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Infectious diseases

Clinical management of lung cancer patients with respiratory symptoms during the COVID-19 pandemic

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Abstract

Objective: There are many clinical conditions, such as lung cancer, that need to be followed up and treated during a pandemic. Providing health care for patients who are immune-suppressive requires extra care.

Method: Among 108 lung cancer patients who had been hospitalized during the COVID-19 pandemic, 18 with respiratory symptoms were evaluated retrospectively.

Results: The patients' median age was 64 ± 9.4 with a male predominance (male n = 16, female n = 2). Thirteen had non-small cell lung cancer (NSCLC), and 5 had small cell lung cancer (SCLC). Nine (50%) patients were receiving chemotherapy. The most common symptom was shortness of breath (n = 14, 77.8%), followed by fever (n = 10, 55.6%). The findings confirmed on computed thorax tomography (CTT) were as follows: consolidation (n = 8, 44.4%), ground glass opacities (n = 8, 44.4%) and thoracic tumour/mediastinal-hilar lymphadenopathy (n = 3, 16.7%). Hypoxia was seen in 11 patients (61.1%), twelve patients had an elevated LDH (median = 302 ± 197) and lymphopenia (median = 1055 ± 648) and 5 (27.7%) were highly suspected of having contracted COVID-19. None of their nasopharyngeal swaps was positive. Two of these 5 patients received COVID-19 specific treatment even though they thrice had negative reverse transcription polymerase chain reaction (RT-PCR) results. The two patients responded well to both clinical and radiological treatments. For one case with SCLC receiving immunotherapy, methylprednisolone was initiated for radiation pneumonitis after excluding COVID-19.

Conclusion: In line with a country's health policies and the adequacy of its health system, the necessity of a multidisciplinary approach in the management and treatment of complications in patients with lung cancer has become even more important during the COVID-19 pandemic.

1 | INTRODUCTION

Due to outbreak of the novel severe acute respiratory syndrome (SARS) coronavirus 2019-nCoV (COVID-19) at the end of 2019, almost all efforts of health care workers and a large part of health centres have had to be allocated to cope with the resulting pandemic. As the prevalence of COVID-19 increased, the routine diagnosis and treatment procedures of most chronic illnesses have been affected. To prevent virus transmission from other patients or health care providers, strict protections have been put in place. Therefore, the vital guidance and updates prepared by the World Health Organization (WHO) should be followed.[2] As each country's COVID-19 epidemiological and clinical data accumulate, it can modify its patient approach and clinical practice according to its own guidance, as in our country, Turkey.[1]

Oncology practice is a more difficult clinical situation due to the immunosuppression secondary to tumours and the treatments

given. Epidemiological data from China have revealed that, while total COVID-19 mortality is 2.3%, it is 5.6% among patients with malignant tumours.[3] Among patients with cancer, lung cancer (5/18, 28%) is the most common type, but patients with lung cancer have no higher incidence of malignant events during the pandemic (20% and 62%, respectively, $P = .294$).[4] When compared with normal populations, patients with cancer tend to be older and have more polypnea. They have also already had severe baseline tomographic findings. Overall, according to Cox regression analyses, patients with cancer are at risk of severe events (intensive care unit requiring invasive ventilation or death) and of deteriorating rapidly (Fisher's exact $P = .0003$).[4] Therefore, additional concern is needed, depending on the capabilities of a country's health system.

Underlying comorbidities are related to increased case fatality rates (CFR = %). Cancer is one such comorbidity, but among all types of malignancies there are many risk factors specific to COVID-19 complications in lung cancer patients.[5] These patients have structural lung injuries due to smoking, decreased functional capacity, treatment-related immune suppression and defects secondary to pulmonary mass and treatments (surgery and radiotherapy).[5] More common complications in hospitalised lung cancer patients are pneumonia, pneumonitis and acute respiratory distress syndrome.[6] Moreover, systemic steroids used to treat lung cancer patients for many reasons (cranial metastasis, vena cava superior syndrome or emesis) can suppress the symptoms of COVID-19. Many clinical conditions, especially pulmonary infections, present with cough, fever and dyspnoea similar to COVID-19 in patients without cancer.[6] Additionally, tomographic findings secondary to lung tumours can overlap with COVID-19 radiology.[9] As a result, the early detection of COVID-19, management of differential diagnosis and scheduling treatment should be processed carefully by a multidisciplinary team for this group of patients.[5,7]

Another difficulty is the differential diagnosis of infection-related complications in lung cancer patients, especially during the pandemic. If a suspected or confirmed case of COVID-19 pneumonia is diagnosed in a lung cancer patient, transfer to a specially prepared hospital department for isolation must be provided.[7] The possibility of false-negative detection of nasopharyngeal swabs for new coronavirus nucleic acids should be a concern, and in case of persistent clinical suspicion, secondary sampling should be done.[10] While awaiting COVID-19 test results, other causes related to infection or non-infection (radiation pneumonia, immune-checkpoint inhibitor-associated pneumonia, cancer progression, pulmonary embolism, cardiac insufficiency, etc) must be examined so as not to lose time if treatment is required.[9]

After thoracic surgery for lung cancer, in the case of indications for adjuvant therapy, decisions should be made case by case. If a patient in pathological stage IB-IIA is elderly and in poor physical condition, the follow-up treatment plan should be considered using a network platform with the relevant physician(s).[7,8] For patients in pathological stage IIB-IIIA, the time frame for adjuvant chemotherapy can be extended. In the presence of pathological N2 or epidermal growth factor receptor (EGFR), gene mutations may be evaluated as one possible adjuvant treatment option.[11]

What's known

1. During the novel coronavirus pandemic, among patients with a history of malignant tumours, lung cancer is the most common cancer, but patients with lung cancer have shown no higher incidence of malignant events.
2. Cytotoxic therapies should be continued under the required isolation, and a multidisciplinary approach is necessary for these patients.
3. In a patient with respiratory symptoms, if COVID-19 pneumonia is excluded, the initiation of required treatments for other infectious agents should not be delayed.
4. For following up patients, telemedicine is a good alternative.

What's new

1. This study reflects the real experience of a thoracic oncology palliative care unit during the COVID-19 pandemic.
2. It has been demonstrated that radiological or clinical findings differ in patients with lung cancer presenting pulmonary symptoms compared to the normal population.

In advanced stage patients without a targetable mutation, the initiating or continuing of chemotherapy must be comprehensively evaluated. Being engaged in the process of consolidation chemotherapy or two and above line protocols and/or becoming fragile from prior chemotherapies are clinical factors involved in extending the intervals of chemotherapy, which should be considered in close communication with the patient's physician(s).[7,8]

Therefore, this study aimed to reveal how lung cancer patients with respiratory symptoms were managed during the COVID-19 pandemic in a thoracic oncology unit.

2 | METHOD

The study was conducted in a thoracic oncology palliative care unit in the Atatürk Chest Disease and Thoracic Surgery Training and Research Hospital. We retrospectively analysed lung cancer patients who were hospitalised due to respiratory symptoms from 11 March 2020, the date COVID-19 was first diagnosed in Turkey. Among 108 hospitalised patients, 18 were included. Respiratory symptoms were defined as cough, sputum, shortness of breath, haemoptysis, fever and the coexistence of these symptoms. If patients had other symptoms strongly indicating hospitalisation along with their respiratory symptoms, they were excluded. Patients' demographic data, including age, gender, TNM stage, therapies before hospitalisation, physical examination findings (transcutaneous oxygen saturation (hypoxia was defined as ≤88%), bronchospasm, dyspnoea or tachypnoea),

laboratory parameters (LDH with a range of 0-247 IU/L, hemogram analyses and C reactive protein), and radiological findings on chest X-ray and high resolution thorax tomography (HRTT) were recorded. In our clinic, all patients with signs of respiratory tract infection are examined for acid-resistant bacillus (ARB) and given a bacterial and fungal culture examination. When required, considering the patient's epidemiological history and clinical symptoms, nasopharyngeal swabs for new coronavirus nucleic acids were obtained according to the local guidance for COVID-19.[1] In Turkey, a patient suspected of being infected with COVID-19 completes the diagnosis and treatment process in the hospital. Patients with a suspected contact or high risk for COVID-19 are transferred to a specially prepared department for centralised isolation and treatment in the hospital. In case of continuing clinical suspicion, a second test swab was taken. In the meantime, the necessary tests for differential diagnosis were continued, and empirical antibacterial treatment was started in all cases.

This study was approved by our hospital ethical committee (number 673-14.05.2020), and the necessary permission was obtained from the Turkish Ministry of Health (application number 2020-05-08T00_20_42).

3 | RESULTS

Eighteen patients with a median age of 64 ± 9.4 were included. There was male predominance (male n = 16, female n = 2). Among the cases, 13 of them were non-small cell lung cancer (NSCLC) (including 8 squamous cell and 5 adenocarcinoma), and 5 of them were small cell lung cancer (SCLC). The distribution of TNM stages was as follows: 10 patients with stage IV, 6 patients with stage III and 2 patients with early stage cancer. The number of patients receiving chemotherapy was 9 (50%), only 1 of whom was undergoing adjuvant therapies. Other treatments were palliative cranial radiotherapy (RT) for 1 patient, best supportive care for 3 patients, chemoradiotherapy for 2 patients, immunotherapy for 1 patient and follow-up after the completion of planned treatment for 2 patients (Table 1).

The most common symptom was shortness of breath (n = 14, 77.8%), followed by fever (n = 10, 55.6%). Five patients had a cough along with other symptoms. But in 16 patients (88.9%), at least two but sometimes more, respiratory symptoms were present together. All patients had fatigue, whereas 3 patients had severe myalgia (Table 1).

According to the results of the radiological evaluations, 14 (77.8%) patients presented a pathology on their chest X-rays (eg consolidation, pleural effusion, cavity or solid opacities). The findings confirmed on computed thorax tomography (CTT) were consolidation (n = 8, 44.4%), ground glass opacities (n = 8, 44.4%) and thoracic tumour/mediastinal-hilar lymphadenopathy (n = 3, 16.7%). Five patients (27.8%) were revealed to have pleural effusion on their CTT examinations. The parenchymal findings of these 5 patients were in the form of consolidation or secondary changes to the tumour. No pleural effusion was detected by CTT in patients having ground glass opacities (Table 1). Hypoxia was seen in 11 patients (61.1+%), whereas in 12 patients, an elevated LDH (median = 302 ± 197) and lymphopenia (median = 1055 ± 648) were observed (Table 1).

There were 5 (27.7%) patients highly suspected of having contracted COVID-19 and thus requiring a nasopharyngeal swab test. None of them was positive for COVID-19. Two of these 5 patients received COVID-19 specific treatment while a differential diagnosis was ongoing (Table 2, case numbers 1 and 3). Regarding the radiological features of these patients, 4 presented ground glass opacities on CTT. One patient presented with consolidation and tumour progression on CTT, but due to having a fever that did not respond to broad-spectrum antibiotics, he was required to take a COVID-19

TABLE 1 General characteristics of study population

Variables	n/%
Age (mean ± SD)	64 ± 9.4
Gender (male/female)	16/2
Histopathology	
SCLC	5 (27.8%)
NSCLC	13 (72.2%)
Adenocarcinoma	5 (27.8%)
Squamous cell carcinoma	8 (44.4%)
TNM stage	
Stage I-II	2 (11.1%)
Stage III	6 (33.3%)
Stage IV	10 (55.6%)
Therapy	
Chemotherapy	9 (50%)
Palliative radiotherapy	1 (5.6%)
Immunotherapy	1 (5.6%)
Best supportive care	3 (16.7%)
Chemo-radiotherapy	2 (11.1%)
Treatment completed	2 (11.1%)
Symptom	
Fever	10 (55.6%)
Shortness of breath	14 (77.8%)
Sputum purulence	5 (31.2%)
Cough	5 (31.2%)
Myalgia	3 (18.7%)
Pathology on X-ray	14 (77.8%)
Hypoxia	11 (61.1%)
Lymphopenia	12 (75%)
Elevated lactate dehydrogenase	12 (75%)
Tomography findings	
Consolidation	8 (44.4%)
Ground glass opacities	8 (44.4%)
Thoracic mass/lymphadenopathy	3 (16.7%)
Pleural effusion	5 (27.8%)

Abbreviations: SCC, squamous cell lung cancer; NSCLC, non-small cell lung cancer.

TABLE 2 Features of COVID-19 suspicious patients

Case number	Age/ gender	Histopathology/ TNM stage	Treatment	CTT findings	PCR result	COVID treatment	Major symptoms	Lymphopenia/ elevated LDH	Stay in COVID-specific service (day)
1.	63	Adenocarcinoma/ Stage II	Pneumonectomy	Bilateral ground glass opacities	Negative	Yes	Fever Cough Dyspnea	+/+	14
2.	50	SCLC/Limited disease S	Immunotherapy[a]	Bilateral ground glass opacities	Negative	Yes	Cough Dyspnea	+/+	7
3.	71	SCC// Stage III	Chemo-radiotherapy	Bilateral ground glass opacities +alveolar consolidation	Negative	Yes	Dyspnea Myalgia	+/+	10
4.	54	SCC/Stage IV	Chemotherapy	Consolidation	Negative	No	Dyspnea Fever	+/+	3
5.	47	SCC/Stage III	Chemotherapy	Progression of malignancy	Negative	No	Fever Dyspnea	+/−	0

Note: Abbreviations: SCC, squamous cell lung cancer; SCLC, small cell lung cancer.

[a]Immunotherapy following chemo-radiotherapy within the scope of international, multi-centre study.

PCR test, the results of which were negative (Table 2, case number 5). Gram negative bacillus growth in the sputum was the most common microbiological feature.

Among the patients suspected of having COVID-19, (n = 5), 3 responded to broad-spectrum antibiotic therapy. In 1 case (Table 2, case number 2) with SCLC receiving immunotherapy following chemo-radiotherapy within the scope of an international, multi-centre clinical trial, the patient was diagnosed with radiation pneumonitis after excluding COVID-19 with a negative nasopharyngeal swab test. He responded well to methylprednisolone treatment (Figure 1). For 2 patients (Table 2, case numbers 1 and 3), although 3 RT-PCRresults were negative, they were hospitalised in the isolated service, and significant clinical and radiological results were obtained with COVID-19 specific treatment (Figures 2 and 3).

During the pandemic, our unit tended to avoid unnecessary minimal invasive procedures such as bronchoscopies or endobronchial ultrasound (EBUS). Only 1 patient required a bronchoscopy to obtain intrabronchial secretion clearance, and his bronchial lavage culture was positive for *Escherichia coli*.

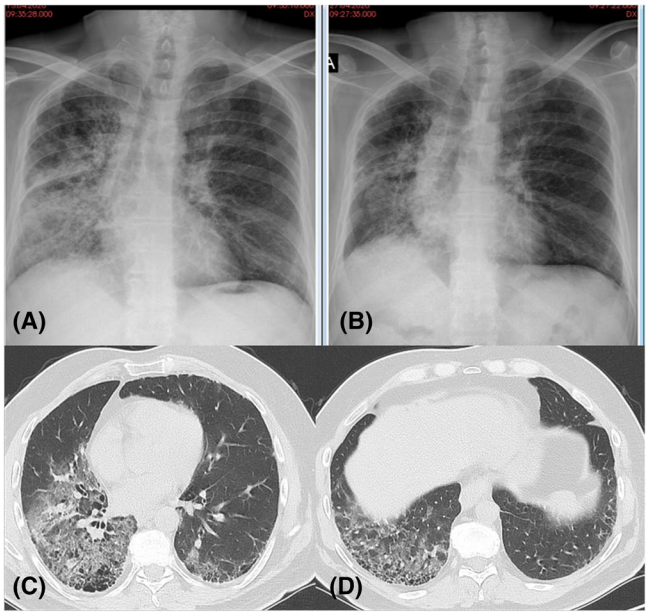

FIGURE 1 Radiological features of patient with SCLC (limited disease) receiving immunotherapy after chemoradiotherapy with COVID-19 negative nasopharyngeal swap, diagnosed with radiation pneumonitis. A, X-ray findings before on his first admission. B, X-ray findings 10 days after metilprednisolone therapy. C,D, Bilateral ground glass opacities with right side predominance on CTT during first admission

4 | DISCUSSION

Chronic diseases are currently more difficult to manage due to the global COVID-19 pandemic. Cancer patients constitute the most important part of this group.[3] Lung cancer cases, which have been shown to increase in frequency, are an important subgroup.[4] Each country strives to plan according to the adequacy and possibilities of its own health care services for the management of patients receiving cancer treatment. The main issue this study focuses on is the symptoms that overlap for both lung cancer and COVID-19, the main symptoms for which are fever, cough, fatigue and slight dyspnoea. This can cause confusion in lung cancer patients[7] because many reasons secondary to tumour or cancer treatments (surgery, chemotherapy, radiotherapy, immunotherapy or targeted therapies) can cause these symptoms to appear. During this pandemic, it is important to maintain the follow-up and treatment

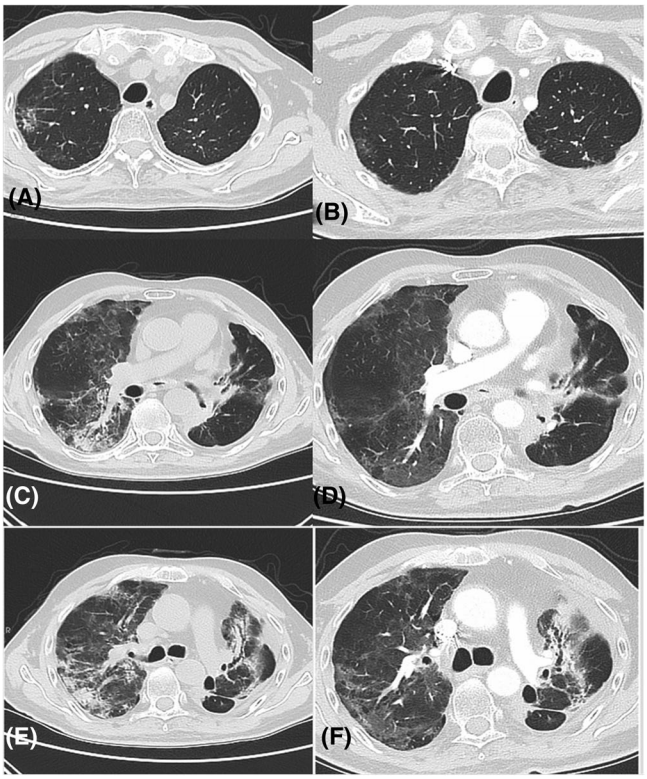

FIGURE 2 Radiological features of patient with NSCLC (locally advanced) who completed chemo-radiotherapy. Although his nasopharyngeal swab was negative for 3 times, he responded well to COVID-specific treatment both clinically and radiologically. A,C,E, Bilateral ground glass opacities +alveolar consolidations on CTT during first admission. B,D,F, Resolutions of CTT findings after completion of COVID-19 therapy

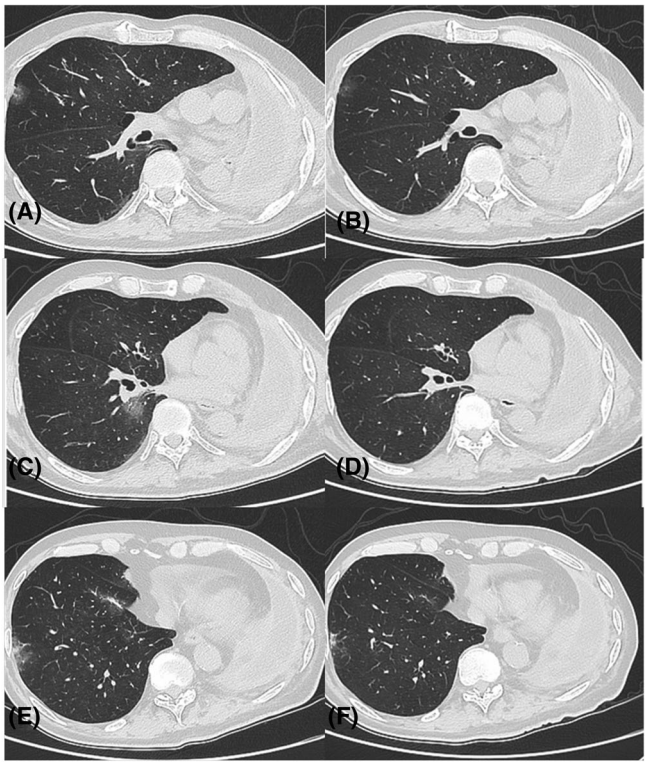

FIGURE 3 Radiological features of patient who underwent left pneumonectomy. Although his nasopharyngeal swab was negative for 3 times, he responded well to COVID-specific treatment both clinically and radiologically. A-C-E, Patchy ground-glass opacities on right hemithorax on CTT during first admission. B,D,F, Resolutions of CTT findings after the completion of COVID-19 therapy

process of lung cancer patients while minimising the risk of COVID-19 transmission.

When comparing the clinical characteristics of our study population to the features of COVID-19 patients, it is noteworthy that both have age (60 years and older) and gender predominance (male).[12] According to some suggestions on the diagnosis of and treatment strategies for lung cancer patients from China, where the outbreak began and was dealt with first, highly suspected or confirmed patients must be transferred to a specially prepared isolated department of the hospital.[7] Five patients in the current study suspected of contracting COVID-19 were admitted to the outpatient clinic of our chemotherapy unit, and the differential diagnosis process took place in an isolated area until COVID-19 was ruled out.

Each case should be handled separately, especially in terms of the treatments (chemotherapy, targeted therapies, immune-checkpoint inhibitor, radiotherapy, etc) they receive at the time of admission. Their history of suspected contact(s) and visits to another country are important issues.[10] In total, 11 (61.1%) patients were receiving chemotherapy (including concurrent chemoradiotherapy).

Even though ground glass opacities are a widely accepted radiological presentation of COVID-19 pneumonia, they can be presented in different manifestations in lung cancer patients.[13] There are a small number of cases in the literature. One is a case of diagnosed lung adenocarcinoma with a simultaneous diagnosis of COVID-19 by the RT-PCR technique. Even though the patient had no COVID-19 specific symptoms, she had been in contact with an infected physician. There were no typical patient's CTT findings (showed diffuse, irregular, small, ground-glass opacities with partial consolidation in bilateral lungs), even at the beginning (when she had no symptoms) and after symptoms appeared. Finally, her complaints and radiological findings were determined to be obstructive pneumonia caused by the tumour.[14] Another reported case is a 73-year-old male who had been operated on for NSCLC in 2016. Even though he had no suspected COVID-19 symptoms, the patient was diagnosed with COVID-19 with PET-CT taken during re-staging. Bilateral diffuse, peripheral predominant ground-glass opacities suggesting active inflammatory processes on 18F-FDG PET/CT were the condition leading to the suspicion of COVID-19.[15] The most common radiological findings in our cases were consolidation (44%) and GGOs (44%), even in 5 cases considered highly suspicious for COVID-19 (Table 2).

Five (27.8%) patients presented with pleural effusion. However, in none of patients was the pleural fluid considered to be related to COVID-19. Thus, in the highly suspected group (Table 2), there were no patients with pleural fluid. Although cancer patients are

not included, according to a meta-analysis of 4121 patients, pleural effusion (5.3%) was reported as the rarest CTT imaging feature of COVID-19.[16]

Although the complete clinical manifestation is not yet clear, fever, lymphopenia, leukopenia, new pulmonary infiltrates on chest radiography and no response to antibiotic treatment are the most reliable symptoms for a COVID-19 diagnosis. Such a diagnosis must be confirmed by the RT-PCR technique,[16] but we already know that there can be a discrepancy between RT-PCR results and CTT findings. According to data from China, although the positive rates of RT-PCR assays were 59% (601/1014), CTT imaging showed 88% (888/1014) positivity in patients suspected of having COVID-19. A total of 308 patients with negative RT-PCR results but having COVİD-19, suggesting radiology. When evaluated together with clinical findings, CTT findings are quite reliable for diagnosis.[17] Considering that RT-PCR is not the gold standard in the diagnosis of COVID-19, clinical and radiological suspicion seems to be sufficient to start treatment early, especially in patients with lung cancer. In our study population, there were 2 patients who had negative RT-PCR results along with highly suspected clinical and radiological findings (Table 1, case numbers 1 and 3). Both responded well to COVID-19-specific therapies not requiring intensive care unit (ICU) support (Figure 2).

Another case presentation is a stage IV lung adenocarcinoma patient from Italy. The patient had been undergoing Nivolumab therapy as part of a multicentre clinical trial for almost 6 months and was experiencing a partial response. He was admitted with severe dyspnoea, hypoxia, lymphopenia, increased C-reactive protein, transaminases and lactate dehydrogenase. His chest X-ray revealed reticular-interstitial addensative findings, and his nasal swab was positive for COVID-19. Due to his rapidly worsening clinical condition, the patient died without receiving any COVID-19-specific treatment.[18]

Of course, it is not possible to predict the treatment approach and prognosis in the presence of COVID-19 in cancer cases receiving immunotherapy. In this sense, we would like to contribute to current research by detailing a case in our study, a male receiving immunotherapy following chemoradiotherapy within the scope of an international, multi-centre clinical trial (Table 2, case number 2). On his first admission to the outpatient chemotherapy clinic, he presented with severe dyspnoea with 83% oxygen saturation in the room air. His laboratory results revealed increased LDH, C reactive protein and lymphopenia. There were bilateral heterogeneous opacities on the patient's chest X-ray and bilateral ground glass areas with right hemithorax predominance on his CTT. The patient was quickly taken to isolated service. After his nasal swabs for COVID-19 were negative three times, he was transferred to the general ward. Since he had been administrated immunotherapy for only one cycle, it was too early to expect immunotherapy-related interstitial pneumonitis. His chemoradiotherapy had been completed almost 4-6 months ago, and his radiological features appeared on the radiotherapy side (right hemithorax). Hence, he was diagnosed with radiation pneumonia and responded well to methylprednisolone therapy (Figure 1).

5 | CONCLUSION

With this study, we aimed to emphasise that the diagnosis, treatment and management of complications in lung cancer patients require more care than in the normal population during the current pandemic. In the face of a multifactorial clinical condition, including the type of treatment, dose, duration of cytotoxic therapy and stage of the disease, as clinicians we should carry out the differential diagnosis process quickly to minimise the risk of transmission. We need to accumulate more knowledge concerning patients whose immunity has already been suppressed and whose cytokine responses have differentiated.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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