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CASE REPORT

Report of a Fatal Pediatric Case of Hemophagocytic Lymphohistiocytosis Associated with Pandemic Influenza A (H1N1) Infection in 2009

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An acute viral infection may lead to death, as seen in the recent novel 2009 influenza A (H1N1) virus pandemic that rapidly spread worldwide. Hemophagocytic lymphohistiocytosis (HLH) is a systemic disorder with high mortality rates and can be triggered by various etiological agents, including viral infections. H1N1-associated HLH is a very rare condition that may cause extremely severe complications leading to multiple organ failure (MOF) and death. We report an unusual case of a rapidly progressive and fatal H1N1 infection that was complicated with HLH and MOF in a previously healthy 8-year-old Asian female who initially presented with fever and abdominal pain. To enable early recognition and proper treatment, physicians should be aware of the possibility of this fatal complication, which may present with unusual initial symptoms.

1. Introduction

In early April 2009, the US Centers for Disease Control and Prevention reported novel swine influenza A (H1N1) infection

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in two children. The virus promptly became a pandemic and caused 2500—6000 deaths.[1,2] Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disorder, characterized by a fulminant picture of nonremitting high fever, pancytopenia, hepatosplenomegaly, lymphadenopathy, liver dysfunction, coagulopathy, and neurological symptoms or encephalopathy; it can be explained by high amounts of proinflammatory cytokines such as interferon-gamma (IFN-γ), interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) resulting in the clinical characteristics of a cytokine storm.[3—5] Beutel et al[6] considered HLH associated with influenza A (H1N1) infection to be strongly associated with multiple organ failure (MOF) and death. There are very few reports of influenza-induced HLH in children.[7,8] We report an unusual case of a rapidly progressive H1N1 infection that presented with unusual initial symptoms of fever and abdominal pain and was complicated by HLH and fatal MOF in a previously healthy 8-year-old female.

2. Case Report

An 8-year-old Asian female presented on September 25, 2009 with acute colicky abdominal pain, rhinorrhea, a mild cough, and a high-grade fever that had been present for 4 days. On admission, the patient was conscious and cooperative, but restless, with a core body temperature of 39.7°C, pulse of 140 beats per minute, respiratory rate of 23 breaths per minute, and blood pressure of 90/45 mmHg. Skin examination showed no jaundice, pallor, cyanosis, rash, or purpuric lesions. There was generalized lymphadenopathy. An abdominal examination revealed a tender abdomen, and hepatosplenomegaly was noted, with the liver edge palpated at 3 cm below the right costal margin and the spleen palpated at 3 cm below the left costal margin. There were no clinically detectable ascites. The chest and cardiac examinations revealed no abnormalities. Results of the laboratory investigation are summarized in Table 1. A chest X-ray was normal (Figure 1A), and abdominal ultrasonography revealed liver and spleen enlargement, gallbladder wall edema, peripancreatic retroperitoneal lymph node enlargement, and mild ascites. A computed tomography (CT) scan of the abdomen confirmed the ultrasonographic findings (Figure 1B). Surprisingly, bone marrow aspiration, which was performed to exclude malignancy, revealed typical hemophagocytosis (Figure 1C). A throat swab specimen was collected and sent for analysis for pandemic influenza A (H1N1) 2009 virus [by reverse-transcription ploymerase chain reaction (RT-PCR)]. Based on the persistent fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, hypertriglyceridemia, and hemophagocytosis in the bone marrow, HLH was diagnosed. Treatment was started with rehydration, omeprazole, methylprednisolone at 30 mg/kg/dose, and intravenous immunoglobulins (IVIG) at 400 mg/kg/day.

On the 2nd day after admission, the child was transferred to the pediatric intensive care unit due to a rapid deterioration in her general condition, persistence of fever, development of generalized tonic colonic convulsions, jaundice, multiple purpuric eruptions, oliguria, and cyanosis with a percutaneous oxygen saturation rate that dropped to 67%. At this stage, the child was ventilated mechanically. The majority of the laboratory values deteriorated, as summarized in Table 1. That day, the patient died from MOF. Throat swab specimens were found to be positive for pandemic influenza A (H1N1) 2009 virus by RT-PCR, but unfortunately, these results were not available until after the patient died.

Table 1 Laboratory investigation results of the child.

Investigations	1st day	2nd day
Hemoglobin (g/dL)	8.5	8.0
WBC (/mm^3)	2900	2500
Neutrophils (%)	59.0	69.6
Lymphocytes (%)	38.0	27.4
Monocytes (%)	2.0	2
Platelets (/mm^3)	29,000	22,000
PT (s)	16	45
PTT (s)	60	80
Serum ferritin level (ng/dL)	12,000	12,200
Serum triglycerides (mg/dL)	390	400
ESR (mm/h)	15	—
C-reactive protein (mg/dL)	14.78	—
Liver function		
Total bilirubin (mg/dL)	2	9
Aspartate aminotransferase (U/L)	280	1200
Alanine aminotransferase (U/L)	150	450
Serum albumin (g/dL)	3.5	3.4
Sodium (mg/dL)	135	125
Potassium (mg/dL)	3.5	5
Serum creatinine (mg/dL)	0.9	1.3
Virology		
Epstein—Barr virus	Negative	
Cytomegalovirus	Negative	

ESR = erythrocyte sedimentation rate; PT = prothrombin time; PTT = partial thromboplastin time; WBC = white blood cells.

3. Discussion

HLH is a life-threatening condition caused by excessive activation and proliferation of T cells and macrophages.[9] These cellular responses can be triggered by a variety of viral, bacterial, fungal, and parasitic infections, as well as by genetic conditions, collagen-vascular diseases, and malignancies.[4]

Infection-related HLH is most commonly caused by viral infections; in Taiwanese patients with infection-related HLH, mortality rates were approximately 50—60%.[10—12] Despite aggressive treatment, most patient deaths resulted from refractory bleeding, pulmonary edema, and MOF.[12]

In 2009, novel human influenza A (H1N1) became a pandemic, which started in Mexico and spread worldwide. The mortality rates from infections with H1N1 were higher in patients who developed HLH and MOF.

The clinical presentation of HLH is usually acute and can be dramatic, causing fatalities. Typically, most clinical features and laboratory findings can be explained by the widespread dissemination of hyperactivated lymphocytes and macrophages, and are compatible with the biologic effects of several T-lymphocyte- and macrophage-derived