



SARS-CoV-2, a virus with many faces: a series of cases with prolonged persistence of COVID-19 symptoms

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Summary Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as the causative agent of the ongoing pandemic, has spread into more than 200 countries to date. The disease which is caused by the virus is termed COVID-19. In most cases, it presents at first like common flu with cough and other respiratory symptoms. Nevertheless, other symptoms have been reported, such as a feeling of extreme fatigue, gastrointestinal symptoms, or acute onset of olfactory and gustatory dysfunction. Here we report a series of 10 cases (1 male, 9 females) observed between February and April 2020, with an undulating appearance and disappearance of symptoms. Weeks passed before the diagnosis was established. Symptoms resolved rapidly after treatment with hydroxy-

chloroquine. It seems that the course of COVID-19 can be mild or moderate but with a long persistence of symptoms, and may therefore remain obscure. This may cause a public health issue because of the long infectivity of these patients.

Keywords COVID-19 · SARS-CoV-2 · Iran · Prolonged symptomatology · Public health

Introduction

Despite the great progress of medical approaches, viral diseases continue to represent a serious threat to public health. Several viral epidemics, including the severe acute respiratory syndrome coronavirus (SARS-CoV) developing 2002 to 2003, H1N1 influenza emerging in 2009, and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012, drew massive attention and effort [1–3].

Most recently, a new respiratory infection was reported in Wuhan, China, which has led to a worldwide pandemic. The new virus which was initially called 2019-nCoV, termed SARS-CoV-2 virus according to the International Committee on Taxonomy of Viruses (ICTV) based on its similarity to the SARS causing virus (SARS-CoV) [4–6].

The most important feature of the new virus is the contagious potency and high rate of spread globally. This potential to become a pandemic worldwide seems to be a serious public health threat. The main route of viral spread is from person to person, through inhaling small infectious droplets which can also land on different surfaces and be picked up by others. Moreover, aerosols containing the virus as a result of medical procedures could be breathed in by nearby individuals and easily lead to progression of the infection [7, 8]. Currently, the therapeutic strategies to handle the infection are mostly supportive, al-

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though several clinical trials are underway to come up with a preventive or therapeutic vaccine simultaneously [9, 10].

According to the WHO report on 18 June 2020, there have been 8,061,550 COVID-19 confirmed cases from 216 countries and, unfortunately, 440,290 related deaths [11]. Since February 15, 96,091 confirmed cases were reported in Iran with the recovery rate of 76,318 and 5574 total deaths [12]. The most common COVID-19 symptoms include fever, dry cough, weakness, and fatigue. Other symptoms including myalgia, malaise, shortness of breath, sore throat, nasal congestion, or diarrhea have been also observed in some patients. These symptoms are normally mild, develop gradually, and could be very limited in some people who normally recover from the symptoms after 10–14 days. The majority of infected individuals (nearly 80%) recover from the disease without any hospital treatments; however, they are supposed to stay at home according to the standard guideline of quarantine and isolation. Around 20% of people who get COVID-19 develop serious illness and experience difficulty in breathing with severer symptoms such as dyspnea and heavy chest feeling. Moreover, people with underlying medical conditions like diabetes, high blood pressure, heart and lung problems, or cancer could be exposed to a higher risk of developing a serious form of the illness resulting in respiratory failure that requires mechanical ventilation and support in an intensive care unit (ICU) [1, 11, 13, 14].

Case series of patients suffering from prolonged COVID-19 symptoms

Apart from these two groups, there has recently been another presentation of the illness in which infected people suffer from respiratory symptoms for a long time, but these problems were not severe nor were they fully resolved. In fact, they represented a chronic condition with on and off cough or fever and weakness which lasted for 2 months. It's a long-lasting situation which can overwhelm patients. This condition has been observed in 10 cases, including 1 male and 9 females who referred to the Department of Clinical Research, Pasteur Institute of Iran, and also the Valiasr Hospital of Arak University of Medical Sciences to seek medical care in early April, 2020. They had referred to the other medical centers in February, when the disease was not a pandemic. Therefore, seasonal allergic events or bacterial sinusitis were diagnosed. However, most of the symptoms were still there after allergic-related medicine and several antibiotics such as azithromycin, amoxicillin, and levofloxacin were taken for 2 months based on the clinical assessment. The applied medicines were not effective to overcome the symptoms. Then, at the time of these patients visiting, we considered the predominant circulating virus in our country according to the insufficient treatment outcome. In addition, due to some positive cases of COVID-19 existing in their relatives, we suggested these cases to be tested for COVID-19 by real-time PCR and/or spiral lung CT scan according to patient symptoms and conditions. Finally, we found

Table 1 Synopsis of cases identified during February through April 2020 at a tertiary hospital in Iran with long persistence of COVID-19 symptoms before diagnosis

Case	Age (years)	Sex	Previous health condition	COVID-19 symptoms	Duration before diagnosis	Previously suspected disease	PCR result
1	68	Male	Chronic high blood pressure	Dry cough, headache, severe sweating, shivering, loss of smell, mild on/off fever, and diarrhea	1.5-2 months	Flu plus sinusitis and allergy	Positive
2	39	Female	No underlying diseases	Progressive dry cough, nasal congestion, high diaphoresis, loss of smell, and weight loss for 2 months	2 months	Flu plus sinusitis and suspicious of malignancy	Positive
3	42	Female	No underlying diseases	Mild on/off fever, dry cough, fatigue	41 day	Common cold and allergy	Positive
4	38	Female	No underlying diseases	Dry cough, weakness	48 days	Common cold and allergy	Positive
5	41	Female	No underlying diseases	Dry cough, nasal congestion, weakness	52 days	Allergy plus sinusitis	Positive
6	50	Female	No underlying diseases	Mild on/off fever, dry cough, fatigue, nasal congestion	58 days	Flu plus sinusitis	Positive
7	43	Female	No underlying diseases	Dry cough, fatigue	44 days	Common cold and allergy	Positive
8	32	Female	No underlying diseases	Dry cough, fatigue	59 days	Common cold and allergy	Positive
9	30	Female	No underlying diseases	Dry cough, fatigue	45 days	Common cold and allergy	Positive
10	49	Female	No underlying diseases	Dry cough, nasal congestion	48 days	Common cold plus sinusitis	Positive

that these cases had been suffering from COVID-19 for a long time.

Among the cases, there was a 68-year-old man who had chronic high blood pressure and suffered from dry cough, headache, severe sweating, shivering, loss of smell, mild on/off fever, and diarrhea. These symptoms had lasted for 1.5–2 months, shifting mostly to severe dry cough before he referred to us. According to the patient's description, most of his symptoms were resolved during 2 months, except the dry cough which overwhelmed him. When the COVID-19-related test was applied to him, he was characterized as infected and the chest CT confirmed this finding as well.

The other case was a 39-year-old woman with no underlying condition, suffering from progressive dry cough, nasal congestion, high diaphoresis, loss of smell, and weight loss for 2 months. Most of her symptoms were resolved and she gained weight after 2 months. However, the dry cough and extreme feeling of weakness made her visit again after 2 months and she was tested for COVID-19 which led to a positive result. The related data are shown in Table 1.

The rest of the cases were females aged from 30 to 50 years with no underlying diseases who experienced prolonged mild on/off fever, cough, nasal congestion, and extreme feeling of weakness and fatigue for nearly 2 months. The presence of SARS-CoV-2 was proved by the standard tests.

The standard treatment based on the national COVID-19 guideline, 250 mg of hydroxychloroquine, was applied twice a day on an outpatient basis for 5 days for all cases. The follow-up showed that they were fully recovered after medicine consumption and the patients even declared that they felt much better 2 days after the beginning of treatment.

Discussion

SARS-CoV-2 has affected the global population with no effective vaccine yet. The current coronavirus disease 2019 (COVID-19) outbreak is considered a worldwide emergency. Its rapid spread and high mortality rate have led to many challenges. COVID-19-infected patients can develop pneumonia, severe symptoms of acute respiratory distress syndrome (ARDS), and multiple organ failure [15–17]. Serology tests have been widely applied to assess IgG in COVID-19 patients, which have shown varying durations in individuals. Protective and long-lasting immune responses to viral infections usually arise from the combined actions of both immune arms, i.e., humoral and cellular directed by B cell and T cell activation [18–21].

The majority of viral infections in humans induce both CD4+ and CD8+ T cell activation and proliferation. Therefore, SARS-CoV-2 infection is not unique in this regard. CD4+ T cell depletion in SARS-infected patients resulted in less production of neutralizing antibodies and Th1 cytokines and subsequently induced lower recruitment of inflammatory

monocytes in the lung, suggesting that the CD4-mediated control of COVID-19 infection most probably operates through antibody-/cytokine-dependent mechanisms. Therefore, COVID-19 prolongation may stem from weak antibody generation, short-lived antibodies, or lack of cellular immunity activation [22–25].

In this study we applied hydroxychloroquine for the prolonged form of the disease with mild presentation, which resulted in patients' recovery. Hydroxychloroquine has been widely used in Iran in COVID-19 patients who present mild to moderate clinical symptoms, specifically those who suffer from fever. This treatment has been evaluated as practical although it is not applicable in severe forms of the disease. Moreover, its antiviral and immunomodulatory effect for these patients was effective enough.

Conclusion

SARS-CoV-2 shows different presentations in individuals, from an asymptomatic level to a long-lasting situation or even a severe condition which leads to death in up to 11%[26]. Although most infected people are characterized to have mild symptoms for 10–14 days, the newly reported cases reveal other unknown facts of the virus. Considering this issue, it could be suggested that COVID-19-related test application for a chronic allergic-like condition is highly valuable to detect COVID-19 without losing time in order to stop its transmission and support the infected individuals at the right time. Taken together, this observational study indicated that prolonged COVID-19 presentation with mild symptoms can endure for several weeks and hydroxychloroquine consumption was found practical for patients' resolution.

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Compliance with ethical guidelines

Conflict of interest M. Sofian, A.A. Velayati, M. Banifazl, F. Fotouhi, M.S. Larijani, N. Afzali, and A. Ramezani declare that they have no competing interests.

Ethical standards The study design was approved by the Arak University of Medical Sciences Ethical Committee (IR.ARAKMU.REC.1399.002).

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