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TITLE: Covert Covid-19: CBCT Lung Changes in An Asymptomatic Patient Receiving Radiotherapy

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Abstract:

Running Title: Covid-19 Consistent Changes Detected on CBCT

Introduction: COVID-19 profoundly impacted the United States, with New York City (NYC) rapidly becoming the epicenter of the disease. Cancer patients represent a vulnerable population in this pandemic, with data suggesting a higher risk for severe events and unfavorable outcomes. Timely identification of COVID-19 in cancer patients has been thwarted by the lack of outpatient testing for SARS-CoV-2. Chest computed tomography (CT) plays a major role in the identification of COVID-19 pneumonia, with radiologic hallmarks including bilateral, peripheral ground-glass opacities (GGOs) and consolidation. Cancer patients undergoing radiotherapy (RT) commonly have daily cone beam computed tomography (CBCT) obtained for image-guided radiotherapy (IGRT), and such imaging frequently includes the chest.

Methods: We retrospectively reviewed the CBCTs of an initially asymptomatic patient undergoing IGRT for breast cancer, who developed COVID-19 symptoms during the second week of RT. Lung windows of daily CBCTs were reviewed with Diagnostic Radiology to survey for changes consistent with COVID-19. Diagnostic CTs obtained at the time of recovery were obtained and compared with the CBCTs.

Results: Five consecutive CBCTs were retrospectively reviewed. Bilateral, peripheral GGOs were noted on the 4th and 5th CBCTs in the two days prior to symptom onset. CBCT on the day of RT resumption demonstrated substantial worsening of the GGO compared with those obtained during the asymptomatic phase. Diagnostic CTs demonstrated bilateral, peripheral GGOs and mediastinal lymphadenopathy, findings suggesting COVID-19 pneumonitis. Repeat diagnostic CT three days later showed improved pulmonary findings and the patient resumed RT without incident.

Conclusion: Familiarity with typical CT changes of COVID-19 pneumonitis may allow for early detection in cancer patients undergoing CBCT for RT treatment. Prompt review of the lung windows is recommended in order to identify such changes, with the hope that pre-symptomatic diagnosis leads to expedited patient management, improved outcomes, and a reduction of inadvertent COVID-19 dissemination.

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Introduction:

Since the initial cases of COVID-19 were reported in December 2019 in Wuhan, China [1], the SARS-CoV-2 virus disseminated internationally, rapidly reaching pandemic proportions. The United States has reported the largest number of cases worldwide and New York City has become the epicenter of the crisis [2]. In the face of COVID-19, cancer patients represent a particularly vulnerable population with data suggesting a higher risk for severe events such as ICU admission, ventilator requirement, or death compared to the general population [3, 4]. There is a wide variation in clinical presentation with up to 80% of patients estimated to be asymptomatic [5], and the remainder experiencing symptoms ranging from transient fever, dry cough, and dyspnea, to respiratory failure, multi-organ failure, and death [6]. Rare symptoms including anosmia and ageusia, as well as gastrointestinal symptoms have also been described [7, 8]. Adverse outcomes and death are more common in the elderly and those with comorbidities, with a fatality rate ranging from 4-11% [9].

There have been several reports documenting the pulmonary imaging abnormalities associated with COVID-19, including in the setting of subclinical disease [10-13]. A study from China reported on temporal patterns of SARS-CoV-2 pneumonia on computed tomography (CT); the most common CT patterns in such patients were ground-glass opacities (GGO), air bronchograms, crazy-paving patterns, and thickening of the adjacent pleura [10]. Cone Beam Computed Tomography (CBCT) is a medical imaging technique capturing cone-shaped X-ray beam images that are reconstructed to form a 3D axial representation of the patient [14]. CBCT is one of many image-guided radiotherapy (IGRT) tools used for the verification of patient set-up to ensure accurate radiotherapy (RT) delivery [15]. In patients undergoing breast or thoracic RT, the lungs are encompassed in the daily CBCT, allowing the unique opportunity to monitor lung findings over several weeks. Typically, bone and soft tissue windows are utilized to allow for anatomic matching on specified structures for RT targeting. However, timely review of lung windows on CBCT may afford the opportunity to assess for lung changes indicative of asymptomatic SARS-CoV-2 infection.

Patients undergoing RT must present to a health care facility for treatment as delay, interruption, and/or premature termination of RT is associated with suboptimal oncologic outcomes [16-19]. Unfortunately, daily travel to a health care facility increases the risk of exposure to SARS-CoV-2 and, in the case of asymptomatic patients, inadvertent dissemination of the virus to other patients, healthcare professionals, and administrative staff. Rapid recognition of COVID-associated lung abnormalities on routine daily CBCTs may allow for early clinical assessment and the prompt initiation of appropriate precautions and/or treatment for these patients. The purpose of this case-report is to describe an initially asymptomatic patient in our radiation oncology clinic who was noted to have imaging changes consistent with SARS-CoV-2 pulmonary changes on CBCT prior to the onset of symptoms.

Description:

The patient is a postmenopausal female diagnosed as having pathologic T2N0M0, moderately differentiated invasive ductal carcinoma of the right breast, ER+/PR+/HER2-. The patient was treated with lumpectomy and sentinel-lymph node biopsy, to be followed by adjuvant hypofractionated whole breast radiotherapy (4256 cGy in 16 fractions) and endocrine therapy, as per multidisciplinary tumor board recommendations. At the time of CT simulation, the patient did not report fever or respiratory symptoms and her lung parenchyma on the CT simulation was normal. Approximately 2 weeks later, in March 2020, RT was initiated and the patient remained asymptomatic. The patient was treated on our Varian Halcyon unit, utilizing daily KV CBCTs for patient set-up. During the first week of treatment, no radiographic pulmonary abnormalities were noted on daily review of the CBCT soft tissue windows.

The patient presented on Monday morning for her 6th fraction of RT and upon COVID-19 verbal screening at the entrance to the cancer center, she reported a 2-day history of fatigue and fever, with a peak temperature of 101F. She had no other complaints and denied respiratory symptoms. Her vital signs were within normal limits, and her oxygen saturation was at her baseline of 95-98% on room air. Lung auscultation revealed good air entry bilaterally with no adventitious sounds. Due to the limited access of SARS-CoV-2 testing in New York City, outpatient testing was not available, and the patient's symptoms were not severe enough to warrant referral to the emergency room. As per departmental guidelines based on CDC recommendations [20], the patient's RT was held until she became afebrile without antipyretics for at least 72 hours and at least 7 days from symptom onset.

The patient's 5 CBCTs from the first week of RT were reviewed retrospectively and peripheral, predominantly right lower lobe GGOs were noted on the CBCT obtained at the 4th and 5th fractions, in the two days prior to her symptom onset (Figure 1). The patient was monitored daily via telemedicine. She remained febrile with fatigue and anorexia. On the 4th day after symptom onset, she reported a transient mild dry cough, dysgeusia ("everything tastes salty") and dysosmia ("smelling coffee all day"). The patient defervesced on the 8th day after symptom onset and she was no longer symptomatic. On the 11th day after symptom onset, the patient met our departmental criteria for resuming RT with the appropriate precautions for COVID-recovered patients. CBCT that day showed substantial worsening of the GGO, bilaterally (Figure 2). The case was reviewed with Diagnostic Radiology and Infectious Disease; given the severity of the radiologic findings and the unknown consequence of RT in a patient recovering from probable SARS-CoV-2 pneumonia, it was decided to hold RT again and obtain serial diagnostic imaging in order to monitor the progression of lung disease.

The patient underwent diagnostic CT chest on the 13th day after symptom onset, demonstrating bilateral peripheral GGO most prominent on the right side, as well as lymph nodes in the pre-tracheal space and AP window measuring up to 1.2cm (Figure 3, Column A). Diagnostic impression was consistent with a viral pneumonitis, including COVID-19 pneumonia. Comparison made with CBCT from two days prior showed stable to improved pulmonary findings. Repeat diagnostic CT chest was performed on the 16th day after symptom onset, demonstrating improvement in bilateral, peripheral GGOs with decreased lymphadenopathy, suggesting an amelioration (Figure 3, Column B). The patient resumed RT and remained asymptomatic with continued improvement in her pulmonary GGO on subsequent CBCTs.

Discussion:

COVID-19 infection disproportionately impacts patients with underlying comorbidities, including cancer [21]. Given that cancer patients require frequent medical visits to treatment facilities, the risk of inadvertent dissemination of COVID-19 poses a serious threat to this vulnerable patient population. Adding to this challenge is the covert nature of the SARS-CoV-2 virus, with rates of asymptomatic infection being reported as high as 80%. Up to 50% of asymptomatic patients can have radiographic abnormalities prior to the onset of symptoms [22]. Radiographic imaging findings are important in the diagnosis and treatment of this disease. In cancer patients receiving CBCT as part of their RT, review of lung windows to screen for COVID-19 changes could lead to early detection of the infection in asymptomatic patients.

Studies have described the radiographic characteristics of distinct groups of patients and temporal changes associated with disease progression [10]. The imaging features of this viral pneumonia are diverse, typically ranging from normal appearance to diffuse changes in the lungs; patients with multiple comorbidities are more likely to have bilateral and diffuse disease [10]. Overall, there is a slight predilection for the right lower lobe. The extent of disease on CT increases gradually from the subclinical period throughout the first 3 weeks, then decreases thereafter [10], but radiographic changes may continue to evolve beyond 26 days of symptoms [10, 12]. Asymptomatic patients are more likely to have unilateral, multifocal GGOs. After symptom onset, bilateral and diffuse GGOs are predominant. In the progressive stage, GGOs are relatively decreased in frequency, with a transition to consolidation and mixed-pattern development. As the disease peaks, GGOs decrease further, and peak lung involvement is characterized by increasing crazy-paving patterns, reticulation, along with bronchiolectasis and thickening of the adjacent pleura. The resolving stage demonstrates decreasing consolidation and absence of crazy-paving patterns following the first 2-3 weeks of disease [11-13, 23-25]. Our patient's radiographic changes were generally consistent with the above findings; during the subclinical period, GGO's were predominantly located in the peripheral right lower lobe and progressed in the symptomatic stage to become more diffuse and bilateral. Based on our patient's available imaging, her CT lung abnormalities appeared to peak in severity approximately 11 days after symptom onset, followed by gradual resolution of GGO's as demonstrated in her diagnostic CTs (Figure 3).

Radiographic evolution of the disease typically mirrors the clinical course, with time to medical ventilation and intensive-care unit admission paralleling the severity of CT findings [26]. Timely detection has been shown to be associated with improved clinical outcomes and prognosis [27]. One retrospective series demonstrated as many as 75% of patients with negative RT-PCR COVID-19 testing had positive CT findings; some patients continued to test negative on repeat RT-PCR before eventually testing positive, indicating CT findings may have greater sensitivity than RT-PCR. Interestingly, 40% of patients had improvement in CT findings prior to serial RT-PCR results converting from positive to negative [13], suggesting RT-PCR results lag behind radiographic findings.

Patients undergoing therapeutic radiation typically undergo radiographic confirmation of set-up prior to treatment delivery. Modalities include KV port-films using 2D x-ray and/or cone-beam CT scans [15, 28]. Traditionally, patients treated with breast tangent RT do not undergo daily IGRT, but rather weekly portal imaging. The Varian Halcyon 2.0 platform utilizes KV CBCT, and iterative CBCT imaging for improved soft tissue definition [29]. Patients with thoracic and breast malignancies undergoing treatment on the Halcyon receive CBCT for set-up verification, which opportunely encompasses the lungs. Pulmonary infiltrates potentially indicative of infection with SARS-CoV-2 may be identifiable on routine daily CBCTs, which would not otherwise have been appreciable with KV orthogonal imaging or weekly portal imaging. Given the relatively high proportion of breast cancer patients treated in most radiation oncology departments, Halcyon's daily KV CBCT imaging presents a unique opportunity for lung evaluation during the COVID-19 pandemic. Suppli et al. have reported on early pulmonary findings discovered on retrospective review of daily CBCTs done in a lung cancer patient admitted to the ICU during RT, who ultimately died of COVID-19 infection [30].

In our institution, this case prompted the initiation of a protocol for the prospective review of thoracic CBCTs in patients undergoing RT in an effort to detect pulmonary changes suggestive of COVID-19 pneumonitis. With the limited access to SARS-CoV-2 testing in NYC and the risk of false negative RT-PCR despite abnormal CT chest findings, the utility of a laboratory test in identifying asymptomatic or suspected infected cancer patients may be impractical. Given that imaging characteristics have been shown to correlate with clinical severity and progression of disease, the combination of clinical and laboratory findings, and acquaintance with typical radiographic COVID-19 related changes may facilitate the prompt diagnosis of these patients, leading to immediate quarantine and/or treatment and decreased risk of unintended dissemination.

Conclusion:

COVID-19 has impacted the United States on a level not seen since the influenza pandemic of 1918, and NYC rapidly became the epicenter of the pandemic. Due to the high prevalence of asymptomatic patients and the limited availability of outpatient SARS-CoV-2 testing, a combination of screening for symptoms, clinical acumen, and use of available technology is necessary for the prompt identification and management of these patients. As many cancer patients undergo routine CBCT during RT, familiarity with COVID-related lung changes may lead to earlier detection, diagnosis and treatment, while decreasing inadvertent dissemination amongst this vulnerable patient population.

References:

1. Rothan, H.A. and S.N. Byrareddy, *The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak.* J Autoimmun, 2020: p. 102433.
2. Organization, W.H. *Coronavirus disease (COVID-2019) situation reports*. 2020 9 April 2020 [cited 2020 10 April 2020]; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports.
3. Xia, Y., et al., *Risk of COVID-19 for patients with cancer.* Lancet Oncol, 2020. **21**(4): p. e180.
4. Zhang, L., et al., *Clinical characteristics of COVID-19-infected cancer patients: A retrospective case study in three hospitals within Wuhan, China.* Ann Oncol, 2020.
5. Medicine, C.f.E.-B. *COVID-19: What proportion are asymptomatic?* 2020; 6 April 2020:[Available from: https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/.
6. Adhikari, S.P., et al., *Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review.* Infect Dis Poverty, 2020. **9**(1): p. 29.
7. Gautier, J.F. and Y. Ravussin, *A New Symptom of COVID-19: Loss of Taste and Smell.* Obesity (Silver Spring), 2020.
8. Tian, Y., et al., *Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission.* Aliment Pharmacol Ther, 2020.
9. Singhal, T., *A Review of Coronavirus Disease-2019 (COVID-19).* Indian J Pediatr, 2020. **87**(4): p. 281-286.
10. Shi, H., et al., *Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study.* Lancet Infect Dis, 2020. **20**(4): p. 425-434.
11. Bernheim, A., et al., *Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection.* Radiology, 2020: p. 200463.
12. Pan, F., et al., *Time Course of Lung Changes On Chest CT During Recovery From 2019 Novel Coronavirus (COVID-19) Pneumonia.* Radiology, 2020: p. 200370.
13. Ai, T., et al., *Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases.* Radiology. **0**(0): p. 200642.
14. Scarfe, W.C. and A.G. Farman, *What is cone-beam CT and how does it work?* Dent Clin North Am, 2008. **52**(4): p. 707-30, v.
15. Yan, H., et al., *Progressive cone beam CT dose control in image-guided radiation therapy.* Med Phys, 2013. **40**(6): p. 060701.
16. Bese, N.S., P.A. Sut, and A. Ober, *The effect of treatment interruptions in the postoperative irradiation of breast cancer.* Oncology, 2005. **69**(3): p. 214-23.
17. Chen, M., et al., *The impact of overall treatment time on outcomes in radiation therapy for non-small cell lung cancer.* Lung Cancer, 2000. **28**(1): p. 11-9.
18. Dong, Y., et al., *Effects of interruptions of external beam radiation therapy on outcomes in patients with prostate cancer.* J Med Imaging Radiat Oncol, 2018. **62**(1): p. 116-121.
19. Gonzalez Ferreira, J.A., et al., *Effect of radiotherapy delay in overall treatment time on local control and survival in head and neck cancer: Review of the literature.* Rep Pract Oncol Radiother, 2015. **20**(5): p. 328-39.

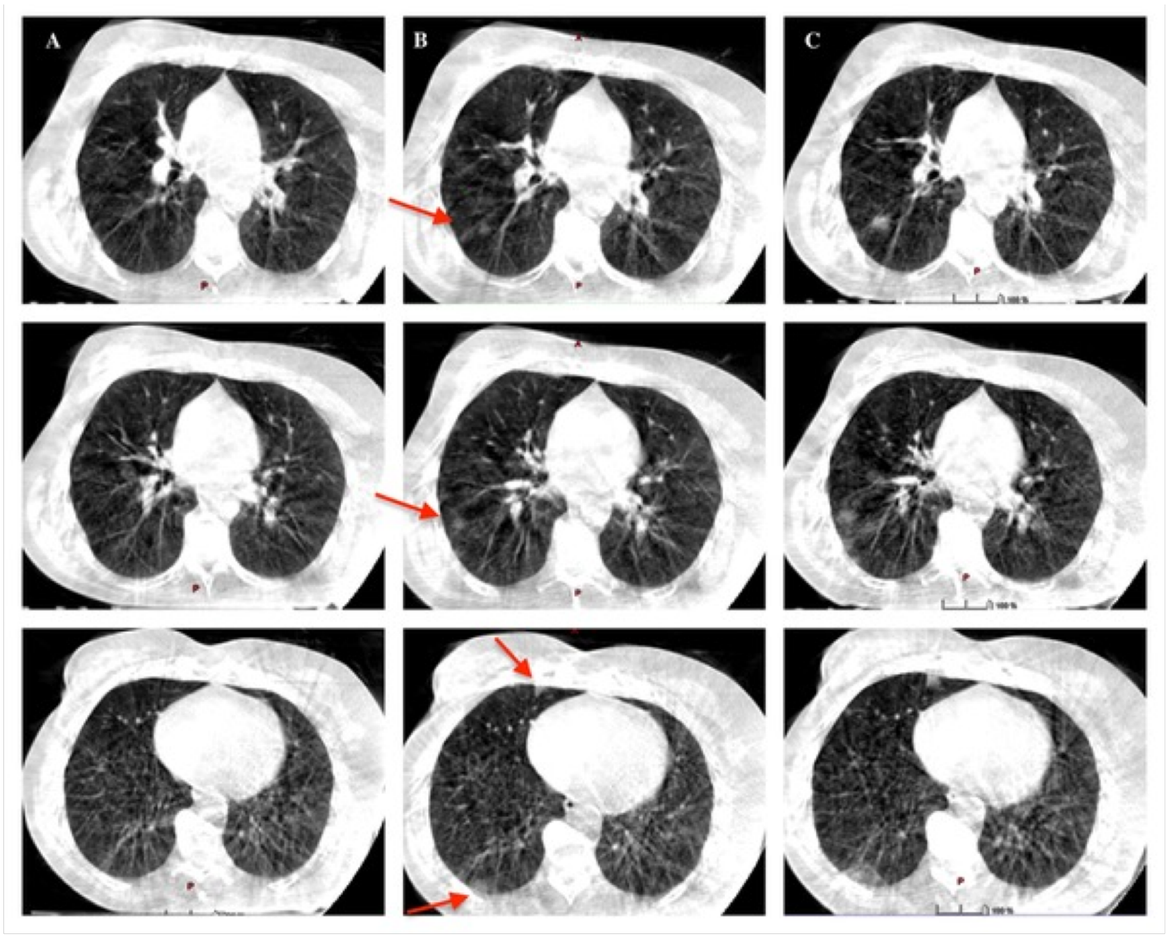
20. *Discontinuation of Isolation for Persons with COVID-19 Not in Healthcare Settings (Interim Guidance)*. Coronavirus Disease 2019 (COVID-19) 2020 [cited 2020 21 April]; Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html.
21. Jordan, R.E., P. Adab, and K.K. Cheng, *Covid-19: risk factors for severe disease and death.* BMJ, 2020. **368**: p. m1198.
22. Inui, S., et al., *Chest CT Findings in Cases from the Cruise Ship "Diamond Princess" with Coronavirus Disease 2019 (COVID-19).* Radiology: Cardiothoracic Imaging, 2020. **2**(2): p. e200110.
23. Chung, M., et al., *CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV).* Radiology, 2020. **295**(1): p. 202-207.
24. Lei, J., et al., *CT Imaging of the 2019 Novel Coronavirus (2019-nCoV) Pneumonia.* Radiology, 2020. **295**(1): p. 18.
25. Ng, M.-Y., et al., *Imaging Profile of the COVID-19 Infection: Radiologic Findings and Literature Review.* Radiology: Cardiothoracic Imaging, 2020. **2**(1): p. e200034.
26. Huang, C., et al., *Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China.* Lancet, 2020. **395**(10223): p. 497-506.
27. Huang, G., et al., *Timely Diagnosis and Treatment Shortens the Time to Resolution of Coronavirus Disease (COVID-19) Pneumonia and Lowers the Highest and Last CT Scores From Sequential Chest CT.* AJR Am J Roentgenol, 2020: p. 1-7.
28. Sterzing, F., et al., *Image-guided radiotherapy: a new dimension in radiation oncology.* Dtsch Arztebl Int, 2011. **108**(16): p. 274-80.
29. Cai, B., et al., *Characterization of a prototype rapid kilovoltage x-ray image guidance system designed for a ring shape radiation therapy unit.* Med Phys, 2019. **46**(3): p. 1355-1370.
30. Suppli, M.H., et al., *Early appearance of COVID-19 associated pulmonary infiltrates during daily radiotherapy imaging for lung cancer.* J Thorac Oncol, 2020.

Figure 1: Column A: Baseline CBCT. Column B: CBCT at 4th fraction. Column C: CBCT at 5th fraction. Serial CBCT's demonstrate increasing peripheral ground-glass opacities, predominantly in the right lower lobe (red arrows)

Figure 2: Selected images from CBCT obtained on the 11th day after symptom onset, after the patient had a complete clinical recovery and was eligible to resume RT based on departmental guidelines. The CBCT demonstrates worsening peripheral GGO's with greater bilateral involvement.

Figure 3: Left panel: Diagnostic CT obtained the 13th day after symptom onset demonstrating bilateral peripheral GGOs, more prominent on the right side. Right Panel: Diagnostic CT obtained the 16th day after symptom onset, with improvement and diminished volume of GGOs.

Figure 1:



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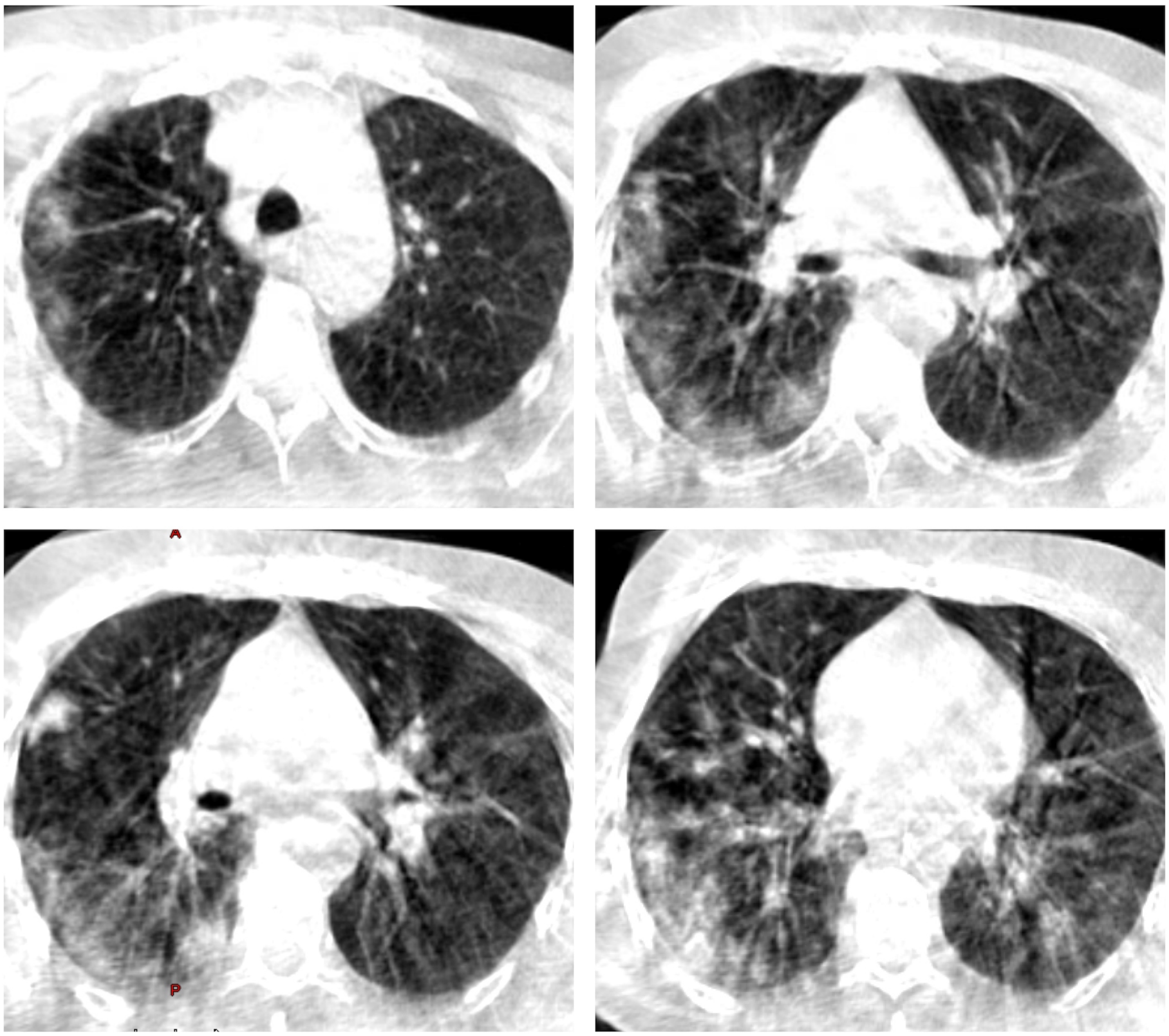

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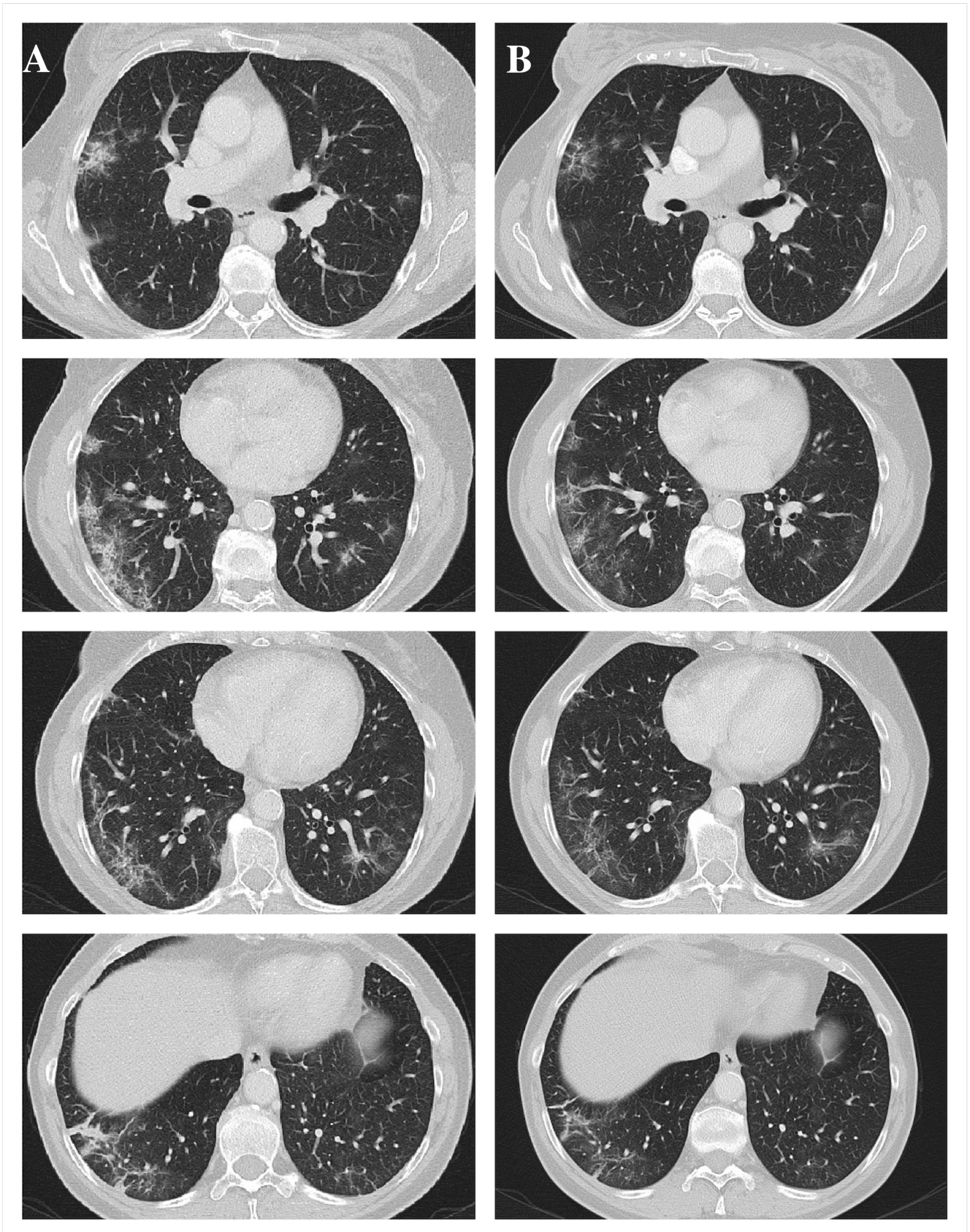
Figure 3



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