Pembrolizumab-related pneumonitis in a patient with COVID-19 infection

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CASE DESCRIPTION

The impact of the COVID-19 pandemic on medicine is undoubtedly significant, resulting in alterations to layouts, workflow and protocols of many hospitals. Owing to the similarities in clinical presentation and imaging features between COVID-19 and other types of pneumonia and lung diseases, it also creates diagnostic problems in clinical practice. We herein present a case of an oncological patient who tested positive for COVID-19, with underlying treatment-related changes, and posed a clinical and diagnostic dilemma to the managing team.

Our patient, a 66-year-old Chinese man with multiple comorbidities, initially presented to the hospital in September 2019 with haemoptysis, dysphagia and weight loss. Computed tomography (CT) of the thorax (Fig. 1a) revealed an 8.5-cm × 6.0-cm mass in the lower lobe of the right lung with extensive vascular, bronchial and oesophageal invasion. Ultrasonography-guided, endobronchial fine-needle aspiration of the mass revealed adenocarcinoma of lung origin. 18-Fluorodeoxyglucose positron emission tomography-CT also showed multiple osseous metastases in the axial skeleton.

In view of the metastatic disease on presentation, the patient was referred to the oncology team and commenced on pembrolizumab, an immune checkpoint inhibitor. Palliative radiotherapy 18 Gray (Gy) to the thorax was also given to relieve his dysphagia from extrinsic tumour compression on the oesophagus. A repeat CT thorax three months later in January 2020 showed significant reduction in the size of the mass. New, well-defined reticular opacities corresponding to the radiation field were observed in the right lower lobe and attributed to radiation-induced lung disease (RILD).

Surveillance CT thorax performed two months later in March 2020 (Figs. 1b & c) showed new ground glass opacities in the periphery of both lungs. Temporal progression of RILD was also

observed, as evidenced by bronchiectasis, volume loss and worsening reticular opacities in the right lower lobe. The patient had fever at this point but reported no respiratory symptoms. COVID-19 nasopharyngeal swabs were negative. It is notable that serological testing was not available at this time. Moreover, COVID-19 testing in oncological patients was implemented only in patients who fulfilled the Ministry of Health criteria for testing. The patient was treated with a course of antibiotics and planned for interval CT imaging.

Follow-up CT thorax on 22 April 2020 (Fig. 1d) demonstrated worsening interlobular septal thickening and ground-glass changes in the middle and right lower lobes and bilateral patchy consolidation. Again, our patient did not report having symptoms of acute respiratory infection. He was not under quarantine, nor was there any history of overseas travel, exposure to local clusters or large group gatherings. Nevertheless, there was a valid concern that he had an asymptomatic COVID-19 infection in view of the CT findings. It was later discovered through contact tracing that our patient had potential exposure to another patient in the oncology clinic on 2 April 2020 who had subsequently tested positive for COVID-19. As such, our patient was recalled to the National Centre for Infectious Diseases (NCID) and admitted. Initial investigations revealed lymphopenia (absolute lymphocyte count of 0.68 × 10^9/L) and elevated C-reactive protein (13.5 mg/L). A nasopharyngeal swab on 22 April 2020 returned positive results for COVID-19 with a cycle threshold value of 38.64, indicating that the patient was infected shortly after his potential exposure. Subsequent swabs performed 24 hours apart on 23 and 24 April 2020 were negative. The patient remained well and asymptomatic, and was discharged on 25 April 2020. Pembrolizumab was held off as we could not exclude immunotherapy-induced pneumonitis as a cause of his radiological findings. There is no known contraindication to continuing pembrolizumab in patients who have recovered from COVID-19, nor is there evidence currently

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that pembrolizumab would cause a flare-up of COVID-19.

A repeat CT thorax on 8 May 2020 (Figs. 1e & f) showed worsening patchy consolidative and ground-glass changes in both lungs. COVID-19 swab performed on admission was negative. The patient was assessed to have pembrolizumab-induced pneumonitis. He subsequently developed dyspnoea and was started on steroid therapy but died shortly thereafter. Fig. 2 indicates the timeline of events from the point when the patient was first diagnosed with cancer to his subsequent death.

**DISCUSSION**

Our case demonstrates the diagnostic challenges of treating lung cancer patients with suspected COVID-19, as these patients often have multiple pathologies present, either as a result of their primary malignancy, post-treatment changes or co-infection with COVID-19 pneumonia, albeit asymptomatic. Furthermore, these entities often present with non-specific symptoms and have overlapping radiological findings on imaging, making patient management more challenging. In the following paragraphs, we will attempt to highlight the various differential diagnoses for such patients, and their associated imaging features.

**COVID-19 pneumonia**

In a patient with suspected COVID-19 pneumonia, chest radiographs are usually the first-line imaging modality for assessment. Early or mild disease may return normal chest radiographs. Chest radiography is less sensitive than CT for detecting COVID-19 lung disease, with a reported baseline chest radiography sensitivity of 69%.\(^1\) The commonest findings of COVID-19 on chest radiographs include lung consolidation and ground-glass opacities (GGOs),\(^2\) with reticular
opacities accompanying areas of GGOs. Often, these findings are seen bilaterally, found in more than one lobe and most frequently in the lower zones. The lung changes could become diffusely coalescent or form a consolidative pattern within 7–21 days following symptom onset, typically peaking around 6–12 days after initial clinical manifestations.\(^{(3,4)}\)

However, these non-specific findings can be seen in numerous other infectious or inflammatory processes, such as acute respiratory distress syndrome. Pleural effusions, pneumothoraces and lung cavities are rare observations in COVID-19 and, when detected on chest radiographs, are likely due to other causes.\(^{(5-7)}\)

Chest CT is performed in symptomatic hospitalised patients for specific indications, mainly for assessment of complications. Commonly reported findings that are of greater specificity for COVID-19 pneumonia are peripheral, bilateral or multifocal GGOs with or without consolidation in lung regions close to pleural surfaces, including the fissures or visible interlobular lines, giving rise to a ‘crazy paving’ pattern.\(^{(8,9)}\) Reverse halo and other findings of organising pneumonia are seen in the later stages of the disease.\(^{(10)}\) Similar to chest radiography, there are usually no pleural effusions, lung cavitation, mediastinal lymphadenopathy or discrete pulmonary nodules (e.g. centrilobular nodules or tree-in-bud opacities).\(^{(11,12)}\)

Our patient remained largely asymptomatic during the course of his illness. Furthermore, the presence of pleural effusions and asymmetric GGOs confounded the diagnosis of COVID-19. Given the potential exposure of our patient to a positive case, it is likely that he had COVID-19 infection. However, the clinical and radiological features of the patient confounded the diagnosis of COVID-19 pneumonia. Unfortunately, serological testing was not readily available at that point of time during the pandemic. A positive COVID-19 serological test would have facilitated confirmation of recent infection, especially given the high cycle threshold value.

In the later stages of the patient’s disease, CT thorax demonstrated persistent and worsening GGOs with reticular opacities. These findings, along with normal inflammatory markers and multiple consecutive negative COVID-19 swab results, made the diagnosis of COVID-19 re-infection very unlikely.

Radiation-induced lung disease

Given the history of radiotherapy, albeit limited, radiation-induced pneumonitis was another consideration for our patient. The lung abnormalities, which appear similar after three-dimensional (3D) conformal radiation therapy and stereotactic body radiation therapy, are largely classified into two distinct well-known clinical and pathological phases: early transient radiation pneumonitis and late chronic radiation fibrosis phases.\(^\text{(13)}\) One should consider the time interval after the completion of radiation therapy to classify the radiation-induced lung changes into early or late phase.\(^\text{(14-16)}\) Radiation-induced pneumonitis usually appears within the first six months after completion of treatment and may result in symptoms of self-limiting dyspnoea, cough and chest discomfort, whereas radiation fibrosis typically manifests 6–12 months after completion of treatment, with possible progressive dyspnoea and persistent dry cough.\(^\text{(17,18)}\) Radiologically, the early phase shows diffuse or patchy GGOs, consolidation, or both, usually in the irradiated lung field. Occasionally, an ipsilateral pleural effusion is seen with lung atelectasis. Although the opacities usually resolve gradually over six months without radiologic sequelae in case of limited injury, progression to fibrosis may occur in more severe cases. The late phase of radiation fibrosis appears radiologically as a well-demarcated area of volume loss with linear scarring or consolidation, parenchymal distortion and traction bronchiectasis conforming to the treatment fields. It may stabilise or continue to evolve for as long as 24 months.

Pulmonary damage occurs rarely after total radiation doses of less than 20 Gy, commonly after doses of 30–40 Gy and almost always after doses of more than 40 Gy.\(^{(19)}\) Patients who receive more than 40 Gy of radiation should be suspected of having RILD if the radiologic manifestations occur within the radiation field, following an appropriate time course. However, RILD can be affected by the patient’s age and concomitant drug administration, and more rapid onset does not exclude RILD.\(^{(20)}\)

Clinical features such as temporality of the GGOs aid differentiation, as CT findings of GGOs and patchy consolidation with thickened interstitium and crazy paving pattern are common to both RILD and COVID-19.\(^{(21)}\) Notwithstanding the limited course of radiation, the time interval, total dose amounting to less than 20 Gy, and bilateral GGO development in the lungs made RILD less likely in our patient.

Progression of lung malignancy

Although the patient showed partial response to the treatment instituted, progression of his underlying malignancy was also a consideration, either in the form of lymphangitis carcinomatosis or local tumour recurrence. Clinically, lymphangitic carcinomatosis mimics RILD and COVID-19 by causing dyspnoea. However, specific CT findings such as smooth or nodular interlobular septal thickening, peribronchovascular interstitial thickening, pleural effusion and mediastinal lymph nodes help to establish a confident diagnosis. Diffuse lung abnormalities outside the radiation fields or bilateral distribution of the specific CT findings facilitate the diagnosis.\(^{(22)}\)

Some changes that suggest tumour progression or recurrence include altered contour and dimensions of the fibrotic area, new homogeneous soft tissue density without air bronchograms and with convex borders, filling-in of bronchi, nodules outside the zone of radiation fibrosis,

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pleural effusion occurring long after completion of therapy, bone destruction or mediastinal involvement. These were not observed in our patient’s serial CT scans, rendering progression of malignancy less likely.

Aspiration pneumonitis

The patient had oesophageal dysphagia from oesophageal tumour involvement and had been consuming food orally against medical advice. This could have contributed to the imaging appearances from intercurrent aspirations of gastric contents leading to chemical lung injury. Aspiration pneumonitis is clinically distinct from aspiration pneumonia and demonstrates airway thickening with GGOs in a peribronchovascular and centrilobular distribution. The imaging findings can occur concurrently with aspiration bronchiolitis. The distribution tends to be diffuse, bilateral and symmetric owing to dispersion by coughing. Aspiration pneumonia, on the other hand, involves the lower lobes and posterior lung as patchy GGOs with or without segmental or lobar consolidations. Aspirated material filling the airways is an important clue to the diagnosis. Centrilobular nodular opacities and a tree-in-bud pattern are common findings in aspiration pneumonia, but are not typical in COVID-19 pneumonia. The bilateral distribution of consolidation and GGO without abscess formation, tree-in-bud opacities or cavitation made this diagnosis unlikely in our patient.

Immunotherapy-induced pneumonitis

Pembrolizumab is a highly selective anti-programmed cell death-1 (PD-1) humanised monoclonal antibody that inhibits PD-1 activity and serves as an immune checkpoint inhibitor (ICI) by T-cell upregulation to treat malignancies lacking a driver mutation. Although the patient’s lung cancer

initially responded to pembrolizumab, the course was complicated by the development of ICI-related adverse effects. In particular, ICI-related pneumonitis, one of the adverse effects of ICIs, mimics COVID-19. However, the outcomes of patients with COVID-19 and ICI-related pneumonitis are mixed at this point in time.\(^{(30-32)}\)

Treatment guidelines are available for ICI-related pneumonitis.\(^{(33)}\) However, the main challenge in implementing treatment is the radiological dilemma in diagnosis due to the abovementioned overlapping imaging findings and limited evidence to suggest differences in the ground-glass changes occurring in COVID-19 pneumonia versus ICI-pneumonitis.\(^{(34)}\) The diagnostic uncertainty may have led to treatment delay, as there were concerns regarding the use of glucocorticoids in the setting of COVID-19 infection in our patient at that juncture.\(^{(35,36)}\)

The CT findings of ICI-related pneumonitis are diverse, with patchy GGOs and areas of consolidation, symmetric distribution and a lower lobe and peripheral predominance. Commonly described patterns include interstitial pneumonia either as non-specific interstitial pneumonia, organising pneumonia, diffuse alveolar damage, hypersensitivity pneumonitis, or simple pulmonary eosinophilia, which are non-specific and overlap with those of COVID-19 pneumonia. Therefore, the following criteria have been proposed to diagnose drug-related pneumonitis: (a) newly detected parenchymal opacities on CT or chest radiography, commonly in a bilateral non-segmental distribution; (b) temporal link at presentation with the initiation of a systemic therapeutic agent; and (c) exclusion of other likely causes.\(^{(37)}\)

**CONCLUSION**

Contemplating the clinical and radiological findings together, one can conclude that the patient had contracted and recovered from asymptomatic COVID-19 pneumonia on a background of
worsening pembrolizumab-induced pneumonitis. Although corticosteroids were commenced to treat the pneumonitis, the patient unfortunately deteriorated and died.

As COVID-19 becomes endemic, the clinical and radiological dilemma of distinguishing COVID-19 infection from other causes will be encountered more frequently. Knowledge of the differentials for GGOs will help to guide treatment and prove useful in patients’ outcomes. This case demonstrates how immunotherapy-related pneumonitis mimics COVID-19 infection and complicates management decisions, especially in oncology patients with lung involvement who are on immunotherapy.\(^{(38)}\)

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FIGURES

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**Fig. 1** Serial axial CT images of the patient’s thorax (a) before treatment in September 2019; (b & c) after radiotherapy and the initial stage of immunotherapy in March 2020; and in (d) April and (e & f) May 2020. (a) CT image shows a soft tissue mass in the right lower lobe, with an associated right pleural effusion (asterisk). There is invasion of the right lower pulmonary vein (white arrow) and right lower lobe segmental bronchus (dashed arrow), and oesophagus by the mass. (b) CT image shows significant reduction in the mass after treatment. Interval development of fibrotic changes is seen along with new ground-glass opacities (GGOs) (dashed arrow). (c) Serial axial CT image of the thorax in March 2020 shows GGOs in the left upper lobe (white arrow). (d) CT image of the thorax shows GGOs and interlobular septal thickening in the right lower lobe (white arrows). (e) CT image shows progression of GGOs in the upper lobes (white arrows) and (f) the left lower lobe posterior segment as well as the left inferior lingular segment (dashed arrows), in keeping with pembrolizumab-related pneumonitis.

**Fig. 2** Timeline shows the chronology of the imaging scans and COVID-19 swab results of the patient from diagnosis of cancer to the patient’s death.