

Coronavirus Pandemic

Long-term application of hydroxychloroquine could not prevent the infection of COVID-19

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Abstract

Introduction: Current pandemic of the coronavirus induced disease 2019 (COVID-19) presents an urgent issue to the world due to lack of vaccine and medication. Hydroxychloroquine (HCQ) has generated a lot of controversies whether it is effective in prevention and treatment of COVID-19. Current report presents a 63-year-old woman who has taken HCQ for many years but still infected by COVID-19.

Case presentation: A patient with rheumatoid arthritis came to the clinic with fever and sore throat. The patient has been treated with 200 mg HCQ per day since 2016. Laboratory tests showed that the patient had lymphopenia, increased levels of high-sensitive C-reactive protein (hs-CRP) and serum Interleukin-6 (IL-6). Chest radiography showed that the patient had pneumonia. Throat swab test confirmed COVID-19 positive. On admission, she was treated with nebulized interferon alfa-2b, oral Lopinavir/Ritonavir, and ceftriaxone sodium for the COVID-19 in addition to HCQ. The patient stayed in hospital for 18 days, recovered from oxygen intake, and eventually discharged from hospital. Follow up investigation showed the patient developed antibody against COVID-19.

Conclusions: Long-term application of HCQ could not prevent COVID-19 infection, but whether HCQ exerts benefit to alleviation of clinical symptoms and duration of hospital stays remains to be further investigated.

Key words: COVID-19; case report; hydroxychloroquine; treatment; prevention.

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Introduction

Global pandemic of COVID-19 is a serious emergent public health concern because the virus is highly contagious. According to the latest statistics of the World Health Organization, more than 49 million people have been confirmed to be infected and a total of 1.2 million deaths was reported on 8 November 2020 [1]. Although several antiviral drugs such as Interferon alfa, Remdesivir, Lopinavir/Ritonavir, and Arbidol have been used to treat COVID-19, no specific and effective drugs have been identified so far. Recently, HCQ has been suggested to treat patients with SARS-

CoV-2 infection due to an *in vitro* report [2]. HCQ is derived from quinoline (CQ) and has been used to treat not only malaria, but also autoimmune disorders such as lupus and rheumatic diseases due to its immunomodulatory effects [3]. Therefore, HCQ may not have direct antiviral effects against COVID-19 [4, 5]. In order to provide some information of HCQ in the prevention and treatment of COVID-19, we report a COVID-19 patient who has taken HCQ for many years to evaluate the feasibility of HCQ for patients with COVID-19 infection.

Case presentation

On 23 January 2020, a 63-year-old woman, who came back from Wuhan on 16 January 2020, presented to the urgent care clinic in Ningbo Medical Center Lihuli Hospital, with a 2-day history of fever as high as 39.5°C, mild cough and sore throat. This patient has a medical history of rheumatoid arthritis and has been treated with oral HCQ (200 mg per day) since 2016. She denied to have history of the hypertension, diabetes mellitus and cardiovascular diseases. The laboratory tests showed low lymphocyte percentage (12.2%) and high hs-CRP value (10.0 mg/L) (Table 1). Chest radiography showed increased markings in both lungs and reduced opacity in the lower lobe of the left lung (Figure 1). Throat swab tests were positive for SARS-CoV-2 by PCR analysis. Therefore, the patient was admitted to hospital as COVID-19 on 24 January 2020. On admission, the physical examination showed body temperature of 38.2°C, pulse of 92 beats per minute, respiratory rate of 18 breaths per minute and blood pressure of 145/92 mmHg. During hospital stay, the patient still took oral HCQ (200 mg) once per day to treat rheumatoid arthritis. At the same time, she

received nebulized interferon alfa-2b (6,000,000 international units) twice per day and oral Lopinavir/Ritonavir (200 mg/50 mg) twice per day for

Figure 1. Chest Radiographs (Jan 23, 2020) showed increased markings in both lungs and reduced opacity in the lower lobe of the left lung.

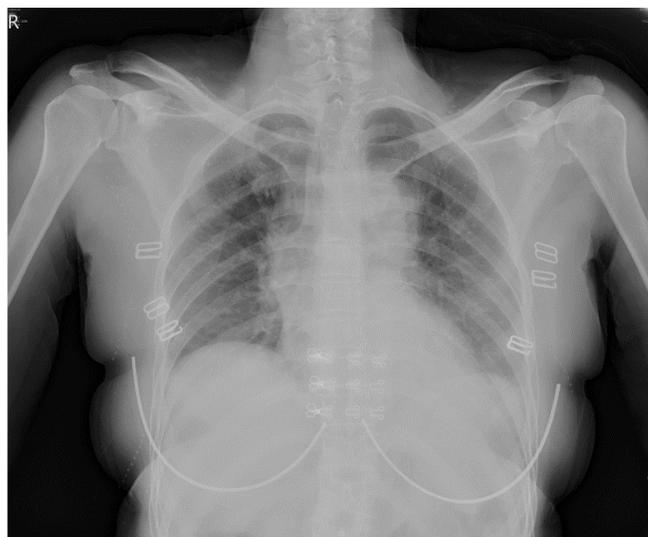


Table 1. Clinical Laboratory Results.

Measure	Jan 23, 2020	Jan 25, 2020	Jan 29, 2020	Feb 1, 2020	Feb 5, 2020	Feb 8, 2020	Feb 10, 2020	Apr 27, 2020
White blood cell(/mm ³)	5,400	4,200	4,800	7,400	4,300	5,600	—	5,200
Neutrophil, %	79.3*	71.3	75.0	77.4*	75.5*	79.1*	—	76.3*
Lymphocyte, %	12.2*	21.1	14.3*	11.6*	15.0*	13.0*	—	16.6*
Monocyte, %	7.9	7.4	10.1*	10.5*	7.4	7.0	—	5.3
Eosinophil, %	0.2*	0.0*	0.2*	0.4	2.0	0.9	—	0.9
Hemoglobin (g/L)	116	117	108*	110*	97*	100*	—	128
Platelet (/mm ³)	245,000	215,000	229,000	328,000	490,000*	458,000*	—	327,000
Total bilirubin (μmol/L)	—	5.2	9.4	9.0	2.8	2.8	—	—
AST (IU/L)	—	20	28	22	20	22	—	—
ALT (IU/L)	—	14	15	17	17	23	—	—
Albumin (g/L)	—	39.8	34.9	39.0	32.2	34.0	—	—
Creatinine (μmol/dL)	—	67.8	69.0	62.0	54.0	53.6	—	—
Urea (mmol/L)	—	3.35	3.20	2.95	3.48	4.48	—	—
Prothrombin time (s)	—	11.4	10.9	12.8*	11.3	10.9	—	—
Pro-calcitonin (ng/mL)	—	0.032	0.090	0.090	< 0.100	< 0.100	—	< 0.100
Hs-CRP (mg/L)	10.00*	29.40*	83.41*	124.90*	16.23*	15.06*	—	< 3.10
IL-2 (pg/ml)	—	—	—	1.42	—	—	—	—
IL-4 (pg/ml)	—	—	—	1.80	—	—	—	—
IL-6 (pg/ml)	—	—	—	24.23*	—	—	—	—
IL-10 (pg/ml)	—	—	—	4.59	—	—	—	—
TNFα (pg/ml)	—	—	—	1.32	—	—	—	—
IFNγ (pg/ml)	—	—	—	2.74	—	—	—	—
SARS-CoV-2 virus nucleic acid	Positive	—	—	—	Positive	Negative	Negative	Negative
(COVID-19)IgM antibody	—	—	—	—	—	—	—	Negative
(COVID-19)IgG antibody	—	—	—	—	—	—	—	Positive

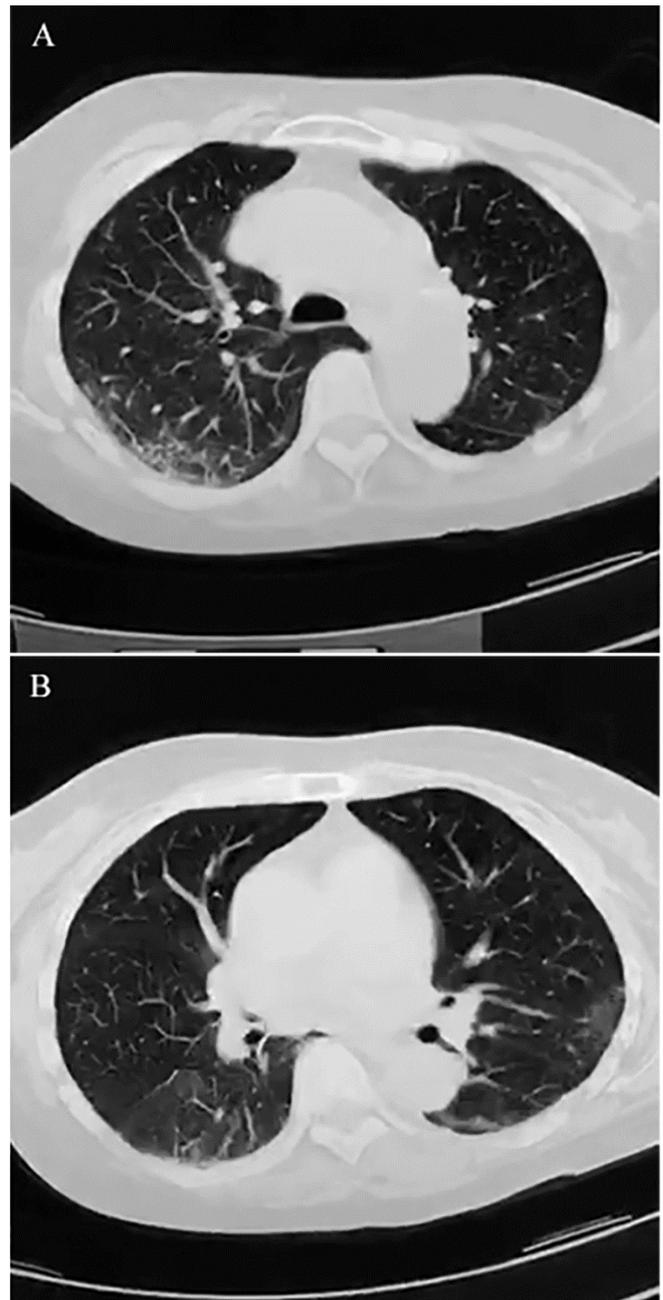
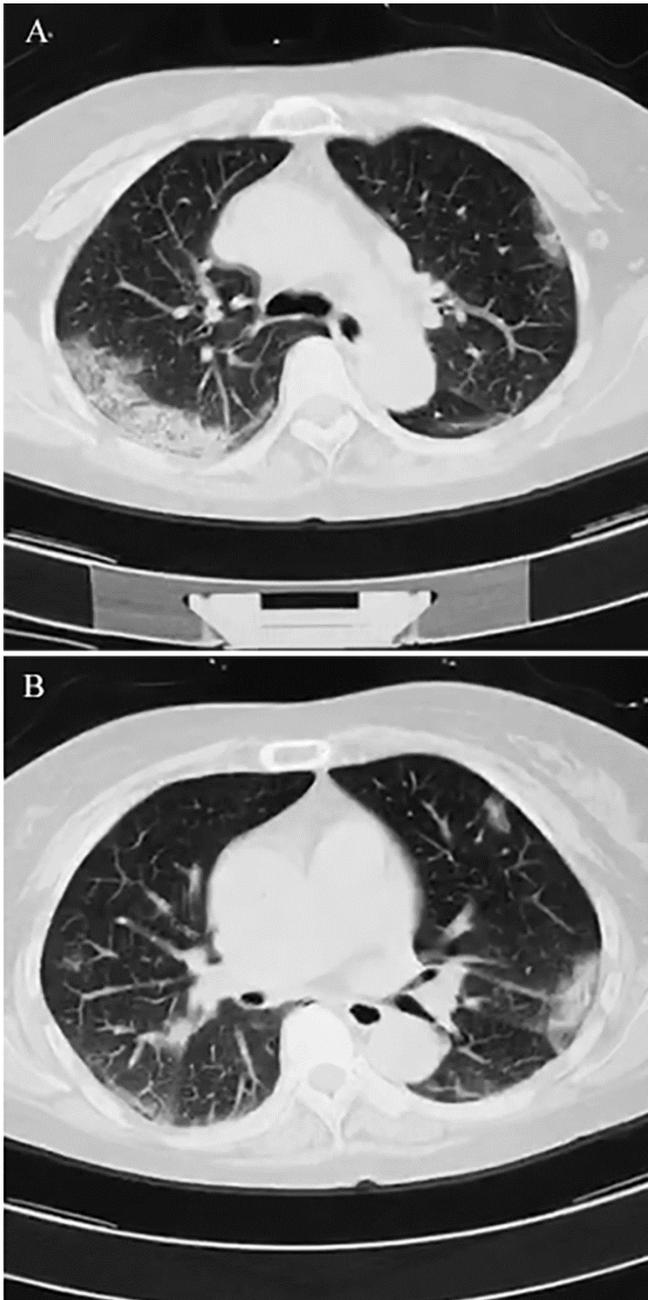
AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; hs-CRP: High-sensitive C-reactive protein; IL: interleukin; TNFα: Tumor Necrosis Factor-alpha; IFNγ: Interferon-gamma; COVID-19: Coronavirus induced disease 2019; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; Ig: immunoglobulin.

the treatment of COVID-19. Considering presence of bacterial infections, she was also given intravenous ceftriaxone sodium (2.0g) once per day. On the afternoon of hospital day 2 (26 January 2020), the patient developed diarrhea and retrosternal pain radiated to the shoulder region. The patient had the electrocardiography (ECG) test and results suggested there was no myocardial infarction. She was started on supplemental oxygen, delivered by nasal cannula at 3 liters per minute for 2 days. The patient’s intermittent

fever lasted 15 days and her clinical conditions improved. Laboratory tests displayed that the patient had lymphopenia and increased hs-CRP during hospitalization (Table 1). A chest CT taken on hospital day 6 (29 January 2020) showed multiple ground-glass opacities in both lungs, which presented a hyperdense shadow with hazy borders (Figure 2). On hospital day 13 (Feb 5, 2020), the follow-up chest CT showed an obvious improvement with a reduction of pulmonary exudative lesions compared with the last CT (Figure 3). After two negative detections of SARS-CoV-2 virus

Figure 2. Chest CT (Jan 29, 2020) showed multiple ground-glass opacities in both lungs, which presented a hyperdense shadow with hazy borders.

Figure 3. Chest CT (Feb 5, 2020) showed a reduction of pulmonary exudative lesions.



nucleic acid, she was discharged for outpatient follow-up. On 27 April 2020, the patient was confirmed as COVID-19 IgG positive by an IgM-IgG antibody test at the follow-up (Table 1). This case is one of the ordinary cases of COVID-19. Throat swab tests were first negative for SARS-CoV-2 on hospital day 16. The time of hospitalization was 18 days.

Discussion

Recent research showed that the median duration of viral shedding was 24 days among COVID-19 patients who were mild to moderate [6], and the median hospitalization time was 19 days [7]. In our case, duration of virus shedding was 15 days and hospital length of stay was 18 days. Indexes of liver function and renal function were within the normal range as evidenced by normal aspartate aminotransferase (AST), alanine aminotransferase (ALT) and serum creatinine. Notably, Th1/ Th2 cytokines test showed that the level of serum IL-6 was 24.23 pg/ml, and the levels of serum IL-2, IL-4, IL-10, Tumor Necrosis Factor-alpha (TNF α) and Interferon-gamma (IFN γ) were normal. Previous studies reported that the level of IL-6 was positively correlated with mortality [8]. Although the patient had increased IL-6, she was still fortunately survived. In severe cases, laboratory examination showed elevated levels of IL-6, IL-10, IL-2 and IFN γ , as well as lower counts of CD8⁺ T cells [9]. Our patient may also have immune dysfunction especially T cell function.

Recently, HCQ was given to people to protect them from COVID-19 in a publication from The Indian Council of Medical Research. These people include healthy medical staffs in treatment of the confirmed or suspected COVID-19 patients and/or family members of confirmed COVID-19 patients. Moreover, a study has evaluated the effect of HCQ for prophylaxis of COVID-19. Two hundred and eleven persons were employed to evaluate the post-exposure prophylaxis (PEP) of HCQ and the results showed no confirmed cases at the end of the trial [10]. However, it is inconclusive whether PEP will be safe and effective due to no control group. Moreover, some studies also suggest that prophylaxis application of HCQ for patients with COVID-19 might reduce the morbidity of COVID-19 and protect person during the COVID-19 outbreak [11]. However, our case did not seem to support the role of HCQ in prevention of SARS-CoV-2 infection. The patient had been taking HCQ for a long time due to rheumatoid arthritis, but she was still confirmed to have SARS-CoV-2 infection. The current case suggested that HCQ can not completely prevent

the infection of COVID-19. Other reports also showed prophylaxis use of HCQ in prevention of COVID-19 needs to be further explored [12,13].

On the other hand, HCQ may be a promising drug for treating patients with COVID-19 pneumonia [14]. A recent article in *Lancet* reported that HCQ should be considered as an alternative for patients with COVID-19 [15]. An early clinical trial showed that the use of HCQ in COVID-19 patients in China could significantly shorten the time to clinical recovery (TTCR) and promote the absorption of pneumonia [16]. Moreover, two French trials revealed that HCQ had a significant effect on viral clearance in COVID-19 positive patients and its effect was reinforced by azithromycin [17,18]. In the current case, the patient was also received other anti-infective agents. HCQ and ceftriaxone sodium may synergize to alleviate clinical symptoms of the patient. However, it is still unclear what is the underlying mechanism of HCQ in treatment of patients with COVID-19. Further research is needed to explore the efficacy and potential toxicity of the combination. In previous studies, cytokine storms have been observed in critically ill patients with SARS-CoV-2 infection, as demonstrated by increased concentrations of granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10) and TNF α [19]. Additionally, the overactivation of T cells led to severe immune damage in COVID-19 patients [20]. HCQ is considered as an immunomodulator and can reduce inflammation and organ damage by inhibiting antigen processing and MHC-II-mediated auto-antigen presentation to T cells. This process reduces the expression of CD154, T cell activation and other cytokines (IL-1, IL-6 and TNF α). Moreover, HCQ can inhibit the transcription of pro-inflammatory genes via Toll-like receptor signaling and the nucleic acid sensor cyclic GMP-AMP synthase (cGAS) [3,21]. These findings support the notion that HCQ may have the ability to inhibit the production of cytokines and alleviate the clinical symptoms in patients with COVID-19. In this case, there were elevated levels of hs-CRP and IL-6 suggesting an acute inflammatory reaction and cytokine storm. The case was likely to progress to severe type because of age and the use of immunosuppressive drugs. However, the patient's clinical presentations were not severe just showing the symptoms of fever and radiographic pneumonia. The patient stayed in the hospital for 18 days which is about median hospitalization stay. Therefore, was the patient just an ordinary case of COVID-19 at the beginning? Or did long-term

application of HCQ attenuated severity of the patient, otherwise who may become severe type of COVID-19?

Nevertheless, a study of 30 Chinese patients with mild COVID-19 found no difference in recovery rates by using HCQ [5]. In a study of 11 patients with COVID-19 infection receiving HCQ, eight out of eleven patients still remained positive for SARS-CoV-2 RNA in the nasopharyngeal swab test [4]. Furthermore, another research found that using HCQ alone could increase the mortality of COVID-19 patients [22]. Therefore, these findings highlight a significant caution of using HCQ. Some scholars believed that CQ/HCQ was not only useless but also harmful to COVID-19 patients [23,24]. In addition, HCQ is more distributed in the lung, and its concentration in the lung is one hundred times higher than that in the blood. So the function of the pulmonary compartment could be affected due to the high concentration of HCQ [2,25]. Liver injury has been detected in patients with COVID-19 as well [26]. Therefore, it is necessary to monitor indexes of liver function in the course of HCQ treatment. There are also some adverse reactions due to long-term therapy with HCQ such as retinopathy, arrhythmias, serious cutaneous adverse reactions. Therefore, whether HCQ exhibits therapeutic effects on patients with COVID-19 still needs to be further investigated.

Finally, with the widespread use of HCQ/CQ to prevent and treat COVID-19, there is a shortage of HCQ/CQ for patients with rheumatic disease especially in the United States, where exists a significant lack of HCQ/CQ for patients with rheumatoid arthritis and lupus [27]. Therefore, proper prescription of HCQ in patients with COVID-19 should be considered and the media should present accurate and the most updated information to patients with COVID-19. Anyway, the current case report indicates that long-term application of HCQ could not prevent the infection of COVID-19 but whether the application of HCQ in this case attenuated severity of illness in this patients grants to be further investigated with large randomized and controlled clinical trials.

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funders contributed to data analysis, the clinical patient management and follow-up.

Authors' Contributions

XML, FJJ, PAJ, DHJ and YBY contributed to the diagnosis and treatments of the patient. ZY, FJJ, PAJ, DHJ and YBY contributed to data collection and manuscript preparation. CYP, GYW, WBD, KCH and XML contributed to revision of the manuscript. All authors read and approved the final manuscript.

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