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The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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The WJCC is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor (IF) for WJCC as 1.013; IF without journal self cites: 0.991; Ranking: 120 among 165 journals in medicine, general and internal; and Quartile category: Q3. The WJCC's CiteScore for 2019 is 0.3 and Scopus CiteScore rank 2019: General Medicine is 394/529.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Ji-Hong Lin; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

June 26, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Low symptomatic COVID-19 in an elderly patient with follicular lymphoma treated with rituximab-based immunotherapy: A case report

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Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

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

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and

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Abstract

BACKGROUND

Follicular lymphoma is an indolent lymphoma that may progress to a highly aggressive form requiring immunochemotherapy. Most regimens utilize rituximab, an anti-CD20 monoclonal antibody, which may affect the clinical course of novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections [coronavirus disease 2019 (COVID-19)]. Here we describe the first case of mild COVID-19 during ongoing oncological treatment without significant deterioration after rituximab administration.

CASE SUMMARY

A 74-year-old female with an enlargement of her right palatine tonsil was diagnosed with follicular lymphoma following tonsillectomy and started immunochemotherapy according to the rituximab, cyclophosphamide, vincristine, prednisone regimen. At home before the fourth cycle, she developed nonspecific symptoms (excessive fatigue, loss of appetite and nausea), misdiagnosed as adverse effects of chemotherapy. Unexpectedly, interim positron emission tomography-computed tomography scan, performed shortly before rituximab administration, revealed previously nonexistent pulmonary changes, potentially of infectious etiology. SARS-CoV-2 infection was confirmed by a nasopharyngeal swab (with reverse transcriptase polymerase chain reaction test) performed the following day. Despite rituximab infusion, the patient remained oligosymptomatic and was discharged home for self-isolation. Having reached a negative SARS-CoV-2 status before the subsequently scheduled regimen, the patient

revised according to the CARE Checklist (2016).

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Manuscript source: Unsolicited manuscript

Specialty type: Medicine, research and experimental

Country/Territory of origin: Poland

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: February 8, 2021

Peer-review started: February 8, 2021

First decision: April 4, 2021

Revised: April 13, 2021

Accepted: May 6, 2021

Article in press: May 6, 2021

Published online: June 26, 2021

P-Reviewer: Nagaraju GP, Villalba R

S-Editor: Gao CC

L-Editor: Filipodia

P-Editor: Xing YX



successfully received six cycles of rituximab, cyclophosphamide, vincristine, prednisone and obtained complete remission by positron emission tomography-computed tomography.

CONCLUSION

Our case shows that rituximab-based immunotherapy due to follicular lymphoma may have no evident negative effect on the COVID-19 clinical course.

Key Words: COVID-19; SARS-CoV-2; Follicular lymphoma; Rituximab; Case report

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Core Tip: Follicular lymphoma is an indolent lymphoma requiring immunochemotherapy with rituximab. This anti-CD20 monoclonal antibody depletes malignant and normal B-cells, resulting in a significantly increased risk of infectious complications, including the novel coronavirus, severe acute respiratory syndrome coronavirus 2 infection [coronavirus disease 2019 (COVID-19)]. We present the first case of mild COVID-19 in an elderly patient during ongoing follicular lymphoma treatment, without significant deterioration after rituximab administration. This case highlights that rituximab-based therapy may have no evident negative effect on the clinical course of COVID-19 in patients with follicular lymphoma, which may be significant during the current pandemic.

Citation: Łącki S, Wyżgolik K, Nicze M, Georgiew-Nadziakiewicz S, Chudek J, Wdowiak K. Low symptomatic COVID-19 in an elderly patient with follicular lymphoma treated with rituximab-based immunotherapy: A case report. *World J Clin Cases* 2021; 9(18): 4859-4865

URL: <https://www.wjgnet.com/2307-8960/full/v9/i18/4859.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v9.i18.4859>

INTRODUCTION

Follicular lymphoma (FL) is an incurable, indolent form of non-Hodgkin lymphomas, deriving from follicular center B-lymphocytes, mostly connected with asymptomatic lymphadenopathy. In a few recent decades, the occurrence of this neoplasm has significantly increased, amounting to 5/100000 cases, making it the second most frequent nodal lymphoid malignancy in Western Europe[1]. Diagnosis is made based on a surgical specimen or excisional lymph node biopsy, followed with the pathological and immunohistological tissue examination. Therapeutic management may differ depending on the FL clinical stage, presented symptoms, comorbidities and life expectancy, but the front-line treatment is immunochemotherapy with rituximab-based regimens[2]. This chimeric anti-CD20 monoclonal antibody causes rapid and prolonged (up to 12 mo) depletion of both malignant and normal B-cells[3], resulting in a significantly increased risk of infectious complications, particularly in immuno-compromised patients[4], which seems to be crucial especially during the novel coronavirus disease 2019 (COVID-19) ongoing pandemic.

Although most human coronavirus infections are mild, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel strain of coronavirus causing COVID-19, contributed to numerous severe pneumonia cases, which started in December 2019 in Wuhan (China) and has spread worldwide since then[5].

On March 11, 2020, the World Health Organization announced COVID-19 a pandemic[6]. To date, COVID-19 has affected almost 100 million patients and caused more than 2 million deaths all over the world[7], posing a major global healthcare threat. As reported by Yang *et al*[8], COVID-19 infection in patients under oncological therapy is associated with an increase in mortality. However, during the present pandemic, the benefit/risk ratio of cancer treatment may need to be reconsidered individually[9]. The European Society for Medical Oncology has released new guidelines recommending physicians to watch their patients carefully, and while developing COVID-19 symptoms ongoing treatment should be stopped[10]. Here we report the case of a 74-year-old female patient with FL treated with rituximab-based

immunochemotherapy regimen, unexpectedly diagnosed with oligosymptomatic COVID-19 during the fourth cycle of treatment, which was paused after the administration of rituximab solely. After recovery from COVID-19, she continued oncological therapy.

CASE PRESENTATION

Chief complaints

A 74-year-old female patient presented with an enlargement of her right palatine tonsil accompanied by difficulties with swallowing lasting for 2 mo.

History of present illness

In May 2020, the patient was referred to a laryngologist, and the right-side tonsillectomy was performed, obtaining a surgical specimen measuring 3.5 cm × 2.5 cm × 2.0 cm. This pathological mass with polypoid lesions was sent for pathological, immunohistochemical and genetic analyses, which confirmed Grade 2 FL with the following marker combinations: CD20 (+), CD23 (+), CD3 (-), CD5 (-), bcl-2 (+), bcl-6 (+), CD10 (+) and Ki-67 (80%). Afterwards, in July 2020, she was admitted to the Department of Internal Diseases and Oncological Chemotherapy of the Medical University of Silesia in Katowice to evaluate the advancement of the disease and implement the targeted therapy.

History of past illness

The patient reported suffering from arterial hypertension, hypothyroidism, glaucoma and hyperuricemia. She underwent a radical, right-side nephrectomy 25 years ago due to kidney tumor (the estimated glomerular filtration rate of the remaining kidney was 41 mL/min per 1.73 m²).

Personal and family history

The family history was not relevant as for neoplasms, and there were not any known drug allergies nor use of any psychoactive substances.

Physical examination

On admission, the patient was alert, self-oriented and complained of progressive fatigue (without B symptoms). No additional symptoms on the part of other organs or systems were reported. Her general well-being and activities of daily life were assessed as ECOG 1 (symptomatic but completely ambulatory). General examination, apart from obesity (body mass index 30.5 kg/m²) and the nephrectomy scar, did not reveal any other abnormalities.

Laboratory examinations

Conducted blood tests primarily did not indicate infectious background (lymphopenia 0.89 G/L, C-reactive protein 16.47 mg/L, procalcitonin < 0.05 ng/mL). Reported symptoms were connected to the adverse effects of immunochemotherapy. After infusion of multielectrolyte fluids, the patient felt better.

Imaging examinations

Interim positron emission tomography-computed tomography (PET-CT) scan was performed, as planned, before the fourth cycle, and then rituximab infusion was given (before PET-CT description). The following day, the results of imaging ([Figure 1](#)) demonstrated the regression in metabolism and measurements of affected lymph nodes and spleen.

Nonspecific, previously nonexistent pulmonary changes, predominant in the upper and middle lung areas, were described. The differential considerations in the first instance included ongoing inflammatory processes (especially the viral ones) but also drug toxicity reactions.

Initial treatment

After the initial routine diagnostic process for the patient with FL, including a PET-CT scan of the neck, thorax, abdomen and pelvis (to stage nodal and extranodal site involvement) as well as laboratory tests such as complete blood count, lactate dehydrogenase, beta-2 microglobulin and uric acid, the clinical stage was evaluated as III according to the Ann Arbor classification system (involved nodes on both sides of

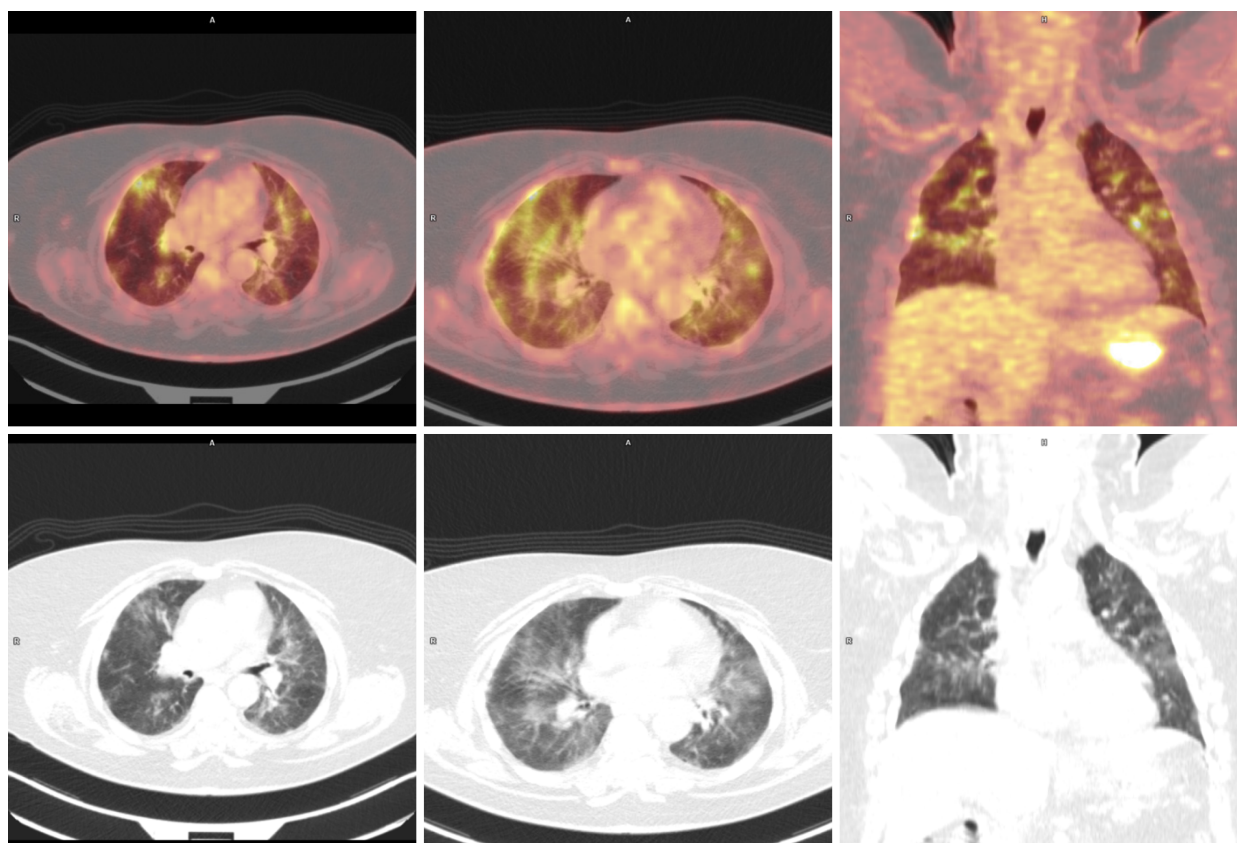


Figure 1 Radiological findings from positron emission tomography-computed tomography. Regression in metabolism and measurement of affected lymph nodes and spleen. Previously nonexistent pulmonary changes, metabolically active, disseminated areas of pulmonary parenchyma in both lungs, with central and subpleural distribution, with greater intensity in the upper and middle lung areas.

the diaphragm and the spleen). Furthermore, Follicular Lymphoma International Prognostic Index was established 3 out of 5 (due to advanced age, anemia and clinical stage III), predicting a poor prognosis of overall life survival. Although European Society for Medical Oncology guidelines prefer rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone regimen as a front-line treatment of FL[11], patient was qualified for immunochemotherapy according to the R-CVP protocol (rituximab: 375 mg/m², cyclophosphamide: 1200 mg, vincristine: 1 mg, prednisone: 10 mg)[12]. The prevention of herpes simplex virus and pneumocystis infections and emetic complications was applied. At home, after the third cycle of therapy, the patient developed excessive fatigue, loss of appetite and nausea deteriorating since the previous week. During the succeeding hospitalization, the patient's physical condition weakened, but ECOG remained 1.

Further diagnostic work-up

Having regard to the current global epidemiological situation, on October 1, 2020 we extended the diagnostics taking a nasopharyngeal swab to test for SARS-CoV-2, which led to a positive result.

FINAL DIAGNOSIS

SARS-CoV-2 infection during FL treatment with rituximab. Given the overall clinical picture and the virus incubation period, we could presume community-acquired infection.

TREATMENT

Initiated therapy was limited to rituximab only, with the discontinuation of other regimen components. Despite implementing immunotherapy, the patient remained

asymptomatic for fever and typical pulmonary symptoms (cough, dyspnea) accompanying COVID-19. Moreover, her general medical state improved, despite the lack of any other complementary drugs, and she was discharged home for self-isolation.

OUTCOME AND FOLLOW-UP

Having reached a seronegative status along with no auscultation abnormalities or other physical examination findings, the patient successfully received six cycles of R-CVP regimen. PET-CT scan was conducted and confirmed complete remission. Then maintenance treatment with rituximab monotherapy was implemented. At the time of this report, the patient received two injections of rituximab.

DISCUSSION

In this paper, we presented the case report of an elderly woman with FL treated with rituximab, who was diagnosed with COVID-19 during oncological therapy. The course of this infectious disease appeared to be oligosymptomatic with uncharacteristic and nonrelevant to respiratory system symptoms. Such a clinical manifestation mainly suggested the adverse effects of ongoing immunochemotherapy.

The recent scientific studies report mild to moderate natural history of SARS-CoV-2 infection as the most frequent one, typically with possible fever, dry cough and tiredness[13]. In COVID-19 positive people, there may also occur other symptoms, in the combination as presented by our patient, but they are not specific enough to test for the novel coronavirus in the first instance. Such a situation can especially be noted in hemato-oncological disorders, where similar manifestations can derive from the targeted treatment as its adverse effects as well as the progression of the neoplasm itself[14].

Furthermore, there is scientific evidence that elderliness and conditions such as hematological malignancies, obesity or arterial hypertension predispose to an increased vulnerability to COVID-19 and particularly high risk of serious events related to it[15-17]. According to observations from Yang *et al*[8], receiving chemotherapy 4 wk before the infection is an unfavorable risk factor. Fortunately, in our case, the course was mild and has not generated any complications so far. Nevertheless, oncologists should always bear in mind the current epidemiological status and have awareness of the possible new viral threat even among asymptomatic people. Similar to our patient, Albano *et al*[18] described five asymptomatic patients undergoing routine PET-CT scans who had radiologically found interstitial pneumonia indeterminate for COVID-19, subsequently proven with reverse transcriptase polymerase chain reaction.

The available literature refers to the treatment during detected COVID-19 in autoimmune and autoinflammatory diseases, such as granulomatosis with polyangiitis, systemic sclerosis, cryopyrin-associated periodic syndrome, spondyloarthritis and pemphigus vulgaris, in which there were severe viral pneumonia or even some fatalities in patients medicated with rituximab[19,20], whereas other drugs widely administered in the foregoing conditions (tumor necrosis factor-alpha antagonists, anakinra or tocilizumab) did not deteriorate the natural course of COVID-19[21-24].

Interestingly, Yasuda *et al*[25] reported persistent COVID-19 pneumonia and failure of seroconversion during rituximab maintenance therapy for FL, underlining that rituximab therapy should be avoided whenever possible during the ongoing pandemic.

Another important issue is how treatment with rituximab may affect the success of a possible future vaccine in the patient. According to Rubin *et al*[26], patients receiving rituximab generally should receive the vaccine ≥ 6 mo after therapy because of their poor immune response. Our patient should wait this long as well.

Given the abovementioned, it is worth emphasizing that we did not find any data concerning the course of COVID-19 while ongoing immunotherapy with monoclonal anti-CD20 antibodies due to oncological purposes. According to our knowledge, the presented patient is the first one ever described with such a favorable course of this infection and therefore becomes the unique case.

CONCLUSION

From our point of view, this case report may be important, especially regarding patients with an oligosymptomatic course of COVID-19 but requiring urgent lymphoma treatment.

The presented course of events was not a standard one, and the rituximab-containing regimen was administered to the SARS-CoV-2 positive patient before having possessed the knowledge about the viral status. Although the described case report shows that rituximab-based therapy may have no evident negative effect on the clinical course of COVID-19 in patients with FL, it should be remembered that the administration of cancer chemotherapy in patients with COVID-19 is associated with increased mortality. Certainly, further research is needed to learn the causes of distinct COVID-19 clinical courses in patients undergoing the same anti-CD20 treatment.

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