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Radiologic Abnormalities in Prolonged SARS-CoV-2 Infection: A Systematic Review

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We systematically reviewed radiological abnormalities in patients with prolonged SARS-CoV-2 infection, defined as persistently positive polymerase chain reaction (PCR) results for SARS-CoV-2 for > 21 days, with either persistent or relapsed symptoms. We extracted data from 24 patients (median age, 54.5 [interquartile range, 44–64 years]) reported in the literature and analyzed their representative CT images based on the timing of the CT scan relative to the initial PCR positivity. Our analysis focused on the patterns and distribution of CT findings, severity scores of lung involvement on a scale of 0–4, and the presence of migration. All patients were immunocompromised, including 62.5% (15/24) with underlying lymphoma and 83.3% (20/24) who had received anti-CD20 therapy within one year. Median duration of infection was 90 days. Most patients exhibited typical CT appearance of coronavirus disease 19 (COVID-19), including ground-glass opacities with or without consolidation, throughout the follow-up period. Notably, CT severity scores were significantly lower during ≤ 21 days than during > 21 days (P < 0.001). Migration was observed on CT in 22.7% (5/22) of patients at ≤ 21 days and in 68.2% (15/22) to 87.5% (14/16) of patients at > 21 days, with rare instances of parenchymal bands in previously affected areas. Prolonged SARS-CoV-2 infection usually presents as migrating typical COVID-19 pneumonia in immunocompromised patients, especially those with impaired B-cell immunity.

Keywords: Prolonged SARS-CoV-2 infection; COVID-19 pneumonia; CT; Immunocompromised; B-cell immunity; Anti-CD20 agent

INTRODUCTION

Over the past three years, the spread and severity of coronavirus disease 19 (COVID-19) have declined. However, a rare and intriguing manifestation of SARS-CoV-2 infection, known as 'prolonged SARS-CoV-2 infection' is garnering attention [1]. This condition encompasses cases of SARS-CoV-2 infection that extend beyond the typical duration of viral shedding in the respiratory tract, which is usually 17–21 days, along with persistent clinical symptoms [2-5]. In some patients, polymerase chain reaction (PCR) tests for SARS-CoV-2 can yield positive results for approximately 80–300 days from the initial positivity [5-7]. Prolonged SARS-CoV-2 infection poses a public health threat as it may lead to a higher number of viral mutations, potentially resulting in the emergence of drug-resistant variants and variants with increased infectivity [8,9].

Imaging is indispensable for the diagnosis and management of COVID-19 [10,11], and CT findings of COVID-19 pneumonia have been reported in multiple studies [12,13]. However, radiological findings associated with prolonged SARS-CoV-2 infection remain underexplored, with only sporadic case reports. Addressing this knowledge gap by characterizing the radiological findings of prolonged SARS-CoV-2 infection is crucial for its timely recognition, diagnosis, and management. Hence, this study aimed to systematically review radiological abnormalities in patients with prolonged SARS-CoV-2 infection.

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Systematic Search and Analysis of Literature

A systematic literature review was conducted to identify studies on prolonged SARS-CoV-2 infection with available CT images. Prolonged infection was defined as persistently positive PCR results for SARS-CoV-2 for more than 21 days [3], with either persistent or relapsed COVID-19 symptoms. Patient characteristics and clinical details were extracted and reviewed. Additional methodological details are provided in Figure 1 and in the Supplementary Methods and Supplementary Tables 1, 2. This review included 19 studies that reported on a total of 24 patients (median age, 54.5 years [interquartile range (IQR) 44–64 years]; 15 male) [7-9,14-29].

Two authors (K.S.B. and S.H.Y.) independently reviewed the CT findings from representative images and reached a consensus regarding the following items: the predominant CT density of pneumonia (ground-glass opacity [GGO], consolidation, or both); the predominant distribution of pneumonia (peripheral, peribronchovascular, or both); category according to the Radiological Society of North America (RSNA) Expert Consensus Document (typical appearance, indeterminate appearance, atypical appearance, or negative for COVID-19 pneumonia) [13]; severity of pneumonia on a scale of 0–4 for the whole lungs (0, no involvement; 1, 1%–25% involvement; 2, 26%–50% involvement; 3, 51%–75% involvement; and 4, 76%–100% involvement); and the presence of migration between two serial CTs (emergence of new lesions with regression of prior lesions). In addition, the reviewers assessed the presence of reticular opacities or parenchymal bands in previously affected areas on subsequent CT scans.

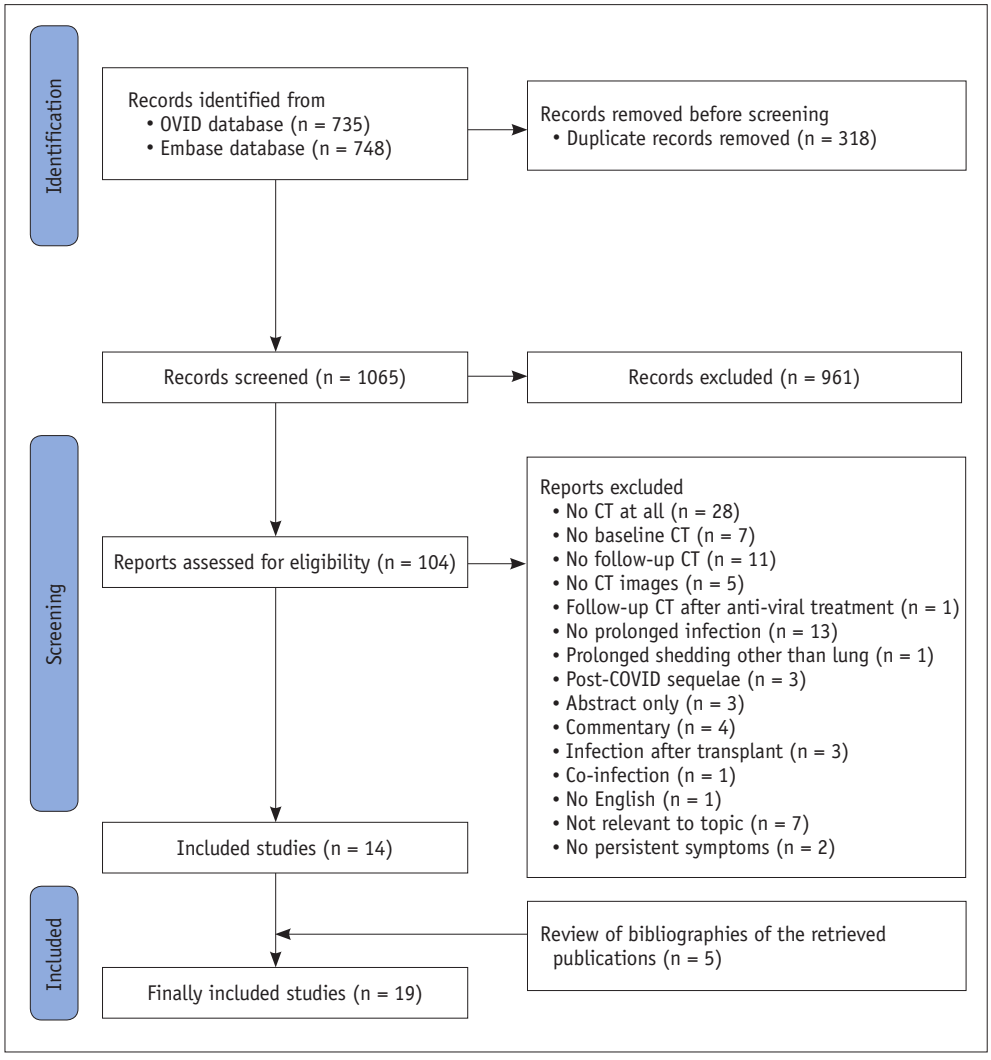

Fig. 1. PRISMA flow diagram of the study selection process.

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Table 1. Summary of clinical characteristics of 24 patients with prolonged SARS-CoV-2 infection

Clinical characteristics	Data
Age, yrs	54.5 (44–64)
Sex, female:male	9 (37.5):15 (62.5)
Continent	
Asia	12 (50.0)
Europe	7 (29.2)
North America	3 (12.5)
South America	2 (8.3)
Underlying disease	
X-linked agammaglobulinemia	2 (8.3)
Lymphoma	15 (62.5)
Leukemia	2 (8.3)
Multiple sclerosis	2 (8.3)
Good syndrome	1 (4.2)
Systemic lupus erythematosus	1 (4.2)
Mixed connective tissue disease	1 (4.2)
Immunocompromised	
Yes	24 (100.0)
No	0 (0)
Treatment with anti-CD20 agent* within 1 year	
Yes	20 (83.3)
No	4 (16.7)
Vaccination against SARS-CoV-2	
Yes	10 (41.7)
No	11 (45.8)
Unknown	3 (12.5)
Detection of anti-SARS-CoV-2 antibody	
Yes	0 (0)
No	14 (58.3)
Unknown	10 (41.7)
Lymphopenia	
Yes	14 (58.3)
No	2 (8.3)
Unknown	8 (33.3)
SARS-CoV-2 subtype	
Original strain	7 (29.2)
Delta variant	2 (8.3)
Omicron variant	10 (41.7)
Unknown	5 (20.8)
Duration of SARS-CoV-2 PCR positivity, days	90 (64.5–115.25)
Number of SARS-CoV-2 PCR tests taken	8.5 (4.75–12)
Time interval between SARS-CoV-2 PCR tests, days	10 (7–14)
Transient negative conversion during prolonged SARS-CoV-2 infection	
Yes	5 (20.8)
No	19 (79.2)
Lowest cycle threshold value during the disease course	18 (14.25–21.75)
Median cycle threshold value during the disease course	
< 20	2 (8.3)
20–30	10 (41.7)
> 30	1 (4.2)
Not available	11 (45.8)

Data are median (interquartile range) or number of patients (percentage).
*Rituximab, obinutuzumab, or odronextamab.
PCR = polymerase chain reaction

Clinical Characteristics of Prolonged SARS-CoV-2 Infection

Patients' clinical characteristics, including symptoms, treatment, and outcomes, are summarized in Table 1 and Supplementary Table 3. All patients were immunocompromised and lymphoma was the most common underlying disease (62.5% [15/24]). Twenty patients (83.3% [20/24]) had undergone treatment with anti-CD20 agents, such as rituximab, obinutuzumab, or odronextamab within one year prior to COVID-19 diagnosis. Anti-SARS-CoV-2 antibodies were not detected in all 14 patients (58.3% [14/24]) who underwent testing. The median duration of SARS-CoV-2 PCR positivity was 90 days, with a median of 8.5 PCR tests performed per patient. The median time interval between PCR tests was 10 days, and 10 patients (76.9% of the 13 patients with available data) demonstrated a median cycle threshold (Ct) value of 20–30.

Bronchoscopic biopsies were performed in three patients [22,25,26], revealing organizing pneumonia upon histopathological examination. To treat prolonged SARS-CoV-2 infection, a high proportion of patients (87.5% [21/24]) received steroids, such as dexamethasone, methylprednisolone, or prednisone, and 22 patients (91.7% [22/24]) received antiviral treatment, including remdesivir, favipiravir, molnupiravir, or lopinavir-ritonavir. Three (12.5% [3/24]), seven (29.2% [7/24]), and seven (29.2% [7/24]) patients received convalescent plasma, intravenous immunoglobulin, and monoclonal antibody, respectively, as treatment for prolonged SARS-CoV-2 infection. Three patients (12.5% [3/24]) were admitted to the intensive care unit and required mechanical ventilation. The median length of hospital stay was 54.5 days. Four patients (16.7% [4/24]) died.

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CT Findings of Prolonged SARS-CoV-2 Infection

Patients underwent a median of three CT scans during prolonged SARS-CoV-2 infection. The findings of the CTs (Fig. 2, Supplementary Fig. 1) taken during SARS-CoV-2 infection, which were categorized into four groups (≤ 21 days, 22–43 days, 44–65 days, and > 65 days from initial diagnosis) based on the period after initial diagnosis, are summarized in Table 2. Further, a box and whisker plot showing CT severity scores according to the timing of the scan is shown in Supplementary Figure 2. The most common findings across all time intervals were typical appearance of COVID-19 pneumonia, as defined by the RSNA CT categorization, and GGO with or without consolidation, regardless of when the CT was performed. On CTs from the initial ≤ 21 days from diagnosis, GGO with a peripheral distribution and a severity score of 1 was most frequently seen. Beyond 21 days from the initial diagnosis, both peripheral and peribronchovascular distributions with severity scores of 2–3 were commonly seen. Migration was observed in 22.7% (5/22) of CTs taken within ≤ 21 days and in 68.2 (15/22) to 87.5% (14/16) of CTs taken after 21 days from the initial diagnosis. Median severity scores for CTs taken during ≤ 21 days, 22–43 days, 44–65 days, and > 65 days from initial diagnosis were 1.0 (IQR 1.0–2.0), 2.0 (IQR 2.0–3.0), 3.0 (IQR 2.0–3.0), and 3.0 (IQR 2.0–3.0), respectively.

A non-parametric Kruskal-Wallis H-test was conducted to determine if there were significant differences in CT severity scores among the four groups. CT severity scores were significantly lower for CTs taken during ≤ 21 days from initial diagnosis ($P < 0.001$), compared to CTs taken after 21 days. Severity scores across CTs taken during 22–43 days, 44–65 days, and > 65 days from the initial diagnosis did not show a significant difference ($P = 0.540$). When migration of airspace opacities was observed on subsequent CT scans, previous airspace opacities tended to show complete resolution.

Further Discussion

In this study, all patients with prolonged SARS-CoV-2 infection were immunocompromised. Notably, 20 patients (83.3% [20/24]) had been treated with anti-CD20 agents, which are known for their B cell-depleting effects, within one year prior to their prolonged SARS-CoV-2 infection. The use of anti-CD20 agents, such as rituximab, can compromise a patient's ability to produce antibody responses following SARS-CoV-2 infection or COVID-19 vaccination. This

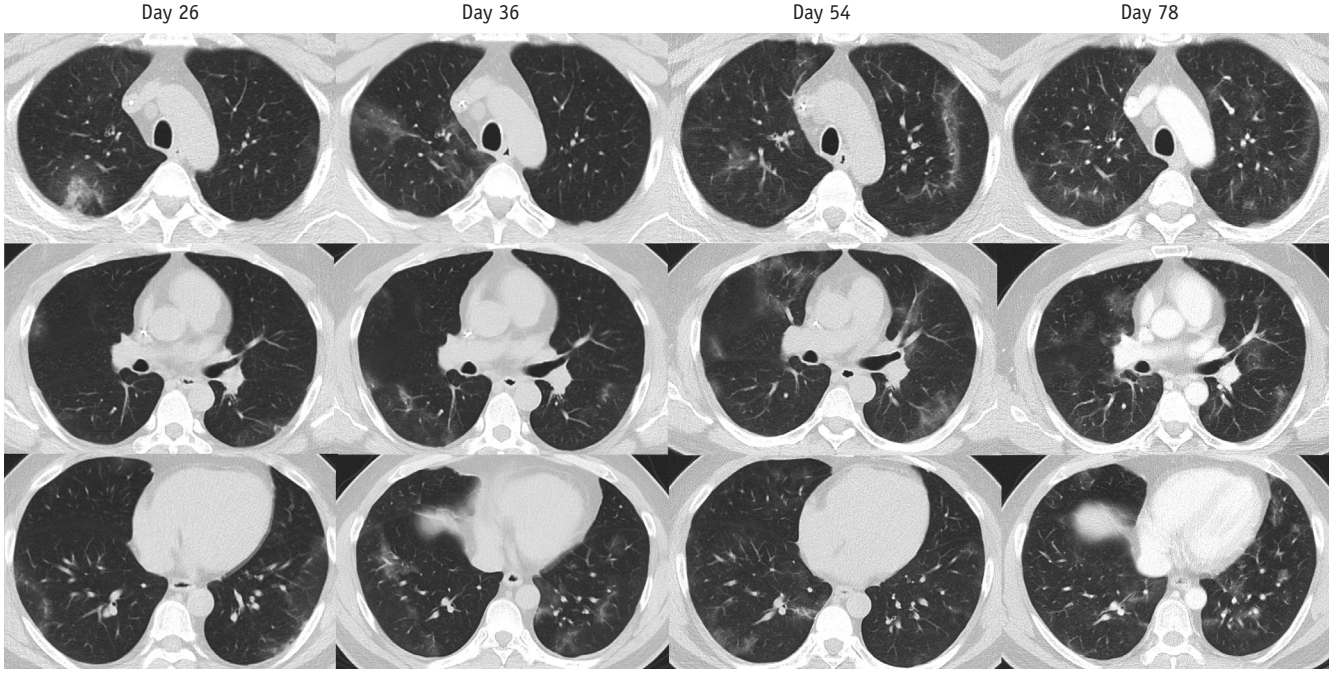

Fig. 2. Migratory pneumonia in a 45-year-old male patient with diffuse large B-cell lymphoma and persistent SARS-CoV-2 infection. Axial chest CT images taken at 26, 36, 54, and 78 days after COVID-19 diagnosis demonstrated migration of multifocal patchy peripheral or peribronchovascular ground-glass opacities, which is clearing of previous opacities with development of new opacities in different locations. The patient had received odronextamab, a bispecific antibody that acts as a B-cell-depleting agent, 9 days prior to COVID-19 diagnosis. Reprinted from Lee et al. *Korean J Radiol* 2023;24:362-370 [7].

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Table 2. Serial CT findings during prolonged SARS-CoV-2 infection

Time of CT exam (days from the 1st positive PCR)	≤ 21 days (n = 22)	22–43 days (n = 22)	44–65 days (n = 17)	> 65 days (n = 16)
Median number of days from the 1st positive PCR	10	31	54	89
RSNA CT categorization of COVID-19 pneumonia				
Typical	19 (86.4)	20 (90.9)	15 (88.2)	14 (87.5)
Indeterminate	3 (13.6)	2 (9.1)	2 (11.8)	2 (12.5)
Atypical	0 (0)	0 (0)	0 (0)	0 (0)
Pattern				
GGO	13 (59.1)	10 (45.5)	12 (70.6)	12 (75.0)
Consolidation	1 (4.5)	0 (0)	0 (0)	0 (0)
Both	8 (36.4)	12 (54.5)	5 (29.4)	4 (25.0)
Distribution				
Peripheral	12 (54.5)	8 (36.4)	4 (23.5)	2 (12.5)
Peribronchovascular	1 (4.5)	2 (9.1)	3 (17.6)	1 (6.2)
Both	9 (40.9)	12 (54.5)	10 (58.8)	13 (81.3)
Severity				
1%–25% involvement	12 (54.5)	3 (13.6)	3 (17.6)	1 (6.2)
26%–50% involvement	7 (31.8)	7 (31.8)	3 (17.6)	4 (25.0)
51%–75% involvement	0 (0)	6 (27.3)	7 (41.2)	7 (43.8)
76%–100% involvement	0 (0)	0 (0)	0 (0)	0 (0)
Unassessable	3 (13.6)	6 (27.3)	4 (23.5)	4 (25.0)
Migration				
Yes	5 (22.7)	15 (68.2)	13 (76.5)	14 (87.5)
No	1 (4.5)	1 (4.5)	3 (17.6)	1 (6.2)
Unassessable	16 (72.7)	6 (27.3)	1 (5.9)	1 (6.2)

Data are number of patients (percentage) unless specified otherwise.
PCR = polymerase chain reaction, RSNA = Radiological Society of North America, GGO = ground-glass opacity

impairment is due to the depletion of B cells in most stages, including memory B cells, which may contribute to prolonged SARS-CoV-2 infection [23]. The relationship between the patients' inability to produce antibody responses and prolonged SARS-CoV-2 infection was clearly evidenced in our study, where 14 patients (58.3% [14/24]) failed to develop anti-SARS-CoV-2 antibodies regardless of their vaccination status or duration of infection.

Our analysis revealed that mild, typical COVID-19 pneumonia with peripheral GGOs were dominant CT findings in the early stages of SARS-CoV-2 infection. This presentation evolved into moderate, typical COVID-19 pneumonia with GGOs showing both peripheral and peribronchovascular distributions on CT during prolonged SARS-CoV-2 infection. Notably, CT scans conducted during prolonged SARS-CoV-2 infection (after 21 days) showed persistently intermediate severity scores, regardless of the timing of the scan. Migration of airspace opacities was seen throughout the whole duration of SARS-CoV-2 infection, even in the early stage (≤ 21 days). These results differ somewhat from previous studies on the temporal changes in CT findings of COVID-19 pneumonia, which identified a peak stage of airspace opacities at 9–13 days after symptom onset and a gradual decrease in airspace opacities with signs of fibrosis, such as parenchymal bands, ≥ 14 days after symptom onset [30-32], reflecting a different course of COVID-19 pneumonia in prolonged SARS-CoV-2 infection in immunocompromised patients. Interestingly, all patients who had used anti-CD20 agents within one year exhibited migration of airspace opacities during SARS-CoV-2 infection. Three additional patients who showed migratory pneumonia during SARS-CoV-2 infection had either X-linked agammaglobulinemia (XLA) [14], which is a condition characterized by an inability to produce B-cells, or were undergoing treatment with tirabrutinib [21], a Bruton's tyrosine kinase (BTK) inhibitor that inhibits pathways associated with B-cell proliferation and development. In fact, BTK is known to be defective in XLA [33], and one study revealed that the pooled antibody responses after COVID-19 vaccination were the lowest (15% and 23%, respectively) for patients who had used anti-CD20 therapy within one year prior to COVID-19 diagnosis and a BTK inhibitor [34].

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From these observations, it can be inferred that patients with impaired B cell immunity who cannot produce proper antibody responses are likely to demonstrate migratory COVID-19 pneumonia during prolonged SARS-CoV-2 infection.

Our observations align with a hypothesis stemming from a report on patients with XLA, which suggests that this migratory phenomenon is likely a result of a lack of immune-mediated response due to impaired humoral (B-cell) immunity, which hinders the establishment of a proper inflammatory reaction in the lungs [14]. Interestingly, in patients with migratory pneumonia, we seldom observed parenchymal bands or reticular opacities in areas where opacities previously existed on CT scans. This observation could be linked to the absence of a proper inflammatory reaction in the lungs. Although the mechanism is not clear, a flawed immune-mediated reaction in conjunction with persistent viral shedding into the lungs despite some clearance of the viruses may be responsible for the development of migratory airspace opacities. Depletion of B-cells may protect the patients from a cytokine storm and severe pneumonia due to dampened inflammatory responses, but the inability to eliminate the virus from the body may result in persistent infection and a protracted disease course [21,27]. Although controversial, many clinicians use Ct values as a proxy for viral load; generally, Ct values around 17–24 and around 40, which is closer to the limit of detection for most assays, are considered high and low viral loads, respectively [35,36]. In our analysis, the median Ct values of 20–30 during the course of prolonged SARS-CoV-2 infection in most patients with available data, coupled with persistently intermediate severity scores on follow-up CTs after 21 days, likely reflect a consistently moderate to high viral load, resulting in an extended disease course.

Histopathological results from the three patients who underwent bronchoscopic biopsies revealed organizing pneumonia. Despite the pathological diagnosis of organizing pneumonia, two patients were identified as having COVID-19 pneumonia and received antiviral therapy along with steroids, eventually showing improvement. Conversely, one patient was regarded as having obinutuzumab-induced organizing pneumonia and only treated with methylprednisolone [24]. It was only after revising the diagnosis to pneumonia due to prolonged SARS-CoV-2 infection and initiating remdesivir treatment that the patient improved. Since histopathological findings of 'COVID-19 pneumonia' is actually organizing pneumonia in about 30%–40% of autopsied patients with COVID-19 [37,38], in patients with impaired humoral immunity and prolonged SARS-CoV-2 infection who show persistent and migratory radiological abnormalities, 'ongoing COVID-19 pneumonia' due to persistent viral shedding should be firstly considered and differentiated. Verifying SARS-CoV-2 PCR results, or recommending SARS-CoV-2 PCR in the absence of recent SARS-CoV-2 PCR results, would assist in the diagnosis. If SARS-CoV-2 PCR results are negative, then the airspace opacities are less likely to be 'ongoing COVID-19 pneumonia,' and alternative diagnoses, such as pneumonia or organizing pneumonia due to other causes or cryptogenic organizing pneumonia, should be considered.

This literature analysis has several limitations. First, this review is based on a relatively small number of retrospective case reports and case series, with a limited study population. Second, heterogeneity existed in the reporting format and content of each study, and not all information was available in every study. Third, imaging findings were analyzed solely through representative CT images with descriptions presented in the published papers, which may not accurately reflect the whole CT images of the patients. Fourth, the descriptive nature of the included studies precluded the classification of symptom severity and the analysis of its relevance to the CT findings. Fifth, information about Ct values was only available for approximately half of the patients, and the values span the entire duration of the prolonged SARS-CoV-2 infection, not solely after 21 days from the initial diagnosis. However, it is worth noting that the majority of the available Ct values were obtained after 21 days from the initial diagnosis. Sixth, this study only included immunocompromised patients. Imaging findings of COVID-19 pneumonia according to immune status should be explored in future studies. Lastly, pathological verification was conducted in only three patients and via bronchoscopic biopsy, which may not provide ample histopathological or molecular evidence for our hypotheses regarding migratory pneumonia.

CONCLUSION

In conclusion, prolonged SARS-CoV-2 infection in immunocompromised patients, especially those with impaired B-cell immunity, predominantly presents as migrating, typical COVID-19 pneumonia. This condition exhibits low severity in the early phase and maintains intermediate severity in the later phases, mimicking the appearance of organizing pneumonia on repeated CT scans.

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When interpreting chest CT images of immunocompromised patients with a history of COVID-19, careful evaluation of imaging findings and patient symptoms, along with verification of recent SARS-CoV-2 PCR results, is warranted.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2023.1149.

Availability of Data and Material

Data generated or analyzed during the study are available from the corresponding author by request.

Conflicts of Interest

Soon Ho Yoon has stocks and stock options of MEDICAL IP, outside this work. Other authors have no potential conflicts of interest to declare.

Author Contributions

Conceptualization: Kyongmin Sarah Beck, Soon Ho Yoon. Data curation: Kyongmin Sarah Beck, Soon Ho Yoon. Formal analysis: all authors. Investigation: all authors. Methodology: all authors. Supervision: Soon Ho Yoon. Validation: all authors. Visualization: Kyongmin Sarah Beck, Soon Ho Yoon. Writing—original draft: all authors. Writing—review & editing: all authors.

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