Annals of Case Reports
Courchesne K, et al. Ann Case Rep: 8: 1372
www.doi.org/10.29011/2574-7754.101372
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Case Report

Acute Anaplasmosis Infection Presenting with Hemophagocytic Lymphohistiocytosis in Quebec

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Citation: Courchesne K, Viens I, St-Arnaud C, Mayette M (2023) Acute Anaplasmosis Infection Presenting with Hemophagocytic Lymphohistiocytosis in Quebec. Ann Case Report. 8: 1372. DOI:10.29011/2574-7754.101372

Received: 10 July 2023, **Accepted:** 14 July 2023, **Published:** 17 July 2023

Abstract

Human granulocytic anaplasmosis (HGA) is a rare and potentially severe tick-borne infection caused by the bacterium Anaplasma phagocytophilum. The incidence of anaplasmosis has increased steadily in the past few years in the United States. In Canada, HGA is only a mandatory reportable disease in the provinces of Quebec and Manitoba and it could be underreported. Most patients present with febrile illness and non-specific symptoms such as fatigue, myalgia, headaches, arthralgia, or gastrointestinal symptoms. We report the case of a 69-year-old male who developed hemophagocytic lymphohistiocytosis as a rare, life-threatening manifestation of acute anaplasmosis.

Introduction

HGA is a rare and potentially severe tick-borne infection. HGA is caused by the bacterium Anaplasma phagocytophilum. This obligate intracellular bacterium resides and replicates in the membrane-bound vacuoles in leukocytes. The bacteria can be seen in an intracellular cluster, called morulae [1]. Ixodes scapularis is the main vector of this zoonosis in Northeastern parts of the US and Canada. Most patients present with febrile illness and non-specific symptoms such as fatigue, myalgia, headaches, arthralgia, or gastrointestinal symptoms. The incidence of anaplasmosis has increased steadily in the past few years, from around a thousand cases in 2008 to 5 655 cases in 2019 [2] in the United States. HGA is most commonly reported in the upper midwestern and northeastern United States and happens usually in June or July. Anaplasma phagocytophilum has been detected in tick populations of all Canadian provinces. HGA is only a mandatory reportable disease in the provinces of Quebec and Manitoba and it could be underreported in Canada. Starting in 2021, an unusual cluster of cases (25 reported cases over a year) has been described in the Estrie region of Quebec, Canada [3]. Appropriate treatment of this disease with antibiotics (doxycycline or rifampin) usually results in improvement within 24-48 hours.

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening syndrome characterized by exaggerated cytokine release, diffuse inflammatory reaction and dysregulated activation of monocytes and macrophages. Multiple organ dysfunction can ensue from active hemophagocytosis. The common findings of HLH are fever, hepatosplenomegaly, cytopenias, hypofibrinogenemia, hypertriglyceridemia, hepatitis, hyperferritinemia and neurological symptoms. Five of the eight diagnostic criterias were established in 1991 and the remaining three were added in 2004. The criteria's are : 1- fever, 2- splenomegaly, 3- cytopenias, 4 - hypertriglyceridemia or hypofibrinogenemia, 5- hemophagocytosis, 6- low or absent natural killer (NK)-cell activity, 7- hyperferritinemia and 8- high level of soluble interleukin-2 receptor (sIL-2R) [4]. This syndrome may be primary, or secondary to various neoplastic

and infectious conditions. Although of similar pathophysiology and clinical presentation, when it is associated with autoimmune rheumatologic conditions, the term macrophage activation syndrome is preferred. Treatment is based on identification and treatment of the cause, and neoplastic or idiopathic cases may require aggressive chemotherapy with the HLH-94 protocol, which is an immunosuppressive and cytotoxic therapy (usually etoposide and dexamethasone] followed by a hematopoietic stem cell transplantation [5].

Objective

We present this case as it combines two rare conditions coincidentally. As the epidemiology of anaplasmosis is evolving, clinicians need to be cognizant of various clinical presentations that may suggest the diagnosis, and critical care specialists need to quickly recognize the hemophagocytic syndrome and its various etiologies to adapt their management and empirical therapies.

Case Report

A 69-year-old man with no significant past medical history and no current medications presented to a referring hospital with fatigue, general malaise, high fever and rapidly progressing confusion evolving over 2 days. He denied any known infectious contacts, but he was a hiking and camping enthusiast. He lived in the Estrie region, the southernmost region of the province of Quebec. He was a retired commercial flight pilot who traveled over the world during his career, but he denied any recent travel. Upon presentation, he had a blood pressure of 115/62 and a heart rate of 83 bpm. He was tachypneic with a respiratory rate of 33/min, a saturation of 94% with 4 L/min of oxygen and a fever of 39.3°C. He appeared toxic, slightly confused, but without nuchal rigidity. His neurologic exam was normal apart from bilateral dysmetria on cerebellar exam. His abdominal exam showed hepatosplenomegaly, without peripheral adenopathies. His physical examination was otherwise unremarkable. His initial blood work revealed pancytopenia (hemoglobin 126 g/L, platelets 48 x 109/L, leukocytes of 2.4 x 109/L), normal renal function and electrolytes apart from mild hyponatremia (132 mmol/L), normal liver enzymes (except from an AST of 199 U/L), coagulation abnormalities (PT 1.24, aPTT 30.6 sec), elevated D-Dimer levels (17 854 mcg/L) and elevated LDH level at 827 U/L. Urinalysis, chest x-ray and computerized tomography of the head were unremarkable. A polymerase chain reaction (PCR) test for COVID-19 was negative, as well as serologies for viral hepatitises, Epstein-Barr virus and human immunodeficiency virus. The patient was admitted and treated with broad-spectrum antibiotics (Vancomycin, Ceftriaxone, Ampicillin, and Acyclovir). A lumbar puncture was postponed due to thrombocytopenia. Over the following 48 hours, the patient's confusion resolved, but he remained febrile without any improvements in shortness of breath and laboratory abnormalities. All cultures remained negative. Seventy-two hours after his initial presentation, the patient was transferred to our university health center. Upon arrival, we suspected a disseminated intravascular coagulation disorder secondary to an inflammatory process. A peripheral blood smear revealed neutrophils with cytoplasmic inclusion bodies suggestive of morulae (Figure 1). No schistocyte was found. Complementary analyses revealed an elevated ferritin level (74 548 mcg/L) and hypertriglyceridemia (4.36 mmol/L), both suggestive of hemophagocytosis.

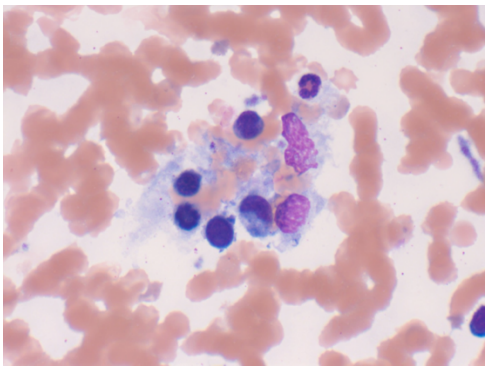

Figure 1: Peripheral blood smear with a 1000x scale showing a morulae of anaplasmosis in the patient's granulocyte.

Because of the clinical presentation, laboratory results, and a recently reported cluster of Anaplasmosis in the Estrie region, the diagnosis of hemophagocytic lymphohistiocytosis secondary to human granulocytic anaplasmosis was suspected and antibiotic treatment was simplified to doxycycline. A bone marrow aspiration confirmed active medullary hemophagocytosis (Figure 2). PCR for Anaplasma phagocytophilum confirmed the diagnosis of anaplasmosis.

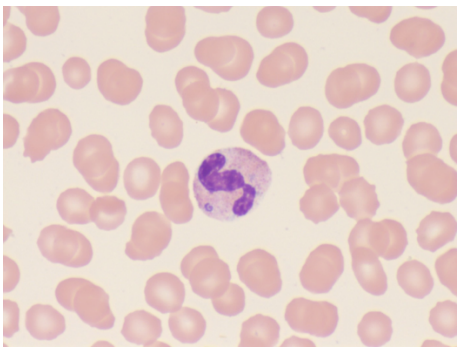

Figure 2: Blood marrow aspirate with a 600x scale showing hemophagocytosis.

Following the initiation of doxycycline, the patient's condition rapidly improved and he was discharged home within 3 days. Doxycycline was prescribed for a total of 14 days. Upon follow-up 2 weeks after discharge, the patient reported complete

resolution of all symptoms. All blood work abnormalities were resolved upon follow up, 6 weeks after discharge.

Discussion

The association between HGA and HLH has been rarely reported in the past [6-9]. This is, to our knowledge, the first case of such association and presentation in Canada. Considering that Anaplasma phagocytophilum has been reported in tick populations in all Canadian provinces and considering the increased incidence of HGA over the past few years, Canadian doctors should be aware of this disease. Clinical presentation of anaplasmosis is highly variable, including severe presentations that may require intensive care. Canadian physicians may be confronted with the disease and should be cognizant of its presentations. HLH is an emergency to be recognized and treated as mortality remains high.

Acknowledgement: We would like to thank Dr. Pierre-Aurèle Morin for his support with the diagnosis and for providing us with the figures.

Funding: All authors declare having not received any source of funding for the submitted work.

Conflict of interest: All authors declare having no conflict of interest related to the submitted work. All authors have contributed to the writing and approval of the manuscript

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