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CASE REPORT

Involuntary Movements Following Administration of Hydroxychloroquine for COVID-19 Pneumonia

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ABSTRACT

Hydroxychloroquine (HCQ) has been used as an investigational drug for patients with moderate to severe coronavirus disease 2019 (COVID-19). There have been concerns of potential harms from side effects of the drug. We present a case of a 38-year-old male who was started on HCQ for COVID-19 pneumonia. He was referred for evaluation of myoclonus of all extremities, which resolved after discontinuation of HCQ. The involuntary movements were first reported after the initiation of HCQ, persisted despite improvement in inflammatory and radiologic parameters and eventually resolved after HCQ discontinuation. This supports a possible causality related to adverse drug reactions from HCQ that have not been commonly reported.

Key Words Adverse drug reactions; COVID-19; Hydroxychloroquine; Involuntary movements; Myoclonus; Tremors.

Hydroxychloroquine (HCQ) has potent immunomodulatory effects, and its inhibitory effects on cytokine production and viral proliferation have led to its use in the management of moderate to severe coronavirus disease 2019 (COVID-19) infection.[1] Although HCQ was initially shown to decrease the time to clinical recovery, high-quality evidence of its benefit for such use is lacking, with concerns of potential harms from adverse drug reactions (ADR).[2,3] To our knowledge, this is the first case report with video documentation of an ADR secondary to HCQ use as treatment for COVID-19.

CASE REPORT

We present a case of a 38-year-old male with known diabetes who sought consultation at our institution in March 2020 due to a nine-day history of productive cough, fever and myalgia. He denied any history of travel abroad but was known to have been exposed to a COVID-19-positive patient. In the emergency department, he was febrile at 38°C with an oxygen saturation of 90% at room air. Lung auscultation revealed bibasal crackles and rhonchi on all lung fields. The neurologic examination was unremarkable. Work-up on admission revealed elevated ferritin [4,100.08 ng/mL, normal value (NV) = 21.81–274.66 ng/mL], D-dimer (689 ng/mL, NV = 0–246 ng/mL), lactate dehydrogenase (529 U/L, NV = 85–227 U/L), and transaminases (aspartate aminotrasferase: 143 U/L, NV = 16–63 U/L; alanine aminotransferase: 174 U/L, NV = 15–37 U/L). The white blood cell count, blood urea nitrogen and creatinine were normal. Chest radiography showed patchy hazy opacities on both upper to lower lungs with peripheral predominance (Figure 1A). The reverse transcription polymerase chain reaction (RT-PCR) test for COVID-19 was positive. He was started on HCQ 200 mg/tablet, 1 tablet twice a day and ceftriaxone 2 g intravenously every 12 hours. On the 2nd hospital day, oral lopinavir + ritonavir 400/100

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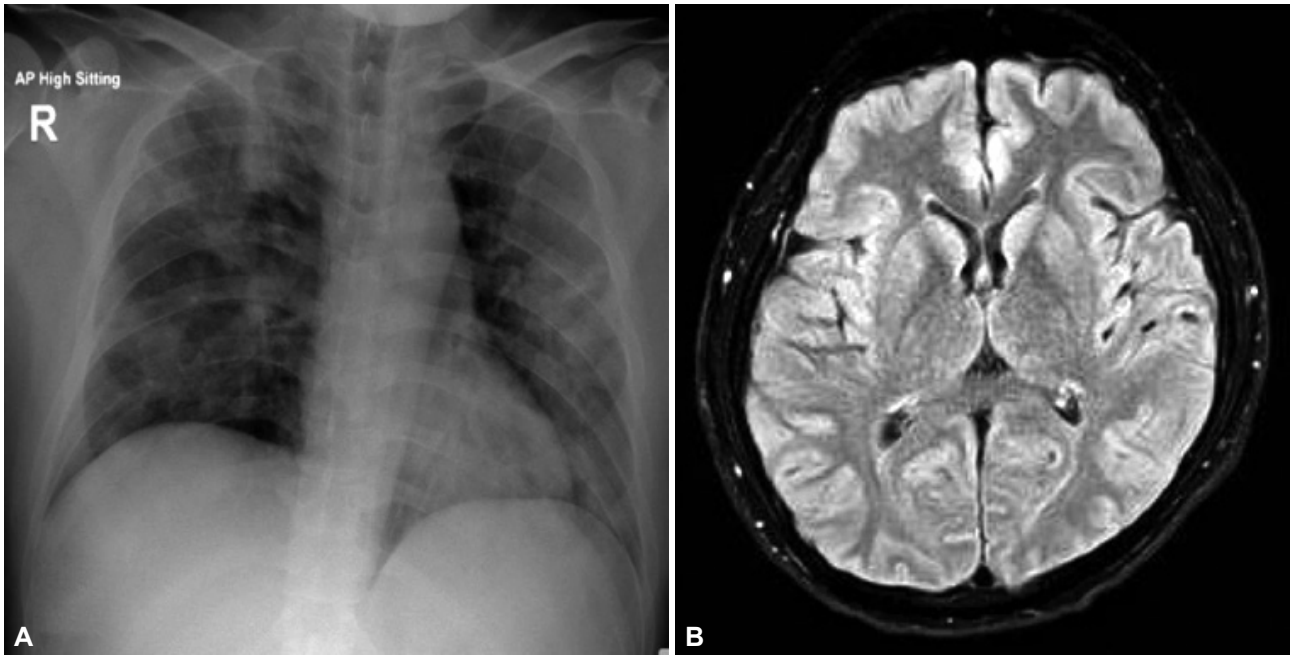

Figure 1. Chest radiography and cranial magnetic resonance imaging of the patient. A: Chest radiography on admission revealed patchy hazy opacities on both upper to lower lungs with peripheral predominance on the left. B: Cranial magnetic resonance imaging with a fluid attenuated inversion recovery sequence was unremarkable.

mg tablet twice a day was added.

On the 5th hospital day, his COVID-19 showed improvement with regression of infiltrates on chest radiography and decreasing ferritin (1,642.99 ng/mL, NV = 21.81−274.66 ng/mL). However, the patient was noted to have involuntary movements that prompted referral to the movement disorders service. On examination, bilateral, asynchronous, irregular myoclonus of the upper limbs was noted (Supplementary Video 1 in the online-only Data Supplement). He was also bedbound due to moderate to severe myoclonus of the bilateral proximal lower limbs, most prominent during attempts to stand from a sitting position (Supplementary Video 2 in the online-only Data Supplement). At this time, his acid-base status, thyroid function tests, and ammonia were within the normal range with improved liver function test results. Plain cranial magnetic resonance imaging was unremarkable (Figure 1B). Due to the persistence of the involuntary movements, HCQ was discontinued on the 7th day. On the 9th day, the upper limb myoclonus was no longer observed. The lower limb myoclonus resolved on the 12th day, allowing the patient to stand up from the bed and ambulate unassisted (Supplementary Video 3 in the online-only Data Supplement). Repeat RT-PCR on the 22nd hospital day was negative. He was discharged with total resolution of all involuntary movements.

DISCUSSION

A total of 105 COVID-19 patients were admitted to our institution between March and April 2020, and approximately 80 were given HCQ. This is the only documented case of myoclonus among these patients.

The safety profile of HCQ is well established in malaria and autoimmune diseases. However, its use for COVID-19 is not well established.[3,4] The therapeutic profile of HCQ in symptomatic COVID-19 patients is largely influenced by metabolic derangements, comorbidities including hepatic and renal dysfunction or the complications of COVID-19 itself.[5] Although the patient's renal function was normal, mild hepatic dysfunction was noted on admission, which was improved on repeat blood exam prior to the onset of involuntary movements.

The myoclonus may be caused by several factors. Our patient was on ceftriaxone, which has been reported to also cause myoclonus. Myoclonus, along with seizures and encephalopathy, were previously reported as manifestations of cephalosporin-related neurotoxicity.[6] However, these were seen in patients with renal dysfunction administered excessive dosages. Neither of these was applicable to our patient. Despite continuing ceftriaxone in our patient, the myoclonus resolved, indicating that ceftriaxone was unlikely to be the cause.

Generalized myoclonus can be seen in several patients with COVID-19, suggesting the possibility of a parainfectious immune-mediated mechanism related to COVID-19.[7] However, the onset of the myoclonus in our patient occurred when the inflammatory parameters for COVID-19 had already begun showing significant improvement.

Neurologic adverse effects such as diplopia, muscular weakness, dyskinesias, and seizures have been reported with HCQ use.[5] However, cases of extrapyramidal adverse events such as parkinsonism, oculogyric crisis and dystonia are reportedly rare, and the dose or duration of treatment that can lead to these symptoms has yet to be explored. One case of dystonia was documented after the administration of a single standard dose of chloroquine.[8] The reduction in involuntary movements and eventual resolution were noted only after discontinuation of HCQ. Although a therapeutic dose of HCQ was given to our patient, comorbidities that may alter blood and target tissue concentrations must be taken into consideration.[9] Our patient had mild hepatic dysfunction on admission, which may have contributed to an altered metabolism of HCQ, possibly predisposing our patient to an ADR.[5] Drug-to-drug interactions should also be considered.

Electromyography could not be performed due to hospital restrictions on procedures during the COVID-19 pandemic. HCQ blood levels were also not requested. Nevertheless, the temporal sequence, resolution after discontinuation and absence of other etiologic candidates or concomitant drug-drug interactions all support a possible causal relationship relating to an ADR.[10]

In conclusion, this case report highlights an ADR from HCQ. The occurrence of myoclonus after HCQ initiation, its persistence despite improvement in inflammatory and radiologic parameters and eventual resolution after drug discontinuation strengthen the possible causality of HCQ-related ADR.

Supplementary Video Legends

Video 1. Upon referral, bilateral, asynchronous, irregular myoclonus of the upper limbs were noted when the arms were outstretched.

Video 2. Moderate to severe myoclonus of the bilateral proximal lower limbs was noted to be most prominent during attempts to stand from a sitting position.

Video 3. The patient was able to ambulate unassisted 2 weeks after discontinuation of hydroxychloroquine.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20091.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Emmaline Zantua Fernando, Jeryl Ritzi Tan Yu, Roland Dominic Go Jamora. Data Curation: Emmaline Zantua Fernando, Jeryl Ritzi Tan Yu, Roland Dominic Go Jamora. Formal Analysis: all authors. Investigation: all authors. Methodology: Emmaline Zantua Fernando, Jeryl Ritzi Tan Yu, Roland Dominic Go Jamora. Project administration: Emmaline Zantua Fernando, Jeryl Ritzi Tan Yu, Roland Dominic Go Jamora. Supervision: Roland Dominic Go Jamora. Validation: Salvador Miclat Abad Santos, Roland Dominic Go Jamora. Visualization: all authors. Writing—original draft: Emmaline Zantua Fernando, Jeryl Ritzi Tan Yu, Roland Dominic Go Jamora. Writing—review & editing: all authors.

Ethical Standards

Consent was secured from the patient for the publication of the information and videos shown in the manuscript.

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