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Case Report

Are there overlapping clinical features between thoracic radiotherapy side effects and covid-19 pneumonia? Radiation pneumonitis outside the radiation ports: Three case reports

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ABSTRACT

Respiratory involvement of COVID-19 infection, with presentations ranging from a mild flu-like illness to potentially lethal acute respiratory distress syndrome, is the main clinical manifestation in adults. Chest imaging shows a pictorial fashion of images due to the severity and stage of the disease, starting from focal nodular or mass-like opacities with air bronchogram to areas of ground glass consolidation or whited out lung. However, during the COVID-19 pandemic, CT findings could yield confounding reporting in the case of cancer patients previously treated with thoracic radiotherapy (tRT) due to atypical radiation pneumonitis occurring outside the radiation ports. Hypersensitivity pneumonitis and radiation-induced bronchiolitis obliterans organizing pneumonitis (RT-BOOP) are accounted for in this report.

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1. Introduction

Severe pneumonia is the main clinical manifestation of COVID-19 infection in adults, leading to fatal events that are overloading the healthcare system worldwide [1]. Studies have assessed the mandatory role of computed tomography (CT) scans in the diagnosis of COVID-19 patients with false negative real-time PCR results [2]. A sensitivity of 98% in detecting and monitoring this disease combined with bronchoalveolar lavage (BAL) fluid, which is an optimal tool for improving the accuracy of virus detection, has been reported. Chest CT images per guideline should describe pulmonary lesions in terms of distribution, quantity, shape, pattern, density, and concomitant signs [3].However, at the peak of the COVID-19 pandemic, these combined CT findings could yield misinterpretations in reporting diagnoses in cancer patients previously treated with tRT. It is well acknowledged that chest CT is the preferred imaging technique for detecting radiation pneumonitis, which is the main side effect of tRT. Typical CT features due to pulmonary fibrosis are unilateral and share parenchymal involvement corresponding to the radiation treatment fields and the distribution of different doses to the lungs [4].

Recently, these concepts have been widely pointed out by Ippolito et al., who highlighted several key points in the differential diagnosis among COVID-19 pneumonia features and radiation pneumonitis pictures [5]. Interestingly, these points refer to the features of "classical" radiation-induced lung injury (RILI). Nevertheless, unusual situations may occur a few months after tRT, such as hypersensitivity pneumonia and bronchiolitis obliterans organizing pneumonia syndromes (RT-BOOP), both of which are primed by thoracic radiation and present with overlapping clinical and radiological features of COVID-19 pneumonia. These syndromes are rare clinical events that share a febrile flu-like syndrome or respiratory failure illness, such as COVID-19 pneumonia, with fever, cough, and dyspnoea. In contrast to classic radiation pneumonitis, in these cases, CT images provide findings that do not correspond with the radiation ports and mimic the wide pictorial fashion of features shown in COVID-19 pneumonia, including the bilateral distribution of ground glass opacities with or without consolidation in the posterior and peripheral lung [6].

These similarities make it difficult to correctly diagnose these diseases, as occurred in our experience in three cases of atypical radiation-induced pneumonitis that developed a few months after tRT during the COVID-19 pandemic.

2. Case 1

A 66-year-old man affected by a resected non-small cell lung cancer (NSCLC) of the right lung with stage pT2 pN1 (with extra-

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capsular extension) M0 received adjuvant RT with 50 Gy on a limited lung volume, including only the right hilum, with 3-dimensional conformal external beam radiotherapy (3D-CRT) consisting of four MLC customized photon fields. The dose-volume histogram (DVH) showed an MLD of 13 Gy and V20 and V5 equal to 25% and 41%, respectively. One month post-radiotherapy, he returned for observation complaining of fever and severe dyspnoea, with oxygen saturation < 70% requiring C-PaP ventilation in an intensive care unit. Anaemia; neutrophilic leucocytosis with lymphopaenia; and high levels of D-dimer, fibrinogen and IL-6 were recorded. Chest CT images and radiography (Fig. 1A, B) described pleural effusion in the right lung with an air bronchogram, massive bilateral alveolar thickening and diffuse ground-glass opacities evolving into a whited out lung. Upon admission, the serology and swab for COVID-19 were negative. The patient died of acute respiratory distress syndrome (ARDS). The autopsy described alveolar disruption with hyaline membranes due to fibrin deposits and serous fluid. Pneumocyte exfoliation, platelet clots with microthrombi and loads of giant macrophages and neutrophils were also found. Taking the information collectively, a diagnosis of hypersensitivity pneumonitis was given.

3. Case 2

A 45-year-old woman, after breast-conserving surgery due to intraductal carcinoma of the left breast, (DCIS), received adjuvant

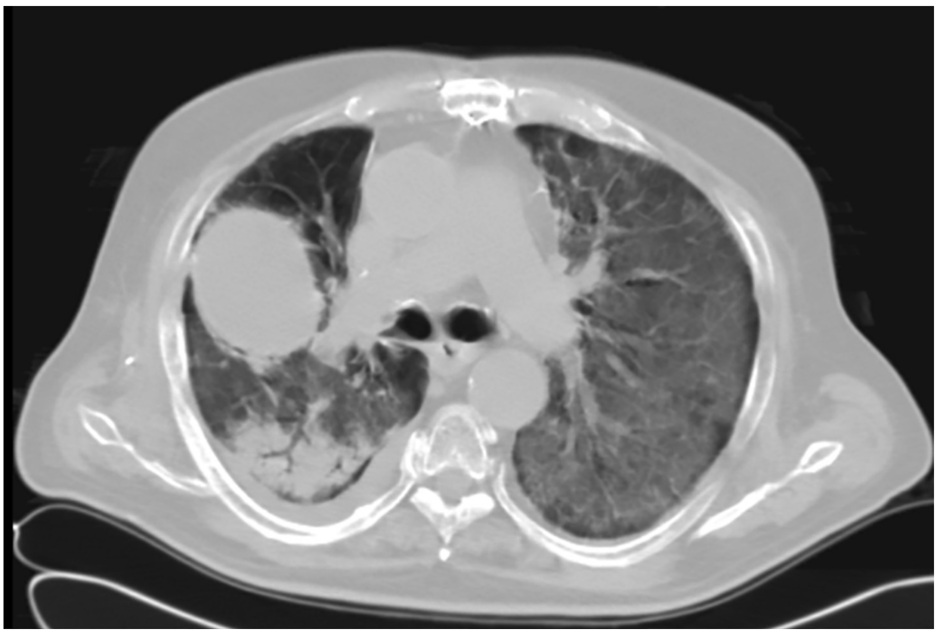

Fig. 1A. Axial chest CT image showing in the right lung a pleural effusion with nodular opacity and air bronchogram while in the left lung the interstitial involvement is present.

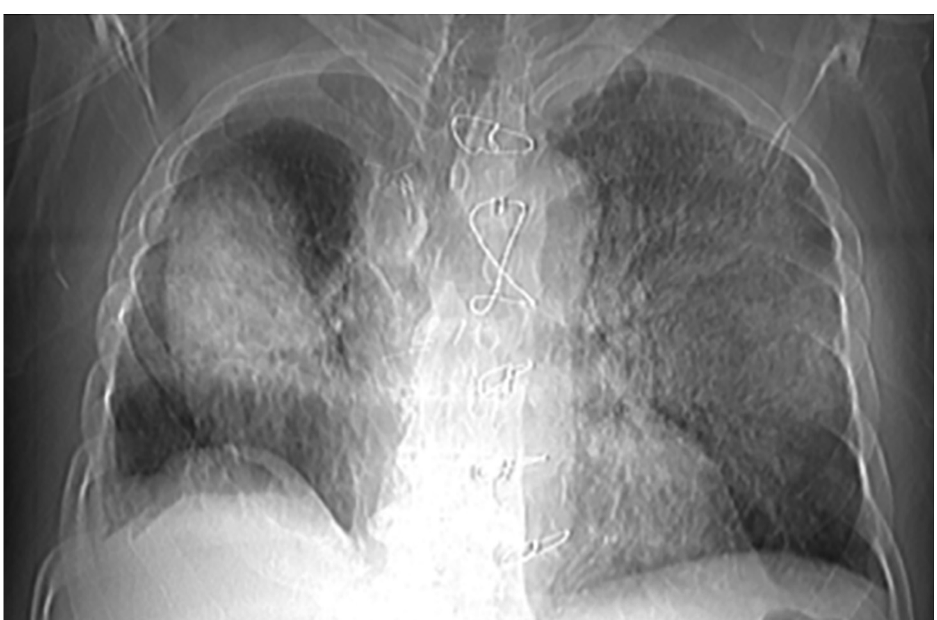

Fig. 1B. Chest radiography indicating the evolution of the process into a whited out lung.

therapy with tamoxifen and postoperative RT 50 Gy on the residual breast with 3D-CRT, with two MLC customized photon tangential hemi-fields. In the DVH analysis, the MLD was 8 Gy, the left lung V20 was 13%, V30 was 10%, and V5 was 30%. Two months after RT, she showed febrile flulike symptoms with cough and mild dyspnoea. High erythrocyte sedimentation rate (ESR) and leucocytosis were found. The CT scan images showed several nodular opacities associated with a vessel sign and air bronchogram in both lungs. Swabs, serology and BAL were negative for COVID-19 infection. Symptoms ameliorated after steroid therapy. Chest CT scan images (Fig. 2A, B) showed complete remission of the findings. Multinodular RT-BOOP was the final diagnosis.

4. Case 3

A 70-year-old man, affected by adenocarcinoma of the left lung in stage pT3 pN2 M0 after upper lobectomy, received sequential adjuvant chemotherapy and radiotherapy 50,4 Gy on the left mediastinum, with 3D-CRT consisting of five MLC customized photon fields. In the DVH analysis, the MLD was 20 Gy, V20 was 30%, V30 was 25% and V5 was 48%. Three months after radiotherapy, he showed mild flulike symptoms with cough and fever lasting one day. Leucocytosis with neutrophilia, lymphopaenia and elevated ESR were observed.

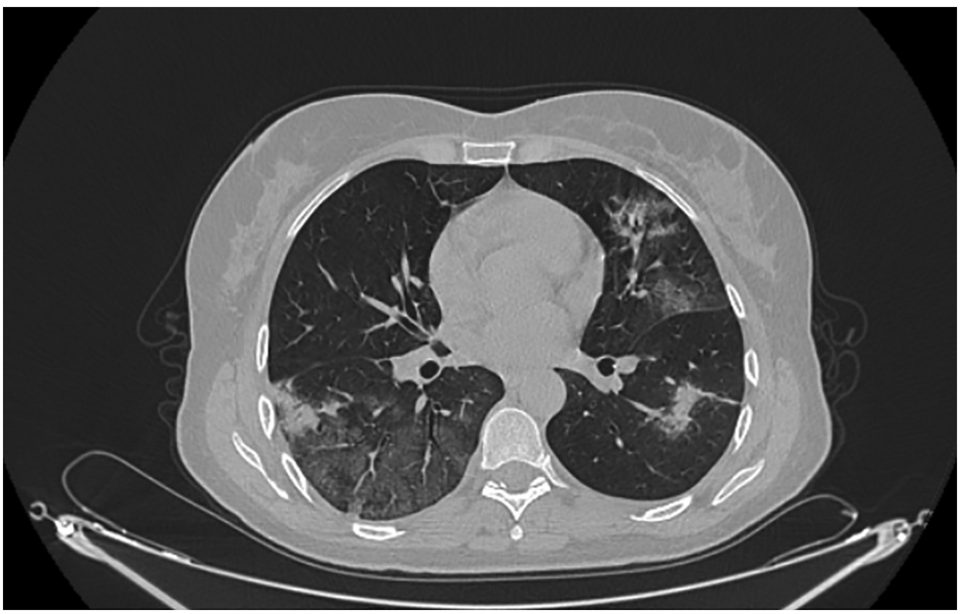

Fig. 2A. Axial chest CT image demonstrating multiple bilateral nodular opacities with vessel and bronchus signs before therapy.

Fig. 2B. Axial chest CT image recording the complete resolution of findings after steroid assumption.

Chest CT scan images (Fig. 3B). A, B) In the posterior right inferior lobe, a single peripheral air-space infiltrate with bronchus signs inside a slight reticular pattern area was recorded. COVID-19 swabs, BAL and serology tests were negative. After steroids and antibiotic therapy, CT scan images resulted in a resolution of the inflammatory process. The final diagnosis was focal nodular RT-BOOP.

5. Discussion

Although COVID-19 is an acute asymptomatic disease in most of the population, it can also be deadly, resulting in a > 2% case fatality rate in Northern Italy at the beginning of March 2020 [7]. Respiratory involvement, with presentations ranging from mild flulike illness to potentially lethal ARDS or fulminant pneumonia, is the dominant clinical manifestation of COVID-19 in adults, although other organs could be involved, such as the heart, vessels, and NCS, depending on ACE-2 cell receptor expression [8]. Post-mortem autopsies have shown the destruction of lung alveolar structures with exfoliated III pneumocytes, giant macrophages, fibrinous exudate in alveolar cavities, thrombosis in micro-vessels, pulmonary tissue haemorrhage and interstitial fibrosis [9].

Studies have assessed the key role of CT scans in the diagnosis of COVID-19 patients with false negative real-time PCR results, showing 98% sensitivity in detecting and monitoring this disease

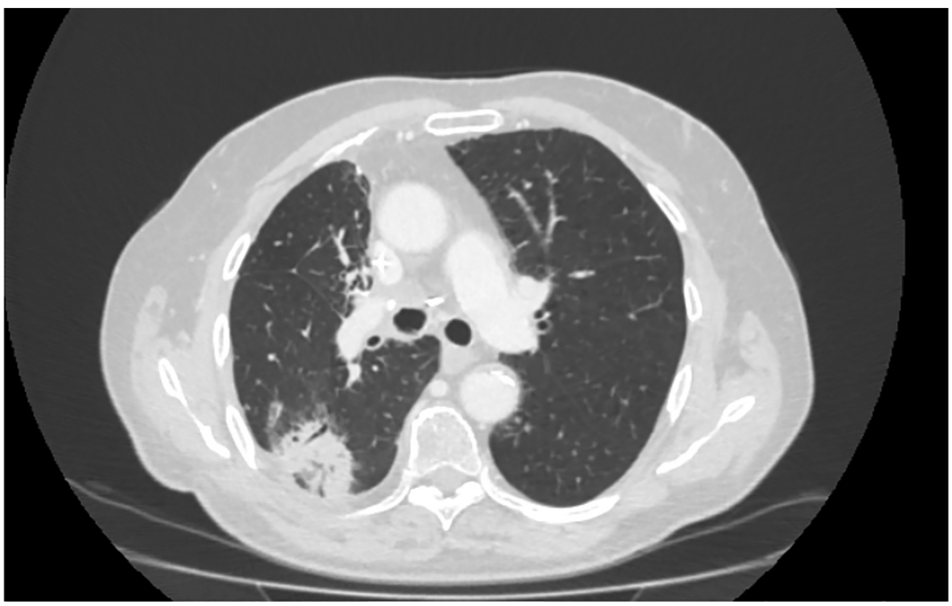

Fig. 3A. Axial chest CT image showing a peripheral nodular opacity in posterior inferior right lung with a bronchus sign.

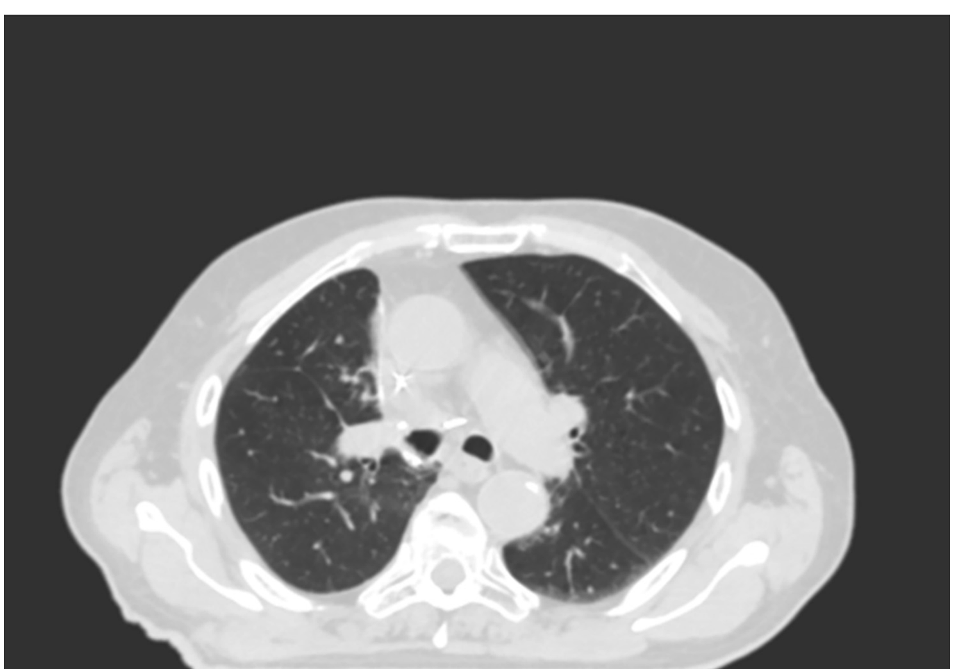

Fig. 3B. Axial chest CT image recording the inflammatory process resolution.

[1,2]. As reported in many series, CT images could manifest different pictorial features according to the disease severity and course, varying from focal or massive bilateral GGO and consolidation as the predominant findings to a "whited out lung" [10]. BAL fluid may improve diagnosis with the detection accuracy of the virus. However, in patients who have received tRT, as in our cases, similar findings could be an expression of several atypical pneumonitis occurring as a side effect of chest radiation due to radiation-induced lung injury (RILI). While the "classic" RILI signs recall the paths of radiation fields [5], unusual pneumonitis features displayed outside the radiation ports are described in atypical RILI, showing similarities with COVID-19 pneumonia findings. This similarity is also found in the autopsy reports. In contrast, BAL fluid shows an inflammatory pattern and negative results for bacterial, mycobacterial, fungal and viral pathogens; a viral cytopathic effect is not found in BAL cells [11].

Hypersensitivity pneumonitis and RT-BOOP are evocated to this concern, as we observed in our experience. Hypersensitivity pneumonitis has been described in the past in women treated with conventional tangential field tRT for breast cancer who developed pneumonitis signs outside the radiation fields, showing diffuse interstitial bilateral pneumonia and evolving into a "whited out lung" [12]. This fatal pneumonitis accounts for "sporadic" RILI, which occurs in approximately 10% of thoracic irradiation cases and is sometimes associated with ARDS [13]. RT-BOOP syndrome is a migratory pneumonitis finding commonly seen in both lungs outside the radiation fields. It has been observed mainly in breast cancer patients a few months after adjuvant tRT, with an incidence of 1.8–2.9% [14]. Several cases have also been recorded in lung cancer tRT [15].

From all the reported series, a spectrum of CT findings in RT-BOOP have been described, ranging from focal nodular, mass-like opacities to areas of consolidation resembling pneumonia or patchy ground glass infiltrates. Interestingly, in nodular opacities, either a feeding vessel or bronchus sign, such as an air bronchogram, has been identified as a characteristic sign [16]. Likewise, COVID-19 pneumonia, an immunologically mediated mechanism due to an overactive immune system triggered by radiation, has also been postulated in radiation pneumonia [17]. Given these similarities and the exceptional rarity of these events, recognizing and differentiating these entities from COVID-19 pneumonia is now a major challenge for radiologists who are beginning to become familiar with this infectious disease. Recently, Carotti et al. outlined how the CT findings of COVID-19 truly overlapped with the CT findings of other pulmonary diseases, including drug-induced acute lung injury [6]. Thus, why not consider the event of radiation pneumonitis outside the radiation ports?

Sharing information may be useful to solve the question. In our experience, the anamnesis of a previous tRT together with the negativity of COVID-19 tests and BAL fluid, were helpful to exclude viral infection. In conclusion, because CT imaging pictures are not specific in COVID-19 pneumonia [6], diagnostic doubt should alert radiologists to the hypothesis of atypical radiation-induced pneumonitis in cancer patients previously treated with thoracic irradiation. Diagnosis of hypersensitivity pneumonitis and RTBOOP should be taken into account.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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