MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 11(2) pp. 040-044, February, 2023
Available online http://www.meritresearchjournals.org/mms/index.htm

DOI: 10.5281/zenodo.7653420

Case Report

Long Covid Case Report: Post SARS-CoV-2 Infection Evolution in Follicular Non-Hodgkin's Malignant Lymphoma, under Monoclonal Anti-CD20 Antibodies Treatment

Mihaela Andreescu[1,2*], Nicoleta Ilie[2], Andreea Lacatusu[2], Tudor Tony Andrei[2], Laura-Gabriela Tirlea[2], Andreea Brasoveanu[2], Ionescu Rozeta[2], Viola Popov[2]

[1]"Department of Clinical Sciences, Hematology, Faculty of Medicine, Titu Maiorescu University of Bucharest, 040051 Bucharest, Romania

[2]Department of Hematology, Colentina Clinical Hospital, 01171 Bucharest, 10 Romania

*Corresponding Author's E-mail: tevetmihaela@gmail.com

Abstract

Patients with malignant etiologies often exhibit unfavorable outcomes in COVID-19 infections. Due to the depleted humoral response by cytotoxic therapies and malignant conditions, such patients demonstrate prolonged shedding of SARS-CoV-2. In the current study, we present a case of 52 years old woman who presented with mild symptoms which were confirmed as SARS-CoV-2 infection by subsequent PCR test. Even after the initial correction of symptomatology, she manifested recurrent symptoms including fatigue, dyspnoea at medium efforts, coughing syndrome, and loss of appetite. Rigorous diagnostic efforts were made to identify the underlying etiology of this recurrent behavior. Our investigations revealed that the current case is not a relapse of the malignant disease but rather a prolonged case of SARS-COV-2 infection.

Keywords: Histopathology, Immunohistochemistry, Infection, Lymphoma, SARS-CoV-2

INTRODUCTION

Patients undergoing hematological malignancies generally show poorer COVID-19-related outcomes. Immuno-suppressant conditions can increase the risk of severe infections or death by up to 25-34% in hospitalized patients (Vijenthira et al., 2020). Underlying malignant etiologies and cytotoxic treatment therapies impair the immune system which diminishes its ability to fight infections. Of all the malignancies, lymphoma patients exhibit a greater risk of adverse COVID-19 consequences. Although rare, lymphomas comprise heterogeneous malignancies that are classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphomas (NHLs), both arising from the clonal proliferation of lymphocytes (Jiang et al., 2017). The underlying pathophysiology of lymphoma is attributed to the dysfunction of innate and adaptive importance which affects the viral clearance ability, consequently resulting in prolonged COVID-19 (Helleberg et al., 2020).

The prolonged post-COVID syndrome is characterized by progressive and persistent dyspnoea manifested by the necessity of repeated hospitalization. Furthermore, anticancer compounds like anti-CD20 monoclonal antibodies also deplete humoral response in patients as they not only destroy malignant B lymphocytes but also normal B lymphocytes which decreases the memory-driven responses to new pathogens, increasing the infection recurrence (Tvito et al., 2022).

Patients receiving anti-CD-20 monoclonal antibodies exhibit a greater risk of COVID-19 infection as they are unable to develop anti-SARS-COV-2 antibodies, resulting in prolonged COVID-19 infections. The combined effects of immunosuppressive factors lead to reduced seroconversion post-vaccination and serious health-related risks in natural infection (Bonuomo et al., 2021).

Table 1. Laboratory data values during infection evolution

	October	December	January	February	March	April	May	June	July
Hemoglobin (g/dl)	14.3	13.3	12.7	12.5	13.4	13.5	11.7	11.8	10.7
WBC/uL	2.98	6.69	7.94	7.55	12.56	8.51	6.81	7.91	5.61
PLT/uL	188,000	225,000	251,000	158,000	418,000	208,000	149,000	322,000	272,000
ESR (mm/1h)	5	25	48	107	60	111	73	90	63
Fibrinogen (mg/dl)	360	579	709	921	720	1080	659	911	724
C-reactive protein(mg/L)	1.2	27.16	49.3	55.15	26.49	56.7	35.87	96.94	56.21
D-Dimers (ng/ml)	765	455	560	1140	453	772	651	1170	690

We are presenting a case of post-SARS COV 2 infection evolution in symptomatic COVID-19 with comorbid non-Hodgkin's lymphoma who was receiving chemotherapy.

Case presentation

Ourpatientwas a 52-years-old female who presented to the Emergency Department (ED) of Colentina clinical hospital, Bucharest on 13th October 2020 with anosmia, ageusia, fever (38.7°C), migraine syndrome, and myalgia. Her previous history revealed that she was diagnosed with grade 3A follicular Non-Hodgkin B-cell malignant lymphoma, categorized as intermediate risk according to the International Follicular Lymphoma Prognostic Factor Project (FLIPI) in February 2019. Following the malignancy diagnosis, she underwent chemotherapeutic treatment according to the R-CHOP protocol, with a complete response detected on PET-CT after the 6 courses. Later, she followed 7 maintenance courses with Rituximab, once every two months, until she presented a positive RT-PCR test for SARS-COV-2.

Upon presentation to our ED, she exhibited mild COVID-19 symptoms, for which she was recommended dexamethasone 6mg/day for 30 days, Quarelin® 500 mg/day for five days, Zinnat® 500 mg/day for five days, and Vit D3 daily for 30 days. After 5 days of treatment, the symptoms improved significantly and the case wasframed as a mild case of COVID-19.

However, two and half months after the initial diagnosis of COVID-19 infection, the patient's condition started to deteriorate, with the re-appearance of fatigue, dyspnoea at medium efforts, coughing syndrome, and loss of appetite. Further diagnostic efforts revealed a negative PCR test for SARS-CoV-2.

At this juncture, the suspicion of a relapse of the lymphoid disease vs an underlying infectious substrate of the symptomatology was raised. Upon chest computerized tomography (CT) scan, several interstitial lung lesions manifesting "frosted glass" density, isolated and confluent overlapping with alveolar foci were visible in both lungs. The initial interpretation concluded an underlying infectious (SARS-COV-2) cause of symptomatology, with minimal to moderate damage.

To ascertain the etiological factors, numerous interdisciplinary consultations were carried out. From the broncho-alveolar lavage, an RT-PCR test was performed and SARS-COV-2 came out positive which confirmed a COVID prolonged syndrome. Following a thoracic surgery consultation, a lung biopsy was recommended, to exclude any possible relapse of the hematological disease. Throughout the study period, the patient exhibited inflammation of varying degrees (Table 1). Higher levels of inflammation were controlled by corticosteroid therapy.

During the patient's infection evolution, various chest CT scans were performed that showed the emergence of new infectious foci, manifesting a migratory behavior. In January 2021, the CT scan showed several "frosted glass" interstitial lung lesions, isolated and confluent isolated and confluent overlapping with alveolar foci, visible in both lung fields (predominantly the right side) (Figure 1). The CT scan conducted in March 2021 demonstrated bilateral lung lesions, some in regression (the upper lobes, from the medium lobe) and others in progression (lower lobes and upper lobes). In May 2021, the CT scan showed numerical and dimensional remission of interstitial infiltrates with a "frosted glass" appearance and of the pulmonary condensation foci. Pulmonary fibrotic changes were present in the lower lobes segments, at the level of the lingula, and in the medial segment of the LM.

A final PET-CT scan was performed in August 2021 to evaluate the metabolic activity of the pulmonary lesions and identify areas of increased radiotracer activity, which may indicate a relapse of the disease (Figure 2). The PET-CT examination revealed: multiple areas of infiltration, with a "frosted glass" appearance located

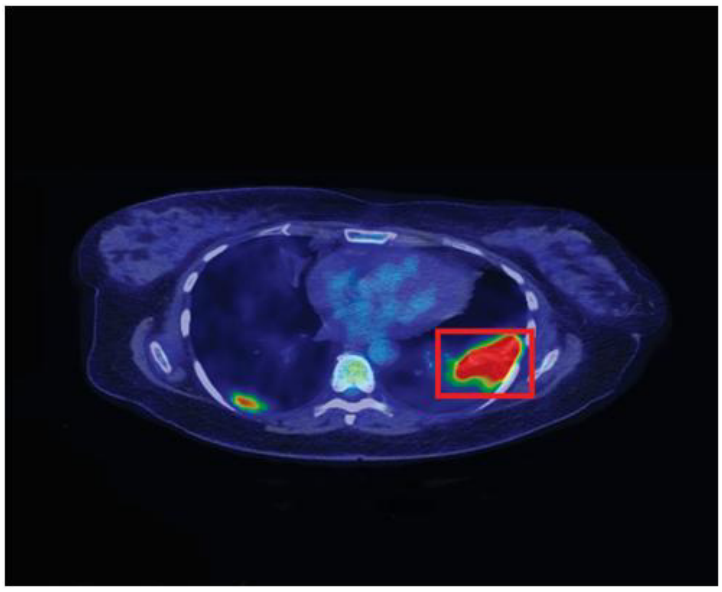

Figure 1. The PET-CT examination revealed — pulmonary frosted-glass opacities and interstitial lung lesions, isolated and confluent isolated and confluent overlapping with alveolar foci, visible in both lung fields (predominantly the right side).

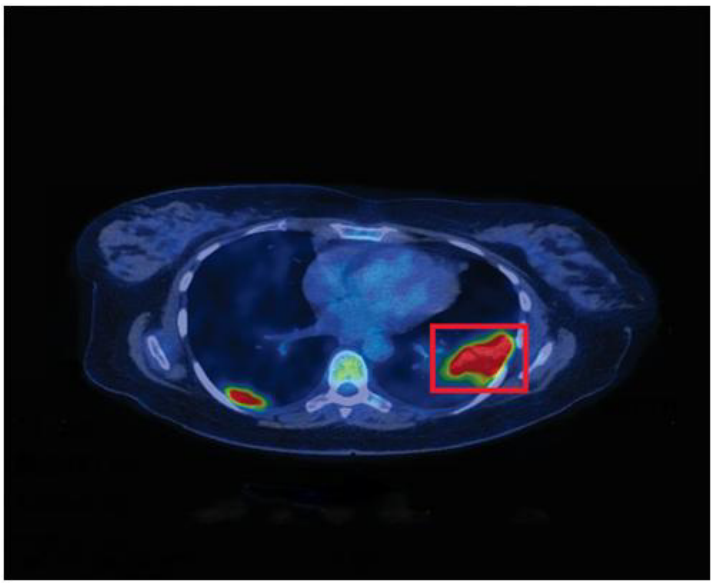

Figure 2. The PET-CT examination revealed — multiple areas of infiltration, with a "frosted glass" appearance located predominantly in subpleural, peripheral, and peri fissural areas, demonstrating SARS-COV-2 antecedents.

predominantly in subpleural, peripheral, and perifissural areas, associated with several areas of consolidation in the subsegmental lung; the lesions were metabolically active with SUV lbm up to 10.04 in the apical inferior segment and left latero-basal, the areas of condensation presenting air bronchogram images. We concluded that active lung lesions were more probably in the context of SARS-COV-2 antecedents.

For further clarification of the underlying etiology, we performed a lung biopsy for histopathological and immunohistochemical examinations. The histopathological examination showed chronic interstitial pneumonia, with lesions of bronchiolitis and macrophage desquamative reaction, localized in the LIS and LSS. These aspects could be associated with residual lesions of viral pneumonia. The immunohistochemical examination showed the following: CD3 was positive in frequent small reactive T lymphocytes being grouped interstitially; CD20 was positive in isolated reactive small B lymphocytes; Pancytokeratin AE1/AE3 was positive in the lung parenchyma. Immunohistochemical findings indicated a chronic interstitial pneumonic process. From all that, we were able to confirm with certainty that the lung lesions and the prolonged inflammatory syndrome were indeed caused by the SARS-COV-2 infection.

DISCUSSION AND CONCLUSION

Patients with Non-Hodgkin's lymphoma, especially those undergoing anti-CD20 monoclonal antibodies treatment present a dilemma for healthcare experts as hematological disease and immunosuppressive treatment therapies worsen the COVID-19 related outcomes. Current literature revealed that patients with hematological malignancies demonstrate severe COVID-19 symptoms and prolonged inflammatory syndrome (Bonuomo et al., 2021). In the current study, we described the case of a 52-year female patient with non-Hodgkin's lymphoma who received anti-CD20 monoclonal antibodies treatment. Rituximab, an anti-CD 20 drug has been associated with the depletion of normal B-cells along with malignant B-lymphocytes which results in impaired humoral immunity (Yasuda et al., 2020). Salles et al. reported that the continuation of rituximab treatment therapy for two years resulted in more frequent infections in patients who receive rituximab (Salles et al., 2011). Some clinical experts propagate the idea of sparinganti-CD20 antibody-based maintenance therapy during the COVID-19 pandemic whenever possible to avoid persistent immunosuppression (Kuderer et al., 2020).

The presented case initially reported mild COVID-19 symptomology that was resurrected with at-home treatment with corticosteroids, antibiotics, and multi-vitamin supplements. Lester et al. showed significant beneficial effects of dexamethasone in the treatment of COVID-19 (Lester et al., 2020). However, two and half months after the initial diagnosis, worsening symptoms were exhibited by the patient which indicated prolonged COVID-19. Kos et al. reported a case of prolonged COVID-19-associated pneumonia in a patient with a prior history of nodal marginal zone lymphoma, receiving rituximab treatment (Kos et al., 2020). Yasuda et al., in a case report, demonstrated that patients who receive rituximab fail to develop anti-SARS-CoV-2 antibodies, which results in prolonged COVID-19 infections (Yasuda et al., 2020). In our study, the CT scan demonstrated the frosted glass density of lung lesions. Our results were supported by Zhang et al. who demonstrated frosted glass density in 45.2% of participants. They graded chest CT density as 0 = normal attenuation, 1=frosted glass density, 2=ground-glass attenuation, and 3=consolidation (Zhang et al., 2020).

One interesting finding observed in the current study was regarding the negative RT-PCR test after 48 days but the presence of a positive RT-PCR test of COVID in the broncho-alveolar lavage (BAL), with the persistence of the clinical syndrome of pneumonia. Such observations are explained by Baron et al. who shared that BAL has a higher ability to confirm COVID-19 even in cases when nasopharyngeal swab(s) are negative in patients (Baron et al., 2021). In the current study, histopathological examination revealed chronic interstitial pneumonia, with lesions of bronchiolitis and macrophage desquamative reaction which could be indicators of prolonged COVID-19.Buja et al. demonstrated interstitial pneumonia with diffuse alveolar damage (DAD) in COVID-19 autopsies (Buja et al., 2020). Immunohistochemical parameters in the current study showed CD3-positive T lymphocytes and CD 20 positive lymphocytes. Similar findings were reported by Oprinca and Muja who showed lymphocyte infiltrates reactive to CD3 and CD5 whereas scattered lymphocytes were positive in CD 20 in SARS-CoV-2 autopsies (Oprinca and Muja, 2021). Fluctuating clinical conditions made it impossible for the patient to resume the maintenance treatment with monoclonal antibodies until today.

CONCLUSION

In conclusion, significant evidence indicates unsatisfactory outcomes in COVID-19 comorbid patients with lymphomas. Due to the depleted humoral response in such patients, they show prolonged COVID-19 symptomatology. In this report, we showed a patient with non-Hodgkin lymphoma with a history of chemotherapy, presented a mild clinical course of COVID-19 infection. Although a real diagnostic challenge, we managed to certify, using high-performance diagnostics such as PET-CT examination and lung biopsy (with histopathological and immunohistochemical examination), that the current case is not a relapse of the disease but rather a chronic interstitial pneumonic process, most likely due to SARS-COV-2 infection.

Author Contributions

Conceptualization, M.A.; Methodology, M.A.; Validation, M.A.; Formal analysis, M.A.; Investigation, M.A.,N.I., A.L., L.T., V.P. resources, M.A.; data curation, M.A. and T.T.A.; writing—original draft preparation, M.A.; writing—review and editing, M.A., T.T.A., E.I.; visualization, M.A.,N.I., A.L., L.T., V.P.; supervision, M.A.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

Baron A, Hachem M, Tran Van Nhieu J, Botterel F, Fourati S, Carteaux G, De Prost N, Maitre B, Mekontso-Dessap A, Schlemmer F (2021). Bronchoalveolar Lavage in Patients with COVID-19 with Invasive Mechanical Ventilation for Acute Respiratory Distress Syndrome. Ann Am Thorac Soc, 18, 723-726, doi:10.1513/AnnalsATS.202007-868RL.

Bonuomo V, Ferrarini I, Dell'Eva M, Sbisà E, Krampera M, Visco C (2021). COVID-19 (SARS-CoV-2 infection) in lymphoma patients: A review. World Journal of Virology, 10, 312.

Bonuomo V, Ferrarini I, Dell'Eva M, Sbisà E, Krampera M, Visco C (2021). COVID-19 (SARS-CoV-2 infection) in lymphoma patients: A review. World J Virol, 10, 312-325, doi:10.5501/wjv.v10.i6.312.

Buja LM, Wolf DA, Zhao B, Akkanti B, McDonald M, Lelenwa L, Reilly N, Ottaviani G, Elghetany MT, Trujillo DO, et al. (2020). The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): Report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. Cardiovasc Pathol, 48, 107233, doi:10.1016/j.carpath.2020.107233.

Helleberg M, Niemann CU, Moestrup KS, Kirk O, Lebech AM, Lane C, Lundgren J (2020). Persistent COVID-19 in an Immunocompromised Patient Temporarily Responsive to Two Courses of Remdesivir Therapy. J Infect Dis, 222, 1103-1107, doi:10.1093/infdis/jiaa446.

Jiang M, Bennani NN, Feldman AL (2017). Lymphoma classification update: T-cell lymphomas, Hodgkin lymphomas, and histiocytic/dendritic cell neoplasms. Expert Rev Hematol, 10, 239-249, doi:10.1080/17474086.2017.1281122.

Kos I, Balensiefer B, Roth S, Ahlgrimm M, Sester M, Schmidt T, Thurner L, Bewarder M, Bals R, Lammert F, et al. (2020). Prolonged Course of COVID-19-Associated Pneumonia in a B-Cell Depleted Patient After Rituximab. Front Oncol, 10, 1578, doi:10.3389/fonc.2020.01578.

Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Hsu CY, Desai A, de Lima Lopes G. Jr, et al. (2020). Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet, 395, 1907-1918, doi:10.1016/s0140-6736(20)31187-9.

Lester M, Sahin A, Pasyar A (2020). The use of dexamethasone in the treatment of COVID-19. Ann Med Surg (Lond), 56, 218-219, doi:10.1016/j.amsu.2020.07.004.

Oprinca GC, Muja LA (2021). Postmortem examination of three SARS-CoV-2-positive autopsies including histopathologic and immunohistochemical analysis. Int. J. Legal Med., 135, 329-339, doi:10.1007/s00414-020-02406-w.

Salles G, Seymour JF, Offner F, López-Guillermo A, Belada D, Xerri L, Feugier P, Bouabdallah R, Catalano JV, Brice P, et al. (2011). Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet, 377, 42-51, doi:10.1016/s0140-6736(10)62175-7.

Tvito A, Ronson A, Ghosheh R, Kharit M, Ashkenazi J, Magen S, Broide E, Benayoun E, Rowe JM, Ofran Y, et al. (2022). Anti-CD20 monoclonal antibodies inhibit seropositive response to Covid-19 vaccination in non-Hodgkin lymphoma patients within 6 months after treatment. Exp Hematol, 107, 20-23, doi:10.1016/j.exphem.2021.12.396.

Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, Martín-Moro F, Razanamahery J, Riches JC, Zwicker J, et al. (2020). Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood, 136, 2881-2892, doi:10.1182/blood.2020008824.

Yasuda H, Tsukune Y, Watanabe N, Sugimoto K, Uchimura A, Tateyama M, Miyashita Y, Ochi Y, Komatsu N (2020). Persistent COVID-19 Pneumonia and Failure to Develop Anti-SARS-CoV-2 Antibodies During Rituximab Maintenance Therapy for Follicular Lymphoma. Clin Lymphoma Myeloma Leuk, 20, 774-776, doi:10.1016/j.clml.2020.08.017.

Zhang J, Meng G, Li W, Shi B, Dong H, Su Z, Huang Q, Gao P (2020). Relationship of chest CT score with clinical characteristics of 108 patients hospitalized with COVID-19 in Wuhan, China. Respir Res, 21, 180, doi:10.1186/s12931-020-01440-x.