

PEDIATRIC ASTHMA

Emergence of Oseltamivir-Resistant Pandemic H1N1 in an Immunocompetent Child with Severe Status Asthmaticus

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Introduction. Pandemic influenza A (H1N1) may cause severe illness in pediatric patient with chronic lung disease. **Case Report.** We describe the emergence of oseltamivir resistance in an immunocompetent child with status asthmaticus triggered by pandemic influenza A (H1N1). This case highlights the possible relationship between influenza viral load and risk of resistance emergence in children with asthma. Influenza vaccination should continue to be emphasized as the mainstay of prevention in children with chronic lung disease. **Conclusion.** Influenza virus can lead to severe status asthmaticus and can develop oseltamivir resistance in immunocompetent children.

Keywords children, chronic lung disease, drug resistance, influenza, neuraminidase inhibitor

INTRODUCTION

In 2009–2010, pandemic influenza A (H1N1) emerged and caused significant morbidity and mortality in the pediatric population. The CDC reported the highest influenza-associated pediatric death number since 2004, with 279 deaths during that season (1). Prompt empiric antiviral therapy was recommended for infants, children, and adolescents presenting with suspected or confirmed influenza requiring hospitalization (2). Progressive, severe, or complicated illness and risk factors for severe illness including asthma were also indications for empiric therapy (2). Asthma was the single most frequent risk factor of severe diseases encountered in hospitalized pandemic H1N1 (pH1N1)-infected children cohorts (21–67%) (3–6). Available options for treating children included neuraminidase inhibitors, oseltamivir or zanamivir, with the latter licensed for children 7 years and older without underlying respiratory disease. Previous reports have shown that children infected with seasonal H1N1 are at higher risk of developing antiviral drug resistance when compared with adults (7). Limited reports of oseltamivir-resistant pH1N1 in immunocompetent children are available (8). We describe the emergence of the H275Y mutation conferring oseltamivir resistance in a 7-year-old immunocompetent child presenting with severe status asthmaticus and respiratory failure requiring mechanical ventilation secondary to pH1N1 infection.

CASE REPORT

A 7-year-old former 27-week preterm infant with a history of bronchopulmonary dysplasia and asthma, manifesting as recurrent wheezing with upper respiratory tract infections, presented to our emergency department. He had a past history of status asthmaticus requiring mechanical ventilation in February 2009 secondary to seasonal influenza A, and since that time had been maintained on inhaled fluticasone/salmeterol controller therapy. On the evening of 24 September 2009, the patient started coughing. The following day, he developed marked wheezing poorly responsive to albuterol and was admitted to the local hospital. Progressive respiratory distress despite treatment with inhaled bronchodilators and systemic corticosteroids precipitated transfer to our facility. Upon arrival, he was in severe hypoxic respiratory failure (oxygen saturation of 75%) and severe respiratory acidosis (pH of 6.94 and pCO₂ > 130 mmHg) necessitating intubation and mechanical ventilation. He required treatment with methylprednisolone (2 mg/kg/day), terbutaline (3 µg/kg/min), aminophylline, heliox, magnesium sulfate, and muscle relaxant. At presentation to our hospital, physical exam was significant for bilaterally decreased breath sounds and prolonged expiratory phase with diffuse expiratory wheezes. His initial chest X-ray, prior to intubation, showed marked hyperinflation without infiltrates (Figure 1A). The patient's maximum temperature on admission was 39.2°C. The reverse transcriptase polymerase chain reaction (RT-PCR) test performed on a nasal wash collected on the first hospital day detected pH1N1. Oseltamivir was started on the second day of illness at a dose of 45 mg twice daily (4 mg/kg/day) via nasogastric tube and increased to 60 mg twice daily (5 mg/kg/day) the following day according

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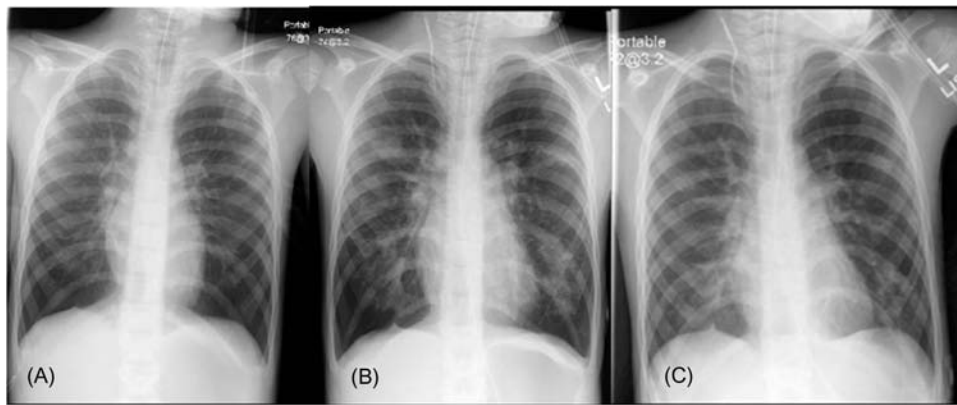


FIGURE 1.—Chest radiography (A) hospital day 1 showing hyperinflation, diaphragmatic retraction, and absence of infiltrate; (B) hospital day 3 showing apparition of bilateral patchy infiltrate compatible with viral pneumonia; and (C) hospital day 6 showing improvement of inflation and infiltrate.

to CDC recommendations. One dose of ceftriaxone was given empirically. The patient developed patchy bilateral pulmonary opacities with negative blood culture and endotracheal bacterial culture (Figure 1B and C). He remained febrile for 5 days and was successfully extubated on hospital day 6. The duration of the oral oseltamivir treatment was 5 days.

Virologic data for this patient include an initial nasal wash RT-PCR positive for influenza with a viral load of $9.3 \log_{10}$ copies/ml. This initial sample was determined to be wild type at position H275 by allele-specific RT-PCR and therefore susceptible to oseltamivir (9). Repeat nasal wash and tracheal aspirate on hospital day 3 revealed influenza viral loads of $9.3 \log_{10}$ copies/ml and $7.7 \log_{10}$ copies/ml, respectively; viruses from both specimens were determined to be wild type. Influenza RT-PCR was also performed on the patient's serum on hospital day 3 and was negative. The nasal wash obtained on hospital day 6, following extubation, revealed a viral load of $6.3 \log_{10}$ copies/ml with a mixed population of wild-type (85%) and mutant H275Y (15%) viruses. Oseltamivir was stopped on day 5 of treatment and the patient discharged to home on hospital day 11.

DISCUSSION

Emergence of the H275Y mutation in seasonal influenza A (H1N1) has been recognized to occur in children at higher rates than adults (7). Previous studies reported oseltamivir resistance rates between 16 and 18% among seasonal H1N1 influenza obtained from children after initiating therapy (10, 11). Delayed cell-mediated immunity in response to a virus encountered for the first time has been suggested as the potential explanation for higher viral loads in young children (12). This higher viral load could contribute to the selection of drug-resistant quasiespecies. pH1N1 has been associated with a relatively low rate of oseltamivir resistance (1.1%) (1). However, more than 300 cases of oseltamivir-resistant infection have been reported to the World Health Organization (WHO) and almost 100 have been published. With few exceptions, all

isolates carried the H275Y mutation, which prevents the neuraminidase conformational change that is required for oseltamivir to inhibit the release of newly formed viruses. According to the WHO, 24% of resistant viruses were recognized in immunocompromised patients, 32% were associated with treatment in immunocompetent patients, and a few were related to post-exposure prophylaxis.

Immunosuppression and younger age are two of the most significant risk factors for drug resistance emergence in influenza virus. Only few cases of immunocompetent children with oseltamivir-resistant pH1N1 have been reported. One large-scale study in South Korea identified 10 cases of resistant pH1N1 through a national surveillance program. Six of these cases were children, including one immunocompetent child with asthma (13). Another case report described an 11-year-old boy with severe neurological disease and complicated pH1N1 who also developed the H275Y mutation and recovered despite 21 days of potentially ineffective oseltamivir and intravenous immunoglobulins (IVIG) (8).

Our case report highlights the potential severity of bronchospasms triggered by pH1N1 influenza infections in children with asthma as previously shown in two adult patients (14). Asthma has been identified as the single most frequent underlying comorbidity in hospitalized patients with pH1N1, occurring in 21–67% of hospitalized children with pH1N1 (3–6). One study compared inpatient non-severe illness with inpatient severe illness in children infected with influenza and found that a history of asthma and acute exacerbation of asthma at the time of influenza diagnosis were significantly associated with severe disease (15). Interestingly, two other studies found that children admitted with pH1N1 were significantly more likely to have asthma than children hospitalized for seasonal H1N1 during previous years (22% vs. 6%; $p < .001$ and 67% vs. 12%; $p < .001$) (4, 5). Both studies also highlighted the high rate of pneumonia caused by pH1N1 in hospitalized asthmatic children (50–73%) (4, 5). Studies in outpatient settings have also shown the burden of pH1N1 in patients with reactive airway disease. Asthmatic children with severe exacerbation presenting to pediatrician's office had more risk to have

concomitant influenza-like illness (16.5%) than asthmatic children without exacerbation (3.9%) ($p < .0001$) (16). Adults presenting to emergency departments with pH1N1 infection identified asthma as a pre-existing condition in 31% of cases versus 14% of controls presenting for other reasons (OR: 2.6; 95% CI: 1.3–5.4) (17). Asthmatic patients were also the only high-risk group experiencing significantly higher than expected emergency department visits for influenza-related illness (18).

Our patient was admitted twice, 8 months apart, to the pediatric intensive care unit because of status asthmaticus, both triggered by influenza infection. At the first episode, the patient was unvaccinated, and at the second episode, the pandemic influenza vaccine was not yet available. The lack of available pH1N1 vaccine at the time of the 2009 influenza pandemic was problematic, but influenza vaccination of asthmatic children and their families should be emphasized as the best way to reduce morbidity in that population. In times of limited vaccine availability, high-risk children such as our patient with a history of severe asthma should be considered to be at highest priority to receive influenza vaccine. One randomized open-label study has shown that monovalent-inactivated 2009 pH1N1 vaccine was safe and provided a robust immune response in asthmatic patients under 60 years of age (19).

Asthma is associated with more severe influenza disease, but whether asthma is associated with higher viral load or more resistance of influenza viruses is unknown. The study by Li et al. reported higher viral loads in throat swabs from children with pneumonia compared with children with bronchitis or upper respiratory tract infection (12). They also described longer shedding of viruses in children under 13 years compared with children older than 13 years (11 days vs. 7 days). Interestingly, asthma was present in 23% of the patients under 13 years compared with none of the older children. We hypothesize that chronic airway inflammation or use of topical corticosteroids could lead to higher viral load or longer shedding in patients with asthma and possibly contribute to resistance development. Many studies in immunocompromised patients have shown that systemic corticosteroids were associated with prolonged influenza viral shedding, but no reports correlating topical corticosteroid use with prolonged shedding are available (20).

CONCLUSION

We describe a case of status asthmaticus triggered by pH1N1 with emergence of the H275Y mutation leading to oseltamivir resistance. Influenza in patients with asthma has been associated with more severe disease, but the relationship to viral load and risk of resistance emergence remains incompletely understood. Influenza caused by oseltamivir-resistant virus in patients with chronic lung disease could potentially lead to severe outcome since the only alternative treatment, zanamivir, is

actually contraindicated in this population because of the risk of bronchospasm. More studies looking at resistant influenza in this high-risk population are needed and newer treatment strategies involving intravenous antiviral medications should be evaluated. Influenza vaccination should continue to be emphasized as the mainstay of prevention in this patient population.

DECLARATION OF INTEREST

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