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Commentary

Host tolerance contributes to persistent viral shedding in COVID-19

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Host resistance and host tolerance are two main mechanisms by which the host responds to the infection. Host resistance refers to the ability of the host to eradicate the infection from the body by employing innate and adaptive immunity. In contrast, the host tolerance refers to the ability of the host to withstand the presence of pathogens without mounting an immune response or with a minimal immune response that is not detrimental to the host tissue [1]. Currently, it is unclear how these mechanisms play roles during current coronavirus disease 2019 (COVID-19).

COVID-19 manifestations vary from asymptomatic or very mild disease to severe disease that can lead to death [2,3]. It remains unclear how host resistance and host tolerance mechanisms contribute to the disease severity in COVID-19. Host inflammatory response including those mediated by antiviral interferons, are important contributors of host tolerance by promoting the viral clearance, but also have potential to contribute to the pathology. Interestingly, reports are emerging where patients continue to shed virus for prolonged periods. Currently, it is not clear whether failure to mount strong resistance or increased host tolerance contribute to the viral persistence.

In this report, we show clinical characteristics of three patients with persistent viral presence for at least 50 days (Timeline given in Fig. 1). All three patients were in their 50 s or early 60 s and were admitted to the PLA general hospital in Beijing, China and had confirmed COVID-19 measured by viral qPCR of throat swabs. The viral quantitative PCR was performed either at the China Center for Disease Control or in the hospital laboratory using Multiple Real-Time PCR Kit for Detection of SARS-CoV-2 (XABT, Beijing Applied Biological Technologies Co. Ltd). The lab test results showed that various parameters like blood WBC counts, CRP, IL-6, D-Dimer, CD4 T cells, CD8 T cells are in the normal range. These patients were treated with IFN-α together with lopinavir/ritonavir and arbidol.

Patient 1 is a 52-year-old female who was tested for possible SARS-CoV-2 infection without any symptom due to her close contact with a known COVID-19 patient. She did not show any disease symptom during her stay to the hospital (quarantine) for 56 days. Two lobes of her lung (lower lobes of left and right lung) had signs of pathology as observed in the chest CT. Ground glass opacity (GGO) was observed in these CT scans, which resolved when second CT was obtained at 26 days post hospital admission. Her viral persistence was at least for 54 days from the symptom onset as measured by qPCR of throat swabs and sputum. The patient reported a history of skin rash or allergy for 40 years with intermittent drug treatment (details are not available). The patient also has a 12-year history of hypertension and was being treated with telmisartan, amlodipine and bisoprolol fumarate. The person also has a 1-year history of diabetes and is on metformin therapy for one year; however, the blood glucose control remained unknown.

Patient 2 is a 62-year-old female with a history of occasional elevated blood pressure but was not on any medication for hypertension. The patient had her gall bladder excised and has type 2 diabetes but was not on any medications but was maintaining a healthy diet and lifestyle. The patient had a fever (one day) and cough (18 days) with the involvement of three lobes of her lung observed in chest CT which showed presence of GGO. The CT scan show resolution of GGO when CT scan was performed at 32-day post admission. The viral persistence was observed for 51 days in this patient.

Our third patient is a 58-year-old male with a history of gout. The patient did not receive any therapy for gout. The patient was also diagnosed with hypertension during his hospital stay for COVID-19 and was treated with amlodipine besylate. The patient had a fever for two days with no other symptoms. However, imaging analysis showed the presence of pathology in all five lobes of his lung. The patient had a persistent viral presence for 51 days. GGO and infiltrating shadows in both lungs were resolved remarkably when checked after 51 days post hospital admission.

Surprisingly, all three patients had underlying comorbidities, including hypertension and diabetes, both of which have been a well-established risk factor for disease severity and death due to

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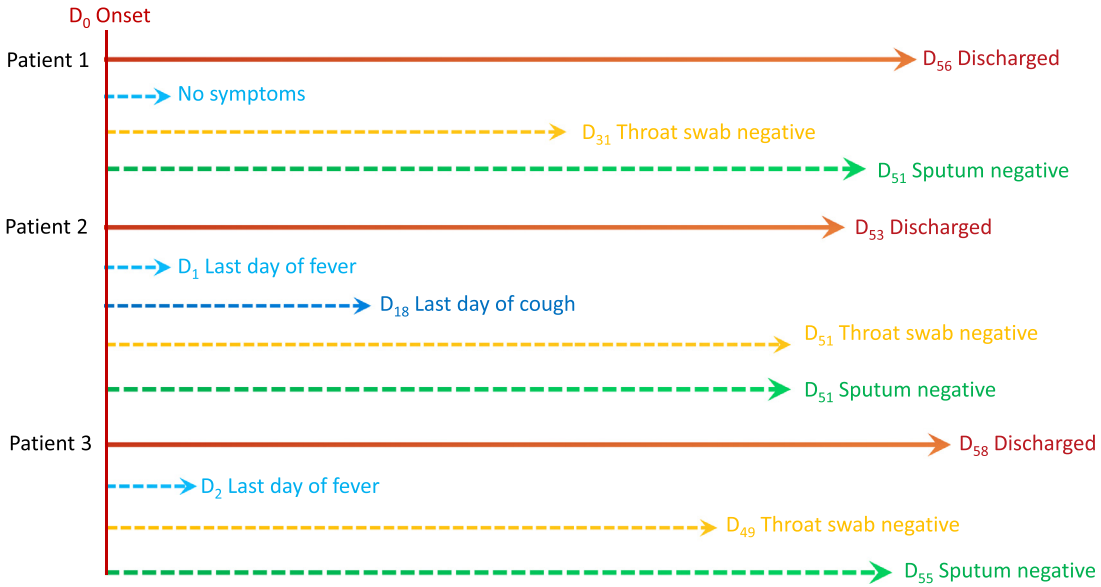

Fig. 1. The timeline of three patients are shown in Fig. 1. The continuous red line denotes the duration of the hospital stays for each patient. The dotted blue line represents the duration of symptoms indicated for each symptom. The broken orange line indicates the period of viral positivity measured by throat swab while the green line denotes the length of viral positivity measured by sputum samples. D0 represents the day of the symptom onset in patient 2 and 3 while the day of first positive test in patient 1.

COVID-19 [2,4]. Despite these underlying morbidities, these patients had minimal to no symptoms but had a persistent viral presence for prolonged periods. This evidence suggests the presence of host tolerance mechanisms that can explain both mild disease and prolonged presence of the virus in the host.

We propose that due to high tolerance to the virus, these patients mounted limited host antiviral and anti-inflammatory response that led to minimal or no symptoms. At the same time, limited host antiviral and anti-inflammatory response allowed the virus to persist for prolonged periods. Previous studies have shown that viral shedding continues even after symptom resolution in milder infections [5]. In addition, patients can harbor very high viral titers after the resolution of symptoms and can be infective [6]. It is possible that these patients with a high tolerance may be contributing to the disease spread due to persistent shedding for prolonged periods. However, it is unclear whether persistent viral positivity reflects active viral replications and risk of transmissions for entire duration of PCR positivity. Minimal host antiviral response and persistent viral presence have been well established in mouse model of LCMV infection where infection in neonatal mice do not develop any symptoms and harbors the virus throughout the life [7]. Similarly, owing to minimal host defense against Simian Immunodeficiency Virus (SIV), the non-human primates never develop acquired immuno-deficiency syndrome (AIDS), as seen with Human Immunodeficiency Virus (HIV) [8]. Currently, it remains unknown why a fraction of human population can stay positive for SARS-CoV-2 for prolonged periods without developing a severe disease.

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Declaration of Competing Interest

The authors declare that there are no competing interests.

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