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Need for Caution in the Diagnosis of Radiation Pneumonitis in the COVID-19 Pandemic

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Abstract:	Introduction : Patients with cancer are at high-risk for mortality from coronavirus-disease 2019 (COVID-19). Radiation pneumonitis (RP) is a common toxicity of thoracic radiotherapy with overlapping clinical and imaging features with COVID-19, however, RP is treated with high-dose corticosteroids, which may exacerbate COVID-19-associated lung injury. We reviewed patients who presented with symptoms of RP during the intensification of a regional COVID-19 epidemic to report on their clinical course and COVID-19 testing results. Methods : The clinical course and chest computed tomography (CT) imaging findings of consecutive patients who presented with symptoms of RP in March 2020 were reviewed. The first regional COVID-19 case was diagnosed on 3/1/2020. All patients underwent COVID-19 qualitative RNA testing. Results : Four patients with clinical suspicion for RP were assessed. Three out of four patients tested positive for COVID-19. All patients presented with symptoms of cough and dyspnea. Two patients had a fever, of whom only one tested positive for COVID-19. Two patients started on an empiric high-dose corticosteroid taper for presumed RP, but both had clinical deterioration, and ultimately tested positive for COVID-19 and required hospitalization. Chest CT findings in patients suspected of RP, but ultimately diagnosed with COVID-19 showed ground-glass opacities mostly pronounced outside the radiation field. Conclusions : As this pandemic continues, patients with symptoms of RP require diagnostic attention. We recommend that patients suspected of RP be tested for COVID-19 before starting empiric corticosteroids and for careful attention be paid to chest CT imaging in order to prevent potential exacerbation of COVID-19 in these high-risk patients.

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Title:

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Summary

Radiation pneumonitis (RP) is a common toxicity of thoracic radiotherapy with overlapping clinical and imaging features with coronavirus-disease-2019 (COVID-19). Based on the clinical courses of the patients described in this letter, we recommend that patients suspected of RP be tested for COVID-19 before starting empiric corticosteroids and for careful attention to chest CT imaging in order to prevent potential exacerbation of COVID-19 in these high-risk patients.

Abstract:

Introduction:

Patients with cancer are at high-risk for mortality from coronavirus-disease 2019 (COVID-19). Radiation pneumonitis (RP) is a common toxicity of thoracic radiotherapy with overlapping clinical and imaging features with COVID-19, however, RP is treated with high-dose corticosteroids, which may exacerbate COVID-19-associated lung injury. We reviewed patients who presented with symptoms of RP during the intensification of a regional COVID-19 epidemic to report on their clinical course and COVID-19 testing results.

Methods:

The clinical course and chest computed tomography (CT) imaging findings of consecutive patients who presented with symptoms of RP in March 2020 were reviewed. The first regional COVID-19 case was diagnosed on 3/1/2020. All patients underwent COVID-19 qualitative RNA testing.

Results:

Four patients with clinical suspicion for RP were assessed. Three out of four patients tested positive for COVID-19. All patients presented with symptoms of cough and dyspnea. Two patients had a fever, of whom only one tested positive for COVID-19. Two patients started on an empiric high-dose corticosteroid taper for presumed RP, but both had clinical deterioration, and ultimately tested positive for COVID-19 and required hospitalization. Chest CT findings in patients suspected of RP, but ultimately diagnosed with COVID-19 showed ground-glass opacities mostly pronounced outside the radiation field.

Conclusions:

As this pandemic continues, patients with symptoms of RP require diagnostic attention. We recommend that patients suspected of RP be tested for COVID-19 before starting empiric corticosteroids and for careful attention be paid to chest CT imaging in order to prevent potential exacerbation of COVID-19 in these high-risk patients.

Introduction:

The coronavirus-disease-2019 (COVID-19) pandemic has resulted in significant global mortality. Early published reports have found patients with cancer to be disproportionately affected with nearly 40% requiring mechanical ventilation, ICU admission or death from COVID-19 (1). Furthermore, data also suggest patients with lung cancer to be more susceptible to COVID-19 infection (2). Radiation pneumonitis (RP) is a well-described toxicity of thoracic radiotherapy that can cause significant morbidity and has an incidence ranging up to 40% in patients with lung cancer (3).

The overlapping clinical and imaging features of RP and COVID-19-induced pulmonary disease require attention by providers to prevent misdiagnoses and poor outcomes, particularly since the treatment of these two pathologies are substantially different. Herein, we review patients who presented with symptoms consistent with RP at our tertiary cancer center located in the New York City metropolitan area, an epicenter of the COVID-19 pandemic, during the first month of our regional epidemic. We report on their clinical course and COVID-19 testing results, and offer recommendations to providers on the management of RP as this pandemic continues.

Methods:

Medical records of consecutive patients who presented with symptoms of RP in March 2020 were reviewed. The first regional COVID-19 case was diagnosed on 3/1/2020. All patients underwent COVID-19 qualitative RNA testing. Patient imaging and clinical course data were reviewed as were COVID-19 testing results. This study was completed under an institutional review board approved protocol.

Results:

Four patients with clinical suspicion for RP were assessed. Three out of four patients tested positive for COVID-19. All patients presented with symptoms of cough and dyspnea. Two patients had a fever, of whom only one tested positive for COVID-19. Two patients started on an empiric high-dose corticosteroid taper for presumed RP, but both had clinical deterioration, and ultimately tested positive for COVID-19 and required hospitalization.

Patient 1: A 73-year-old female with an American Joint Committee on Cancer (AJCC) 8th edition T2bN3M0, Stage IIIB, small-cell lung cancer (SCLC) treated with carboplatin/etoposide/atezolizumab and sequential definitive thoracic radiation (56 Gy in 28 fractions due to a large field involving the bilateral hilum). Six weeks after radiation, she developed a non-productive cough, which was initially managed conservatively. One week later her symptoms progressed and she was started on empiric high-dose corticosteroids for presumed RP. One week later, her symptoms of cough and dyspnea

progressed, and she presented to the Emergency Department (ED) with hypoxia. She was tested for COVID-19 and was found to be positive. Chest computed tomography (CT) revealed diffuse ground-glass opacities, mostly pronounced outside the radiation field (Figure 1).

Patient 2: A 56-year-old male with a T1cN3M0, Stage IIIB, non-small-cell lung cancer (NSCLC) treated with definitive thoracic radiation (60 Gy in 30 fractions) with concurrent cisplatin/pemetrexed. Eleven weeks after radiation, he developed a non-productive cough and mildly increased dyspnea on exertion and was managed conservatively. Approximately four weeks later, he presented with fever and worsening cough and dyspnea. A fever work-up including a standard viral respiratory panel was negative. COVID-19 testing was unavailable at the time. Chest CT imaging revealed mild inflammatory changes within the radiation field, and he was started on empiric high-dose corticosteroids for presumed RP. One week after starting corticosteroids, his symptoms progressed, and he presented to the ED with hypoxia. He was tested for COVID-19 and was found to be positive.

Patient 3: A 66-year-old female with a T1bN2M0, Stage IIIA SCLC treated with definitive twice-daily thoracic radiation (45 Gy in 1.5Gy fractions) with concurrent carboplatin/etoposide. Eight weeks after radiation, she reported a new onset non-productive cough and increased dyspnea requiring increased albuterol use. She denied fever, fatigue or decreased appetite. Out of caution, COVID-19 testing was recommended, which returned positive, and she was not treated for RP.

Patient 4: A 65-year-old female with a history of a T1N2M0, stage IIIA adenocarcinoma of the right lung treated with definitive concurrent chemoradiation in 2006 (59.4 Gy in 33 fractions), who then developed an in-field recurrence and was treated with definitive re-irradiation (60 Gy in 30 fractions) concurrent with cisplatin/pemetrexed followed by consolidative durvalumab. Sixteen weeks after reirradiation, she presented with a progressive non-productive cough and dyspnea. Chest CT imaging demonstrated mild inflammatory-changes within the radiation field, and empiric short-course corticosteroids were prescribed, which initially improved symptoms. After completing an initial short-course of corticosteroids, she presented with fever and worsening cough and dyspnea. COVID-19 testing was recommended which returned negative. She was then started on a high-dose corticosteroid taper for RP, which improved symptoms.

Discussion:

This report illustrates the overlapping symptoms and imaging features of RP and COVID-19, and the need for diagnostic caution in the management of these findings.

COVID-19 and RP are both characterized by similar symptoms including cough, dyspnea and fever (4, 5). Ground-glass opacities and consolidations are characteristic Chest CT radiographic findings of both pathologies, but data indicate differences in the

distribution of these features between these pathologies (6). Chest CT findings of COVID-19 are present in approximately 80% of symptomatic patients. Early reports indicate up to 85% of patients have imaging findings in more than one lobe and 90% of patients have bilateral chest CT findings (7, 8). This contrasts to RP, where opacities are classically noted mostly within the radiation field (9).

Currently available diagnostic testing for COVID-19 commonly identify viral RNA in nasopharyngeal and/or oropharyngeal samples through nucleic acid amplification. These tests, while mostly specific, have a clinical sensitivity that is yet to be fully determined. Early reports indicate a significant false negative rate and the potential for higher sensitivity using lower respiratory track samples (10, 11). Therefore, clinical judgement and continuous reassessment of pulmonary symptoms remains critical in patients who test negative for COVID-19.

The treatment of RP and COVID-19 are substantially different. The treatment for symptomatic RP includes a high-dose corticosteroid taper. However, there is data-driven concern that corticosteroids can worsen COVID-19-associated lung injury, with prior studies finding corticosteroid therapy to delay clearance of Middle East Respiratory Syndrome (MERS) coronavirus and Severe Acute Respiratory Syndrome (SARS) coronavirus from the respiratory track and plasma (12, 13). This may have been the case in the first two patients presented, where the use of empiric high-dose corticosteroids may have contributed to their clinical deterioration.

We, therefore, recommend these steps in the managements of patients with a differential diagnosis that includes RP (Figure 2):

1) Review of imaging findings to characterize the nature and distribution of pulmonary changes in relation to the radiation treatment field.

2) Prioritization of COVID-19 testing prior to starting high-dose corticosteroids to prevent potential exacerbation of COVID-19 in these high-risk patients.

3) Close monitoring of pulmonary symptoms, particularly among patients who initially test negative for COVID-19, to assess for superimposed conditions including COVID-19.

As the pandemic continues, this diagnostic dilemma will become increasingly present for providers. Given that cancer patients, particularly those with lung cancers, are at increased risk for severe events, close monitoring of these patients and the impact of their oncologic therapies on COVID-19 outcomes are warranted.

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Figure Legends:

Figure 1: Chest computed tomography (CT) imaging of Case 1 illustrating:

Top Row: Radiation treatment planning scan from 11/6/2019 with the radiation dose distribution set at the 50% isodose line

Middle Row: CT imaging at the initial presentation of pulmonary symptoms demonstrating minimal inflammatory changes.

Bottom Row: CT imaging upon the diagnosis of COVID-19 with ground-glass changes most pronounced outside the radiation field (circled in red).

Figure 2: Flow chart illustrating a recommended approach to cases with concern for radiation pneumonitis during the COVID-19 pandemic. *An abnormal CT chest is not specific for COVID-19 diagnosis, patients with clinical and radiographic features consist with COVID-19 should be tested when possible.

Figure 1

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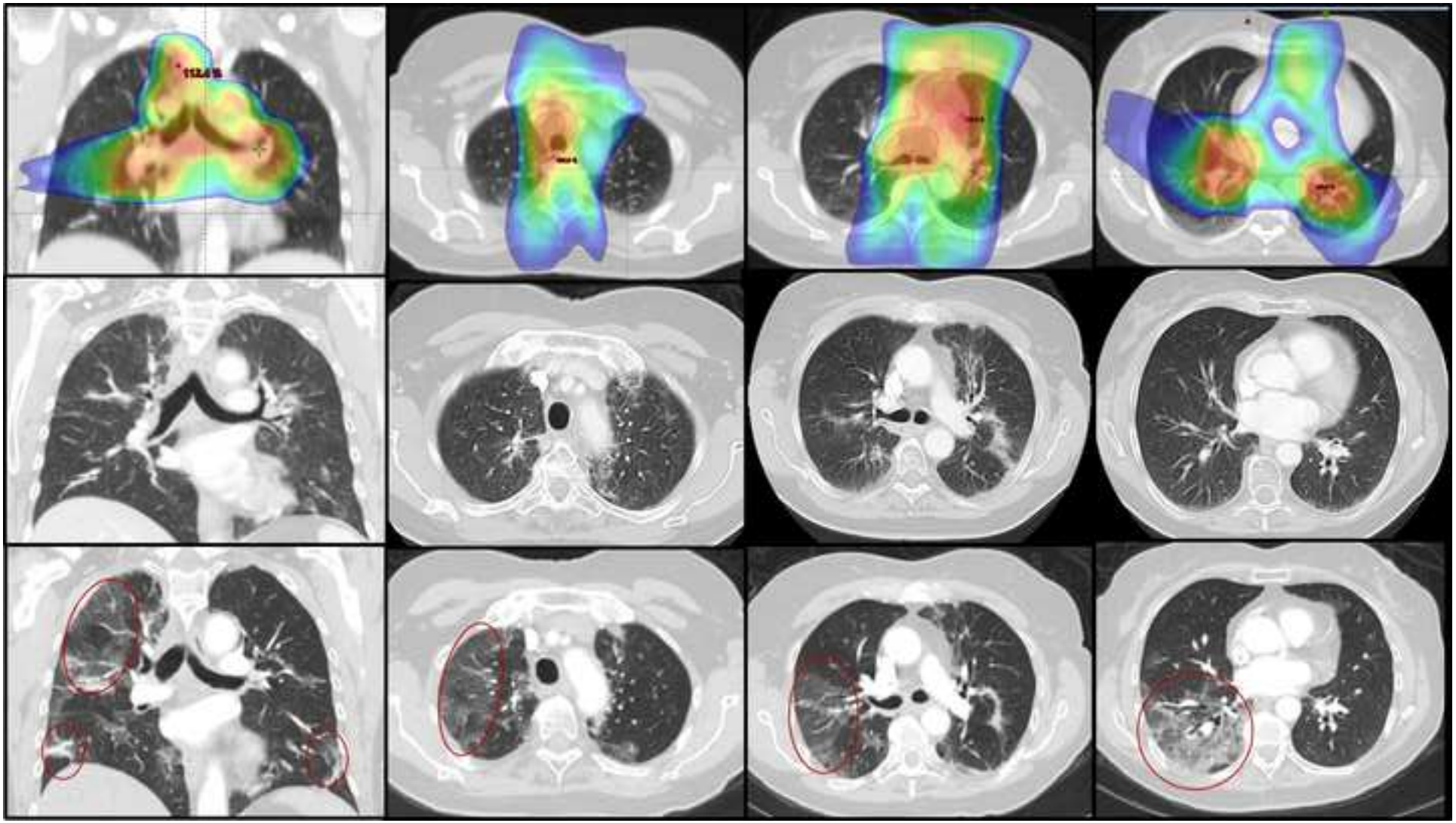

Figure 2

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