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Letter to the Editor

COVID-19 reinfection in healthcare workers: A case series



To the Editor

To date, few reports have been published documented cases of SARS-CoV 2 infection which turned polymerase chain reaction (PCR) negative in nasopharyngeal swab at discharge with resolution of symptoms and subsequently returned PCR positive in follow-up swab tests.^{1–3} Usually, the patients had mild to moderate symptoms and the time of recurrence of positive tests ranged from few days to several weeks after discharge.⁴ Several hypothesis have been postulated to explain these findings: false negative PCR at the time of discharge due to improper sampling, transport or processing or laboratory errors or low viral load; all these conditions possibly related to false negative results. As a consequence, as in all these case series viral culture and genetic analysis were not performed, these recurrences could be re-infections, viral relapses or laboratory errors.^{5–6} However, such uncertain results have significant implications regarding the variable presence of viral infection, the risk of re-infection and the need of quarantine for prolonged periods to prevent the spread of infection. It has been recently documented from Hong Kong a case of COVID-19 re-infection by a phylogenetically distinct strain;⁷ this finding led to several assumptions on long-term immunity, sampling technique standardization, viral mutation and efficacy of herd immunity. As a consequence, SARS-CoV-2 may continue to circulate among the global population despite herd immunity due to natural infection or vaccination. In particular, this case has a time gap of over 4 months, a laboratory proven different genotype resembling the European virus and the patient was also returning from Europe; all these considerations make it more likely that it is a re-infection rather than a recurrence. This evidence might pay particular attention to those subjects that during the pandemic period have been continuously exposed to SARS-CoV2 infection; among these, healthcare workers certainly represent a population at particularly high risk of re-infection.

We prospectively collected data on nasopharyngeal swabs by healthcare workers of ASST Rhodense, Milan Province, Italy, starting from the very beginning of the pandemic (in Italy, March 2020) to February 2021, when database was finally closed. As for Regional protocols, from March to September 2020 (first wave), nasopharyngeal swabs were collected only in symptomatic subjects, in those who had a close contact with a positive patient or in those with a positive serological test identifying S1/S2-neutralizing IgG, that was available in our Hospital from May 2020. Serological tests were systematically performed in May in all the healthcare workers that did not develop symptoms in the previous 2 months. From October 2020 (second wave), a massive screening program was introduced in our Hospital and all the healthcare workers underwent periodically to nasopharyngeal swabs, regardless of the presence

of clinical symptoms (approximately, once a month). All the subjects with a documented SARS-CoV 2 re-infection (defined as a nasopharyngeal swabs positive in the first wave which turned initially negative and then got positive again during the second wave or as a positive serological test at May with a contextual negative nasopharyngeal swab followed by a positive nasopharyngeal swab during the second wave). All these individuals were tested with chest X-ray, blood tests (complete blood count, d-dimer, lactate dehydrogenase, C-reactive protein, procalcitonin, creatinine, transaminases) and arterial blood gas analysis at the time of re-infection. One month after re-infection viral clearance, all the patients underwent to spirometry, 6-minutes walking test and DLCO (diffusing capacity of the lung for carbon monoxide). Finally, the times to viral clearance of the primary infection and of the re-infection were evaluated.

A total of 677 subjects had at least a positive nasopharyngeal swab in the study period, 328 during the first and 349 during the second wave. Furthermore, 16 individuals had a positive serological test at May 2020 with a negative nasopharyngeal swab, as for previous infection. Thirteen patients (1.9%) were diagnosed with a re-infection: 7 had nasopharyngeal swabs positive in both the first and the second wave and 6 had a positive serological test at May and a positive nasopharyngeal swab during the second wave. Interestingly only 4/13 (30.8%) subjects worked in COVID-19 dedicated wards or in the Emergency. Symptoms were mild in all the subjects and nobody was hospitalized; in particular, 3 subjects were symptomatic during the first infection (all had fever) and 7 during the re-infection (6 fever, 1 myalgia). All the other subjects were completely asymptomatic. Chest X-rays showed pneumonia in only 1 subject who had fever with persistently normal respiratory parameters (blood oxygen saturation 96% at arterial blood gas analysis). D-dimer was slightly elevated in only 1 subjects (322 mg/dL, normal limit < 150), without any sign of thrombosis or pulmonary embolism. Other blood tests were normal in all the subjects. Spirometry, DLCO and 6-minute walking tests were also normal. Finally, the re-infection was associated with a mean shorter time to achieve viral clearance than primary infection (34 vs 16 days).

SARS-CoV2 re-infection has been occasionally documented in the last year; no case series has been at the moment published. At our knowledge, this is the largest population being re-infected by SARS-CoV2 ever described. The implication of re-infections in healthcare workers might be serious for the entire health system. In our population, re-infections were never associated with COVID-19 severe diseases; this finding, though on a limited number of cases, might suggest that asymptomatic subjects discovering by change to be SARS-CoV2 infected are at risk of being re-infected when immune protection disappears. Finally, re-infection was associated with a more rapid viral clearance than first infection, probably due to the presence of immune memory. In con-

clusion, our study demonstrates that re-infection is an unusual but possible event in subjects continuously exposed to SARS-CoV2 such as healthcare workers; usually subjects with re-infection develop mild diseases without significant complications.

References

1. Yuan J, Kou S, Liang Y, et al. PCR assays turned positive in 25 discharged COVID-19 patients. *Clin Infect Dis* 2020 Apr 8; doi: 10.1093/cid/ciaa398.
2. Bongiovanni M, Basile F. Re-infection by COVID-19: a real threat for the future management of pandemia? *Infect Dis* 2020;52(8):581–2 Aug.
3. Wu J, Liu X, Liu J, et al. Coronavirus disease 2019 test results after clinical recovery and hospital discharge among patients in China. *JAMA Netw Open* 2020;3(5) May 1. doi:10.1001/jamanetworkopen.2020.9759.
4. Ye G, Pan Z, Pan Y, et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. *J Infect* 2020;80(5):e14–17.
5. Batisse D, Benech N, Botelho-Nevers E, et al. Clinical recurrences of COVID-19 symptoms after recovery: viral relapse, reinfection or inflammatory rebound? *J Infect* 2020 Jun 30; S0163-4453(20)30454-0.
6. Bongiovanni M, Vignati M, Giuliani G, et al. The dilemma of COVID-19 recurrence after clinical recovery. *J Infect* 2020;81(6):979–80 Dec.
7. To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis* 2020;25:ciaa1275 AugDoi: 10.1093/cid/ciaa1275.

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