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Case Reports

Hemophagocytic lymphohistiocytosis associated with influenza A (H1N1) infection in a patient with chronic lymphocytic leukemia: an autopsy case report and review of the literature☆

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Abstract H1N1 influenza A virus can trigger fatal hemophagocytic lymphohistiocytosis in immunocompromised patients and in immunocompetent hosts, usually children. We present a case of a 50-year-old man with low-burden chronic lymphocytic leukemia who had sudden reactivation of his leukemia triggered by influenza A (H1N1) infection with hemophagocytic lymphohistiocytosis during the 2009 H1N1 pandemic. His rapid course was complicated by acute respiratory distress syndrome with diffuse alveolar damage, a 6-fold rise in lymphocyte count, disseminated intravascular coagulation, and, ultimately, cardiac arrest. Major findings at autopsy included: bilateral H1N1 pneumonitis with diffuse alveolar damage, intra-alveolar pulmonary hemorrhage, pulmonary microthromboemboli, pulmonary hemorrhagic infarction, hemophagocytic lymphohistiocytosis in multiple locations, and diffuse chronic lymphocytic leukemia. Hemophagocytic lymphohistiocytosis is a serious and often fatal condition, which may be primary or secondary. It may be associated with high-grade lymphoproliferative malignancies, especially in patients with therapy-related leukocytopenia, but only rarely is it seen in uncomplicated chronic lymphocytic leukemia. Hemophagocytic lymphohistiocytosis may be triggered by a variety of infections (viral, fungal, bacterial and parasitic), but H1N1 influenza A-associated hemophagocytic lymphohistiocytosis is often rapidly fatal, especially in children. This adult patient's clinical presentation with low tumor burden and leukocytosis is thus unique. We review the recently published autopsy findings in fatal influenza A (H1N1) infection and the association with resultant secondary hemophagocytic lymphohistiocytosis. Published by Elsevier Inc.

Keywords: Influenza A (H1N1); Diffuse alveolar damage; Pulmonary infarction; Hemophagocytic lymphohistiocytosis; Acute pneumonitis; Chronic lymphocytic leukemia

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening disease in which the immune system loses its regulatory function due to genetic disorders, malignancies, or overwhelming infections caused by viruses, bacteria, or parasites. It is characterized by prominent hemophagocytosis and lymphohistiocytosis with activated macrophages engulfing many formed elements of blood including red blood cells, lymphocytes, plasma cells, polymorphonuclear cells and cellular debris. Hemophagocytic lymphohistiocytosis is

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often associated with high-grade T-cell or natural killer-cell (NK-cell) leukemias and lymphomas, usually with leukocytopenia [1]. Epstein-Barr virus is one of the most commonly reported viral triggers for HLH. Recently, several studies have demonstrated an association between influenza A (H1N1) infection and HLH in clinically critical and fatal cases during the 2009 H1N1 pandemic [2-4]. This pandemic caused an estimated 12,470 deaths in the United States from April 9, 2009, to April 10, 2010 [5]. Most fatal H1N1 cases in published reports had known previous medical histories of underlying co-morbidities, most commonly including: obesity, hypertension, diabetes mellitus, cardiovascular disease, pulmonary disease, and pregnancy [2-4]. We report a case of a 50 year-old man with a history of chronic lymphocytic leukemia (CLL) showing an unusual presentation of pneumonia at the height of the 2009 H1N1 pandemic. He had a rapid clinical course with the subsequent autopsy revealing confirmed influenza A (H1N1) infection and pathologic findings of secondary HLH.

Examination of the post-mortem findings of patients with influenza A (H1N1) infection and certain co-morbid conditions may help better our understanding of which underlying chronic diseases can predispose individuals to become more vulnerable to adverse outcomes, such as secondary HLH. Patients with hematologic malignancies are more vulnerable to develop fatal outcomes from H1N1 infection when compared with the general population, which could be related to secondary HLH in some cases. Understanding the risk factors and pathologic changes, including morphology and pathogenesis, of fatal H1N1 infection is crucial for future disease surveillance, prevention, and treatment.

2. Clinical history

The patient was a 50-year-old African-American man who presented acutely with a 10-day history of fever up to 105°F, chills, sore throat, shortness of breath, nausea, and diarrhea on September 28, 2009. He was previously treated for a presumed upper respiratory tract bacterial infection with antibiotics, including cefiatrixone and azithromycin, 1 week before admission at an outpatient clinic. He was employed as a substitute school teacher and had extensive exposure to children with respiratory illnesses before his presentation. His medical history was significant for CLL originally diagnosed in 2004. He was subsequently treated for his CLL with multiple cycles of chemotherapy including fludarabine, cyclophophamide, and rituximab. He had remained in remission for 4 years and had been doing well until August 10, 2009, 1 month before his admission, when he presented to the oncology clinic with a two-month history of night sweats and a weight loss of 10 to 15 pounds. He was thought to have CLL relapse with low tumor burden at that time due to his symptoms as well as an increased white blood cell count of 11.9 K/cmm (reference range, 3.5-10 K/cmm) with 56% lymphocytes (reference range, 15%-47%) and moderate smudged lymphocytes seen on the peripheral blood smear. No additional testing (flow cytometry analysis or bone marrow biopsy) was deemed necessary. Anti-leukemic treatment was not initiated given the low burden disease and the patient's stable condition.

At the time of presentation, his chest x-ray revealed diffuse airspace opacities and perihilar infiltrates, suggestive of pneumonia. Because of his condition, he was admitted the same day for further evaluation. On admission, his vital signs included: fever of 101.4° F, heart rate of 88 beats per minute, respiratory rate of 18 per minute, and blood pressure of 104/67 mm Hg. The chest and abdominal examination was notable for decreased basilar breath sounds in the bilateral lungs, costovertebral angle tenderness and increased bowel sounds in the abdomen. He then developed rapidly progressive respiratory failure and hypoxemia and was transferred to the medical intensive care unit for pulmonary and circulatory support. Subsequent chest computed tomography (CT) scan also showed bilateral moderately extensive airspace consolidations, suggestive of pneumonia (Fig. 1). In addition, CT scan demonstrated multiple enlarged lymph nodes in several regions including the supraclavicular, axillary, mediastinal, and periaortic areas. Significant laboratory findings during hospitalization included the following: leukocytosis with a white blood cell count of 61.8 K/cmm with 74% lymphocytes, anemia with an erythrocyte count of 2.1 M/cmm (reference range, 4.0-5.9 M/cmm), hemoglobin of 6.9 g/dL (reference range, 12-18 g/dL), a hematocrit of 20.9% (reference range, 36.0%-52%), and a coagulopathy with a prothrombin time of 16.9 seconds (reference range, 12.0-14.7 seconds) and a partial thromboplastin time of 63.2 seconds (reference range, 23.6-33.6 seconds). He also had thrombocytopenia with a platelet count of 62 K/cmm (reference range, 150-450 K/cmm). He showed increasing renal insufficiency, decreased immunoglobulins of 651 mg/dL (reference range, 751-1560 mg/dL),

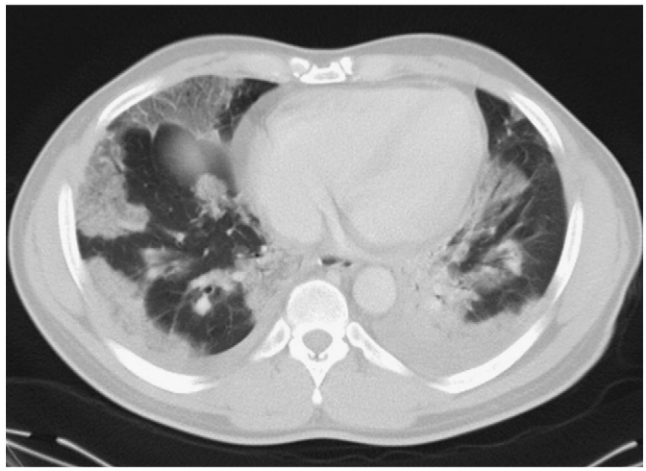

Fig. 1. Chest CT scan revealing bilateral diffuse pulmonary airspace opacities and consolidations, suggestive of pneumonia.

and hyperferritinemia with a ferritin of 1761 ng/ml (reference range, 11-336 ng/ml). Review of his peripheral blood smear showed smudge cells, indicative of CLL but no overwhelming predominance of lymphocytes or evidence of Richter's transformation. Fiberoptic bronchoscopy revealed edema and erythema in the proximal airways with no distal endobronchial lesions. Cytologic examination of bronchoalveolar lavage fluid was interpreted as negative for malignant cells with no fungal organisms on Gömöri methenamine silver stain. Nasal swab test by polymerase chain reaction for H1N1 (influenza A RNA and 2009 H1 gene) was inconclusive due to low viral titers. Further studies searching for an infectious etiology including sputum, stool, bronchoalveolar lavage and blood cultures, and cryptococcal serum antigen test were also negative. He was diagnosed as having relapsed CLL, pneumonia with respiratory failure and adult respiratory distress syndrome (ARDS), early disseminated intravascular coagulation, and renal failure. He was treated with multiple broad-spectrum antimicrobial agents, antiviral agent (osteltamivir), mechanical ventilation, and other supportive care. However, his condition progressively deteriorated. He subsequently developed intermittent episodes of myoclonic jerking/seizure activity and expired with pulseless electrical activity arrest 10 days after admission despite full resuscitation efforts. An autopsy was performed to further characterize the cause of death.

3. Pathologic findings

The major pathologic findings were within the respiratory and reticuloendothelial systems. Grossly, the lungs were heavy and boggy (combined lungs weight: 3000 g; expected: 685-1050 g). The pulmonary parenchyma was red-brown to gray with bilateral diffuse congestion and edema, more prominent on the right side (Fig. 2A and B). The lower lobes were firm and consolidated. There was a large demarcated dark red-brown area with hemorrhage involving one half of the right lower lobe (Fig. 2A and B). Multiple dark red blood clots/thrombi in large and small segmental branches of the right lower lobe pulmonary artery were present. Bilateral pleural effusions with clear serous fluid were noted (right, 100 mL; left, 300 mL). The tracheal mucosa was pink to red with scattered congestion and petechial hemorrhages. There were multiple bilateral, enlarged, tan-gray hilar lymph nodes containing anthracotic pigment, ranging in size from 0.5 to 2.0 cm. Significant lymphadenopathy was also seen in the cervical and abdominal regions. There was also splenomegaly (weight: 400 g; expected: 125-195 g) with congestion.

Microscopic examination revealed diffuse intra-alveolar hyaline membranes (hallmark of diffuse alveolar damage, Fig. 3A) correlating with clinical ARDS, alveolar capillary congestion, intra-alveolar fibrinous exudates, lymphoplasmacytic inflammatory infiltrates, and intraparenchymal hemorrhage in all lobes, more severe on the right side (Fig. 3B). Multifocal bilateral microthrombi were present within

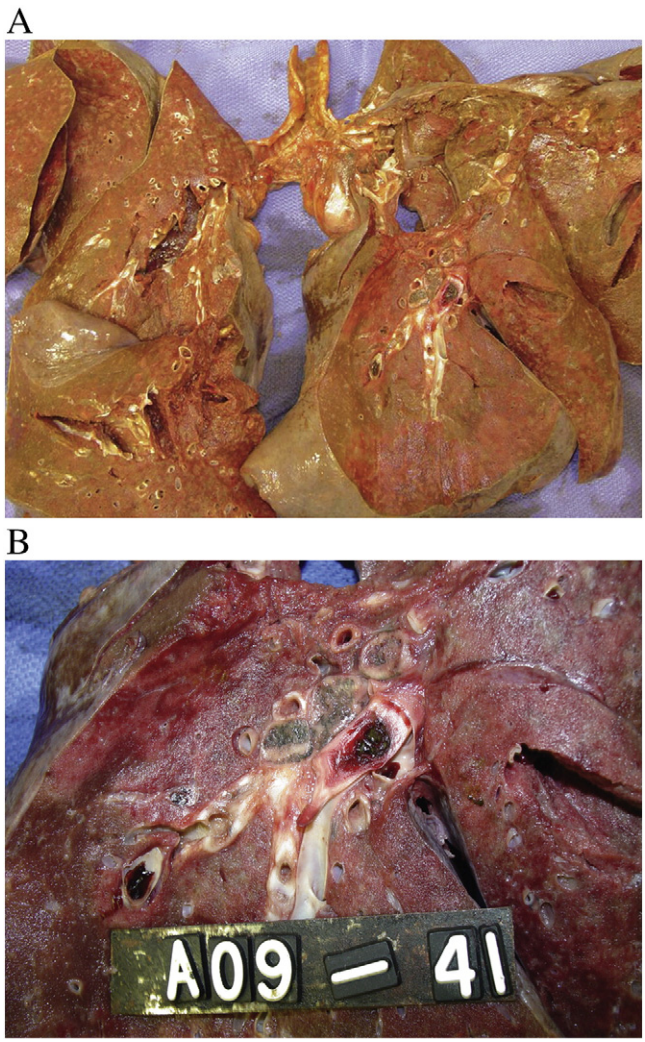

Fig. 2. A and B, Gross appearance of lungs. Hemorrhagic-appearing pulmonary parenchyma with congestion, edema, consolidation, and tracheal mucosa with hemorrhage and congestion. A, Bilateral lungs. B, Right lower lobe.

small and medium-sized vessels in the right middle and left upper lobes, consistent with clinical disseminated intravascular coagulation (Fig. 3C). There were associated infarcts with hemorrhage, fibrin deposition, and alveolar septa destruction in the right lower lobe with focal organization (Fig. 3D). Multifocal type II pneumocyte hyperplasia and squamous cell metaplasia associated with hemorrhage and infarction were present bilaterally (Fig. 3B). There was also acute tracheitis with mucosal congestion and hemorrhage. Pulmonary hilar lymph nodes and bilateral lung parenchyma (mainly the right lung) demonstrated prominent hemophagocytic lymphohistiocytosis with ingestion of hematopoietic cells by macrophages/histiocytes (Fig. 4A-C). Immunohistochemical stains demonstrated CD5 and CD20 positive CLL cells engulfed by macrophages. Hemophagocytic lymphohistiocytosis was also noted in the spleen, multiple cervical and abdominal lymph nodes, and in the bone marrow. Many of the lymphocytes in the lung parenchyma

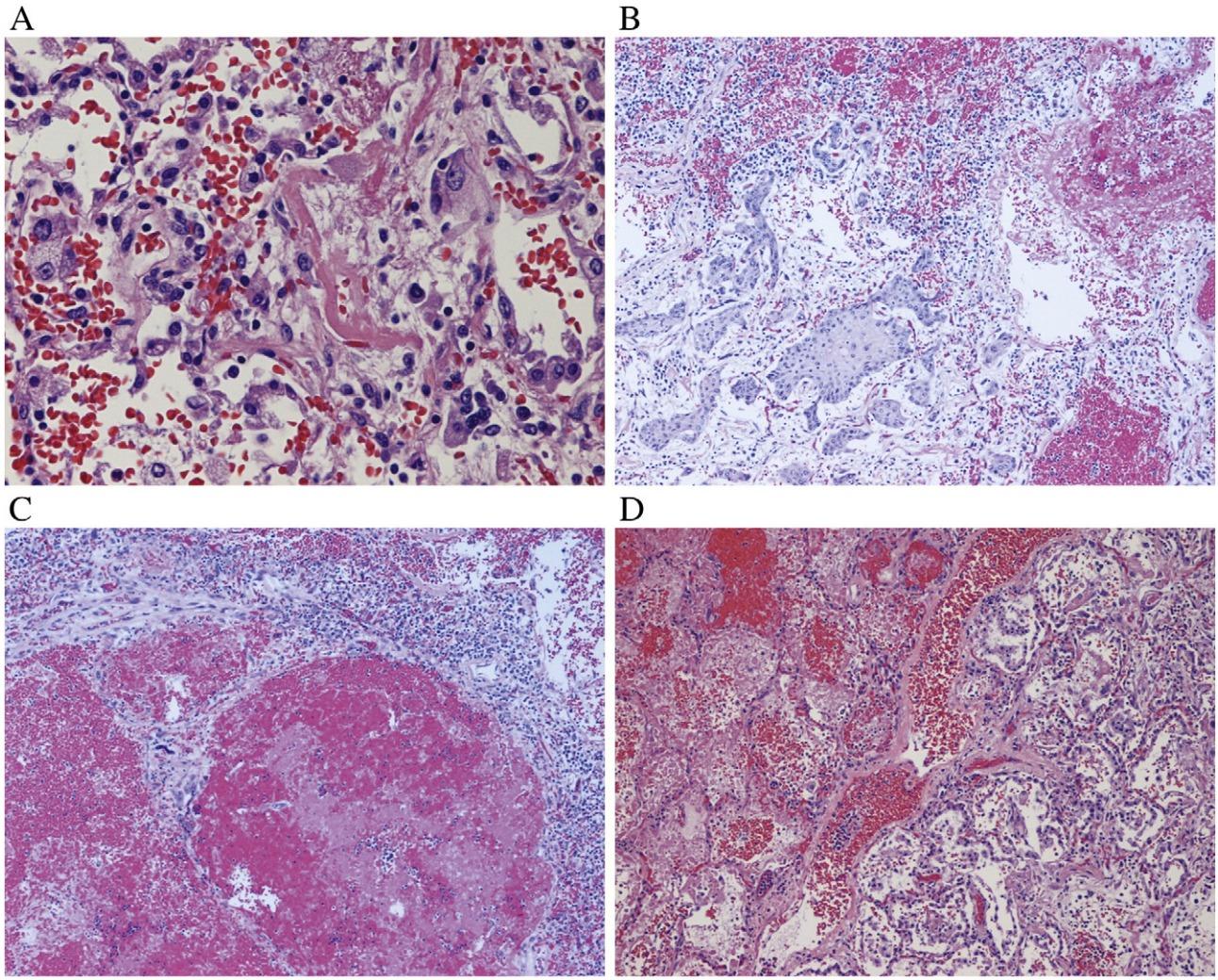

Fig. 3. A-D, Lung sections illustrating changes associated with H1N1 infection. A, Hyaline membranes, prominent type II pneumocytes and increased intra-alveolar macrophages. B, Pneumonitis with fibrinous exudates, capillary congestion, alveolar hemorrhage, inflammatory infiltrates and abundant squamous metaplasia. C, Microthrombus and surrounding lymphocytic infiltrates. D, Hemorrhagic infarct (left) adjacent to viable lung parenchyma (right).

were slightly enlarged, hyperchromatic, and monotonous in size and shape, consistent with leukemic involvement. Gram stain performed on a section of right middle lung revealed scattered Gram-positive cocci. Gömöri methenamine silver stains on sections of the right lower and right middle lungs were negative for fungal microorganisms. Immunohistochemical stain performed on a section of left lower lung was negative for herpes simplex virus I and II. Molecular testing of lung tissue for pandemic influenza A (H1N1) viral RNA by reverse transcriptase polymerase chain reaction performed at the Centers for Disease Control and Prevention (Atlanta, GA) was confirmed to be positive. The lung culture showed rare *Staphylococcus epidermidis*. The above changes are consistent with bilateral acute viral pneumonitis caused by influenza A (H1N1) infection.

Sections of multiple cervical, mediastinal and abdominal lymph nodes showed dense atypical monotonous lymphocytic infiltrates with effacement of the normal architecture (Fig. 5). Immunohistochemical studies on a right hilar lymph node showed that the atypical lymphocytes stained with CD5, CD20, CD23, BCL-2, and PAX5 but lacked CD10, BCL-6, and cyclin D1 expression. This staining pattern is consistent with CLL involvement of the lymph nodes. Flow cytometry of his peripheral blood at autopsy demonstrated an abnormal B-lymphocyte population with CD19 expression (86% of gated cells), confirming relapsed CLL. There was evidence of diffuse CLL in multiple other organs including the bone marrow, spleen, liver and thyroid.

Other pathologic findings included moderate to severe atherosclerosis of the coronary arteries and aorta, mild arteriolosclerosis of the kidneys, mild acute tubular necrosis of the right kidney, nodular hyperplasia of the prostate, and focal nodular hyperplasia of the liver. There were no specific findings in any other organ systems. Severe autolysis in the gastrointestinal mucosa and pancreas precluded precise evaluation. Postmortem blood cultures were positive for *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Enterococcus* species.

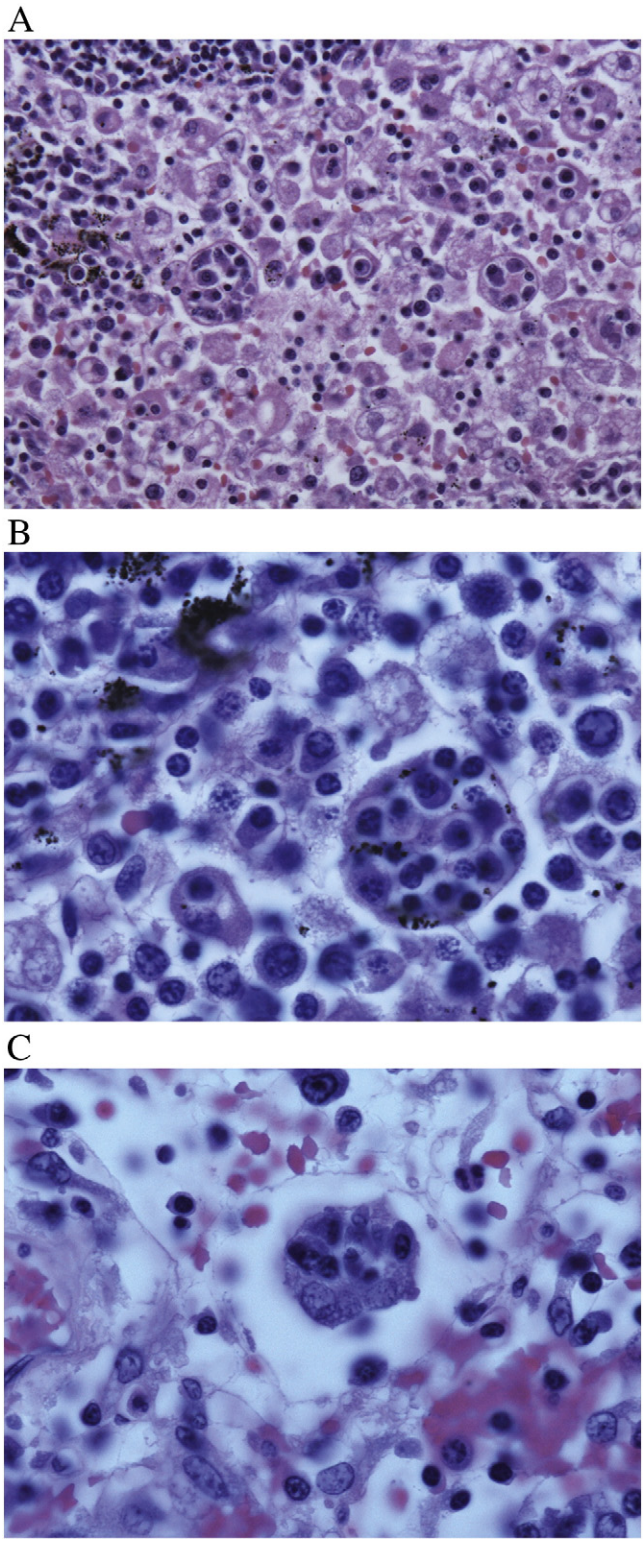

Fig. 4. A-C, Hemophagocytosis with ingestion of plasma cells and lymphocytes by macrophages. Note surrounding lymphohistiocytosis and adjacent small monotonous lymphocytes. A and B, Pulmonary hilar lymph node (B, high power). C, Lung parenchyma (high power).

4. Discussion

Shortly after two cases in Mexico and two in the United States of influenza viral infection were identified in March and April of 2009, respectively, the World Health Organization confirmed an outbreak of human infections with a novel H1N1 influenza A virus and declared an H1N1 influenza pandemic in June of 2009 [3,6]. This novel influenza A (H1N1) viral infection spread worldwide with a rising morbidity and mortality rate throughout 2009. The first autopsy series describing the systemic pathologic findings in 21 fatal novel human influenza A H1N1 infection cases from Brazil was published in press online in October 2009 [2]. This was followed by several other autopsy series and case reports [3,4,6,7-9].

Pathologic changes of fatal pandemic influenza and H1N1 infection have been described previously and are often associated with concurrent bacterial infections [10]. Diffuse alveolar damage (DAD) of the lungs is the most common significant and consistent finding in fatal H1N1 infections (Table 1) [2-4,7,8,11]. As seen in most other cases, the major pathologic finding in our case was diffuse bilateral pulmonary hyaline membranes with DAD, manifested clinically as ARDS with refractory hypoxemia on oxygen therapy. This feature is similar to that observed in avian influenza (H5N1) infection [12-15]. DAD is a well-recognized complication of numerous and diverse conditions, including both direct injuries to the lungs and systemic disorders. Common direct lung injuries causing DAD are viral infections (such as adenovirus, human herpes virus, respiratory syncytial virus, and influenza virus), oxygen toxicity, inhalation of toxins, and other irritants. In some circumstances, DAD is related to extracorporeal membrane oxygenation for treatment of hypoxemia [4]. However, extracorporeal membrane oxygenation was not used to manage the patient in our case. Diffuse alveolar damage is characterized by hyaline membranes consisting of fibrin-rich edematous fluid mixed with the cytoplasmic and

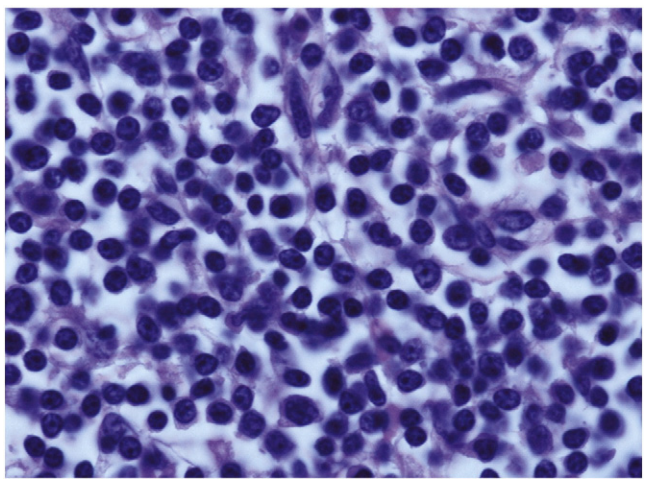

Fig. 5. Section of pulmonary hilar lymph node showing abundant small monotonous lymphocytes consistent with chronic lymphocytic leukemia.

Table 1
Published pathologic findings in autopsy/histology series with influenza A (H1N1)

Pathology findings	Gill et al	Mauad et al	Shieh et al	Hajjar et al	Harms et al	Current
Diffuse alveolar damage	25/34 (74%)	20/21 (95%)	85/85 (100%)	4/5 (80%)	8/8 (100%)	Present
Alveolar hemorrhage	5/34 (15%)	11/21 (52%)	58/100 (58%)	NA	7/8 (88%)	Present
Tracheitis	6/34 (18%)	NA	22/85 (26%)	NA	4/8 (50%)	Present
Necrotizing bronchitis	NA	6/21 (29%)	NA	5/5 (100%)	3/8 (38%)	Not present
Bacterial pneumonia	NA	3/9 (33%)	29/100 (29%)	4/5 (80%)	6/8 (75%)	Present
Pulmonary thrombus	NA	8/21 (38%)	16/85 (19%)	1/5 (20%)	5/8 (63%)	Present
Splenic white pulp depletion	NA	21/21 (100%)	NA	5/5 (100%)	NA	Not present
HLH	NA	21/21 (100%)	25/41 (61%)	NA	8/8 (100%)	Present

NA indicates not available.

lipid remnants of necrotic epithelial cells. The management of DAD/ARDS can be very difficult, and regardless of etiology, this disorder is frequently fatal [16]. Similar to reported findings of the 2009, 1968, and 1918 pandemics with H1N1, histologic findings of diffuse pneumonitis, pulmonary hemorrhage, hemorrhagic infarction, and microthrombosis were identified in our case [7,17]. These changes in tandem with the DAD interfered with ventilation and caused ventilation-perfusion mismatching and refractory hypoxemia.

Hemophagocytic lymphohistiocytosis is another important piece to the pathologic puzzle found in our case as well as in other fatal influenza deaths. Increased numbers of macrophages with phagocytosis of hematopoietic cells were observed in the lungs, lymph nodes, spleen, and bone marrow. This in conjunction with clinical fever, cytopenias (erythrocytopenia and thrombocytopenia), splenomegaly, and hyperferritinemia constitutes HLH based on the diagnostic guidelines proposed by the International Histiocyte Society [18-20]. Some critical collaborative laboratory data, including a fibrinogen level, interleukin-2 receptor level, and NK-cell activity were unavailable because HLH was not suspected prior to his death. HLH is a systemic hyper-inflammatory response seen in various disease conditions with exaggerated phagocytosis by activated macrophages or histiocytes [18]. There are 2 recognized types: a rare primary, autosome-recessive disorder and an acquired or secondary disorder related to or instigated by another underlying disease. Secondary HLH is not found in association with known genetic mutations. Like primary HLH, however, it is often associated with a fatal outcome. Secondary HLH can be triggered by infections (viral, bacterial, fungal, or parasitic), exposure to toxins, and autoimmune or inflammatory diseases [18,21-23]. Malignancy-associated HLH has also been reported [24-26]. It is more commonly seen in T-cell or NK-cell leukemias and lymphomas [24]. In recent years with recognition of this disorder, HLH has been known to be associated with severe inflammatory reactions in response to exposure to certain viruses including Epstein-Barr virus, human immunodeficiency virus, avian influenza H5N1 virus, and hepatitis B and C virus [18,20]. Numerous studies have also shown a link between fatal H1N1 influenza infection and hemophagocytosis (Table 1) [2-4]. Fatal H1N1 cases with HLH in immunocompetent hosts, including many children, have also been reported [8,27].

It was recently postulated that HLH results from impaired functions of NK-cells and cytotoxic T-lymphocytes, which causes an abnormality in the functional proteins perforin and granzyme [20]. These proteins subsequently reduce apoptosis and cytotoxicity of target antigen-presenting cells. Therefore, the transformed and infected cells cannot be cleared, and the virus may propagate instead of being eliminated. Janka et al postulated that the excessive antigens may further activate T-lymphocytes and macrophages/histiocytes, promoting release of cytokines such as interferon-γ, interleukin (IL)-6, IL-10, IL-12, IL-16, IL-18 and tumor necrosis factor-α [22]. Hypercytokinemia leads to excessive phagocytosis with resultant cytopenias and underlies the progressive organ dysfunction that results in the clinical syndrome, which can eventually lead to death in affected patients [18,20,22,23]. Anomalies of the NK-cell and cytotoxic T-lymphocytes proteins have also been described in septic patients and increased plasma concentrations of these proteins may be predictive of severe sepsis [20,28,29]. Hemophagocytosis was found in 64.5% of critically ill patients, and all patients with hemophagocytosis had concurrent infection [20,30]. Therefore, HLH is a life-threatening condition with a high mortality rate [20].

Bacterial coinfections in severe and fatal influenza cases have been well documented in previous influenza pandemics and seasonal epidemics (Table 1) [2-4,11,31,32]. *Staphylococcus aureus* and *Streptococcus pneumoniae* were the most commonly reported causative bacteria. In our case, sections of the lungs failed to show evidence of severe bacterial pneumonia. However, Gram stain revealed scattered Gram-positive cocci, and lung and blood cultures were positive for rare *S. epidermidis*, which is consistent with a superimposed bacterial infection.

By using immunohistochemistry, Shueh et al was able to identify influenza A viral antigen in respiratory epithelial cells, submucosal glands and pneumocytes [3]. In about half of the cases, the type II pneumocytes were the major cellular target with macrophages as the second location [3]. Antigens were also seen in association with material in the hyaline membranes. Gill et al also showed immunohistochemical evidence of viral antigen detection in the alveolar

macrophages and pneumocytes [7]. These findings indicate respiratory epithelium, pneumocytes and macrophages as the target cells of viral replication. Furthermore, the evidence of viral antigen within pneumocytes and its association with hyaline membranes suggests a direct viral cytopathic effect as a major pathogenic mechanism [3]. No immunohistochemical staining for the H1N1 viral antigen was performed in our case due to lack of availability. However, extensive type II pneumocyte reaction with hyperplasia, squamous cell metaplasia and abundant alveolar macrophages were observed, suggesting a cellular response to viral replication. Type II pneumocytes are known to play an important role in tissue restitution after acute lung injury and are also known to secrete pulmonary surfactants, which reduce surface tension to preserve the integrity of alveolar spaces and play important roles in modulating inflammation and enhancing pathogen clearance. Interference with this role in injury repair can result in progression of the disease and cell death. Additional studies have shown that some of the pulmonary abnormalities of fatal influenza viral pneumonia might be induced by the release of host inflammatory mediators rather than by a direct viral cytopathic effect [7,33]. Viral replication-induced cytokines, Toll-like receptor 3, CD8 T-cells and interferon-γ are considered to be associated with viral pathogenesis [34]. Consistent with other findings, our case showed no morphologic cytopathic effect of inclusion bodies [2,6]. No evidence of viral replication-associated changes in extrapulmonary tissue was seen. The histologic findings in non-respiratory tissues other than HLH in this patient, were nonspecific and most likely due to his underlying conditions.

5. Conclusion

Chronic lymphocytic leukemia patients are at risk for infection due to inherent humoral and cell-mediated immune defects as well as therapy-related immunosuppression [35]. These individuals are at greater risk of developing severe complications from H1N1 infection compared with the general population. Hemophagocytic lymphohistiocytosis is most often seen in children with H1N1 infections and is associated with fatal outcomes. It is also seen in adults with influenza, but its role has perhaps been underemphasized. Further investigation of the pathomechanism and significance of this entity in H1N1 infection may shed some light on prevention of severe outcomes and help meet some of the challenges of future pandemics. The clinical presentation (fever, organomegaly, cytopenia, elevated ferritin, low fibrinogen, and hypertriglyceridemia) can overlap the findings seen in influenza. Bone marrow or lymph node biopsy may be needed to establish the diagnosis. Retrospectively, the series of autopsies reviewed suggest that if the patient's condition worsens with pancytopenia, HLH will often be present. Identifying this entity and developing therapeutic protocols may lead to improved treatments and outcomes.

In summary, this is a fatal case of novel influenza A (H1N1) infection with all of the primary findings that are known to be associated with severe disease. Our patient had rapid reactivation of his CLL, either related directly to the H1N1 infection, or it surfaced concurrently. Compared with the general population, his increased susceptibility to the rapid course of the infection was likely due to impaired humoral and cell-mediated immunity, but further investigation of the exact mechanisms is still warranted. We believe this fatal case of novel influenza A (H1N1) infection demonstrates the need for increased surveillance and prophylactic measures including vaccination for patients with lymphoproliferative disorders such as CLL during the influenza season. Infection with novel H1N1 can be rapidly fatal, even in patients deemed to have low tumor burden and who have previously achieved remission.

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