H1N1 is a novel subtype of the influenza A virus. Since its reemergence in 2008, it has been reported to cause a variety of illnesses ranging from mild flu-like symptoms to severe multiorgan failure. We report a case of a young immunocompetent man who presented with progressive shortness of breath and rapidly developed multiorgan dysfunction, including pancytopenia from H1N1 infection during the 2010-2011 influenza season. His H1N1 pneumonia caused severe acute respiratory distress syndrome, respiratory failure requiring mechanical ventilation, rhabdomyolysis, myocarditis, hepatitis, encephalitis, and renal failure. During the diagnostic workup, a bone marrow biopsy was performed, showing hemophagocytosis secondary to the H1N1 infection. Unfortunately the patient died despite aggressive measures. Published reports contain only a few records of H1N1-induced hemophagocytosis. This is the first case report from Saudi Arabia with H1N1-induced secondary hemophagocytosis. It also highlights the fact that the virus is still very virulent and will pose a major annual health risk along with the seasonal influenza for at least the next few years.

In Saudi Arabia, cases of the H1N1 influenza infection during the 2009 pandemic were similar to those in other regions of the world.1 Most patients presented with respiratory symptoms, and mortality was reported to be low in patients with preexisting ailments.2 The fatal cases usually had multiorgan involvement. A few postmortem case reports in patients from the United States and China showed secondary hemophagocytosis because of the H1N1 virus; however, this was not reported in patients from Saudi Arabia.3,4 We report here a unique case of an immunocompetent Saudi patient who was admitted with severe H1N1 infection during the current 2010-2011 influenza season, and developed not only severe multiorgan dysfunction, but also secondary hemophagocytosis because of the H1N1 virus.

CASE
A 29-year-old Saudi male, with a history of insulin-dependent diabetes mellitus, presented with shortness of breath and fever to our hospital. There was no history of sick contacts. The patient did report stomach upset after eating at a restaurant the day prior. On admission, he had bilateral infiltrates on the chest radiograph and was admitted to the medical ward and treated for community-acquired pneumonia. Over the next 2 days, however, his condition failed to improve, and he started having more respiratory distress and became more confused. A toxicology screen was performed, showing a negative result. Laboratory evaluation showed an elevated creatinine kinase level of 439 U/L. He was then transferred to the medical intensive care unit (ICU) for impending respiratory failure. By that time, the bilateral infiltrates had worsened and involved the whole lungs. He was intubated and placed on the ventilator in a pressure-regulated volume control mode. Because of his rapid deterioration, broad-spectrum antibiotics including meropenem, vancomycin, colistimethate, doxycycline, caspofungin, trimethoprim/sulfamethoxazole, moxifloxacin, and metronidazole were administered to cover all strains of bacterial infections. Oseltamivir at a dose of 150 mg orally twice
daily was also started on admission to the ICU to cover for influenza. A transthoracic cardiac echocardiogram showed that the patient had a severely depressed ejection fraction of 15%. This was acute decompensation of his heart function as he did not have any cardiac problems before. Liver transaminases also significantly increased, and he developed pancytopenia on presentation to the ICU. At that time, a flexible bronchoscope was done and bronchoalveolar lavage was sent for bacterial and fungal cultures and viral testing. The patient went into severe acute respiratory distress syndrome requiring 100% oxygen and a positive end-expiratory pressure of 15. A bone marrow biopsy was done as part of the workup for pancytopenia while awaiting the bronchoalveolar lavage results. By the second day in the ICU, he had developed multiorgan failure, with creatinine levels rising up to 358 µmol; creatinine kinase levels increased from 439 U/L to more than 10 000 U/L, indicating massive rhabdomyolysis and necessitating continuous renal replacement therapy. His hemoglobin level dropped from 106 g/L to 67 g/L with no evidence of bleeding or hemolysis. The white blood cell (WBC) count decreased from 5.8×10⁹/L to 1.68×10⁹/L and the platelet count decreased from 229×10⁹/L to 50×10⁹/L. He had not received any heparin products. Gradual deterioration in coagulation parameters despite antibiotics and antivirals indicated disseminated intravascular coagulation. Laboratory test results for identifying the underlying cause of pancytopenia, such as the presence of parvovirus B19, hepatitis B, hepatitis C, or HIV, were negative, as were the serology tests for coxsackie virus and cytomegalovirus, varicella, the IgM test for Epstein-Barr virus, and two independent peripheral blood smears for malarial parasites. Blood cultures were negative for bacterial or fungal infection. The test results for acid-fast bacilli were also negative. Since his mental condition was deteriorating despite brain computed tomographic images being normal, a lumbar puncture was performed after correcting his coagulation status and transfusing platelets. The fluid obtained was sent for cultures, and on microscopic and cytological analyses it was reported to be normal. The autoimmune profile including rheumatoid factor, anti-neutrophil antibody, classical anti-neutrophil cytoplasmic antibody, protoplasmic-staining antineutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody was normal, and hence lupus and other autoimmune diseases were ruled out. He required repeated transfusions to maintain his hemoglobin level and fresh frozen plasma to correct coagulation parameters. After ruling out all the other possibilities, the bone marrow was examined for malignancy or other causes of pancytopenia. Surprisingly, the bone marrow showed significant hemophagocytosis, with histiocytic engulfment of red blood cells, WBCs, and platelets (Figures 1, 2, 3). CD68 staining to confirm the identity of the histiocytes was strongly positive (Figure 4). At the same time, positive polymerase chain reaction (PCR) results on two specimens taken at the time of ICU admission were positive for H1N1 (influenza virus type A), with negative avian influenza PCR. Other parameters in favor of hemophagocytosis were a
low fibrinogen of 1.00 g/L, a high ferritin of 1966 µg/L, a triglyceride of 2.6 mmol/L, and a high CSF protein of 560 mg/dL. Even though the patient was started on a high dose of oseltamivir on admission to the ICU, it did not control the massive multiorgan dysfunction precipitated by the virus. Unfortunately, the patient did not recover from the acute viral infection and its complications and died on the 8th hospital day from intractable shock and hypoxemia.

DISCUSSION

According to the February 2011 CDC report, influenza activity (including H1N1 influenza) was low until December 2010; however after that a progressive increase in activity was observed. Approximately 79% of reported viruses were influenza A and 21% were influenza B. Among the 1794 influenza A viruses that were subtyped, approximately 57% were influenza A (H3N2) viruses and 43% were 2009 H1N1. These viruses were similar to the viruses chosen for the 2010-2011 flu vaccine and susceptible to both oseltamivir and zanamivir. Our patient presented in October of 2010, and the virulence of the viral attack was fatal. This is in contrast to the United States, where the fatalities from H1N1 surfaced only starting in December 2010. This is probably due to the millions of people from all over the world visiting during the Ramadan and Hajj season.

The primary event after the transmission of H1N1 is the invasion of the respiratory epithelium after an incubation period that varies from 1 to 7 days. The virus is shed for an average duration of a week, starting from 1 day before the start of symptoms until 7 days later. Besides the usual involvement of the lungs, some unusual symptoms that have been seen, but are less common are conjunctivitis and parotitis. Parotitis was reported in a child with influenza of swine origin. In two sporadic cases of the disease caused by a similar reassorted swine-origin H1N1 virus, much before the onset of this pandemic, atypical features of hemophagocytic syndrome in one and extensive bowel involvement with mesenteric vessel thrombosis in the other have been reported. The occurrence of hemophagocytic syndrome in that patient was attributed to immune dysregulation. Besides this, the vaccine may have the potential to precipitate the Guillain-Barré syndrome and a progressive postvaccinal encephalopathy.

Our patient was noted to have the hemophagocytic syndrome. The cardinal symptoms of hemophagocytic lymphohistiocytosis (HLH) are prolonged high fever, hepatosplenomegaly and cytopenias, lymphadenopathy, and icterus; neurological symptoms such as cranial nerve palsies or seizures may also be present. Characteristic laboratory findings include high triglycerides, ferritin, transaminases, and bilirubin and decreased fibrinogen. The clinical picture of HLH can be induced by a variety of infectious organisms, mostly viruses, but also bacteria, protozoa, and fungi. The patients in the original report by Risdall and colleagues were mostly adults with a viral infection following organ transplantation. Subsequently, it became clear that nonviral agents could trigger HLH, and the term virus-associated hemophagocytic syndrome was redesignated infection-associated hemophagocytic syndrome. In the majority of cases, hemophagocytosis is not observed in the initial bone marrow aspirate, and only increased monocytes and monohistiocytic cells may be present. A myelodysplastic syndrome is sometimes suspected because of marked dysplastic changes in the red cell precursors.

In summary, our patient had a severe fatal case of H1N1 infection with resultant hemophagocytosis. This is a grim reminder that in the next coming years the H1N1 virus will remain virulent, especially in Saudi Arabia, and physicians need to be extra vigilant during the influenza season.

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