รายงานผู้ป่วยที่ตรวจพบ SARS-CoV-2 RNA ซ้ำหลังการติดเชื้อไวรัสโคโรนา 2019: ความท้าทายในการแยกแยะจากการกำเริบหรือการติดเชื้อซ้ำ

A case report of recurrent SARS-CoV-2 RNA positivity after COVID-19: challenges to differentiate from reactivation and reinfection

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บทคัดย่อ

วัตถุประสงค์

รายงานผู้ป่วยนี้เป็นกรณีศึกษาของผู้ป่วยที่ตรวจพบ SARS-CoV-2 RNA ซ้ำหลังติดเชื้อโควิด-19 และคำแนะนำสำหรับแพทย์และนักระบาดวิทยาในการดูแลผู้ติดเชื้อ

รายงานผู้ป่วย

ผู้ป่วยหญิงอายุ 50 ปี ไม่มีโรคประจำตัว ตรวจพบว่าติดเชื้อโควิด-19 จากผล RT-PCR โดยมีอาการเล็กน้อย ได้แก่ ไข้ต่ำๆ ปวดกล้ามเนื้อและจมูกไม่ได้กลิ่น ผู้ป่วยได้รับการตรวจ RT-PCR ซ้ำเป็นลบ (หลังจากพบการติดเชื้อครั้งแรก 29 วัน) และตรวจพบแอนติบอดี IgG ต่อ SARS-CoV-2 อย่างไรก็ตาม ในวันที่ 42 หลังจากพบการติดเชื้อครั้งแรก ผู้ป่วยตรวจพบผล RT-PCR บวกซ้ำโดยไม่มีอาการใดๆ ผลการตรวจ RT-PCR ซ้ำอีกครั้งวันที่ 44 ให้ผลเป็นลบ

อภิปรายผล

การพบ SARS-CoV-2 RNA ซ้ำในกรณีนี้น่าจะเกิดจากการขับไวรัสในทางเดินหายใจที่นานกว่าปกติ (prolonged viral shedding) เนื่องจากตรวจพบแอนติบอดีต่อเชื้อ SARS-CoV-2 แล้ว รวมทั้งตรวจไม่พบยีน subgenomic E จากการตรวจวิเคราะห์เพิ่มเติม อย่างไรก็ตามแพทย์ควรพิจารณาจากประวัติและอาการของผู้ป่วย รวมถึงหลักฐานทางระบาดวิทยาและการตรวจทางภูมิคุ้มกันเพื่อหาสาเหตุของการพบ RNA ซ้ำ หากไม่พบหลักฐานของการแบ่งตัวของไวรัส (active replication) ผู้ป่วยสามารถกลับมาทำกิจกรรมตามปกติได้

คำสำคัญ: ไวรัสโคโรนา 2019, โควิด-19, SARS-CoV-2 ซ้ำ, การขับไวรัสนานกว่าปกติ

Abstract

Objective

Here, we report a case of recurrent SARS-CoV-2 RNA positivity and suggestions for clinicians or epidemiologists in clinical management.

Case report

A 50-year-old healthy female with no previous illnesses was tested positive for COVID-19 by RT-PCR. She presented with mild symptoms including low-grade fever, myalgia and anosmia. She was tested negative 29 days since initial positive RT-PCR test together with detectable SARS-CoV-2 IgG antibody. However, on Day 42, recurrent RNA positivity was detected with no signs or symptoms of COVID-19. She was subsequently tested negative again on Day 44.

Discussion

Recurrent SARS-CoV-2 RNA positivity in this case was probably from prolonged viral shedding. This is supported by the evidence of positive antibody to SARS-CoV-2 and absence of sub-genomic E gene from further analysis. Clinicians should correlate with the patients' clinical course, epidemiological and immunological investigations to determine the cause of recurrent viral shedding. In the absence of active replication evidence, the patients can be dismissed from re-diagnosing with COVID-19 infection and be advised to return to their normal activities.

Keywords: COVID-19, SARS-CoV-2, recurrent positivity, prolonged viral shedding

Introduction

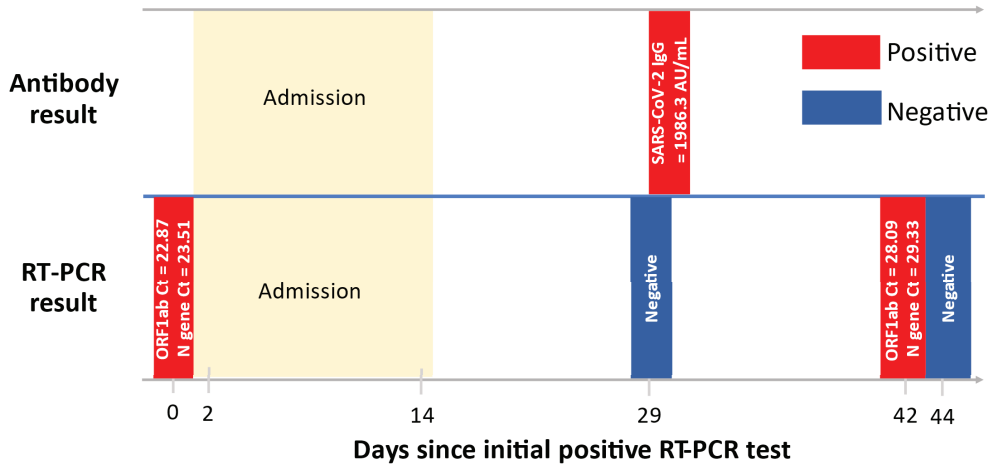
SARS-CoV-2 infection most often presents as asymptomatic or mild symptoms. Recurrent COVID-19 upper respiratory tract viral shedding has frequently been reported.[1] Recurrent viral shedding is challenging as clinicians face a dilemma of deciding whether recurrent positivity was either from prolonged non-transmissible virus shedding or from reactivation or reinfection in which patients need to be isolated further. Here, we report a case of recurrent SARS-CoV-2 RNA positivity and suggestions for clinicians or epidemiologists in clinical management.

Case report

This is the case of a 50-year-old healthy Thai female office worker in a company in Pathum Thani, Thailand. She denied of any previous illnesses or any allergic history. Outbreak investigation reported her close contact with an infected colleague at work on 20th April, 2021. She started feeling feverish and myalgia on 2th May, 2021. Two days later, she developed anosmia and nasal congestion. She was then tested positive by nasopharyngeal swab RT-PCR on 6th May, 2021 with ORF1ab cycle threshold (Ct) value of 22.87 and N gene Ct value of 23.51. The case was then hospitalized for isolation between 8th – 20th May, 2021 (day 2- day 14 since initial positive test) in which she presented with unremarkable renal and live function, no thrombocytopenia and normal chest x-ray. Her mild symptoms subsided with no complications. After discharge, she undergone self-quarantine at home for another 14 days. Before returning to work, she was tested negative by RT-PCR on 4th June, 2021 (29 days since initial positive test) and reactive SARS-CoV-2 IgG against receptor binding domain (RBD) of S1 subunit of spike protein with the level of 1986.3 AU/mL (Abbott SARS-CoV-2 IgG II QuantTM[2]) on 5th June, 2021. The recovered patient then returned to work at her office as usual. On 14th June, 2021 another colleague was tested positive for COVID-19, making her a low-risk contact. As a special precaution, she was tested again on 17th June, 2021 (42 days since initial positive test), showing a positive RT-PCR with ORF1ab Ct value of 28.09 and N gene Ct value of 29.33 and being confirmed again by another laboratory with RdRp gene Ct value of 38.03, N gene Ct value of 35.26 and E gene Ct value of 30.86. Further analysis showed N1 gene Ct value of 35.00 but subgenomic E gene and N2 gene showed negative results. Subsequently, she was tested negative by RT-PCR on 19th June, 2021.

In conclusion, this COVID-19 case had recurrent positive RT-PCR test 42 days after her initial diagnosis. She was tested reactive for SARS-CoV-2 IgG and this RNA positivity was documented 13 days from the first negative result (Figure 1).

Figure 1: Timeline of COVID-19 patient testing



Discussion

A recent systematic review showed that recurrent SARS-CoV-2 RNA positivity after COVID-19 was as high as 14.8% (95% CI 11.44-18.19) with the interval from disease onset to recurrence of 35.4 days (95% CI 32.65-38.24).[1] The plausible causes of recurrent RNA positivity are prolonged viral shedding, reactivation or reinfection. The longest SARS-CoV-2 virus shedding in upper respiratory tract was 83 days, while shedding in stools can be found up to 126 days. No studies, however, detected live virus beyond day 9 of illness. Younger age patients were also more likely to experience recurrent viral shedding.[1] Depending on the type of specimens and RT-PCR test sensitivity, viral genomes may be detected again due to initial false-negative results.[3] Previous studies also suggested that most recurrent positive test in recovered patients were related to viral genomic fragments rather than transmissible virus.[4] Reinfection can be confirmed by viral culture or isolation of a complete genome in the second episode, identification of 2 different virus strains in 2 episodes of infection, by immunological responses and epidemiological investigations.[5] Reactivation is indicated if whole-genome sequencing corresponded to the same strain involved in the first episode.[6,7]

Recurrent RNA positivity in this case report was probably from prolonged viral shedding in the patient's respiratory tract. This is supported by the evidence of positive antibody to SARS-CoV-2 and absence of N2 gene sub-genomic E gene from specific primers and probes for RT-PCR. This implied that this was an incomplete RNA genome. Although viral isolation of SARS-CoV-2 is an indication of active replication and contagiousness, the technique has to be done in a biosafety level 3 (BSL-3) laboratory, requiring weeks for the result.(8) Providing evidence of replicative intermediates of the virus rather than residual viral RNA, sub-genomic RNA (sgRNA) has been used as a virus viability marker for SARS-CoV-2. Studies also demonstrated association between culture-positive specimens and detectable sgRNA.[9-11] Furthermore, previous clinical evidences showed that there were no transmission to close contacts of infected case after 6 days of symptom onset (95% CI 0%-0.4%) regardless of RT-PCR results. (12) Therefore, recurrent RNA positivity from reactivation or reinfection was less likely in this case.

Clinicians should correlate with the patients' clinical course, epidemiological and immunological investigations to determine the cause of recurrent viral shedding. sgRNA analysis is a more convenient, faster alternative investigation to viral culture. In the absence of active replication evidence, the patients can be dismissed from re-diagnosing with COVID-19 infection and be advised to return to their normal activities.

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Conflict of interest

All authors have declared no conflicts of interest.

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