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**Oncology patients with pulmonary infiltrates in the COVID-19 era: a case series**

Edwin Chong Yu Sng<sup>1,2</sup>, MBBS, MRCP, Shuting Han<sup>3</sup>, MBBChir, MRCP, Valerie Shiwen Yang<sup>3,4</sup>, MBBChir, PhD, Ban Hock Tan<sup>1</sup>, MBBS, FRCP

<sup>1</sup>Department of Infectious Diseases, Singapore General Hospital,

<sup>2</sup>Department of Infectious Diseases, Changi General Hospital,

<sup>3</sup>Division of Medical Oncology, National Cancer Centre Singapore,

<sup>4</sup>Institute of Molecular and Cell Biology, A\*STAR, Singapore

**Correspondence:** Dr Edwin Chong Yu Sng, Associate Consultant, Department of Infectious Diseases, Changi General Hospital, 2 Simei Street 3, Singapore 529889. [edwin.sng.c.y@singhealth.com.sg](mailto:edwin.sng.c.y@singhealth.com.sg)

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## INTRODUCTION

The clinical spectrum of symptomatic COVID-19 ranges from a mild upper respiratory tract infection to a severe pneumonia with respiratory failure.<sup>(1)</sup> When there is lower respiratory tract involvement, typical findings on computed tomography (CT) scan of the lungs are ground-glass opacities (GGOs) with or without consolidation. Lung changes are more likely to be bilateral, peripheral, and involving the lower lobes.<sup>(2,3)</sup> However, the CT findings are non-specific. The diagnosis of COVID-19 is confirmed by a positive test for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR).

In oncology patients, pulmonary infiltrates are commonly encountered, and may be due to infection, fluid overload, drug pneumonitis, the underlying malignancy or any combination of these.<sup>(4,5)</sup> In this current COVID-19 pandemic, excluding COVID-19 is an additional consideration, further complicating the diagnostic algorithm. Yet a prompt and accurate diagnosis is crucial for both patient care and infection control.

Singapore saw its first case of COVID-19 on 23 January 2020 in a Chinese national visiting from Wuhan. Since then, the outbreak has evolved into a pandemic. As of May 2021, more than 61,000 cases of COVID-19 have been diagnosed in Singapore. In oncology patients who present with pulmonary infiltrates, it is often prudent to exclude COVID-19. Over a 10-week period from 5<sup>th</sup> February-15<sup>th</sup> April 2020, 431 oncology patients who were on follow-up with National Cancer Centre Singapore (NCCS) underwent PCR testing for COVID-19. Only 1 tested positive for SARS-CoV-2. We juxtapose 3 oncology patients with pulmonary infiltrates to depict the challenges clinicians face in differentiating COVID-19 from the other causes of pulmonary infiltrates in the oncology patient.

## CASE DESCRIPTION

### Case 1

He was a 65-year-old Chinese man with hypertension, hyperlipidaemia and human epidermal growth factor receptor 2 (HER2) positive gastroesophageal junction adenocarcinoma, with metastases to the lymph nodes and spine, but no pulmonary metastases. He had undergone decompression laminectomy, resection of epidural tumour and posterior instrumentation, and was staying in a subacute care hospital for rehabilitation. Despite radiotherapy to the spine for local control, he developed cord compression. Repeat surgery to the spine was deemed unhelpful. He was initiated on outpatient palliative chemotherapy with 3-weekly capecitabine, cisplatin and trastuzumab. In April 2020 on day 15 of the first cycle of chemotherapy, he developed a dry cough with low grade fever. Laboratory evaluation showed lymphopenia ( $0.30 \times 10^9/L$ ), thrombocytopenia ( $86 \times 10^9/L$ ), elevated C-reactive protein (30.4 mg/L) and normal procalcitonin (0.11 ng/mL). Chest radiograph (CXR) was unremarkable. Intravenous piperacillin-tazobactam was started, and cycle 2 of chemotherapy was withheld. The bicytopenia was attributed to chemotherapy. He continued to have low-grade fevers for the next 2 weeks, and subsequently desaturated requiring supplementary oxygen. A repeat CXR showed bilateral diffuse opacities (Figure 1). He was transferred to a nearby acute care hospital's negative-pressure airborne isolation room where his nasopharyngeal swab tested positive for SARS-CoV-2 by RT-PCR. He continued to deteriorate with progressive CXR changes and increasing oxygen requirement. In view of the patient's metastatic cancer with a poor prognosis, the goal of care was palliative. No trial drug or steroid treatment was administered. He passed away shortly after.

**Case 2**

He was a 78-year-old Chinese man with history of hypertension. He was an ex-smoker and was diagnosed with stage III (T3N2M0) right lower lobe lung squamous cell carcinoma with PD-L1 5%. A multi-disciplinary tumour board deemed the primary tumour unresectable. He subsequently underwent curative chemoradiotherapy (chemoRT). He achieved partial response after 2 cycles of induction chemotherapy with paclitaxel and carboplatin. Radiotherapy was then initiated with subsequent cycles of chemotherapy. He presented in February 2020 with fever (38.4 °C) on his planned 24<sup>th</sup> radiotherapy dose. He was haemodynamically stable, and did not require supplementary oxygen. Laboratory evaluation showed lymphopenia ( $0.10 \times 10^9/L$ ), elevated C-reactive protein (104 mg/L) and normal procalcitonin (0.09 ug/L). CXR demonstrated stable ill-defined air space opacities at the right lower zone, corresponding to the site of the primary tumour. Oropharyngeal swabs for SARS-CoV-2 and common respiratory viruses by RT-PCR were negative. Intravenous piperacillin-tazobactam was started. CT thorax on Day 8 of admission revealed diffuse lower lobe ground-glass change with patchy peripheral ground glass upper lobe opacities and bilateral pleural effusions (Figure 2). Because of concerns of false-negative SARS-CoV2 PCR in early COVID-19, he remained under airborne precaution in a negative-pressure isolation room. Within hours, he developed tachycardia and electrocardiogram (ECG) changes suspicious for an acute coronary syndrome. He was intubated and mechanically ventilated, and underwent emergency coronary angiography, which suggested stress-induced cardiomyopathy. During this time, a blood sample for cytomegalovirus (CMV) PCR was positive (1685 IU/ml), hence intravenous ganciclovir was initiated for presumptive CMV pneumonitis. Endotracheal aspirates for SARS-CoV-2 on day 9 and 10 of admission were negative. He improved after intravenous dexamethasone was initiated for presumptive taxane-induced pneumonitis, and was successfully extubated. On Day

17 of admission, he developed massive rectal bleeding. End-of-life issues were discussed, and palliative care was initiated.

### Case 3

She was a 63-year-old woman who underwent a left mastectomy in October 2019 for early stage pT2N0M0 breast invasive carcinoma. Histology revealed a 45mm, grade 3 poorly differentiated invasive carcinoma of no special type, with a minor sarcomatoid (spindle cell) component. Stains were weakly positive for oestrogen (oestrogen receptor 1 +, 10%) but negative for progesterone receptors (< 1%) and HER2 receptors (1+). She was advised for adjuvant chemotherapy, with 12 cycles of weekly paclitaxel, followed by 4 cycles of 3-weekly doxorubicin and cyclophosphamide (AC). In March 2020 on day 10 of cycle 1 of AC, she presented to another hospital with 2 days of fever without localising symptoms. Laboratory evaluation showed neutropenia ( $0.5 \times 10^9/L$ ), lymphopenia ( $0.4 \times 10^9/L$ ), thrombocytopenia ( $133 \times 10^9/L$ ), elevated C-reactive protein (96.8 mg/L) and normal procalcitonin (0.10 ug/L). Initial CXR was unremarkable. Intravenous vancomycin, aztreonam and amikacin were started. She remained febrile and developed shortness of breath. 6 days into her admission, she requested a transfer to our hospital. On arrival, she was febrile, but haemodynamically stable, and did not require supplementary oxygen. Repeat laboratory evaluation was similar. CXR showed basal atelectasis with prominent interstitial lines. Oropharyngeal swabs for SARS-CoV-2 were negative. Following “swab-clearance”, she was de-isolated. The next day she was identified as a contact of a confirmed case of COVID-19 (both having been in the emergency room at the same time), and was transferred into a single room and placed under quarantine order. Over the next few days, she remained febrile. Her oxygen saturation ranged from 88% to 95% on room air. CT thorax showed ill-defined peripheral ground glass changes in the lungs, predominantly in the lower lobes, raising concerns for COVID-19 that may present with a similar CT appearance (Figure 3). Additional swabs for SARS-CoV-2 were negative but paired

blood cultures taken from both the porta-cath and peripheral vein yielded *Staphylococcus epidermidis* (4 of 4 bottles). She was diagnosed with catheter-related blood stream infection and started on intravenous vancomycin. Her port-a-cath was planned for removal. Over the following days, the fever subsided, and her oxygenation improved without steroid treatment. The lung infiltrates were ascribed to possible taxane-induced pneumonitis.

## DISCUSSION

From February to April 2020, there was ongoing community transmission of COVID-19 in Singapore, and excluding COVID-19 was crucial for both patient care and infection control. Yet the clinical manifestations of COVID-19 and its associated radiographic changes mimic diseases processes that commonly occur in oncology patients, especially those undergoing chemotherapy. The 3 patients in this series depict the challenges clinicians face in differentiating COVID-19 from the other causes of pulmonary infiltrates in the oncology patient.

Case 1 demonstrates that COVID-19 can mimic the common side effects of chemotherapy, to which his fever and bicytopenia were initially attributed. When his respiratory status worsened with progressive bilateral opacities on CXR, an infective process was considered, and COVID-19 was eventually diagnosed. Since the median time to deterioration in COVID-19 is around 8 days,<sup>(6)</sup> his deterioration after 2 weeks of fever shows how challenging it is to determine the actual onset of COVID-19 in patients with multiple concomitant disease processes. There was a delay in the diagnosis of COVID-19 in case 1. He had been in the subacute care hospital for 2 weeks before he developed dry cough and fever, and he had neither epidemiological exposures nor known COVID-19 contacts. Consequently, COVID-19 was not initially considered. In retrospect, he should have been tested for COVID-19 earlier, as there was significant community transmission in April 2020 during his stay at the

subacute care hospital. Fortunately, even though he was not tested for COVID-19, he was moved into a single room when he first became febrile. Investigations revealed no secondary cases in the subacute care hospital. Extensive contact tracing did not reveal any cases linked to him. When there is ongoing community transmission, a low threshold to test for SARS-CoV-2 is crucial for both patient care and infection control.

Case 2 illustrates that several causes of pulmonary infiltrates may co-exist in an oncology patient undergoing chemotherapy. Paclitaxel-induced pneumonitis was a chief consideration as he was then undergoing chemoRT. However, the CT findings of GGOs that were predominantly peripheral with a few regions demonstrating a rounded appearance (Figure 2) raised concerns for COVID-19. When he deteriorated on day 7 with worsening pulmonary infiltrates and ECG changes, an acute coronary syndrome had to be excluded, though deterioration at around day 7 – 8 of illness would fit the clinical course of COVID-19.<sup>(6)</sup>

It is difficult to differentiate drug-induced pneumonitis from other aetiologies of pulmonary infiltrates. The diagnosis of drug-induced pneumonitis requires not only a compatible clinical pattern and exposure history, but also the exclusion of other causes.<sup>(7)</sup> Bronchoscopy with bronchoalveolar lavage is often required to exclude other conditions. However, bronchoscopy is aerosol-generating, and risks transmission of COVID-19 to healthcare workers when COVID-19 is not yet confidently excluded. While he had CMV reactivation, CMV disease is uncommon in patients undergoing chemotherapy for solid tumours.<sup>(8,9)</sup> Radiological manifestations of COVID-19 can resemble CT findings in patients with lung cancer.<sup>(10)</sup> The development of an acute coronary syndrome heightened suspicions for COVID-19, even though he already had negative PCR tests for SARS-CoV-2.<sup>(11)</sup> The discovery that SARS-CoV-2 is able to directly infect vascular endothelial cells provides a pathophysiological explanation for the cardiovascular complications associated with COVID-19.<sup>(12)</sup> Even with SARS-CoV-2 PCR testing, excluding COVID-19 remains a challenge.<sup>(13)</sup>

Although publications suggest that SARS CoV-2 viral load peaks early,<sup>(14,15)</sup> oropharyngeal/nasopharyngeal swabs taken early in the disease have been reported to be negative.<sup>(13)</sup> While Case 2 already had negative swabs for SARS-CoV-2 at the time he deteriorated, the first had been done just hours after his initial symptoms, raising concern for false-negative results. His deterioration on day 7 of symptoms also coincided with the median time to deterioration in COVID-19.<sup>(6)</sup> Hence, additional testing to rule out COVID-19 was ordered, and he underwent coronary angiography with full infection prevention precautions - a major logistical undertaking.

In Case 3, the clinical assessment of the patient was complicated by the fact that she was discovered to be in contact of a confirmed case of COVID-19 after she was de-isolated to a cohort cubicle. She was issued a quarantine order, and had to be transferred back into a single room. Those patients whom she shared a cubicle with were tracked by the Epidemiology department, lest she subsequently developed COVID-19. Despite early negative SARS-CoV-2 PCR tests, new events (e.g. fever) necessitated repeat swabs. Eventually, paired blood cultures taken from both the porta-cath and peripheral vein yielded *Staphylococcus epidermidis*, leading to the diagnosis of catheter-related bloodstream infection. The true cause of her respiratory symptoms and lung infiltrates was never conclusively established, though the mild hypoxemia, spontaneous resolution and onset around 4 weeks after completion of 12 cycles of paclitaxel suggested taxane-induced pneumonitis. This case illustrates the importance of a systematic approach to the evaluation of fever that consists of detailed clinical history, physical examination, laboratory investigations, and takes into consideration each patient's unique medical history and treatment. In this case, while evaluation was ongoing to exclude COVID-19, the clinical suspicion for a catheter-related blood stream infection in a febrile patient with a porta-cath in-situ prompted repeated blood cultures that helped clinch the diagnosis.



A limitation of our case series is that the case series took place relatively early in the pandemic. The optimal respiratory specimen for COVID-19 testing was still uncertain, and the role of serology testing was limited to epidemiological studies. Consequently, oropharyngeal swabs were used for PCR testing for SARS-COV-2 for cases 2 and 3. Serology testing were also not performed for the 3 patients.

In conclusion, there are many causes of pulmonary infiltrates in an oncology patient. In this current COVID-19 pandemic, excluding COVID-19 is crucial for both patient care and infection control. However, distinguishing COVID-19 from the other aetiologies of pulmonary infiltrates in the oncology patient is challenging. Clinicians should be familiar with the clinical presentation of COVID-19, and the limitations of the various diagnostic tests. A systematic approach to pulmonary infiltrates in oncology patients, which takes into consideration each patient's unique medical and treatment history, should be undertaken to ensure the correct diagnosis is reached, while protecting public health.

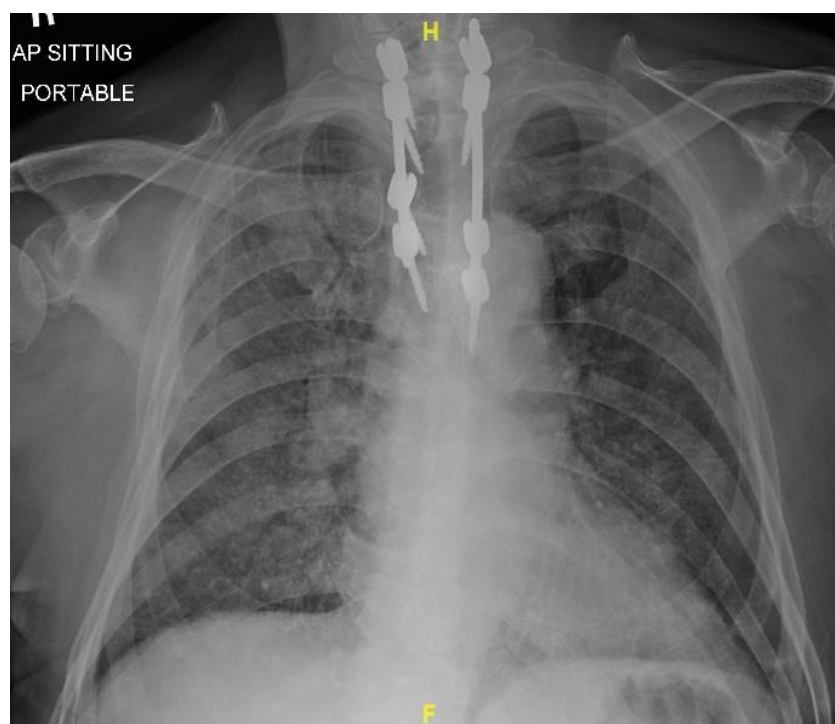
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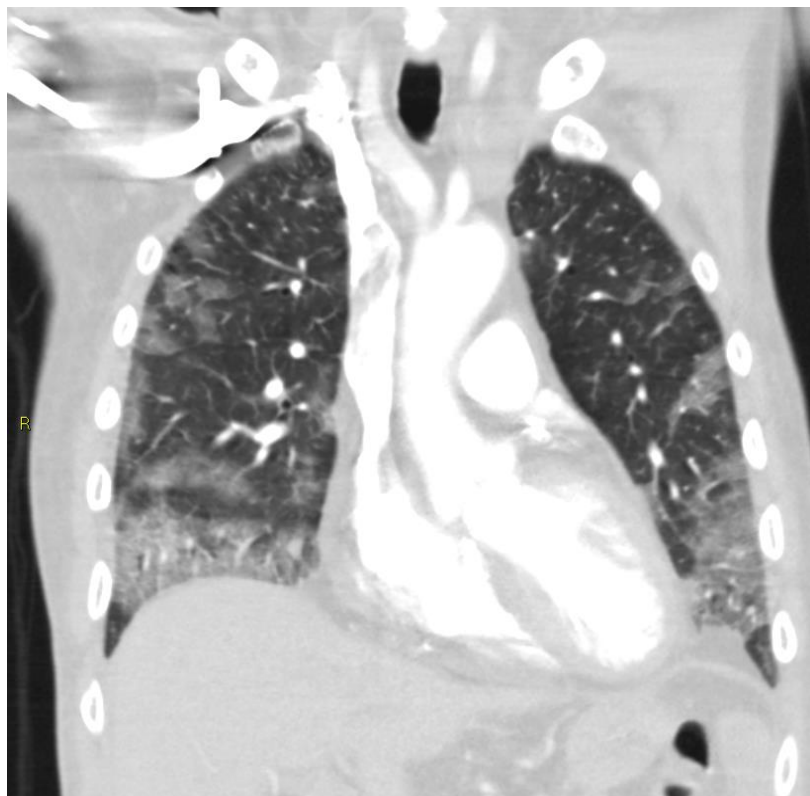
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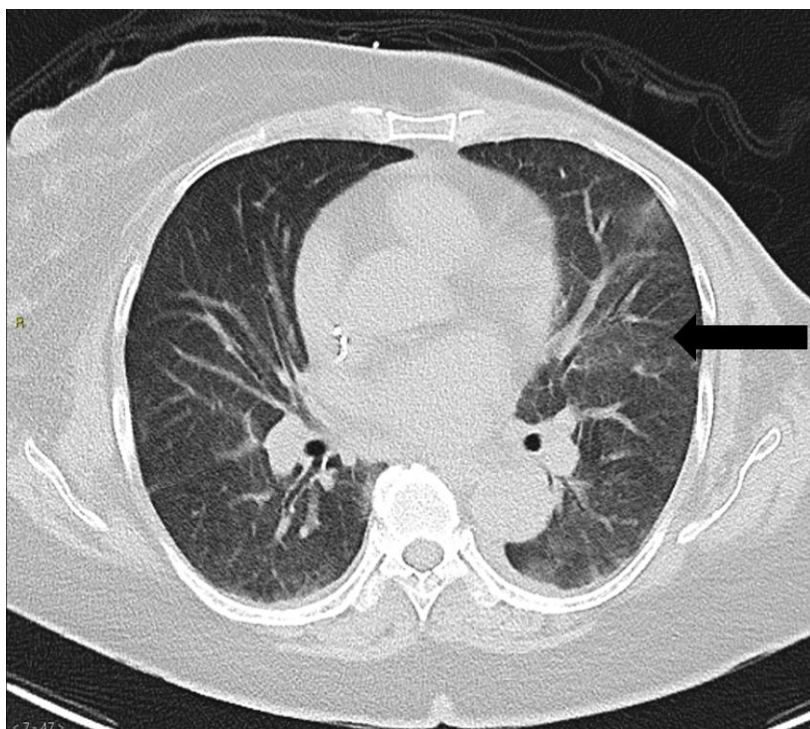
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**Figure 1:** CXR showing bilateral diffuse opacities (Case 1)



**Figure 2:** CT thorax showing diffuse lower lobe ground-glass change with patchy peripheral ground glass upper lobe opacities and bilateral pleural effusions (Case 2)



**Figure 3:** CT thorax showing ill-defined peripheral ground glass changes in the lungs, predominantly in the lower lobes (Case 3)