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Annals of Diagnostic Pathology 16 (2012) 477 – 484

Annals of DIAGNOSTIC PATHOLOGY

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

☆ Note: This material has been presented in part as a poster at College of American Pathologists (CAP'10), the Pathologists' Meeting, Chicago, IL, September 26 to 29, 2010.

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1092-9134/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.anndiagpath.2011.03.009

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),

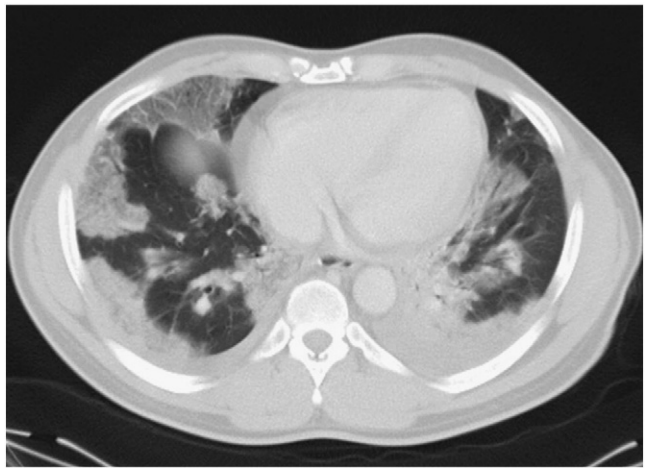

Fig. 1. Chest CT scan revealing bilateral diffuse pulmonary airspace opacities and consolidations, suggestive of pneumonia.

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