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Does immune privilege result in recovered patients testing positive for COVID-19 again?

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SUMMARY Recently, an increasing number of reports have indicated that a few patients who were believed to have recovered from COVID-19 initially tested negative but later tested positive. Several hospitals in different countries have detected SARS-CoV-2 RNA in the semen and cerebrospinal fluid of patients with severe COVID-19. Given the fact that the testes and central nervous system are both immune privilege sites and the fact that Ebola virus and Zika virus can avoid immune clearance and continue proliferating and spreading by hiding in those sites, the question of whether SARS-CoV-2 is present in immune privilege sites, it attacks those sites, and it spreads again after proliferating in those sites needs to be investigated.

Keywords SARS-CoV-2, COVID-19, immune privilege, re-detectable positive, semen, CNS

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused nearly 4 million cases of coronavirus disease 2019 (COVID-19) worldwide, including over 274,000 deaths, as of 11 May 2020 (*1*). Generally, COVID-19 is less severe and less fatal than SARS, but some patients, and especially those who are elderly with co-morbidities, are prone to develop more severe symptoms and require emergent medical interventions (*2*). An increasing number of patients with COVID-19 have been discharged and undergone regular follow-up and observation. Studies have reported that some recovered patients have test positive again for SARS-CoV-2 RNA (*3*-*5*). There may be two reasons why patients test positive again for SARS-CoV-2 RNA: first, the patients were re-infected by another carrier of the virus; second, the virus was not completely cleared and instead reappeared in recovered patients. Since there is little evidence that recovered patients were re-infected, Vineet Menachery, a virologist at the University of Texas Medical Branch, said testing positive after recovery could simply mean that the test result was a false negative and that the patient was still infected (*6*). The leads to the question of whether the virus is still in the bodies of patients and, if so, where it is hiding. After considering a number of possibilities, the current authors hit upon immune privilege.

Certain sites in the human body have immune privilege, meaning that they are able to tolerate the introduction of antigens without eliciting an inflammatory immune response. Immunologically privileged sites include: the eyes, the placenta and fetus, the testicles, the central nervous system (CNS), and the anagen hair follicles (*7*) (Figure 1). Immune privilege is thought to be an evolutionary adaptation to protect vital structures from the potentially damaging effects of an inflammatory immune response. Inflammation in the brain or eye can lead to loss of organ function, while immune responses directed against a fetus can lead to a miscarriage. Thus, these are niches where viruses may be protected from the host immune response. Immunoprivileged sites gained attention as places where viruses can persist after disease recovery during the 2013-16 West African Ebola virus outbreak (*8*). In addition, Zika virus can also be detected in the semen of recovered patients (*9*). There are reports of patients who had these viruses in their semen months after they were originally infected even though the viruses had been cleared from elsewhere in their bodies. Ebola virus was still detectable in the semen of some survivors for more than three years, and Ebola virus transmission through sexual intercourse can occur months after the patient has recovered. In one of the most extreme cases, Zika virus was detected in the semen of a man in Italy at least 134 days after symptoms of the disease (mainly a fever) first emerged, even though blood and saliva samples revealed no trace of the virus. A semen test on day 188 still indicated the presence of virus (his blood and saliva were not tested). The testes seem to be a particularly understudied area among immune-privileged sites, which also include the eye and the

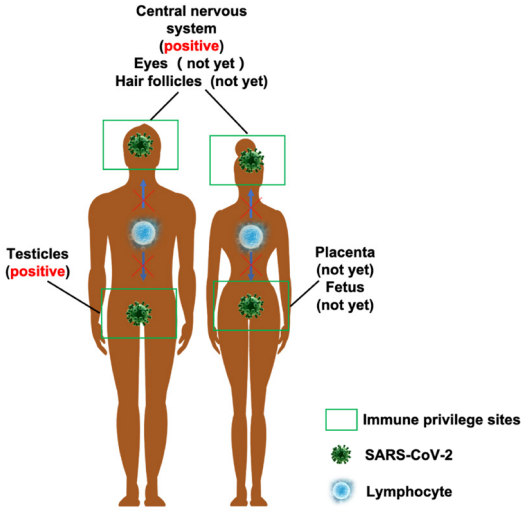

Figure 1. SARS-CoV-2 could hide in immune privilege sites to avoid immune clearance. To date, SARS-CoV-2 has been detected in the central nervous system and semen but not in the eyes, hair follicles, placenta, or fetus.

brain (*10*). Coincidentally, SARS-CoV-2 shares some characteristic with those viruses.

A study of 38 patients undergoing treatment for severe COVID-19 at a Chinese People's Liberation Army General Hospital looked for SARS-CoV-2 in their semen (*11*). Fifteen of the patients provided a semen sample during the acute phase of their illness and 23 shortly after recovering. SARS-CoV-2 RNA was found in semen samples from 4 of the 15 patients with acute disease and 2 of the 23 recovering patients. These new findings differ from the results of an earlier study involving 12 COVID-19 patients and a case report which suggested that semen of infected patients tested negative (*12,13*). However, the earlier studies focused on patients with mild disease after they had recovered, whereas the more recent study focused on hospitalized patients with severe disease, and all samples in this latest study were collected while symptoms were evident or very shortly after recovery. In fact, all of the semen samples from recovering patients that were found to have viral RNA were collected 2 or 3 days after recovery. Thus, different findings from the earlier studies and the more recent one are probably the result of differences in disease severity and the timing of sample collection. Other studies found that infected patients had neurologic manifestations (*e.g.* cerebrovascular disease and impaired consciousness) and skeletal muscle injury, and SARS-CoV-2 RNA was even detected in the cerebrospinal fluid of an infected patient (*13,14*).

However, the presence of viral RNA in immunologically privileged sites in patients does not necessarily mean that an infectious virus is present. Thus, what must be determined is whether infectious viruses can also be isolated from immunologically privileged sites in COVID-19 patients and survivors. Isolation of SARS-CoV-2 in those sites would lead to 3 questions: first, will the virus attack eyes, CNS, testes, or a fetus; second, will SARS-CoV-2 spread through sexual transmission or pregnancy; and third, can detection of SARS-CoV-2 in immunologically privileged sites serve as a prognostic marker or is it a necessary indicator for recovered patients, and especially those who with severe disease. In the future, more studies need to investigate whether immunologically privileged sites play an important role in SARS-CoV-2infection and the recurrence of COVID-19. In the meantime, the sensible move would be for patients recovering from COVID-19 to remain in self-isolation until further research determines how long the virus remains in immunologically privileged sites.

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