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CASE REPORT

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Concurrent lung adenocarcinoma hidden among multiple shadows of COVID-19 pneumonia: A rare and instructive case report

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Abstract

A 40-year-old man was admitted with a diagnosis of COVID-19 pneumonia. Although most of multiple ground-glass opacities and consolidations on computed tomography improved, a round ground-glass opacity with consolidation remained unchanged and was suspected to be a part-solid nodule of lung adenocarcinoma. Pathologic diagnosis of resected tumor was papillary adenocarcinoma.

KEYWORDS

consolidation, COVID-19, ground-glass opacity, lung adenocarcinoma, part-solid nodule

1 | INTRODUCTION

Ground-glass nodule, a technical term of an initial finding of early stage lung adenocarcinoma, is often seen in lung fields on computed tomography (CT).[1] As the solid component of a ground-glass nodule increases, it is referred to as a part-solid nodule, and further as a solid nodule.[2] Radiologic ground-glass nodule corresponds with a pathologic pattern of lipidemic growth and is a sign of noninvasive cancer.[3] On the other hand, a radiologic solid component in the center of the lesion represents pathologic fibrotic foci derived from tumor invasion.[4] A recent study reported that a high ratio of solid component to ground-glass component (consolidation tumor ratio [CTR]) in thin-section CT images is an independent factor for poor prognosis in patients with clinical stage IA lung adenocarcinoma.[5] These studies suggest that early diagnosis of lung adenocarcinoma, at the stage in which the ground-glass component predominates and the solid component is limited on CT images, is associated with substantially better prognosis than lung adenocarcinoma diagnosed in a more advanced stage with increased solid component.

The global pandemic of coronavirus disease 2019 (COVID-19) has been ongoing for more than 2.5 years, since December 2019.[6] Pneumonia is often observed in patients with COVID-19, but its incidence differs according to the strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[7,8] Before the appearance of SARS-CoV-2 variants, the incidence of pneumonia

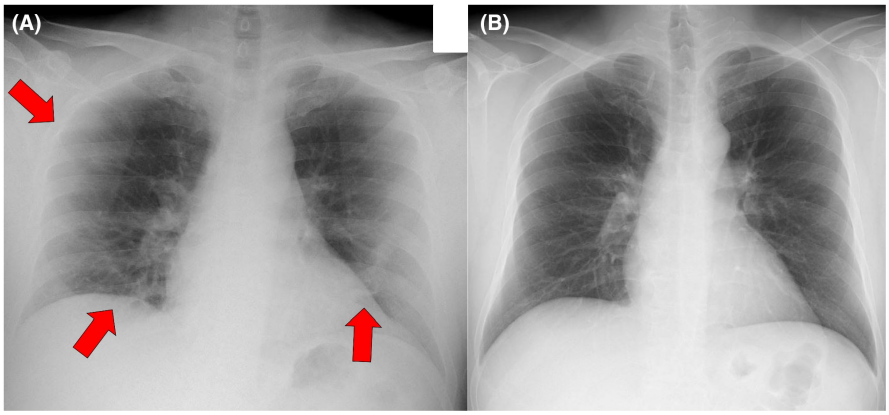

FIGURE 1 Chest radiography images. (A) Chest radiograph on the day of admission for COVID-19 showing ground-grass opacities and infiltrative shadows in both the lung fields (red arrows). (B) Chest radiograph taken 6 months after admission for COVID-19, showing no obvious signs of lung adenocarcinoma.

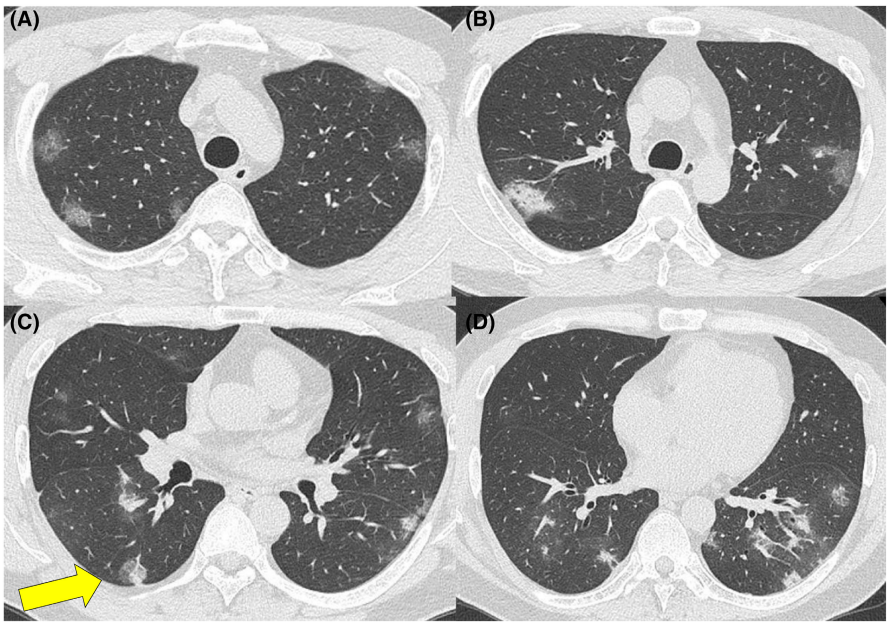

FIGURE 2 Chest computed tomography images on the day of admission for COVID-19. (A-D) Multiple round to elliptical ground-glass opacities, consolidations, are present in the peripheral lower lung fields, suggestive of bilateral COVID-19 pneumonia. (C) A round ground-glass opacity containing a consolidation in the superior segment (S^6) of the right lower lobe (yellow arrow) was subsequently found to be a lung adenocarcinoma. The length of the ground-glass opacity and consolidation are 21.4 mm and 9.3 mm, respectively (consolidation tumor ratio: 0.435).

in patients with COVID-19 was reported to be 86.6% in Japan.[7] However, we recently reported that the incidence of COVID-19 pneumonia was 77.0% in the Alpha and Delta waves, and 34.2% in the Omicron wave.[8]

Ground-glass opacity is the most frequent shadow type seen in patients with COVID-19 pneumonia, which appears as the earliest manifestation.[9] As organizing change appears in pneumonia, consolidations appear in the ground-glass opacities.[9] Song et al.[10] reported that in patients with COVID-19, pure ground-glass opacities were seen in 77% (39/51) of patients, and ground-glass opacities with consolidation was seen in 59% (30/51) of patients.

Thus, ground-glass opacities, with or without consolidations, as seen in COVID-19 pneumonia, are similar to ground-glass nodules or part-solid nodules, as seen in patients with lung adenocarcinoma. COVID-19 pneumonia often reveals multiple shadows with a variable ratio of ground-glass opacities and consolidations in their time course change. Whereas clinicians generally have a cognitive awareness that lung adenocarcinoma can exist among multiple COVID-19 pneumonic shadows, it is difficult even for specialists in CT interpretation to detect lung adenocarcinoma in patients with concurrent COVID-19 pneumonia in clinical practice, not only due to the similarity in shadow patterns, but also because once a diagnosis of COVID-19 pneumonia has been made, clinicians generally do not consider the possibility of other concurrent lung diseases with similar CT findings.

Here, we report a rare and instructive case of lung adenocarcinoma, that appeared as a part-solid nodule on CT images. It was initially missed because it was hidden among multiple ground-glass opacities of COVID-19 pneumonia, with and without consolidations. Repeated CT examinations and interpretation of the CT findings by multiple respiratory physicians fortunately enabled us to diagnose lung adenocarcinoma at the curatively operable stage.

2 | CASE PRESENTATION

In the early April 2020, a 40-year-old man presented with a 1-week history of fever (approximately 37.0–38.0°C) and

a 3-day history of disorder in the sense of taste and smell. He was diagnosed with COVID-19 based on a positive polymerase chain reaction (PCR) test result for SARS-CoV-2 in a nasopharyngeal sample and was admitted to our hospital 7 days after the onset of his fever. He was an ex-smoker with a Brinkman index of 260 and had quit smoking 8 years previously. He had no notable medical history.

On admission, the patient had a clear level of consciousness, with a body temperature of 37.8°C, a blood pressure of 114/83 mmHg, a heart rate of 99 beats/min with a regular rhythm, and a percutaneous arterial oxygen saturation (SpO_2) of 99% breathing room air. His height, body weight, and body mass index were 170.0 cm, 78.0 kg, and 27.0 kg/m^2, respectively. His respiratory and heart sounds were normal, without any cardiac murmurs. He had no palpable lymphadenopathy. There was no peripheral edema.

A chest radiograph revealed bilateral ground-glass opacities and infiltrative shadows (Figure 1A). On CT images, multiple round to elliptical ground-glass opacities and consolidations were seen bilaterally, with some consolidations within the ground-glass opacities (Figures 2A–D). We attributed all of the shadows to COVID-19 pneumonia.

Laboratory tests revealed a normal white blood cell count (4300 cells/μL; normal: 3300–8600 cells/μL) with mildly elevated neutrophil percentage (70.8%; normal: 40.0–70.0%), and mildly elevated levels of alanine aminotransferase (50 U/L; normal: 40–42 U/L), lactate dehydrogenase (234 U/L; normal: 124–222 U/L), and C-reactive protein (6.16 mg/dL; normal: <0.14 mg/dL). The serum Krebs von den Lungen-6 level was within normal limits (218 U/mL; normal: 0–499 U/mL).

We prescribed 200 μg of inhaled ciclesonide: two inhalations, twice daily, which was being used as study drug to treat COVID-19 according to a clinical research protocol.[11] We also prescribed oral levofloxacin (500 mg, once daily) to treat latent secondary bacterial infection. The patient's body temperature decreased to below 37.0°C on the fourth day of admission, and his SpO_2 remained >95% throughout his hospital stay. Based on the negative results of nasopharyngeal SARS-CoV-2 PCR tests, performed on the 18th and 19th days of admission, he was discharged on the 20th day of admission.

A follow-up CT was performed 1 month after the patient's admission (Figures 3A–D). The CT images revealed marked improvement in the ground-glass opacities and consolidations, so we assumed that remaining shadows would gradually disappear. We explained the result of the CT findings to the patient and discontinued follow up. However, at a clinical conference held 6 months after the patient's admission, we noticed that a round ground-glass opacity containing a consolidation (the length of the ground-glass opacity and consolidation: 21.4 mm and 9.3 mm, respectively) in the superior segment (S^6) of right lower lobe remained unchanged in the form and size on the second CT images (yellow arrow in Figure 3C) compared with that on the initial CT images taken on the day of admission (yellow arrow in Figure 2C).

The patient was thus asked to return for follow-up CT. A follow-up CT was performed 6 months after the patient's admission; the CT images showed that the round ground-glass opacity containing the consolidation in the right S^6 was still present and had increased slightly in size (the length of the ground-glass opacity and consolidation: 23.1 mm and 10.3 mm, respectively) (Figures 4A–C). We

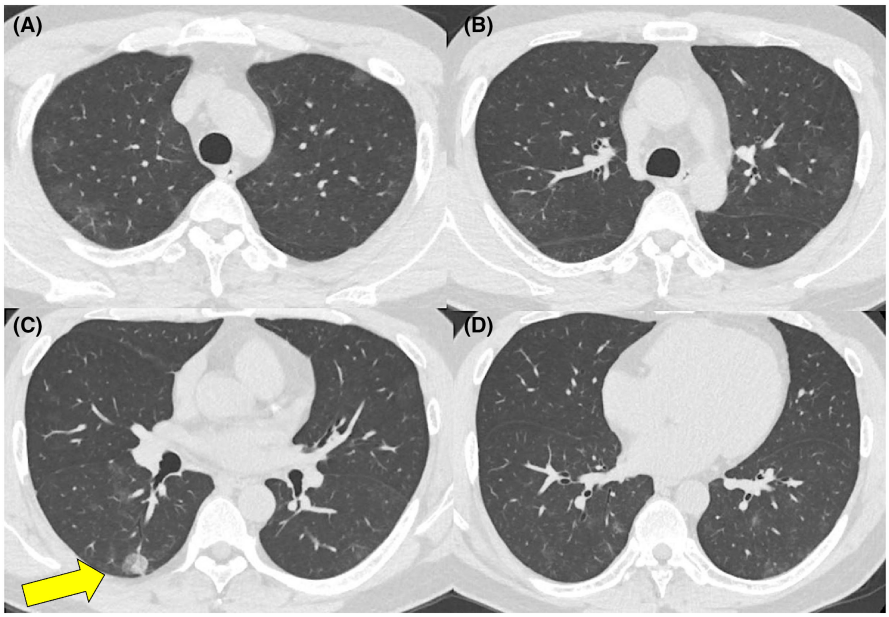

FIGURE 3 Chest computed tomography (CT) images taken 1 month after admission for COVID-19. (A-D) Most of the ground-glass opacities, consolidations or a mixture of both have improved. (C) A round ground-glass opacity containing a consolidation in the superior segment (S^6) of the right lower lobe remains unchanged in the form and size compared with that on the initial CT images on the day of admission (yellow arrow). This lesion was subsequently found to be a lung adenocarcinoma.

did not detect this shadow on a chest radiograph performed at the same time (Figure 1B).

Moreover, we realized that this ground-glass opacity containing the consolidation had characteristic features of a lung adenocarcinoma, such as vessel convergence (Figure 4A), pleural indentation (Figures 4B, C), and notch formation (Figure 4C).[12] At this point, we suspected the persistent shadow in the right S^6 on CT images to be a part-solid nodule of lung adenocarcinoma, not COVID-19 pneumonia, which is often seen in the process of the growth of lung adenocarcinoma. In the initial and the second CT images, the CTR was 0.435 (9.3/21.4 mm) (Figures 2C, 3C) and in the third CT images taken 6 months after the patient's admission, the CTR had increased to 0.446 (10.3/23.1 mm) (Figures 4A-C). On all three occasions, the CT was performed without using a contrast agent, and no metastatic lesions were detected in other organs such as the liver, adrenal gland, and bone. There were no signs of pleural dissemination, pleural effusion, pericardial effusion, or ascites, nor any mediastinal, hilar, or supraclavicular lymphadenopathy.

^{18}F-fluorodeoxyglucose positron emission tomography coupled with CT (FDG-PET/CT) revealed that the rounded ground-glass opacity with consolidation had a maximum standardized uptake value of 2.0, which was lower than the commonly used cutoff value of 2.5 (Figure 4D).[13] No marked FDG accumulation was found in the lymph nodes or any other organs. No brain metastases were observed on contrast-enhanced magnetic resonance imaging and the serum carcinoembryonic antigen level was within normal limits (1.73 ng/ml; normal: ≤5.0 ng/ml).

According to the tumor-node-metastasis (TNM) classification of primary lung cancer, 8th Edition,[14] we provisionally diagnosed lung adenocarcinoma with clinical stage T1bN0M0, Stage IA2. Based on his good performance status of 0 according to the criteria of the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale[15] and cardiopulmonary function, we performed video-assisted thoracoscopic pulmonary resection of the right S^6 and dissection of the lymph nodes around the segmental bronchus (#13) approximately 7 months after the patient's admission for COVID-19.

Macroscopic findings of the resected tumor were as follows: the color was mixture of yellowish white and grayish white, and the total size was 14.0 × 11.0 mm in length and breadth, respectively (Figure 5A). The tumor had pleural indentation (Figure 5A), which was also visible on histology (Figure 5B). Based on the predominant growth pattern on histology, the pathologic diagnosis was papillary adenocarcinoma (Figures 5B,C).

The surgical margin was negative (R0) and there was no sign of pleural invasion (pl0). No malignant cells were found in the resected lymph node (pN0). Based on these results, we judged lung adenocarcinoma was curatively resected and confirmed that the pathologic stage was the same as the clinical stage: T1bN0M0, Stage IA2. At the patient's most recent follow-up visit, 2 years after the resection, there were no signs of recurrence or distal metastases on the CT images.

3 | DISCUSSION

Adenocarcinoma is the most frequent pathologic type in whole lung cancer, and the number of newly diagnosed patients with adenocarcinoma has been increasing.[16,17] Because lung adenocarcinoma usually occurs in peripheral lung lesions, respiratory symptoms such as cough, sputum, or dyspnea rarely appears especially while the tumor size is small and noninvasive. Considering that it is often difficult to find small peripheral lung adenocarcinoma lesions on chest radiograph alone at this stage, early detection of ground-glass nodules in lung adenocarcinoma on CT images, especially at the stage in which the solid component is limited, improves the prognosis.[5,18] Xi et al.[5] reported that in patients with clinical stage IA lung adenocarcinoma, the 5-year recurrence-free survival was significantly longer in patients with a CTR ≤ 0.53 than in those with a CTR greater than 0.53. From this perspective, we considered that the patient would have a good prognosis based on a CTR of 0.446 immediately before the surgery.

According to expert consensus,[19] the use of routine screening CT to detect COVID-19 pneumonia is not currently recommended by most radiology societies. However, in Japan, CT examination is still often performed to detect pneumonia not only in patients diagnosed with COVID-19 but also in some persons under investigation to rule out false-negative in SARS-CoV-2 antigen or PCR test results.[19,20]

One of the main reasons for performing CT examination is the consistent recommendation in the guidelines for COVID-19 published by the Ministry of Health, Labour and Welfare in Japan (versions 2 to 8.1)[21,22]: "to the extent possible, performing chest CT is desirable to evaluate the existence of pneumonia, with careful attention to nosocomial infection" (author's translation). Versions 2 to 8.1 of these guidelines[21,22] have recommended different ways of management according to the existence of COVID-19 pneumonia. For example, patients with COVID-19 pneumonia have been consistently classified as having higher than moderate severity. In this population, hospital admission is recommended, and remdesivir is usually administered for 5 days (up to 10 days).[21–23] In contrast, patients without COVID-19 pneumonia are classified as having

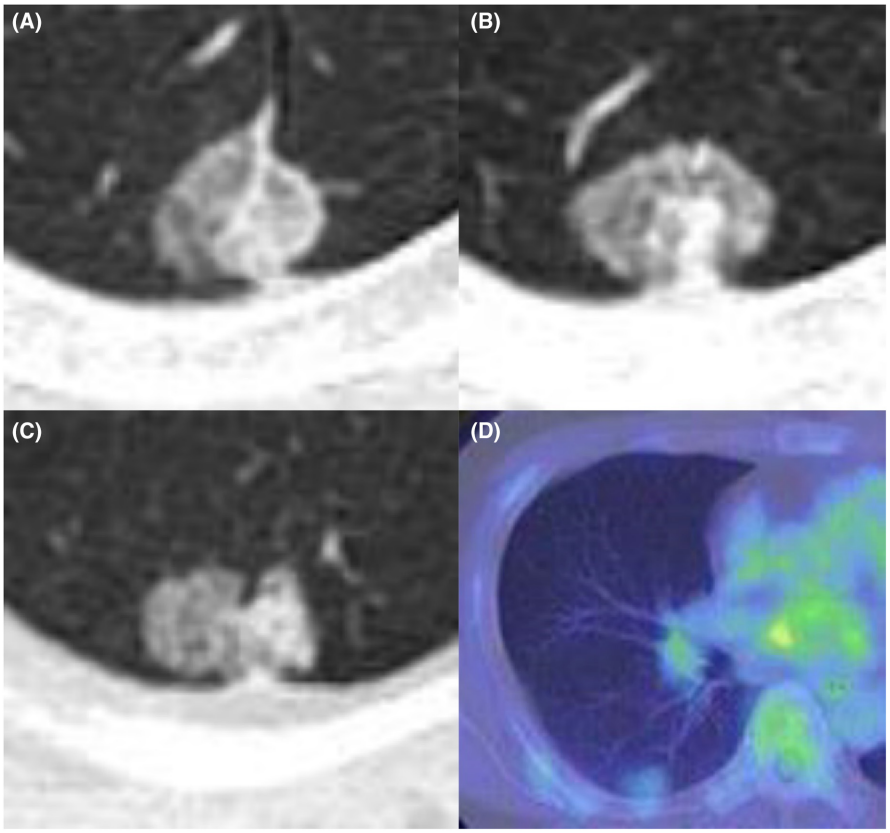

FIGURE 4 Chest computed tomography (CT) images and ^{18}F-fluorodeoxyglucose positron emission tomography coupled with CT (FDG-PET/CT) images taken 6 months after the admission for COVID-19. (A-C) The round ground-glass opacity containing a consolidation in the superior segment (S^6) of the right lower lobe has slightly increased in size (the length of the ground-glass opacity and consolidation: 23.1 mm and 10.3 mm, respectively [consolidation tumor ratio: 0.446]). This shadow has typical features of lung adenocarcinoma: (A) vessel convergence, (B, C) pleural indentation, and (C) notch formation. (D) The FDG-PET/CT has a low maximum standardized uptake value of 2.0.

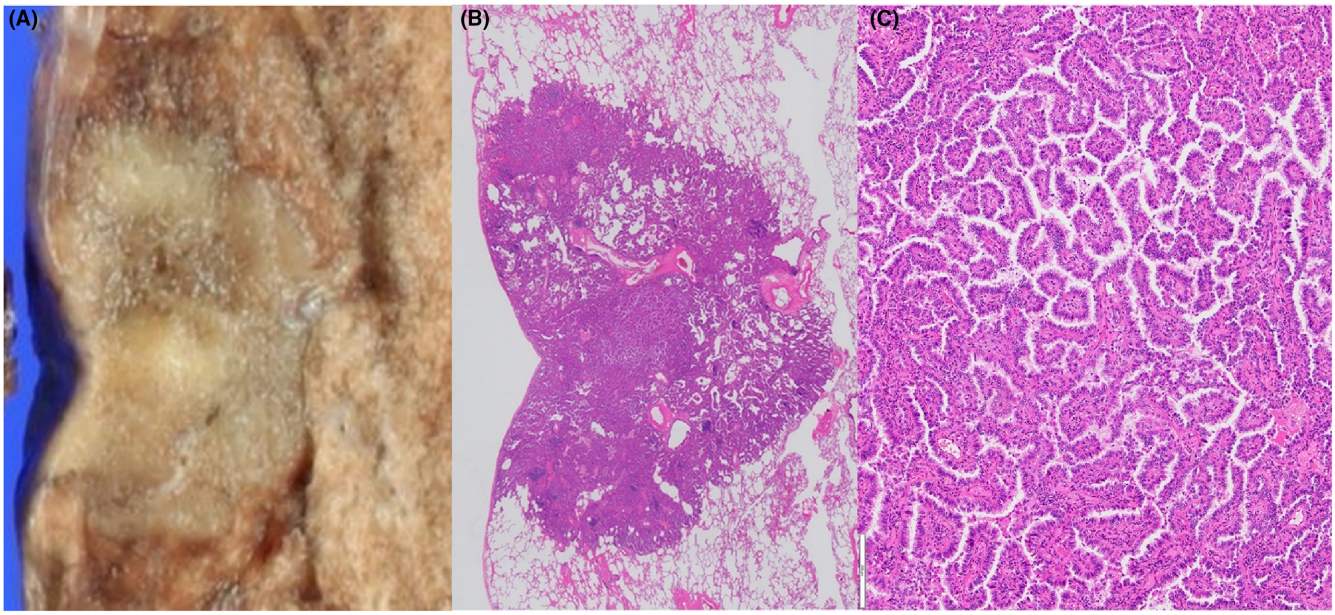

FIGURE 5 Macroscopic and microscopic findings of the resected tumor in the superior segment (S^6) of the right lower lobe. (A) Cut surface of the resected tumor. The color of the tumor is a mixture of yellowish white and grayish white. The total size is 14.0 × 11.0 mm in length and breadth, respectively. The tumor has pleural indentation. (B, C) Hematoxylin–eosin staining of the resected tumor. (B) The pleural indentation is also visible on histology (magnification, ×100). (C) The pathologic diagnosis is papillary adenocarcinoma, based on its predominant growth pattern (magnification, ×100).

mild disease severity, and since March 18, 2022, off-label administration of remdesivir for 3 days has been permitted without requiring hospital admission in case they have risk factors for developing severe disease state.[24]

In this case, CT examination was not necessarily needed because we could detect COVID-19 pneumonia on the chest radiograph and the patient was in his early 40s without any risk factors for progression to severe disease

state. However, this patient was admitted only 3 months after COVID-19 first appeared in Japan. Owing to the unavailability of effective medication or vaccine and lack of disease severity classification for COVID-19 in version 1 of the guidelines (published on March 17, 2020),[25] all patients with COVID-19 were required to be admitted to hospital for monitoring and to prevent the spread of COVID-19, regardless of symptoms.

Considering that it is often difficult to detect COVID-19 pneumonia on chest radiograph in early phase and some patients with COVID-19 pneumonia rapidly progress to acute respiratory failure, we performed both chest radiography and CT in all patients with COVID-19, so as not to overlook COVID-19 pneumonia and underestimate the disease severity. It was fortuitous for both the patient and our medical team that the repeated CT examinations for the diagnosis and monitoring of COVID-19 pneumonia enabled us to discover the lung adenocarcinoma as an incidental finding at a stage in which curative resection was possible.

In this case, the diagnosis of COVID-19 pneumonia was based on high fever and a positive SARS-CoV-2 PCR test result. We assumed that all shadows were caused by COVID-19 pneumonia and did not consider the possibility of more than one pathology causing similar shadows. Several types of disease in addition to COVID-19 and lung adenocarcinoma can produce solitary or multiple ground-glass opacities on CT images, including focal interstitial fibrosis, aspergillosis, cryptococcosis, eosinophilic pneumonia, organizing pneumonia, intrathoracic endometriosis, focal traumatic lung injury, and bleeding site of granulomatosis with polyangiitis or Henoch–Schönlein purpura.[26] If CT images show multiple similar shadows in both the lung fields, clinicians tend to narrow down the differential diagnosis to one diagnosis, taking other clinical information into consideration. However, clinicians should bear in mind that more than one pathology can be present in the lung concurrently, producing similar shadows in both the lung fields on CT images.

In this case, as most of the COVID-19 pneumonia had resolved by the time of the second CT examination, we wrongly assumed that all of the residual shadows were attributable to COVID-19 pneumonia without careful evaluation of the features of each shadow. Thus, we did not initially consider the possibility of lung adenocarcinoma. However, we fortunately had an opportunity to evaluate the time course change in CT findings objectively with several other respiratory physicians at a clinical conference 6 months after the patient's admission for COVID-19. This review alerted us to the possibility of lung cancer from the persistence without changes in the form and size of the round ground-glass opacity containing the consolidation in the right S^6.

4 | CONCLUSION

Patients with malignancy, including lung cancer, are prone to severe disease state if they develop COVID-19.[27] From a survival perspective, clinicians are concerned about the management of patients with COVID-19 who have been treated for lung cancer. However, this case illustrates a new aspect of the relationship between lung cancer and COVID-19: the clinical importance and difficulty in interpretation of ground-glass opacities, with or without consolidations on CT images.

Considering the difficulty in detecting signs of early stage lung adenocarcinoma on chest radiograph and based on the fact that CT examination is not routinely performed for detecting pneumonia in patients with COVID-19, this is a rare case and clinicians are unlikely to encounter similar cases in their clinical practice. However, given that the incidence of lung adenocarcinoma is increasing[16,17] and that the COVID-19 pandemic is ongoing,[6] the incidence of concurrent undiagnosed lung adenocarcinoma in patients with COVID-19 pneumonia may be higher than is generally recognized. In the interpretation of CT findings, clinicians should be careful not to overlook other concurrent undiagnosed lung diseases, especially lung adenocarcinoma, which may be hidden among the multiple shadows of COVID-19 pneumonia.

AUTHOR CONTRIBUTIONS

Yoshihiro Kitahara: Writing – original draft. **Motoki Matsuura:** Supervision; writing – review and editing. **Rie Yamasaki:** Supervision; writing – review and editing. **Kanako Nakamoto:** Data curation; writing – review and editing. **Shinji Kakumoto:** Writing – review and editing. **Shinpei Tada:** Writing – review and editing. **Noriaki Ito:** Writing – review and editing. **Kei Miwata:** Writing – review and editing. **Mafumi Okimoto:** Writing – review and editing. **Toshiro Takafuta:** Supervision; writing – review and editing.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data are included in the report and the associated images.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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