Case Report: Novel Swine-Origin Influenza A (H1N1) Virus-Associated Hemophagocytic Syndrome—A First Case Report

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Abstract. Secondary or reactive hemophagocytic syndrome (HPS) is frequently related to viral infections. However, the novel swine-origin influenza A (H1N1) virus associated HPS has never been reported. On October 10, 2009, a 17-year-old female child with no past medical history, complaining of severe asthenia, pneumonia, myalgia, and high fever, was admitted to our department, and H1N1 DNA was detected. Five days after her hospitalization, all signs and symptoms aggravated into HPS. After treatment for H1N1 influenza, the patient had a recovery and clearance of H1N1 infection 10 days after hospitalization. Three weeks later, the patient was discharged without any complaints, indicating the etiological role of H1N1 infection in HPS.

INTRODUCTION

Hemophagocytic syndrome (HPS) is a clinical condition characterized by infiltration of the bone marrow and reticuloendothelial system by macrophages and activated histiocytes, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes, and precursor cells. This syndrome is classified as primary or acquired, the latter being more frequent.1 The acquired type is associated with several etiologies, including viral, bacterial, fungal, and protozoa infections, malignancies (lymphomas), and other conditions like rheumatic diseases. Among these viral infections, the most likely to be associated with hemophagocytic syndrome are Epstein–Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus type 6 (HHV-6), and human herpesvirus type 8 (HHV-8).2 However, the novel swine-origin influenza A (H1N1) virus with hemophagocytic has never been reported.

MATERIALS AND METHODS

Informed consent was obtained from all human adult participants and from parents or legal guardians of minors with the name of the appropriate institutional review board that approved the project. We report a case of HPS associated with the new H1N1 virus infection. A 17-year-old female child with no past medical history complained of severe asthenia, pneumonia, myalgia, and high fever and was hospitalized for the first time on October 10, 2009. During 21 days, her H1N1 DNA was monitored.

RESULTS

The patient’s severe asthenia, pneumonia, myalgia, and high fever symptoms developed 10 days before her hospitalization. After admission in our hospital, chest contrast-enhanced computerized tomography (CT) scan revealed interstitial pneumonia. She was given an empiric treatment of pneumonia based on chest CT scan finding. After admission in our hospital, chest contrast-enhanced computerized tomography (CT) scan revealed interstitial pneumonia. After admission, the patient had a recovery and clearance of H1N1 infection 10 days after hospitalization. Three weeks later, the patient was discharged without any complaints.

DISCUSSION

The sudden emergence and rapid spread of oseltamivir-resistant H1N1 viruses with neuraminidase (NA) gene H274Y amino acid substitution has been the hallmark of global seasonal influenza since January 2008.3–5 Viruses carrying this mutation are widely presumed to exhibit attenuated pathogenicity,6 compromised transmission,7 and reduced lethality.8 The case described herein has complied with all diagnostic criteria and is the first case of H1N1 virus-associated HPS to be reported.

The HPS was first described in 1979 in immunosuppressed patients with viral infections.9 It is characterized by fevers, lymphadenopathy, hepatosplenicomegaly, maculopapular rash, cytopenias, and hyperferritinemia caused by dysregulated activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes, and their hematopoietic precursors throughout the reticuloendothelial system. Familial HPS seems to have a genetic etiology, whereas acquired HPS may be associated with malignancy, autoimmune disease, or infection.

The pathophysiological mechanism for HPS remains poorly understood. In patients with HPS, the expression of major histocompatibility complex MHC-I and MHC-II molecules increased, suggesting that splenic macrophages were activated.10

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The prognosis of the HPS relies mainly on the severity and duration of the cytopenias. Long-term neutropenia increases the risk of severe infections from gram-positive bacteria like *Staphylococcus aureus*. Thrombocytopenia should be monitored because of the possibility of spontaneous bleeding, which can occur in the central nervous system (CNS) as a fatal outcome. Anemia is a risk factor for infections and can induce organ dysfunctions, such as heart failure and tissue hypoxia. In addition to cytopenias, some cases of HPS developed disseminated intravascular coagulation and fatal organic dysfunction because of severe sepsis, which contributed to the mortality of more than 40% in the largest series.11

The treatment of HPS is not well-defined because of lack of controlled studies.12 Some supportive therapies corrected the severe cytopenias and treated the causal infection. The effective use of prednisolone or plasma exchange against HPS has been reported,13–16 however, whether or not these treatments were effective against HPS in our patient is still unknown.17

H1N1 influenza is one of many infections that can cause a secondary hemophagocytic syndrome, and it is possible that the patient carried falciparum H1N1 infection with continuing anaemia after successful anti-virus therapy.

We report a case of H1N1 virus-associated HPS, which is an uncommon event described in critical patients and thus, might be underdiagnosed. Treatment of the underlying infection can improve clinical outcomes, and therefore, early diagnosis and treatment of H1N1 virus-associated HPS are essential in clinical practice (Figure 1).

**Laboratory findings in a patient with HPS and H1N1**

<table>
<thead>
<tr>
<th>Laboratory finding</th>
<th>Oct. 10</th>
<th>Oct. 20</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/L)</td>
<td>78</td>
<td>97</td>
<td>131–172</td>
</tr>
<tr>
<td>Leukocyte (cells/L)</td>
<td>0.5 x 10⁹</td>
<td>0.9</td>
<td>3.97–9.15</td>
</tr>
<tr>
<td>Platelet (x10⁹/L)</td>
<td>28 x 10⁹</td>
<td>21</td>
<td>85–303</td>
</tr>
<tr>
<td>DB (µmol/L)</td>
<td>47</td>
<td>19</td>
<td>3.0–17.0</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>52</td>
<td>23</td>
<td>0–33</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>23</td>
<td>227</td>
<td>0–27</td>
</tr>
<tr>
<td>Fe (ng/mL)</td>
<td>1,500</td>
<td>20–200</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>214.4</td>
<td>0–10</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>2.35</td>
<td>0.4–1.5</td>
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</tr>
<tr>
<td>Reticulocyte (%)</td>
<td>0.87</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>214.4</td>
<td>0–10</td>
<td></td>
</tr>
<tr>
<td>Fe (ng/mL)</td>
<td>1,500</td>
<td>20–200</td>
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<tr>
<td>LDH (U/L)</td>
<td>1,657</td>
<td>230–460</td>
<td></td>
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</tbody>
</table>

**REFERENCES**


**Figure 1.** Bone-marrow smear results. Blank arrow, macrophages with hemophagocytosis (HE staining ×400). This figure appears in color at www.ajtmh.org.
H1N1-ASSOCIATED HEMOPHAGOCYTIC SYNDROME


