Diagnosis of influenza from lower respiratory tract sampling after negative upper respiratory tract sampling

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In this retrospective cohort study, we demonstrate that PCR-confirmed diagnoses of influenza were made solely by lower respiratory sampling in 6.9% of cases, as traditional upper respiratory tract tests were negative, indeterminate or not performed. Clinical features of these cases are presented. Clinicians should consider lower respiratory tract sampling in select cases of influenza-like illness for diagnosis.

Introduction

Clinicians are often faced with the challenge of patients presenting with an influenza-like syndrome despite negative routine influenza investigations. These investigations usually include nasal or nasopharyngeal rapid influenza screens, direct fluorescent antibody (DFA) or PCR tests. Occasionally these diagnostic tests may be falsely negative due to their low sensitivity, as in the case of many rapid-influenza tests,1 poor technique in specimen collection, delayed transport to the laboratory or the presence of viral inhibitors.2 Clinicians rely heavily on these investigations as they are readily available and guide therapeutic decisions.

Most influenza infections affect the upper respiratory tract, while lower tract infection typically represents extension from upper airways and may be diagnosed with lower respiratory sampling such as bronchoscopy.2,3 Occasionally a diagnosis of influenza is missed with upper respiratory tract sampling if pulmonary symptoms are present, and concerns have been raised regarding missing pandemic strain of H1N11 and Avian influenza A (H5N1), which have both been shown to infect the lower respiratory tract.4,5 We present data from our institution where lower respiratory tract sampling aided the diagnosis of influenza and discuss clinical features of these patients.

Methods

The Institutional Review Board at the Massachusetts General Hospital reviewed and approved this study. We performed a retrospective cohort analysis of all cases of PCR-confirmed influenza between December 2009 and April 2011 at the Massachusetts General Hospital [Simplexa™ Influenza A H1N1 (2009), Focus Diagnostics]. We identified all patients where lower respiratory sampling (induced sputum, endotracheal aspiration or bronchoscopy) was used to diagnose influenza. Only cases that were confirmed as PCR-positive were included. Using a standardized data collection form, we recorded patient demographics, influenza diagnostic testing, radiographic features, oxygenation supplementation, clinical features, accompanying comorbid conditions, and outcomes. Obesity was defined by body mass index (BMI) equal to or greater than 30. Patients were defined as immunocompromised if they were taking prednisone (or equivalent) > 15 mg per day for over 2 mo, on active chemotherapy, HIV with CD4 T cell counts less than 200 cells/ml or on other immunomodulatory medications such as biologic therapies like tumor necrosis factor α antagonists.

Results

One hundred and sixteen patients were identified with PCR-confirmed influenza virus between December 2009 and April 2011. Forty-six were typed as pandemic H1N1 and 70 as seasonal influenza A. The average age was 56.6 y (range 1–95) with 60 (51.7%) females. Ninety-four patients (81%) were hospitalized and a total of 6 (5.1%) of died. Sixty-seven (57.8%) had a comorbid condition portending severe influenza. Of these 116 PCR-positive patients, 15 (12.9%) underwent lower respiratory sampling to aid in diagnosis (age range 11–81 y). Ten of these 15 patients (66.7%) were positive for influenza virus in lower respiratory samples. Of these 10, a diagnosis of influenza was made solely by lower respiratory sampling in eight cases (6.9% of total PCR positive cases), as rapid tests, nasopharyngeal DFA or PCR tests were either negative, indeterminate or not performed.

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Influenza viruses initially infect the upper airways but can directly extend to the lower airways in severe cases, resulting in a viral pneumonia with significant morbidity and mortality. Patients initially present with upper respiratory symptoms, but typically deteriorate from a respiratory standpoint if lower tract symptoms develop, frequently requiring hospitalization or intensive care. Clinicians should be aware that sampling of the upper airways might not be adequate to diagnose these cases. In our series, 6.9% of PCR-documented influenza had negative upper airway sampling, and were diagnosed by either BAL, endotracheal aspiration, or induced sputum. Certain influenza strains such as Avian H5N1 virus are reported to infect lower airways, and the average white blood cell count on presentation was 7.3 cells/ml (range 3.2–16.2) on admission. Radiographic features included 6 (60%) with acute respiratory distress syndrome (ARDS), and 3 (30%) with single or multi-lobar consolidative processes. One patient had no obvious radiographic changes from his underlying interstitial lung disease. Eight (80%) patients required care in an ICU and two (20%) patients ultimately died of their illness.

Discussion

Influenza viruses initially infect the upper airways but can directly extend to the lower airways in severe cases, resulting in a viral pneumonia with significant morbidity and mortality. Patients initially present with upper respiratory symptoms, but typically deteriorate from a respiratory standpoint if lower tract symptoms develop, frequently requiring hospitalization or intensive care. Clinicians should be aware that sampling of the upper airways might not be adequate to diagnose these cases. In our series, 6.9% of PCR-documented influenza had negative upper airway sampling, and were diagnosed by either BAL, endotracheal aspiration, or induced sputum. Certain influenza strains such as Avian H5N1 virus are reported to infect lower airways, and the average white blood cell count on presentation was 7.3 cells/ml (range 3.2–16.2) on admission. Radiographic features included 6 (60%) with acute respiratory distress syndrome (ARDS), and 3 (30%) with single or multi-lobar consolidative processes. One patient had no obvious radiographic changes from his underlying interstitial lung disease. Eight (80%) patients required care in an ICU and two (20%) patients ultimately died of their illness.

Table 1. Characteristics of patients with lower respiratory specimens positive for influenza A (pandemic and seasonal)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Rapid test</th>
<th>NP DFA</th>
<th>NP PCR</th>
<th>Comorbidities</th>
<th>Lower respiratory tract sampling</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>F</td>
<td>- (1)</td>
<td>- (1)</td>
<td>n/a</td>
<td>Nil</td>
<td>ETA</td>
<td>Died</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>n/a</td>
<td>- (2)</td>
<td>n/a</td>
<td>Renal transplant</td>
<td>BAL</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>F</td>
<td>n/a</td>
<td>- (2)</td>
<td>+</td>
<td>Pregnant, obese</td>
<td>BAL</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>n/a</td>
<td></td>
<td>+</td>
<td>ILD</td>
<td>BAL</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>F</td>
<td>- (1)</td>
<td>- (1)</td>
<td>i(1)</td>
<td>Nil</td>
<td>BAL</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>F</td>
<td>- (2)</td>
<td>- (2)</td>
<td>- (1)</td>
<td>Nil</td>
<td>BAL</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>73</td>
<td>M</td>
<td>n/a</td>
<td>- (1)</td>
<td>n/a</td>
<td>ILD</td>
<td>BAL</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>F</td>
<td>n/a</td>
<td></td>
<td>- (1)</td>
<td>Nil</td>
<td>ETA</td>
<td>Survived</td>
</tr>
<tr>
<td>9</td>
<td>81</td>
<td>M</td>
<td>n/a</td>
<td>- (1)</td>
<td>n/a</td>
<td>Nil</td>
<td>BAL</td>
<td>Survived</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>M</td>
<td>- (1)</td>
<td>- (1)</td>
<td>- (1)</td>
<td>HIV, asthma</td>
<td>IS</td>
<td>Survived</td>
</tr>
</tbody>
</table>

NP, nasopharyngeal; DFA, direct fluorescent antibody; i, indeterminate; BAL, bronchoalveolar lavage; ETA, endotracheal aspirate; IS, induced sputum; ILD, interstitial lung disease.
nasopharyngeal sampling techniques must be employed, and such
tests may ultimately be negative due to inadequate specimen
collection. Other possibilities include low levels of viral shedding
in the nasopharynx at the time of sampling as the infection has
progressed to the lower respiratory tract. 1 Animal models
demonstrate more viral replication in the trachea, bronchi and
bronchioles with pandemic H1N1 compared with seasonal
H1N1, which is restricted primarily to the nasopharynx. 2
Lastly, those with risk factors for severe influenza such as obesity,
an immunocompromised state, asthma or pregnancy 3 may be at
greater risk of lower respiratory tract involvement and a poor
gnosis. Future prospective studies should assess diagnostic
characteristics of influenza in relation to the time of sample
collection, risk factors for severe disease and clinical disease
progression.

Traditional nasopharyngeal diagnostic techniques may miss
cases of influenza affecting the lower respiratory tract. Clinicians
should have a high degree of suspicion in patients with lower-tract
symptoms and a syndrome compatible with influenza, particularly
in the setting of pregnancy, obesity or in immunocompromised
states. Empiric antiviral therapy is often warranted 4 and sampling
of the lower tract by bronchoscopy, endotracheal aspirate or
induced sputum may yield a diagnosis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Faix DJ, Sherman SS, Waterman SH. Rapid-test
   sensitivity for novel swine-origin influenza A (H1N1)
   http://dx.doi.org/10.1056/NEJMn0904264
3. Centers for Disease Control and Prevention (CDC). Swine influenza A (H1N1) infection in two children–
   Southern California, March-April 2009. MMWR Morb Mortal Wkly Rep 2009; 58:400-2; PMID:19390508
   PMID:19230162; http://dx.doi.org/10.1016/j.vaccine.2008.07.025
5. Yeh E, Luo RF, Dyner L, Hong DK, Banaei N, Baron EJ, et al. Preferential lower respiratory tract infection in
   10.1086/649875
   Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in
   virulent influenza A(H1N1) variants in the lower respiratory tract of critically ill patients during the
   journal.pone.0028332
8. Connolly MG, Jr., Baughman RP, Dohn MN, Linnemann CC, Jr.. Recovery of viruses other than
   dx.doi.org/10.1378/chest.105.6.1775
   Diagnostic Utility Of Blind Endotracheal Aspirate In Intubated Patients With False Negative Realtime
   Reverse Transcriptase Polymerase Chain Reaction Assays From Nasopharyngeal Samples. Am J Respir
   Crit Care Med 2010; 181:A2623.
10. Falsey AR, Formica MA, Walsh EE. Yield of sputum for viral detection by reverse transcriptase PCR in adults
    1128/JCM.05841-11
11. Munster VJ, de Wit E, van den Brand JMA, Herfst S, Schrauwen EJA, Bestebroer TM, et al. Pathogenesis and
    transmission of swine-origin 2009 A(H1N1) influenza virus in ferrets. Science 2009; 325:481-8; PMID:19574548
    Working Group for Risk Factors for Severe H1N1pdm Infection. Risk factors for severe outcomes following 2009
    dx.doi.org/10.1371/journal.pmed.1001055
    Diseases Society of America. Seasonal influenza in adults and children–diagnosis, treatment, chemoprophylaxis,
    and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America.
    Clin Infect Dis 2009; 48:1003-32; PMID:19281331; http://dx.doi.org/10.1086/598513