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Pneumocystis and Severe Acute Respiratory Syndrome Coronavirus 2 Coinfection: A Case Report and Review of an Emerging Diagnostic Dilemma

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We present a case of a critically ill patient with coronavirus disease 2019 (COVID-19) found to have acquired immune deficiency syndrome and *Pneumocystis jirovecii* pneumonia (PCP). Coronavirus disease 2019 and PCP co-occurrence is increasingly reported and may complicate diagnostic and therapeutic strategies. Patients with severe COVID-19 should be screened for underlying immunocompromise and coinfections should be considered.

Keywords. coinfection; COVID-19; HIV; *Pneumocystis*; SARS-CoV-2.

With mounting global cases of coronavirus disease 2019 (COVID-19), there has been increasing recognition of fungal coinfection complicating COVID-19 care. Although *Aspergillus* spp appears to be the predominant fungal pathogen in persons with COVID-19 pneumonia [1], there are emerging reports of *Pneumocysits jirovecii* pneumonia (PCP) co-occurring with or after COVID-19.

In this study, we present a case of a patient hospitalized with hypoxemic respiratory failure attributed to COVID-19 and was found to have a new diagnosis of acquired immune deficiency syndrome (AIDS) and PCP. We review all published literature to date of co-occurring COVID-19 and PCP.

CASE REPORT

A 36-year-old man with no known past medical history presented to an emergency room complaining of shortness of breath, fever, nausea, and diarrhea for 3 weeks. Additional review of systems was positive for chills, sinus congestion, sore throat, and cough. He denied anosmia and chest pain. He was Hispanic and lived with 2 relatives who were asymptomatic. He worked in construction and reported close contacts with coworkers with similar symptoms.

On admission, his temperature was 38.7°C, heart rate 121 beats per minute, blood pressure 94/59 mmHg, respiratory rate 40 breaths per minute, and oxygen saturation 89% on 15L high flow nasal cannula, improved in prone positioning. He was ill-appearing, in respiratory distress, and without abnormal lung sounds. The white blood cell count was 8600/μL (reference range, 4800 to 10 800); absolute lymphocyte count was 400/μL (reference range, 1200 to 3400); absolute neutrophil count was 7800/μL (reference, 1400 to 6500); C-reactive protein was 197.72 mg/L (reference, <10); ferritin was 1276.1 ng/mL (reference range, 10–300); lactate dehydrogenase was 789 IU/L (reference range, 100–220); and procalcitonin was 1.87 ng/mL (reference, <0.50). A swab for influenza A and B viruses was negative. An oropharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) was positive. Chest radiograph showed diffuse hazy pulmonary opacifications. A contrasted computed tomography angiography of the chest showed diffuse upper and lower lobe ground-glass alveolar airspace disease without pulmonary embolism.

The patient was admitted to intensive care and started on remdesivir, as well as cefepime and vancomycin for possible bacterial pneumonia. Over the next 48 hours he experienced persistent hypoxemia requiring intubation and transfer to our facility. As part of our institutional protocols for patients admitted with COVID-19 at the time of this encounter, routine screening with a fourth-generation human immunodeficiency virus (HIV)-1/2 antigen/antibody test was performed and reactive. Reflex HIV ribonucleic acid testing revealed a viral load of 578 876 copies/mL. His absolute CD4 cell count was <10 cells/μL and 2% of lymphocytes. Due to the patient's critical illness and clinical condition, additional social and medical history was unobtainable, but medical record review did not report a history of HIV and noted no outpatient medications. A new chest radiograph was reported as heterogeneous bilateral lung opacities with scattered air bronchograms (Figure 1), but treating providers felt the opacities were less dense than expected for COVID-19 and for his level of hypoxemia. He continued remdesivir via emergency use authorization, received a transfusion of COVID-19 convalescent plasma, and antibacterial medications were narrowed to ceftriaxone and azithromycin.

Given the patient's prolonged, subacute symptoms and x-ray findings, an evaluation for PCP was undertaken and

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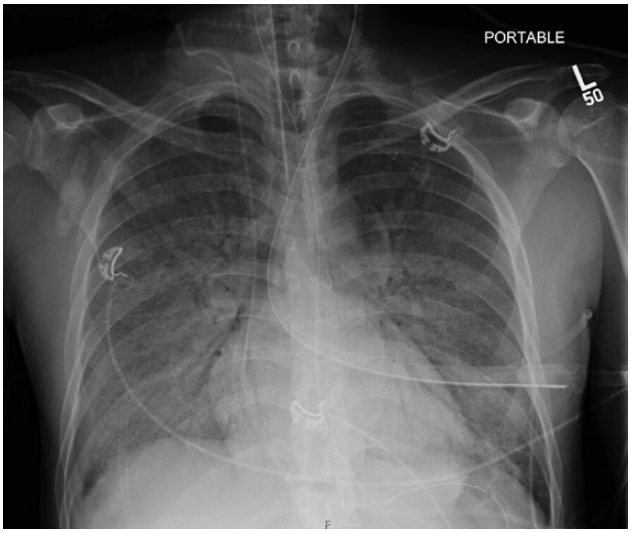

Figure 1. Chest X-ray on transfer to our facility, showing diffuse hazy opacities.

he was started on empiric trimethoprim-sulfamethoxazole and prednisone. A tracheal aspirate acid-fast stain, bacterial culture, and *P jirovecii* direct fluorescent antibody stain (DFA) were all negative. Positive serological studies included (1→3)-β-D-glucan >500 pg/mL as well as a weakly positive serum histoplasma antigen that was below the level of quantification. A QuantiFERON-TB Gold test was indeterminate. Urine histoplasma antigen and blood cultures for bacteria and molds were negative. On hospital day 7, he underwent bronchoscopy with bronchial alveolar lavage that yielded positive *Pneumocystis* DFA and PCR tests, positive SARS-CoV-2 PCR, and bacterial, fungal, and mycobacterial cultures that remain negative to date.

The patient completed a course of remdesivir. He received a 21-day course of trimethoprim-sulfamethoxazole and prednisone for PCP, and he started dolutegravir with combination tenofovir alafenamide/emtricitabine for HIV. His course was complicated by ventilator-associated pneumonia due to *Pseudomonas aeruginosa*, labial ulcer due to herpes simplex virus type 1, persistent hypoxemia, and ongoing fevers. He was evaluated for extracorporeal membrane oxygenation but deemed not to be a candidate due to his prolonged ventilation and his immunocompromised state. He continued to experience refractory hypoxemia despite maximal ventilator settings, paralytic agents, and prone positioning. On hospital day 26, he developed asystolic cardiac arrest and died. No autopsy was performed.

Patient Consent Statement

Consent was unable to be obtained from the patient due to patient being intubated and altered throughout his hospitalization. No family or next of kin was available, and, if they had been, obtaining consent would have risked potentially unwanted disclosure of the patient's HIV status. All identifying details of the patient have been removed in accordance with our institutional policy and Oxford University Press publishing policy. Ethical board approval was not believed to be indicated because this did not involve human subjects research.

Literature Review

A literature search of Medline with the string "[COVID-19 and pneumocystis] or [SARS-COV-2 and pneumocystis] or [COVID-19 and PJP] or [SARS-COV-2 and PJP] or [COVID-19 and PCP] or [SARS-COV-2 and PCP]" was conducted in September 2020. This search yielded 28 results (Supplementary Figure 1). Thirteen articles were case reports, 5 of which were case reports of patients with both COVID-19 and PCP (Table 1). Of these, 3 were also HIV positive. Two cases were in people newly diagnosed with HIV, underscoring the need for HIV testing in individuals hospitalized for COVID-19 who would not be expected to have a severe course of illness. In one case, the patient was diagnosed with COVID-19, treated with tocilizumab and glucocorticoids, and later diagnosed with PCP, raising the possibility that immunomodulatory treatment for COVID-19 contributed to the development of PCP [2]. The other 8 case reports described cases of either PCP or COVID-19 and the challenge in distinguishing between them.

DISCUSSION

This case emphasizes that PCP and COVID-19 can present as co-occurring disease processes and a broad differential should be maintained, especially in immunocompromised patients. *Pneumocystis jirovecii* is an opportunistic fungal pathogen that primarily causes disease in immunocompromised individuals. Although historically associated with advanced HIV, PCP now often impacts persons who are immunosuppressed for other reasons as well, including malignancy [3], organ transplant [4], and those requiring other immunosuppressive drugs, particularly corticosteroids [5]. All 5 previously reported cases of COVID-19 and PCP coinfection identified during our literature review had a documented immunocompromising condition. It is notable that none of the other cases of COVID-19 and PCP died. This may be attributable to extent of immunosuppression in our patient as well as his late presentation to care.

Pneumocystis jirovecii pneumonia and moderate-to-severe COVID-19 share many clinical characteristics, making them difficult to distinguish. Both often present with fever, cough, and hypoxia [6] and can have a wide range of radiographic findings including diffuse ground-glass opacities [7]. The similarities in presentation may be due to similar underlying mechanisms of pathogenicity between the 2 infections and their interaction with pulmonary surfactant [8]. Given these similar findings, there is a growing recognition of PCP as a COVID-19 mimicker in severely ill patients [9].

Table 1. Case Reports of PCP and COVID-19 Coinfection

Reference	Age/Sex	Comorbidities	Immune Suppression	Method of PCP Diagnosis	Clinical Course	Outcome
Cai et al [2]	72/Female	Rheumatoid arthritis	HCQ, leflunomide	High-throughput sequencing	Diagnosed with COVID-19, treated with steroids and toculizumab, initially improved then worsened over several weeks. Repeat COVID-19 RNA PCR negative, but high-throughput testing positive for *Aspergillus fumigatus* and PCP. Treated with steroids and antimicrobials.	Recovered, discharged from hospital
Bhat et al [24]	25/Male	HIV	HIV, new diagnosis, CD4 32 cell/μL on admission. HIV RNA not reported	PCP antigen testing on BAL	Intubated, treated with remdesivir, TMP/SMX, and steroids.	Extubated, discharged from hospital
Menon, et al [25]	83/Female	Ulcerative colitis, asthma, mitral valve prolapse	Budesonide, sulfasalazine	1,3-β-D-glucan 305 pg/mL, positive PCP PCR from tracheal aspirate	Intubated, treated with TMP/SMX	Extubated, discharged
Mang et al [26]	52/Male	HIV	HIV, new diagnosis, CD4 12 cells/μL on admission, HIV RNA 360 000 copies/mL	BAL fluid positive for PCP, method of detection not specified	Intubated, bronchial aspirate positive for multiple bacteria. Blood cultures positive for vancomycin-resistant *Enterococcus faecium* and *Staph*ylococcus *epidermidis*. Blood PCR positive for CMV infection. Treated with linezolid, meropenem, TMP/SMX, prednisone, ganciclovir.	Extubated, improving but remained hospitalized at time of publication
Coleman et al [9]	55/Male	HIV, asthma	Well controlled HIV, last CD4 422 cells/μL before admission, HIV RNA <20 copies/mL	Induced sputum positive for PCP by PCR	Diagnosed first with PCP, then with COVID-19 on hospital day 3. Treated with TMP/SMX, steroids.	Recovered and discharged
Current case	36/Male	HIV	HIV, new diagnosis, CD4 <10 cells/μL, HIV RNA 578 000 copies/mL	BAL positive for PCP DFA and PCR testing. Serum 1,3-β-D-glucan >500 pg/mL	Diagnosed with COVID-19, intubated, started on remdesivir and antibiotics. Transferred to our hospital and diagnosed with HIV and PCP. Started on TMP/SMX and steroids, completed 5 days of remdesivir, and received COVID-19 convalescent plasma. Developed *Pseudomonas aeruginosa* VAP.	Cardiac arrest and death

Abbreviations: BAL, bronchoalveolar lavage; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; DFA, direct fluorescent antibody stain; HCQ, hydroxychloroquine; HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia; PCR, polymerase chain reaction; RNA, ribonucleic acid; TMP/SMX, trimethoprim/sulfamethoxazole; VAP, ventilator-associated pneumonia.

In the case of our patient, the 3-week symptom duration before presentation was atypically long for COVID-19. For comparison, a large series of patients with COVID-19 alone reported a median 7 days of symptoms preceding hospitalization [10]. Coinfection with both SARS-CoV-2 and *P jirovecii* can lead to diagnostic dilemmas. Although COVID-19 testing is now readily available via nasopharyngeal swabs with fast turnaround time by most hospital laboratories [11, 12], PCP is less easy to diagnose. Bronchial alveolar lavage fluid remains the gold standard for PCP diagnosis due higher sensitivity [13], but performing a bronchoscopy to obtain a bronchial alveolar lavage specimen is an invasive procedure that cannot always be readily performed in severely hypoxic patients, and it requires additional procedural caution due to the risk of aerosolization of SARS-CoV-2. Although the serum fungal marker 1,3-β-D-glucan can be used to aid in the diagnosis of PCP [14], additional testing and a compatible clinical presentation are required to confirm the diagnosis. Colonization with *P jirovecii* is common in patients with COVID-19, a finding that may further impact challenging diagnostic scenarios. A recent study of 108 critically ill patients with COVID-19 found that 9% had a positive PCR test for *P jirovecii* on bronchial alveolar lavage [15]. The use of corticosteroids for severe COVID-19 may further delay diagnosis of co-occurring PCP, because such patients may theoretically experience transient improvement, given the known beneficial effect of steroids in severe PCP. As targeted immunomodulators are studied in COVID-19, physicians should be mindful of the risk they may pose for PCP. For example, the anti-interleukin-6 monoclonal antibody tocilizumab, which was pursued as a potentially promising therapy for COVID-19, has been associated with PCP in the treatment of rheumatoid arthritis (0.28 events per 100 patient-years) [16].

Finally, this case of COVID-19 and AIDS in a Latinx male highlights the disparities intertwined with both COVID-19 and HIV in the United States. Coronavirus disease 2019 has disproportionately affected the Latinx and black communities in the United States [17]— populations that experience a greater incidence and prevalence of HIV, have a high rate of progression to AIDS, and encounter barriers to HIV testing and care [18–21]. The HIV testing efforts and the continuity of care among these vulnerable populations may be disrupted as healthcare resources are shifted toward the pandemic and traditional models of healthcare delivery are redesigned [22, 23]. However, the pandemic also presents new opportunities to engage patients in HIV screening and other preventive care as they seek COVID-19 testing or treatment. Incorporating HIV screening of all patients admitted for COVID-19 into institutional protocols is a sensible approach that would benefit individual patients and impact public health disparities.

CONCLUSIONS

In summary, there is increasing recognition of PCP co-occurring with or succeeding severe COVID-19, primarily in immunocompromised individuals. Diagnostic uncertainty and anchoring biases can potentially delay diagnosis due to substantial overlap in the clinical presentation. Providers caring for patients with severe COVID-19 should retain a broad differential diagnosis if the clinical syndrome is atypical for COVID-19 or in patients with immunocompromising conditions. It is sensible to consider routine testing of HIV in all patients admitted with COVID-19 as a means of mitigating this diagnostic dilemma and benefitting our public health efforts.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Hoenigl M. Invasive fungal disease complicating COVID-19: when it rains it pours. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa1342.
2. Cai S, Sun W, Li M, Dong L. A complex COVID-19 case with rheumatoid arthritis treated with tocilizumab. Clin Rheumatol **2020**; 39:2797–802.
3. Cooley L, Dendle C, Wolf J, et al. Consensus guidelines for diagnosis, prophylaxis and management of *Pneumocystis jirovecii* pneumonia in patients with haematological and solid malignancies, 2014. Intern Med J **2014**; 44:1350–63.
4. Brakemeier S, Pfau A, Zukunft B, et al. Prophylaxis and treatment of *Pneumocystis jirovecii* pneumonia after solid organ transplantation. Pharmacol Res **2018**; 134:61–7.
5. Chew LC, Maceda-Galang LM, Tan YK, Chakraborty B, Thumboo J. *Pneumocystis jirovecii* pneumonia in patients with autoimmune disease on high-dose glucocorticoid. J Clin Rheumatol. **2015**; 21:72–5.
6. Parker A, Shaw J, Karamchand S, et al. HIV and SARS-CoV-2 co-infection: the diagnostic challenges of dual pandemics. S Afr Med J **2020**; 110:473–5.
7. Hanfi SH, Lalani TK, Saghir A, et al. COVID-19 and its mimics: what the radiologist needs to know. J Thorac Imaging **2020**; 36:W1–W10.
8. Kanduc D, Shoenfeld Y. On the molecular determinants of the SARS-CoV-2 attack. Clin Immunol **2020**; 215:108426.
9. Coleman H, Snell LB, Simons R, et al. Coronavirus disease 2019 and *Pneumocystis jirovecii* pneumonia: a diagnostic dilemma in HIV. AIDS **2020**; 34:1258–60.
10. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA **2020**; 323:1061–9.
11. Patel R, Babady E, Theel ES, et al. Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: value of diagnostic testing for SARS–CoV-2/COVID-19. mBio **2020**; 11:e00722–20.
12. Younes N, Al-Sadeq DW, AL-Jighefee H, et al. Challenges in laboratory diagnosis of the novel coronavirus SARS-CoV-2. Viruses **2020**; 12:582.
13. Masur H, Brooks JT, Benson CA, et al.; National Institutes of Health; Centers for Disease Control and Prevention; HIV Medicine Association of the Infectious Diseases Society of America. Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: updated guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis **2014**; 58:1308–11.
14. Hammarström H, Grankvist A, Broman I, et al. Serum-based diagnosis of *Pneumocystis* pneumonia by detection of *Pneumocystis jirovecii* DNA and 1,3-β-D-glucan in HIV-infected patients: a retrospective case control study. BMC Infect Dis **2019**; 19:658.
15. Alanio A, Dellière S, Voicu S, et al. The presence of *Pneumocystis jirovecii* in critically ill patients with COVID-19. J Infect **2020**. doi:10.1016/j.jinf.2020.10.034.

16. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. Ann Rheum Dis **2011**; 70:2148–51.
17. Centers for Disease Control and Prevention. Communities, Schools, Workplaces, & Events. Available at: https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/race-ethnicity.html. Accessed 1 December 2020.
18. Levison JH, Levinson JK, Alegría M. A critical review and commentary on the challenges in engaging HIV-infected Latinos in the continuum of HIV care. AIDS Behav **2018**; 22:2500–12.
19. Hall HI, Byers RH, Ling Q, Espinoza L. Racial/ethnic and age disparities in HIV prevalence and disease progression among men who have sex with men in the United States. Am J Public Health **2007**; 97:1060–6.
20. Levy ME, Wilton L, Phillips G 2nd, et al. Understanding structural barriers to accessing HIV testing and prevention services among black men who have sex with men (BMSM) in the United States. AIDS Behav **2014**; 18: 972–96.
21. Centers for Disease Control and Prevention. HIV Surveillance Reports. Available at: https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed 1 December 2020.
22. Jiang H, Zhou Y, Tang W. Maintaining HIV care during the COVID-19 pandemic. Lancet HIV **2020**; 7:e308–9.
23. Chenneville T, Gabbidon K, Hanson P, Holyfield C. The impact of COVID-19 on HIV treatment and research: a call to action. Int J Environ Res Public Health **2020**; 17:4548.
24. Bhat P, Noval M, Doub JB, Heil E. Concurrent COVID-19 and *Pneumocystis jirovecii* pneumonia in a severely immunocompromised 25-year-old patient. Int J Infect Dis **2020**; 99:119–21.
25. Menon AA, Berg DD, Brea EJ, et al. A case of COVID-19 and *Pneumocystis jirovecii* coinfection. Am J Respir Crit Care Med **2020**; 202:136–8.
26. Mang S, Kaddu-Mulindwa D, Metz C, et al. *Pneumocystis jirovecii* pneumonia and severe acute respiratory syndrome coronavirus 2 coinfection in a patient with newly diagnosed HIV-1 infection. Clin Infect Dis **2020**. doi:10.1093/cid/ciaa906.