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ID TEACHING CASES

Anaplasmosis-Induced Hemophagocytic Lymphohistiocytosis: A Case Report and Review of the Literature

Jacob Scribner,[1] Benita Wu,[2] Andre Lamyaithong,[2] Victor Arcega,[1] and Daphne-Dominique Villanueva[1]

[1]Department of Medicine Section of Infectious Diseases, West Virginia University, Morgantown, West Virginia, USA, and [2]Department of Internal Medicine, West Virginia University, Morgantown, West Virginia, USA

Cases of anaplasmosis have increased steadily and are appearing in states where it is less common. While symptoms are usually mild, in rare cases it can cause hemophagocytic lymphohistiocytosis. Here, we present a case of polymerase chain reaction–confirmed *Anaplasma phagocytophilum* with morulae on peripheral blood smear associated with biopsy-proven hemophagocytic lymphohistiocytosis.

Keywords. *Anaplasma phagocytophilum*; anaplasmosis; hemophagocytic lymphohistiocytosis; tick-borne.

Recognized as a human disease in 1994, and previously known as human granulocytic ehrlichiosis, anaplasmosis is a bacterial infection caused by *Anaplasma phagocytophilum* [1]. This obligate intracellular organism is transferred into its human host via *Ixodes scapularis* (black-legged tick) and grows within the membrane-bound vacuoles of leukocytes [1–3]. This infection can range from a spectrum of benign self-limited symptoms of fevers, chills, headaches, nausea, and diarrhea to life-threatening illness with respiratory failure, organ failure, and hemophagocytic lymphohistiocytosis (HLH) [1, 3]. Symptoms typically occur within 1–2 weeks following a tick bite [2]. Anaplasmosis can lead to death from HLH or severe symptoms, with laboratory abnormalities showing thrombocytopenia and signs of liver failure, or both [2, 4]. Risk factors that predispose individuals to severe illness are delayed treatment, age, and weakened immune systems [5, 6].

CASE REPORT

A 78-year-old male West Virginia resident presented to the hospital in the fall of 2022 for the evaluation of generalized weakness, fever, and chills. His medical history was notable for gout, hypertension, hypothyroidism, and chronic kidney disease stage 3. He worked as an automobile mechanic and was an avid outdoor gardener. Thirty days prior to symptom onset, he noticed a tick bite. He did not notice a rash around the bite site. He had not traveled outside of West Virginia. His symptoms started abruptly with decreased appetite and generalized weakness. He did not seek medical attention at that time. Eleven days after symptom onset, he developed fever and chills. Fourteen days after symptom onset, he was unable to ambulate due to severe weakness and that prompted him to seek evaluation at his local emergency department before transferring to our hospital for further management. Upon admission, he was febrile with a temperature of 38.8°C (101.9°F), tachycardic at 104 beats per minute, and tachypneic at 28 breaths per minute. Physical examination revealed an irregular rhythm and a palpable liver 2 cm below the costal margin. Initial laboratory examination revealed leukopenia of 3.3 × 1000 cells/μL, thrombocytopenia of 16 × 1000 cells/μL, acute kidney injury with a creatinine level of 3.96 mg/dL (baseline of 1.4 mg/dL), and transaminitis (aspartate aminotransferase of 330 U/L and alanine aminotransferase of 183 U/L). Viral hepatitis panel was negative for acute or chronic hepatitis infection. Initial peripheral blood smear identified neutrophils with toxic changes without morulae. A computed tomographic scan of the chest, abdomen, and pelvis without intravenous (IV) contrast was significant for bilateral perinephric stranding, leading to a concern for a urinary source of sepsis. He was started on IV ceftriaxone 2 g every 24 hours although urinalysis was negative for nitrites, leukocytes, and bacteria. Oral doxycycline 100 mg twice a day was added the following day due to concern for tick-borne illness. The patient's ferritin was markedly elevated at >33 511 ng/mL (reference range, 20–300 ng/mL) and other inflammatory markers were high. Due to concern for HLH, a bone marrow biopsy was performed and he was started on dexamethasone. Serum cytomegalovirus polymerase chain reaction (PCR) was negative while Epstein-Barr virus (EBV) quantitative was positive at a low level of 120 IU/mL. On day 3 of admission, 1 of 4 blood culture bottles came back positive with gram-positive cocci (GPC) in pairs and chains. Due to the

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Correspondence: Jacob Scribner, DO, Department of Medicine Section of Infectious Diseases, West Virginia University, 64 Medical Center Drive, Box 9163, Morgantown, WV 26506 (jacobscribner4@gmail.com); Daphne-Dominique Villanueva, MD, Department of Medicine Section of Infectious Diseases, West Virginia University, 64 Medical Center Drive, Box 9163, Morgantown, WV 26506 (ddvillanueva.md@gmail.com).

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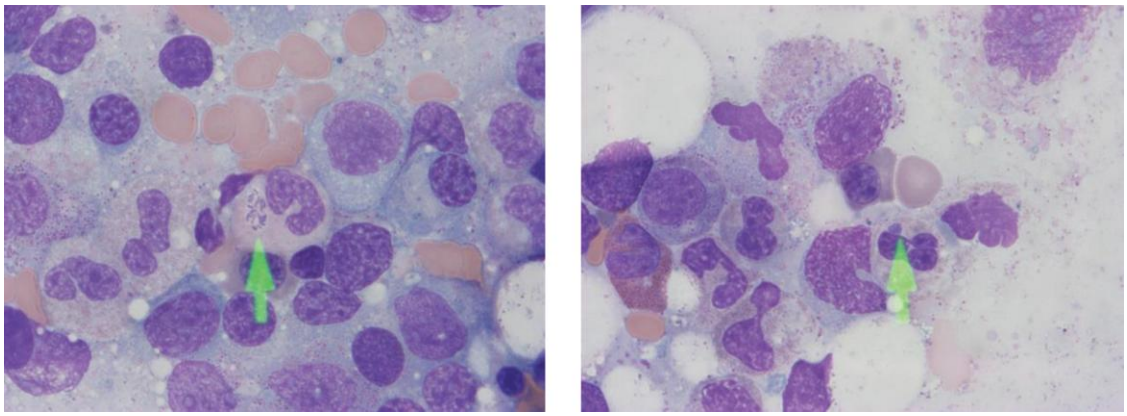

Figure 1. Bone marrow biopsy showing intracellular organisms consistent with *Anaplasma* (arrows).

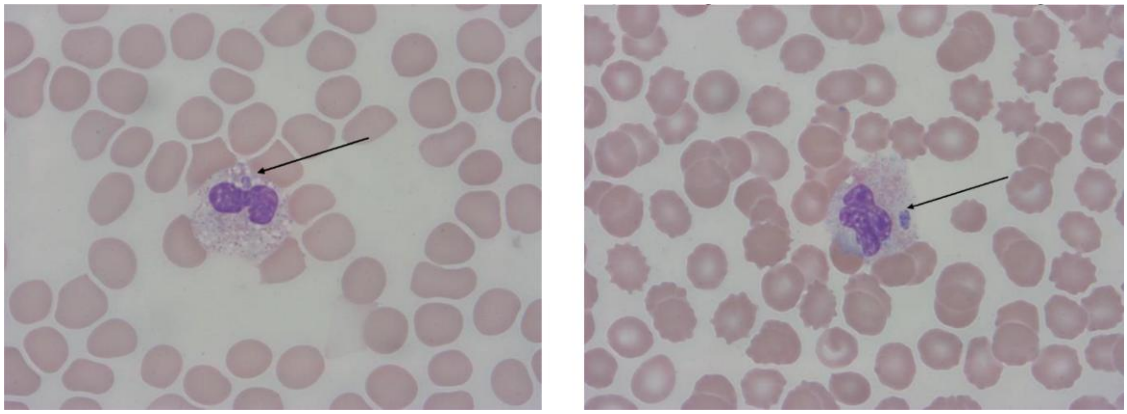

Figure 2. Peripheral blood smear with arrows pointing toward intracellular organisms.

positive blood culture and negative urine culture, ceftriaxone was changed to renally dosed IV ampicillin-sulbactam 3 g every 12 hours. On day 4 of hospitalization, bone marrow biopsy results showed neutrophils with intracellular organisms consistent with *Anaplasma* species (Figure 1). Additionally, there were scattered histiocytes with predominantly intracellular red blood cells and rare intracellular white blood cells consistent with hemophagocytosis. With these findings the patient met the diagnostic criteria for HLH with fever, hyperferritinemia, hypertriglyceridemia, elevated soluble interleukin 2 receptor, and hemophagocytosis present on bone marrow biopsy. Concomitantly the peripheral smear was reviewed and intracellular organisms were seen (Figure 2).

On the same day, serum PCR returned positive for *A phagocytophilum*. The patient was treated with a total of 21 days of oral doxycycline 100 mg twice a day for his anaplasmosis infection and he completed 14 days of renally adjusted oral amoxicillin-clavulanate 500/125 mg twice a day for the GPC in the blood that was sent to a reference laboratory for identification and was pending at the time of his discharge. The GPC was later identified as *Facklamia ignava* after 11 days; by that time the patient had completed his antibiotic course. On the follow-up visit, the patient stated his symptoms were dramatically improved. See Table 1 for a summary of the patient's laboratory results on admission and throughout therapy.

DISCUSSION

Since anaplasmosis became a nationally notifiable disease in the United States in 1999, the incidence of cases has increased by 40% [1, 7, 8]. With the highest incidences in the summer and the fall, 4151 cases are documented annually, primarily concentrated in the Northeastern and northern Midwestern regions of the United States—with the highest number of cases in New York, Rhode Island, Wisconsin, and Connecticut. However, cases are appearing in states where it is typically less common [1, 2, 5, 9–11]. Although there has been a drastic

Table 1. Laboratory Results at Initial Presentation, After 7 Days of Doxycycline Therapy, and at End of Therapy

Laboratory Test	Reference Range	On Admission	Day 7 of Doxycycline Therapy	Day 21 of Doxycycline (End of Therapy)
WBC count, × 1000 cells/μL	3.7–11.0	3.3	9.6	7.9
ANC, × 1000 cells/μL	1.5–7.70	3.17	6.95	4.74
Hemoglobin, g/dL	13.4–17.5	13.9	12.3	12.0
Platelet count, × 1000 platelets/μL	150–400	16	45	224
Creatinine, mg/dL	0.75–1.35	3.96 (Baseline 1.4)	2.61	2.86
AST, U/L	8–45	330	48	25
ALT, U/L	10–55	183	150	40
Triglycerides, mg/dL	<150	448	…	…
Ferritin, ng/mL	20–300	>33 511	…	…
Fibrinogen, mg/dL	200–400	256	…	…
LDH, U/L	125–220	1337	…	…
Soluble IL-2 receptor, pg/mL	175.3–858.2	31 673.1	…	…
D-dimer, ng/mL	≤232	>5000	…	…

Abbreviations: ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; IL-2, interleukin 2; LDH, lactate dehydrogenase; WBC, white blood cell.

Table 2. Previously Reported Cases of Anaplasma Associated With Hemophagocytic Lymphohistiocytosis in the United States

Author, Year of Publication	Time of Year and Geographic Location	Age/ Sex	Comorbidities	Treatment and Duration	Outcome
Zhang et al, 2022 [3]	Unreported time of year, Pennsylvania	67/M	Prior Lyme	IV doxycycline 100 mg every 12 h, etoposide, dexamethasone	Extubated and discharged with symptom resolutions
Rocco et al, 2020 [6]	June, Pennsylvania	74/M	Coronary artery disease	2 wk of doxycycline	Discharged with resolution of symptoms and laboratory abnormalities
Rocco et al, 2020 [6]	September, Pennsylvania	83/M	Atrial fibrillation, hypothyroidism	10-d course of doxycycline, anakinra, dexamethasone	Discharged with resolution of encephalopathy, hypotension, renal failure
Song et al, 2022 [27]	Unreported time of year, traveled to upstate New York	62/M	Hypertension	10-d course of doxycycline	Discharged with resolution of fevers and pancytopenia
de Jesus et al, 2022 [28]	Unreported time of year, Connecticut	54/M	COPD	10-d course of doxycycline, 14-d course of dexamethasone 20 mg daily with taper	Discharged with resolving laboratory abnormalities
Johnson et al, 2017 [29]	Unreported time of year, Valhalla, New York	63/M	Dental abscess status post–root canal surgery, mechanical aortic valve replacement and aortic root graft from valvular insufficiency and ascending aortic aneurysm	Doxycycline	Discharged with resolution of fevers, lethargy, and laboratory abnormalities
Al Amri et al, 2021 [30]	Unreported time of year, Pennsylvania	76/M	Unknown	IV doxycycline	Discharged after extubation, with resolution of fever, altered mental status, and malaise

Abbreviations: COPD, chronic obstructive pulmonary disease; F, female; IV, intravenous; M, male.

rise in diagnosis of Lyme disease and the spread of *I scapularis* in West Virginia, it is one of the states known to have few cases of anaplasmosis with a total of only 7 cases reported from 2015 to 2020 [12]. This geographic spread is likely multifactorial and could be explained by climate changes that alter the life cycle and survivability of ticks, and continued fragmented reforestation providing the habitat for tick-borne vectors [7, 13–17]. Increases in *Ixodes* population present a public health challenge as unfamiliarity with tick-borne diseases, such as anaplasmosis, can lead to delayed treatment and unfortunate outcomes. The aim of this case is to remind healthcare providers, especially in states where *A phagocytophilum* is rare, to consider anaplasmosis as this disease can progress into the rare and deadly HLH.

Commonly associated with malignancy, HLH can be observed in autoimmune, rheumatologic, hereditary, and viral, bacterial, fungal, and parasitic infections. Viral infections, particularly EBV, are the most common trigger of HLH; however, infections from *Leishmania* spp, *Cryptococcus* spp, *Mycobacterium tuberculosis*, and *Anaplasma* have been observed [1, 18–20]. With symptoms of fever and hepatitis overlapping with severe anaplasmosis, HLH occurs due to dysregulation of innate and adaptive immune responses and a proinflammatory state with elevated cytokine levels as seen in a cytokine storm [21, 22]. HLH is usually treated with immunosuppressive therapies [21]. Due to the cellular location that *Anaplasma* occupies within the human host, there have been studies showing clonal expansion of gamma and delta T cells in relation with infection [11]. In general, HLH mortality is high with a secondary mortality rate of 50%–80%, and there have been documented cases in the past of patients dying from anaplasmosis-induced HLH [6]. Our patient had elevated EBV viral load and *Facklamia* isolated in blood cultures. With 33% of EBV-infected patients developing secondary HLH, it could be argued that the positive EBV viral load could make it difficult to determine the etiology of the patient's HLH [23]. However given the low viral load, EBV was unlikely to be the cause for this case. Immune dysregulation could explain the patient's blood growing the rare gram-positive facultative anaerobic cocci seen in cases of bacteremia associated with infective endocarditis, chorioamnionitis, central nervous system infections, and necrotizing gangrene [24]. The positive blood cultures might also be secondary to contamination as the collected sets of blood cultures were not all positive.

Based on current literature on anaplasmosis-induced HLH, only 7 cases are documented in the United States. The demographics and clinical characteristics of these patients are described in Table 2. All 7 patients were male with a mean age of 68.4 years. Like this case, the patients were all discharged and had good clinical outcomes. Four of the 7 patients were from Pennsylvania. Bordering West Virginia, Pennsylvania is not on the list of states with the highest number of anaplasmosis cases; however, it does have significant cases of tick-borne illnesses [12]. Some patients reported in the literature tend to have more severe disease as they require intubation and intensive care–level medical management. Given that <50% of the documented cases required standard HLH treatment with immunosuppressive therapy, appropriate and timely treatment of anaplasmosis is imperative in patient survival and in resolution of the significant immune dysregulation. In other literature, the mortality rate of anaplasmosis is significantly higher in immunocompromised patients than immunocompetent patients [2]. In addition, the literature also suggests that morbidity and mortality increase with delay in treatment >48 hours [2]. Given his chronic kidney disease and age, the patient in this case could be considered immunocompromised. These 2 risk factors, in addition to his delayed presentation to the hospital, could lead to severe complications. Approximately 17 days had passed prior to the patient starting appropriate therapy for anaplasmosis. Given the patient's nonspecific symptoms, laboratory abnormalities, and the West Virginia location, the delayed diagnosis of anaplasmosis was challenging as HLH diagnostics were pursued first. In addition, the initial peripheral blood smear did not show intracytoplasmic granulocytic morulae to suggest anaplasmosis. This diagnostic test is challenging. Despite a specificity of 100%, sensitivity ranges from 21% to 60% [6, 25]. For diagnosis, a combination of serology and PCR would be ideal as PCR sensitivity ranges from 67% to 90% and serology has a sensitivity of 84% and specificity of 94% [25, 26]. Based on patient history, the seasonality of the presentation, and symptoms, healthcare providers should have a high index of suspicion of tick-borne illness to complete the appropriate diagnostic workup and start the appropriate antibiotics—in the case of anaplasmosis, doxycycline 100 mg every 12 hours for 5–14 days or rifampin 300 mg every 12 hours for 7–10 days for those who are pregnant or have allergy to doxycycline [26].

Given the limited number of cases reported in the United States and the inconsistency of immunosuppressive use in anaplasmosis-induced HLH, an international analysis of other cases and management may be useful for determining the specific role of immunosuppressive therapies in the treatment of anaplasmosis.

Anaplasmosis should be suspected in cases of HLH with corresponding symptoms and endemic risk factors, with timely diagnostics and prompt treatment to prevent morbidity and mortality.

Notes

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