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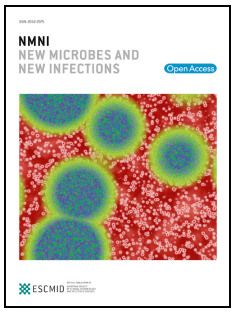

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COVID-19 re-infection or persistent infection in patient with Acute Myeloid Leukemia M3 ; A mini review

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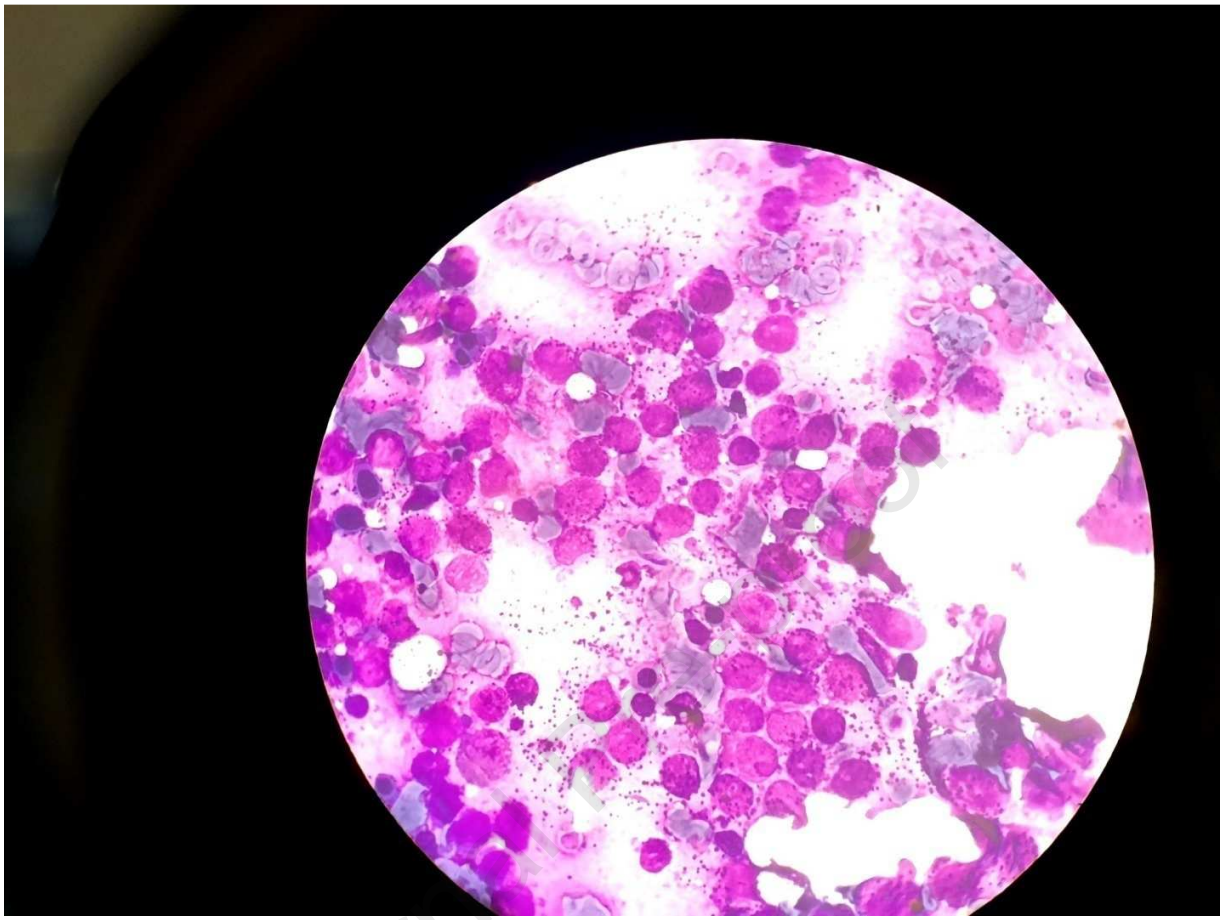
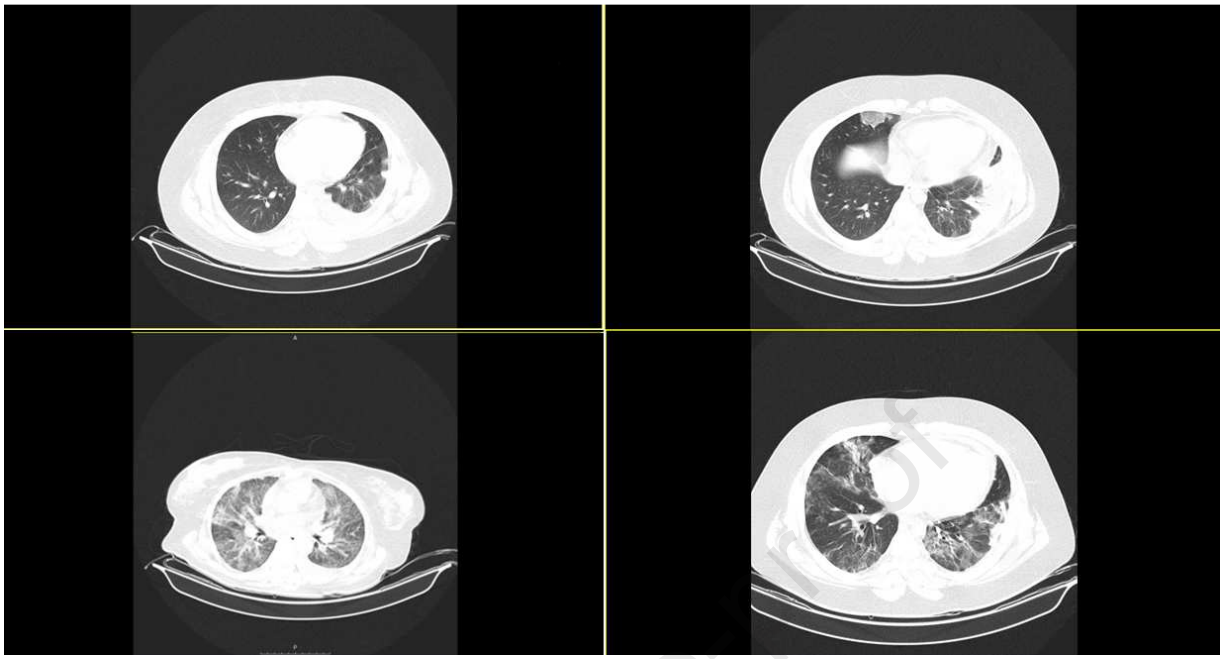


BMA shown diffuse infiltration of promyelocytes



Upper Left : CT-Scan at first day of admission in the hospital

Upper Right : CT-Scan shown a new infiltration in RLL after patient became febrile with neutropenia

Lower Left : CT-Scan shown bilateral infiltration suggesting new episode of COVID-19 infection

Lower Right : CT-Scan at the day of discharge consistent with partial healing

Abstract

Up to now, COVID-19 pandemic affected more than 40 million of people worldwide. Some of the patients had episodes of symptoms recurrence after the first episode of infection with variable intervals. There are multiple issues and hypotheses about re-infection or re-activation of COVID-19 virus, especially in immunocompromised patients. In this paper first, we present a case with a recent history of COVID-19 infection who proceeded to Acute Myeloid Leukemia M3 and immunosuppression by chemotherapy, then we review some recently published articles about possible re-infection or re-activation.

Keywords: COVID-19, Re-infection, AML

Case

A 15-year-old boy was referred to our hematology clinic because of pancytopenia (WBC: 3200/µl , Hb: 10.5 mg/dl, PLT: 88000/µl). Her mother complained of her son's sudden icteric sclera. In history, he had no past medical, surgical and medication history. One month ago, he had an episode of COVID-19 infection with signs and symptoms of cough, dyspnea and patchy infiltration in the left lung. He had two negative PCR tests. After that, gradually, symptoms become resolved, and only some residual patchy infiltration was visible in lung CT-Scan. In the physical exam, there were not any signs of lymphadenopathies nor splenomegaly. COVID19-PCR was negative, but the COVID19 antibody was positive for IgG (33 IU/ml with typically less than 5 IU/ml) but negative for IgM (3.5 IU/ml with typically less than 5 IU/ml).

He became a candidate for bone marrow biopsy and aspiration. Results for bone marrow biopsy, aspiration and flow cytometry were compatible with Acute Myeloid Leukemia M3 with positive PML-RARα. After admission, he had no signs or symptoms of active infection, So the chemotherapy regimen started with ATRA ($45mg/m^2$) and Arsenic Trioxide (0.15mg/kg) daily. After about ten days of treatment, his weight increased about 10 kilograms, and WBC count reached up to 29000/µl. As with differentiation syndrome, we started Dexamethasone 8 mg twice daily and a single dose of Idarubicin $12mg/m^2$, although he had not any sign of respiratory distress. After three days, the WBC count decreased to 13000/µl and again started to rise about 23000/µl three days after that, so another single dose of Idarubicin $12mg/m^2$ was administered. With this second dose, WBC count drop to 800/µl, Hb to 7.5 mg/dl and PLT to 15000/µl. By continuing Arsenic Trioxide and holding the ATRA, the WBC count started to decrease, we started ATRA $45mg/m^2$ thereafter. With this decrement, his weight returned to normal.

In the admission course, as he was neutropenic, he became febrile with a temperature of about 39.0 C. He had a cough, Shivering, and myalgia. We continued ATRA and Arsenic Trioxide but evaluated him for febrile neutropenia etiologies. In Lung CT-Scan, a new patchy infiltration in his right lung was seen. In this situation, empirical antibiotics (Meropenem, Vancomycin and Levofloxacin) were administered. As the patient's general condition worsened we added antifungal agent Amphotericin liposomal 3mg/kg to empirical antibiotics.

About 24 hours later, he became severely dyspneic, and O2 saturation drop to 75% and in CT-Scan severe bilateral ground-glass patchy infiltrations compatible with COVID-19 lung involvement became visible. The patient was intubated and concomitantly pulmonologist performed a bronchoscopy and took mini

bronchoalveolar lavage and sent it for galactomannan and gram smear, culture, and COVID-PCR. After 48 hours, bronchoalveolar lavage Galactomannan was negative, but viral load measured by COVID RT-PCR cycle threshold (CT levels) was 521868217 copies per milliliter of mini bal sample.

We started Interferon Beta 1.2 million units subcutaneously every other day and remdesivir 200 mg in day one and then 100 mg for four days after that with three days of Methylprednisolone 500mg and after that Dexamethasone 8 mg twice daily continued. Although ATRA and Arsenic trioxide continued during the anti-viral treatment. He was also evaluated for pulmonary thromboembolism with pulmonary CT-Angiography, which was consistent with thromboembolism. We transfused platelets and maintained the platelet count above 50000/µl, and started Enoxaparin 60 units subcutaneously twice daily. After five days on mechanical ventilation, O2 saturation began to rise and some pieces of evidences of respiratory recovery were seen. On day eight, the patient became extubated. Antibiotics and antifungal treatment were continued for 14 days, then we hold them. We tapered Dexamethasone gradually and continuously. By continuing ATRA and Arsenic Trioxide administration platelet count increased gradually and the patient became transfusion independent. After six weeks of admission, the patient was discharged with the good general condition and without any dependency on oxygen. WBC was 5600/µl, Hb 10.5 mg/dl and PLT were 145000/µl at the time of discharge. Anti-coagulant continued after discharge.

Discussion

Up to October 2020 COVID-19 virus affects more than 40 million people with more than one million death worldwide. Two significant concerns about COVID-19 are re-infection and prolonged viral shedding [1,2]. Some patients have positive COVID-19 PCR earlier after the recovery of infection despite antibody production [3]. Some studies have shown that these antibodies titers begin to drop about two months later [4]. It would be possible that the virus may persist in the body in respiratory secretions while the patient has no symptoms. it can spread throughout the body into the different organs such as the spleen, lymph nodes, which cannot be detected by nasopharyngeal swab [5]. It has been suggested that antibodies produce against viral spike proteins, which can be mutated and lead to reduce neutralization [6,7]. In the second infection, IgG antibodies were undetectable after the diagnosis, which would be justifiable for the low burden of the disease in the first episode of infection in some patients. [8,9]. Of note T cell immunity may have a pivotal role in the long-term

protection against the virus by providing targets against spike protein with helper and cytotoxic T cells [10,11]. In the convalescence period, viral shedding is still ongoing. There is some evidence that patients with immunodeficiency, such as glucocorticoids use have prolonged viral shedding [12]. In a report from the COCOREC study group in France, they reported 11 patients with confirmed viral re-infection at least three weeks later than the first episode. Four of them had a mild relapse and 7 of them had severe relapses who were admitted to ICU. They suggested that in patients with mild relapse prolonged exposure and reduced immunity made them susceptible to re-infection. However, in severe relapses, suboptimal control of infection leads to second infection [13,14]. There are several reports of COVID-19 re-infection with mild clinical pictures or without any symptoms. The latter may be diagnosed with a positive PCR test in which it can be sample contamination or misdiagnosis due to detecting non-infectious RNA. PCR test can not differentiate between infectious and non-infectious RNA, so all test positivity would not be a clinical relapse [15-18]. Guido Lancman et al. reported a 55-year-old woman with Acute lymphoblastic leukemia who had positive for COVID-19 infection after induction chemotherapy with severe respiratory signs and symptoms. After receiving remdesivir and clinical improvement, she became infected again with positive PCR one month later after consolidation therapy. Results of the antibody were negative despite prior positive results. They supported the COVID-19 re-activation issue because of a short interval between consolidation therapy and PCR positivity [19]. In this paper, we reported a patient with acute myeloid leukemia who had previously been infected with COVID-19 with positive IgG serology and with negative PCR at the time of admission. However, as he became leukopenic and lymphopenic in the course of treatment, he infected again with COVID-19 and became severely symptomatic, which was confirmed by lung imaging and positive PCR test result. There are some proposed issues about re-infection. First, it may be possible that after the first infection, the virus would not fully remove from body secretions, lymphatic system or pulmonary infiltration as in our patient, So it can be quiescent until an immunosuppression event occurred and it becomes activated again. Chemotherapeutic agents that interact with B cell function, such as Anti-CD20 agents, may impact antibody production against COVID-19. Lia Philips et al. reported a case with Acute lymphoblastic leukemia who had severe COVID-19 infection before initiating induction chemotherapy. He received only steroids and non-myeloablative chemotherapeutic agents until the critical period of infection passed, then he received a full course of chemotherapy. In this paper Lia et al recommended that after passing the critical phase of infection chemotherapeutic agents could be introduced [20]. However, it needs more attention than our report and Guido et al. [19] report had a new episode of infection with COVID-19 after myeloablative chemotherapy and

starting chemotherapy would not be completely safe. A recently published report from Memorial Sloan Kettering Cancer Center in New York, demonstrated severe COVID-19 infection in 20% of patients with cancer and a 12% case fatality rate. Treatment with immune checkpoint inhibitors predicted both hospitalization and severe disease [21]. A recent report published in New England Journal of Medicine by Bina Choi et al [22], they reported a 40-years-old man with antiphospholipid syndrome, who had received immunosuppressive agents because of alveolar hemorrhage. In the course of first infection with COVID-19 until death, he had four course of COVID-19 infection, new infection and three recurrences.

Second, it may be possible that the virus can transform into a new mutational status, which is more virulent [23], or secondary infection with a new viral strain. However, it is necessary to define the exact genome in each course of infection. Nevertheless, because the previous result of PCR was negative, it would not possible to compare the genomic study results in the two episodes of COVID-19 infections. In the case of new mutational status, it would be possible that a new mutation interacts with different lymphocyte colony and make them replicative which lead to another phase of cytokine release. So, it may be possible significantly immunocompromised patients acquire this infection several times. This issue needs further investigations to confirm these observations.

In summary we reported a case with AML-M3, who had previous history of COVID-19 infection. After administration of chemotherapeuting agents he became infected again with positive findings in CT-Scan and also PCR test. This may be due to re-activation or re-infection that needs further investigation.

Compliance with ethical standards:

Conflict of interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the Helsinki declaration.

Informed Consent: Informed consent was obtained from all individuals.

References:

1.Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb 15;395(10223):514-523.

2.Kelvin Kai-Wang To, Vincent Chi-Chung Cheng, Jian-Piao Cai, Kwok-Hung Chan, Lin-Lei Chen, Lok-Hin Wong, Charlotte Yee-Ki Choi, Carol Ho-Yan Fong, Anthony Chin-Ki Ng, Lu Lu, Cui-Ting Luo, Jianwen Situ, Tom Wai-Hin Chung, Shuk-Ching Wong, Grace See-Wai Kwan, Siddharth Sridhar, Jasper Fuk-Woo Chan, Cecilia Yuen-Man Fan, Vivien W M Chuang, Kin-Hang Kok, Ivan Fan-Ngai Hung, Kwok-Yung Yuen. Seroprevalence of SARS-CoV-2 in Hong Kong and in residents evacuated from Hubei province, China: a multicohort study.The Lancet Microbe, Volume 1, Issue 3, 2020, Pages e111-e118.

3.To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, Yip CC, Cai JP, Chan JM, Chik TS, Lau DP, Choi CY, Chen LL, Chan WM, Chan KH, Ip JD, Ng AC, Poon RW, Luo CT, Cheng VC, Chan JF, Hung IF, Chen Z, Chen H, Yuen KY. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. Lancet Infect Dis. 2020 May;20(5):565-574.

4. Robbiani DF, Gaebler C, Muecksch F, Lorenzi JCC, Wang Z, Cho A, Agudelo M, Barnes CO, Gazumyan A, Finkin S, Hägglöf T, Oliveira TY, Viant C, Hurley A, Hoffmann HH, Millard KG, Kost RG, Cipolla M, Gordon K, Bianchini F, Chen ST, Ramos V, Patel R, Dizon J, Shimeliovich I, Mendoza P, Hartweger H, Nogueira L, Pack M, Horowitz J, Schmidt F, Weisblum Y, Michailidis E, Ashbrook AW, Waltari E, Pak JE, Huey-Tubman KE, Koranda N, Hoffman PR, West AP Jr, Rice CM, Hatziioannou T, Bjorkman PJ, Bieniasz PD, Caskey M, Nussenzweig MC. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. Nature. 2020 Aug;584(7821):437-442.

5. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, Mou HM, Wang LH, Zhang HR, Fu WJ, Luo T, Liu F, Guo QN, Chen C, Xiao HL, Guo HT, Lin S, Xiang DF, Shi Y, Pan GQ, Li QR, Huang X, Cui Y, Liu XZ, Tang W, Pan PF, Huang XQ, Ding YQ, Bian XW. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020 May 8;49(5):411-417. Chinese.

6. Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, Luo Y, Chan JF, Sahi V, Figueroa A, Guo XV, Cerutti G, Bimela J, Gorman J, Zhou T, Chen Z, Yuen KY, Kwong PD, Sodroski JG, Yin MT, Sheng Z, Huang Y, Shapiro L, Ho DD. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. Nature. 2020 Aug;584(7821):450-456.

7. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, Lorenzi JCC, Muecksch F, Rutkowska M, Hoffmann HH, Michailidis E, Gaebler C, Agudelo M, Cho A, Wang Z, Gazumyan A, Cipolla M, Luchsinger L, Hillyer CD, Caskey M, Robbiani DF, Rice CM, Nussenzweig MC, Hatziioannou

T, Bieniasz PD. Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. bioRxiv [Preprint]. 2020 Jul 22:2020.07.21.214759.

8. Liu L, To KK, Chan KH, Wong YC, Zhou R, Kwan KY, Fong CH, Chen LL, Choi CY, Lu L, Tsang OT, Leung WS, To WK, Hung IF, Yuen KY, Chen Z. High neutralizing antibody titer in intensive care unit patients with COVID-19. Emerg Microbes Infect. 2020 Dec;9(1):1664-1670.

9. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, Hu JL, Xu W, Zhang Y, Lv FJ, Su K, Zhang F, Gong J, Wu B, Liu XM, Li JJ, Qiu JF, Chen J, Huang AL. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020 Aug;26(8):1200-1204.

10. Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, Chng MHY, Lin M, Tan N, Linster M, Chia WN, Chen MI, Wang LF, Ooi EE, Kalimuddin S, Tambyah PA, Low JG, Tan YJ, Bertoletti A. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature. 2020 Aug;584(7821):457-462.

11. Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, Hippenstiel S, Dingeldey M, Kruse B, Fauchere F, Baysal E, Mangold M, Henze L, Lauster R, Mall MA, Beyer K, Röhmel J, Voigt S, Schmitz J, Miltenyi S, Demuth I, Müller MA, Hocke A, Witzenrath M, Suttorp N, Kern F, Reimer U, Wenschuh H, Drosten C, Corman VM, Giesecke-Thiel C, Sander LE, Thiel A. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. Nature. 2020 Jul 29.

12. Ling Y, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, Wu F, Song ZG, Huang W, Chen J, Hu BJ, Wang S, Mao EQ, Zhu L, Zhang WH, Lu HZ. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. Chin Med J (Engl). 2020 May 5;133(9):1039-1043.

13. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Fu Y, Ge S, Liu L, Zhang J, Xia N, Zhang Z. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. Clin Infect Dis. 2020 Mar 28:ciaa344.

14. Gousseff M, Penot P, Gallay L, Batisse D, Benech N, Bouiller K, Collarino R, Conrad A, Slama D, Joseph C, Lemaignen A, Lescure FX, Levy B, Mahevas M, Pozzetto B, Vignier N, Wyplosz B, Salmon D, Goehringer F, Botelho-Nevers E; in behalf of the COCOREC study group. Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound? J Infect. 2020 Jun 30:S0163-4453(20)30454-0.

15. Sah R, Rodriguez-Morales AJ, Jha R, Chu DKW, Gu H, Peiris M, Bastola A, Lal BK, Ojha HC, Rabaan AA, Zambrano LI, Costello A, Morita K, Pandey BD, Poon LLM. Complete Genome Sequence of a 2019 Novel Coronavirus (SARS-CoV-2) Strain Isolated in Nepal. Microbiol Resour Announc. 2020 Mar 12;9(11):e00169-20.

16. Chen LD, Li H, Ye YM, Wu Z, Huang YP, Zhang WL, Lin L. A COVID-19 patient with multiple negative results for PCR assays outside Wuhan, China: a case report. BMC Infect Dis. 2020 Jul 16;20(1):517.

17. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020 May 12;323(18):1843-1844.

18. Chaturvedi R, Naidu R, Sheth S, Chakravarthy K. Efficacy of Serology Testing in Predicting Reinfection in Patients With SARS-CoV-2. Disaster Med Public Health Prep. 2020 Jun 24:1-3.

19. Lancman G, Mascarenhas J, Bar-Natan M. Severe COVID-19 virus reactivation following treatment for B cell acute lymphoblastic leukemia. J Hematol Oncol. 2020 Oct 2;13(1):131.

20. Phillips L, Pavisic J, Kaur D, Dorrello NV, Broglie L, Hijiya N. Successful management of SARS-CoV-2 acute respiratory distress syndrome and newly diagnosed acute lymphoblastic leukemia. Blood Adv. 2020 Sep 22;4(18):4358-4361.

21. Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, Bogler Y, Caldararo M, Figueroa CJ, Glickman MS, Joanow A, Kaltsas A, Lee YJ, Lucca A, Mariano A, Morjaria S, Nawar T, Papanicolaou GA, Predmore J, Redelman-Sidi G, Schmidt E, Seo SK, Sepkowitz K, Shah MK, Wolchok JD, Hohl TM, Taur Y, Kamboj M. Determinants of COVID-19 disease severity in patients with cancer. Nat Med. 2020 Aug;26(8):1218-1223.

22. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, Solomon IH, Kuo HH, Boucau J, Bowman K, Adhikari UD, Winkler ML, Mueller AA, Hsu TY, Desjardins M, Baden LR, Chan BT, Walker BD, Lichterfeld M, Brigl M, Kwon DS, Kanjilal S, Richardson ET, Jonsson AH, Alter G, Barczak AK, Hanage WP, Yu XG, Gaiha GD, Seaman MS, Cernadas M, Li JZ. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. N Engl J Med. 2020 Nov 11.

23. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, Laverdure C, Verma SC, Rossetto CC, Jackson D, Farrell MJ, Van Hooser S, Pandori M. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis. 2020 Oct 12:S1473-3099(20)30764-7.