A Case of COVID-19 and *Pneumocystis jirovecii* Coinfection

To the Editor:

Lymphocytopenia has been identified as a common laboratory finding in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, particularly among those with more severe presentations (1); however, there are limited data on which specific lymphocyte populations may be affected or the clinical sequelae. In this report, we describe the case of a woman with hypoxemic respiratory failure found to have coinfection with SARS-CoV-2 and *Pneumocystis jirovecii*, a pathogen commonly seen in patients with defects in T-cell immunity.

An 83-year-old female nonsmoker presented to our hospital on March 12, 2020, with fevers, malaise, headache, dry cough, and dyspnea. She had a history of mild intermittent asthma, managed with an albuterol inhaler as needed, mitral valve prolapse with moderate to severe mitral regurgitation, and mild to moderate ulcerative colitis, which was well controlled on oral budesonide (3 mg daily and being tapered) as well as maintenance-dose sulfasalazine (1,500 mg twice daily). Her symptoms had started approximately 2 weeks prior to presentation, shortly after travel from Florida to Massachusetts, and had failed to improve with courses of azithromycin and amoxicillin-clavulanate. In the emergency department, she had a fever of 39.3°C and oxygen saturation of 86% on room air, which improved to 95% on 5 L/min of supplemental oxygen by nasal cannula. Initial laboratory evaluation revealed leukocytosis and relative lymphocytopenia (absolute lymphocyte count, 1,090 cells/μl) (Table 1). Chest computed tomography was notable for diffuse bilateral ground-glass opacities with patchy bands of atelectasis and small nodular foci of consolidation with a distribution suggestive of a viral pneumonia. Subtle cystic changes were also seen in the affected regions (Figure 1). She was admitted to the medical intensive care unit and placed on strict isolation precautions given concern for community-acquired SARS-CoV-2. She developed worsening tachypnea with a respiratory rate of 40 breaths/min and hypoxia with an oxygen saturation of 80% requiring supplemental oxygen through a nonrebreather mask at a rate of 15 L/min. An arterial blood gas measurement showed a Pa_{O_2} of 63 mm Hg on 15 L/min of supplemental oxygen. She was intubated for hypoxemic respiratory failure and supported on low V_T ventilation according to the Acute Respiratory Distress Syndrome Network

lower V_T protocol. Her Pa_{O_2}/Fi_{O_2} was consistent with moderate acute respiratory distress syndrome.

A broad infectious workup for viral, bacterial, and fungal organisms (Table 1) confirmed the diagnosis of SARS-CoV-2 infection based on positive detection for the presence of SARS-CoV-2 RNA from a nasopharyngeal swab (Nucleocapsid [N]1 target [Cycle threshold (Ct) 31.33]; N2 target [Ct 33.38]; RNase P control [Ct 25.66]), a qualitative test result (positive when Ct <40.00 for N1 and N2 targets) reported by the Massachusetts State Public Health Laboratory, using its Food and Drug Administration Emergency Use Authorization–approved CDC 2019-nCoV Real-Time RT-PCR Diagnostic Panel. In addition, a serum (1,3)-β-D-glucan level was markedly elevated at 305 pg/ml (reference value <80 pg/ml), prompting additional testing for *P. jirovecii* with a qualitative real-time PCR assay from a tracheal aspirate, which was positive (fluorescent value 0.160 at melting temperature of 62.4°C; minimum fluorescent signal intensity for positive test ≥0.020). Notably, she had no apparent clinical characteristics associated with false-positive (1,3)-β-D-glucan measurements, such as exposure to hemodialysis membranes, intravenous immunoglobulin, albumin, gauze packing, or intravenous β-lactam antibiotics. HIV-1/2 antibody/antigen testing was nonreactive. However, a CD4+ T lymphocyte count was low at 291 cells/μl (reference value, 441–2,156 cells/μl), as was the CD4+/CD8+ ratio (1.18; reference value, 1.20–5.30). She was treated with trimethoprim-sulfamethoxazole and successfully extubated on hospital day 7. A follow-up serum (1,3)-β-D-glucan level obtained 1 week after initiating treatment was significantly reduced (90 pg/ml). Moreover, a follow-up CD4+ T lymphocyte count obtained 10 days after initial presentation demonstrated improvement (730 cells/μl).

CD4+ T lymphocytes play a critical role in the immune response against *P. jirovecii*. Classically, when patients with untreated HIV develop severe CD4+ lymphocytopenia (<200 cells/μl), the risk of *Pneumocystis* pneumonia increases significantly (2). In the present case, we hypothesize that SARS-CoV-2 infection led to a state of functional immune suppression related to CD4+ lymphocytopenia, which then predisposed the patient to *P. jirovecii* infection. Although the patient's CD4+ T-cell count was >200 cells/μl, the sample was collected nearly a week into her course after her total lymphocyte count had started to recover. It is also possible that an underlying immune defect predisposed the patient independently to SARS-CoV-2 and *P. jirovecii* infection; however, the patient did not have a known underlying immunodeficiency, nor did she have any classical risk factors for *Pneumocystis* pneumonia, such as malignancy, organ transplantation, or prolonged exposure to systemic corticosteroids. Although patients with inflammatory bowel disease on systemic corticosteroids, biologics, and other immunosuppressants may be at increased risk of *Pneumocystis* pneumonia (3), the overall incidence in ulcerative colitis is low (approximately 8/100,000 person-years) (4) and has not been associated with oral budesonide use (5). Given the high sensitivity of *P. jirovecii* PCR (6), *Pneumocystis* colonization cannot be completely excluded. However, taken together, the highly positive PCR test, significant elevation in (1,3)-β-D-glucan, cystic lesions on chest imaging, progressive hypoxemia in the setting of CD4+ lymphocytopenia, and response to trimethoprim-

Table 1. Clinical Laboratory Results

Measure	Result	Reference
Hematology and chemistry		
Hb, g/dl	8.9	11.5–16.4
Hematocrit, %	27.3	36–48
Leukocytes, $\times 10^3/\mu$l	15.2	4–10
Differential, %		
Neutrophils	89.5	40–70
Lymphocytes	7.2	22–44
Monocytes	2.4	4–11
Eosinophils	0.0	0–8
Basophils	0.2	0–3
Platelets, $\times 10^3/\mu$l	562	150–450
Ferritin, μg/L	54	13–150
Procalcitonin, ng/ml	0.1	0.00–0.08
Lactate dehydrogenase, U/L	348	135–225
Microbiology		
Respiratory culture (tracheal aspirate)	3+ neutrophils, negative Gram stain, and no growth on culture	No growth
Blood culture	No growth	No growth
SARS-CoV-2 (COVID-19 PCR)	Positive	Negative
Influenza A and B PCR	Negative	Negative
Parainfluenza PCR	Negative	Negative
Adenovirus PCR	Negative	Negative
Respiratory syncytial virus PCR	Negative	Negative
Human metapneumovirus PCR	Negative	Negative
Rhinovirus PCR	Negative	Negative
S. pneumoniae urine antigen	Negative	Negative
Legionella urine antigen	Negative	Negative
Histoplasma urine antigen	Negative	Negative
Coccidioides urine antigen	Negative	Negative
Blastomyces urine antigen	Negative	Negative
Cryptococcal antigen	Negative	Negative
Galactomannan antigen	0.08	0–0.49
(1,3)-β-D-glucan, pg/ml	305	<80
Pneumocystis jirovecii PCR	Positive	Negative
Immunology		
CD4$^+$ T lymphocytes (absolute)	291	441–2,156

Definition of abbreviations: COVID-19 = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; *S. pneumoniae* = *Streptococcus pneumoniae*.

sulfamethoxazole therapy are highly supportive of a diagnosis of *Pneumocystis* pneumonia.

Respiratory viral infections, particularly influenza, predispose patients to the development of secondary bacterial infections (7) and invasive fungal infections, including aspergillosis, most notably in immunocompromised patients (8). Although no cases of *Pneumocystis* pneumonia have been reported in patients infected with SARS-CoV-1 or Middle East respiratory syndrome coronavirus, coinfection with *P. jirovecii* has been reported in HIV and hematopoietic stem cell transplant patients with influenza A infection (9, 10). Furthermore, two cases of *Pneumocystis* pneumonia and H1N1 influenza A coinfection have been reported in immunocompetent patients, possibly secondary to influenza-induced CD4$^+$ lymphocytopenia (11).

There is emerging evidence that patients with SARS-CoV-2 are at high risk for coinfection (12), and this case highlights the importance of being vigilant about excluding treatable respiratory pathogens, including *P. jirovecii*. Because COVID-19 and *Pneumocystis* pneumonia may share common clinical features (e.g., bilateral multifocal infiltrates and profound hypoxemia),

coinfection with *P. jirovecii* may not be appreciated in patients with severe SARS-CoV-2 infection. It may therefore be reasonable to consider additional diagnostic testing for *P. jirovecii* in patients with SARS-CoV-2 infection, particularly when there are other clinical characteristics that may support coinfection (e.g., elevated lactate dehydrogenase, cystic findings on chest computed tomography), even in the absence of classical *P. jirovecii* risk factors. Finally, this case extends the potential utility of (1,3)-β-D-glucan testing for diagnosing *Pneumocystis* pneumonia (13) in patients with suspected SARS-CoV-2 infection, which is particularly relevant given concerns about healthcare transmission associated with performing bronchoscopy in these patients. ∎
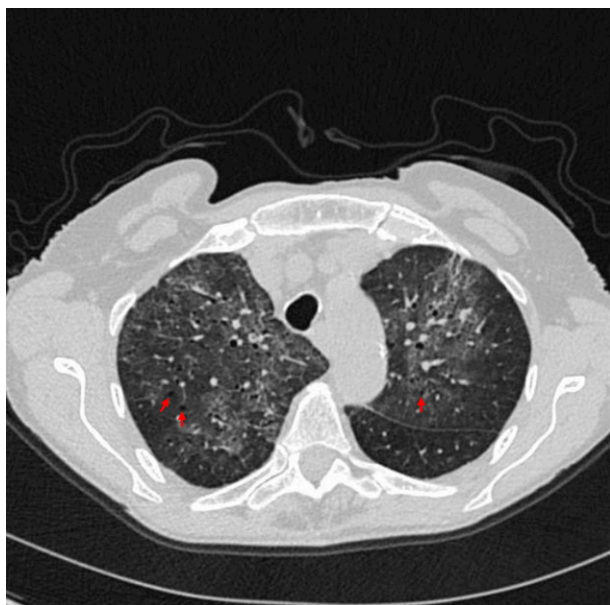
Figure 1. Chest computed tomographic image. Shown is a representative axial image from the patient's chest computed tomography scan. Red arrows indicate cystic changes.

Disease and Laboratory Sciences, for assistance with interpretation of the results of the SARS-CoV-2 real-time RT-PCR assay.

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Right Ventricle–to–Left Ventricle Diameter Ratio Measurement Seems to Have No Role in Low-Risk Patients with Pulmonary Embolism Treated at Home Triaged by Hestia Criteria

To the Editor:

It remains challenging to determine which patients with acute pulmonary embolism (PE) may qualify for outpatient treatment. Current guidelines emphasize the importance of early risk stratification of patients with PE to facilitate assessment of prognosis and guide therapeutic decision making (1–3). There is a continuous debate on whether right ventricular (RV)