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
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.

Key words / MeSH words
Covid-19, SARS-CoV2, HIV, Immunosuppression, PCR test, CT value

Key Clinical Message
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.

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) 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.

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 co-morbidities 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 $0.32x10^3$/ul), 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 49pg/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 (>38C) 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 (Image 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 cells count of 3.0 only. In light of HIV with a reduced CD4 count and ground glass changes on the CT chest (Image 1), co-trimoxazole was started for suspected Pneumocystis jirovecii pneumonia (PJP). Co-trimoxazole, 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 (non-infectious). 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 non-infectious after a total of 6 weeks of ART. During this period his CD4 count gradually improved to 42.

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.

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, an active hematological malignancy and those receiving chemotherapy, corticosteroids or immunomodulators etc. 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 etc. [3,4,5,6]. We summarize these risk factors in table 1.

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 healthcare [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 non-viable virus (non-contagious) 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 [7,8,9]. 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]. To curb and limit the transmission of SARS CoV-2, diagnostic testing, isolation of positive cases and contact tracing is 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.

Course of Covid-19 co-infection in HIV with Immunosuppression

Although the jury is still not out, it has been hypothesised 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 [11,12]. 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 co-infection is similar in both Non-HIV and HIV infected patients, It is worth noting that most of the studies on Covid-19 co-infection 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 [13, Table 2].

Kanwugu et al in his review shows 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= 0.275). A binary regression analysis of their data shows that CD4 count <200 cells per µL increases the risk of progression to severe Covid-19 by almost 5 [14]. Vizcarra et al in his case series of 51 also shows that those with a low CD4 T cell count may have severe disease and prolonged viral shedding [15]. Kanwugu et al also shows 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 co-infection suggesting that HIV patients who are compliant to ART and have achieved viral suppression are less likely to progress to severe/complicated Covid-19 [16,17].

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 summarise some larger HIV/AIDS observational studies in Table 2.

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 remains sparse when it comes to Covid-19 co-infection with HIV, especially in those with immune suppression and a low CD-4 cell count of<200 cells/µL. The outcomes of Covid-19 co-infection in HIV therefore remains 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.

AUTHORSHIP CONTRIBUTIONS

1. **Muhammad Yousaf:** Conception, design, manuscript writing, revision and final approval
2. **Mansoor Hameed:** Design, flow, data acquisition, manuscript writing, revision and final approval
3. **Hussam Alsoub:** Contributed to HIV discussion, data acquisition, revision and final approval
4. **Mohamad Khatib:** Final approval and review
5. **Wasim Jamal:** Review, editing and final approval
6. **Mushtaq Ahmad:** Contributed to revision and final approval

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1. **Image 1:** CT Chest shows bilateral ground glass changes
2. **Table 1**: Summaries various studies looking at prolonged viral shedding in SARS-CoV2 and risk factors associated with prolonged viral shedding.
3. **Table 2**: Summary of salient large observational studies (case series) on HIV in Covid-19

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