe and Asia (7, 12, 16, 17). Thus, control of HAdV7 spread is crucial. However, it is difficult to differentiate pneumonia caused by HAdVs from other types of viral pneumonia, and culturing and typing of HAdVs are not routinely performed in hospitals (18). Therefore, the inevitable delay of several days after the index case's onset of symptoms leads to nosocomial transmission of the virus.

### TABLE 1 Patient characteristics and laboratory results

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Underlying condition</th>
<th>Clinical symptoms</th>
<th>Laboratory results</th>
<th>X-ray results</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index case</td>
<td>23</td>
<td>None</td>
<td>Fever, cough, sore throat</td>
<td>Neutrophilia, 71.94%; C-reactive protein, 19 mg/ml</td>
<td>Increase of right lung markings; later, lung consolidation developed</td>
<td>Death</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>None</td>
<td>Fever, sore throat</td>
<td>Mononucleosis, 11.14%; lymphocytosis, 54.24%</td>
<td>Normal</td>
<td>Recovered after 6 days of hospitalization and was discharged 7 days later</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>Acute pancreatitis, fatty liver</td>
<td>Fever</td>
<td>Normal leukocyte count; mononucleosis, 11.74%</td>
<td>Pulmonary shadows</td>
<td>Recovered after 9 days of hospitalization and was discharged 7 days later</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>None</td>
<td>Fever, sore throat</td>
<td>Normal leukocyte count; mononucleosis, 10.74%</td>
<td>Normal</td>
<td>Recovered after 6 days of hospitalization and was discharged 7 days later</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>Respiratory infections</td>
<td>Fever</td>
<td>Mononucleosis, 10.85%; lymphocytosis, 52.68%</td>
<td>Normal</td>
<td>Recovered after 7 days of hospitalization and was discharged 7 days later</td>
</tr>
</tbody>
</table>

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**FIG 1** Timeline of critical events for the index patient and nosocomial infection. (Top) Key events during the index patient’s illness are shown. (Bottom) Each bar indicates the period for an infected patient from first contact with the index case to symptom onset.
FIG 2 Phylogenetic analysis of a portion of the hexon gene for strain HAdV7 309-1B described in this study and other reference strains of adenovirus. The phylogenetic tree was generated using the neighbor-joining method. Bootstrap values are shown at branching points. Scale bars indicate nucleotide substitutions per site. (A) Strains HAdV7 309-1B compared to other subgenotype of HAdV reference strains; (B) HAdV7 309-1B compared to other HAdV7 reference strains.
days in the recognition of HAdV infections probably promoted the transmission. One study of adenovirus infection reported the incubation period to be 5 to 6 days (19), and another study of secondary infections in families found the mean incubation period to be 10 days (20). In this study, therefore, it was concluded that patient 4, who developed fever 11 days after first contact with the index case, was also infected by him. When the pathogen was identified, an infection control response was initiated immediately, on 8 February. Efforts to prevent the spread of HAdV7 included the use of disposable gowns and gloves, strict hand hygiene, and disinfection of common areas, such as floors and toilets. Furthermore, the four patients with HAdV7 infection were transferred to single rooms. The symptomatic patients had recovered well after 5 to 8 days of hospitalization and were discharged after 7 days of isolation.

In summary, we suggest that more importance should be given to the early diagnosis and treatment and proper transmission control of HAdV7, which causes acute respiratory illness. Therefore, hospitals should improve their diagnostic capabilities for rapid detection of HAdV infection, as well as their infrastructure to institute proper case management and transmission control.

Nucleotide sequence accession numbers. The hexon gene sequences of the isolates were deposited in the GenBank database (accession numbers KJ783432 to KJ783436).

ACKNOWLEDGMENTS

We thank all the participants at the hospital for help in recruiting patients and all the patients for agreeing to be included in this study.

This work was supported by Mega-projects of Science and Technology Research grants (grant no. 2012ZX10004215, 2013ZX10004607, 2013ZX10004218, and 2012ZX10004801) and by the National Nature Science Foundation of China (grant no. 81171554 and 81202252). The authors declare that they have no competing interests.

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