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BRIEF REPORT

Anaplasmosis Presenting With Respiratory Symptoms and Pneumonitis

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Anaplasmosis is a now common tick-borne illness that is characterized by the presence of fever, myalgias, thrombocytopenia, and elevated liver function tests. We report 4 cases with an atypical presentation with pulmonary symptoms and imaging findings, along with the characteristics of each patient, clinical course, and response to therapy.

Keywords. anaplasma phagocytophila; anaplasmosis; pneumonia; pneumonitis; tick-borne illness.

Human granulocytic anaplasmosis (HGA) refers to human ehrlichiosis caused by the obligate intracellular bacteria *Anaplasma phagocytophillum*. Patients often present with high fever, leukopenia, increased serum transaminases, and thrombocytopenia. This disease is most notable during the spring, summer, and early fall [1, 2]. Here we describe 4 cases of confirmed anaplasmosis presenting with significant pulmonary disease.

CASE 1

A 70-year-old female presented with weakness, cough, mild shortness of breath (SOB), difficulty with ambulation, and history of a tick bite mark in the right groin. On admission, she was noted to have a temperature of 101.7°F and atrial fibrillation with rapid ventricular response (RVR). Initial laboratories showed a white blood cell (WBC) count of 4750 cells/uL with lymphopenia, hemoglobin of 12.8 g/dL, and platelets of 100 000 cells/uL. Renal function and liver function tests were within normal limits. Empirical broad-spectrum antibiotics were started. Infectious workup included blood cultures, urine cultures, and respiratory virus panel, which were ultimately negative. Chest x-ray (CXR) showed subtle ill-defined ground-glass opacities in the left lung. She continued to spike fevers and developed altered mental status, along with hypoxia and oxygen saturation at 80% on room air, requiring supplemental oxygen up to 50%. Echocardiogram showed a preserved ejection fraction (EF). A chest computed tomography (CT) scan (Figure 1A) showed worsening ground-glass opacities along the right-center and left lung base with diffuse interlobular septal thickening bilaterally. Complete blood work showed elevations in transaminases to 5 times the normal limits as well as thrombocytopenia with a platelet count of 49 000 cells/uL. *Legionella* antigen, *Streptococcus pneumonia* antigen in urine, and Lyme serology were negative. Doxycycline was started with suspicion of anaplasmosis. Supplemental oxygen decreased to 2–3 liters and was discontinued within 2 days of therapy with doxycycline, which she received for 10 days. The presence of morulae on peripheral smear (Figure 1E) and positive polymerase chain reaction (PCR) for *Anaplasma phagocytophilum* confirmed the diagnosis.

CASE 2

A 63-year-old female presented with fevers, cough, chest pain (CP), SOB, body aches, and ear pain with a history of splenectomy. Laboratories showed a WBC of 10 220 cells/uL with neutrophilic predominance and lymphopenia, lactic acid of 2.6 mmol/L, and elevated transaminases 4 times the normal upper limit. CT of the chest, abdomen, and pelvis showed mild emphysematous changes in the lungs and a calcified granuloma in the left lower lobe with no enlarged lymphadenopathy. She was started on vancomycin and piperacillin/tazobactam empirically after obtaining blood and urine cultures, which ultimately did not grow any organisms. The patient continued to have fevers despite antibiotic therapy and developed hypoxia, requiring oxygen supplementation up to 2–3 liters. A viral respiratory panel, Lyme serology, and abdominal ultrasound all returned negative. Echocardiogram showed a preserved EF. A repeated CT of the chest (Figure 1B) showed new ill-defined centrilobular ground-glass opacities in the right upper and middle lobes. Intravenous antibiotics were stopped, and doxycycline was started empirically. PCR for tick-borne illnesses was positive for anaplasmosis, and peripheral smear showed morulae (Figure 1F). The patient improved with complete resolution of hypoxia and SOB with ambulation within 2 days of starting doxycycline. She was discharged on oral doxycycline for a total of 10 days.

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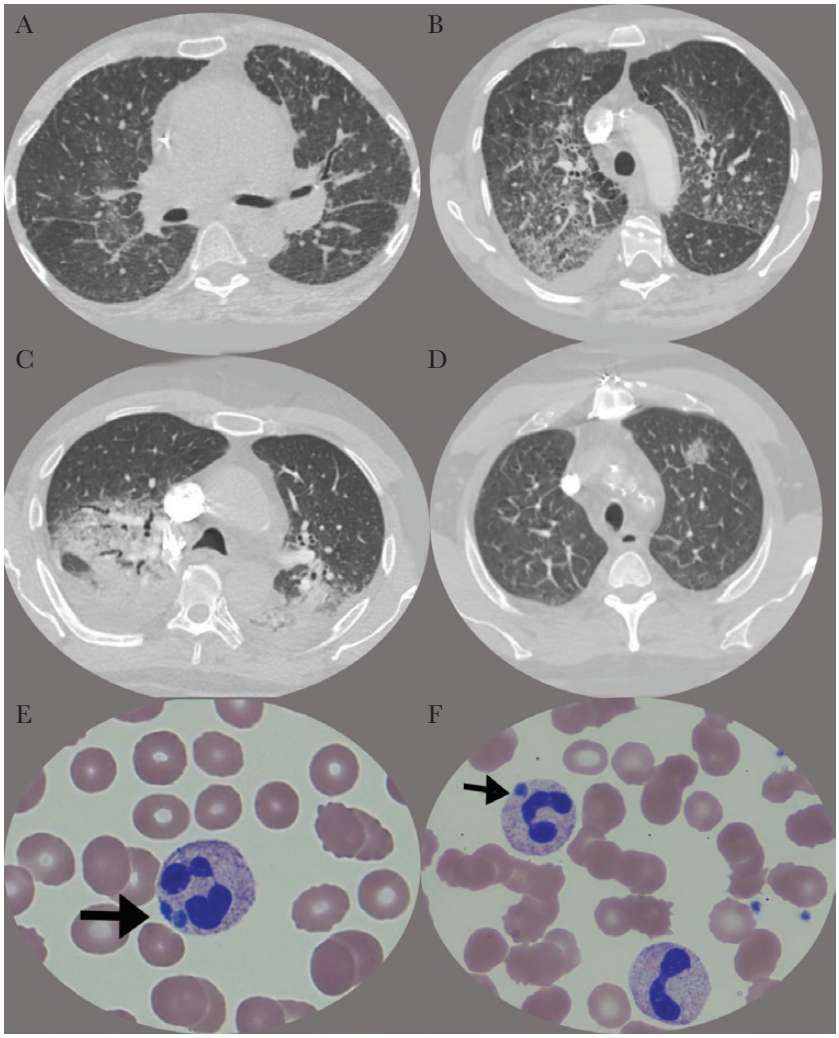

Figure 1. Represented are the pulmonary findings associated with each of the cases described above. A, Findings showed the presence of a greater involvement of the right lung. B, Significant involvement of the right lung with mild right-sided pleural effusion. C, Bilateral ground-glass opacities and pleural effusion. D, Very minimal left-sided ground-glass opacities with significant bilateral pleural effusion. E and F, Presence of morulae (arrows) in neutrophils on peripheral smear.

CASE 3

A 64-year-old male presented with a history of CP, SOB, and atrial fibrillation with RVR. The patient required supplemental oxygen for hypoxia requiring 4 liters of oxygen. Initial laboratories showed a WBC of 5450 cells/uL with neutrophil predominance and lymphopenia. Platelets were 140 000 cells/uL. Liver function tests were within normal limits, with an elevated lactic acid. A CT chest showed peripheral ground-glass opacities within the right middle and left upper lobe. Echocardiogram showed a preserved EF with severe aortic stenosis. The patient developed increased oxygen requirements and work of breathing, requiring bilevel positive airway pressure (BiPAP) and diuretics. BiPAP therapy contributed to decreasing the oxygen requirements to 2 liters. He continued to have fevers and leukocytosis with lymphopenia. A repeat chest CT (Figure 1C) showed the presence of scattered small round ground-glass opacities within upper lung lobes with an interlobular septal thickening. Respiratory viral panel and blood cultures were negative. Transaminases trended up to 6 times the normal upper limit levels. Broad-spectrum antibiotics were stopped, and doxycycline was administered empirically with suspicion of anaplasmosis given the above findings. PCR came back positive for *Anaplasma phagocytophillum*. There was a significant clinical improvement with resolution of oxygen requirement within 1 day of starting doxycycline, and he was eventually discharged home to complete a total of 10 days of therapy.

CASE 4

A 78-year-old male presented with severe malaise, fever, productive cough, and dyspnea on exertion (DOE). Initial vital signs were unremarkable, and laboratory studies revealed a hemoglobin of 14.4 g/dL, WBC count of 6600 cells/μL with

lymphopenia, and platelet count of 91 000 cells/μL. The rest of the laboratory workup showed an aspartate aminotransferase (AST) of 84 U/L and alanine aminotransferase (ALT) of 58 U/L. Chest radiograph showed nodular patchy left basilar opacity for which he was treated with vancomycin, piperacillin-tazobactam, and azithromycin. Infectious workup including respiratory viral panel, *Legionella* urine antigen, *Streptococcus pneumonia* urine antigen, Lyme serology, peripheral blood smear, and blood cultures was unrevealing. The patient deteriorated, developing acute kidney failure, worsening SOB, and hemoptysis, requiring pressor support, mechanical ventilation, and continuous renal replacement therapy. CT of the chest with contrast (Figure 1D) showed moderate bilateral pleural effusions with minimal scattered ground-glass opacities. Bronchoscopy revealed dark blood on the tracheobronchial tree consistent with diffuse alveolar hemorrhage. The serum PCR for *Anaplasma phagocytophilum* was positive, and the patient was started on doxycycline. Within 3 days of beginning doxycycline, he was off pressor support and extubated subsequently. Repeat imaging showed resolution of previously seen lung infiltrates. The patient completed a 3-week course of doxycycline and was discharged to a skilled nursing facility.

DISCUSSION

The association between human anaplasmosis and interstitial pneumonia is neither common nor well understood. We report 4 cases of anaplasmosis who presented with pulmonary complications as well as more classic findings such as fever, lymphopenia, and thrombocytopenia.

Most infections with anaplasmosis are mild; however, up to 36% of patients require hospitalization, with 3% of those having life-threatening complications. Some of these complications include toxic shock–like syndrome, acute respiratory distress syndrome, invasive opportunistic infections with both viral and fungal agents, rhabdomyolysis, pancarditis, acute renal failure, hemorrhage, and neurologic diseases [3–6]. There are few cases in the literature reporting a pulmonary association; 1 case of interstitial pneumonitis was reported in Europe [7], 1 in the United States with interstitial pneumonia and pleural effusion [8], and 1 of acute respiratory distress syndrome (ARDS) [9]. The pathophysiology is not well understood but is thought to be mediated by the capacity of *A. phagocytophilum* to infect neutrophils and stimulate an exaggerated inflammatory response. Simply speaking, the host deals with an exaggerated immune-mediated inflammatory response with a dysfunctional defense mechanism. *A. phagocytophilum* can deactivate and concomitantly recruit neutrophils. It can survive inside neutrophils by inhibiting their apoptotic signals and antimicrobial functions by downregulating granulocytic RAC2 and CYBB (gp91phox) transcription, resulting in the cessation of phagocytic oxidase activity. Affected neutrophils are no longer able to bind and transmigrate through the endothelium, inhibiting phagocytic activity [4]. In summary, *A. phagocytophilum* alters cellular mechanisms to facilitate endocytic entry to the cell, alters phagocytosis to facilitate survival inside the cell, and upregulates chemokines such as interleukin (IL)-8 and IL-10 to recruit neutrophils and support population expansion [10].

Tissue injury appears to be mediated by interferon-gamma and other proinflammatory cytokines that activate local effector cells and effector molecules such as superoxide radicals or nitric oxide. This pathogenesis is similar to macrophage activation and hemophagocytic syndromes, as it can also present increased inflammatory cytokine response, thrombocytopenia, anemia, hepatic injury, and infiltration of hemophagocytic cells in the bone marrow, spleen, and lymph nodes [11]. Interstitial pneumonitis and pulmonary hemorrhage could be counted as part of that inflammatory immunologic response [10]. Other details that can help elucidate the pulmonary presentation are a monocytic margination within the pulmonary veins and infiltration of the interstitium by monocytes seen on histopathology [8].

In our series, the most prominent pulmonary findings were SOB or symptomatic hypoxia with associated ground-glass opacities seen on imaging of the chest. The patients with previous lung disease showed severe findings, but this did not correlate with the severity of the clinical presentation. None of the patients had a previous blood transfusion. Pleural effusion was noted in 2 of the 4 cases, but its significance in the respiratory manifestation of anaplasmosis is yet to be determined. It is also seen in other tick-borne illnesses such as babesiosis and perhaps can be explained by increased microvascular permeability due to the inflammatory process discussed above, but this could certainly be a nonspecific finding as other mechanisms and comorbidities could contribute. Although current data suggest that cough and other respiratory symptoms are uncommon findings, our cases indicate that pulmonary manifestations should be considered part of an inflammatory-mediated clinical syndrome caused by *A. phagocytophilum*. In conclusion, we recommend that anaplasmosis be included in the differential diagnosis for atypical respiratory presentations in the appropriate clinical setting.

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References

1. Dumler JS, Madigan JE, Pusterla N, Bakken JS. Ehrlichioses in humans: epidemiology, clinical presentation, diagnosis, and treatment. Clin Infect Dis **2007**; 45(Suppl 1):S45–51.
2. Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Vector-Borne Diseases

(DVBD). Anaplasmosis. Epidemiology and Statistics. Available at: https://www.cdc.gov/anaplasmosis/stats/index.html. Accessed May 2020.
3. Dumler JS. Anaplasma and ehrlichia infection. Ann N Y Acad Sci **2005**; 1063:361–73.
4. Bakken JS, Dumler JS. Clinical diagnosis and treatment of human granulocytotropic anaplasmosis. Ann N Y Acad Sci **2006**; 1078:236–47.
5. Bakken JS, Dumler JS. Human granulocytic anaplasmosis. Infect Clin Dis **2015**; 29:341–55.
6. Dahlgren FS, Heitman KN, Drexler NA, Massung RF, Behravesh CB. Human granulocytic anaplasmosis in the United States from 2008 to 2012: a summary of national surveillance data. Am J Trop Med Hygiene **2015**; 93:66–72.
7. Remy V, Hansmann Y, De Martino S, et al. Human anaplasmosis presenting as atypical pneumonitis in France. Clin Infect Dis **2003**; 37:846–8.
8. Tsibris AMN, Shepard JAO, Zukerberg LR. Case 6-2011: a 77-year-old man with dyspnea, weakness, and diaphoresis. N Engl J Med **2011**; 364:759–67.
9. Kaphle U, Kheir F, Thammasitboon S. A rare case of ARDS from human anaplasmosis. Respir Care **2015**; 60:e125–7.
10. Ismail N, McBride JW. Tick-borne emerging infections: ehrlichiosis and anaplasmosis. Clin Lab Med **2017**; 37:317–40.
11. Dumler JS. The biological basis of severe outcomes in *Anaplasma phagocytophilum* infection. FEMS Immunol Med Microbiol **2012**; 64:13–20.