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Research Article

Asymptomatic SARS-CoV-2 infection: Incidental findings on FDG PET/CT

Ricardo Bello Martinez, Munir Ghesani, Nasrin Ghesani and Somali Gavane*

Division of Nuclear Medicine; Department of Radiology, Icahn School of Medicine at Mount Sinai; 1 Gustave L. Levy Pl, New York, NY 10029, United States

ABSTRACT

Rationale and Objectives: Identify the incidental findings of Covid-19 pneumonitis on ^{18}F-FDG PET/CT scan in asymptomatic oncologic patients. The goal was to detect clinically unsuspected Covid-19 infections to prevent community spread.

Materials and Methods: Retrospective analysis was conducted to recognize the pattern of metabolic and radiographic alterations on ^{18}F-FDG PET/CT scans in Covid-19 patients. 492 ^{18}F-FDG PET/CT scans were reviewed for pulmonary and systemic abnormalities.

Results: ^{18}F-FDG PET/CT demonstrated new lung infiltrates in 29 asymptomatic patients. 13/29 patients had Covid-19 infection confirmed by nasopharyngeal nucleic acid PCR test. The most common lung abnormality was pure ground-glass opacity (GGO) (90%) in peripheral distribution (100%), involving 1 lobe in four patients (30.8%), 2–3 lobes in four patients, and 4-5 lobes in five patients (38.4%). Mean SUVmax was 4.7 (range 1.3–13.1). Ten patients developed symptoms, mainly fever, fatigue, and dry cough, within 6.4 ± 7.8 days (range 1–24). Of the available laboratory data of 12 patients, eight developed lymphopenia, and five patients had neutrophilia. Five patients required hospitalization, and two died of complications.

Conclusion: For a given geographic region in the later stage of a pandemic, such as Covid-19, community spread of the disease is common. Therefore, it is not surprising to find it in asymptomatic being imaged for other indications. Recognition of its manifestation and effectively mounting mitigation protocols is essential to further reduce SARS-CoV-2 spread, especially to susceptible groups, predominantly the elderly and people with comorbidities.

Keywords: Severe acute respiratory syndrome coronavirus 2; SARS-CoV-2 ; PET/CT; Covid-19

RÉSUMÉ

Justification et objectifs: Identifier les constats fortuits de la pneumonie à COVID-19 sur un scan TEP/TDM au 18F-FDG chez des patients oncologiques asymptomatiques. L'objectif était de détecter des infections à COVID-19 cliniquement insoupçonnées afin de prévenir la propagation dans la communauté.

Matériel et méthodologie: Une analyse rétrospective a été menée pour reconnaître le schéma des altérations métaboliques et radiographiques sur les scans TEP/TDM au 18F-FDG chez les patients atteints de la COVID-19. 492 scans TEP/TDM au 18F-FDG ont été examinés pour détecter des anomalies pulmonaires et systémiques.

Résultats: La TEP-TDM au 18F-FDG a mis en évidence de nouveaux infiltrats pulmonaires chez 29 patients asymptomatiques. Treize patients sur 29 présentaient une infection à Covid-19 confirmée par le test PCR de l'acide nucléique nasopharyngien. L'anomalie pulmonaire la plus courante était l'opacité en verre dépoli pure (90%) en distribution périphérique (100%), impliquant 1 lobe chez quatre patients (30,8%), 2 à 3 lobes chez quatre patients et 4 à 5 lobes chez cinq patients (38,4%). Le SUVmax moyen était de 4,7 (fourchette de 1,3 à 13,1). Dix patients ont développé des symptômes, principalement de la fièvre, de la fatigue et une toux sèche, en 6,4 ± 7,8 jours (fourchette de 1 à 24). Sur les données de laboratoire disponibles concernant 12 patients, huit ont développé une lymphopénie et cinq patients ont présenté une neutrophilie. Cinq patients ont dû être hospitalisés, et deux sont morts de complications.

Conclusion: Pour une région géographique donnée au stade avancé d'une pandémie, comme la COVID-19, la propagation communautaire de la maladie est courante. Par conséquent, il n'est pas surprenant de la trouver en mode asymptomatique en étant imagée pour d'autres indications. La reconnaissance de sa manifestation et la mise en place de protocoles d'atténuation efficaces sont essentielles pour réduire davantage la propagation du SRAS-CoV-2, en particulier dans les groupes sensibles, principalement les personnes âgées et les personnes présentant des comorbidités.

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Introduction

The Covid-19 pandemic has drastically compromised many daily routines worldwide since December 2019. Over 49 million confirmed cases and more than 1,240,000 deaths have been reported worldwide [1]. The novel coronavirus SARS-CoV-2 was initially associated with a seafood market in China where live animals were sold [2]. Its transmission is primarily person to person, occurring in close contact mainly via respiratory droplets [3]. The virus uses the angiotensin-converting enzyme 2 (ACE2) as a cell receptor for cellular entry, mainly present in the human respiratory epithelium from where it can disseminate to other organs [4]; it can result in lung injury, and severe cases progress to severe respiratory distress syndrome or multi-organ failure [5].

Early-stage Covid-19 infection can be seen in chest CT as lung parenchymal ground-glass opacification (GGO) or consolidation that is likely to be bilateral and peripheral in distribution [6]. Asymptomatic or presymptomatic carriers contribute to the viral spread, and recognition of imaging findings suggestive of Covid-19 pneumonia plays a crucial role in detection and mitigation strategies, mainly when imaging is performed for SARS-CoV-2 unrelated reasons [7]. Elderly oncologic patients, who are susceptible to severe Covid-19 due to immunosuppression caused by anticancer treatment and malignancy, often have the absence of symptoms or are atypical, attributed to underlying conditions [8].

Imaging metabolic pathways with ^{18}F-FDG PET/CT in oncologic applications aid accurate diagnosis, assessing disease status, and response to treatment on serial imaging [9]. Not infrequently, whole-body PET scans detect incidental like Covid-19 pneumonia characterized with a high degree of uptake [10]. ^{18}F-FDG PET/CT plays a role in evaluating infectious and inflammatory diseases, monitoring disease progression and assessing treatment response, improving patient outcomes [11]. The discovery of new lung infiltrates on routine PET/CT suggestive of infection should raise suspicion, given the pandemic situation [12].

Despite public health plans to control the spread, the United States has more cases than any other country accounting for over 9 million confirmed cases [1]. As an international hub and its dense population, New York City became the pandemic's epicenter in early 2020 [13]. We present Covid-19 infection FDG PET/CT findings in asymptomatic oncologic patients during the disease outbreak.

Material and methods

Retrospective analysis of PET/CT scan performed between March 10, 2020, and April 20, 2020, in a multicenter urban health system during the Covid-19 outbreak. Patients with unknown Covid-19 infection with incidental findings suggestive of infection were included. Clinical and demographics data were extracted from electronic medical records. Real-time polymerase chain reaction (RT-PCR) assays of the nasopharyngeal mucosa were used for microbiologic diagnosis. ^{18}F-FDG PET/CT studies were performed on Biograph Vision system, with an axial PET FOV of 25.6 cm, continuous bed motion 1.2 mm/s, 220 x 220 matrix, using PSF and TOF corrections, and reconstructed using OSEM with 2 iterations and 21 subsets (Siemens Healthcare); and on a Biograph mCT Flow PET/CT system, with an axial PET FOV of 21.6 cm, continuous bed motion 1.1 mm/s, 200 x 200 matrix, using PSF and TOF corrections and reconstructed using OSEM with 4 iteration and 5 subsets (Siemens Healthcare). Images were acquired after a fasting period of at least 6 hours, patients' blood glucose levels were <200 mg/dL at the time of tracer injection with 4.6-4.8 MBq/Kg of ^{18}F-FDG. Delta time was 50–65 min, the low mA, non-diagnostic CT images from PET/CT were used for attenuation correction and anatomic localization. The PET data were used to calculate the maximum SUV, a semi-quantitative parameter. A region of interest (ROI) was placed over abnormal lung parenchyma consolidations and mediastinal/hilar lymph nodes. The maximal activity in the ROI was calculated as the activity over lung consolidation/lymph node relative to the normal injected activity normalized by body weight. Imaging review was performed by a nuclear medicine physician at an Encore (version 6, MIM Software) workstation. The institutional Ethics Committee approved the study, and patients' informed consent was waived (Figures 1–5).

Results

492 PET/CT scans were performed between March 10, 2020, and April 20, 2020. Twenty-nine asymptomatic patients had new lung infiltrates suspicious for an infectious/inflammatory process. 13/29 (45%) had Covid-19 infection that was diagnosed by RT-PCR subsequently. Patients' clinical and PET characteristics are summarized in (Table 1). The mean age was 65.7 ± 10.7 years (range 49–79). Ten patients developed symptoms 6.4 ± 7.8 days (range 1–24) after PET/CT study. Mean time from PET/CT to positive RT-PCR was 15.6 ± 15.4 days (range 0–50). The most frequent symptoms were fever (70%), fatigue (70%), and dry cough (50%). Chills (30%), emesis (20%), myalgias (20%), altered mental status (20%), diarrhea (10%) and sore throat (10%) presented in lower proportions. Five patients required hospitalization, and two succumbed to complications.

Nine patients had only GGO, three patients had consolidation with GGO, and one patient had consolidative changes. Bilateral lung involvement was seen in nine patients. Four patients (30.8%) had 1 lobe affected, four patients had 2–3 lobes

Abbreviations: GGO, Ground-glass opacification; ACE2, Angiotensin-converting enzyme 2; RT-PCR, Real-time polymerase chain reaction.

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* Corresponding author.
E-mail address: somali.gavane@mountsinai.org (S. Gavane).

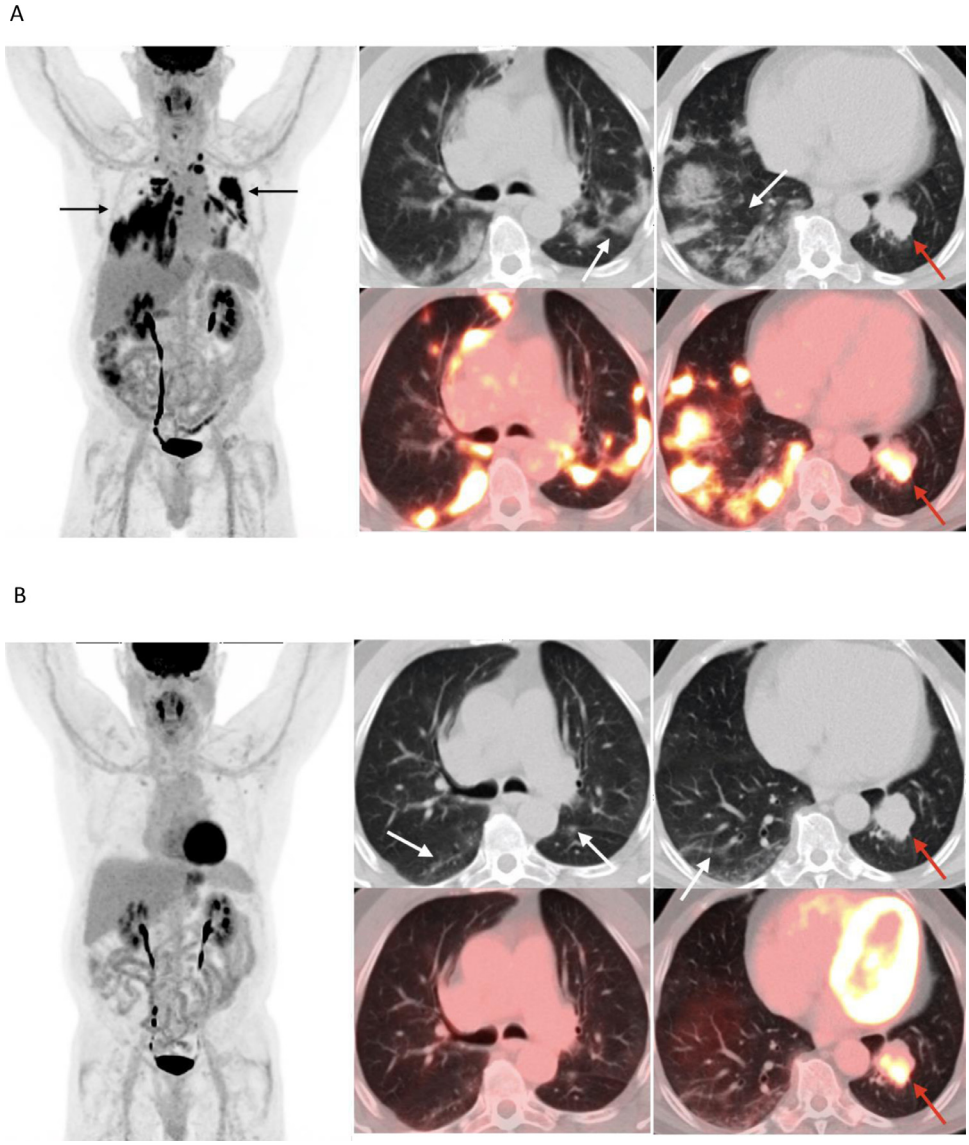

Figure 1. 70-year-old male with lung adenocarcinoma on alectinib presenting for routine PET/CT. (Panel A) MIP image shows hypermetabolic lesions in bilateral lungs (black arrows). Axial CT and fused PET images show multifocal bilateral hypermetabolic ground-glass opacities and consolidation (white arrows) consistent with Covid-19 pneumonia, as confirmed by RT-PCR. Hypermetabolic left lower lobe mass (red arrow) consistent with primary malignancy. (Panel B) PET/CT obtained two months after shows near-complete resolution of bilateral opacities with minimal residual GGO. Subpleural parenchymal bands can be seen in the right lower lobe and left fissure thickening (white arrows). Persistent hypermetabolic left lower lobe mass (red arrow).

involved, and five patients (38.4%) had 4–5 lobes. All patients had a peripheral distribution of opacities. The mean SUVmax of the opacities was 4.7 (range 1.3–13.1). FDG avid thoracic lymphadenopathy was seen in seven patients. Out of the 12 patients with labs available for review, eight patients developed lymphopenia (66.7%) and five neutrophilia (41.7%).

Discussion

Lung infiltrates on PET/CT of cancer patients may be the first sign of SARS-CoV-2 infection, as demonstrated in our series of asymptomatic patients with microbiological confirmation. Identification of typical Covid-19 pneumonia allowed prompt prevention of viral spread and close follow-up of our cohort. However, 16 patients presented with chest CT findings suggestive of infection but resulted in an alternative diagnosis due to negative RT-PCR test for SARS-CoV-2. The most common diagnostic test used for SARS-CoV-2 is the nasopharyngeal nucleic acid amplification test with high specificity but variable sensitivity to exclude infection [14]. It is essential to note the limitations of diagnostic test accuracy of the nasopharyngeal swab. First, it is unclear how different manufacturers assess their test performance under flexible regulations allowed by emergency use authorizations (EUA) of these tests granted by The Food and Drug Administration (FDA). The diagnostic test's clinical sensitivity and specificity also vary by the specimen source, quality of sampling technique, disease course timing, and illness severity. Additionally, no robust data assessing

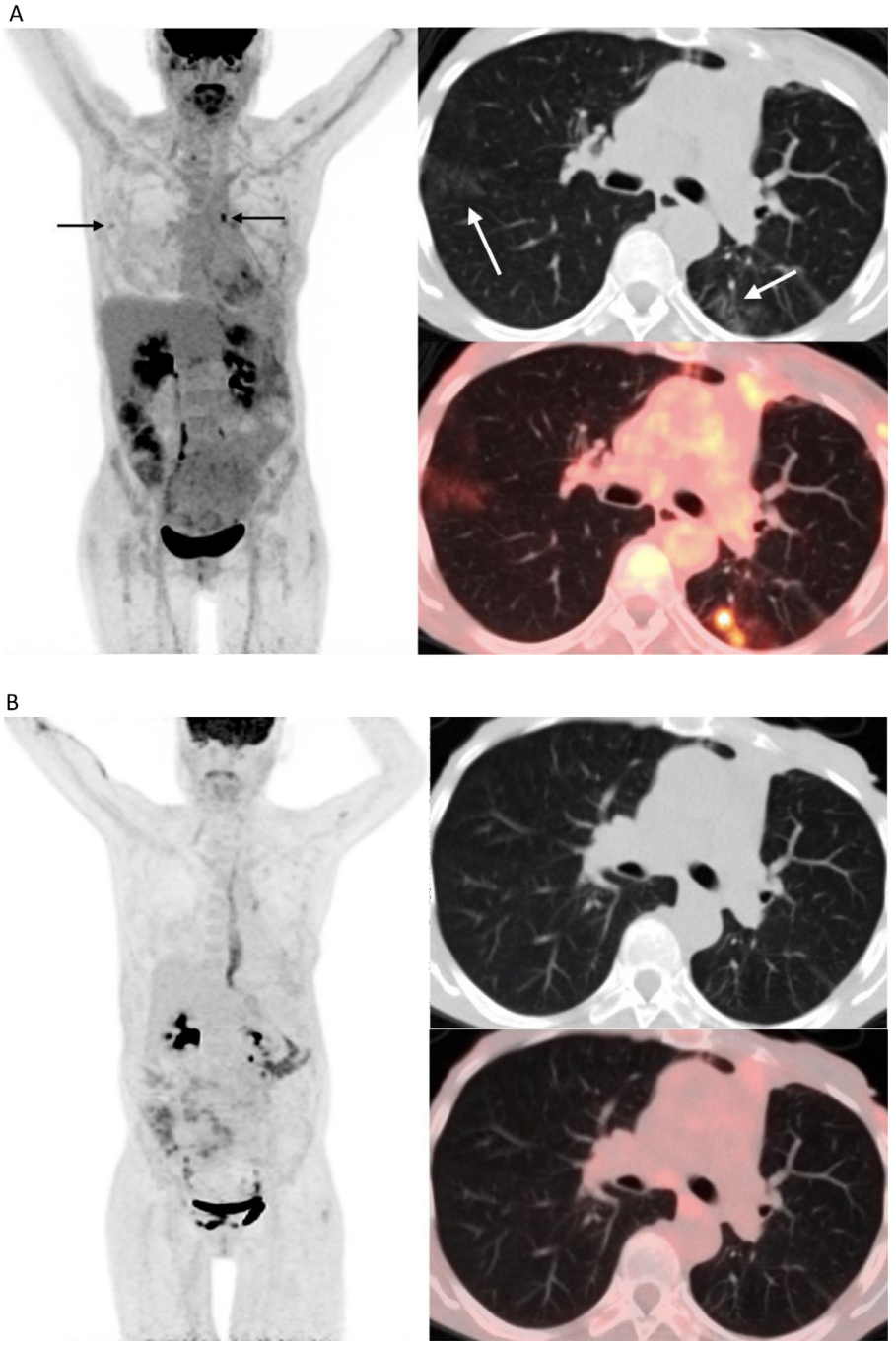

Figure 2. 67-year-old female with lung adenocarcinoma on maintenance pemetrexed and bevacizumab presenting for routine PET/CT. (Panel A) MIP image shows foci of uptake in the bilateral chest (black arrows) corresponding to hypermetabolic peripheral ground-glass opacities (white arrows) in axial images. (Panel B) Follow-up PET/CT obtained four months after demonstrating complete resolution of lung opacities.

the nasopharyngeal test sensitivity on asymptomatic infected individuals exist. Given our cohort's high pretest probability for having been located in a prevalent area, one needs a highly sensitive test to reliably deemed true-negatives; hence we might have underestimated our positive cases [15].

Nonetheless, testing allows tracking the viral spread and isolation of infected cases, estimates local prevalence, necessary in the risk-benefit assessment of safety of performing routine nonurgent radiologic care or postponing any examination given the risk of healthcare-acquired Covid-19, considering patients' demographics and comorbidities [16]. RT-PCR is also used to triage before debilitating interventions like surgery or chemoradiation that can be complicated by a severe infectious process.

Many asymptomatic carriers lack radiographic abnormalities or have a false negative RT-PCR that undermines prevention measurements based on the presence of symptoms, imaging findings, or laboratory results [17]. It is essential to adapt universal prevention strategies as masking, physical distancing,

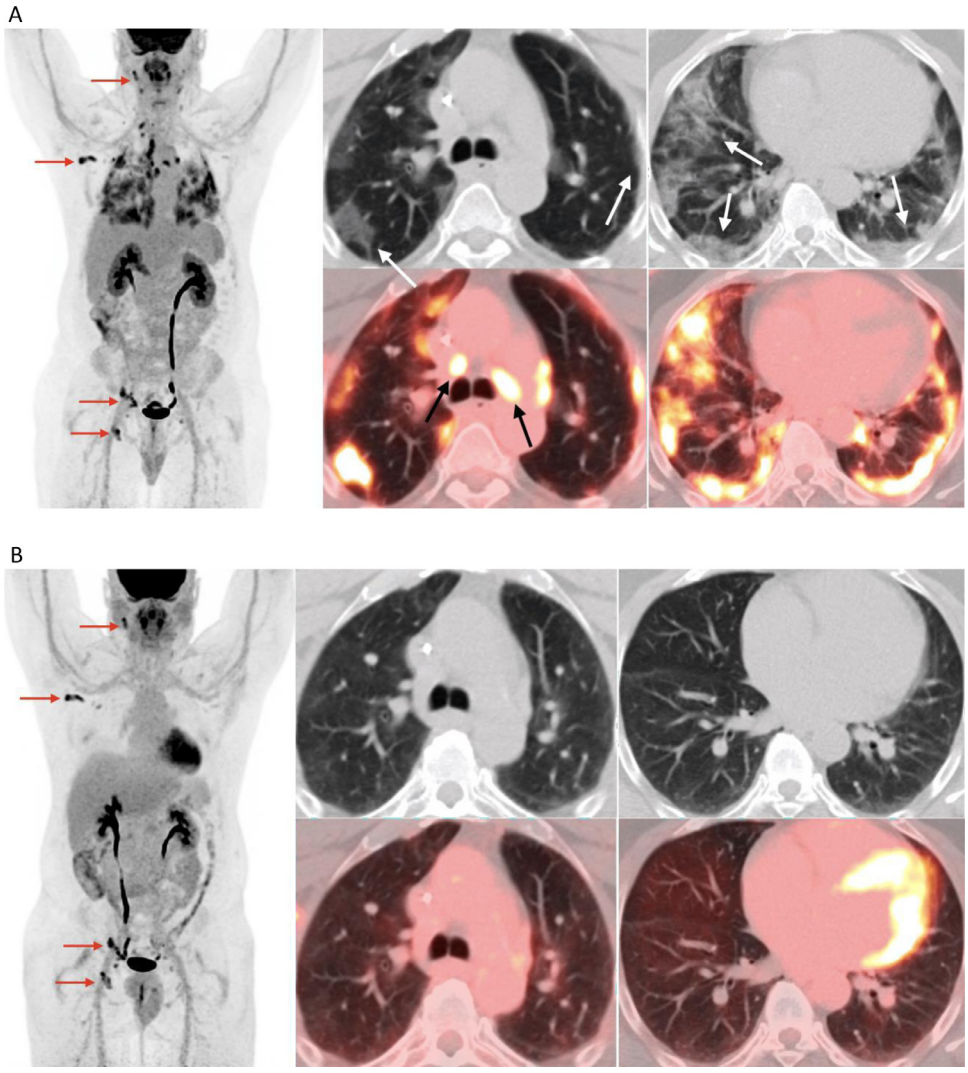

Figure 3. 56-year-old male with Hodgkin's lymphoma presents for follow-up PET/CT complaining of neck discomfort. (Panel A) MIP image shows uptake in bilateral lungs and mediastinum and bilateral neck, right axilla, right pelvis, and inguinal regions (red arrows). Axial PET/CT shows bilateral ground-glass opacities in the upper lobes and patchy consolidations in the lower lobes (white arrows) with associated mediastinal lymphadenopathy (black arrows). (Panel B) PET/CT obtained four months after shows residual ground-glass opacities and resolution of mediastinal lymphadenopathy. MIP images show persistent cervical and right axillary, pelvic, and inguinal lymphadenopathy (red arrows) related to lymphoma.

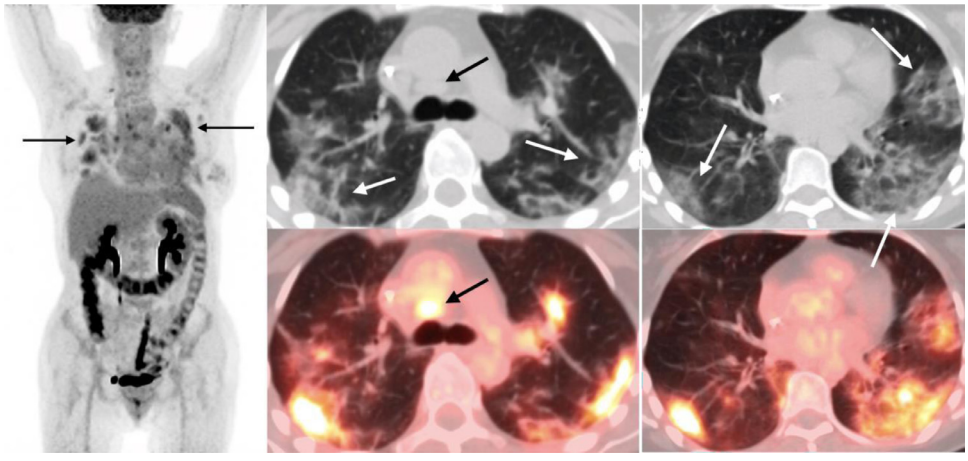

Figure 4. 54-year-old female with breast cancer on chemotherapy presents for restaging PET/CT. MIP images demonstrate hypermetabolic foci in the lungs and mediastinum (black arrows). Axial PET/CT shows bilateral confluent ground-glass opacities (white arrows) and precarinal lymph node (black arrow).

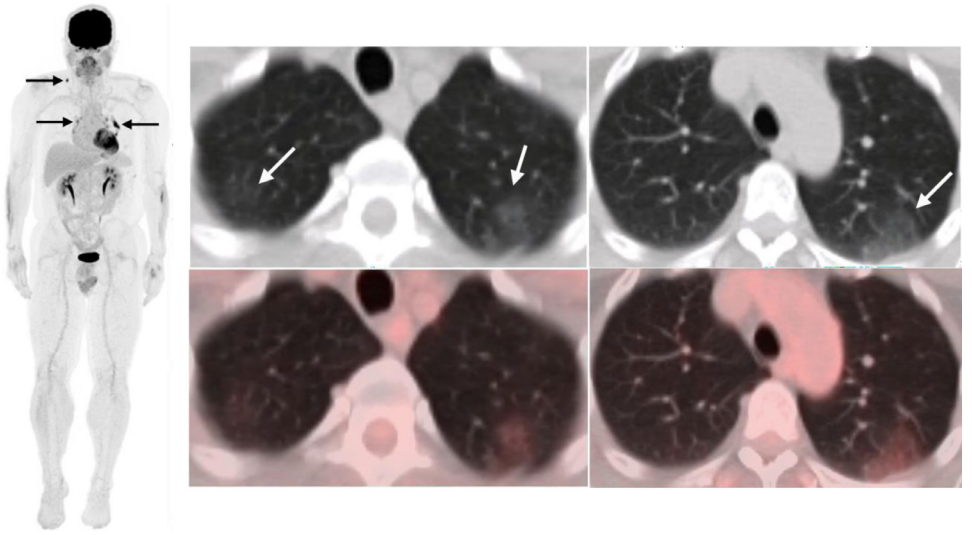

Figure 5. 54-year-old male with lacrolentiginous melanoma on nivolumab. MIP image shows metastatic left lower lobe nodule and right scapula lesion with mediastinal lymphadenopathy (black arrows). Axial PET/CT shows bilateral upper lobes lung opacities with mild uptake (white arrows). RT-PCR done resulted negative.

Table 1
Demographic data, clinical and PET/CT findings.

	Sex	Age	Primary Cancer	Symptoms	Type of lung abnormality	Nº of Lobes Affected	Lung findings SUVmax	Outcome
1	F	67	Lung	Asymptomatic	GGO	3	4.8	Recovered
2	M	78	Urothelial	Fever, Fatigue, Emesis	GGO	4	1.3	Recovered
3	M	65	DLBCL	Fever, Fatigue, Cough	GGO	1	1.9	Recovered
4	M	79	DLBCL, EBV associated	Fever, Fatigue, AMS	GGO	3	2.1	Recovered
5	F	67	Lung	Fever	GGO	2	2.4	Deceased
6	M	56	Hodgkin's Lymphoma	AMS	GGO with consolidation	5	10.0	Recovered
7	F	76	DLBCL	Fever, Fatigue, Cough	Consolidation	1	2.6	Recovered
8	F	64	Multiple myeloma	Fever, Fatigue, Cough, Myalgia	GGO	5	1.7	Deceased
9	F	79	Colon	Fatigue, Emesis	GGO	1	1.6	Recovered
10	F	50	Transformed DLBCL	Fatigue, Cough, Myalgia	GGO	2	7.9	Recovered
11	M	49	HER2+ Esophageal adenocarcinoma	Asymptomatic	GGO with consolidation	1	7.1	Recovered
12	F	54	Breast	Asymptomatic	GGO	5	4.6	Recovered
13	M	70	Lung	Fever, Cough	GGO with consolidation	5	13.1	Recovered

F=female; M=male; DLBCL=diffuse large B cell lymphoma; GGO=ground-glass opacity; AMS=altered mental status

and hand hygiene to prevent asymptomatic spread and exposure to vulnerable patients. Five of the presented cases were subsequently hospitalized, and two died, reflecting the vulnerability of elderly oncologic patients. In health care centers where exposure risks are higher, comprehensive measures as Covid-19 safety algorithms, readily available personal protective equipment, and protocols for staff and patients are the cornerstone for safe operations. Telehealth, as the remote delivery of care and tools for employees attesting their health status before each shift, should also be implemented when feasible [18,19].

The oncologic population commonly presents with benign infectious/inflammatory lung processes, often treatment-related, that nor radiographic or scintigraphy findings can differentiate from other viral or non-viral atypical types of pneumonia [20]. Imaging should be used as an adjunct to patient management [21]. FDG PET/CT is useful in assessing infectious and inflammatory cardiopulmonary processes. It allows quantification of radioactivity, providing a biomarker of the inflammatory process in vivo [22]. It is also sensitive for detecting lymph node involvement and assesses response to treatments; however, PET/CT scan currently does not have a role in the management of Covid-19. The long-time interval between PET/CT scan RT-PCR in our population can be explained by testing-supply shortage at that time

and isolated patients after PET/CT that sought medical care later.

Conclusions

Incidental findings seen on nonurgent radiologic care suggestive of Covid-19 pneumonia in asymptomatic patients should be interpreted along with clinical, laboratory, and epidemiologic information for an accurate diagnosis and preventive measures. Protocols to deliver care, minimizing the risk of exposure are of utmost importance to protect susceptible patients from Covid-19 infection and hospital staff.

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