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Case Report

Secondary Hemophagocytic Lymphohistiocytosis due to Anaplasmosis; When Infection meets Hyper-Inflammation: Consider Adjuvant Dexamethasone

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ABSTRACT

Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening hyper-inflammatory condition characterized by excessive immune activation and multi-organ dysfunction. HLH can be inherited (primary HLH) or acquired (Secondary HLH) due to autoimmune disorders or infections. We report a case of a 72-year-old woman who developed sepsis with HLH features secondary to Anaplasma phagocytophilum infection. Despite appropriate antimicrobial therapy with doxycycline, she experienced rapid clinical deterioration necessitating intensive care and vasopressor support. Adjunctive treatment with a short course of intravenous dexamethasone was associated with marked clinical improvement, resolution of vasopressor dependence and recovery of organ function. This case highlights the importance of early recognition of MAS in infectious contexts and supports consideration of corticosteroid therapy alongside antimicrobials in selected patients.

Keywords: Anaplasma phagocytophilum; Macrophage activation syndrome; Doxycycline; Dexamethasone; Multi-organ dysfunction; Tick-borne infection, Hemophagocytic Lymphohistiocytosis

Introduction

Anaplasma phagocytophilum is an obligate intracellular bacterium transmitted by ticks, causing human granulocytic anaplasmosis (HGA). While most infections are self-limited or mild, severe cases may manifest with systemic inflammation, cytopenias and organ dysfunction. Rarely, HGA can trigger Hemophagocytic Lymphohistiocytosis (HLH) due to overwhelming immune activation and cytokine storm resulting in clinical features suggestive of sepsis, cytopenia's and multi-organ dysfunction. HLH can be inherited (primary HLH) or acquired (Secondary HLH) due to autoimmune disorders or infections[1,2].

HLH should be suspected if the patient presents with sepsis like syndrome along with cytopenias, liver dysfunction, hyper-ferritinemia, coagulopathy and elevated inflammatory cytokines. Prompt recognition and treatment are critical, as untreated HLH carries high mortality[3,4]. While antibiotics targeting the underlying infection are essential, adjunctive immunomodulation with corticosteroids may be lifesaving.

We present a case of 72-year-old woman with severe HLH secondary to A. phagocytophilum infection successfully managed with doxycycline and adjuvant dexamethasone.

Case Presentation

A 72-year-old previously healthy woman presented with a 7-day history of progressive generalized weakness and fever. On

admission, she was febrile and appeared ill but hemodynamically stable. Broad-spectrum antibiotics (vancomycin and meropenem) were initiated pending diagnostic evaluation.

A detailed history obtained from her spouse revealed a tick bite approximately 10 days prior, with no prophylactic treatment. Peripheral blood smear demonstrated Howell-Jolly bodies and intracellular inclusions consistent with Anaplasma species **(Figure 1)**. Doxycycline was started and broad-spectrum antibiotics were discontinued. Serology was positive for Anaplasma phagocytophilum IgG antibody >1:2048 by immunoblot.

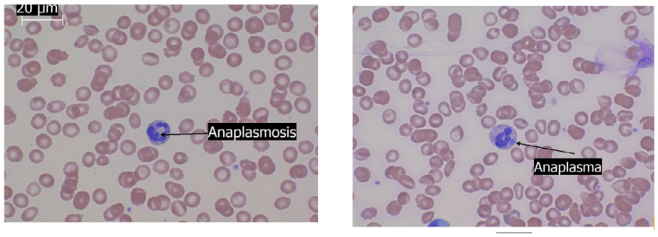

Figure 1: Peripheral blood smear obtained on the patient revealed intracellular inclusions consistent with Anaplasma. Also noted is Howell jolly bodies (nuclear remnants inside red blood cell) and echinocytes (crenated red cells)

Within 12 hours of admission, the patient developed profound hypotension requiring norepinephrine infusion and was transferred to the intensive care unit. She experienced a lower gastrointestinal bleed and worsening mental status, necessitating intubation. Computed tomography angiography excluded active gastrointestinal bleeding or biliary obstruction. Echocardiography showed hyper dynamic left ventricular function.

Laboratory evaluation revealed worsening liver enzymes (AST 357 U/L, ALT 178 U/L, alkaline phosphatase 349 U/L, total bilirubin 5.9 mg/dL), acute kidney injury (serum creatinine 2.6 mg/dl), thrombocytopenia (60 ×10^3/µL), prolonged partial thromboplastin time (54.6 sec) and coagulopathy (fibrinogen 109 mg/dL, D-dimer 6940 ng/mL FEU). White blood cell count was 0.8 ×10^3/µL. **(Table 1)** for laboratory values.

Table-1: Laboratory values of our patient at the time of ICU admission.

Test	Patient value	Normal range
Lactate Dehydrogenase	868 U/L	100-190 U/L
Triglycerides	750 mg/Dl	<150 mg/dL
Ferritin	27,621 ng/mL	13-150 ng/mL
Interleukin-6 (IL-6)	157 pg/mL	<7 pg/mL
Soluble IL-2 Receptor	25,918.8 pg/mL	223-710 pg/mL
Aspartate Transminase (AST)	357 U/L	10-40 U/L
Alanine Transminase (ALT)	178 U/L	7-56 U/L
Alkaline Phosphatase	349 U/L	44-147 U/L
Total Bilirubin	5.9 mg/dL	0.1-1.2 mg/dL
Serum creatinine	2.6 mg/dl	0.9 mg/dl
White Blood Cell Count	0.8 ×103/µL	4.0-10.5 ×103/µL
Platelets	60 ×103/µL	150-450 ×103/µL
Partial Thromboplastin Time	54.6 seconds	25-35 seconds
INR	1	0.8-1.1
D-dimer	6940 ng/mL FEU	<500 ng/mL
Fibrinogen	109 mg/dL	200-400 mg/dL

Despite initiation of doxycycline, vasopressor requirements increased over the subsequent 24 hours (norepinephrine up to 1.5 mcg/kg/min plus vasopressin 0.03U/min) and the patient remained oliguric with worsening renal function (serum creatinine 2.6 mg/dl). Patient was already receiving hydrocortisone at 50 mg Q6hrs intravenously for refractory hypotension. Further laboratory evaluation revealed elevated ferritin (27,621 ng/mL), triglycerides (750 mg/dL), lactate dehydrogenase (868 U/L). Due to elevated triglycerides, ferritin, abnormal liver function tests and cytopenias, secondary HLH was strongly suspected. Subsequently IL-6 came back at 157 pg/mL and soluble IL-2 receptor was significantly elevated at 25,918.8 pg/mL strongly supporting a diagnosis of HLH or secondary macrophage activation syndrome.

As patient had refractory hypotension and worsening multiorgan dysfunction including acute kidney injury (AKI), on day 3, shared decision was made with her husband and intravenous dexamethasone was initiated at 10 mg/m² (23 mg), resulting in a rapid decrease in vasopressor requirements within 4 hours. Norepinephrine was discontinued within 24 hours. Ferritin decreased to 6415 ng/mL over the following days **(Figure 2)**.

Effect of Dexamethasone 23 mg > 10 mg > 8 mg

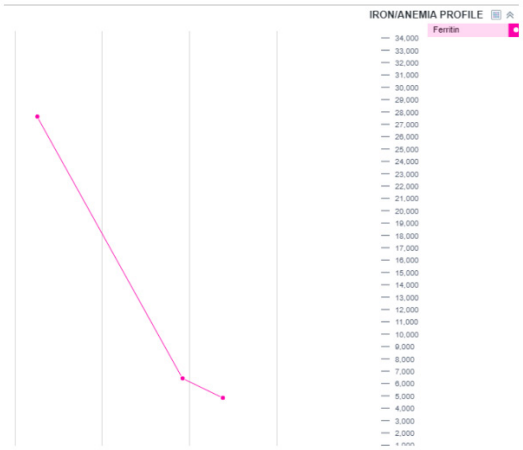

Figure 2: After administration of dexamethasone, ferritin levels decreased significantly with simultaneous improvement in vasopressor need

24 hours after intravenous dexamethasone, her vasopressor requirements gradually increased over the next 12 hours needing nor-epinephrine at 0.3 mcg/kg/min and hence a subsequent dose of dexamethasone was given at 10mg/day. Following the administration of second dose of dexamethasone, the nor-epinephrine could be weaned off. Dexamethasone was then tapered over 3 days (10 mg followed by 8 mg), during which organ dysfunction and laboratory indices improved significantly **(Figure 3)**.

She never required renal replacement therapy during the hospital course; however, required 48 hours of bumetanide infusion for fluid management. Hyper-leukocytosis developed transiently but resolved within 48 hours. She was successfully extubated on day 8 and ultimately recovered fully.

Discussion

Anaplasma phagocytophilum is an obligate intracellular bacterium transmitted by Ixodes ticks, responsible for human granulocytic anaplasmosis (HGA). HGA typically presents as a nonspecific febrile illness with symptoms such as fever, malaise,

myalgia, leukopenia, thrombocytopenia and mild hepatic enzyme elevation. Although many cases are self-limiting or mild, severe disease with multi-organ dysfunction can occur, particularly in elderly or immunocompromised patients[1,2].

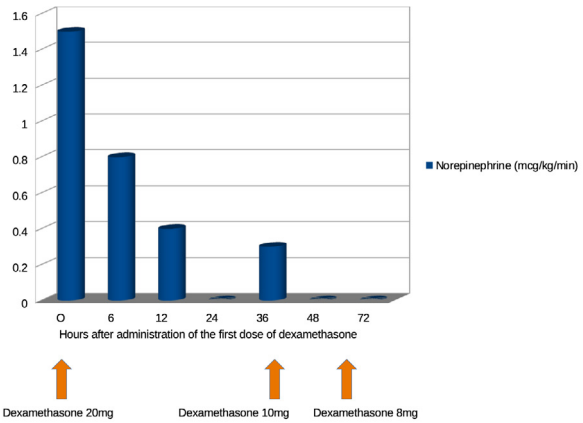

Figure 3: Effect of dexamethasone on vasopressor need. Nor-epinephrine dose needed to maintain target mean arterial pressure decreased gradually after administration of first dose of dexamethasone and patient remained vasopressor free by 24 hours of dexamethasone administration. However, in the next 12 hours, she required progressively increasing doses of nor-epinephrine and hence received an additional 10mg of dexamethasone with significant improvement in hemodynamics. Subsequently, she was completely weaned off vasopressors and organ function indices improved significantly.

A rare but life-threatening complication of HGA is secondary Hemophagocytic Lymphohistiocytosis (HLH), also known as macrophage activation syndrome (MAS). Secondary HLH/MAS is a hyper-inflammatory syndrome characterized by excessive activation and proliferation of macrophages and cytotoxic T-cells, resulting in a massive cytokine storm, multi-organ failure and high mortality if untreated[3-5].

The pathogenesis of HLH/MAS in infections such as Anaplasma involves immune dysregulation triggered by persistent antigenic stimulation. Anaplasma infects neutrophils and evades immune clearance by impairing phagocytic killing and modulating apoptosis pathways. This leads to an exaggerated immune response with impaired cytotoxic function, culminating in macrophage over activation and hemophagocytosis[3,6,7].

Clinical and laboratory features indicative of HLH/MAS include persistent high fever, cytopenia's, hyper-ferritinemia, hyper-triglyceridemic, hypo-fibrinogenaemia, elevated soluble IL-2 receptor (sCD25) and hemophagocytosis on bone marrow or tissue biopsy. Although bone marrow biopsy may aid diagnosis, it is not always definitive; clinical suspicion should guide early management[3-5].

Our case illustrates the potential for A. phagocytophilum infection to induce secondary HLH. The initial presentation is like septic shock as seen in our case; however, laboratory findings including bi-cytopenia, hyper-ferritinemia, hyper-triglyceridemic and elevated soluble IL-2 receptors are suggestive of secondary HLH or macrophage activation.

Although secondary HLH/MAS triggered by A. phagocytophilum infection is rare, several case reports describe this complication in elderly patients presenting with severe systemic illness, including cytopenias, liver dysfunction, coagulopathy and rapidly progressing organ failure[5,6]. The diagnostic challenge arises because the clinical picture mimics severe sepsis and delayed recognition of HLH/MAS can adversely affect outcomes.

Whether secondary HLH is considered a specific phenotype of sepsis or a separate entity mimicking sepsis is a matter of perspective, but this condition needs to be identified. As a typical sepsis, it should induce a robust Interleukin-6 response unlike secondary HLH, as seen in our case where soluble IL-2 had a severe elevation compared to IL-6. One should strongly suspect secondary HLH in any case of "sepsis" if there are findings suggestive of bi-cytopenia, abnormal coagulation (low fibrinogen and elevated d-dimer) and multi-organ dysfunction. Further probability can be gauzed by ferritin and triglyceride levels as abnormal coagulation and multi-organ dysfunction can be signs of sepsis or disseminated intravascular coagulation (DIC). Of note, DIC can be a feature of HLH. If needed IL-2R (also referred to as soluble CD25) and IL-6 can be obtained that will help to identify this sub-phenotype of secondary HLH presenting as sepsis. **(Figure 4)** for proposed flowchart for the diagnosis of secondary HLH.

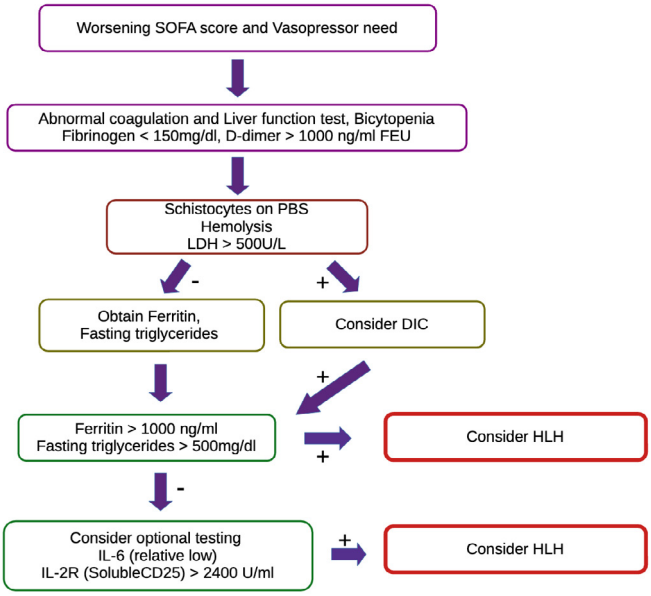

Figure-4: Proposed flow chart for the diagnosis of secondary HLH in suspected septic shock patients. See text for further description. The cut-offs used in this algorithm are higher than the traditional values used for the diagnosis of HLH, as sepsis by itself can increase the levels of d-dimers, ferritin, LDH. These cut-off values represent author's personal opinion. IL-6 will be elevated from baseline and relatively low compared to IL-2R.

Abbreviations

PBS: peripheral blood smear, SOFA: Sequential organ failure assessment score, IL: Interleukin, LDH: Lactate dehydrogenase.

Our case demonstrates this severe hyper-inflammatory phenotype. Despite appropriate antimicrobial therapy, the patient's condition deteriorated with increasing vasopressor requirements, worsening cytopenias, markedly elevated ferritin and other biochemical markers consistent with HLH.

While doxycycline is the treatment of choice for Anaplasma, adjunctive immunosuppressive therapy, particularly corticosteroids, has been employed successfully in severe cases to dampen the hyper-inflammatory response[6,7].

Standard treatment of HGA involves doxycycline; however, in cases complicated by HLH, antimicrobials alone may not suffice to arrest the cytokine storm and hyper-inflammation. Our patient demonstrated a dramatic clinical response to corticosteroids, consistent with other reports emphasizing immunosuppressive therapy in secondary HLH/MAS triggered by infections. Of note there was significant temporal variation in the vasopressor need with the administration of dexamethasone. The rapid clinical improvement following initiation of dexamethasone supports its role in interrupting the cytokine storm and immune-mediated tissue damage. In our case, administration of dexamethasone resulted in significant clinical improvement, including rapid reduction of vasopressor needs and recovery of organ function.

Corticosteroids down regulate the excessive macrophage and T-cell activation driving HLH[3]. There is always a concern of worsening infection with corticosteroids and hence only a short and tapering course of steroid was employed in our case. The short course of dexamethasone used in this case was well tolerated and temporally correlated with clinical stabilization and improvement in vasopressor requirements.

Corticosteroids are typically first-line agents due to their anti-inflammatory effects and safety profile for short-term use. Dexamethasone is the preferred anti-inflammatory agent in this condition as hydrocortisone due to its weak anti-inflammatory action alone may not be sufficient. Other therapies, such as etoposide or cytokine inhibitors (e.g., anakinra), are reserved for refractory cases or primary HLH[3,4].

The rarity of Anaplasma-induced HLH/MAS means current management is largely based on case reports and expert opinion. Large prospective studies are needed to define optimal immunosuppressive regimens, corticosteroid dosing duration and time of initiation. Identification of reliable biomarkers to predict progression to hyper-inflammatory states could facilitate earlier diagnosis and improve patient outcomes. We recommend obtaining ferritin in patients with multi-organ dysfunction and new onset bi-cytopenia. If ferritin is > 1000 ng/ml, HLH should at least be in the differential. Further assessments can be done by fasting triglyceride levels, Il-2 and Il-6 levels.

Conclusion

Physicians should maintain a high index of suspicion for HLH in patients with tick-borne infections who deteriorate despite appropriate antimicrobial therapy, especially in the presence of cytopenias, coagulopathy and hyper-ferritinemia. Early diagnosis and initiation of adjunctive corticosteroids (for example dexamethasone) alongside doxycycline can be lifesaving. Further research is warranted to define optimal immunomodulatory strategies in infection-associated MAS.

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