Incidental radiological findings suggestive of COVID-19 in asymptomatic patients

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Abstract

Despite routine screening of patients for coronavirus disease 2019 (COVID-19) symptoms and signs at hospital entrances, patients may slip between the cracks and be incidentally discovered to have lung findings that could indicate COVID-19 infection on imaging obtained for other reasons. Multiple case reports and case series have been published to identify the pattern of this highly infectious disease. This article addresses the radiographic findings in different imaging modalities that may be incidentally seen in asymptomatic patients who carry COVID-19. In general, findings of COVID-19 infection may appear in computed tomography (CT), magnetic resonance imaging, positron emission tomography-CT, ultrasound, or plain X-rays that show lung or only apical or basal cuts. The identification of these characteristics by radiologists and clinicians is crucial because this would help in the early recognition of cases so that a rapid treatment protocol can be established, the immediate isolation to reduce community transmission, and the organization of close monitoring. Thus, it is important to both the patient and the physician that these findings are highlighted and reported.

Key Words: Incidental; Asymptomatic COVID-19; Chest computed tomography; Positron emission tomography-computed tomography; Magnetic resonance imaging; Ultrasound; Oncology patients
INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Infection has a major global influence on social, health, and economic issues. COVID-19 is considered the most significant major health epidemic since the Spanish flu 100 years ago[1]. It first appeared in Wuhan, China, in December 2019 and was officially declared a pandemic by the World Health Organization (WHO) on March 11, 2020, extending rapidly worldwide thereafter and becoming an outbreak. By the end of 2020, more than 78 million people were infected, leading to over 1.7 million deaths[2]. Unlike infections with other coronaviruses, asymptomatic COVID-19 patients are infectious, leading to the rapid spread of infection worldwide[1,3]. The most common modes of transmission of the virus are person-to-person spreading during intimate contact with an infected person (or asymptomatic infected carriers), inhalation of respiratory droplets, and contact with surfaces contaminated with respiratory droplets or aerosols, which can penetrate the lungs through the nose or mouth[2,4,5]. SARS-CoV-2 virus uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry. ACE2 receptors are present in high amounts on epithelial cells, which are more predominant in oral mucosa and lungs, than in heart, blood vessels, brain, and other organs, leading to a diversity in the disease presentation[5-8]. The clinical presentation of COVID-19 ranges from asymptomatic to critically ill, and the most common manifestations are mild to moderate respiratory illness, where recovery occurs without requiring special treatment[6-8]. However, many nonspecific symptoms, such as fever, fatigue, shivering, anorexia, headache, olfactory dysfunction and loss of taste, shortness of breath, cough with or without expectoration, dyspnea, chest tightness, diarrhea, nausea, vomiting, abdominal pain, and muscle soreness, overlap with other viral infections[2,5-12]. Despite most patients with COVID-19 complaining of mild symptoms, the death rate is considerable, ranging from 0.3%–13.1%, with more susceptibility to severe forms of the disease in older patients, especially those with underlying disease, such as diabetes mellitus, cardiovascular disease, respiratory disease, hyperlipidemia, obesity, and chronic renal and hepatic disease[4,10,11].

COVID-19 DIAGNOSIS

A confirmed case of coronavirus disease 2019 (COVID-19) is defined by World Health Organisation as a patient with a positive reverse transcription-polymerase chain reaction (RT-PCR) test, irrespective of clinical signs and symptoms[12]. This test directly assesses the viral load from a nasopharyngeal swab, sputum, or endotracheal lavage[13]. It has impressive specificity of up to 100% owing to its specificity to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genome sequence, but has imperfect sensitivity of 89% (95%CI: 81%–94%)[14]. A positive result denotes the presence of viable virus only, and a negative result does not rule out COVID-19 infection[13,15]. False-negative RT-PCR results may occur if the test is performed too early or late in infection course, the viral load is insufficient, or the specimen is of poor quality.
CLASSICAL IMAGING CRITERIA OF COVID-19

To prevent the spread of infection in hospital patients or healthcare workers, chest radiography is considered the first-line imaging modality to be performed in patients with suspected coronavirus disease 2019 (COVID-19) or to exclude the presence of COVID-19 infection in patients who need to receive medical or surgical treatment[10, 13,17,18,24-29]. Most radiological imaging modalities are beneficial in characterizing COVID-19 infection.

Chest X-ray

Chest X-ray (CXR) findings in COVID-19 patients usually appear at 10–12 d from symptom onset as bilateral lower zone consolidation patches or diffuse airspace opacities with peripheral distribution[10,11,30]. The CXR may be normal in up to 63% of cases, particularly in the early stages[28], and it has a great value in patients with moderate to severe disease who have acute respiratory distress syndrome, showing bilateral diffuse alveolar consolidation that may progress to white lung with or without mild pleural effusion[26,31-33].

Yasin et al[7] studied the association of COVID-19 severity and X-ray findings among 350 positive COVID-19 patients. Of them, 62.9% had an abnormal baseline CXR, and the most common findings were consolidation opacities (81.3%), followed by reticular interstitial thickening (39.9%) and ground glass opacities (GGOs) (32.5%). An example of CXR findings in a patient with COVID-19 is presented in Figure 1.

Chest computed tomography

Chest computed tomography (CT) plays a pivotal role in the early detection of COVID-19 pneumonia and has better sensitivity (98%) compared with RT-PCR (89%), particularly in the early course of the disease. However, it also has low specificity (25%) due to the overlap between COVID-19 pneumonia and other types of viral pneumonia[5,8,30,31]. Radiologists must be familiar with the different imaging findings of COVID-19 pneumonia to differentiate it from other types of pneumonia[11, 13,30]. Early COVID-19 chest CT findings include bilateral multiple GGOs with a peripheral, subpleural, and posterior distribution, with or without consolidation. In the late phase, the consolidation patches, linear opacities, “crazy-paving” pattern, reversed halo sign, and vascular enlargement become more common[5,9,10,18,32]. The pulmonary histologic findings of COVID-19 resemble those of other coronavirus infections, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV)[4], which also shows similarities in chest CT findings[23,33,34]. Great variability is observed in chest CT findings in COVID-19 patients according to the stage and severity of the disease[6,9,15, 24,25,35,36]. The Radiological Society of North America classifies the chest CT findings into four categories related to COVID-19 diagnosis: (1) Compatible with viral pneumonia; (2) Indeterminate; (3) Atypical (suggestive of other diagnoses); and (4) No evidence of pneumonia[37].

The Fleischner Society[38] recommends performing a chest CT in moderate to severe infections presenting with hypoxemia and moderate to severe dyspnea, regardless of the RT-PCR test result[39], while RT-PCR is indicated if incidental findings on CT suggest the presence of viral pneumonia[14,19,34,38,39]. Chest abnormalities associated with COVID-19 may be incidentally detected in the visualized lungs.
Figure 1 Postero-anterior chest X-RAY in one asymptomatic patient with coronavirus disease 2019 pneumonia from our institution. It shows interstitial infiltrates and ill-defined, patchy, peripheral opacities in bilateral lung fields.

parenchyma in CT examinations of other body regions, such as in the lower lung base in abdominal CT (Figure 2), the lung apex in head and neck CT studies (Figure 3), and the lung tissues seen in dorso-lumbar spine CT[18,40]. Several studies have been published reporting incidental chest CT findings of COVID-19 in the visualized lung parenchyma in patients with acute abdomen without respiratory manifestation who undergo abdominal CT in the scenario of an acute pandemic[41-47](Table 1).

Lung ultrasound
A lung ultrasound (US) in COVID-19 pneumonia is usually performed using a portable US machine at the bedside to minimize the spread of infection to other patients and healthcare workers[48]. The classical appearance is bilateral irregular pleural lines, subpleural consolidation, areas of thick white lung tissue, and thick irregular vertical artifacts suggesting interstitial alveolar damage[48-50]. In the pediatric age group, lung US has an advantage over CT because it does not use ionizing radiation. Vertical artifacts (70%) and pleural irregularities (60%) were the most common abnormalities detected in 10 symptomatic pediatric patients with confirmed COVID-19 who underwent a chest US while awaiting RT-PCR results. Notably, pleural effusions were absent in all 10 patients[44,50,51]. The follow-up of lung US findings to monitor pulmonary involvement in symptomatic COVID-19 patients is preferable to the use of repeated CT scans, especially in critically ill patients or patients on a ventilator, owing to the difficulty in transporting such patients to the CT equipment[5,8,50]. Additionally, US can detect pneumothorax and other complications. However, a major disadvantage is the prolonged close exposure of the operator to the infection and also the need for careful sterilization of the device and the use of transducer and keyboard covers[10]. No reports about incidental lung US findings are available because this is not a routine examination, and it is only performed in certain circumstances.

Magnetic resonance imaging
Although magnetic resonance imaging (MRI) plays no role in the diagnosis of COVID-19 pneumonia, there are many reports of the detection of incidental COVID-19 in MRIs performed for other diagnostic purposes in asymptomatic patients[8,40,42]. After an extensive review of the literature, we found many cases of reported COVID-19 findings in upper lung cuts that appear in brain, neck, and cervico-dorsal spine MRIs and in lower cuts in abdomen and liver MRI studies[4,52-55]. COVID-19 infection appears as peripheral areas of high signal on T2-weighted short tau inversion recovery imaging caused by edema or alveolar opacities. A high T1 signal is observed due to higher tissue density, and partial alveolar collapse with focal areas of restricted diffusion is observed on diffusion-weighted imaging because of increased cell density from the inflammatory reaction. Partial collapse with a heterogeneous enhancement pattern is observed after contrast administration. Thus, radiologists should be alert and look carefully for these findings[34,42,54-56]. Figure 4 shows an example of cardiac MRI findings in a COVID-19 patient. Ates et al[52] studied thorax CT and MRI findings in 32 COVID-19 patients who underwent chest CT and then MRI within 24 h after the chest CT. They reported that MRI had a sensitivity of 91.67% and a specificity
Table 1 Summary of incidental asymptomatic COVID-19 studies

| Ref.          | Imaging modality used | Number of incidental asymptomatic COVID-19 cases/total number of cases | Setting                                                                                     |
|---------------|-----------------------|------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| Ali et al[41] | 18F-FDG PET-CT        | 87/764; only 3 of which were RT-PCR negative                            | Asymptomatic oncology patient                                                              |
| Ferrando-     | 18F-FDG PET-CT        | 1                                                                      | COVID-19 asymptomatic cancer patient for routine oncological indication                    |
| Castagnetto et al[47] |            |                                                                      |                                                                                            |
| Pallardy et al[44] | 18F-FDG PET-CT    | 20/529                                                                 | COVID-19 asymptomatic cancer patients for routine oncological indication                    |
| Wallfie-Corieh et al[68] | 18F-FDG PET-CT | 23/1079, only 14 of which were RT-PCR positive                           | COVID-19 asymptomatic cancer patients for routine oncological indication                    |
| Mo et al[66]  | 18F-FDG PET-CT        | 1                                                                      | COVID-19 asymptomatic cancer patients for routine oncological indication                    |
| Franceschi et al[67] | 18F-FDG PET-CT    | 1                                                                      | Asymptomatic diffuse large B-cell lymphoma patient                                          |
| Setti et al[64] | 18F-FDG PET-CT        | 5/13                                                                   | COVID-19 asymptomatic cancer patients                                                      |
| Albano et al[65] | 18F-FDG PET-CT     | 6/65 patients                                                           | COVID-19 asymptomatic oncology patient                                                     |
|                  | SPECT-CT              | 1/12 patients                                                           | Asymptomatic patient with treated differentiated thyroid carcinoma                           |
| Angelini et al[42] | Whole-body MRI     | 1                                                                      | COVID-19 asymptomatic multiple myeloma patient under follow-up                            |
| Deen et al[57] | Liver MRI (basal chest cuts) | 1                                                                  | Emergency patient with hepatic focal lesion                                                |
| Di Girolamo et al[43] | MRI of the abdomen  | 1                                                                      | COVID-19 asymptomatic cancer patient for routine oncological indication                    |
| Ap Dafydd et al[22] | Chest CT            | 9/240 of CTs were reported as abnormal, only one of which was RT-PCR positive. | Asymptomatic patients prior to major thoracic or abdominal surgery                         |
| Siegel et al[59] | CT of the abdomen and pelvis (basal chest cuts) | 3                                                                      | Patients presented to emergency department with abdominal pain                              |
| Ali et al[26]  | Chest CT (for other causes) | 44                                                                  | COVID-19 asymptomatic cases                                                                |
| Hyne et al[60] | Cerebral angiography | 1                                                                      | Patient presented to emergency department with neurological manifestations                   |

COVID-19: Coronavirus disease 2019; FDG-PET/CT: Fluorodeoxyglucose-positron emission tomography-computed tomography; SPECT/CT: Single photon emission computed tomography; MRI: Magnetic resonance imaging.

Figure 2 Axial-basal chest cut in urinary tract computed tomography in a patient presenting with renal colic at our institution who was diagnosed with asymptomatic coronavirus disease 2019 due to the presence of peripheral small focal areas of ground glass veiling.

of 100%. Furthermore, rapid limited study using a T2-weighted spin echo sequence, which is widely available in all scanners and can detect GGOs or consolidative patches with no exposure to radiation, was suggested. Angelini et al[42] reported a case of incidental COVID-19 pneumonia in a 60-year-old male with multiple myeloma and negative respiratory symptoms who underwent whole-body MRI as routine follow-
Figure 3 Axial-apical chest cut in brain computed tomography in a patient presenting with head trauma at our institution who was diagnosed with asymptomatic coronavirus disease 2019 due to the bilateral presence of multiple peripheral small foci of ground glass veiling with mild interstitial thickening.

Figure 4 Cardiac magnetic resonance images of a patient with coronavirus disease 2019 who presented to our institute for a viability study showing multifocal peripheral areas of abnormal signal in both lungs that appear as high signal intensity areas localized in the coronal plane (A), high T2 signals (B), and faint heterogeneous enhancement in post-contrast sequences (C).

up. The COVID-19 pneumonia presented as peripheral posterior GGOs in the lung in T2-weighted sequences. Deen et al[57] reported the detection of incidental basal lung lesions on liver MRI in a 49-year-old woman with a negative RT-PCR result for COVID-19 who presented at the emergency department with vague symptoms. An abdominal US revealed a liver mass, and subsequent MRI examination identified it as a hemangioma, while the scanned lung base showed peripheral high T2-weighted focal areas with restricted diffusion in the left lower lobe. Consequently, the patient underwent a chest CT that confirmed presence of bilateral multiple GGOs. Di Girolamo et al[43] reported a 71-year-old woman with T4a colorectal cancer who underwent an abdominal MRI for routine follow-up of hepatic metastasis that led to the incidental detection of bilateral lower lobe GGOs in the scanned lung. Thereafter, the patient underwent RT-PCR, which confirmed that they were positive for COVID-19. MRI can help in the early recognition of cases so that a rapid treatment protocol can be established, the immediate isolation to reduce community transmission, and the organization of close monitoring. Thus, it is important to both the patient and the physician that these findings are highlighted and reported.

ASYMPTOMATIC COVID-19 PATIENTS IN ELECTIVE AND EMERGENCY SURGERIES

On April 15, 2020, the Royal College of Surgeons and Royal College of Radiologists published guidelines on the use of preoperative reverse transcription-polymerase chain reaction (RT-PCR) and chest computed tomography (CT) during the coronavirus
Thus, FDG PET-CT imaging plays a role in localizing foci of infection and pathological etiologies, including infections, inflammatory processes, and neoplasms. PET-CT imaging, which demonstrates the increased uptake across a variety of related to the use of fluorodeoxyglucose (FDG) positron emission tomography-CT within the context of following cancer patients. However, the most attractive data was the accidentally discovered COVID-19 signs in different imaging modalities performed may need to be reconsidered in certain patients treatment, especially in newly discovered cases or patients receiving their treatment as asymptomatic, isolated, and tested patients and is not recommended for screening preoperative chest CT screening does not add to the detection of COVID-19 in asymptomatic or with nonspecific symptoms, like fever, cough, dyspnea, fatigue, myalgia, and headache. Furthermore, many upper respiratory infections in children, such as influenza virus, rhinovirus, and others, present the same symptoms as COVID-19, and coinfection of SARS-CoV-2 may also occur. Thus, the surgical committee must follow established guidelines to facilitate the workflow and prevent virus transmission, and every patient should be tested by RT-PCR. However, if rapid intervention is crucial in an emergency and RT-PCR results are not available soon enough, the assessment can be based on clinical conditions and/or chest imaging findings.

The guidelines for preoperative COVID-19 testing for elective cancer surgery of 15 April, 2020, were updated on May 14, 2020, to document accumulating evidence that preoperative chest CT screening does not add to the detection of COVID-19 in asymptomatic, isolated, and tested patients and is not recommended for screening before elective cancer surgery. Thus, chest CT should only be considered for screening in preoperative planning in asymptomatic patients who are not isolated when RT-PCR test results are unavailable.

**ASYMPTOMATIC COVID-19 ONCOLOGY PATIENTS**

Oncology patients are a very special group of because of their high vulnerability to infections caused by risk factors due to their impaired immune systems, such as leukopenia, long-lasting immunosuppression (steroids, antibodies), or low immunoglobulin levels. Oncology patients infected with COVID-19 may present as asymptomatic or with nonspecific symptoms, like fever, cough, dyspnea, fatigue, myalgia, and headache. Also, because oncology patients need to continue their treatment, especially in newly discovered cases or patients receiving their treatment as chemotherapy, radiotherapy, or other forms, the benefit: risk ratio of cancer treatment may need to be reconsidered in certain patients. Some reports are describing the accidentally discovered COVID-19 signs in different imaging modalities performed within the context of following cancer patients. However, the most attractive data was related to the use of fluorodeoxyglucose (FDG) positron emission tomography-CT (PET-CT) imaging, which demonstrates the increased uptake across a variety of pathological etiologies, including infections, inflammatory processes, and neoplasms. Thus, FDG PET-CT imaging plays a role in localizing foci of infection and inflam-
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Figure 5 Axial fused thoracic 18F-Fluorodeoxyglucose-positron emission tomography-computed tomography showing multiple variable-sized metabolically active and mainly subpleural subsegmental consolidative lesions with an SUV$_{\text{max}}$ of up to 10.9 as well as metabolically active lymph node seen in the aorto-pulmonary window in a patient with thyroid cancer and asymptomatic coronavirus 2019.

Infection with COVID-19 may remain asymptomatic and appears as incidental findings in nuclear imaging procedures performed for standard oncologic indications [43,55,66]. PET-CT findings are considered sensitive for the detection of early COVID-19 infection, even before its detection as nasal viral carriage [41,55,66]. It appears in 18F-FDG PET-CT as multiple areas of GGOs showing increased FDG uptake (SUV$_{\text{max}}$ is usually around 5.5) [41,55,66]. Some theories explain the FDG activity detected in COVID-19 pulmonary lesions is the result of viral replication after the viral particles penetrate the cells. This replication starts to overwhelm the cellular structure, inciting a proinflammatory state that disrupts the infected and adjacent endothelium, leading

mation in cases of fever of unknown origin. PET-CT permits detailed evaluation of both functional and anatomical/pathological processes [58,44]. Albano et al [65] reported a case series performed in the nuclear medicine units in Northern Italy from March 16–24, 2020. This included 65 asymptomatic patients referred for PET-CT with no suspicion of COVID-19 infection. Of them, six (9%) showed 18F-FDG-avid interstitial pneumonia, suggesting COVID-19 infection. The study also included 12 patients who were admitted for whole-body 131I scintigraphy followed by single photon emission CT 3–4 d after radiiodine administration, and 1 of these patients showed peripheral GGOs, suggesting COVID-19 infection, but not an increase in radiiodine uptake. All of the patients with findings suggestive of COVID-19 infection were confirmed positive upon further workup. Mo et al [66] reported similar findings in another asymptomatic 60-year oncology patient in the United States with human papillomavirus, and Franceschi et al [67] reported a similar scenario in an asymptomatic 61-year-old patient with treated primary diffuse large B-cell lymphoma. Wakfie-Corieh et al [68] retrospectively reviewed 1079 oncologic 18F-FDG PET-CT scans performed between February 2 and May 18, 2020 to identify lung and extraparenchymal lung involvement in asymptomatic cancer patients with COVID-19. The authors concluded that FDG PET-CT-positive findings were usually limited to thoracic structures, and silent, distant involvement was infrequent. An example of PET-CT findings in COVID-19 infection is shown in Figure 5. Another retrospective review discussed the incidental findings suggestive of COVID-19 in asymptomatic cancer patients in France who underwent 18F-FDG PET-CT from January 1 to February 21, 2020, in the era before COVID-19 (n = 867 PET-CT scans) and from March 16 to April 17, 2020, in the era of socially spread COVID-19 (n = 529 PET-CT). They noticed a 1.6% increase in parenchymal lung changes during the COVID-19 era [44].
to increased FDG uptake[67].

Landete et al[28] reported some correlation between the degree of FDG uptake in pulmonary lesions and COVID-19 infection, which may be used as a predictor for the recovery time because the patients with pulmonary lesions had a higher SVU max and took longer to recover. However, a larger sample size is necessary to confirm the predictive value. Many authors did not recommend the use of PET-CT as a primary diagnostic modality for investigating cases of suspected COVID-19 in the emergency setting because PET is an expensive imaging modality associated with prolonged acquisition times and increased radiation burden in comparison with conventional CXR and chest CT[18,44,56].

Nuclear medicine has no primary role in the diagnosis of COVID-19, yet awareness of the pattern of COVID-19 in this type of patient who is either asymptomatic or in the early stage of the disease before manifestations may have great implications in the further management of oncology patients with underlying immunosuppression, either by malignancy or oncologic therapeutics, because the virus is highly contagious and PET requires a much longer time in the unit than most other investigations.

CONCLUSION

In some asymptomatic patients with coronavirus disease 2019 (COVID-19) pneumonia on different radiological tools, reverse transcription-polymerase chain reaction, the definitive test for COVID-19, may be false negative. As community transmission of the COVID-19 increases and isolation restrictions are lifted, incidental findings highly suspicious of COVID-19 pneumonia on imaging modalities of asymptomatic patients may become more common. It is crucial to be aware of such appearances and the difficulties that come with them. Radiologists must be alert to signs of COVID-19 that may become more common. It is crucial to be aware of such appearances and the difficulties that come with them. Radiologists must be alert to signs of COVID-19 infection in various imaging modalities because many asymptomatic patients present to the radiology department for other reasons and could be already infected with COVID. If it remains unrecognized, these patients can transmit COVID-19 to the community and to healthcare workers.

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