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65-Year-Old Man With Weight Loss and Dyspnea on Exertion

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A 65-year-old man, a nonsmoker, presented to the hospital in mid-February 2021 with a 30- to 40-lb weight loss over 2 to 3 months and profound fatigue. He also endorsed dyspnea on exertion, a productive cough, and profuse watery diarrhea for several days. Clinical comorbidities included a diagnosis of Mantle cell lymphoma (MCL) in remission after treatment with chemotherapy (cyclophosphamide, vincristine, doxorubicin), autologous stem cell transplant (ASCT) in May 2019 and maintenance rituximab every 8 weeks, hypogammaglobinemia, hypertension on lisinopril, type 2 diabetes mellitus (T2DM) on metformin, and coronary artery disease on aspirin and atorvastatin. He also had COVID-19 pneumonia in November 2020, treated with remdesivir, as well as a C. difficile infection in January, treated with vancomycin. Routine testing during December and January 2020 to 2021 revealed his serum immunoglobulin G level was 429 mg/dL (ref 767 to 1590 mg/dL), and hemoglobin A1c was 6.4% (ref 3.5% to 6.0%). Rituximab was held after October 2020 because of the COVID-19 diagnosis.

Initial testing included a gastroenterologic pathogen panel that was positive for C. difficile and a nasopharyngeal (NP) swab that was negative for severe acute respiratory syndrome coronavirus-2 reverse transcription polymerase chain reaction (SARS CoV-2 rt-PCR). He had been treated with oral vancomycin for 4 days and stopped having diarrhea but continued to have daily fevers, anorexia, dyspnea on exertion, dysphagia, and a nonproductive cough. Vitals revealed temperature of 39.3 °C, heart rate of 144, respiratory rate of 26, blood pressure of 120/80, and pulse oximetry 99% on room air. Physical examination findings consisted of a nontoxic patient with no acute distress; no rashes or skin lesions; grossly intact hearing with patent nares; crackles in the bilateral lung bases with normal inspiratory effort; tachycardia with regular rhythm and no murmurs; soft and nontender abdomen; no lower extremity edema; normal gait without gross motor or sensory neurologic deficits; and intact attention with orientation to person, place, and time. Laboratory findings revealed the following (reference ranges shown parenthetically): hemoglobin, 7.5 g/dL (13.2 to 16.6 g/dL), which had dropped slightly over several days from 9.0 g/dL on admission; white blood cell count 4.7 x 10^9/L (3.4 to 9.6 x 10^9/L); neutrophils, 3.6 X 10^9 (1.56 to 6.45 x 10^9); lymphocytes, 0.65 x 10^9/L (0.95 to 3.07 x 10^9/L); sodium, 137 mmol/L (135 to 145 mmol/L); glucose, 115 mg/dL (70 to 140 mg/dL); and creatinine, 0.74 mg/dL (0.74 to 1.35 mg/dL). Imaging included a computed tomography (CT) of the abdomen and pelvis with intravenous (IV) contrast material, which revealed no acute abnormalities. A CT chest without IV contrast material revealed numerous peribronchovascular and peripheral ground-glass opacities throughout the lungs that had migrated since a positron emission tomography/CT (PET/CT) scan obtained a month earlier for surveillance of MCL. Notably, peribronchovascular and peripheral ground-glass opacities were first noticed 2 1/2 months earlier after the initial COVID-19 diagnosis on CT angiography of the chest.

1. **Given the patient's history and hospital course to date, which is the most likely etiology of his recurrent fever?**
   a) Relapsed MCL
   b) Aspiration pneumonia
   c) Drug-induced fever

See end of article for correct answers to questions.

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d) Persistent C. difficile
e) Atypical or opportunistic lung infection

Relapsed MCL is a consideration as the patient has been experiencing weight loss and fevers, but is less likely in the context of a PET/CT scan in January that did not reveal relapse and lack of lymphadenopathy on CT imaging of the chest, abdomen, and pelvis. Aspiration pneumonia is a consideration in the context of dysphagia but generally infiltrates associated with aspiration reflect dependency and are located either in the lower lobes or the posterior lobes, and some of the patient's symptoms—such as weight loss and anorexia—are not commonly associated with aspiration. The patient's long-term medications (metformin, lisinopril, aspirin, and atorvastatin) are not likely to cause fever; rituximab had been held for months; and although antibiotics commonly cause drug-related fever, oral vancomycin is unlikely to cause fever. Furthermore, drug-related fever is a diagnosis of exclusion, so other possibilities should be ruled out before choosing this diagnosis. Persistent C. difficile infection could cause continued fevers, but the patient has been treated with vancomycin for several days with resolution of diarrhea, making this diagnosis less probable. Because of the patient's history of immunosuppression with rituximab, pulmonary symptoms, and new scattering pulmonary ground-glass opacities on chest CT scan, atypical or opportunistic lung infection is high in the differential diagnosis as a source of his persistent symptoms.

The infectious disease service was consulted, and they believed that an atypical infection was probable, so they recommended additional testing for infection, including a nasopharyngeal respiratory pathogen panel and serum testing for aspergillus, histoplasma, and Blastomyces, the results of which were negative.

2. **Which one of the following is the most appropriate next step for this patient?**
   a) Repeat chest CT scan in 2 days
   b) Bronchoscopy for bronchoalveolar lavage (BAL)
   c) Initiation of therapy with ceftriaxone and azithromycin
   d) Repeat C. difficile stool testing
   e) Wait for results of conservative testing

Repeating a chest CT may reveal interval evolution of the ground-glass opacities, but it will not yield the etiology of an infection. Bronchoalveolar lavage is established as an excellent means of diagnosing opportunistic infections such as *Aspergillus* or *P. carinii* in immunocompromised hosts and increases probability of diagnosing these types of infections compared with noninvasive testing.[1] Our patient has a history of immunosuppression and presented with chronic symptoms, which makes an opportunistic infection more probable. Initiating therapy with ceftriaxone and azithromycin would treat community-acquired pneumonia (CAP) empirically. However, this diagnosis is unlikely in this patient with chronic symptoms, hemodynamic stability, and normal oxygen saturation on room air. It is more appropriate to focus on diagnoses associated with atypical pathogens that cause disease more consistent with his history. Repeating C. difficile stool testing will not yield valuable information because the patient is no longer experiencing diarrhea or other gastrointestinal symptoms, and without symptoms, positive C. difficile stool testing results are not indicative of active infection. Fungal testing can take days to yield results, and serum testing has lower sensitivity than BAL testing; considering that the patient is immunosuppressed and symptomatic, pursuing bronchoscopy is more appropriate.

Infectious disease recommended consulting pulmonology for a bronchoscopy with BAL using an immunocompromised host testing protocol.

3. **Which of the following choices is the most likely diagnosis for this patient?**
   a) Persistent COVID-19 pneumonia
   b) Post COVID-19 syndrome
   c) Subacute invasive pulmonary aspergillosis
   d) Influenza
   e) Legionnaire disease

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This immunosuppressed patient has persistent symptoms of dyspnea on exertion and cough since his COVID-19 pneumonia and has persistent CT imaging findings like his initial findings after being diagnosed with COVID-19 pneumonia. Furthermore, the fact that he has persistent fevers implies active inflammation. There are documented case reports of persistent COVID-19 pneumonia in immunosuppressed patients treated with remdesivir, and some were diagnosed on bronchoscopy after negative nasopharyngeal swab testing for SARS-CoV-2.[2,3] Based on his presentation, medical comorbidities, immunosuppressed status, and imaging findings, persistent COVID-19 pneumonia is the most probable diagnosis.

Post−COVID-19 syndrome consists of the persistent symptoms after COVID-19 infection that are not associated with active viral infection.[4] There is a broad range of reported residual symptoms, but in a prospective study of 277 patients, none experienced fevers as a component of post-COVID syndrome, indicating that this is not the most likely possibility.[4] Subacute invasive pulmonary aspergillosis is more common in immunosuppressed patients but is characterized by chest CT findings of progressive cavitary pulmonary lesions and hyphal invasion throughout the lungs, not migrating ground-glass opacities.[5] Influenza can present broadly, but even in immunocompromised patients, influenza is rarely detectable for longer than 1 month, and considering the patient's known previous COVID-19 infection, influenza is not the most likely diagnosis.[6] Legionnaire disease can be distinguished from other lung infections via its association with hyponatremia, gastrointestinal symptoms, and unilateral pneumonia: all inconsistent with this patient.

Ultimately, the BAL revealed a positive SARS CoV-2 on RT-PCR testing, whereas all other infectious work-up results performed were negative, including testing for fungal infections, legionella, and pneumocystis. His medical team determined that his symptoms were caused by persistent COVID-19 pneumonia. The results of a serum COVID-19 total nucleocapsid antibody test were negative.

4. **Which one of the following is <u>most predisposing</u> to this patient's condition?**
   a) Autologous stem cell transplant
   b) Vincristine treatment
   c) Type 2 diabetes mellitus
   d) Cyclophosphamide treatment
   e) Rituximab treatment

The patient had ASCT in May 2019, more than 1 1/2 years before his original COVID-19 infection. Because bone marrow ablation is necessary before ASCT, patients are at higher risk for infection before and after the procedure. However, over time, the patient's B cells engraft and begin to function normally, and, after 1 year, it is unlikely that a patient would still be experiencing significant immunosuppression as a result of ASCT, although some T-cell dysregulation could persist. Vincristine inhibits microtubule formation and has side effects including neuropathy and ototoxicity but would be unlikely to cause immunosuppression after 2 years. T2DM is known to impair immune function through hyperglycemia, causing suppression of cytokine production, thereby impairing the body's innate immune response to infection.[7] However, the patient's most recent hemoglobin A1c before hospitalization was 6.4%, which is not indicative of prolonged hyperglycemia, and his hospital blood glucose values were not significantly elevated. Cyclophosphamide is an alkylating agent with many side effects, including hemorrhagic cystitis and pulmonary fibrosis, but the patient has no evidence of pulmonary fibrosis on his CT imaging, and it would be unusual for persistent immunosuppression 2 years after stopping therapy.

Rituximab functions by causing apoptosis of B cells, and the patient had been receiving rituximab therapy through October 2020. B cells are a vital component of adaptive humoral immunity, as they are the precursors to plasma cells that produce antibodies against specific antigens. SARS-CoV-2 enters most cells by using its spike

protein to bind with an extracellular receptor called angiotensin-converting enzyme 2 (ACE2).[8] To date, the most effective protective measures against COVID-19 have been the COVID-19 vaccines that use mRNA that encode for COVID-19 components, such as the spike protein, to be created and serve as antigenic targets for the host's adaptive immune system.[8] If a patient is unable to mount an adaptive response with antibodies because of B-cell depletion, it could result in longer lasting SARS-CoV-2 infections with evolving pneumonic infiltrates.

An immune cell subset assessment was conducted after the patient was found to have SARS-CoV-2 positivity on BAL. The patient had reduced numbers of cellular immune subsets in peripheral blood: 69 CD4 T cells/mcL (365 to 1437 cells/mcL), 51 CD8 T cells/mcL (80 to 846 cells/mcL), 30 NK cells (59 to 513 cells/mcL), and 0 CD19 B cells/mcL (45 to 409 cells/mcL). His medical team thought his lack of B and reduced T and NK cells reflected the effect of his previous malignancy and treatments and most prominently implicated his rituximab therapy.

5. **Which one treatment would be most appropriate for this patient?**
   a) Lopinavir
   b) Remdesivir
   c) Hydroxychloroquine
   d) High-titer convalescent plasma
   e) Dexamethasone

Lopinavir is a viral protease inhibitor, but interim results of the World Health Organization Solidarity randomized control trial (RCT) revealed that there is no benefit of lopinavir therapy for mortality or hospitalization duration with COVID-19 infection.[9] Remdesivir inhibits the RNA-dependent RNA polymerase of coronaviruses, and RCTs have revealed mixed results in terms of efficacy. One RCT of 1062 patients, published in October 2020, revealed an improvement in time to recovery of patients treated with remdesivir, whereas the Solidarity RCT revealed no benefit to hospitalization duration or mortality.[9,10] Considering that our patient had remdesivir therapy previously without resolution of infection, it does not represent the best therapeutic option. Hydroxychloroquine is an anti-inflammatory medication with an unknown mechanism of action that has not been shown to have efficacy in treating COVID-19 infection.[9]

Convalescent plasma therapy (CPT) consists of donating plasma from people who have recovered from COVID-19 infection to those who are actively fighting it, thereby providing antibodies against COVID-19 antigens. An RCT published in June 2020 evaluated 189 patients with COVID-19 infection treated with CPT that revealed a reduction in the length of hospitalization as well as decreased need for mechanical ventilation.[11] Furthermore, a study published in November 2020 evaluated the effect of CPT in a population of 17 patients with profound B-cell lymphopenia, which revealed that within 48 hours all but 1 patient experienced improvement.[12] Considering that our patient's B cells were depleted and thus incapable of mounting an effective antibody response against SARS-CoV-2, convalescent plasma from a high-titer donor is the best therapeutic choice.

Dexamethasone is a potent steroid that has been evaluated for clinical efficacy in COVID-19 infection in the RECOVERY RCT, which compared 2104 patients who received dexamethasone therapy with 4321 patients who received supportive care.[13] Results indicate that patients who received dexamethasone had an improved rate of mortality if they required supportive oxygen therapy or mechanical ventilation but did not have benefit if they were on room air.[13] Our patient was on room air and would not likely benefit from dexamethasone.

The patient was treated with 2 treatments of high-titer CPT and given another course of remdesivir therapy. He felt improved shortly after CPT and felt back to baseline at a follow-up appointment 2 months after discharge.

DISCUSSION

COVID-19, an infection caused by SARS-CoV-2, is the most recent species of the

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beta coronavirus family to cause infection in humans.[8] It has transformed life around the world because of its transmissibility and associated morbidity and mortality. SARS-CoV-2 has a crown-shaped appearance similar to other coronaviridae, but differs in that it enters cells primarily by binding to the N-terminal helix of the ACE2 protein and then uses its spike protein to pinch inside.[8] The primary pathology of COVID-19 is within the respiratory tract, with the majority of mortality stemming from acute respiratory distress syndrome.[8]

However, COVID-19 infection is new and has many manifestations that have not yet been well characterized. Our patient presented with features of persistent COVID-19 pneumonia in the context of rituximab-associated immunosuppression. Persistent COVID-19 infection has the potential to affect many people owing to the prevalence of rituximab therapy in addition to other medications and pathologies that cause similar immunosuppression.

Identifying hosts at risk for persistent SARS-CoV-2 infection has implications for diagnosis and treatment. The standard of diagnosis for COVID-19 infection is NP swab, but for an immunocompromised host at risk for persistent SARS-CoV-2 infection, bronchoscopy with BAL may be necessary for diagnosis.[2,3] Furthermore, based on the most accurate data available now, remdesivir, dexamethasone, and CPT all have treatment benefits in COVID-19 in certain settings.[9-11,13] However, both our case and the case series described by Hueso et al. suggest that immunosuppression by rituximab resulting in severe B-cell depletion sets the stage for prolonged COVID-19 pneumonia, and therapy regimens including high-titer CPT enable the best host immune response, leading to viral clearance and clinical recovery for this population.[12]

It is also important to distinguish persistent SARS-CoV-2 infection from other long-term sequelae of COVID-19, including post-acute COVID-19 syndrome, because of the differing management implications. Reports indicate that between 40% and 90% of patients who experience COVID-19 will have lingering persistent symptoms.[4] Baseline clinical characteristics that predispose people to postacute COVID-19 syndrome have not been well defined, but the management of postacute COVID-19 syndrome consists primarily of supportive care, whereas persistent SARS-CoV-2 infection represents actively replicating virus that may respond to therapy.[4] Based on our patient and a case series of 277 patients with postacute COVID-19 syndrome, persistent SARS-CoV-2 infection may be distinguishable by the presence of persistent fevers and a host with depressed humoral immunity.[4]

Recognizing hosts at risk for persistent SARS-CoV-2 infection will enable providers to more rapidly distinguish this condition from other opportunistic infections that endanger immunosuppressed individuals. Patients such as ours—with histories of MCL status post-ASCT and maintenance rituximab therapy—are at risk for many opportunistic pathogens, so recognizing imaging patterns, host features, and symptomatic presentations consistent with persistent COVID-19 pneumonia will facilitate more rapid diagnosis and efficacious treatment.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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CORRECT ANSWERS: 1. e. 2. b. 3. a. 4. e. 5. d.

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