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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.[1,2] Nevertheless, rare cases of suspected COVID-19 "recurrence" 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.[3–6]

Similarly, the COCOREC (Collaborative study COvid RECurrences) 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 CLInician 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 dysgeusia; 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.[7] 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 reinfection 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 faint in this young population with no invasive infection.[8] 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[5] 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.[9]

Immunosuppressive factors such as drugs or pathological conditions could contribute to impair viral clearance and favour SARS-CoV-2 reactivation.[10] Three of the 7 severe patients of our series, and 3 of 4 patients reported by Ye[3] 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).

Patients characteristics				First episode			2nd episode				
Case	Age	Sex	Past medical history	Clinical characteristics	Treatments	1st Clinical cure	2nd ep onset	Clinical characteristics	Treatments	Duration of 2nd episode (days)	Outcome
1	19	F	None (HCW)	FLS with no fever-cough-dyspnoea-AO-DG -headache-diarrhoea-otalgia-	None	D18	D26	FLS-cough-dyspnoea -chest pain	None	on-going	home care
2	32	F	None (HCW)	Cough-AO-myalgia-headache	None	D29	D36	FLS	None	10	cured
3	33	F	First trimester pregnancy (HCW)	Myalgia-headache-fatigue-nasal congestion-sore throat	None	D13	D27	Fatigue-nasal congestion-sore throat-chills	None	8	cured
4	43	M	None (HCW)	FLS-AO- headache	None	D14	D24	Cough-AO-myalgia headache-diarrhoea-fatigue	None	29	cured
5	85	M	Bronchiectasis - CHD - pace maker - arrhythmia	Fever-cough-dyspnoea-fatigue-confusion-falls	O2, ATB	D17	D44	Cough-dyspnoea-fatigue-chest pain-confusion-acute heart failure	O2	6	cured
6	54	M	HT	Fever-cough-dyspnoea -severe ARDS-fatigue	ICU, OTI, ATB, LPV/rtv, CTS	D41	D45	Cough-dyspnoea-diarrhoea-ARDS-fatigue	ICU, OTI, ECMO, ATB	34	death
7	91	F	CHD - HT-CVD-atherosclerosis-arrhythmia- DM	Fever-dyspnoea-fatigue-pleural & pericardial effusion	O2, ATB, CTS	D13	D25	Dyspnoea-fatigue	none	9	cured
8	55	M	CLD, cirrhosis Child C	Fever-headache-fatigue	ATB	D21	D27	Dyspnoea-headache-diarrhoea -fatigue	ICU-HFNIV-OTI ATB	20	cured
9	72	M	Anti MAG neuropathy (rituximab, bendamustine)	Fever- cough-dyspnoea-worsening neuropathy	O2, ATB	D21	D27	Fever- cough-dyspnoea -fatigue – worsening neuropathy	ICU-HFNIV-OTI, ATB remdesivir	29	death
10	73	M	DLBCL (chemotherapy D-22)	Fever-fatigue-abdominal cutaneous rash	ATB	D13	D24	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	D49	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-corporeal 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: patients1–4; hospitalized patients: patients 5–11).

	First episode (onset = D1)			No symptom Minimal CRP Maximal L PCR if available	2nd episode				
Case	Blood tests	SARS CoV2 PCR			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	NA	D29	E 35 - IP2 37 - IP4 42	D58	POSITIVE total Ig
2	NA	D18	E 23,9- N NA - RdRP 23,6	NA	NA	D36 D55	E 31,5- N NA - RdRP 30,3 NEGATIVE	NA	NA
3	NA	D3	30,5	NA	L 1800	D28	32,7	D27	POSITIVE IgG IgM
4	NA	D3	POSITIVE, CT NA	NA	L 1300 Eo 90CRP 1	D38	21.5	D31, 45	slighly POSITIVE IgG, NEGATIVE IgM
5	L 290 Eo 0 CRP 33	D1	E8 - N11- RdRP 12	L 870 CRP 17 PCR D36 : + E35	L700 Eo 30 CRP 15	D46	E 33 - N 33 - RdRP 32 Viral culture NEGATIVE	NA	NA
6	L 690 CRP 365	D16 D 38, 44	IP2 29,4 - IP4 29.9 NEGATIVE	L 2750 CRP 28	L 690 Eo 50 CRP 247	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	L 1000 Eo 160 CRP 188	D26	ORF1 29,7	D27	POSITIVE IgG IgM
8	L 629 Eo 0 CRP 74	D6	16	L 1400 CRP 33	L 800 Eo 10 CRP 73	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	L 360 Eo 0 CRP 85	D 23, 32, 36	POSITIVE, CT NA	D41	NEGATIVE
10	L 60 Eo 0 CRP 112.8	D6	17 Cutaneous PCR neg	L 80 CRP 18	L 60 Eo 30 CRP 160	D35	18	D25	NEGATIVE
11	L 770 CRP 88	D11	IP4 31	L 1180 CRP 4.2	L 480 CRP 346	D50	IP4 16,7 Viral culture POSITIVE	D53	NEGATIVE

L : lymphocytes (per mm^3)– Eo = Eosinophils polymorphonuclar leukocytes (per mm^3). 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)1.

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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