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LETTER TO THE EDITORS

Atypical hemolytic uremic syndrome associated with H1N1 influenza A virus infection

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Sirs,

Atypical nonfamilial HUS can be caused by infections, medications, systemic diseases, malignancy, and pregnancy [1]. Infection with influenza A or Epstein Barr virus has been rarely associated with atypical HUS. The 2009 pandemic of influenza A due to a novel swine-origin influenza A:H1N1 strain in the spring of 2009 has been characterized by widespread illness in young children and an increase in the number of fatal cases in the pediatric age group [2]. We report the first case of atypical HUS associated with confirmed pandemic influenza A:H1N1 infection and describe the clinical course of this illness.

A 5-year-old girl had a history of reactive airway disease and hospitalization for pneumonia 1 year prior to presentation. Her immunizations were up to date, and she had received the seasonal influenza but not the 2009 pandemic influenza A:H1N1 vaccine. Three days prior to admission, she presented with 3 days of fever (103°F), frontal headaches, sinus pain, cough, abdominal pain, and vomiting, but no diarrhea. She was treated with nebulized albuterol and amoxicillin. The patient was first seen in a local hospital 1 day prior to admission. A nasopharyngeal swab was positive for influenza A and negative for influenza B using a rapid antigen detection test.

The following day, the child had worsening vomiting and increased difficulty breathing. She was treated with albuterol, methylprednisolone, and supplemental oxygen (O_2). Laboratory tests included white blood cells (WBC) 8.6, hemoglobin (Hb) 11.4, hematocrit (Hct) 33.3, and platelet count 254,000. Renal function was normal. A chest radiograph showed a right upper lobe infiltrate. Treatment with oseltamivir and ceftriaxone was initiated, and continuous positive airway pressure (CPAP) was begun. Her condition worsened, prompting transfer to Cohen Children's Medical Center (CCMC).

On admission to the Pediatric Intensive Care Unit, the patient was grunting and in moderate respiratory distress. Oseltamivir and ceftriaxone were continued, and vancomycin was added. Her urinalysis had 25 mg/dl protein with small ketones but was negative for blood and nitrites. A nasal swab submitted to detect respiratory viruses by nucleic acid amplification assay was positive for influenza A nonsubtypable. On the second hospital day, she was placed on a ventilator. On admission, a comprehensive metabolic panel revealed blood urea nitrogen (BUN) 16 and serum creatinine 0.27 mg/dl. The following day, she passed dark-colored urine, and urinalysis revealed numerous red blood cells and 500 mg/dl protein. On day 3, laboratory testing indicated a serum sodium 126 mmol/L, calcium 6.9 mg/dl, and rising blood urea nitrogen BUN and serum creatinine levels, 37 and 2.79 mg/dl, respectively. Over this same period,

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she developed microangiopathic anemia with fragmented red cells, a decline in Hct from 30.3 to 24.2 vol%, and thrombocytopenia with a drop in platelet count from 160,000 to 27,000/mm^3. The patient experienced bleeding of the oral mucosa. Her coagulation profile was normal, but she had markedly elevated D-dimer and normal fibrinogen levels. She was given vitamin K, platelets, and a transfusion of packed red blood cells (PRBC).

The patient became oliguric, and on the third hospital day, she was started on continuous venovenous hemofiltration with dialysis. She remained anuric for 15 days and was transitioned to intermittent hemodialysis. She was maintained on renal replacement therapy until she gradually began to void, and dialysis was stopped 4 weeks after being hospitalized.

Nasopharyngeal swab specimens, transported in universal transport media, obtained on days 1, 4, and 5 of hospitalization at CCMC tested positive for nonsubtypable influenza A:H1N1 using the Luminex xTAG Respiratory Virus Panel (RVP) real-time polymerase chain reaction (RT-PCR) assay. The identity of the initial isolate was confirmed to be 2009 pandemic influenza A:H1N1 by RT-PCR using the method developed by the United States Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA). In addition, a nasopharyngeal swab specimen was cultured using R-Mix cells (Diagnostic Hybrids), and influenza A virus was isolated. The influenza A isolate was confirmed to be 2009 pandemic influenza A:H1N1 by the CDC RT-PCR assay, as described above.

An in-house-developed quantitative influenza A RT-PCR assay, which utilizes the Gen-Probe/Prodesse ProFlu+ reagents (Gen-Probe/Prodesse, Waukesha, WI, USA) [3] determined that the patient's influenza A viral titer was 3.5×10^6 copies/ml on day 1, 2.5×10^7 copies/ml on day 4, and 3.7×10^7 copies/ml on day 5. Nasopharyngeal samples tested at days 10, 13, and 14 of hospitalization were negative for influenza A and B RNA.

Three months after discharge, the child was well and was taking no medications. Her physical examination was normal. Laboratory testing indicated a normal complete blood count (CBC) and full recovery of kidney function, with a serum creatinine of 0.64 mg/dl and calculated glomerular filtration rate (GFR) 90 ml/min/1.73 m^2. The urine protein:creatinine ratio in a first morning sample was 1.1 (mg:mg).

This child satisfied the three diagnostic criteria for HUS. Because of the absence of a prodromal diarrhea and the presence of a localized pulmonary infiltrate, consideration was given to pneumococcus-related HUS. However, the patient's WBC was not elevated, and she did not have disseminated intravascular coagulation. Her blood and endotracheal tube cultures were negative for bacteria. Viral studies confirmed that the pneumonia was caused by the 2009 pandemic influenza A:H1N1 virus, with high viral titers in the respiratory tract through day 5. Moreover, severity and resolution of the thrombotic microangiopathy coincided with the clinical course of the respiratory infection. Although we cannot definitively exclude a combined viral–bacterial infection, this is the first report in a child of atypical HUS that was triggered by this new pandemic influenza A:H1N1 strain.

Infection by the 2009 pandemic influenza A:H1N1 strain has been associated with widespread and possibly more severe disease in pediatric patients. The risk of death was tenfold higher in pediatric patients with pandemic influenza A:H1N1 infection in 2009 compared with those who had seasonal influenza in previous years [2]. Although there is a recent report of two pediatric patients—a 7-year-old girl and a 13-year-old boy—who had macroscopic hematuria as a prodromal complaint in association with 2009 pandemic influenza A:H1N1 infection [4], there are no prior reports linking this virus with the occurrence of atypical HUS. The risk of atypical HUS may be higher after infection with the 2009 pandemic influenza A:H1N1 strain than with seasonal influenza strains, or occurrences may reflect the large number of children infected. Nonetheless, the full recovery in our patient suggests that the outcome of atypical HUS associated with 2009 pandemic influenza A:H1N1 virus infection may not be worse than for other strains.

References

1. Constantinescu AR, Bitzan M, Weiss LS, Christen E, Kaplan BS, Cnaan A, Trachtman H (2004) Non-enteropathic hemolytic uremic syndrome: causes and short-term course. Am J Kidney Dis 43:976–982
2. Libster R, Bugna J, Coviello S, Hijano DR, Dunaiewsky M, Reynoso N, Cavalieri ML, Guglielmo MC, Areso MS, Gilligan T, Santucho F, Cabral G, Gregorio GL, Moreno R, Lutz MI, Panigasi AL, Saligari L, Caballero MT, Egües Almeida RM, Gutierrez Meyer ME, Neder MD, Davenport MC, Del Valle MP, Santidrian VS, Mosca G, Garcia Domínguez M, Alvarez L, Landa P, Pota A, Boloñati N, Dalamon R, Sanchez Mercol VI, Espinoza M, Peuchot JC, Karolinski A, Bruno M, Borsa A, Ferrero F, Bonina A, Ramonet M, Albano LC, Luedicke N, Alterman E, Savy V, Baumeister E, Chappell JD, Edwards KM, Melendi GA, Polack FP (2010) Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Argentina. N Engl J Med 362:45–55
3. Chandrasekaran A, Zhang F, Lotlikar M, Ginocchio CC (2010) Development of a normalized quantitative influenza A real-time RT-PCR assay. 26th Clinical Virology Symposium, Pan American Society for Clinical Virology. Daytona, FL. April 2009. Abstr S78
4. Ghiggeri GM, Losurdo G, Ansaldi F, Canepa A, Magnasco A (2010) Two cases of swine H1N1 influenza presenting with hematuria as prodrome. Pediatr Nephrol 25:779–780