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CASE BASED REVIEW

Inflammatory arthritis: a unique presentation of human anaplasmosis

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Abstract

Human granulocytic anaplasmosis (HGA) is a tickborne rickettsial disease caused by the bacterium *Anaplasma phagocytophilum*. Reported cases have increased with the highest incidence in the Northeast. To our knowledge, this is the first report of anaplasmosis associated with an inflammatory arthritis. A 64-year-old man, with a history of Crohn's disease controlled on budesonide, presented to the emergency room in August 2017 with a week history of headache, sore throat, fever, myalgias, rash, and joint pain. There was no clinical evidence of active Crohn's disease. He lives in Nassau County and participates in outdoor activities. His exam was notable for a maculopapular rash over the trunk, arms, and thighs as well as synovitis of several proximal interphalangeal joints. Lab tests revealed transaminitis and elevated inflammatory markers. When evaluated by rheumatology, he had marked polyarthritis of wrists and hands as well as extremely painful motion of the shoulders, elbows, hips, knees, and ankles despite ibuprofen. Prednisone 20 mg daily resulted in significant improvement in his arthritis. Because of an *Anaplasma phagocytophilum* IgM of 1:320 (normal < 1:20; IgG < 1:64; normal < 1:64) that returned few weeks after presentation, he was prescribed 4 weeks of doxycycline. Convalescent *Anaplasma* serologies revealed negative IgM and IgG > 1:320. He fully recovered and was able to discontinue steroids. HGA presents acutely with a spectrum of manifestations ranging from a flu-like illness to severe complications such as respiratory failure. Myalgias and arthralgias are common, but an inflammatory arthritis has not been described.

Keywords Anaplasmosis · Inflammatory arthritis · Rickettsial disease · Tickborne disease

Human granulocytic anaplasmosis (HGA) is a tickborne rickettsial disease caused by the bacterium *Anaplasma phagocytophilum*. It is a gram-negative intracellular bacterium transmitted by *Ixodes scapularis* tick in the northeast region of the United States (US). Reported cases have increased in the US with the highest incidence in the Northeast [1]. Typical symptoms of HGA include fever, malaise, headache, myalgias, and occasionally arthralgias [2]. We report a case of anaplasmosis infection in a patient who presented with acute polyarthritis. To our knowledge, this is the first report of anaplasmosis associated with an inflammatory arthritis.

A 64-year-old man, with a history of Crohn's disease controlled on budesonide, presented to the emergency room (ER) in August 2017 with a week history of headache, sore throat, daily fevers of 101 °F, myalgias, rash, and joint pain affecting the knees, shoulders, and hands bilaterally. He lived in Nassau County and routinely participated in outdoor activities.

The patient's vital signs were as follows: temperature, 98.3 °F; blood pressure, 110/74 mmHg; pulse, 90 beats per minute; and oxygen saturation, 98% on room air. His exam was notable for a faint maculopapular rash over the trunk, arms, and thighs. His musculoskeletal exam was significant for tenderness of bilateral shoulders and knees and synovitis of several proximal interphalangeal joints. His cardiac, pulmonary, and neurological exams were normal. He had no lymphadenopathy.

Initial laboratory tests revealed WBC 12 k/μL with lymphopenia, hemoglobin 12.7 g/dl, platelets 290 k/μL, alkaline phosphatase 124, AST 55, ALT 66, ESR 36, and CRP 21 (Table 1). Because of concern for an infectious etiology, a lumbar puncture (LP) was performed. An extensive infectious serological workup was obtained that evaluated viral, bacterial, and tickborne illnesses (Table 2). Cerebrospinal fluid (CSF) analysis was unremarkable; blood and CSF cultures were sterile. A chest radiograph was normal.

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Table 1 Laboratory results at initial presentation

Lab test	Result	Reference range
WBC (k/μL)	12	3.8–10.5
Hemoglobin (g/dL)	12.7	13–17
Platelets (k/μL)	290	150–400
Creatinine (mg/dL)	0.89	0.5–1.3
Bilirubin, total (mg/dL)	1.2	0.2–1.2
Alkaline phosphatase (U/L)	124	40–120
AST (U/L)	55	10–40
ALT (U/L)	66	10–45
ESR (mm/h)	36	0–20
CRP (mg/dL)	21	0.00–0.4
Ferritin (ng/mL)	441	30–400
Lactate dehydrogenase (U/L)	305	50–242
Procalcitonin (ng/mL)	0.12	0.00–0.04
Uric acid (mg/dL)	3.5	3.4–8.8

The patient received supportive care with intravenous hydration and a non-steroidal anti-inflammatory medication before discharge. Because of persistent arthritis despite ibuprofen, he was evaluated by rheumatology. There was no clinical evidence of active Crohn's disease. On exam, he had marked polyarthritis of wrists and hands as well as extremely painful motion of the shoulders, elbows, hips, knees, and ankles. With prednisone 20 mg daily, his arthritis improved.

Few weeks after his initial presentation, a lab result revealed an *Anaplasma phagocytophilum* IgM titer of 1:320 (normal < 1:20) and IgG < 1:64 (normal < 1:64). He was therefore prescribed 4 weeks of doxycycline. Convalescent *Anaplasma* serologies 2 months after presentation revealed negative IgM and an IgG titer > 1:320. The patient had a full recovery and was able to discontinue steroids.

Table 2 Infectious workup

Lab test	Result
EBV (U/mL)	VCA IgM +, IgG − EA Ab − NA IgG +
Parvovirus	IgM −, IgG −
CMV (AU/mL)	IgM −, IgG −
Lyme	ELISA IgG/IgM − Western blot IgG −
Rocky Mountain spotted fever	IgM −
Babesia microti	IgM −, IgG −
Ehrlichia chaffeensis	IgM −, IgG −
Anaplasma phagocytophilum	IgM 1:320; IgG −
West Nile	IgM −, IgG −

VCA viral capsid antigen, *EA* early antigen, *NA* nuclear antigen

This patient had several epidemiological risk factors that raised concern for a tickborne illness, such as his presentation in the summer, living in a wooded area in the Northeast, and doing outdoor activities. Because of his potential exposure to ticks, the differential diagnosis included babesiosis, Lyme disease, Rocky Mountain spotted fever, ehrlichiosis, and anaplasmosis. Given the seroconversion, human granulocytic anaplasmosis was the best explanation for this patient's initial presentation.

According to the latest CDC report, the number of anaplasmosis cases has increased from 348 cases in 2000 to 4151 cases in 2016 with an increase in the annual incidence from 1.4 to 6.1 cases per million persons during those 16 years. The peak in cases typically occurs during the summer months, with the highest incidence in the upper Midwest and Northeast regions of the US.

In the eastern and midwestern areas of the US, the vector is the *Ixodes scapularis* tick, whereas in the western regions, the tick is *Ixodes pacificus*. This becomes important when considering a diagnosis of a tickborne illness, as the *Ixodes* ticks are commonly coinfected with other organisms and can potentially transmit *Borrelia burgdorferi*, *Babesia*, and *Ehrlichia*. In the US, the most common reservoir is the white-tailed deer; other possible reservoirs include squirrels and rats. Once the infection is acquired, *Anaplasma phagocytophilum* can induce a pro-inflammatory response leading to neutrophil activation and degranulation. Interleukin-10, interleukin-12, and IFN-γ are some of the major cytokines involved in tissue injury [3]. Schotthoefer et al. [4] examined the serum of patients infected with HGA and found a clinical correlation with certain pro-inflammatory cytokines and clinical disease. For instance, higher levels of IL-1β, IL-8, IL-6, IL-10, and TNF-α correlated with severity of thrombocytopenia. This highlights the role of the inflammatory immune response in the pathophysiology of HGA.

Human granulocytic anaplasmosis occurs at any age with the highest incidence in men above the age of 40 [2]. Patients can present with a spectrum of manifestations ranging from a flu-like illness to severe complications such as respiratory failure in immunocompromised individuals. A typical presentation of acute anaplasmosis in an immunocompetent host would include fevers, malaise, myalgias, and headaches. A comprehensive review of available literature describing cases of human granulocytic anaplasmosis failed to reveal any similar reports of inflammatory arthritis as part of the clinical spectrum. The presence of a rash in HGA is less common compared to other tickborne illnesses, occurring in fewer than 10% of anaplasmosis cases [5].

The majority of patients will have at least one blood abnormality such as leukopenia, thrombocytopenia, or elevated aminotransferase levels; the presence of all three abnormalities is seen in only a minority [6]. The absence of leukopenia and thrombocytopenia in our patient could have been secondary to hemoconcentration as a consequence of dehydration.

Several methods can be used to establish the diagnosis including identification of morulae on the peripheral blood smear, detection of DNA by PCR, and serology using indirect fluorescent antibody (IFA). The case definition of HGA used by the CDC requires that an IgG IFA assay be performed on paired acute and convalescent serum samples collected 4 weeks apart to demonstrate a 4-fold seroconversion. Fever and most other symptoms typically subside within 48 to 72 h after the initiation of treatment. A 10- to 14-day course of doxycycline is the treatment of choice.

To the best of our knowledge, this case is the first report of an inflammatory arthritis seen in acute human granulocytic anaplasmosis infection.

Compliance with ethical standards

Disclosures None.

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