CASE RECORDS *of the* MASSACHUSETTS GENERAL HOSPITAL

Case 5-2023: A 67-Year-Old Man with Interstitial Lung Disease, Fever, and Myalgias

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PRESENTATION OF CASE

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CME
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Dr. Peter W. Croughan (Medicine): A 67-year-old man was admitted to this hospital because of fever, myalgias, and one previous episode of vomiting.

Nine months before this admission, the patient was admitted to another hospital with cough and shortness of breath, and coronavirus disease 2019 (Covid-19) pneumonia was diagnosed. He received remdesivir, dexamethasone, and supplemental oxygen, which was delivered through a high-flow nasal cannula. His clinical condition gradually improved, and he was discharged home with supplemental oxygen, which was to be administered through a nasal cannula at a rate of 4 liters per minute.

While the patient was recovering at home, cough persisted and shortness of breath worsened, despite treatment with prednisone. Two weeks after discharge from the hospital, organizing pneumonia was diagnosed. Pulmonary-function testing revealed a severe restrictive ventilatory defect with impaired gas exchange, and findings on computed tomography (CT) of the chest were consistent with organizing pneumonia superimposed on fibrotic interstitial lung disease. Treatment with pirfenidone and mycophenolate mofetil was initiated, and the dose of prednisone was increased. Despite the use of these treatments, there was no decrease in dyspnea; consequently, treatment with pirfenidone was stopped, and the dose of prednisone was tapered over the course of the 2 months before the current admission. Because of persistent severe dyspnea on exertion, the patient was listed for lung transplantation 2 weeks before the current admission.

Two days before the current admission, myalgias and nausea developed, and an episode of vomiting occurred. The tympanic temperature, as measured by the patient at home, was 40.0°C. There was also a slight increase in shortness of breath, and the patient began to administer supplemental oxygen at an increased rate of 5 liters per minute. One day before the current admission, a home test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen was negative. The patient presented to the emergency department of this hospital for further evaluation.

In the emergency department, the patient reported a chronic dry cough that was unchanged. Other medical history included gastroesophageal reflux disease,

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission	Hospital Day 2
Hematocrit (%)	41.0–53.0	43.0	39.1
Hemoglobin (g/dl)	13.5–17.5	14.0	12.7
White-cell count (per µl)	4500–11,000	5770	3040
Differential count (per µl)			
Neutrophils	1800–7700	4860	2800
Lymphocytes	1000–4800	210	160
Monocytes	200–1200	570	30
Eosinophils	0–900	0	50
Basophils	0–300	50	0
Bands	0–100	80	0
Platelet count (per µl)	150,000–400,000	225,000	59,000
Alkaline phosphatase (U/liter)	45–115	109	167
Alanine aminotransferase (U/liter)	10–55	48	76
Aspartate aminotransferase (U/liter)	10–40	61	115
Total bilirubin (mg/dl)	0.0–1.0	0.4	0.4
Direct bilirubin (mg/dl)	0.0–0.4	<0.2	<0.2
Albumin (g/dl)	3.5–5.0	4.0	4.0
International normalized ratio	0.9–1.1	—	1.2
Lactate dehydrogenase (U/liter)	110–210	—	572
C-reactive protein (mg/liter)	<8.0	—	273.8
Haptoglobin (mg/dl)	30–200	—	258
Fibrinogen (mg/dl)	150–400	—	459

* To convert the values for bilirubin to micromoles per liter, multiply by 17.1.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

obstructive sleep apnea, and prostate cancer that had been treated surgically 4 years before this admission. Medications included albuterol, calcium carbonate, cholecalciferol, ipratropium–albuterol delivered by nebulizer, mycophenolate mofetil, pantoprazole, prednisone, and trimethoprim–sulfamethoxazole. He had no known drug allergies. He drank three or four alcoholic drinks per week and was a lifelong nonsmoker. He lived in a rural area of New England on five acres of land with woods. He used well water at home, but he boiled drinking water before consumption. He owned a dog, and he spent time outdoors, including mowing the lawn 1 week before this admission. He had had mosquito bites but no known tick bites. He was retired from previous work as a welder.

On examination, the temporal temperature was 36.6°C, the blood pressure 126/67 mm Hg, the pulse 91 beats per minute, the respiratory rate 28 breaths per minute, and the oxygen saturation 97% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 5 liters per minute. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 24.8. Respirations were slightly labored, and the patient spoke in short sentences. He was alert and oriented and answered questions appropriately. No oral thrush was present. There were crackles at the bases of both lung fields. There was no hepatosplenomegaly. The remainder of the examination was normal. The blood levels of electrolytes and glucose were normal, as were the results of
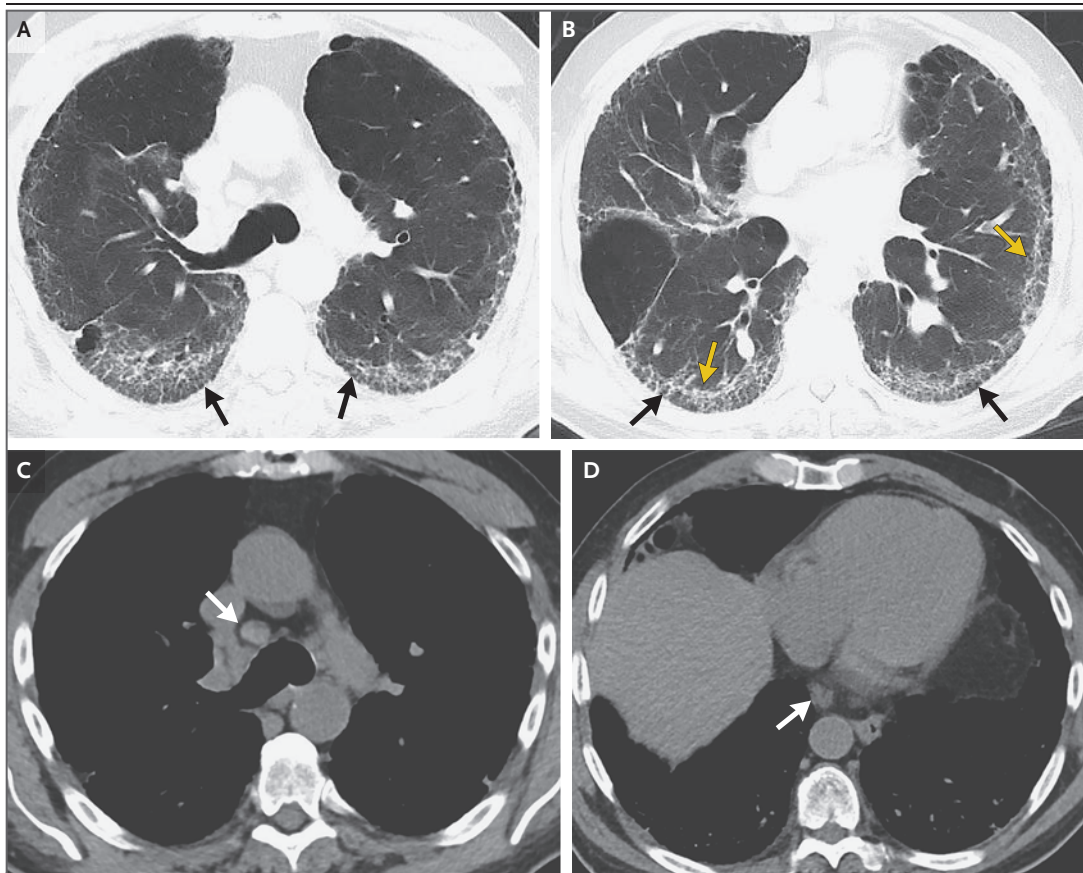
Figure 1. CT of the Chest on Admission.

Axial images obtained with lung windows (Panels A and B) show resolution of peripheral consolidation and multifocal ground-glass opacity, which had been observed on CT scans obtained 7 and 9 months earlier, and new peripheral curvilinear opacity (Panel B, yellow arrows). There is subpleural reticulation with associated ground-glass opacity, architectural distortion, traction bronchiolectasis, and honeycombing (Panels A and B, black arrows). These findings are consistent with a CT pattern of usual interstitial pneumonia. The new peripheral curvilinear opacity is consistent with previous severe acute respiratory syndrome coronavirus 2 infection. As compared with the CT scans obtained 7 and 9 months earlier, the mediastinal windows show a decrease in mediastinal lymphadenopathy (Panel C, arrow) and a new paraesophageal lymph node on the lower right side (Panel D, arrow).

kidney-function tests. Urinalysis results were normal. The blood level of 1,3-β-D-glucan was less than 31 pg per milliliter (reference value, <60), and the blood galactomannan index was 0.13 (reference range, 0.00 to 0.49). Tests for Lyme disease and human immunodeficiency virus (HIV) were negative; other laboratory test results are shown in Table 1. A respiratory viral panel that included testing for SARS-CoV-2 nucleic acids was negative. Imaging studies were obtained.

Dr. Amita Sharma: Chest radiography revealed bilateral peripheral reticular opacities that were similar in appearance to those observed in studies obtained 7 and 9 months earlier and were consistent with the patient's reported history of interstitial lung disease, with no new focal consolidation. CT of the chest (Fig. 1), performed without the administration of intravenous contrast material, showed resolution of multifocal air-space opacities and new peripheral curvilinear opacity. There was peripheral reticulation that was unchanged from that seen in the studies obtained 7 and 9 months earlier, basilar-predominant architectural distortion, and traction bronchiectasis with evidence of honeycombing in the lung bases. There was a slight decrease in mediastinal lymphadenopathy as compared with the earlier studies and a single new paraesophageal lymph node on the right side.

Dr. Croughan: Blood and urine cultures were obtained, and treatment with intravenous cefepime was initiated. Twelve hours after the patient presented to the emergency department, the temporal temperature was 38.8°C, the blood pressure 82/53 mm Hg, the pulse 78 beats per minute, the respiratory rate 20 breaths per minute, and the oxygen saturation 99% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 5 liters per minute. One liter of intravenous fluids was administered, and the blood pressure increased to 108/52 mm Hg. Owing to the patient's acute illness, the dose of prednisone was increased, and he was admitted to the hospital.

On hospital day 1, fever persisted; the maximum temporal temperature was 39.9°C. The blood pressure remained stable; treatment with intravenous vancomycin was added.

On hospital day 2, pancytopenia developed, and the results of liver-function tests had worsened; laboratory test results are shown in Table 1. Blood and urine cultures showed no growth. A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Hemal N. Sampat: This immunosuppressed 67-year-old man with interstitial lung disease presented with high fever, worsening hypoxemia and dyspnea, myalgias, nausea, and vomiting. Subsequently, pancytopenia developed, along with elevation of aminotransferase levels. Each of these presenting signs and symptoms has a potentially broad differential diagnosis, but the combination of fever, pancytopenia, and elevation of aminotransferase levels suggests a state of immune activation, so I will begin by constructing a differential diagnosis that focuses on immune activation and fever.

FEVER

Causes of fever generally fall into three broad categories: infection, cancer, and inflammation. Initial investigations for infection in this patient revealed negative blood and urine cultures, a negative respiratory viral panel, a normal blood level of 1,3-β-D-glucan, a normal blood galactomannan index, and negative tests for HIV and Lyme disease. In consideration of cancer as a cause of fever in this patient, there was no smoking history, no weight loss or night sweats, and no palpable lymphadenopathy or hepatosplenomegaly on examination. Other than an increase in lymphadenopathy, findings on chest radiography and chest CT were unchanged from previous studies. Without evidence of an apparent infection or cancer in this patient, I will first focus on inflammatory causes of fever.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND RECENCY BIAS

Before I initially reviewed this patient's clinical presentation, I had recently attended a case conference in which a colleague discussed a patient who had had a similar presentation of fever, pancytopenia, and elevated aminotransferase levels and had received a diagnosis of hemophagocytic lymphohistiocytosis (HLH). HLH is a hyperinflammatory syndrome in which the presence of various triggers results in the failure of the immune system to downregulate activated macrophages and cytotoxic T cells.[1] It primarily affects children, but it has been described in adults up to 70 years of age. HLH is characterized by fever, both anemia and thrombocytopenia (from immune destruction of red cells and platelets), an elevated blood level of ferritin, and hepatosplenomegaly. Recency bias probably contributed to my early consideration of HLH. However, this patient had relatively mild anemia and clinically significant leukopenia, which make HLH an unlikely diagnosis.

COMPLICATIONS OF COVID-19

Could this patient's history of Covid-19 be contributing to his current illness? Shortly after the Covid-19 pandemic began, a new hyperinflammatory syndrome similar to Kawasaki's disease was described in children with Covid-19: multisystem inflammatory syndrome in children (MIS-C).[2] Soon thereafter, a similar Covid-19–related complication was described in adults: multisystem inflammatory syndrome in adults (MIS-A). In addition to fever, the diagnosis of MIS-A requires the presence of either severe cardiac illness or both rash and nonpurulent conjunctivitis, plus several secondary criteria.[3] The diagnosis also requires a recent positive SARS-CoV-2 test and elevation of at least two inflammatory markers. Although this patient's C-reactive protein level was markedly elevated, MIS-A is an unlikely cause of his fever, given that Covid-19 was diagnosed 9 months before the

current admission, and there is no cardiac illness, rash, or nonpurulent conjunctivitis.

TREATMENT WITH MYCOPHENOLATE MOFETIL

There are case reports of an acute inflammatory syndrome that is associated with the use of mycophenolate mofetil. It is characterized by fever, arthralgia, arthritis, myalgia, and elevated inflammatory markers in the absence of infection.[4-8] However, this syndrome typically occurs within 1 week after the initiation of mycophenolate mofetil therapy or after a change in the dose. This patient had been receiving a stable dose of mycophenolate mofetil for 6 months. Although an inflammatory syndrome related to mycophenolate mofetil is possible in this patient, this syndrome is rare.

INFECTION

Given that this patient had been treated for interstitial lung disease with mycophenolate mofetil and prednisone, he was at risk for various infections that are associated with immunosuppressive therapy. Leukopenia could be caused by an acute illness, or it could be an effect of mycophenolate mofetil therapy. Although the prednisone dose had been tapered over the course of the 2 months preceding this admission, I consider this patient to be moderately immunocompromised.

What other clues can help determine whether this patient had an infectious disease? He had chronic hypoxemia and dyspnea due to interstitial lung disease, but these symptoms had worsened abruptly. A nonpulmonary source of infection could cause worsening dyspnea and hypoxemia by further stressing his already chronically ill lungs. However, the worsening dyspnea and hypoxemia could also be clues to a pulmonary source of infection.

PULMONARY INFECTION

Chest imaging showed no evidence of bacterial, viral, or atypical pneumonia or of pulmonary tuberculosis. The patient had been receiving trimethoprim–sulfamethoxazole prophylactically for *Pneumocystis jiroveci* pneumonia, which makes this diagnosis unlikely. The blood level of 1,3-β-D-glucan was not elevated, which further argues against a diagnosis of *P. jiroveci* pneumonia. In addition, the blood galactomannan index was normal. How do these negative fungal markers help refine the differential diagnosis, when considering pathogens such as aspergillus?

The polysaccharide 1,3-β-D-glucan is a constituent of the cell wall of many fungi. The 1,3-β-D-glucan assay to diagnose invasive fungal infection has a sensitivity of 50 to 77% and a specificity of 85 to 99%.[9,10] Galactomannan is a more specific polysaccharide constituent of the cell wall of aspergillus species and several other fungi. The galactomannan assay to identify aspergillus infection or colonization has a sensitivity of 81% and a specificity of 82%.[11] Thus, a normal blood level of 1,3-β-D-glucan and a normal blood galactomannan index do not rule out invasive fungal infection in this patient. However, invasive fungal infections are seen primarily in patients who are severely immunocompromised, such as those with leukemia or those who have undergone bone marrow transplantation. In a moderately immunocompromised patient such as this one, 1,3-β-D-glucan or galactomannan testing is typically not indicated, given the low likelihood of an invasive fungal disease.[12]

SYSTEMIC INFECTION

Could this patient have had a nonpulmonary source of infection? Indeed, there was an important finding on the chest CT that is suggestive of a systemic infection. The degree of mediastinal lymphadenopathy was mildly decreased as compared with that on previous studies, but the finding of a new paraesophageal lymph node was notable. Paraesophageal lymph nodes drain the esophagus and areas below the diaphragm — not the lungs.[13] The presence of a new paraesophageal lymph node suggests either an abdominal source of infection or a systemic source. Although the patient had nausea, vomiting, and elevated aminotransferase levels, there are no other elements of the history or physical examination that would suggest an abdominal process.

Potential systemic sources of infection in this patient with concurrent leukopenia, thrombocytopenia, and elevated aminotransferase levels include viral infections such as Epstein–Barr virus (EBV) infection, cytomegalovirus (CMV) infection, and viral hepatitis. However, I often find it helpful to ask the question, "Why now?" Are there recent events that can be correlated with the onset of his illness?

It is interesting to note that this patient spent substantial time outdoors and that he had

mowed his lawn the week before this admission. In addition, he lived in rural New England, had a dog, and reported recent mosquito bites. Although he had had no known tick bites, he was certainly at risk for them. Although it would be prudent to test for EBV infection, CMV infection, and viral hepatitis in this patient, a mosquito-borne or tickborne illness is more likely to explain his clinical syndrome, given the history of outdoor activity (Table 2).

Infection with a mosquito-borne virus such as West Nile virus or eastern equine encephalitis virus is unlikely in this patient because he did not have encephalopathy. Rocky Mountain spotted fever is also unlikely because he did not have headache or diffuse rash that includes the palms and soles. Babesiosis is unlikely, given the absence of hemolytic anemia.

Ehrlichiosis and anaplasmosis are tickborne illnesses that are characterized by fever, leukopenia, thrombocytopenia, and elevated aminotransferase levels. Persons with anaplasmosis often have pronounced lymphopenia,[14] as was seen in this patient. Ehrlichiosis is associated with rash in 33% of affected patients and with encephalopathy in approximately 20% of patients; rash and encephalopathy are rare in patients with anaplasmosis.[15,17,23] The vector for ehrlichia species is the lone star tick (*Amblyomma americanum*), and ehrlichiosis is most common in the southern and central United States.[24] *Anaplasma phagocytophilum*, the bacterium that causes anaplasmosis, is transmitted by the deer tick (*Ixodes scapularis*), which is also the vector for Lyme disease and babesiosis, in the northeastern and upper midwestern United States.[25] In accordance with the increased activity of their vectors, both ehrlichiosis and anaplasmosis have the highest prevalence in the late spring and early summer months. Although the season during which this patient presented is not specified, we can assume that it was the spring or summer when he would be outside mowing his lawn.

Both illnesses are associated with a high incidence of hospitalization — 57% for ehrlichiosis and 36% for anaplasmosis — and can progress to septic shock or a toxic shock–like illness if left untreated.[26,27] Ehrlichiosis is fatal in 1.0 to 2.7% of affected patients, and anaplasmosis is fatal in 0.3% of patients.[28] Risk factors for severe illness include immunocompromise, an older age, and delayed initiation of treatment.

Table 2. Clinical Features of Tickborne and Mosquito-borne Illnesses as Compared with This Patient's Illness.*

Illness	Fever	Elevated AST or ALT Level	Leukopenia	Thrombocytopenia	Anemia	Rash	Encephalopathy
Anaplasmosis[14]	Present	Present	Present	Present	Present, mild	Absent	Absent
Ehrlichiosis[15-17]	Present	Present	Present	Present	Present, mild	Present in approximately 33% of patients	Present in approximately 20% of patients
Rocky Mountain spotted fever[18-20]	Present	Present	Present or absent	Present	Absent	Present, hallmark feature	Late or severe manifestation if left untreated
Babesiosis[21]	Present	Present	Present or absent	Present	Present, hallmark feature	Absent	Late or severe manifestation if left untreated
Arbovirus infection (e.g., West Nile virus infection, eastern equine encephalitis)[22]	Present	Present	Present or absent	Present or absent	Present or absent	Present	Present, hallmark feature
This patient's illness	Present	Present	Present	Present	Present, mild	Absent	Absent

* AST denotes aspartate aminotransferase, and ALT alanine aminotransferase.

Clinically, ehrlichiosis and anaplasmosis are often indistinguishable, and they are treated the same way. Given the much higher prevalence of anaplasmosis in New England, as well as the presence of lymphopenia in this patient, I suspect that this patient had anaplasmosis. To confirm this diagnosis, I would obtain a specimen of blood for nucleic acid testing for anaplasma, and I would initiate treatment with doxycycline immediately while awaiting the results of that diagnostic test.

DR. HEMAL N. SAMPAT'S DIAGNOSIS

Anaplasmosis.

MICROBIOLOGIC DISCUSSION

Dr. E. Zachary Nussbaum: Nucleic acid amplification testing (NAAT) for ehrlichia species and CMV was negative, as was an examination of thick and thin blood smears for babesia and plasmodium species. Blood tests for hepatitis A, B, and C viruses were also negative. Results of serologic testing for EBV were consistent with previous infection. Ultimately, the diagnosis in this case was confirmed by the presence of *A. phagocytophilum* nucleic acids in a specimen of whole blood.

The diagnosis of anaplasmosis can be achieved by means of direct and indirect methods. Direct diagnostic methods include NAAT and microscopy. The sensitivity of NAAT ranges from 70 to 90% and is highest when the test is performed early in the disease course. The specificity approaches 100%. Given these testing characteristics, NAAT is considered to be the test of choice, particularly during the early stages of disease.[29,30] Microscopic examination of a peripheral-blood or buffy-coat smear (stained with Wright–Giemsa stain) can detect intracytoplasmic inclusions (morulae) in granulocytes, which can support the diagnosis. However, microscopy is time-consuming and highly operator-dependent. The overall sensitivity of microscopic analysis ranges from 25 to 75%.[29]

Indirect diagnostic tests include serologic testing as well as evaluation of the peripheral-blood count and tests of liver function. Serologic testing requires paired serum samples that are obtained during the acute and convalescent phases of infection; test sensitivity is particularly limited in early infection. Supportive, although less specific, laboratory abnormalities noted during this patient's presentation included elevated aspartate aminotransferase and alanine aminotransferase levels as well as leukopenia, thrombocytopenia, and an elevated C-reactive protein level. Increased aminotransferase levels are observed in approximately 80% of affected patients. Thrombocytopenia and leukopenia occur in 75% and 55% of patients, respectively, and C-reactive protein elevations are seen in more than 90% of patients.[31-33] Thrombocytosis and leukocytosis are highly unlikely to occur in patients with anaplasmosis, unless such abnormalities are caused by an alternative process.[34] Anemia occurs in less than one third of patients,[16] and therefore this finding can help to distinguish anaplasmosis from babesiosis, a parasitic infection transmitted by the same ixodes tick species in a similar geographic distribution. Anemia is expected in cases of babesiosis, and the relatively normal hemoglobin level in this patient was a clue that babesiosis was a less likely diagnosis.

MICROBIOLOGIC DIAGNOSIS

Anaplasma phagocytophilum infection.

DISCUSSION OF MANAGEMENT

Dr. Nussbaum: Antimicrobial therapy is warranted in all patients with a confirmed diagnosis of anaplasmosis. This patient received doxycycline for a total of 10 days. Doxycycline is the preferred treatment for adults with anaplasmosis, and there is no documented resistance to this agent.[30] This observation is based primarily on retrospective data, since data from randomized, controlled trials are lacking. Tetracyclines are bactericidal against anaplasma species and are associated with relatively few toxic effects. In addition, coinfection with *Borrelia burgdorferi*, the causative agent of Lyme disease, which is transmitted by the same ixodes tick species that transmits *A. phagocytophilum*, can occur in up to 12% of patients.[35] The risk of coinfection offers additional rationale for the use of doxycycline, which is active against both bacterial species. Rifamycins have shown in vitro activity against

anaplasma species and can be considered if an alternative to doxycycline is needed.

Doxycycline is typically administered for 7 to 10 days. Persistent infection after treatment is extremely uncommon. Counseling about preventive measures to avoid future tick bites, such as the use of repellents and protective clothing, should be provided. No licensed vaccines are currently available, and previous infection does not provide protective immunity against reinfection.

This patient's fever resolved within 24 hours after the initiation of doxycycline therapy. The abnormalities in hematologic function and liver function resolved within several days. One month after the resolution of anaplasmosis, the patient underwent successful bilateral lung transplantation for his underlying interstitial lung disease.

FINAL DIAGNOSIS

Human granulocytic anaplasmosis.

This case was presented at the Medicine Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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