



Case Report

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POSSIBLE COVID-19 REINFECTION IN TWO HEALTHCARE WORKERS: A FIRST CASE REPORT FROM TURKEY WITH REVIEW OF THE LITERATURE

İKİ SAĞLIK ÇALIŞANINDA OLASI COVID-19 REENFEKSİYONU: LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ İLE TÜRKİYE'DEN İLK VAKA RAPORU

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Öz

COVID-19 pandemisinin en yoğun günlerini yaşadığımız bu günlerde hastalığı geçirenlerde bir süre sonra benzer klinik tablolar gözlenmiş olması ve birkaçı sağlık çalışanlarında olmak üzere olası re-enfeksiyon vakalarının rapor edilmesi COVID-19'a karşı kazanılan doğal bağışıklık ile ilgili ciddi endişelere yol açmıştır. Biz burada Türkiye'de ilk kez sağlık çalışanlarında iki olası re-enfeksiyon vakasını rapor ediyoruz. İlk vaka COVID-19 vakalarının izlendiği bir yoğun bakım servisinde çalışan 21 yaşındaki erkek hemşiredir. Halsizlik, şiddetli kas ağrısı ve boğaz ağrısı şikayetleri sonrası 10 Ağustos'ta RT-PCR testi pozitif olarak bildirilmiştir. Toraks BT normal olarak değerlendirilmiştir. İlgili protokole göre tedavi alan ve izlenen hasta 25-26 Ağustos tarihlerinde art arda alınan iki RT-PCR testinin negatif olması üzerine işine geri dönmüştür. Bundan 76 gün sonra halsizlik, şiddetli kas ağrısı, boğaz ağrısı ve ishal şikayetleri ile yeniden başvuran hastanın RT-PCR pozitif olarak rapor edilmiştir. İkinci vaka COVID-19 hastalarının izlendiği bir serviste çalışan 28 yaşındaki kadın doktordur. Sub-febril ateşin eşlik ettiği yorgunluk, şiddetli kas ağrısı, baş ağrısı, öksürük, anozmi ve disguzi şikayetleri sonrası 25 Ağustos'ta gerçekleştirilen RT-PCR testi pozitif olarak rapor edilmiştir. İlgili protokole göre tedavi verilen ve izlenen hasta şikâyetlerinin geçmesi ve 10 ve 15 Eylül'deki RT-PCR testlerinin negatif raporlanması üzerine işine dönmüştür. Bundan 71 gün sonra yorgunluk, kas ağrısı, boğaz ağrısı, baş ağrısı, sub-febril ateş ve ara sıra kuru öksürük şikayetleri sonrası alınan RT-PCR testi pozitif olarak değerlendirilmiştir. Toraks BT incelemesi normal olarak raporlanmıştır. Vakalar, bu konuda literatürde yer alan benzer yayınlar ve her iki klinik durumda izole edilen suşların genom dizilimlerinin incelendiği çalışmaların sonuçları ile ayrıntılı olarak tartışılmıştır.

Anahtar Kelimeler: COVID-19, re-enfeksiyon, Koronavirüs.

Abstract

In these worse days of the COVID-19 pandemic, it was reported that similar clinical pictures were observed after a while in those who suffered from the disease suggesting possible cases of reinfection. Some of these cases were among healthcare workers. These reports have raised serious concerns about the natural immunity gained against COVID-19. We report here two possible cases of reinfection in healthcare workers for the first time in Turkey. The first case was a 21-year-old male nurse working in a COVID-19 intensive care unit. RT-PCR test was reported positive on August 10 after complaints of weakness, severe muscle pain, and sore throat. The patient, who received treatment and was followed up according to the protocol, returned to work when two consecutive RT-PCR tests were negative on August 25-26. After 76 days, the patient who presented with complaints of weakness, severe muscle pain, sore throat, and diarrhea had again a positive RT-PCR. The second case was a 28-year-old female doctor working in a COVID-19 clinic. Her RT-PCR test was performed on 25 August after complaints of fatigue, severe muscle pain, headache, cough, anosmia, and dysgeusia accompanied by sub febrile fever were reported positive. She returned to work after two RT-PCR tests on September 10 and 15 were reported negative. Seventy-one days later, the RT-PCR test taken after complaints of fatigue, muscle pain, sore throat, headache, sub febrile fever, and occasional dry cough was evaluated as positive. The cases were discussed in detail with the review of the literature.

Keywords: COVID-19, re-infection, coronavirus.

Introduction

The pandemic of Coronavirus disease-2019 (COVID-19) has now reached enormous proportions. As of late November, 2020 more than 58 million cases and almost 1.4 million deaths were reported globally.^{1,2} A concerning issue regarding patients who recovered from COVID-19 has been the possibility of re-infection.³ Although it was well-established that neutralizing antibodies against Coronavirus rapidly produced after the infection, it was also reported that the antibody titers declined over time as early as 1-2 months post-infectiously.^{4,5} The clinical importance of this decline is still unknown; however, some possible reinfection cases were reported.⁶⁻¹⁰ These reports raised suspicions about whether these cases represented viral persistence, re-infection, or inflammatory rebound.¹⁰⁻¹² Five recent studies suggested that the second episodes were due to phylogenetically distinct SARS-coronavirus-2 strains confirmed by whole-genome sequencing.^{4,13-16}

We report here two healthcare workers, a 21-year-old male nurse, and a 28-year-old female doctor both working in a Covid 19 Unit who were presented with the second episode of clinical manifestations of COVID-19 after their recovery from initial infection confirmed by negative reverse transcriptase-polymerase chain reaction (RT-PCR) tests from nasopharyngeal swabs suggesting possible re-infections.

Case 1

Patient 1 was a 21-year-old male nurse with no comorbidities working at a Covid-19 unit at a research and training hospital, a referral hospital for patients with COVID-19 in Samsun province. On August 8, he developed symptoms of fatigue and severe myalgia with a sore throat. He reported no fever or cough. He stated that he had diarrhea that lasted a day on the second day of his initial symptoms. On August 9, an RT-PCR test from a nasopharyngeal swab was performed and on August 10 it was reported positive for SARS-CoV-2. Of other laboratory tests, neutrophils count was $3.9 \times 10^9/L$ (Normal range: $2-6.9 \times 10^9/L$), lymphocytes count was $1.5 \times 10^9/L$ (Normal range: $0.6-3.4 \times 10^9/L$) and C-reactive protein was 0.99 mg/L (Normal range: $0-5 \text{ mg/L}$); all were in the normal range. He also had a low-dose chest CT-scan with no abnormal findings. He was then followed at home with oral Favipiravir (five days) and Vitamin C treatment. His symptoms resolved in four days. Following the national quarantine protocols for health workers, patient 1 returned to work after two consecutive negative RT-PCR tests on 25th and 26th August.

On November 10, 76 days later than the last negative RT-PCR test, the patient started to have similar symptoms like fatigue, myalgia, sore throat, and diarrhea. He also had a dry cough. He reported no fever or dyspnea. His oxygen saturation was 98%. A low-dose chest CT-scan revealed minimal ground glass images in his left lung. RT-PCR test from nasopharyngeal swabs was positive for Covid-19. Of other laboratory tests, neutrophils count was $2.6 \times 10^9/L$ (Normal range: $2-6.9 \times 10^9/L$), lymphocytes count was $1.3 \times 10^9/L$ (Normal range: $0.6-3.4$

$\times 10^9/L$) and C-reactive protein was 3.56 mg/L (Normal range: 0-5 mg/L); all were in the normal range. Oral Favipiravir (five days) was prescribed and the patient was followed at home. His symptoms regressed in two days and apart from an occasional dry cough he was symptom-free after 10 days. Following the new national protocols, he went back to work after ten days. Although the two RT- PCR tests from nasopharyngeal swabs performed on November 22 and 26 (12 and 16 days after the first symptoms presented) were also reported positive. The case continued to work because of the new protocol which did not require a negative RT- PCR for confirmation of recovery.

Case 2

Patient 2 was a 28-year-old female doctor with no comorbidities also working at another Covid-19 unit at the same research and training hospital. On August 25, she had symptoms of fatigue and severe myalgia, headache, cough, anosmia, and dysgeusia accompanied by a sub-febrile fever (37.8 °C). She stated that a sensation of dyspnea but her oxygen saturation was normal. RT- PCR test performed on August 25 from her nasopharyngeal swabs was positive for Covid-19. Of other laboratory tests, neutrophils count was $1.3 \times 10^9/L$ (Normal range: $2-6.9 \times 10^9/L$), lymphocytes count was $2.8 \times 10^9/L$ (Normal range: $0.6-3.4 \times 10^9/L$) and C-reactive protein was 6.74 mg/L (Normal range: 0-5 mg/L).

A low-dose chest CT-scan yielded no abnormal findings. She was then followed at home with oral Favipiravir (five days) treatment. Her symptoms resolved completely in a week. Patient 2 returned to work after ten days following the new protocol. Two negative RT-PCR tests from nasopharyngeal swabs performed on 10th and 15th September were reported.

On November 25, 71 days later than the last negative RT-PCR test, the patient started to have symptoms of fatigue, myalgia, sore throat, headache, low-grade fever (37.6 °C), and occasional dry cough. She reported no dyspnea. A low-dose chest CT-scan revealed no abnormal findings. RT- PCR test from nasopharyngeal swabs was positive for Covid-19. Of other laboratory tests, neutrophils count was $3.3 \times 10^9/L$ (Normal range: $2-6.9 \times 10^9/L$), lymphocytes count was $3.7 \times 10^9/L$ (Normal range: $0.6-3.4 \times 10^9/L$) and C-reactive protein was 3.3 mg/L (Normal range: 0-5 mg/L). Oral Favipiravir (five days) was prescribed and the patient was being followed at home by the time this paper was written.

Discussion

Here we report two medical professionals who had two distinct episodes of Covid-19 clinical symptoms confirmed by RT-PCR with a completely symptom-free interval for more than two months, suggesting

reinfection of the disease. Suspected reinfection cases were reported among medical professionals and it was suggested that reinfections were related to increased risk due to repeated exposure to Covid-19 patients.¹⁰⁻¹⁷

Very recently, Liotti et al. described the results of 176 patients who had recovered from COVID-19 confirmed by two negative RT-PCR test results 24 hours apart. After a mean of 48.6 days from diagnosis, they performed a retest and found that 32 patients (18.2%) had positive RT-PCR results for SARS CoV-2 RNA. They used a specialized assay to determine virus replication and found that only one of these 32 patients (3.1%) had evidence of RNA capable of replication suggesting recurrent infection or reinfection. They concluded that without whole-genome sequencing it was impossible to separate the two. Interestingly, this patient was the only one who had the clinical symptoms of COVID-19 among 32 patients with positive RT-PCR results. Previous studies have also shown that prolonged viral shedding for over one month was possible but these cases were rare and not correlated with clinical symptoms.^{18,19}

Lafaie et al. reported three RT-PCR positive elderly patients with two distinct symptomatic episodes, but they suggested that the absence of IgG antibodies in two of their patients would favor the hypothesis of recurrence which may be related to immunosuppression.⁶ Similarly, Bongiovanni and Basile reported two elderly patients who recovered from RT-PCR confirmed COVID-19 with subsequent negative results. The patients were tested positive again after the emergence of symptoms thirty days later. The authors suggested that age and the presence of comorbidities of these patients may have contributed to the alterations in their immune system, increasing the risk of reinfection.⁷

Batisse et al. described 11 possible COVID-19 reinfection cases (Four of them were healthcare workers) without significant comorbidity similar to our cases. However, the interval was very short and recovery was not confirmed by a negative test result. They concluded that these healthy healthcare workers with mild symptoms at both episodes could present reinfection due to waning immune response from the first non-invasive infection.²⁰

Tomassini et al. tried to set the criteria for the definition of SARS-CoV-2 reinfection as the patient should have an initial COVID-19 confirmed with a positive RT-PCR, a clinical recovery confirmed with a negative RT-PCR test and at least 28 days after the previous negative result another positive RT-PCR test. Both our cases met these criteria.⁵

De Brito et al. reported two doctors working in a reference clinic for COVID-19. Both cases had two distinct clinical episodes with an interval of approximately 30 days. There was no confirmation of recovery from the first episodes with a negative RT-PCR test due to follow-up protocols in Brazil. One of the patients in their report did not have positive serology test results after the first wave of symptoms with RT-PCR positivity indicating the absence of neutralizing antibodies capable of preventing a second infection. However, six weeks

after the second episode, the RT-PCR of the patient was negative, and the serology was positive for both IgG and IgM. In addition, the second patient had positive IgG test results in the first episode, indicating that antibodies were present due to the first infection. The authors concluded that the only way distinguishing cases of reactivation of the previous infection from cases of reinfection was a demonstration of molecularly distinct viruses.¹⁶

We happened to find five studies that tried to address this issue by implementing whole genome sequencing of two viruses isolated at both episodes of suspected reinfections. The first report was from Hong Kong. The researchers performed whole-genome sequencing on a patient's respiratory specimens collected during two episodes of COVID-19 with an interval of 142 days. They found that viral genomes from first and second episodes belonged to different lineages with four amino acid residues that differ in the spike protein between the first and second infection. It was the first confirmation of true reinfection. The patient was asymptomatic at the second episode and there was no reliable serologic evidence for neutralizing antibodies from the first episode.³

The second report from Belgium described a 51-year-old woman without any immunodeficiency having two separate clinical episodes of COVID-19 more than three months apart and found that the initial infection was caused by a lineage B.1.1 SARS-CoV-2 virus and the relapsing infection by a lineage A virus using full-length genome sequencing. The authors identified eleven mutations across the genome of the two strains. There was no serologic evidence from the first episode and the second episode was milder with rhinitis.¹³

The third case from South America, Ecuador described a 46-year-old man with two distinct episodes with an interval of more than 90 days. SARS-CoV-2 genome sequencing revealed the first infection variant belonged to clade 20A and lineage B.1.p9, whereas the second infection variant belonged to clade 19B and lineage A.1.1 with no shared mutations between the two sequences, further suggesting that both variants resulted from distinct evolutionary trajectories. There was serologic evidence that only specific anti-SARS-CoV-2 IgM was present at the beginning of the first episode. The symptoms at the second episode were reported to be worse with odynophagia, nasal congestion, fever of 38.5°C, back pain, productive cough, and dyspnoea.¹⁴

In the fourth report from the US state of Nevada, Tillett et al. described a 25-year-old male with two separate symptomatic episodes 48 days apart. Recovery from the first episode was confirmed by two negative follow-up RT-PCR tests. The patient had worse symptoms at the second episode reported as myalgia, cough, and shortness of breath and required oxygen support in hospital. Chest radiography revealed the development of bilateral patch-like interstitial opacities suggestive of viral pneumonia. The researchers used two different bioinformatic methodologies and found a significant genetic difference between two SARS COV-2 viruses.¹⁵ This case with the Ecuador case presented a worse clinic at the second episode compared with the first

infection. In one of our cases, the male nurse had radiographic evidence of viral pneumonia and dry cough at the second episode which was absent at the first episode. In our other case, the female doctor reported a similar or somewhat milder disease subjectively.

The most recent report was from France. Colson et al. described a 70-year-old immunocompetent man living in a retirement home who had COVID-19 with minimal ground glass images in both lungs and recovered. Recovery was confirmed by subsequent three negative RT-PCR test results. Seroconversion was also shown with IgG positivity. The RT-PCR test performed for a systematic screening was positive after 105 days from the first episode. The patient was asymptomatic. SARS-CoV-2 genome sequencing showed drastically different viral genomes with 34 nucleotide differences.¹⁶

As far as we know this is the second report of suspected COVID-19 reinfection in Turkey. Ozaras et al. described a 23-year-old woman with two symptomatic episodes 116 days apart. Her recovery was confirmed with negative RT-PCR test results after both episodes. Clinical symptoms were similar between the episodes and serologic data was available only after the second episode.²²

In this case, we could not identify possible different strains of the virus causing each episode to confirm true reinfection using whole-genome sequencing. We also did not have any serologic data of our cases because serologic evaluation is not a part of COVID-19 management in Turkey. Nevertheless, the emergence of symptoms suggesting COVID-19 after as long as 71 and 76 days and two consecutive negative RT-PCR tests indicating recovery after the first episodes suggested strongly two distinct episodes due to two different strains of the virus.

Reinfection with the SARS-COV-2 virus has important clinical implications as previous exposure to SARS-CoV-2 even with seroconversion does not necessarily translate to guaranteed total immunity.¹⁵ If that is the case, it may be postulated that the number of reinfection cases will skyrocket as the pandemic worsens throughout the world. All individuals who recovered from COVID-19 should take identical precautions with the people who have not met the virus yet. Another implication involves effective vaccine design which clearly will be a challenge with different pathogenic strains circulating among human populations.

Conflict of interest

The authors declare no conflict of interest.

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