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Migratory Pneumonia in Prolonged SARS-CoV-2 Infection in Patients Treated With B-cell Depletion Therapies for B-cell Lymphoma

Jongmin Lee^{1*}, Raeseok Lee^{2*}, Kyongmin Sarah Beck³, Dae Hee Han³, Gi June Min⁴, Suyon Chang³, Jung Im Jung³, Dong-Gun Lee²

¹Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

²Division of Infectious Diseases, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

³Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea ⁴Department of Hematology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Objective: To report the clinical and radiological characteristics of patients with underlying B-cell lymphoma and coronavirus disease 2019 (COVID-19) showing migratory airspace opacities on serial chest computed tomography (CT) with persistent COVID-19 symptoms.

Materials and Methods: From January 2020 to June 2022, of the 56 patients with underlying hematologic malignancy who had undergone chest CT more than once at our hospital after acquiring COVID-19, seven adult patients (5 female; age range, 37–71 years; median age, 45 years) who showed migratory airspace opacities on chest CT were selected for the analysis of clinical and CT features.

Results: All patients had been diagnosed with B-cell lymphoma (three diffuse large B-cell lymphoma and four follicular lymphoma) and had received B-cell depleting chemotherapy, including rituximab, within three months prior to COVID-19 diagnosis. The patients underwent a median of 3 CT scans during the follow-up period (median 124 days). All patients showed multifocal patchy peripheral ground glass opacities (GGOs) with basal predominance in the baseline CTs. In all patients, follow-up CTs demonstrated clearing of previous airspace opacities with the development of new peripheral and peribronchial GGO and consolidation in different locations. Throughout the follow-up period, all patients demonstrated prolonged COVID-19 symptoms accompanied by positive polymerase chain reaction results from nasopharyngeal swabs, with cycle threshold values of less than 25.

Conclusion: COVID-19 patients with B-cell lymphoma who had received B-cell depleting therapy and are experiencing prolonged SARS-CoV-2 infection and persistent symptoms may demonstrate migratory airspace opacities on serial CT, which could be interpreted as ongoing COVID-19 pneumonia.

Keywords: Coronavirus disease 2019; Computed tomography; Lymphoma; SARS-CoV-2; Rituximab; B-cell depletion

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2),

has had a great impact globally since the first wave of the pandemic in 2020. Because the lung is the most frequently affected organ, many studies have reported computed tomography (CT) findings and the natural history of

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Corresponding author: Kyongmin Sarah Beck, MD, PhD, Department of Radiology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.

• E-mail: sallahbar@gmail.com

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COVID-19 pneumonia. The typical appearance of COVID-19 pneumonia is peripheral, bilateral ground glass opacities (GGOs), or multifocal rounded GGOs with or without consolidation or visible intralobular lines [1]. These lesions are known to usually regress and disappear over time, although some may show residual opacities even after one year [2-7].

Three case reports of COVID-19 patients with lymphoma or chronic lymphocytic leukemia have described "migration" of airspace opacities, in which clearing of preexisting airspace opacities was accompanied by the development of similar-looking opacities in completely different locations [8-10], but they were anecdotal, and detailed radiological and clinical analyses were not available. During our daily practice, we have encountered a similar phenomenon in some patients with hematologic malignancies infected with SARS-CoV-2. This study aimed to describe the clinical and radiological characteristics of these patients.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (approval number:

KC22RISI0546). The requirement for written informed consent was waived.

Patients

The picture archiving and communication system at our institution was searched with the keywords "COVID" in English or "corona" in Korean from January 2020 to May 2022, and electronic medical record (EMR) were reviewed to select 519 patients with COVID-19 and at least one chest CT after acquiring COVID-19. Further medical chart review revealed 116 patients with hematologic malignancies, including leukemia, lymphoma, multiple myeloma, aplastic anemia, myelodysplastic syndrome, and primary myelofibrosis. Of these patients, 57 with at least two chest CTs after acquiring COVID-19 were subjected to CT review (Supplementary Fig. 1).

Image Analysis

Two thoracic radiologists (each with 7 and 26 years of experience) reviewed the chest CT of these 57 patients to determine whether there were migratory airspace opacities, and a consensus was reached for each case. Migration was defined as the clearing of previous opacities with the



Fig. 1. Migratory airspace opacities on serial chest CT images of a 45-year-old male (patient 5) with diffuse large B-cell lymphoma and persistent SARS-CoV-2 infection. Axial chest CT images taken on 26, 36, 54, and 78 days after COVID-19 diagnosis demonstrate migration of multifocal patchy peripheral or peribronchial GGOs, clearing of previous opacities with development of new opacities in different locations. The patient had received odronextamab, a bispecific antibody acting as a B-cell depleting agent, 9 days prior to COVID-19 diagnosis.



development of new opacities at different locations (Figs. 1, 2)

After selecting the patients with migratory airspace opacities, the following radiologic features were assessed: type of airspace opacity (GGO, consolidation, or both), distribution (peripheral, which was defined as predominantly involving the outer one-third of the lung; peribronchial, which was defined as predominantly being close to the bronchi; or other, which was defined as neither peripheral nor peribronchial), and the type of interval change (migration; regression, which was defined as the decrease in size or density of previous opacities without evidence of new lesions; aggravation, which was defined as an increase in size or density of previous opacities with or without new lesions). CTs taken within one week of previous CTs scans were excluded from the analysis.

Clinical Information Collection

The EMR of study patients up to July 2022 were reviewed. Underlying disease status and history of chemotherapy of the study patients were evaluated by a hematology specialist, and variables regarding COVID-19 were evaluated by a pulmonologist and an infectious diseases physician. The follow-up period was defined as the time between COVID-19 diagnosis and the last hospital visit found on the EMR. The severity of COVID-19 symptoms was categorized according to the National Institutes of Health guidelines [11].

RESULTS

Baseline and Follow-Up Characteristics of Study Patients

Among the 57 patients, 7 who met the eligibility criteria for CT findings were enrolled in this study. All seven patients (five females, median age 45 years) were diagnosed with a B-cell lymphoma: four with follicular lymphoma and three with diffuse large B-cell lymphoma. All patients had received B cell depletion therapy prior to COVID-19 diagnosis. Five patients had received rituximabbased chemotherapy, and two had received bispecific antibody treatment in a clinical trial. The median time from the last lymphoma treatment to COVID-19 diagnosis was 26 days (range: 9–92 days). Five patients had received two or more doses of the COVID-19 mRNA vaccine, and all of them showed mild-to-moderate disease severity when initially diagnosed with COVID-19. Detailed baseline demographics and clinical characteristics are presented in Table 1. None of the patients received chemotherapy for



Fig. 2. Migratory airspace opacities on serial chest CT images in a 38-year-old female (patient 2) with follicular lymphoma who had received rituximab 17 days prior to COVID-19 diagnosis.

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Table 1.	Patient Chara	cterist	ics											
Patient	Diagnosis	Age, yr	Sex	Disease Status	HSCT	Last Chemotherpy	B-Cell Depletion Therapy	Time Interval between Diagnosis of COVID-19 and Last Chemotherapy	Completion of Vaccination : before COVID-19	Type of Vaccine	Severity of COVID-19 at Diagnosis	Initial Mangement F of COVID-19	ollow-Up Period	Outcome
	Follicular lymphoma	44	Σ	PR/SD	Auto	5th BR	Rituximab	26	°N	N/A	Mild to moderate	Remdesivir	225 /	Alive; improvement of symptoms
2	Follicular lymphoma	38	ш	CR	None	5th rituximab maintenance	Rituximab	17	Yes (2nd)	mRNA	Mild to moderate	Remdesivir	144 /	Alive; persistent dyspnea
ς	Follicular lymphoma	37	ш	CR	None	3rd rituximab maintenance	Rituximab	6	Yes (3rd)	mRNA	Mild to moderate	Supportive	115 /	Alive; persistent cough and sputum
4	Follicular lymphoma	58	ш	CR	None	8th rituximab maintenance	Rituximab	40	Yes (3rd)	mRNA	Mild to moderate	Supportive	114 /	Alive; persistent hypoxia and on Home O ₂
Ъ	DLBCL	45	Σ	CK	None	4th-line odronextamab (Bispecific antibody)	Bispecific antibody	G	Yes (3rd)	mRNA	Mild to moderate	Supportive	124 /	Alive; persistent cough, sputum, and dyspnea
Q	DLBCL	71	ш	с	Auto	4th-line odronextamab (Bispecific antibody)	Bispecific antibody	13	Yes (3rd)	mRNA	Mild to moderate	Supportive	124 /	Alive; persistent dyspnea
٢	DLBCL	67	ш	Refractory	None	6th R-CHOP	Rituximab	89	No	N/A	Mild to moderate	Paxlovid	1 62	Died

BR = bendamustine/rituximab, CR = complete remission, DLBCL = diffuse large B cell lymphoma, HSCT = hematopoietic stem cell transplantation, N/A = not applicable, PR = partial response, R-CHOP = rituximab-cyclophosphamide/hydroxydaunorubicin hydrochloride/vincristine/prednisone, SD = stable disease, M = male, F= female



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lymphoma during the follow-up period (median 124 days). The patients received a median of 3 (range: 1–9) reverse transcriptase polymerase chain reaction (RT-PCR) assays during the follow-up period, and all PCR tests were positive (Supplementary Fig. 2).

Baseline and Follow-Up Chest CTs of Study Patients

A summary of the patients' treatments, interval changes in CTs, and RT-PCR results is shown in Supplementary Figure 3.

The patients underwent a median of three CTs during the follow-up period (median 124 days). Follow-up intervals for CT varied greatly because the patients underwent chest CTs as deemed necessary by the ordering physicians. Baseline chest CTs of these patients were taken at a median of 15 days (range: 0–45 days) after the diagnosis of COVID-19. On baseline CTs, all patients showed peripherally distributed patchy GGOs typical of COVID-19 pneumonia. Between the diagnosis of COVID-19 and baseline CT, all patients showed COVID-19 symptoms (five mild to moderate and two severe), one patient received antiviral therapy, and one patient received steroid therapy.

The first follow-up CT of the patients were taken after a median of 39 days (range: 21–72 days) from the diagnosis of COVID-19. On the first follow-up CT, one patient showed aggravation of previous opacities (patchy GGOs in the peripheral distribution), and six patients showed migration of airspace opacities. Migratory opacities consisted of peripheral and peribronchial GGO combined with peripheral or peribronchial consolidation in many patients. Between the baseline and first follow-up CTs scans, all patients continued to show the same COVID-19 symptoms as

Table 2.	Baseline	and	Follow-Up	Chest	СТ	Findings

before (five mild to moderate and two severe); no one had received antiviral therapy; and three patients had received systemic corticosteroid therapy.

Six out of seven patients underwent a second follow-up CT, which were taken after a median of 63 days (range: 21–72 days) from the diagnosis of COVID-19. On the second followup CT, one patient showed regression of previous opacities and five patients showed migration of airspace opacities. The migratory opacities were peripheral and peribronchial GGO, and in two to three patients, peripheral and peribronchial consolidations were combined. Between the first and second follow-up CTs, all patients showed COVID-19 symptoms (five patients continued to show mild to moderate symptoms and one patient with severe symptoms aggravated to critical symptoms); no one had received antiviral therapy; three patients had received systemic corticosteroid therapy; one patient received baricitinib.

Three out of seven patients underwent a third followup CT, which took a median of 75 days (range: 45-78 days) after the diagnosis of COVID-19. On the third follow-up CT, all three patients showed migration of the previous opacities. Three patients showed peripheral and peribronchial GGO and two patients showed peripheral and peribronchial GGO with consolidation. Between the second and third follow-up CTs, two patients continued to have mild to moderate COVID-19 symptoms, and one patient with critical symptoms improved to severe symptoms. None of the patients received antiviral therapy, and all three patients received systemic corticosteroid therapy. The findings of the baseline and follow-up CTs (up to the third follow-up) are summarized in Table 2.

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	Baseline CT	1st F/U CT	2nd F/U CT	3rd F/U CT
Time of CT exam (days from	15 (range: 0–45)	39 (range: 21–72)	63 (range: 31–140)	75 (range: 45–78)
diagnosis of COVID-19)*				
CT finding				
GGO				
Peripheral distribution	7/7 (100%)	7/7 (100%)	6/6 (100%)	3/3 (100%)
Peribronchial distribution	0/7 (0%)	6/7 (85.7%)	5/6 (83.3%)	3/3 (100%)
Consolidation				
Peripheral distribution	0/7 (0%)	5/7 (71.4%)	3/6 (50.0%)	2/3 (66.7%)
Peribronchial distribution	0/7 (0%)	4/7 (57.1%)	2/6 (33.3%)	2/3 (66.7%)
Changes	N/A			
Migration		6/7 (85.7%)	5/6 (83.3%)	3/3 (100%)
Regression		0/7 (0%)	1/6 (16.7%)	0/3 (0%)
Aggravation		1/7 (14.3%)	0/6 (0%)	0/3 (0%)

*Median. GGO = ground glass opacity, N/A = not applicable, F/U = follow-up

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Two of the seven patients underwent a fourth followup CT. One patient whose fourth follow-up CT was 112 days after COVID-19 diagnosis showed regression of the previous opacities, despite continuing to demonstrate severe COVID-19 symptoms. Between the third and fourth CT scans, the patient received remdesivir and systemic corticosteroid therapy. The other patient, whose fourth follow-up CT was taken 61 days after COVID-19 diagnosis, once again showed migration of peripherally and peripronchially distributed patchy and irregular-shaped GGOs. This patient continued to demonstrate mild to moderate COVID-19 symptoms and received systemic corticosteroid therapy between the third and fourth follow-up CTs. Only one patient underwent fifth and sixth follow-up CTs, which were taken 87 days and 134 days, respectively, after the diagnosis of COVID-19. The fifth follow-up CT showed migration of peripheral and peribronchial GGOs, and the sixth follow-up CT showed regression of these opacities. The COVID-19 symptoms of this patient continued to be mild to moderate, and the patient received systemic corticosteroid therapy between the fourth and sixth follow-up CTs scans. Serial CT images of the patients are shown in Figures 1 and 2 and Supplementary Figures 4 and 5.

DISCUSSION

Our study has demonstrated that migratory airspace opacities are seen on chest CTs of B-cell lymphoma patients who had recently received B-cell-depleting agents and show persistent SARS-CoV-2 infection. Lymphoma has been reported to worsen the prognosis of COVID-19 because of its underlying immunosuppressive condition and B-cell aplasia due to B cell-depleting agents [12,13]. In addition, many studies have reported prolonged SARS-CoV-2 infection in lymphoma patients [14]. B-cell lymphoma is characterized by the cancerous transformation of B cells and chromosomal translocation involving immunoglobulin loci, and anti-CD20 antibodies that target CD20 on the malignant B cells, such as rituximab, are the mainstay of treatment for B-cell lymphoma [15]. Many studies have demonstrated that rituximab is associated with a reduced protective effect of COVID-19 vaccination and poor prognosis in COVID-19 patients [12,16-18]. In this study, prolonged SARS-CoV-2 infection was confirmed in six of seven patients and suspected in one patient, despite five patients receiving two or more doses of SARS-CoV-2 vaccination. This may be due to impaired humoral immune response caused by

B-cell-depleting agents; diminished anti-spike antibody production and neutralizing antibody response to SARS-CoV-2 were observed in patients receiving B-cell depleting therapy [8,19,20], resulting in damaged viral clearance and prolonged infection even in vaccinated patients [21,22].

On baseline CT scans, all patients demonstrated peripheral GGOs, which are a typical manifestation of COVID-19 pneumonia [1]. However, except for the first follow-up CT of one patient whose CT showed migration of peripheral GGOs. all migratory opacities consisted of both peripheral and peribronchial GGOs, sometimes combined with peripheral and peribronchial consolidations. As "reverse halo sign or other findings of organizing pneumonia" is included in the definition of typical appearance of COVID-19 pneumonia according to an expert panel review [1] and peribronchial GGO or consolidation is a typical imaging finding of organizing pneumonia [23,24], the migratory opacities could be interpreted as 'typical COVID-19 pneumonia.' The persistent COVID-19 symptoms and prolonged positive SARS-CoV-2 PCR results with persistently similar Ct values of the patients in our study further support this interpretation. Our hypothesis is that airspace opacities caused by SARS-COV-2 improve over time, yet due to damaged viral clearance caused by B-cell depletion, persistently shedding viruses arrive in the lungs and initiate a new inflammatory process at different locations (Supplementary Fig. 6).

Migratory opacities have been described in several case reports of prolonged SARS-CoV-2 infection in lymphoma patients with available CT findings. The literature review revealed eight cases of lymphoma patients (four follicular lymphoma, one chronic lymphocytic leukemia, one mantle cell lymphoma, one marginal zone lymphoma, and one Hodgkin lymphoma) with migratory opacities [8-10,14,20,25-27], which are summarized in Supplementary Table 1. Except for one follicular lymphoma patient whose treatment was not specified and one Hodgkin lymphoma patient, all six patients had received rituximab or other B-cell depleting agents, as in our study. Although there seems to be a predilection for B-cell lymphoma and the use of B-cell depleting therapies in developing migratory opacities on chest CT accompanied by prolonged SARS-CoV-2 infection, further studies are needed to elucidate the exact mechanism and risk factors for developing migratory airspace opacities.

The known natural history of COVID-19 pneumonia up to one year is regression of GGOs over time, with residual lung opacities remaining in some cases even after six months or one year [2-7]. However, the host immunity



of the patients in these studies was not specified, and although some studies included patients with comorbidities, it is highly unlikely that the subjects in these studies were immunocompromised or exhibited prolonged SARS-CoV-2 infection. As is evident in our study and other case reports of prolonged SARS-CoV-2 infection, a different natural history of COVID-19 pneumonia, other than regression over time, should be considered for some immunocompromised patients. The presence of migratory airspace opacities may represent one imaging feature of prolonged SARS-CoV-2 infection.

The course of the airspace opacities and the treatments that the patients received seemed to be unrelated. The treatments received varied between patients, and all of them had received different doses of steroid and/or antiviral agents at some point during their follow-up period. Three patients showed regression of airspace opacities on their last follow-up CTs, but the order and combination of treatments these patients received were all different, and whether antiviral agents or steroid therapy had any influence on these outcomes needs to be further investigated.

Our study had some limitations. First, this was a singlecenter retrospective study with a small sample size. Second, although we did discover some common factors among patients with migratory COVID-19 pneumonia, further statistical analysis exploring the risk factors for developing this phenomenon could not be performed because the number of study patients was too small to perform logistic regression analysis with statistically significant results. As this is not a common phenomenon involving a common disease, it cannot be predicted when or if patients with migratory opacities on CT would arrive at our institution; hence, when a sufficient number of patients can be achieved to run a logistic regression analysis remains unknown. The authors believe that reporting this phenomenon in a timely manner is more important, so that other physicians currently treating COVID-19 patients could use this report as a reference. Third, key clinical information related to the development of COVID-19 pneumonia, such as the patients' vaccination status, details about treatments received after COVID-19 diagnosis, SARS-CoV-2 PCR results, and Ct values of SARS-COV-2 PCR, was missing in many patients with hematologic malignancies and without migratory airspace opacities, which could have potentially served as the control group. Further studies with a larger number of patients and an appropriate control group without missing clinical information that explore the risk factors for developing

migratory COVID-19 pneumonia using statistical analyses would be greatly appreciated. Fourth, there may have been COVID-19 patients who were not included in this study because they did not have COVID-19-related keywords in their CT readings. However, as this study involved a group of patients with COVID-19 diagnosis and abnormal findings on serial chest CTs, the authors believed that the non-inclusion of COVID-19 patients without available chest CT or findings related to COVID-19 on chest CT would not pose a significant problem in the general direction of this study. In addition, since the beginning of the COVID-19 pandemic in 2020, there is a consensus among thoracic radiologists at our institution to include "COVID-19 pneumonia" in the differentials of CT readings when there is even a slightest possibility of atypical pneumonia or viral pneumonia on chest CT, making the keyword search sufficient for the purpose of this study. Fifth, the follow-up period for these patients was limited to a median of 124 days. Only three patients showed regression of airspace opacities on the last follow-up CT, and whether these patients would remain stable is unknown. The clinical courses of the other four patients who showed migration of opacities even on the last follow-up CT are also unknown. Longer follow-up of these patients is necessary to gain a greater understanding of migratory pneumonia during prolonged SARS-CoV-2 infection.

In conclusion, COVID-19 patients with B-cell lymphoma who had received B-cell depleting therapy and are experiencing prolonged SARS-CoV-2 infection and persistent symptoms may demonstrate migratory airspace opacities on serial CT, which could be interpreted as ongoing COVID-19 pneumonia.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0844.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.



Author Contributions

Conceptualization: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee. Data curation: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee, Dae Hee Han, Suyon Chang, Jung Im Jung. Formal analysis: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee. Funding acquisition: Dong-Gun Lee. Investigation: all authors. Methodology: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee. Supervision: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee, Dae Hee Han, Dong-Gun Lee. Validation: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee. Visualization: Kyongmin Sarah Beck, Jongmin Lee, Raeseok Lee. Writing—original draft: all authors. Writing—review & editing: all authors.

ORCID iDs

Jongmin Lee

https://orcid.org/0000-0002-0165-5856 Raeseok Lee

https://orcid.org/0000-0002-1168-3666 Kyongmin Sarah Beck

https://orcid.org/0000-0002-9262-1001

Dae Hee Han

https://orcid.org/0000-0002-5239-9207

Gi June Min

https://orcid.org/0000-0001-7636-4693

Suyon Chang

https://orcid.org/0000-0002-9221-8116

Jung Im Jung https://orcid.org/0000-0001-8264-9388

Dong-Gun Lee

https://orcid.org/0000-0003-4655-0641

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