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Letter to the Editor

Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound?

Dear Editor,

The rapidly spreading COVID-19 pandemic resulted in more than 8.5 million cases diagnosed and 450,000 deaths on June 20th, 2020. As described with other coronaviruses, SARS-CoV-2 was first expected to induce a monophasic disease with at least transient immunity. Nevertheless, rare cases of suspected COVID-19 “re-currence” or “reactivation” have been reported, including the description by Ye & Colleagues in this journal of 5 patients with suspected SARS-CoV-2 reactivation after home discharge. Similarly, the COCOREC (Collaborative study COVID REcurrents) study aimed at summarizing clinical and virological data of patients presenting a second confirmed COVID-19 episode, at least 21 days after the first onset, and after a symptom-free interval [oxygen-free and discharge from acute-care unit (ACU), or return to usual clinical state]. Cases were collected retrospectively at a multicenter observational level through the COCLICO (Collaborative CLinicians COVID-19) French study group meeting. A COVID-19 episode was defined by (i) at least one recent major clinical sign of COVID-19 including fever or chills, febrile flu-like-syndrome, dyspnoea, anosmia, or dyseusia; and (ii) a positive SARS-CoV-2 RT-PCR test. Patients were not included if a differential diagnosis (amongst which bacterial, fungal or other viral superinfection, thrombo-embolic complication, secondary organizing pneumonia or interstitial lung disease) could explain the symptom recurrence. After information, all patients agreed with the use of their anonymous medical data. The study has been approved by the Ethic Committee of French Speaking Society of Infectious Disease (CERMIT, number 2020-0503 COVID).

Between April 6th and May 14th, 2020, 11 patients were identified (sex ratio M/F 1.2, median age 55, range [19–91] years). The median duration of symptoms was 18 [13–41] days for the first episode and 10 [7–29] days for the second one for the 7 patients who eventually recovered. Epidemiological and clinical data are summarized in Table 1.

Four healthcare workers (patients 1–4, median age 32.5 [19–43] years) without significant comorbidity had a first mild COVID-19 episode with a complete recovery: three returned to work in COVID units, one had possible COVID re-exposure at home (patient 2). All of them experienced a clinical relapse requiring sick-leave but no hospitalization after a median symptom-free interval of 9 [7–14] days.

In contrast, 7 older comorbid patients (patients 5–11, median age 73 [54–91] years) required ACU hospitalization for both episodes, with a clinical recovery of 11 [4–27] days in the interval. During the first episode, one patient received lopinavir, and three corticosteroids. Six of them required oxygen therapy again during the second episode. Two patients died of ARDS recurrence and another of chronic right heart failure worsening.

All patients had a positive SARS-CoV-2 RT-PCR test in respiratory samples for both episodes (Table 2). They all showed CT scan signs of acute COVID-19 during the second episode, worsening for 4 in 7 when comparison available, including a case of pulmonary embolism without sign of superinfection and no differential diagnosis (supplementary Table). A SARS-CoV-2 serology was available after D21 for nine patients: five were positive, one slightly positive and three negative. A viral culture was performed on Vero E6 cells from naso-pharyngeal swabs of two patients during the second episode; one was positive with a typical cytopathic effect of SARS-CoV-2 and confirmed by RT-PCR; after sequencing, the strain was shown to belong to the B2 European lineage (Rambaut et al., bioRxiv preprint, doi: https://doi.org/10.1101/2020.04.17.046086).

Immunity to SARS-CoV-2 involves both cell-mediated and humoral responses, but its protective role from re-infection along with definitive viral clearance is uncertain. Our case series of 11 patients having experienced two separate symptomatic COVID-19 episodes, associated with viral detection and no evidence for a differential diagnosis, raises two pathophysiological hypotheses underlying these recurrences: viral reactivation or viral reactivation from sanctuaries. In the case of healthy healthcare workers with mild symptoms at both episodes, a re-infection due to the prolonged exposition can be supposed, given the fact that the immune response may fail in this young population with no invasive infection. The second group included vulnerable persons less likely to have met the virus again and having presented two repeated episodes of hypoxemic pneumonia, fatal in three cases. Recurrence might have occurred due to a suboptimal control of the SARS-CoV-2 infection, allowing a second episode of viral replication.

COVID-19 recurrences should be differentiated from secondary complications such as pulmonary embolism or super infection or persistence of traces of viral RNA that can be detected in respiratory samples up to 6 weeks after onset of symptoms in clinically-cured patients.

Immunosuppressive factors such as drugs or pathological conditions could contribute to impair viral clearance and favour SARS-CoV-2 reactivation. Three of the 7 severe patients of our series, and 3 of 4 patients reported by Ye received corticosteroids during the first episode. Furthermore, from our 3 patients who developed no SARS-CoV-2 antibodies more than 21 days after severe symptoms, two received recent chemotherapy and/or rituximab.

An inflammatory rebound triggered by an inappropriate immune response could constitute an alternative explanation to the recurrence of clinical symptoms. Yet, the facts that viral RNA was detected in all patients –some of them with low cycle threshold- and that a viral strain could be cultured during the second episode for one of them rather support re-infection or virus replication's rebound.

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Table 1
Clinical characteristics of COVID 19 first and 2nd episodes, from onset of first episode (D1) to last follow-up (home-care patients: patients1–4; hospitalized patients: patients 5–11).

| Case | Age | Sex | Past medical history | First episode Clinical characteristics | Treatments | 1st Clinical cure | 2nd episode Clinical characteristics | Treatments | Duration of 2nd episode (days) | Outcome |
|------|-----|-----|----------------------|----------------------------------------|------------|------------------|-------------------------------------|------------|-------------------------------|---------|
| 1    | 19  | F   | None (HCW)           | FLS with no fever-cough-dyspnoea-AO-DG | None       | D18              | FLScough-dyspnoea-chest pain        | None       | on-going                       | home care |
| 2    | 32  | F   | None (HCW)           | Cough-AO-myalgia-headache              | None       | D29              | FLS                                 | None       | 10                            | cured    |
| 3    | 33  | F   | First trimester pregnancy (HCW) | Myalgia-headache-fatigue-nasal congestion-sore throat | None | D13 | Fatigue-nasal congestion-sore throat-chills | None | 8 | cured |
| 4    | 43  | M   | None (HCW)           | FLS-AO- headache                       | None       | D14              | Cough-dyspnoea-fatigue              | None       | 29                            | cured    |
| 5    | 85  | M   | Bronchiectasis - CHD - pace maker - arrhythmia | Fever-cough-dyspnoea-fatigue-confusion-falls | O2, ATB | D17 | Cough-dyspnoea-fatigue-chest pain-confusion-acute heart failure | O2 | 6 | cured |
| 6    | 54  | M   | HT                   | Fever-cough-dyspnoea-severe ARDS-fatigue | ICI, OTI, ATB, LPV/rtv, CTS | D41 | Cough-dyspnoea-diarrhoea-ARDS-fatigue | ICI, OTI, ECMO, ATB | 34 | death |
| 7    | 91  | F   | CHD - HT-CVD-atherosclerosis-arrhythmia - DM CLD, cirrhosis Child C | Fever-dyspnoea-fatigue-pleureal & pericardial effusion | O2, ATB, CTS | D13 | Dyspnoea-fatigue | none | 9 | cured |
| 8    | 55  | M   | DM                   | Fever-dyspnoea-pleural & pericardial effusion | O2, ATB, CTS | D21 | Dyspnoea-headache-diarrhoea-fatigue | ICU-HFNIV-OTI, ATB | 20 | cured |
| 9    | 72  | M   | Anti MAG neuropathy (rituximab, bendamustine) DLBCL (chemotherapy n-22) | Fever-cough-dyspnoea-worsening neuropathy | O2, ATB | D21 | Fever-cough-dyspnoea -fatigue – worsening neuropathy | ICU-HFNIV-OTI, ATB | 29 | death |
| 10   | 73  | M   | LBCL/DLBCL          | Fever-fatigue-abdominal cutaneous rash | ATB | D13 | Fever-dyspnoea-fatigue | O2, ATB, CTS | 17 | cured |
| 11   | 84  | F   | CLD / O2T – mild CRD - CHD arrhythmia/ATC - valvulopathy - atherosclerosis - DM | Fever-cough-dyspnoea-AO-fatigue | O2, curative ATC, ATB, CTS | D23 | Fever-cough-dyspnoea-fatigue | O2, HFNIV, ATB, tocilizumab, CTs curative ATC | 30 | death |

Abbreviations: ATB: antibiotics - AO: anosmia – ATC: anticoagulation - CHD: Chronic Heart Disease- CLD: Chronic Lung Disease- CRD: Chronic Renal Disease – CVD: CerebroVascular Disease – CTS: corticosteroids DM: Diabetes Mellitus – DG: dysgeusia - DLBCL: Diffuse Large B Cell Lymphoma – ECMO: extra-corpooreal membrane oxygenation – FLS: Flu Like Syndrome (= fever + myalgia + fatigue +/- sore throat, nasal congestion) – HT: hypertension – HCW: Health Care Worker - HFNIV: High Flow Non Invasive Ventilation - ICU: Intensive Care Unit -LPV/rtv: lopinavir/ritonavir – NA: Non Available - OTI: Oro-Tracheal Intubation - O2: oxygen therapy. 

* No improvement after 7 days of piperacillin-tazobactam; apyrexia 4 days after pip-taz stop and before linezolid.
Table 2
Laboratory findings of COVID-19 first and 2nd episodes, from onset of first episode (D1) to last follow-up.
(home-care patients: patients 1–4; hospitalized patients: patients 5–11).

| Case | Blood tests | SARS CoV2 PCR | No symptom CRP if available | Blood tests | SARS CoV2 PCR | Serology |
|------|-------------|---------------|-----------------------------|-------------|---------------|----------|
|      |             | Days from onset | CT if available °             |             | Days from 1st onset | CT if available ° | Days from 1st onset | Results |
| 1    | NA          | D2            | E 18 - N22 - RdRP 19         | NA          | D29           | E 35 - IP2 37 - IP4 42 | D58 | POSITIVE total Ig |
| 2    | NA          | D18           | E 23.9 - N NA - RdRP 23.6   | NA          | D36 D55       | E 31.5 - N NA - RdRP 30.3 NEGATIVE | NA | NA |
| 3    | NA          | D3            | 30.5                        | NA          | L 1800        | IP2 38.3 - IP4 36.2 | D27 | POSITIVE IgG IgM |
| 4    | NA          | D3            | POSITIVE, CT NA             | NA          | L 1300 Eo     | 90CRP 1         | D31, 45 | slightly POSITIVE IgG, NEGATIVE IgM |
| 5    | L 290 Eo 0 CRP 33 | D1      | E8 - N11 - RdRP 12          | L 1870 CRP 17 PCR D36 : + E35 | D46       | E 33 - N 33 - RdRP 32 Viral culture NEGATIVE | NA | POSITIVE IgG IgM |
| 6    | L 690 CRP 365 | D16 D 38, 44 | IP2 29.4 - IP4 29.9 NEGATIVE | L 2750 CRP 28 | D45       | IP2 38.3 - IP4 36.2 | D31 | POSITIVE IgG IgM |
| 7    | L 720 Eo 10 CRP 143 | D3        | ORF1 18.7 - N 18.1         | L 1500 CRP 34 | D26       | ORF1 29.7       | D27 | POSITIVE IgG IgM |
| 8    | L 629 Eo 0 CRP 74 | D6        | 16                          | L 1400 CRP 33 | D31       | POSITIVE, CT NA | D27 D47 | Ambiguous POSITIVE IgG |
| 9    | L 630 Eo 260 CRP 39 | D7        | POSITIVE, CT NA            | L 750 Eo 90 CRP 8 | D31, 32, 36 | POSITIVE, CT NA | D41 | NEGATIVE |
| 10   | L 60 Eo 0 CRP 112.8 | D6        | 17 Cutaneous PCR neg        | L 80 CRP 18 | D35       | 18             | D25 | NEGATIVE |
| 11   | L 770 CRP 88 | D11        | IP4 31                      | L 1180 CRP 4.2 | D50       | IP4 16.7 Viral culture POSITIVE | D53 | NEGATIVE |

L: lymphocytes (per mm³); Eo: Eosinophils polymorphonuclear leukocytes (per mm³); CRP: C Reactive Protein (mg/l); NA: Non Available.
° SARS CoV2 Polymerase Chain Reaction: cycle threshold (CT), envelope gene (E), nucleocapsid gene (N), ARN polymerase gene (RdRP, IP2, IP4), specific Open Reading Frame (ORF).
This work has some limitations. In addition to the limited number of observations, the cure between episodes was only clinically-defined (except for patient 6) because iterative RT-PCR controls were not recommended by French guidelines. Finally, viral culture could be performed only for two patients, with no phylogenic sequence comparison at this time.

In conclusion, the fact that patients could experience reactivation of a long-lasting virus carriage or might be re-infected, as well as potential long-term effects of drugs or diseases that hamper the immune response, constitutes a substantial point of vigilance for the management of the pandemic at the individual and collective levels. Studies including genomic comparisons of viral strains involved in both episodes, determination of RNA infectivity by viral culture, as well as assessment of innate and adaptive immunity and monitoring inflammatory targets, would be of great value for further understanding the underlying pathophysiology of these COVID-19 recurrences.

Declaration of Competing Interest

None of the authors has any conflict of interest to declare regarding this subject. This work had no financial support.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.06.073.

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