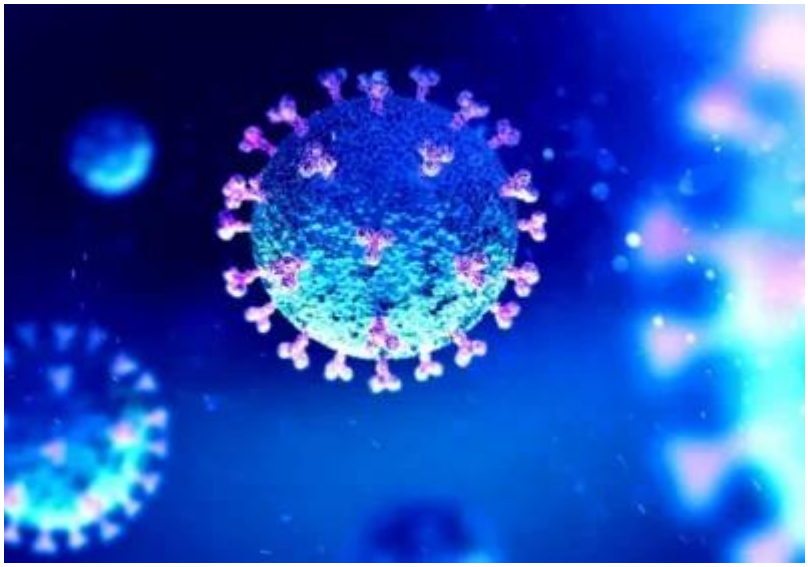
Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to a new disease, known as post-COVID or long COVID syndrome. In this study, the authors from Singapore and Spain investigated the presence of residual SARS-CoV-2 RNA and antigens in tissues of two patients diagnosed with post-COVID syndrome.

The evidence suggests that immune dysregulation plays a significant role in the pathophysiology of post-COVID syndrome. Patients with post-COVID syndrome often test negative for SARS-CoV-2, but viral RNA and/or antigen(s) were found in tissue specimens, especially from the gastrointestinal (GI) tract. Therefore, some authors proposed a pathophysiological model of post-COVID, based on the persistence of the virus that triggers a dysregulation of the immune system. Immune system dysregulation is manifested by elevated release of inflammatory cytokines, chronic inflammation, endothelial damage, hypercoagulability, microthrombosis, and multiorgan injuries in adults and children. Yang C et al. Association of SARS-CoV-2 infection and persistence with long COVID. Lancet Respir Med 2023. https://doi.org/10.1016/S2213-2600(23)00142-X

The GI tract is considered a potential viral reservoir for SARS-CoV-2 and a major viral shedding route. A recent study demonstrated that SARS-CoV-2 infection of the intestinal cells at the apical side (not at the basolateral side) severely damaged the integrity of the intestinal epithelial barrier. This led to viral entry in the blood vessels and the spread of the virus through the body.
https://discovermednews.com/sars-cov-2-infection-of-the-intestinal-cells-at-the-apical-side/



The first case

A 44-year-old woman presented with fever, pharyngitis, bronchospasm, expectoration, nausea, diarrhea, loss of smell and taste, anorexia, headache, and weight loss. Two months after she was diagnosed with COVID-19 by serological testing, she tested negative for SARS-CoV-2 by a polymerase chain reaction (PCR) test, but her symptoms persisted.

During the next months, she developed various symptomatology like chronic fatigue, dizziness, "brain fog", loss of spatial orientation, myalgia, bronchospasm, reactive sinus tachycardia after minimal effort, tongue inflammation, recurrent pharyngitis, tinnitus, and skin flare-ups.

At 426 days after the onset of COVID-19, she experienced generalized abdominal pain and nausea. Laparotomy and appendectomy were performed urgently. She tested negative for SARS-CoV-2 before the surgery. In the appendix and skin tissue samples, the histopathological examination showed reactive lymphoid hyperplasia in the appendix and superficial and deep perivascular dermatitis in the skin.

The SARS-CoV-2-specific antigens, spike (S), and nucleocapsid (N) proteins were detected in the appendix tissue and co-localized with the myeloid and macrophage markers CD68, CD14, CD206, and CD169. SARS-CoV-2 N protein was also detected in the skin macrophages. The SARS-CoV-2 RNA was detected in the extracellular and intracellular spaces of the appendix.

The second case

A 45-year-old woman with ductal carcinoma *in situ* presented with intense headache, upper stomach pain, nausea, diarrhea, myalgia, and fatigue. She was diagnosed with COVID-19 by a PCR test for SARS-CoV-2.

After two months, although she tested negative for SARS-CoV-2, she developed various symptoms of post-COVID syndrome, like headaches, mental confusion, dysarthria, sleep disorder, lack of concentration, tachycardia, stomachache, loss of appetite, pain in the liver and spleen area, arthralgia, and spontaneous bruises.

175 days after the onset of initial symptoms of COVID-19, she underwent partial breast resection and margin control surgery. She tested negative for SARS-CoV-2 before the

surgery. In the breast tissue samples, SARS-CoV-2 N and S proteins were detected in the tumor-adjacent area and co-localized with the myeloid and macrophage markers CD68, CD14, CD206, and CD169. In addition, the SARS-CoV-2 RNA was detected in the extracellular and intracellular spaces of the breast tissue.

Conclusion

This study has shown that residual SARS-CoV-2 RNA and viral-specific antigens were detected in GI and non-GI tissues (appendix, skin, and breast tissues) of two post-COVID patients, 426 and 175 days after the onset of acute SARS-CoV-2 infection.

The authors emphasized that the susceptibility of immunocompromised cancer patients to persistent viral replication and long COVID syndrome needs further investigation.

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Joseph CR, Edwards SG, Neo ZW, et al. Case report: Persistence of residual antigen and RNA of the SARS-CoV-2 virus in tissues of two patients with long COVID. Front. Immunol. 2022; 13: 939989. https://doi.org/10.3389/fimmu.2022.939989