



A Case of SARS-CoV-2 Clinical Relapse after 4 Negative RT-PCR Tests in Greece: Recurrence or Reinfection?

Fotis Konstantinou¹ , Ioanna Skrapari¹, Eleni Baretta¹, Nikolaos Bakogiannis² , Anna-Maria Papadopoulou² and Chris Bakoyiannis³

¹First Department of Internal Medicine, Evangelismos General Hospital, Athens, Greece. ²Medical School, National and Kapodistrian University of Athens, Athens, Greece. ³First Department of Surgery, Laikon General Hospital, Athens, Greece.

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ABSTRACT: SARS-CoV-2 pandemic is the greatest public health concern of the year 2020. There are several worldwide reports of patients who have managed to recover from SARS-CoV-2 infection with negative PCR test results, that for unknown reasons convert back to positive PCR. We report a case of a patient in our hospital who developed positive PCR test results for SARS-CoV-2, after 4 consecutive results that were negative, along with a full-blown clinical syndrome of SARS-CoV-2 infection.

KEYWORDS: Recurrence, reinfection, SARS-CoV-2

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CORRESPONDING AUTHOR: Ioanna Skrapari, First Department of Internal Medicine, Evangelismos General Hospital, Ypsilantou 45-47, Athens 10676, Greece.
Email: iskrapari@yahoo.gr

Introduction

Since the beginning of the 2020 pandemic of SARS-CoV-2, several case studies have reported a fluctuation of the positivity of RT-PCR, during the clinical course and even in the convalescence period. To our knowledge, no large trial has been conducted at the moment, to investigate a possible cause that patients who are discharged with a negative or multiple negative RT-PCR test results, can develop positive test results after some time, with or without clinical symptoms for SARS-CoV-2 infection.

At the time that this paper was written, current national guidelines by the Greek national public health organization recommend a patient is discharged without a negative PCR test result for SARS-CoV-2, provided that they fulfill clinical criteria. If the patient is immunocompromised because of any underlying condition, only then should they have 2 consecutive negative PCR test results with 24 hours time between them.¹

Case Report

A 59-year-old male patient came to the emergency department complaining of diffuse musculoskeletal pain. This patient suffered from oesophageal cancer, with metastasis in both lungs, liver, and bones, hence the diffuse pain. He was administered palliative analgesic treatment and was feeling better, getting ready for discharge.

The past month, he was admitted to another hospital with shortness of breath, and after an initial negative PCR SARS-CoV-2 test, he was found positive to the virus and was treated according to national protocols, with remdesivir and dexamethasone. Before discharge, he had no evidence of clinical illness that could be attributed to SARS-CoV-2 infection, he was afebrile, and he had 2 consecutive negative PCR tests for

SARS-CoV-2 from oropharyngeal swab. During his home stay, he recalled no signs of infection or any clinical syndrome, apart from the intermittent diffuse pain that he had, due to his underlying illness.

At the emergency department of our hospital, he wasn't complaining of any respiratory distress, he had normal temperature and the rest of his vital signs and laboratory tests were unremarkable, apart from mild thrombocytopenia. Because of the recent history of SARS-CoV-2 infection, and despite having already 2 negative PCR tests, increased alertness led us to carry out 2 additional SARS-CoV-2 PCR tests, which were also negative.

During the second day of hospital stay, though, and having received only analgesic treatment, he developed sudden respiratory distress, with productive cough. His temperature raised to 38°C, while he had low blood pressure and low arterial oxygen saturation. At auscultation fine crackles could be detected bilaterally at lower chest areas. His chest X-ray revealed new diffuse consolidations, compared to the previous day and he developed lymphopenia, and increased C-reactive protein levels (Table 1). Because of the alarming clinical syndrome, he was transferred to an isolation chamber, where patients with suspicion for SARS-CoV-2 infection are treated. Two new oropharyngeal PCR tests SARS-CoV-2 were performed which came back positive. The patient died of respiratory failure the same day. The timeline of events in our patient is illustrated in Figure 1.

Discussion

To our perspective, we conclude that there are 4 different scenarios that can explain recurrence of SARS-CoV-2 RNA shedding after RT-PCR negative test results.



Table 1. Laboratory test results at day 1, day 42, and day 44.

	DAY 1 ADMISSION TO PREVIOUS HOSPITAL	DAY 42 ADMISSION TO OUR HOSPITAL	DAY 44 CLINICAL DETERIORATION
WBC (/μL)	6130	8480	6000
NE (/μL)	4200	6530	4300
LY (/μL)	1100	1550	600
HCT (%)	39.5	39.3	38.5
HGB (mg/dL)	12.2	12.1	11.7
PLT (/μL)	60000	45000	15000
CRP (mg/dL)	19	14.2	25

Abbreviations: CRP, C-reactive protein; HCT, hematocrit; HGB, hemoglobin; LY, lymphocyte count; NE, neutrophil count; PLT, platelet count; WBC, white blood cell count.

False negative RT-PCR

Several factors affect the sensitivity or specificity of RT-PCR test. An RT-PCR test can have false negative results at the time of discharge of a patient and be positive at retesting, which can be misinterpreted as a reinfection or recurrence. In a study in hospitalized patients tested before discharge in Wuhan, China, the false negative rate was 12.5% and according to the authors, this is mostly affected by the sampling procedure, laboratory error, or sample transportation.² Of course, with any additional test that gives negative result, the possibility that this is false, is limited. The kits that were used for the PCR technique, were all cobas 8800 by Roche.

Persistence of non-viable RNA of SARS-CoV-2 in the patient, after the primary infection

This scenario assumes that the second event in our patient was caused by a different pathogen. Virological and bacteriological samples were negative, though, except for SARS-CoV-2 RT-PCR. Unfortunately, no sample was taken for viral cultures, which could validate active viral replication. Prolonged nucleic acid conversion for SARS-CoV-2 has been observed, though, even in recovered patients with no symptoms. In fact, Zou et al³ report a 4-fold decrease of the probability of positive RT-PCR SARS-CoV-2 relapse post-discharge, if 3 negative tests are required before discharge, in contrast to current guidelines, that require only 2.

Another possibility is that the worsening clinical syndrome could be attributed to an overwhelming immune reaction, which has manifested post-infection, independently of viral activity. Lafaie et al⁴ report 2 similar cases with negative serological antibody testing during the initial SARS-CoV-2 clinical syndrome, with seroconversion and clinical worsening, and positive RT-PCR relapse, during a second clinical episode, which could be explained by an excess immune activation syndrome post-infection.

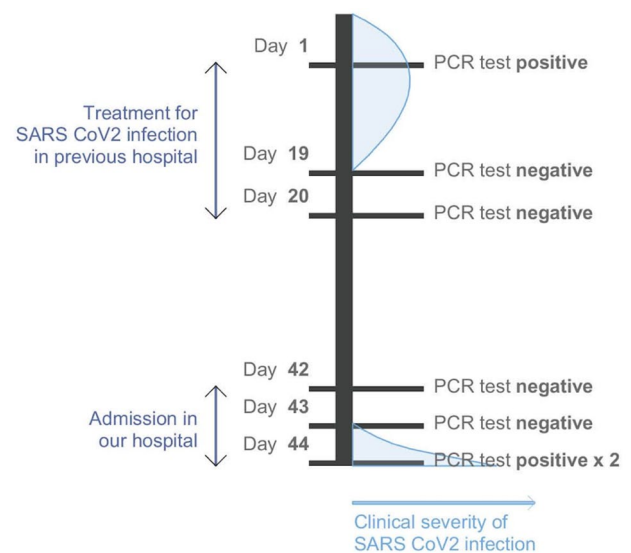


Figure 1. Timeline of events in our patient. After an initial negative seroconversion of PCR test for SARS CoV2, post-infection, with 4 confirmatory PCR tests, the patient tested again positive with severe clinical deterioration.

SARS-CoV-2 reactivation

Small observational studies report a range of 9% to 15% rate of SARS-CoV-2 reactivation, with a time range of recurrence between 4 and 17 days after discharge.^{5,6} In their study, all patients experienced mild clinical symptoms, in contrast to Lafaie et al⁴ patients and our patient, who eventually died, after a more severe clinical syndrome during the second episode. Several factors can affect the chance of reactivation, such as host age and sex, virologic factors, such as high initial viral load, genotype, and treatment response.⁵ An underlying immunosuppressive disorder, the use of immunosuppressive medication or the blunting of immunocompetence post-infection can also play a role. Furthermore, a relationship has been reported, between the chance of a SARS-CoV-2 clinical syndrome

relapse and the slower absorption of exudative lesions in chest CT scans during the recovery period, independently of the initial imaging.⁷

SARS-CoV-2 reinfection

Comparison of strains with sequencing could validate a possible infection by a different SARS-CoV-2 strain. Studies have shown that production of virus neutralizing antibodies after SARS-CoV-2 infection is possible, but this effect on different people is variable and further research is required to understand it.^{8,9}

To sum it all up, our patient survived a first SARS-CoV-2 clinical syndrome and after 4 negative PCR test results, he ended up positive with a worse clinical syndrome that resulted in death. He was an oncologic patient, though, and even if he wasn't treated with any oncologic medication currently, we have to assume that his immune system was compromised.

Considering all the details that we've found in the literature referenced above, the possibility of false negative RT-PCR, even if it is always present, in this case it is highly unlikely because of the multitude of repetitively negative results. The fact that the patient developed a worse clinical syndrome, is most likely attributed to reactivation or reinfection. Unfortunately, no virology genetic testing could be conducted, and this will remain a question.

Conclusion


This is of great importance for public health because, besides patients and asymptomatic carriers, people with supposedly negative RT-PCR for SARS-CoV-2 result could still be infectious. Current guidelines suggest that all discharged patients be isolated for 14 days, which is less than the maximum time some studies have reported for COVID reactivation (17 days post discharge).^{5,6} Perhaps guidelines should be updated regarding a


closer monitoring and longer isolation for discharged patients, until larger studies can shed some more light on the case of SARS-CoV-2 relapse.

Patient Consent Confirmation Statement

We confirm that patient consent was secured to publish the findings of this case study.

ORCID iDs

Fotis Konstantinou  <https://orcid.org/0000-0002-2167-2987>

Nikolaos Bakogiannis  <https://orcid.org/0000-0002-2020-5762>

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