Macrophage Activation Syndrome Secondary to Human Monocytic Ehrlichiosis

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Abstract

Objectives To present a case of human monocytic ehrlichiosis (HME) that was complicated by macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH).

Methods Data was collected from patient's electronic medical records at the University of Alabama at Birmingham. The patient is a part of a larger cohort of patients with all-cause MAS treated at our center.

Case A 63 year old renal transplant recipient male on maintenance immunosuppressive therapy presented with high grade fever, leukopenia, thrombocytopenia and elevated transaminases and initially met clinical criteria for severe sepsis. On further investigation, clinical and laboratory criteria for MAS were met. He was treated with a combination of doxycycline for HME and a novel combination of anakinra (interleukin-1 receptor antagonist), and high dose corticosteroids. The discussion focuses on clinical presentation, pathogenesis and treatment of MAS with an emphasis on MAS secondary to HME.

Conclusion Macrophage activation syndrome or sHLH is a dysfunctional, hyperactive and potentially fatal immune system response that results in multi-organ dysfunction. With increasing incidence of *Ehrlichia chaffeensis* as an emerging pathogen, clinicians should be aware of this fulminant and potentially fatal complication of HME.

Keywords Anakinra · Ehrlichiosis · Hemophagocytic lymphohistiocytosis · Immunosuppressive agents · Macrophage activation syndrome

Introduction

A 63 year-old Caucasian man from Kentucky presented with a 3 week history of a petechial rash involving his upper and lower extremities followed by 1 week of high grade fever and altered mental status. Past medical history was remarkable for type 2 diabetes mellitus and end-stage renal disease with subsequent cadaveric renal transplant in 2003; he received maintenance immunosuppression with sirolimus, mycophenolate mofetil and prednisone. He had recently traveled to the Gulf coast in Alabama. On examination, he was febrile with a temperature of 103 °F; somnolent and disoriented with no meningeal signs or focal neurological deficits, abdominal exam showed hepatosplenomegaly. Laboratory studies showed that white blood cell count was $1.9 \times 10^3/\mu\text{L}$ with 70 % neutrophils, hemoglobin was 8.0 g/dL, and platelet count was $19 \times 10^3/\mu\text{L}$. Prothrombin time was 17.2 s (normal 12.2–14.5) and partial thromboplastin time was 44 s (normal 23–31), liver enzyme elevation was present (aspartate aminotransferase: 658 U/L, alanine aminotransferase: 85 U/L). Renal function was impaired with blood urea nitrogen of 64 mg/dL and creatinine of 4.0 mg/dL (baseline 2.1 mg/dL). CSF and blood cultures were negative. Despite initial treatment for severe sepsis (vancomycin, ceftazidime and supportive care) the patient's clinical status deteriorated which necessitated investigations for MAS/HLH. Workup showed a highly elevated ferritin at 70,097 mg/L (normal 22–322 mg/L), high triglyceride at 436 mg/dL (normal 50–200 mg/dL), low fibrinogen at

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90 mg/dL (normal 220–498 mg/dL), elevated lactate dehydrogenase at 3,209 U/L (normal 120–240 U/L), thereby fulfilling the HLH-2004 criteria for the diagnosis of hemophagocytic lymphohistiocytosis (HLH) [1]. Evaluations for Cytomegalovirus (CMV), Epstein-Barr virus (EBV) and occult malignancies were investigated with negative results. Although serologic tests for *Ehrlichia chaffeensis* were negative; review of the peripheral blood smear showed intracytoplasmic inclusions within monocytes which resembled morulae of *E. chaffeensis*, and polymerase chain reaction for *E. chaffeensis* DNA was positive confirming a diagnosis of human monocytic ehrlichiosis (HME). A repeat serology evaluation showed an IgG titre of 1:256 and an IgM titre of 1:16 during the third week of hospitalization.

The patient was treated for HME and secondary HLH/MAS. He received doxycycline (100 mg twice daily for 2 weeks), high dose steroids (methylprednisolone 1 g daily for 3 days followed by prednisone 1 mg/kg tapered over 6 weeks) and the soluble interleukin-1 receptor antagonist (IL-1 Ra) anakinra (started at 100 mg twice daily for 2 days followed by 100 mg daily for an additional 5 weeks). Over the subsequent 3 weeks, he showed complete recovery and was doing well at follow-up 2 months after discharge.

Discussion

First described in 1952 as “familial hemophagocytic reticulosis”, HLH is a disorder associated with uncontrolled, potentially fatal hyperinflammatory immune system activation. Macrophage activation syndrome (MAS) or secondary HLH is the form most frequently seen in adults. It can be triggered by infections, malignancies and connective tissue diseases [1, 2].

Human monocytic ehrlichiosis, a tick borne illness caused by the obligate intracellular bacteria *E. chaffeensis* is an infrequent trigger of MAS/HLH. It is endemic to areas of the south-central, south-eastern and mid-Atlantic United States in regions where its vector *Amblyomma americanum* (lone star tick) is found [3]. Infections with *E. chaffeensis* may be asymptomatic or present as a non-specific febrile illness associated with laboratory abnormalities such as leukopenia, thrombocytopenia and elevated liver enzymes. Rarely HME may have a fulminant clinical course resembling severe sepsis with multi-organ failure leading to death especially in immunocompromised patients [4, 5]. In our review of published literature we identified only three cases of HLH secondary to HME in children [6, 7]. To the best of our knowledge, *E. chaffeensis* has not been previously reported as a trigger of adult MAS/HLH. A high index of suspicion for secondary HLH/MAS should be

maintained in such patients and immunosuppressive therapy started when features of MAS are present.

Diagnosis is commonly based on the HLH-2004 criteria [1], although these criteria have not been validated for the diagnosis of secondary HLH. Maintaining a high clinical suspicion and early institution of immunosuppressive therapy upon diagnosis is essential in preventing mortality [1, 2]. Although guidelines are not yet established to direct therapy of secondary HLH/MAS, current practice favors treatment of the precipitating cause and immunosuppression with high dose steroids [2], and the presence of elevated inflammatory cytokines in MAS forms the basis for a potential role for biologic therapies targeting these mediators. There are reports of favourable outcomes with the interleukin-1 antagonist anakinra in instances where HLH/MAS occurred secondary to connective tissue disorders such as juvenile idiopathic arthritis and primary cytophagic panniculitis [8, 9]. The success of anti interleukin-1 therapy in our patient suggests a common pathophysiologic pathway for infection and connective tissue disease associated HLH which could be an interesting area for future investigations.

In conclusion we report a case of a patient with MAS secondary to HME successfully treated with doxycycline and anakinra with steroids. Clinicians should remain cognizant of this potentially fatal but treatable complication of HME, especially in patients receiving immunosuppressive therapies.

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