Proper assignation of reactivation in a COVID-19 recurrence initially interpreted as a reinfection

laura Pérez-Lago[1], helena Martínez[2], Jose Antonio pajares[2], Arantxa Diaz Gomez[2], Marina machado[2], Pedro Sola-Campoy[1], Marta Herranz[3], Maricela valerio[2], Maria Olmedo[2], Cristina Andres Zayas[2], Iñaki Comas[4], fernando Gonzalez Candelas[5], Rafael Bañares[2], Pilar Catalán[3], Patricia Muñoz[3], and Darío García de Viedma[2]

[1]Instituto de Investigación Sanitaria Gregorio Marañón
[2]Affiliation not available
[3]Hospital General Universitario Gregorio Marañón
[4]Instituto de Biomedicina de Valencia (IBV-CSIC)
[5]University of Valencia

April 05, 2024

Abstract

A 77-year-old male (Case R) who had had a previous diagnosis of mild COVID-19 episode, with fever without developing pneumonia or other complications, was hospitalized 57 days later, due to an acute cholangitis. He had a prolonged hospital stay with severe biliary and infectious complications. On Day 23 post-admission, the patient developed a second COVID-19 episode, now severe, with bilateral pneumonia, multiorgan failure, and finally died. Initially, Case R COVID-19 recurrence was interpreted as a reinfection due to the exposure to a patient with whom he had shared the hospital room, who also had a subsequent positive SARS-CoV-2 RT-PCR. However, whole genome sequencing data indicated that both cases were infected by different strains and clarified that case R recurrence corresponded to a reactivation of the strain involved in his first episode. Case R reactivation had major consequences, not only leading to a much more severe second episode, but causing a subsequent transmission to another two hospitalized patients, one of them with fatal resolution.

Proper assignation of reactivation in a COVID-19 recurrence initially interpreted as a reinfection

Laura Pérez Lago[1,2+], Helena Martínez Lozano[2,3+], Jose Antonio Pajares Díaz[2,3+], Arantxa Díaz Gómez[2,3+], Marina Machado[1,2], Pedro J. Sola-Campoy[1,2], Marta Herranz[1,2,4], Maricela Valerio[1,2], María Olmedo[1,2], Cristina Andrés Zayas[2,5], Iñaki Comas[6,7], Fernando González Candelas[7,8], Rafael Bañares[9,10], Pilar Catalán[1,2,4], Patricia Muñoz[1,2,4,9], and Darío García de Viedma[1,2,4*] on behalf of Gregorio Marañón Microbiology-ID COVID-19 Study Group

[1]Servicio de Microbiología Clínica y Enfermedades Infecciosas, Gregorio Marañón General University Hospital, Madrid, Spain

[2]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain

[3]Servicio de Digestivo, Gregorio Marañón General University Hospital, Madrid, Spain

[4]CIBER Enfermedades Respiratorias (CIBERES), Madrid, Spain

[5]Genomics Unit, Gregorio Marañón General University Hospital, Madrid, Spain

[6]Instituto de Biomedicina de Valencia-CSIC, Valencia, Spain

[7]CIBER Salud Pública (CIBERESP), Spain

[8]Joint Research Unit "Infection and Public Health" FISABIO-University of Valencia, Institute for Integrative Systems Biology (I2SysBio), Valencia, Spain

[9]Departamento de Medicina, Universidad Complutense, Madrid, Spain

[10]CIBER Enfermedades hepáticas y digestivas (CIBERehd). Madrid, Spain

Corresponding author:dgviedma2@gmail.com*

Phone: (+34) 914265104

Postal address: C/Dr. Esquerdo 46 (28007), Madrid, Spain.

+: these authors contributed equally to this work

Running title : COVID-19 reactivation and nosocomial transmission

Summary

A 77-year-old male (Case R) who had had a previous diagnosis of mild COVID-19 episode, with fever without developing pneumonia or other complications, was hospitalized 57 days later, due to an acute cholangitis. He had a prolonged hospital stay with severe biliary and infectious complications. On Day 23 post-admission, the patient developed a second COVID-19 episode, now severe, with bilateral pneumonia, multiorgan failure, and finally died. Initially, Case R COVID-19 recurrence was interpreted as a reinfection due to the exposure to a patient with whom he had shared the hospital room, who also had a subsequent positive SARS-CoV-2 RT-PCR. However, whole genome sequencing data indicated that both cases were infected by different strains and clarified that case R recurrence corresponded to a reactivation of the strain involved in his first episode. Case R reactivation had major consequences, not only leading to a much more severe second episode, but causing a subsequent transmission to another two hospitalized patients, one of them with fatal resolution.

Keyword s: COVID-19, SARS-CoV-2, reactivation, nosocomial transmission, WGS.

Word count Abstract: 163

Word count text: 1748

Introduction

Whole genome sequencing (WGS) has been essential to clarify a key aspect in the COVID-19 pandemic, namely, the analysis of recurrences, allowing to identify which are due to reinfections (Mulder et al., 2020; Tillett et al., 2020). Genomic research has demonstrated the prolonged persistence of viable SARS-CoV-2 in severely immunosuppressed patients (Baang et al., 2020; Choi et al., 2020), but it has not equally been used to support reactivations, and the scarce reports focus primarily on clinical descriptions (Coppola, Annunziata, Carannante, Di Spirito, & Fiorentino, 2020). Furthermore, the potential relationship between SARS-CoV-2 reactivation and associated nosocomial outbreaks has not been described to date. In this study we present a SARS-CoV-2 reactivation and its consequences in the nosocomial setting.

Patients and Methods

Clinical data

Baseline characteristics and clinical and laboratory parameters at COVID-19 diagnosis and their outcome were obtained from their electronic medical records. The study was approved by the ethical research committee of Gregorio Marañón Hospital (REF: MICRO.HGUGM.2020-042)

Diagnostic RT-PCRs

Viral RNA was extracted and purified from 300 µL of nasopharyngeal exudates with the aid of the KingFisher (Thermo Fisher Scientific, Waltham, Massachusetts) instrument. Next, an RT-PCR was performed, using the TaqPath COVID-19 CE-IVD RT-PCR kit (Thermo Fisher Scientific, USA).

Whole genome sequencing

Eleven µL of RNA were used as template for reverse transcription using Invitrogen SuperScript IV reverse transcriptase (ThermoFisher Scientific, Massachusetts, USA) and random hexamers (ThermoFisher Scientific, Massachusetts, USA). Whole genome amplification of the coronavirus was done with an Artic_nCov-2019_V3 panel of primers (Integrated DNA Technologies, Inc., Coralville, Iowa, USA) (artic.network/ncov-2019) and the Q5 Hot Start DNA polymerase (New England Biolabs, Ipswich, Massachusetts, USA). Libraries were prepared using the Nextera Flex DNA Library Preparation Kit (Illumina lnc, California, USA) following manufacturer´s instructions.

Libraries were quantified with the Quantus Fluorometer (Promega, Wisconsin, USA), before being pooled at equimolar concentrations (4 nM). Next, they were sequenced in pools of up to 17 libraries on the Miseq system (Illumina Inc, California, USA) and the MiSeq Reagent Micro kit v2 (2x151pb) or in pools of up to 96 libraries with the MiSeq Reagent (2x201 pb).

FastQ files above the GISAID thresholds were deposited at GISAID EPI_ISL_654287, EPI_ISL_654203, EPI_ISL_654284, EPI_ISL_654176 and EPI_ISL_1173765. An in-house analysis pipeline was applied to analyse the sequencing reads. The pipeline can be accessed at https://github.com/pedroscampoy/covid_-multianalysis. Briefly, the pipeline goes through the following steps: 1) removal of human reads with Kraken [https://genomebiology.biomedcentral.com/articles/10.1186/gb-2014-15-3-r46]; 2) pre-processing and quality assessment of fastq files using fastp [https://academic.oup.com/bioinformatics/article/34/17/i884/5093234] v0.20.1 (arguments: –cut tail, –cut-window-size, –cut-mean-quality , -max_len1 ,-max_len2) and fastQC v0.11.9 [Andrews S.; S Bittencourt a, "FastQC: a quality control tool for high throughput sequence data – ScienceOpen," Babraham Inst., p. http://www.bioinformatics.babraham.ac.uk/projects/, 2010.]; 3) mapping with bwa v0.7.17 [H. Li and R. Durbin, "Fast and accurate short read alignment with Burrows-Wheeler transform," Bioinformatics, vol. 25, no. 14, pp. 1754–1760, 2009.] and variant calling using IVAR v1.2.3 [https://genomebiology.biomedcentral.com/articles/10.1186/s13059-018-1618-7] using Wuhan-1 sequence (NC_045512.2) as reference; 4) Recalibration of punctual low coverage positions using joint variant calling. When necessary, informative non-covered positions were analysed by standard Sanger sequencing with the corresponding flanking primers from the ARTIC set.

Results

Our case (Case R, Figure 1) was a 77-year-old male with hypertension and dyslipidaemia, a diagnosis of cutaneous B-cell lymphoma in remission, a previous stroke, and chronic obstructive pulmonary disease associated to mild interstitial lung disease without exacerbation nor need of supplemental oxygen. His first positive SARS-CoV-2 RT-PCR was on July 28, 2020 when he had a mild infection with fever without developing pneumonia or other complications. Hospital admission was not required. SARS-CoV-2 serology was not performed at that time.

On September 1, he was admitted to the hospital due to an acute obstructive cholangitis secondary to choledocholithiasis that was removed by endoscopy. The patient received piperacillin-tazobactam. After the endoscopic procedure, he developed mild acute pancreatitis, hemobilia, and acute kidney injury related to acute tubular necrosis. In addition, he developed catheter-related *Enterococcus faecium*bacteraemia successfully treated with vancomycin. During this time, he obtained two negative SARS-CoV-2 RT-PCR tests (September 1 and 14, Figure 1).

On Day 23 following admission, extensive bilateral lung opacities were identified in a control abdominal computed tomography (CT). After these unexpected radiological findings, SARS-CoV-2 RT-PCRs were performed for two consecutive days, both positive (Ct 19, Ct 21). IgG SARS CoV-2 serology was negative

(Figure 1).

Case R developed mild dyspnoea and hypoxemia (oxygen saturation of 92% at room air). He received remdesivir for five days and dexamethasone 20 mg once daily for four days. After a slight improvement, on Day 29, he developed fever and respiratory worsening. On Day 31, high-flow oxygen therapy and a single 400 mg dose of tocilizumab (IL-6 level: 226pg/mL) were administered. The patient was transferred to the ICU where he received full ventilatory support and continuous changing between prone and supine positions. However, the patient rapidly developed multiorgan failure with hemodynamic instability, mixed metabolic and respiratory acidosis, and renal impairment requiring continuous renal replacement therapy. Body CT scan revealed non-specific colitis and worsening of the bilateral pulmonary opacities with pleural effusion. A colonoscopy ruled out ischemic colitis. Despite all therapeutic interventions, the patient developed refractory multi-system organ failure and finally died on Day 34. Retrospectively, we recovered three sera specimens (from days 23, the day the nasopharyngeal RT-PCR result was positive, 27, and 30) and all were positive for SARS-CoV-2 RT-PCR. Clinical outcomes are shown in Figure 1.

Whole genome sequencing analysis

Prior to having the WGS data, several findings, i.e., chronology of SARS-CoV-2 infections, dates of symptom onset, positive SARS-CoV-2 RT-PCRs, and room coincidences, led clinicians to assume that Case R recurrence was a reinfection due to the exposure to a patient with whom he had shared the hospital room (Case A) and who had been admitted 11 days before due to an intestinal obstruction, had a bilateral pneumonia and subsequent positive SARS-CoV-2 RT-PCR. However WGS data (obtained in a larger study analysing a wide nosocomial outbreak in the Gastroenterology ward, under evaluation) indicated that fully different strains were identified in Case A and Case R (Figure 2). In addition, Case R was part of Cluster which also included Cases S and T, infected by an identical strain (0 SNPs, Figure 2). Cases S and T had shared a room, but Case R at the time of his positive-RT-PCR was in a different one. However, tracking back his previous movements revealed that Case R had shared room with case S seven days before, confirming a link between them; SARS-CoV-2 infection in Case S had a fatal outcome.

WGS data ruled out our initial hypothesis of reinfection after nosocomial exposure and led us to consider, alternatively, Case R as a reactivation, causing a subsequent nosocomial transmission. The sequences of the positive specimens collected from Case R first and second episodes (July and September, 2020) belonged to the same lineage (B.1.177) and showed nearly identical sequences; they shared 16 SNPs and differed in two (Figure 3, Supplementary Table). Given the marked diversity of circulating SARS-CoV-2 in the second COVID-19 wave, the high similarity between the sequences strongly supports that Case R recurrence most likely corresponded to a reactivation.

Discussion

This study shows the importance of WGS-based analysis to correctly understand COVID-19 recurrences and, additionally, the true links within nosocomial transmission events. This technique provided key data to describe a COVID-19 reactivation, which was subsequently responsible for another two nosocomial cases.

The similarities between the strains infecting Case R in the July and September episodes may be explained by either a persistent infection or a reactivation. Persistence was ruled out because the patient fully recovered from mild clinical symptoms experienced during his first episode. Furthermore, X-rays at admission did not show abnormal SARS-CoV-2-related findings and two sequential negative PCRs just before being diagnosed again in September (at admission and 14 days later) were obtained. Finally, during the 23 days of hospital stay before reactivation, the patient had close contact with four roommates, none of which had a COVID-19 diagnosis. All these findings rule out a hypothesis of persistence.

An alternative explanation for the high sequence similarities between the specimens collected during the two episodes experienced by Case R would be reactivation. The subtle differences (two different SNPs and 16 identical SNPs) found for this case are similar to those described in a reactivation reported elsewhere (Yadav et al., 2021). Reservoirs for SARS-CoV-2 after the resolution of a COVID-19 episode have not been defined

yet. The involvement of extra-pulmonary tissues (eyes, gastrointestinal tract, liver, and brain) has been reported (Meinhardt et al., 2020; Paizis et al., 2005; Wang et al., 2020), due to the ubiquity of the ACE2 receptors. Moreover, SARS-CoV-2 RNA has been detected in anal swabs for 42 days in an asymptomatic carrier, while nasopharyngeal swabs were negative (Jiang et al., 2020). The presence of SARS-CoV-2 in non-respiratory tissues suggests that further studies are needed to identify other viral reservoirs (Kalkeri, Goebel, & Sharma, 2020).

If the reservoir hypothesis were correct, we would expect reactivations to be mainly associated to immunosuppression, which would trigger the replication of the latent strain. Few studies have proposed reactivation as the explanation for COVID-19 recurrence (Coppola et al., 2020; Lancman, Mascarenhas, & Bar-Natan, 2020), some involving immunosuppression. However, only two were supported with viral genome analyses (Molina et al., 2020) (Yadav et al., 2021). Several factors suggest the presence of immunosuppression in Case R. Firstly, he had stayed hospitalized 23 days suffering of severe conditions before his first positive RT-PCR. Acute care settings is a risk factor of malnutrition. Before the diagnosis of COVID-19, Case R had lymphopenia for 12 days; this may impair immunity, a factor associated to increased morbidity and mortality (Liu Y, 2020; Ziadi A, 2020). Secondly, the patient suffered of severe gastrointestinal conditions (acute cholangitis, post-ERCP acute pancreatitis, and gastrointestinal bleeding requiring blood transfusion) that could have worsened his immune system. Finally, he presented two infections (cholangitis and a catheter-related infection) and acute kidney injury that might have further worsened his already weakened immune system.

A relevant retrospective finding in Case R is the positive SARS-CoV-2 RT-PCR in three sera specimens taken the same day he had his first diagnostic SARS-CoV-2 RT-PCR, and four and six days later. SARS-CoV-2 may be detected in plasma samples from patients with respiratory disease and this may have value to predict the severity of the disease (Veyer et al., 2020). However, this has not been found close to diagnosis, even in cases with pneumonia (Nijhuis et al., 2020). Therefore, the presence of SARS-CoV-2 in plasma in the second episode experienced by Case R, would suggest that we are not facing a new infection but a likely longer-term disease, which may support the reactivation scenario .

In summary, we report genomic viral analysis allowed to identify a reactivation case with major consequences, leading to a more severe second episode with fatal resolution and subsequent nosocomial transmission of the same strain with an additional COVID-19-related death.

Acknowledgements

This work was supported by *Instituto de Salud Carlos III* (Ref COV20/00140: SeqCOVID - *Consorcio para la epidemiologia genomica de SARS-CoV-2 en Espana*) and by *Consejo Superior de Investigaciones Cientificas* (*CSIC*) (*PTI Salud Global*). LPL holds a Miguel Servet Contract CP15/00075). We are grateful to Dainora Jaloveckas (cienciatraducida.com) for editing and proofreading assistance.

Conflict of interests

The authors do not have commercial or other associations that might pose a conflict of interest.

Data availability

The data that support the findings of this study (FastQ files) are openly available in GISAID at https://www.gisaid.org/ . Reference numbers EPI_ISL_654287, EPI_ISL_654203, EPI_ISL_654284, EPI_ISL_654176 and EPI_ISL_1173765.

Figures

Figure 1. Clinical timeline for Case R. ERCP: endoscopic retrograde cholangiopancreatography; RT-PCR: Reverse-transcription polymerase chain reaction; S: serum sample; NP nasopharyngeal sample; (+) Positive result; (-) Negative result; RBC: red blood cells transfusion. CT: computerized axial tomography scan. MO failure: multiorgan failure; HFNC: high-flow nasal cannulas; O. intubation: orotracheal intubation

Figure 2. Network of relationships obtained from whole genome sequencing analysis for the outbreak strains. Each dot corresponds to a single nucleotide polymorphism. When two or more cases share identical genome (zero single nucleotide polymorphisms between them) they are included in the same box. mv: median vector: not sampled recent common ancestor for the two branches. ANC: Wuhan-1 reference strain.

Figure 3. Distribution along the SARS-CoV-2 chromosome of the single nucleotide polymorphisms identified in the two sequential episodes of Case R. Each vertical black bar corresponds to a single nucleotide polymorphism.

Gregorio Maranon Microbiology-ID COVID-19 Study Group

Adan-Jimenez (Javier), Alcala (Luis), Aldamiz (Teresa), Alonso (Roberto), Alvarez (Beatriz), Alvarez-Uria (Ana), Arias (Alexi), Arroyo (Luis Antonio), Berenguer (Juan), Bermudez (Elena), Bouza (Emilio), Burillo (Almudena), Candela (Ana), Carrillo (Raquel), Catalan (Pilar), Cercenado (Emilia), Cobos (Alejandro), Diez (Cristina), Escribano (Pilar), Estevez (Agustin), Fanciulli (Chiara), Galar (Alicia), Garcia (Ma Dolores), Garcia de Viedma (Dario), Gijon (Paloma), Gonzalez (Adolfo), Guillen (Helmuth) Guinea (Jesus), Haces (Laura Vanessa), Herranz (Marta), Kestler (Martha), Lopez (Juan Carlos), Losada (Carmen Narcisa), Machado (Marina), Marin (Mercedes), Martin (Pablo), Montilla (Pedro), Munoz (Patricia), Olmedo (Maria), Padilla (Belen), Palomo (Maria), Parras (Francisco), Perez-Granda (Maria Jesus), Perez-Lago (Laura), Perez (Leire), Pescador (Paula), R Maus (Sandra), Reigadas (Elena), Rico-Luna (Carla Margarita), Rincon (Cristina), Rodriguez (Belen), Rodriguez (Sara), Rodriguez-Grande (Cristina), Rojas (Adriana), Ruiz-Serrano (Maria Jesus), Sanchez (Carlos), Sanchez (Mar), Serrano (Julia), Sola Campoy (Pedro J), Tejerina (Francisco), Valerio (Maricela), Veintimilla (Ma Cristina), Vesperinas (Lara), Vicente (Teresa), de la Villa (Sofia).

References

Baang, J. H., Smith, C., Mirabelli, C., Valesano, A. L., Manthei, D. M., Bachman, M., . . . Lauring, A. S. (2020). Prolonged SARS-CoV-2 replication in an immunocompromised patient. *The Journal of infectious diseases* . doi: 10.1093/infdis/jiaa666

Coppola, A., Annunziata, A., Carannante, N., Di Spirito, V., & Fiorentino, G. (2020). Late Reactivation of SARS-CoV-2: A Case Report. *Frontiers in medicine, 7* , 531. doi: 10.3389/fmed.2020.00531

Choi, B., Choudhary, M. C., Regan, J., Sparks, J. A., Padera, R. F., Qiu, X., . . . Li, J. Z. (2020). Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. *The New England journal of medicine, 383* (23), 2291-2293. doi: 10.1056/NEJMc2031364

Jiang, X., Luo, M., Zou, Z., Wang, X., Chen, C., & Qiu, J. (2020). Asymptomatic SARS-CoV-2 infected case with viral detection positive in stool but negative in nasopharyngeal samples lasts for 42 days. *Journal of medical virology, 92* (10), 1807-1809. doi: 10.1002/jmv.25941

Kalkeri, R., Goebel, S., & Sharma, G. D. (2020). SARS-CoV-2 Shedding from Asymptomatic Patients: Contribution of Potential Extrapulmonary Tissue Reservoirs. *The American journal of tropical medicine and hygiene, 103* (1), 18-21. doi: 10.4269/ajtmh.20-0279

Lancman, G., Mascarenhas, J., & Bar-Natan, M. (2020). Severe COVID-19 virus reactivation following treatment for B cell acute lymphoblastic leukemia. *Journal of hematology & oncology, 13* (1), 131. doi: 10.1186/s13045-020-00968-1

Liu Y, D. X., Chen J, Jin Y, Peng L, Wang HHX, Luo M, Chen L, Zhao Y. (2020). Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. *The Journal of infection, 81* (1), e6-e12.

Meinhardt, J., Radke, J., Dittmayer, C., Franz, J., Thomas, C., Mothes, R., . . . Heppner, F. L. (2020). Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. *Nature neuroscience* . doi: 10.1038/s41593-020-00758-5

Molina, D. A., Fernandez-Cadena, J., Fernandez-Cadena, T., Cardenas, P., Morey-Leon, G., Armas-Gonzales, R., . . . Valiente-Echeverria, F. (2020). A suspected case of SARS-CoV-2 persistence with-reactivation. *Research Square* .

Mulder, M., van der Vegt, D., Oude Munnink, B. B., GeurtsvanKessel, C. H., van de Bovenkamp, J., Sikkema, R. S., . . . Wegdam-Blans, M. C. A. (2020). Reinfection of SARS-CoV-2 in an immunocompromised patient: a case report. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* . doi: 10.1093/cid/ciaa1538

Nijhuis, R. H. T., Russcher, A., de Jong, G. J., Jong, E., Herder, G. J. M., Remijn, J. A., & Verweij, S. P. (2020). Low prevalence of SARS-CoV-2 in plasma of COVID-19 patients presenting to the emergency department. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology, 133* , 104655. doi: 10.1016/j.jcv.2020.104655

Paizis, G., Tikellis, C., Cooper, M. E., Schembri, J. M., Lew, R. A., Smith, A. I., . . . Angus, P. W. (2005). Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. *Gut, 54* (12), 1790-1796. doi: 10.1136/gut.2004.062398

Tillett, R. L., Sevinsky, J. R., Hartley, P. D., Kerwin, H., Crawford, N., Gorzalski, A., . . . Pandori, M. (2020). Genomic evidence for reinfection with SARS-CoV-2: a case study. *The Lancet. Infectious diseases* . doi: 10.1016/S1473-3099(20)30764-7

Veyer, D., Kerneis, S., Poulet, G., Wack, M., Robillard, N., Taly, V., . . . Pere, H. (2020). Highly sensitive quantification of plasma SARS-CoV-2 RNA shelds light on its potential clinical value. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* . doi: 10.1093/cid/ciaa1196

Wang, W., Xu, Y., Gao, R., Lu, R., Han, K., Wu, G., & Tan, W. (2020). Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA, 323* (18), 1843-1844. doi: 10.1001/jama.2020.3786

Yadav, S. P., Thakkar, D., Bhoyar, R. C., Jain, A., Wadhwa, T., Imran, M., . . . Scaria, V. (2021). Asymptomatic reactivation of SARS-CoV-2 in a child with neuroblastoma characterised by whole genome sequencing. *IDCases, 23* , e01018. doi: 10.1016/j.idcr.2020.e01018

Ziadi A, H. A., Admou B, Hazime R, Brahim I, Douirek F, Zarrouki Y, El Adib AR, Younous S, Samkaoui AM. (2020). Lymphopenia in critically ill COVID-19 patients: A predictor factor of severity and mortality. *Int J Lab Hematol., 30* (in press).