Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Fatal relapse of COVID-19 after recovery? A case report of an older Italian patient

Dear Editor,

Even though knowledge on SARS-CoV-2 and COVID-19 improved significantly during the last months, several aspects remain a matter of debate. One of these aspects is related to the recommendation to confirm clearance of SARS-CoV-2, defining recovery and discharge from isolation. The European Centre for Disease Prevention and Control updated the guidance on discharge of people with COVID-19, considering different types of patients.[1] Common criteria for recovery include (1) resolution of fever $\geq$ 3 days or clinical improvement, and (2) two consecutive negative SARS-CoV-2 real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) in a 24-hour interval. Particularly, two consecutive negative SARS-CoV-2 RT-PCR test results are recommended for immunocompromised or severely ill patients, to exclude false negative results, especially in case of transfer to other units within the hospital or discharge to long-term care facilities.

We report a fatal COVID-19 relapse in a very old lady transferred from a COVID-19 area to a COVID-19-free unit.

Case report

On 19 October 2020, a 91-year-old woman presented with respiratory failure to the Emergency Room of our Hospital (Fig. 1A). Her medical history included type 2 diabetes, arterial hypertension, atrial fibrillation, chronic kidney disease, and mixed anxiety-depressive disorder. Chest-X-ray displayed a thickening of the interstitial plot in the right perihilar region (Fig. 1B1). The RT-PCR on the nasopharyngeal swab revealed the presence of SARS-CoV-2. Laboratory results showed a multiple organ dysfunction syndrome (Table 1). The patient was hospitalized in a COVID-19 department and treated with dexamethasone, piperacillin/tazobactam, daptomycin, enoxaparin, furosemide, amiodaron, bisoprolol, basal-bolus insulin therapy, and O_2 by Venturi mask to keep a saturation above 94%.

The patient's conditions improved significantly during the following 10 days, and at the 11th–12th day two consecutive negative SARS-CoV-2 molecular tests from nasopharyngeal swabs were reported. The patient was then transferred to a COVID-19-free department; antibiotic therapy, dexamethasone and oxygen therapy were discontinued on Day 14.

After two days, the patient presented with fever, dyspnea, tachypnea, stranguria; nevertheless, an oxygen saturation of 97% in ambient air was detected. Laboratory exams showed a urinary tract infection sustained by E. faecium. A chest-X-ray described pulmonary venous congestion and diffuse interstitial thickening (Fig. 1B2). A nasopharyngeal swab resulted positive for SARS-CoV-2. A consultation by an infectious disease specialist concluded that the clinical manifestations were caused by a bacterial infection, and a retest positive for SARS-CoV-2 could be interpreted as viral gene fragments without active replication in a recovered patient. Consequently, treatment with paracetamol, cefepime, clarithromycin, and caspofungin was started. During the following two days, the patient remained apyretic and eupnoic, and the oxygen saturation was 95–97% in ambient air. On Day 20, she appeared dyspneic, chest auscultation revealed diffuse rales, and the oxygen saturation in ambient air lowered to 70%. Therapy with furosemide and methylprednisolone was promptly started, and the patient was administered non-invasive ventilation. The day after, chest-X-ray revealed diffuse, confluent pulmonary opacities (Fig. 1B3). A Computed Tomography of the chest showed massive interstitial and alveolar involvement, with bilateral pleural effusion (Fig. 1C). Immunoglobulins for SARS-CoV-2 were negative. Another RT-PCR for SARS-CoV-2 on nasopharyngeal swab resulted positive. An additional specimen was used for SARS-CoV-2 isolation test, as previously reported.[2] The viral replication was confirmed by the specific biomolecular test for SARS-CoV-2, and an impressive cytopathic effect was observed. The patient died on Day 22.

Discussion

The risk of recurrence or re-activation of SARS-CoV-2 infection is a burning topic that needs to be promptly addressed to avoid early discharge and end of isolation in patients with potentially contagious disease. The first retrospective report described a 9% proportion of SARS-CoV-2 re-activation in discharged patients, occurring with mild or no symptoms from 4 to 17 days after negative SARS-CoV-2 tests.[3] A further observation found a 14.5% proportion of COVID-19 patients tested positive after discharge, and mild symptoms in 32% of them.[4] A review considered 62 investigations on newly positive SARS-CoV-2 molecular test in recovered patients, describing that recurrence involved adults rather than older subjects, presenting with no or mild symptoms.[5] Asymptomatic or mild symptomatic course of COVID-19 recurrence could be related to the immune response.[6] Our report is related to a severe relapse of COVID-19, preceded by two negative RT-PCR tests and clinical improvement. We hypothesize that our patient could not develop an efficacious immune response during the first days of COVID-19.

Reasons for SARS-CoV-2 positive tests in previously recovered COVID-19 patients include false results, intermittent viral sloughing, infection with a different strain, or contamination.[7] A high rate of false negative RT-PCR has been described even when two consecutive tests were performed, suggesting prolonged viral clearance rather than recurrence or re-infection.[8] To distinguish between relapse and re-infection, a genetic characterization of the SARS-CoV-2 strain could be performed. A limitation of this report is related to the absence of viral sequencing analysis; nev-

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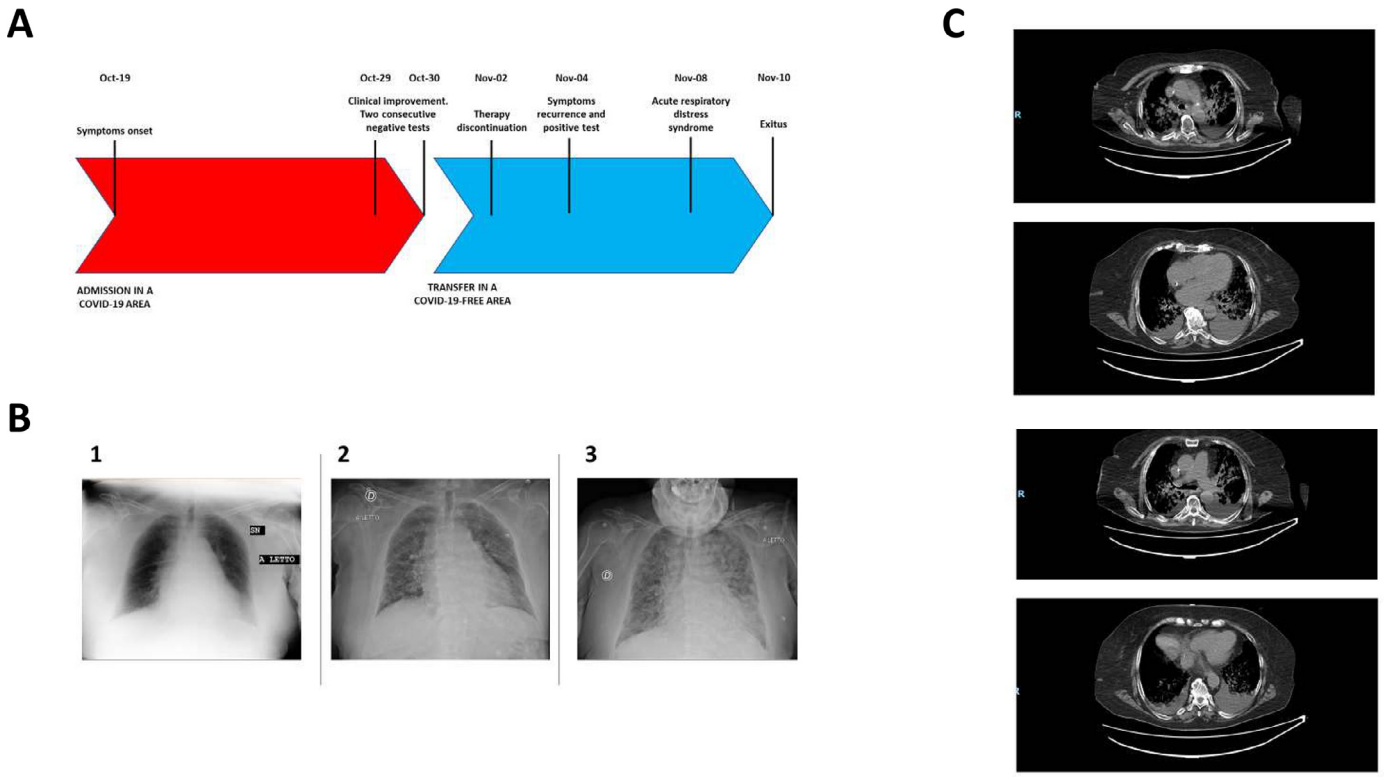

Fig. 1. A: Case report timeline. B: Chest x-rays taken on admission (1), on day 16 (2), and on day 21 (3). Please refer to the main text for full description. C: Computed tomography of the chest at day 21, showing massive interstitial and alveolar involvement, and bilateral pleural effusion.

Table 1
Laboratory results.

Variable	Reference range	Admission	Day 5	Day 9	Day 13	Day 16	Day 20
C-reactive protein (mg/L)	0.0–5.0	236.6*	66*	20.3*	3.1	92.5*	187.6*
HS-Troponin I (ng/L)	< 10.8	1250.2*	269.0*	161.9*	197.5*		
D-dimer (ng/mL)	< 500	698*	469	385	303		
Sodium (mmol/L)	136–146	126^	137	139	137	136	144
Potassium (mmol/L)	3.5–5.3	5.0	3.9	4.0	4.6	4.2	5.0
Chloride (mmol/L)	97–110	90^	102	98	110	106	116*
Oxygen (mmHg)	> 80	49^	165	89	82	69^	39^
Carbon dioxide (mmHg)	35 - 45	28^	29^	27^	24^	27^	29^
Bicarbonates (mmol/L)	22–26	26.1*	26.8*	27.6*	20.9^	21.7^	14.3^
Blood urea nitrogen (mg/dL)	10–50	100*	154*	109*	73*	54*	
Creatinine (mg/dL)	0.20–1.10	2.94*	2.06*	2.16*	1.70*	1.60*	
Glucose (mg/dL)	70–110	585*	292*		155*	143*	
Calcium (mg/dL)	8.8–10.6	9.6			8.4^		
Total protein (g/dL)	6.1–8.3	6.8			4.9^		
Albumin (g/dL)	3.2–5.0	2.8^			2.76^		
Globulin (g/dL)		0.5			0.42		
Aspartate aminotransferase (U/L)	2–40	1145*	22	29	21		
Alanine aminotransferase (U/L)	2–40	821*	245*	78*	36		
Total bilirubin /mg/dL)	0.2–1.2	0.84			0.34		
Gamma glutamyl-transpeptidase (U/L)	7–38	28			27		
Alkaline phosphatase (U/L)	30–120	96			57		
Procalcitonin	< 0.5	14.8*	2.71*	0.42	0.11	1.00*	1.88*
White-cell count (per mm^3)	4000–10,000	21,410*	10,920*		13,170*	15,540*	8070
Hemoglobin (g/dL)	12–16	11.8^	11.5^		10.5^	10.4^	10.0^
Hematocrit (%)	36–48	36.0	35.2^		32.6^	33.2^	30.4^
Platelet count (1000 per mm^3)	130–450	215	324		308	174	112^
Absolute neutrophil count (per mm^3)	1.6–6.5	18.67*	9.17*		10.73*	14.35*	7.18*
Absolute lymphocyte count (per mm^3)	0.8–4.5	1.46	0.95		1.55	0.78	0.62^
NT-BNP (pg/mL)	< 1800	34,700*			5460*		

*The value in the patient was above the normal range. ^The value in the patient was below the normal range. HS, High Sensitivity; NT-BNP, N-Terminal Brain Natriuretic Peptide.

ertheless, we hypothesize that the patient suffered of a persistent infection in which RT-PCR from two consecutive nasopharyngeal swabs resulted false negative, rather than a recurrence. Another reason for re-detectable SARS-CoV-2 RNA in RT-PCR from nasopharyngeal swab after two negative tests may be related to permanence in the lower respiratory tract, and further replication followed by transport to the pharynx through the mucociliary apparatus.[9] An important issue is related to contagiousness of this patient after the negative tests. The sample from our patient provided cultivable SARS-CoV-2, sustaining the hypothesis that she could be contagious.

To conclude, this report suggests that SARS-CoV-2 infection may persist in the respiratory tract and give rise to fatal disease following an apparent recovery. Despite the need of larger studies, we recommend further monitoring of patients with predisposing factors to slow viral clearance because of immune system alterations. Notwithstanding pressure on healthcare system, these patients require to be checked for longer periods before discharge or transfer to COVID-19-free areas, to prevent the spread of SARS-CoV-2.

Declaration of Competing Interest

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