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CASE REPORT

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COVID-19: Prolonged viral shedding in an HIV patient with literature review of risk factors for prolonged viral shedding and its implications for isolation strategies

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Abstract

Our work highlights patients at risk of prolonged viral shedding in COVID-19 and its implications for isolation strategies and explores possible solution by PCR-CT value testing (cycle threshold value). We also review the impact of HIV on COVID-19.

KEYWORDS

COVID-19, CT value, HIV, immunosuppression, PCR test, SARS-CoV-2

1 | BACKGROUND

We present prolonged viral shedding in an immunocompromised HIV patient with a literature review of risk factors for prolonged viral shedding and its implications for isolation strategies. We explore the role of PCR-CT-value (cycle threshold) as an instrument for guiding isolation policies and the impact of HIV on COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has presented health organizations across the world, with significant challenges in planning infection control strategies to contain the ongoing pandemic.[1] Asymptomatic infections and persistent viral shedding after clinical recovery poses a dilemma in containing the spread of the virus.[2] We present a case of COVID-19 coinfection in an immunocompromised HIV patient with the longest period of prolonged viral shedding reported to date. Evidence base in immunocompromised HIV cases and COVID-19 coinfection is limited to observational case reports or series only. We discuss the impact of HIV on the course of COVID-19 and the risk factors of prolonged viral shedding and its relation to infectivity.

2 | CASE REPORT

A 28 years old Kenyan gentleman presented to the emergency department with fever, dry cough, and generalized body aches of 5 days duration. There was no associated shortness of breath, hemoptysis, or chest pain. He was a current smoker and worked as a laborer on a construction site. Systematic review did not yield any other symptoms, and there were no known comorbidities or any significant family history of note.

On examination, he appeared unwell with a respiratory rate of 36 breaths/min, heart rate of 140 beats/min, and a

blood pressure of 147/98 mm (Hg). On admission, his oxygen saturations were 93% on air, and he required 4 liters of oxygen soon after admission to maintain saturations of 98%. A chest X-ray showed bilateral lower zone infiltrates, radiologically compatible with COVID-19 pneumonia. This was confirmed with real-time reverse transcription polymerase chain reaction (rRT-PCR) testing positive for COVID-19. He was started on treatment as per the local guidelines, at the time for severe COVID-19 pneumonia, on ceftriaxone, azithromycin, and hydroxychloroquine. By day 7, he had come off oxygen but continued to spike temperatures. His blood work showed leucopenia, lymphopenia (Lowest $0.32 \times 10^3/\mu L$), a raised D-Dimer, and a high CRP (up to 192) with a normal Procalcitonin. His Interleukin-6, which is considered to be a marker for cytokine inflammatory storm in COVID-19, was within normal limits at 49 pg/mL.

On day 8, he developed chest pain and an ECG showed acute anterior wall myocardial infarction. He successfully underwent primary PCI to LAD. This was thoroughly investigated and was thought to be a thrombotic complication of COVID-19.

His temperature spikes (>38°C) continued, and a full septic screen including blood, urine, and sputum for general microbiology and AFBs was negative. Computerized tomography (CT) chest revealed diffuse mosaic attenuation in both lung fields with multiple patchy areas of ground glass changes and multifocal segmental consolidation in keeping with COVID-19 infection (Figure 1). CT abdomen and pelvis were unremarkable. As part of his investigation, a Human immunodeficiency virus (HIV) PCR was also sent with his consent. His antimicrobial therapy was switched to Piperacillin/tazobactam and teicoplanin, and consequently over the next week, he came off oxygen and CRP (down to 16) and temperature spikes settled.

His HIV PCR reported back as positive. Further blood work up revealed ongoing lymphopenia with a remarkably reduced CD4 T-cell count of 3.0 only. In light of HIV with a reduced CD4 count and ground glass changes on the CT chest (Figure 1), cotrimoxazole was started for suspected Pneumocystis jirovecii pneumonia (PJP). Cotrimoxazole, a week later, was switched to clindamycin and primaquine for 21 days. His chest X-ray at this point showed clearing of the subtle ground glass changes. He was later started on antiretroviral therapy (ART) for HIV, which included a combination of Bictegravir, Emtricitabine, and Tenofovir with a follow-up in HIV clinic planned on discharge.

Our hospital has facilities to check for both COVID-19 rRT-PCR and rRT-PCR CT value (real-time polymerase chain reaction cycle threshold value). An rRT-PCR CT value of below 30 (reference range as per our lab) in our hospital indicates ongoing COVID-19 infectiousness.

Despite clinical recovery and ART, his COVID-19 PCR test continued to be positive with an average rRT-PCR CT value <30, thought to be secondary to his immunosuppression. He was transferred to a COVID-19 positive quarantine facility where he stayed until his rRT-PCR was negative and the CT value reached 30 (noninfectious). He remained PCR positive with CT values less than 30 (infectious) for a total period of 85 days. The rRT-PCR CT value started to improve two weeks after commencing ART reaching a value of 30, considered as noninfectious after a total of 6 weeks of ART. During this period, his CD4 count gradually improved to 42.

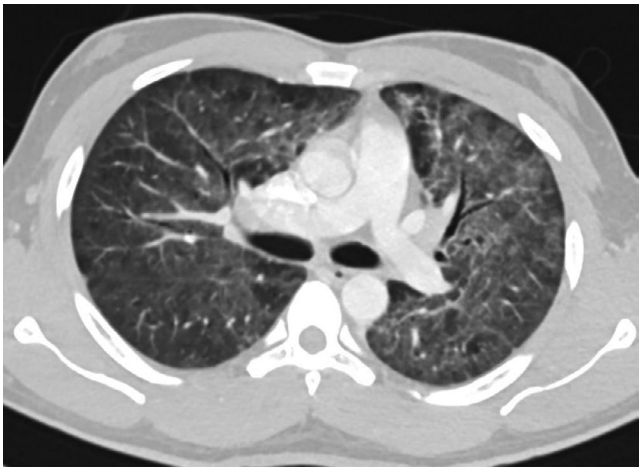

FIGURE 1 CT Chest shows bilateral ground glass changes

3 | DISCUSSION

We present a unique case of significantly prolonged viral shedding (85 days) in a HIV positive patient with acquired immunodeficiency syndrome (AIDS). The patient had a protracted and severe course of COVID-19 but without fatal pneumonia. Our discussion involves three aspects including risk factors for prolonged viral shedding, infectivity, and infection control strategies and the impact of HIV on the course of COVID-19.

3.1 | Risk factors for prolonged viral shedding

Prolonged viral shedding is not an uncommon phenomenon in COVID-19. To the best of our knowledge, our case represents the longest viral shedding period reported in COVID-19. Many studies have looked into it reporting a median duration ranging from 11 to 31 days, with the longest period of up to 55 days.[3] It is well known that viral shedding in COVID-19 may be prolonged in cases of immunosuppression, as in our case.[3,4] Corsini et al shows that patients with a solid organ transplant, active hematological malignancy, receiving chemotherapy, corticosteroids, or immunomodulators may also have a period of prolonged viral RNA shedding and

detection.[3] Similar studies in COVID-19 have described various other factors associated with prolonged viral shedding like male sex, delayed admission, mechanical ventilation, severity of illness, severe or critical disease, corticosteroid therapy, and pyrexia.[3–6] We summarize these risk factors in Table 1.

3.2 | Viral Shedding and the Infectivity dilemma

It is known that viral RNA shedding can persist beyond infectivity.[7,8] The prolonged viral shedding may pose a challenge, for many patients, in terms of infection prevention leading to an unnecessarily extended quarantine, affecting their physical and mental well-being and access to health care.[7,8]

Viral RNA shedding as determined by rRT-PCR test may not be a reliable surrogate marker for determining the infectious risk of COVID-19 patients as the viral RNA detected could either be from nonviable virus (noncontagious) or from viable replicating virus (infectiousness).[3,8] This limitation of rRT-PCR test has significant implications in cases of prolonged viral shedding, resulting in their quarantine for a longer duration of time then possibly necessary due to persistent positivity of rRT-PCR test.

Cycle threshold (CT) value of rRT-PCR, however, appears to be a better marker of infectivity (as defined by viral growth in cell culture) than rRT-PCR alone and hence may prove more valuable in guiding isolation decisions in instances of prolonged viral shedding.[7–9] CT value refers to the number of cycles in an rRT-PCR assay needed to amplify viral RNA to reach a detectable level. The CT value can thus indicate the relative viral RNA load in a specimen with lower CT values reflective of higher viral loads and thus infectivity.[7,9] A study by Bullard et al assessed the correlation of the rRT PCR CT values, with the growth of SARS-CoV-2 in cell cultures. In their study, a rRT PCR CT value of >24 showed a strong correlation with reduced recovery of SARS-CoV-2 in cell cultures depicting reduced infectivity.[7] A study by La Scola et al also showed a similar significant relationship between viral RNA load (CT value) and culture positivity.[9]

Although the mortality caused by COVID-19 is lower than that of severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), the infectivity and transmissibility of the virus is higher.[10,11] To curb and limit the transmission of SARS-CoV-2, diagnostic testing, isolation of positive cases, and contact tracing are extremely important.[8] Our case report is unique as it not only represents the longest viral shedding period, determined by rRT-PCR positivity but also a prolonged period of infectivity as determined by the CT value. Quarantine strategy in our case was based on both the rRT-PCR positivity and its CT values.

3.3 | Course of COVID-19 coinfection in HIV with Immunosuppression

Although the jury is still out, it has been hypothesized that immunosuppression in COVID-19 could delay viral clearance and prolong the course of the disease and may help to avoid fatal pneumonia and severe COVID-19 by blunting a hyperimmune or intense cytokine inflammatory response.[12,13] Our scenario relates to this hypothesis with a prolonged disease course, viral shedding but without fatal pneumonia. Although the European AIDS clinical society suggests based on limited evidence that the disease course of COVID-19 coinfection is similar in both non-HIV and HIV infected patients, it is worth noting that most of the studies on COVID-19 coinfection in HIV mostly include patients with well controlled HIV who are on antiretroviral therapy with a high CD4 T-cell count and suppressed HIV-RNA levels[14] (Table 2).

Kanwugu et al in his review show a strong association of HIV with immunosuppression (CD4 count <200 or ≥200 cells per μL) to an increased severity of COVID-19 (P = .005) but not clinical outcome (P = .275). A binary regression analysis of their data shows that CD4 count <200 cells per μL increases the risk of progression to severe COVID-19

TABLE 1 Summaries various studies looking at prolonged viral shedding in SARS-CoV2 and risk factors associated with prolonged viral shedding

Study	Sample size	Median duration of viral shedding	Risk factors for prolonged viral Shedding
Sun J, et al[5] Wuhan, China	49	15	Possibly severity of illness
Kaijin Xu, et al[6] Wuhan, China	113	17	Male sex, delayed admission, mechanical ventilation
Corsini C C, et al[3] Mayo Clinic, USA	251	23	Immunosuppression, asthma
Tong-Zeng Li, et al[4] Beijing, China	101	11	Disease severity, corticosteroid therapy, fever >38.5°C
Yan D, et al[7] Hubei, China	120	19	Older age, lack of lopinavir/ritonavir treatment

TABLE 2 Summary of salient large observational studies (case series) on HIV in COVID-19

Study	Sample size	Median CD4 Counts	Outcome/Comments
Cristina et al[19] Italy	47	636	Risk of severe disease or death similar to non-HIV COVID-19 cases
Härteret al.[20] Germany	33	670	No excess morbidity & mortality among symptomatic COVID-19 with HIV and viral suppression on ART
Noga et al[21] USA	31	396	Similar clinical characteristics/outcomes with other hospitalized cohorts Comments All patients were virologically suppressed on ART
Vizcarra et al[16] Spain	51	565	Similar clinical, laboratory, radiographical features as non-HIV COVID-19 Comments Lower CD4 counts may affect disease severity and viral kinetics Median viral shedding 68% had for 18 day and 32% had >40 days
Okoh et al[22] USA	27	551	Similar in presentation to non-HIV COVID-19 cases Comments All had well-controlled HIV evidenced by elevated CD4 count levels and low viral loads

by almost 5.[15] Vizcarra et al in his case series of 51 also show that those with a low CD4 T-cell count may have severe disease and prolonged viral shedding.[16] Kanwugu et al also show that there is no evidence that viral suppression and being on ART has any meaningful impact on either severity of COVID-19 or clinical outcome. This is contrary to earlier studies on coinfection suggesting that HIV patients who are compliant to ART and have achieved viral suppression are less likely to progress to severe/complicated COVID-19.[17,18]

It is fair to say that the evidence base on COVID-19 in HIV is limited by the retrospective observational designs and small sample sizes of the studies, and hence, it is difficult to draw a definitive conclusion based on them. We summarize some larger HIV/AIDS observational studies in Table 2.

4 | CONCLUSION

Our case report highlights the impact of HIV/AIDS on the course of COVID-19, prolonged viral shedding, and its implications for patients and infection control. Definitive data remain sparse when it comes to COVID-19 coinfection with HIV, especially in those with immune suppression and a low CD-4 cell count of <200 cells/μL. The outcomes of COVID-19 coinfection in HIV therefore remain inconclusive, and further research is needed to clarify the impact of HIV related immunosuppression and outcomes in COVID-19. Furthermore, rRT-PCR CT values may be a better tool to guide quarantine decisions in cases of prolonged viral shedding; however, more research is needed to validate the use of CT values in guiding quarantine during the current pandemic. We would suggest that an attempt should be made to determine the CT value at least, particularly in patients at high risk of prolonged viral shedding like immunosuppressed patients to avoid a prolonged and unnecessary isolation period for them and to reduce the burden on already strained healthcare services.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Muhammad Yousaf: involved in conception, design, manuscript writing, revision, and final approval. Mansoor Hameed: involved in design, flow, data acquisition, manuscript writing, revision, and final approval. Hussam Alsoub: contributed to HIV discussion, data acquisition, revision, and final approval. Mohamad Khatib: involved in final approval and review Wasim Jamal: involved in review, editing, and final approval. Mushtaq Ahmad: contributed to revision and final approval.

ETHICAL APPROVAL

The study was approved by the Institutional Review Board of Hamad Medical Corporation (MRC-04-20-914).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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