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Differential Diagnosis in the Age of COVID-19 and the Need to Maintain a Broad Differential

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Abstract During the coronavirus pandemic, patients admitted to emergency departments (ED) with constitutional symptoms, respiratory complaints, and/or history of sick contacts have high clinical suspicion for COVID-19 regardless of whether initial screening tests are negative. Although communities seek daily coronavirus infection rates of less than one percent, physicians can be highly focused on narrow differentials despite adequate history and physical exams. This case report focuses on an elderly patient with a past medical history of hypertension, chronic kidney disease (CKD), and gout who presented with three days of fevers, chills, body aches, and shortness of breath and reported a home oxygen saturation of 89%. The patient was a health care worker with high risk of contracting COVID-19, and on admission was febrile and found to have lymphopenia. Nevertheless, COVID-19 Polymerase Chain Reaction (PCR) testing returned negative on two separate occasions prompting the team to broaden their differential. Leukopenia, thrombocytopenia and mildly elevated transaminases can all be due to COVID-19, but should also lead medical teams to include tick-borne illnesses as a potential etiology. Parasite serology returned positive for *Babesia microti* via IgG antibodies (1:512) and *Anaplasma phagocytophilum* via PCR and the patient was discharged on appropriate antimicrobial therapy. It is important for providers to understand and recognize the following: 1) overlapping symptoms of tick-borne disease and COVID-19, 2) proper diagnosis and management of babesiosis and anaplasmosis, and 3) benefits of broad differentials for patient care during the COVID-19 pandemic.

Keywords: *coronavirus, COVID-19, d-dimer, babesiosis, anaplasmosis, tick-borne*

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1. Introduction

In the United States a surveillance report to the Centers for Disease Control revealed a range of symptoms associated with COVID-19: cough in 50%, fever (subjective or > 100.4°F) in 43%, myalgia in 36%, headache in 34%, dyspnea in 29%, sore throat in 20%, diarrhea in 19%, nausea/vomiting in 12%, anosmia/ageusia in 10% [1]. The variety of possible symptoms along with inquiries about travel history and sick contacts may cause premature bias and mislabel cases as COVID-19 despite negative screening tests results. Certainly, false negative nasopharyngeal swabs have ultimately returned positive in some cases [2,3]. In communities with declining rates, however, efforts should be taken to broaden patient differential diagnoses. Key geographical regions during the summer months are known for tick-borne diseases and can present with similar symptoms described above. Here we report a case of a 61-year-old male with a past medical history of hypertension, CKD, and gout who presented with three days of fever, chills, body aches, and complaints of shortness of breath, possibly indicating COVID-19, but was found to have *B. microti* coinfection with *A. phagocytophilum*.

2. Case Presentation

A 61-year-old male with a past medical history of hypertension, CKD, and gout presented with three days of fever (up to 103 °F), chills, body aches, and reported shortness of breath. He reported a home oxygen saturation of 89% via pulse oximeter. The patient was a healthcare worker who had been working during the pandemic and up until his ED arrival. Of note, the patient's wife is also a healthcare worker and tested positive for COVID-19 three months prior; however, the patient claimed he tested negative on two separate occasions. The patient had known recent travel outside of New York State and known sick contacts aside from his wife for the past three months.

On presentation, he was febrile at 101.4 °F, heart rate 88, blood pressure 116/77, breathing 18 breaths per minute, and saturating 97% on room air. On physical exam, the patient was resting comfortably without nasal discharge and had clear breath sounds and no accessory muscle use. His skin was warm and dry and no rashes were noted on the extremities. Shown in Table 1 are his pertinent admission labs. His venous blood gas (VBG) was unremarkable with a pH of 7.37 and pCO2 of 36. The

urinalysis was notable for trace protein, small blood, and bacteria despite no white blood cells. Blood and urine cultures returned negative for growth. Initial COVID-19 PCR testing from the ED was negative. Lower extremity duplex ultrasound was done for elevated D-Dimer and did not show venous thrombosis. On the second day of admission a repeat COVID-19 PCR was sent, and the patient's labs were notable for the following: leukopenia (3.48 K/μL; normal 3.80-10.50 K/μL), thrombocytopenia (113 K/μL; normal 150-400 K/μL), and mildly elevated transaminases (AST 47 U/L, normal 10-40 U/L; ALT 59 U/L, normal 10-45 U/L).

Given that the second consecutive COVID-19 test returned negative, in conjunction with continuously high fevers and the aforementioned lab abnormalities, the primary team broadened their differential and interviewed the patient again. Further history revealed that the patient owned a home in Long Island, NY and was splitting his time between there and New York City during the pandemic. Moreover, he had done extensive yard work days before symptom onset. Based on this information a tick-borne workup was pursued for *A. phagocytophilum*, *B. microti*, *Borrelia burgdorferi*, and *Ehrlichia chaffeensis*. The patient was empirically dosed with doxycycline 100 mg twice a day, atovaquone 750 mg daily, and azithromycin 500 mg daily with clinical improvement in fevers and labs over the next 48 hours. Serology ultimately returned positive for *B. microti* with serum IgG ratio 1:512 and *A. phagocytophilum* via PCR (no Anaplasma antibodies). On the day of discharge, he was afebrile and saturating 99% on room air. He was sent home on a 10-day course of appropriate antimicrobial therapy and set up with outpatient follow up with an infectious disease expert.

Table 1. Laboratory data

Variable	Reference range	On ED presentation
Sodium (mEq/L)	135-145	140
Potassium (mEq/L)	3.5-5.3	3.9
Chloride (mEq/L)	96-108	105
Carbon dioxide (mEq/L)	22-31	21
Anion Gap	5-17	14
Creatinine (mg/dL)	0.50-1.3	1.75
Glucose (mg/dL)	70-99	136
Calcium (mg/dL)	8.4-10.5	9.1
Magnesium (mg/dL)	1.6-2.6	2.0
Aspartate Aminotransferase (U/L)	10-40	47
Alanine Aminotransferase (U/L)	10-45	59
Total Bilirubin (mg/dL)	0.2-1.2	0.30
WBC Count (K/μL)	3.80-10.50	3.48
Hemoglobin (g/dL)	13.0-17.0	15.1
Platelet Count (K/μL)	150-400	113
Auto Lymphocyte (%)	13-44	15.7
D-Dimer (ng/mL)	<230	2180
Fibrinogen (mg/dL)	258-438	430
Lactate Dehydrogenase (U/L)	50-242	156
C-Reactive Protein (mg/dL)	0.00-0.40	9.53
Ferritin (ng/mL)	30-400	743
Procalcitonin (ng/mL)	0.02-0.10	0.45
Lactate, blood (mmol/L)	0.5-2.0	2.6
Creatine Kinase (U/L)	30-200	160

3. Discussion

This case highlights the need to maintain a broad differential diagnosis even with COVID-19 related symptoms. Initially, the patient was admitted to a COVID-19 unit for acute hypoxic respiratory failure, despite having appropriate oxygen saturation and no respiratory distress on room air. While the patient was empirically started on azithromycin, there was no consideration for tick-borne disease until 36 hours into admission when collateral history revealed Long Island travels and recent yard work. This delay in proper management has the potential to compromise patient care in more severe cases. COVID-19 certainly remains a public health crisis, but clinical reasoning skills should not be limited by the pandemic.

Babesiosis and anaplasmosis should be suspected in the setting of relevant epidemiologic exposure, tick season, typical clinical manifestations, and laboratory test abnormalities. As with this patient, most infections with *B. microti* and *A. phagocytophilum* are acquired between the months of May and September. Babesia coinfection with Lyme disease, Ehrlichiosis, and human granulocytic anaplasmosis can occur due to transmission by the same *Ixodes* tick vector and was evident on this patient's positive PCR result for *A. phagocytophilum* [4]. One article evaluated co-infection rates across multiple studies, but the data remains significantly varied [5].

Common complaints of Babesiosis include fever, fatigue, chills, myalgia, headaches, and dry cough - a constellation of symptoms that can mimic those of COVID-19. Atypical physical findings may demonstrate scleral icterus, jaundice, and mild pharyngeal erythema [6]. Rash is rarely seen, but if so, concurrent Lyme disease should be suspected. Laboratory abnormalities may reveal leukopenia, hemolytic anemia, thrombocytopenia, and/or elevated aminotransferases.

Human granulocytic anaplasmosis (HGA) is commonly caused by *A. phagocytophilum*, which was formerly known as E. phagocytophila and E. equi. Data from 2008-2012 revealed an annual incidence of anaplasmosis of 6.3 cases per million in the United States [7]. Analogous to Babesiosis, most patients are febrile and develop nonspecific constitutional symptoms. In a small study of 18 adults with HGA, fever appeared an average of 5.5 days after a tick bite was noticed [8]. Not surprising, both anaplasmosis and babesiosis share similar geographical prevalence and result in leukopenia, elevated aminotransferases, and thrombocytopenia. Rash is a rare finding in HGA, as evident in a retrospective case study that showed positive finding in 1 of 41 patients [9].

Diagnostic tools for babesiosis and anaplasmosis include blood smear (tetrad-forms/Maltese Cross and morulae, respectively), PCR, and serology. In our patient, IgG titers were 1:512. In the acute phase, *B. microti* IgG titers usually exceed 1:1024, but typically decline to ≤1:64 within 6 to 12 months [10]. IgM antibody is typically detected two weeks after illness onset and the correlation between titers and symptoms is poor [11]. Unfortunately, IgM levels were not drawn given that the patient was only ill for 3 days. Based on the IgG titer (1:512) and lack of IgM data the determination of acute vs. chronic infection cannot be exactly determined.

PCR-based testing, as was done for this patient and returned positive, is more widely used to diagnose HGA than antibody tests. Indirect fluorescent antibody can be performed; however, antibodies typically become detectable 2-3 weeks after illness onset so the result was unsurprisingly negative in this case [12]. For most mild to moderate *B. microti* infections, a 7- to 10-day treatment with oral azithromycin plus oral atovaquone is recommended. No antimicrobial therapy is suggested for asymptomatic infection. Appropriate antibiotic coverage is also necessary for coinfections, such as the 10-day doxycycline course for *A. phagocytophilum* in the patient case described herein.

An additional teaching point from this case arises in relation to this patient's lab abnormalities. It has become common practice during the COVID-19 pandemic to trend D-dimers as a way of risk stratifying patients who need anticoagulation. This patient had presented with an elevated D-dimer, but had no evidence of thrombosis. Since little is known about the variation of D-dimer levels in other medical conditions (such as tick-borne illnesses), elevated levels should be interpreted with caution before initiating anticoagulation in a given clinical scenario.

4. Conclusion

Analogous to the Head-to-Toe assessment on history and physical exams - clinicians during the coronavirus pandemic should resort to broad differentials for viral complaints. Babesiosis and other tick-borne diseases can mimic COVID-19 symptoms, but appropriate history (e.g. geographical location and season) along with physical exam and laboratory findings can guide physicians on appropriate diagnosis and management. The alarming coronavirus death counts and high infectivity certainly poses a challenge, but with increased testing and public health measures, physicians should continue utilizing their pre-COVID-19 medical reasoning skills.

Declarations

Ethics approval and consent to participate.
Not applicable

Consent for Publication

Consent obtained at time of discharge.

Availability of Data and Material

Not applicable.

Competing Interests

The authors declare that they have no competing interests

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