Human Granulocytic Anaplasmosis as a COVID-19 Mimicker

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ABSTRACT

Introduction: Human granulocytic anaplasmosis (HGA) is a tick-borne illness caused by the bacterium *Anaplasma phagocytophilum*. HGA has a widely variable clinical presentation and can be life-threatening.

Case description: A 77-year-old man was transferred from an outside facility with altered mental status, a fever of up to 40.5°C, and shortness of breath. Laboratory analysis revealed a progressively worsening pro-inflammatory state and abnormalities in the patient's coagulation studies. With clinical and laboratory evidence concerning for potential COVID-19 infection, the patient was placed in isolation as a precaution. The results of two COVID-19 tests, given approximately 24 hours apart, were negative. The patient's spouse confirmed a bug bite to his upper extremity while working outdoors. His symptoms resolved completely after a 10-day course of empiric doxycycline.

Discussion: The diverse clinical presentations of HGA necessitate a broad differential diagnosis, including viral, bacterial and non-infectious aetiologies. In severe cases, a cytokine-mediated immune cascade can occur (namely, cytokine storm) leading to devastating downstream effects. This cytokine storm can be seen in many other diseases, but most recently it has been demonstrated in the novel coronavirus disease 2019 (COVID-19).

Conclusion: Here we present a case of HGA in which diagnosis was delayed due to mimicry of COVID-19 infection. This case highlights the importance of taking clinical and social histories, seasonality and geography into account during diagnosis, and maintaining a broad differential with non-specific symptoms. Despite the current COVID-19 pandemic, we recommend that HGA remains in the differential diagnosis of a pro-inflammatory state with an atypical respiratory presentation.

LEARNING POINTS

- Human granulocytic anaplasmosis (HGA) has a widely variable clinical presentation and can be life-threatening.
- When presented with non-specific symptoms, it is critical to consider clinical and social histories, seasonality and geography while maintaining a broad differential.
- Cytokine storm can be seen in HGA and other diseases, but most recently it has been observed in the novel COVID-19. However, despite the prevalence of COVID-19, we recommend that HGA remain in the differential diagnosis of a pro-inflammatory state with an atypical respiratory presentation.

KEYWORDS

INTRODUCTION

Human granulocytic anaplasmosis (HGA), first identified in 1990, is a bacterial zoonotic disease characterized by the infection of peripheral granulocytes. It is increasingly being identified as a source of febrile illness following tick bites in several geographical regions in the United States, including New England, Mid-Atlantic states, the Upper Midwest, Northern California, and several areas of Europe [1]. HGA has a broad spectrum of clinical presentations, with the most frequent manifestations being fever, malaise, myalgia and headache [2]. Those infected can suffer life-threatening complications, with 36% of patients requiring hospitalization and up to 17% requiring admission to an intensive care unit [2]. When left untreated, HGA can be fatal; it is for this reason that, in the face of a non-specific presentation, maintaining a broad differential is crucial. Here, we present a case of HGA in which the diagnosis was delayed due to similarities with other infectious inflammatory diseases, including COVID-19 infection.

CASE DESCRIPTION

A 77-year-old man with a medical history of coronary artery disease, hypertension and hyperlipidemia, was transferred from an outside facility with several days of altered mental status, a fever of up to 40.5°C, and shortness of breath. Initial work-up including a computed tomography (CT) scan of the head and sinuses, was negative. CT of the abdomen and pelvis revealed possible ileus/enteritis. A lumbar puncture was also performed, but was not consistent with bacterial or viral meningitis, and infectious serologies from a CSF sample were largely unrevealing. The patient was empirically started on broad-spectrum intravenous antibiotics including piperacillin-tazobactam, vancomycin and ceftriaxone. Over the course of his hospital stay at the outside facility, laboratory abnormalities were trended, with C-reactive protein peaking at 19.8 and platelet count dropping from 127,000 to 24,000. The ferritin level was also significantly elevated. Peripheral smear was performed and according to the records did not reveal schistocytes. Due to worsening thrombocytopenia, altered mental status and ongoing fevers, the patient was transferred to our facility for a higher level of care.

At our facility, the patient was initially in respiratory distress requiring non-invasive positive pressure ventilation. Laboratory analysis (*Table 1*) revealed a progressively worsening pro-inflammatory state, and several abnormalities in the patient's coagulation studies. CT of the chest was performed due to hypoxic respiratory failure, but failed to reveal a pattern consistent with parenchymal or interstitial cause, and was read as largely unremarkable. Amidst the COVID-19 pandemic, with clinical and laboratory evidence concerning for potential COVID-19 infection, the patient was placed in isolation as a precaution. He was subsequently tested for COVID-19 on two separate occasions approximately 24 hours apart, and both test results were negative.

	Day 1	Day 2 (doxycycline)	Day 9
WBC (k/µl)	2.87	2.87	12.04
Relative lymphocyte count (%)	9	39	53
Haemoglobin (g/dl)	10.7	9.5	8.9
Platelets (k/µl)	16	25	59
LDH (U/l)	930	853	521
Ferritin (ng/ml)	33,798	39,013	5,784
D-dimer (µg FEU/ml)	30.29	29.01	2.58
CRP (mg/dl)	25.4	23.6	3.2
SARS-CoV-2	Negative	Negative	

Table 1. Key laboratory values on Days 1, 2 and 9 at our facility

Empiric doxycycline was started on Day 2. Leukopenia and relative lymphopenia, thrombocytopenia and inflammatory markers improved 1 week after the initiation of empiric doxycycline

Upon further questioning, the patient reported that he had been in his normal state of health until approximately 1 week prior to presentation to the outside facility. His spouse confirmed a bug bite to his upper extremity while working outdoors, which was followed by erythema and pain, and then by black and blue discoloration of the area. The patient was then started on empiric intravenous doxycycline while Anaplasma and Ehrlichia PCR testing was performed. Within 24–48 hours of receiving IV doxycycline, the patient defervesced, and inflammatory markers began to trend downwards. Other empiric antibiotics were discontinued. The patient began to improve in terms of mental and respiratory status. Fever trend after initiation of doxycycline is shown in *Fig. 1*. He was discharged to a skilled nursing facility with a total 10 days of empiric doxycycline. Shortly after discharge, anaplasmosis PCR returned positive. The patient's symptoms resolved completely after a 10-day course of empiric doxycycline.
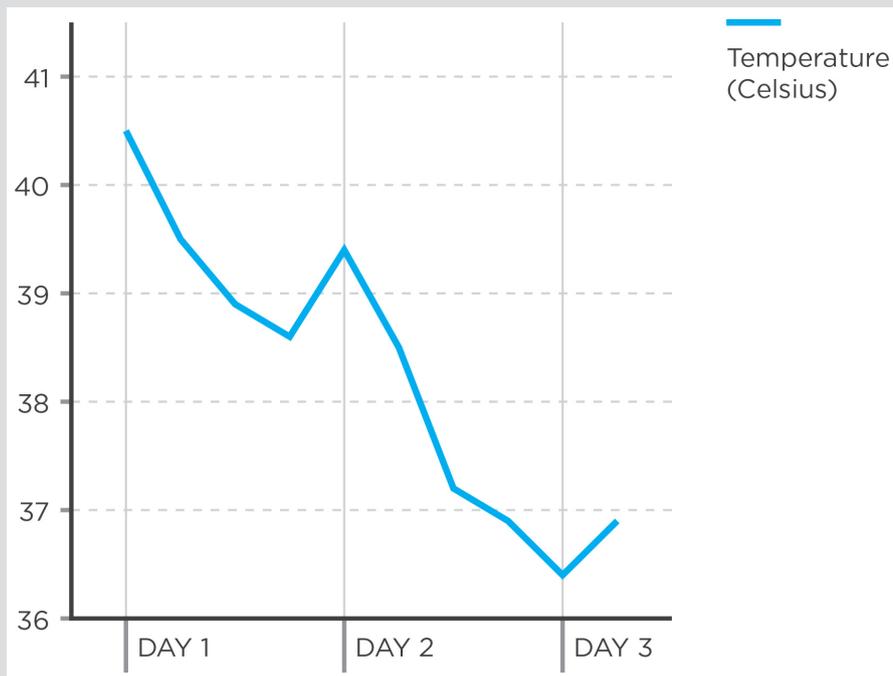

Figure 1. Fever trend after initiation of doxycycline

DISCUSSION

HGA has a wide spectrum of clinical presentations, with the most frequent manifestations as described in one meta-analysis being malaise (94%), fever (92%), myalgia (77%) and headache (75%), and a smaller proportion of patients experiencing arthralgias or involvement of gastrointestinal, respiratory, hepatic or central nervous systems [1]. Common laboratory abnormalities include leukopenia with left-shift, thrombocytopenia, mild to moderate elevations in hepatic transaminases, and elevations in inflammatory markers (such as C-reactive protein and erythrocyte sedimentation rate) [3, 4].

Anaplasma phagocytophilum is transmitted via *Ixodes scapularis* ticks in the United States, along with *Borrelia burgdorferi* and *B. mayonii* (Lyme disease), *Babesia microti* (Babesiosis) and Powassan virus [2]. Because of the non-specific presentation of HGA, and the potential for coinfection with multiple entities via the same tick bite, the differential diagnosis is expansive, and includes other viral illnesses such as enterovirus infection, Epstein-Barr virus infection, human herpes virus-6 infection, human parvovirus B19 infection, viral hepatitis, West Nile virus infection and Chikungunya fever; bacterial infections such as endocarditis, disseminated gonococcemia, meningococcemia, secondary syphilis and septic shock syndrome; and non-infectious aetiologies, such as allergic reaction, idiopathic thrombocytopenic purpura, immune-complex-mediated disease, thrombotic thrombocytopenic purpura, and hemophagocytic and macrophage activation syndromes [2]. More recently, the differential has expanded to include COVID-19 disease. Differences and similarities between HGA and COVID-19 are summarized in *Table 2*.

Diagnosis of HGA is laboratory-confirmed by examination of Wright- or Giemsa-stained peripheral blood smear during the early stage of infection, which often reveals morulae (bacterial clusters) in the cytoplasm of peripheral blood neutrophils [2, 3]. PCR amplification testing for bacterial isolates in culture is also available, albeit in limited laboratory and clinical settings. Serological testing is available; however,

Disease	Coronavirus disease-19 (COVID-19) and human granulocytic anaplasmosis (HGA)	Differentiating factors
Symptoms	Fever, myalgias, headache, malaise, nausea, vomiting, diarrhoea, confusion, altered mental status	Ageusia, anosmia, sore throat is common with HGA
Complications	ARDS, DIC, acute renal failure, toxic shock syndrome	Hypercoagulability and myocarditis are more common with COVID-19
Laboratory work up	Leukopenia or leucocytosis, lymphopenia, elevated CRP, ferritin, D-dimer, LDH	Thrombocytopenia is more common with HGA while elevated CK is more commonly seen with COVID-19
Diagnostic test	RT-PCR is test of choice for COVID-19 and PCR is also the gold standard test for anaplasmosis. Morulae can be seen in peripheral smear in granulocytes	Acute and convalescent serology can be done for both disease but often takes >4 weeks for diagnosis
Treatment	Supportive therapy in both cases. COVID-19 requires strict droplet and contact precautions along with social distancing. Airborne precautions for aerosol generating procedures for COVID-19	COVID-19 therapies Medications such as steroids, antivirals and immunomodulators depends on severity of disease. HGA: doxycycline for 10 days

Table 2. COVID-19 compared with HGA

ARDS, acute respiratory distress syndrome; CK, creatinine kinase; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; LDH, lactate dehydrogenase; RT-PCR, reverse transcriptase polymerase chain reaction

IgM tests are often only reactive during the first 40 days after infection and have been shown to be less sensitive than IgG antibodies even at this stage [2, 5]. Notably, patients infected by *A. phagocytophilum* will develop antibodies that react with *Ehrlichia chaffeensis* (human monocytic ehrlichiosis), and therefore definitive diagnosis of one clinical entity requires antibody titres for both pathogens [2].

The pathogenesis of HGA involves direct infection of and propagation within host neutrophils by the obligate intracellular bacterium *A. phagocytophilum*, leading to upregulation of pro-inflammatory cytokine expression, deactivation of infected neutrophils, and promotion of infected neutrophil degranulation leading to further release of bacteria [6, 7]. Interestingly, limited histopathological analysis of patients with HGA has revealed that generally less than 1% of neutrophils are infected. The associated pancytopenia cannot be explained by bacterial cytolysis alone, however, and is likely related to cytokine-mediated activation of macrophages [8].

The cytokine storm is a feature seen in cases of HGA. This phenomenon is characterized by dysregulation of the immune response with highly elevated cytokine levels and immune-cell hyperactivation. It often causes constitutional symptoms, systemic inflammation, and multiorgan dysfunction and/or failure [9]. Symptoms include fever, fatigue, anorexia, rash, headache, arthralgia, myalgia and neuropsychiatric abnormalities. Cytokine storm can quickly progress to disseminated intravascular coagulation (DIC) with its downstream effects, and can cause renal or hepatic injury, cardiomyopathy or acute respiratory distress syndrome (ARDS). This constellation of pathologies, including renal dysfunction, endothelial cell death, and acute-phase hypoalbuminemia leading to capillary leak syndrome and anasarca, has also been seen in patients with cancer treated with high doses of interleukin-2, a cytokine involved in the immune response to a pathogen [9, 10].

Both HGA and COVID-19 infection, among other aetiologies, have been associated with cytokine storm. The pathophysiology of anaplasmosis and cytokine storm is not well understood but is thought to be mediated by infected neutrophils stimulating an exaggerated immune response [2]. Various studies have demonstrated the direct activation of pro-inflammatory cytokines (including, but not limited to, interleukin (IL)-1β, IL-6, IL-8 and tumour necrosis factor (TNF)-α), albeit to variable degrees [7, 11–13]. In the case of COVID-19, it has not yet been elucidated whether it is immune hyperactivity, failure to resolve inflammatory response triggered by the virus, or underlying immune dysregulation that causes the associated cytokine storm [14]. The immune hyperactivation in cytokine storm can be initiated at several points in the typical immune cascade. This hyperactivation can be due to inappropriate pathogen detection, inappropriate or ineffective

amplitude of immune response, overwhelming pathogen burden (as in sepsis), uncontrolled infection with prolonged immune activation, or failure to return to immune homeostasis [9]. So far, there has not been a unifying criterion that defines cytokine storm, as it remains difficult to distinguish this entity from the natural pathophysiology of critical illness [9, 14]. Three criteria are proposed for cytokine storm: elevated circulating cytokine levels, acute systemic inflammatory symptoms, and either secondary organ dysfunction or cytokine-driven organ dysfunction [9].

Amidst the COVID-19 pandemic, overlooking other diagnoses becomes all too easy, with our intrinsic and anchoring biases coming to the forefront. This case highlights the importance of the patient's clinical and social histories, seasonality and geography in making important clinical diagnoses. It also emphasizes maintaining a broad differential especially when considering the wide range of aetiologies that can present with non-specific symptoms. Despite the current COVID-19 pandemic, we recommend that HGA remain in the differential diagnosis of a pro-inflammatory state with atypical respiratory presentation, in the appropriate clinical setting. Timely diagnosis of HGA can lead to the appropriate treatment of this potentially life-threatening disease.

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