

A case series of recurrent clinical symptoms of COVID-19 among tunisian healthcare workers

N. MECHERGUI, H. ZIEDI, A. MGHIRBI, I. YOUSSEFI, H. BEN SAID, I. YOUSSEF N. LADHARI

Occupational health department of Charles Nicolle Hospital of Tunis

ABSTRACT

Introduction : Healthcare workers(HCW) are the most exposed to SARS COV-2 infection due to their repeated exposure to infected patients. Some cases of reinfection with the novel coronavirus among HCW have been reported.

Methods : We collected cases of recurrent symptoms of COVID-19 with positive RT-PCR after a symptom-free interval of more than one month, among HCW from Charles Nicolle hospital of Tunis who consulted the occupational health department, during the period from September 2020 to May 2021.

Results : we collected 12 cases. Ten were female. Their mean age was 39 years. The median time between the onset of symptoms in the two episodes was 61.5days [32-168 days].In the first episode, the main symptoms were: asthenia (9/12), cough (9/12), headache and arthralgia(7/12). In the second episode, both dyspnea, and arthralgia were reported in seven cases, anosmia and fever were reported in six cases. Among the reported cases, three had a negative RT-PCR test in the period between the two symptomatic episodes. All cases tested positive for SARS-Cov-2 antibodies, with an average delay of 32.5 days after the onset of symptoms in the second episode.

Conclusion : The probability of SARS-CoV-2 reinfection may increase with time after recovery, because of waning immunity and continued widespread transmission of the virus. Enhancing infection prevention and control measures as well as immunization among HCW is thus needed.

Keywords : COVID-19, SARS-CoV-2, Healthcare worker, Recurrence, Reinfection.

INTRODUCTION

The first confirmed case of COVID-19 in Tunisia was reported on March 3, 2020 [1]. Preventive strategies were implemented. Viral transmission has been slowed down thus, with no daily active reported cases between May 20, and June 14, 2020[2]. The second wave of COVID-19 has occurred after the reopening of the borders on June 27, 2020. Then, daily reported cases increased from September 2020 to March 2021. Healthcare workers (HCW) are the most exposed to SARS COV-2 infection due to their repeated exposure to infected patients. Some cases of reinfection with the novel coronavirus among HCW have been reported [3,4]. The magnitude of this problem is explained by the repeated exposition of the HCW, the first-line fighters against COVID-19. This study aims to report a case series of 12 HCW presenting a second episode of clinical manifestations of COVID-19 virologically confirmed by RT-PCR, after a symptom-free interval.

METHODS

It was a retrospective study collecting all cases of recurrent symptoms of COVID-19 with positive RT-PCR after a symptom-free interval of more than one month, among HCW from Charles Nicolle hospital of Tunis who consulted the occupational health department, during the period from September 2020 to May 2021. Data were collected using a pre-established form containing socio-demographic information (age, gender, and profession) and medical reports (comorbidities, symptoms in the first and second episode, date of the RT-PCR, and result of the serology after the first and the second episode). We elected to use the WHO severity definitions based on clinical indicators, adapted from the WHO COVID-19 disease severity categorization in January 2021 [5].

Free agreement of all patients included in the study was obtained before the consultation of the medical records. The anonymity of the medical data was respected.

CASES PRESENTATION

During the period from September 2020 to May 2021, we collected 12 cases. It was about four nurses, three employees, three biology technicians, and two medical doctors. Ten were female. Their age ranged between 27 to 58

years, with a mean age of 39 ± 9 years. Six patients had comorbidities: asthma (3/12), diabetes (2/12), high blood pressure (1/12), hypothyroidism (1/12), anemia (1/12), and scleroderma (1/12) (Table 1).

All cases underwent to nasopharyngeal swab RNA tests for SARS-Cov-2, which were positives between one to seven days after symptom onset (Table 1).

SARS-CoV-2 ELISA (semi-quantitative enzyme-linked immunosorbent assay) serological tests (IgM and IgG antibodies) were performed between 21 to 60 days (mean = 32.5 days) after the first episode and were reported negative in 11 cases. Later, all cases tested positive for SARS-Cov-2 antibodies, between 13 to 47 days (mean = 28 days) after the onset of symptoms in the second episode.

Among the reported cases, three underwent RT-PCR testing in the period between the two symptomatic episodes, with negative results.

The time elapsed between the onset of symptoms of the two episodes ranged from 32 to 168 days (median = 61.5 days). Thus a long symptom-free period of 60 days on average was observed.

In the first episode, the main symptoms were: asthenia (9/12), cough (9/12), headache and arthralgia (7/12), diarrhea (5/12), chest pain (4/12), fever and dyspnea (3/12) (Table 2). In the second episode, both dyspnea and arthralgia were reported in 7 cases, and fever was reported in 6 cases. Anosmia was observed only in one case in the first episode but in 6 cases in the second episode (Table 2).

None of our cases presented with severe or critical COVID-19. All cases progressed without complications in both episodes under symptomatic medications.

All cases were not yet vaccinated at the time of our study.

DISCUSSION

1. Reinfection or reactivation?

In this study, we reported 12 cases of HCW (four nurses, three employees, three biology technicians, and two medical doctors) who had two episodes of symptoms related to COVID-19. All cases were confirmed by RT-PCR, with a long symptom-free period and negative serological tests between the two episodes, and three had a negative RT-PCR test in the period

between the two symptomatic episodes suggesting reinfection.

The time elapsed between the onset of symptoms in both episodes ranged from 32 to 168 days (median = 61.5 days) which is in the line with the short window duration of 28 days to 60 days in the literature.

There are numerous reports of patients who tested positive again after two consecutive negative PCR tests or after clinical recovery [6, 7]. In some studies, this has been attributed to false-negative PCR results at discharge, prolonged shedding of SARS-CoV-2, or increased replication of the virus following discontinuation of the drug after recovery from clinical symptoms [8, 9].

SARS-CoV-2 reinfection criteria remain not fully clarified. In terms of diagnostic testing criteria, several public health organizations proposed different practices for identifying and counting possible SARS-CoV-2 reinfection cases. The Centers for Disease Control and Prevention (CDC) examined appropriate periods following initial SARS-CoV-2 infection or illness to investigate reinfection. Since August 2020, CDC has recommended against the need for retesting persons with asymptomatic infection within 90 days of the first SARS-CoV-2 infection or illness because evidence to this date suggests that reinfection does not occur within this time window [10]. In their update, on 27 October 2020, CDC proposed two-time windows for investigation for suspected cases of SARS-CoV-2 reinfection: a time window of 90 days after initial infection or illness for persons with or without COVID-19-like symptoms or a time window of 45–89 days after initial infection/illness for persons with COVID-19-like symptoms [11]. Moreover, a case definition for suspected COVID-19 reinfection was developed and published by the European Centre for Disease Prevention and Control (ECDC) on 15 March 2021. A suspected COVID-19 reinfection case was defined as a positive PCR or rapid antigen test (RAT) sample ≥ 60 days following a previous positive RT-PCR, a previous positive RAT, or a previous positive serology (anti-spike IgG Ab) [12,13].

We reported cases of recurrence of COVID-19 symptoms concomitant with positive RT-PCR results that could represent either a viral reactivation or reinfection. A control RT-PCR following clinical recovery was performed in only three of our patients. The interpretation of this

phenomenon is subject to discussion because the detection of the viral genome by RT-PCR persisted in some cases for up to 6 weeks [14]. Another factor supporting a new SARS-CoV-2 infection is the presence of anosmia and ageusia in five of our patients during the second episode. These signs have shown high specificity and positive predictive value for COVID-19 in outpatients [15]. These results allow us to suggest reinfection rather than viral reactivation.

2. Challenges in defining Long COVID-19

As of the end of 2020, the time of our study, at least 239 papers and preprints about the post-acute effects of COVID-19 had been released, and approximately 20 additional papers become available each month [16]. No standard framework has been established for identifying symptoms associated with Long COVID at this date. Most of the studies analyzed in a systematic review [17] reported more than 50 long-term effects of COVID-19. The authors concluded that the symptoms of Long COVID are extremely heterogeneous and that the assessment of these symptoms varies widely among studies. No consensus has been reached on the definition and chronology associated with persistent COVID-19 symptoms until the latest WHO document of 6 October 2021[18], where the term 'post-COVID-19 condition' has been proposed to describe 'individuals with a history of probable or confirmed SARS V-2 infection, usually three months from the onset of COVID-19 with symptoms and that last for at least two months and cannot be explained by an alternative diagnosis. Ambiguity in defining the Long COVID is based on an elapsed acute infectious period, but in our study timeline, the relationship between the timing of COVID-19 symptoms in consecutive SARS-CoV-2 infections was not well understood [19].

3. Host susceptibility to the virus

Three elderly patients with two episodes of SARS-COV2 infection were reported by Lafaie & al [20]. These patients presented a recurrence of clinical signs concomitant with positive RT-PCR results within more than 30 days; however, as the symptom-free period was short, the authors suggested a recurrence of symptoms and not reinfection. According to the authors, the absence of IgG antibodies in two of the patients

would support the hypothesis of a recurrence and could be related to the immunodepression in elderly patients. In our series, 50 % of our patients had comorbidities but they were mainly young. A long symptom-free period of 60 days on average was observed, which is longer than the average time reported for the negatization of the RT-PCR test.

Napoli et al [21, 22] showed in their studies that the severe form of COVID-19 occurs especially in the elderly population (65 years and older) probably owing to the higher rate of pre-existing cardiovascular comorbidities as well as increased frailty and immunosenescence. The role of comorbidities as predictors of symptomatic SARS-CoV-2 reinfection was not particularly analyzed in our study since the lack of multiple analyses [23].

4. Immune response against SARS-CoV2

In our series, serological tests performed between the two episodes of infection were reported as negative in 11 patients. Later, all cases tested positive for SARS-Cov-2 antibodies after the onset of symptoms in the second episode. Several studies have discussed the immune response against SARS-CoV-2. The humoral response against SARS-CoV-2 was found to be similar to that against other coronavirus infections, involving the characteristic production of IgM and IgG. At the onset of SARS-CoV2 infection, B cells elicit an early response against protein N, while antibodies against protein S can be detected 4-8 days after the onset of the first symptoms [24,25].

IgA, IgG, and IgM antibodies specific to SARS-CoV2 have been detected after the onset of symptoms at different times in infected patients. A persistent level of IgG was detected for a longer period, while IgM levels started to decline after 3 months [26].

The relationship between clinical presentation and antibody response was unclear. The patients reported in our cases presented with the first episode with mild symptoms that failed to generate a satisfactory immune response, hence the lack of seroconversion. This is in the line with the consideration of Jing Lu and al in their research paper. They proposed a possible explanation for the re-positive detection of the SARS-CoV-2 genome, which is that some patients with COVID-19 may have insufficient immune responses and neutralizing antibodies

to completely clear the infection [27]. The results of a Chinese study revealed that patients with severe clinical COVID-19 infection produced higher antibody titers, including critical patients who showed significantly higher serum antibody values than non-critical cases at 2 weeks of symptom onset [28]. However, antibody detection and higher titers have not always been found to correlate with clinical improvement, and mild symptoms of COVID-19 disease may disappear before seroconversion which is the case in our series [29, 30]. The emergence of new viral strains of SARS-CoV-2 with increased virulence is a new matter of concern, particularly about possible reinfection. Some studies suggested considering criteria for true reinfection, including isolation of the complete genome and identification of different viral strains in both episodes of infection (not just genomic fragments). The evidence of virus infectivity in the second episode by virus culture in addition to the comparison of immune responses in two episodes and the re-exposure to a COVID-19 patient in the second event should also be considered [31].

Limitations: Some limitations were found during this study as the absence of cell culture and genomic sequencing in both episodes of infection. Therefore, the hypothesis of reactivation or prolonged excretion of the virus cannot be ruled out. Also, the effective role of comorbidities and age as predictors of COVID-19 reinfection was not proven since the lack of multiple analyses.

CONCLUSION

The probability of SARS-CoV-2 reinfection may increase with time after recovery, because of waning immunity and continued widespread transmission of the virus. The risk of reinfection also depends on the host susceptibility, the immune status, and the likelihood of re-exposure to new viral variants of COVID-19. HCW infected with COVID-19 will likely require post-recovery surveillance of symptoms, with retesting for SARS-CoV-2 for those who present recurrent clinical manifestations of the disease. We emphasize the importance of maintaining the use of PPE and hand hygiene even after curing COVID-19 when returning to work.

COMPETING INTERESTS

The authors declare no competing interest.

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Table 1: Demographic, clinical, and laboratory characteristics of the cases.

<i>Variables</i>	<i>Patient 1</i>	<i>Patient 2</i>	<i>Patient 3</i>	<i>Patient 4</i>	<i>Patient 5</i>	<i>Patient 6</i>	<i>Patient 7</i>	<i>Patient 8</i>	<i>Patient 9</i>	<i>Patient 10</i>	<i>Patient 11</i>	<i>Patient 12</i>
Age (years)	30	37	27	36	34	44	34	58	38	35	55	40
Gender	Male	Female	Female	Female	Male	Female	Female	Female	Female	Female	Female	Female
Comorbidities	Asthma	-	Asthma, anemia	-	-	Asthma	-	Scleroderma HTA	Insulin dependent diabetes	-	Diabetes Hypothyroidism	-
Date of first infection	September 19, 2020	November 5, 2020	October 2, 2020	December 1, 2020	September 15, 2020	November 2, 2020	December 4, 2020	December 7, 2020	December 13, 2020	October 2, 2020	December 25, 2020	December 15, 2020
Time between symptoms and RT-PCR (days)	2	1	3	3	-	1	1	2	2	3	1	1
Date of first RT-PCR	September 21, 2020	November 6, 2020	October 5, 2020	December 4, 2020	September 15, 2020	November 3, 2020	December 5, 2020	December 9, 2020	December 15, 2020	October 5, 2020	December 26, 2020	December 16, 2020
RT-PCR between the two episodes	Negative (06/10/2020)	-	-	-	Negative (29/09/2020)	-	-	-	-	Negative (20/10/2020)	-	-
Result of the serology after the first episode	Negative	Negative	Negative	Negative	-	Negative	Negative	Negative	Negative	Negative	Negative	IgM/IgG/IgA positive
Time between first episode and serology (days)	23	32	30	29	-	36	40	21	29	60	30	28
Date of second infection	October 29, 2020	December 12, 2020	December 19, 2020	January 2, 2021	January 16, 2021	January 7, 2021	January 26, 2021	January 26, 2021	February 8, 2021	March 19, 2021	April 1, 2021	April 26, 2021
Date of second RT-PCR	October 31, 2020	December 17, 2020	December 26, 2020	January 5, 2021	January 17, 2021	January 8, 2021	January 27, 2021	January 27, 2021	February 12, 2021	March 21, 2021	April 3, 2021	April 30, 2021
Time between episodes (days)	40	37	75	32	123	66	53	50	57	168	96	132
Time between two RT-PCR (days)	40	41	82	32	124	66	53	49	59	167	98	135
Time between second episode and serology (days)	34	13	25	32	18	27	23	37	27	24	47	-
Result of the second serology	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgM and IgG positive	IgG positive	-

Table 2: Symptoms in the first and the second episode.

Patient		1		2		3		4		5		6		7		8		9		10		11		12	
Episode Number		1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd	1 st	2 nd
Symptoms	Fever	N	Y	N	Y	N	Y	N	Y	N	N	N	Y	Y	N	Y	Y	N	N	N	N	Y	N	N	N
	Dyspnea	Y	Y	N	Y	Y	N	N	Y	N	N	N	Y	N	N	N	Y	N	N	Y	Y	N	Y	N	N
	Thoracic pain	N	N	N	N	Y	N	N	N	N	N	N	N	Y	Y	N	N	N	N	Y	Y	Y	N	N	N
	Cough	N	N	Y	N	Y	Y	Y	N	Y	N	Y	N	N	N	Y	N	Y	N	N	Y	Y	Y	Y	N
	Headache	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	N	Y	Y	Y	N	N	N	N	N	N	Y	Y
	Asthenia	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	N	Y	Y	N	N	N	Y	Y	Y	Y	Y
	Arthralgia	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	N	N	N	N	Y	N
	Anosmia	N	Y	N	Y	N	Y	Y	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	Y	N	N
	Dysgeusia	N	Y	N	Y	N	Y	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	N	N	Y	N
	Diarrhea	N	Y	N	Y	N	Y	Y	N	N	N	N	Y	N	Y	Y	Y	N	N	Y	Y	N	N	Y	N
	Emesis	N	N	N	Y	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Nausea	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N
	Sore throat	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Rhinorrhea	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N	N	N	N	N	N	N	N

Y: Yes N: No