

## Influenza virus B-associated hemophagocytic lymphohistiocytosis

Jackson Gao,<sup>1</sup> Jeremiah Pasion,<sup>2</sup> Gabriela Sanchez-Petitto,<sup>3</sup> Jennie Law<sup>3</sup>

<sup>1</sup>Department of Medicine and

<sup>2</sup>Department of Pathology, University of Maryland School of Medicine,

Baltimore, MD; <sup>3</sup>University of Maryland School of Medicine, Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA

### Abstract

This original report describes the diagnosis and management of a male with hemophagocytic lymphohistiocytosis (HLH) triggered by influenza B virus infection. The patient was diagnosed with HLH-2004 clinical criteria and a bone marrow biopsy demonstrating hemophagocytes. Therapy consisted of etoposide and dexamethasone while monitoring hemoglobin and platelet levels. To enable early recognition and prompt treatment for this disease, physicians should be aware of this association.

### Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a disease characterized by overwhelming inflammation and tissue destruction due to a dysregulated immune system. HLH can be separated into primary and secondary HLH. Primary HLH, or familial HLH, is inherited and can present during infancy and has a high mortality rate.<sup>1</sup> Secondary HLH is acquired, and can be triggered by a multitude of infections, malignancies, or rheumatological disorders.

Among the infections that can incite HLH, Epstein-Barr virus (EBV) is the most well-known.<sup>2</sup> Roupheal *et al.* described a case of a young adult woman who passed away from HLH triggered by EBV.<sup>3</sup> Other infectious triggers include cytomegalovirus (CMV), parvovirus, herpes simplex virus (HSV), human immunodeficiency virus (HIV), and H1N1 influenza virus.<sup>4-6</sup> The association between influenza B virus and HLH in adult patients has not been well documented in the literature. Previously, a group reported on a patient who developed HLH due to mixed infection by influenza virus and *S. Pneumoniae*, but could not further clarify which of these two pathogens

caused HLH.<sup>7</sup> Another group reported a case of an adult male with systemic lupus erythematosus who developed influenza virus B-associated hemophagocytic syndrome and cardiac tamponade that ultimately required pericardiocentesis.<sup>8</sup> In the pediatric population, there has been one reported case of influenza virus B-associated HLH in a 10-month old female infant.<sup>9</sup>

We report an unusual case of influenza B complicated by HLH in a previously healthy 54-year old male. Written informed consent for publication was obtained from the patient.

### Case Report

A 54-year old male presented to the emergency department in March 2019 with acute abdominal pain, fever and watery diarrhea that had been present for three days. He had refused the influenza vaccination the previous year. The patient was disheveled-appearing, and with core body temperature of 38.8° C, pulse of 120 beats per minute, respiratory rate of 18 breaths per minute, and blood pressure of 101/61 mmHg. An abdominal exam revealed generalized tenderness to palpation, but no hepatomegaly or splenomegaly. Initial laboratory testing was notable for a hemoglobin level of 6.1 g/dL, and platelet count of 94 K/mcL. A chest x-ray did not show any acute cardiopulmonary abnormality. A molecular viral panel did not detect any respiratory viruses, including EBV, HSV and CMV. HIV testing was negative for p24 antigen and HIV-1 and HIV-2 antibodies. However, a nasopharyngeal swab was positive for Influenza B antigen. The patient was treated with seven days of oseltamivir but continued to have fevers despite negative blood cultures as well as persistent anemia and thrombocytopenia. Additional laboratory testing was notable for a ferritin level of >36,000 ng/mL (reference range <464 ng/mL), triglyceride level of 221 mg/dL (reference range <150 mg/dL), NK (CD 56) 9% (reference range 4-26%), and soluble CD25 level of 2832 pg/mL (reference range <1033 pg/mL). He was diagnosed with HLH most likely related to influenza B virus infection.

Bone marrow biopsy results demonstrated hemophagocytosis (Figure 1). Treatment was started on hospital day 13 with etoposide and dexamethasone. The patient defervesced three days after initiating therapy, and remained afebrile throughout the rest of the hospitalization. His thrombocytopenia gradually improved and hemoglobin returned to baseline prior to discharge.

Correspondence: Jackson Gao, Department of Medicine, University of Maryland School of Medicine, 22 S. Greene Street, Baltimore, MD, 21201, USA.

Tel.: +1.443-722-5389

E-mail: ypgao44@gmail.com

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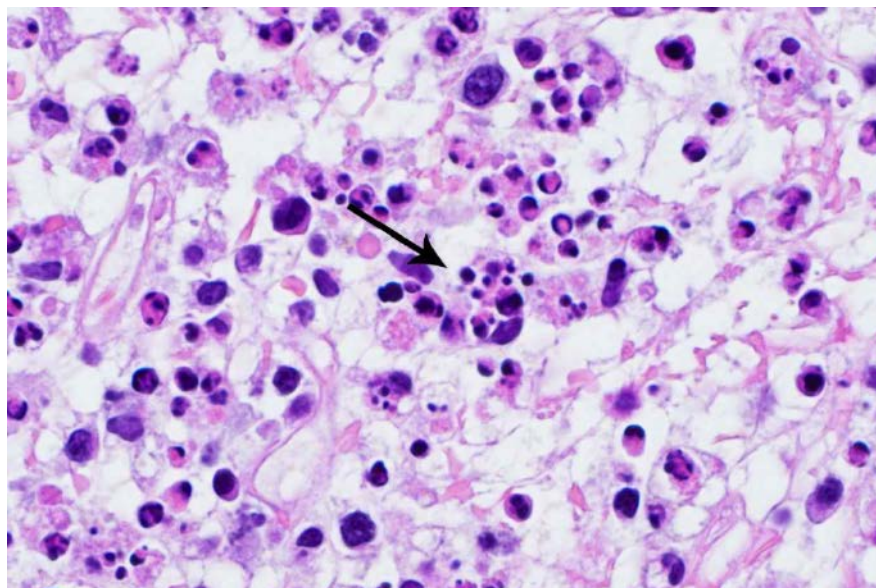
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### Discussion and Conclusions

Early detection and treatment of HLH is key. Previous studies have shown that without therapy, survival of patients with active HLH is approximately 2 months.<sup>10</sup> Despite this demonstrated urgency, the diagnosis of HLH is oftentimes delayed. This could be due to a variety of factors, including the rarity of HLH, the complex diagnostic criteria and the concern for alternative diagnoses. In addition, initial bone marrow biopsy may not demonstrate hemophagocytosis, further complicating the diagnosis.<sup>11</sup> After the diagnosis of HLH is established, immediate treatment based on HLH-2004 protocol with eight weeks of etoposide and dexamethasone is considered standard of care.<sup>12</sup> The original study with the HLH-94 protocol had enrolled over 200 eligible patients and resulted in a 5-year survival of 54%.<sup>12,13</sup> This was a remarkable improvement in long-term survival in HLH compared to three decades ago when the overall survival in HLH was less than 5%.<sup>10</sup> Thus, prompt recognition of HLH and treatment is of utmost importance in order to reduce mortality.

Our patient was diagnosed almost two



**Figure 1. Bone marrow aspirate showing phagocytosis of neutrophils, erythrocytes, and platelets by hemophagocyte (black arrow). H&E stain.**

weeks after his initial presentation to the hospital. Fortunately, the patient had a good clinical response to the treatment as well as a decrease in his inflammatory markers and an increase in his blood counts. We present this case to alert physicians that in adult patients presenting with influenza B virus with concurrent fever and pancytopenia, HLH should be thought of as a possible complication to facilitate early identification and prompt treatment of the disease. In addition, ordering an initial respiratory viral panel may contribute towards finding the specific trigger for HLH in a given patient.

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