Thieme

Nuclear medicine in SARS-CoV-2 pandemia: ^{18}F-FDG-PET/CT to visualize COVID-19

Nuklearmedizin zu Zeiten der SARS-CoV-2 Pandemie: ^{18}F-FDG-PET/CT zur Visualisierung von COVID-19

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ABSTRACT

The current outbreak of coronavirus SARS-CoV-2 has reached multiple countries worldwide. While the number of newly diagnosed cases and fatalities is rising quickly, far-reaching measures were enacted to prevent further spread. Diagnosis relies on clinical presentation, exposure history, PCR using specimens from the respiratory tract together with computed tomography (CT) imaging. One of the hallmarks of a critical course of COVID-19 is the development of severe acute respiratory distress syndrome (ARDS). As management of COVID-19 can be considered a multi-disciplinary approach involving various medical specialties, we here review the first ^{18}F-FDG-PET/CT scans of COVID-19 to discuss how Nuclear Medicine could contribute to management of this disease.

ZUSAMMENFASSUNG

Der Ausbruch des Coronavirus SARS-CoV-2 hat inzwischen viele Länder weltweit erreicht. Trotz weitreichender Maßnahmen zur Eindämmung der Ausbreitung steigen die Fallzahlen kontinuierlich weiter. Die Diagnose der durch SARS-CoV-2 hervorgerufenen COVID-19 Erkrankung erfolgt mittels Polymerasekettenreaktion aus Proben des Respirationstrakts und computertomographischer Bildgebung der Lunge. Die Erkrankung kann asymptomatisch oder mild verlaufen und sich mit Fieber oder trockenem Husten manifestieren. Eine gefürchtete schwere Verlaufsform von COVID-19 ist die Entwicklung eines ARDS (acute respiratory distress syndrome). Da insbesondere schwere Krankheitsverläufe oftmals eine multidisziplinäre Vorgehensweise erfordern, besprechen wir hier anhand einiger ^{18}F-FDG-PET/CT Fallbeispiele, welche Rolle die Nuklearmedizin bei COVID-19 einnehmen könnte.

SARS-CoV-2/COVID-19 Outbreak

In December 2019, novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) first emerged in Wuhan, China, and rapidly spread across the world, confronting us with a pandemic situation [1]. Despite the placement of far-reaching measures to limit further transmission of SARS-CoV-2, the virus continues to spread and poses a major health challenge for the entire population and putting enormous pressure on national health care systems. On January 30th, the World Health Organization (WHO) declared a Public Health Emergency of International Concern.
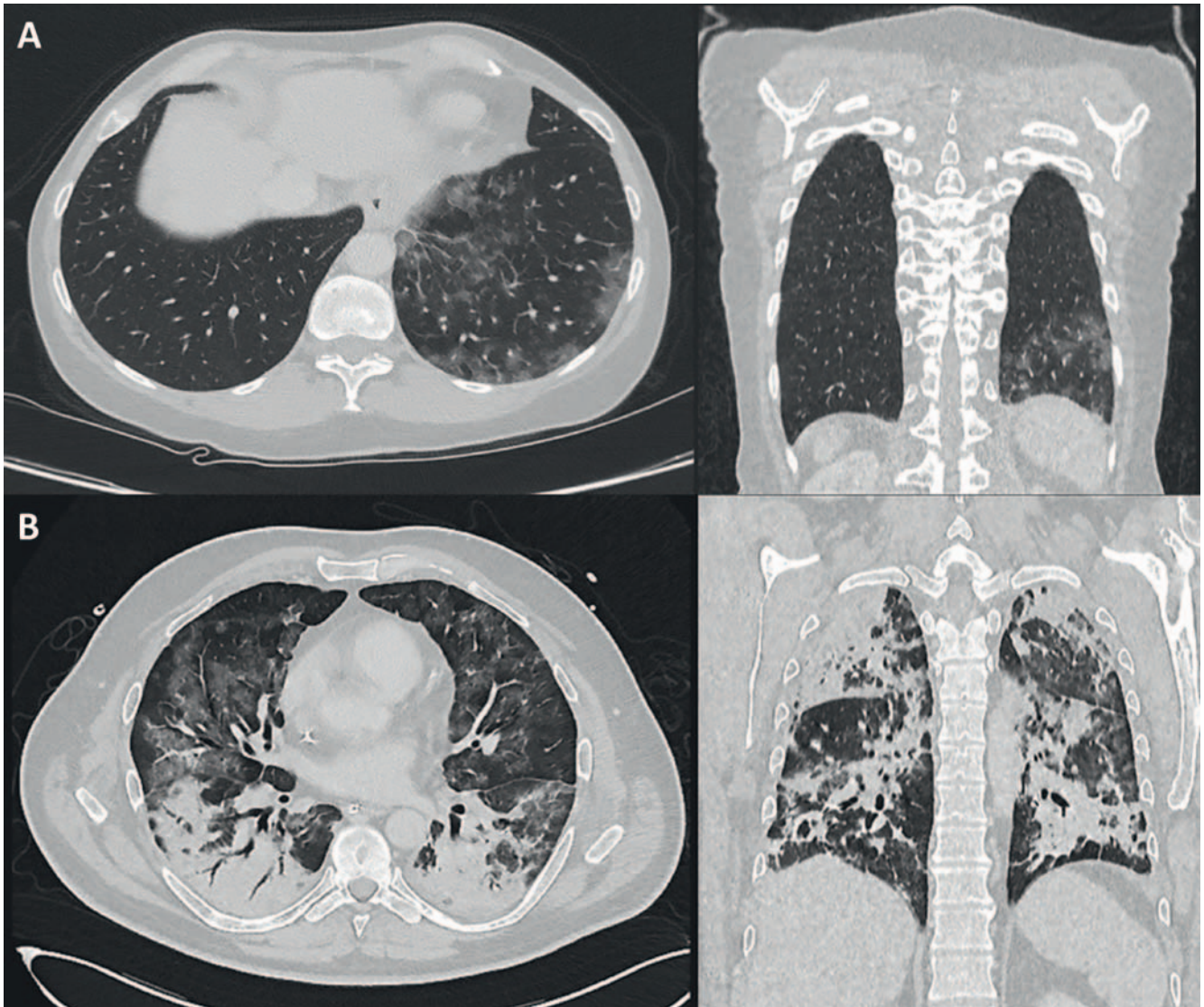
► **Fig. 1** Transversal and coronal CT images of two patients with COVID-19 pulmonary manifestations. **A** (upper panel): Incidental finding of SARS-CoV-2 infection in an asymptomatic 60-year old female patient, showing peripheral groung-glass opacities in basal segments of the right lung. PCR confirmed SARS-CoV-2 infection on molecular level. **B** (lower panel): 51-year old, SARS-CoV-2-positive, male patient with pronounced bilateral pulmonary involvement of COVID-19, hospitalized in an intensive care unit. Typical lesion spread to the center of the lungs and consolidation is present.

SARS-CoV-2 infection causes Corona Virus Disease 2019 (COVID-19), which can remain asymptomatic or lead to a large variety of clinical symptoms including fever, cough, and malaise/fatigue [2]. While the majority of patients survive the infection without complications, a considerable percentage of patients develops severe symptoms including pneumonia with dyspnea, tachypnea and disturbed gas exchange in the form of acute respiratory distress syndrome (ARDS) [2]. Some studies report that up to 5% of the infected patients becomes critically ill with severe lung dysfunction, need for ventilation, shock or extrapulmonary organ failure [3].

While infectious diseases frequently cause severe symptoms in a rather short time span of hours to a few days, the course of COVID-19 can be rather protracted leading to slow deterioration of pulmonary function. Median time from onset of symptoms to admission to an intensive care unit is 10 days [3].

Viral transmission occurs interpersonal human-to-human through droplets from respiratory and close contact. At present, polymerase chain reaction (PCR) technology is used for diagnosis of SARS-CoV-2 infection, samples are obtained from upper and lower respiratory tract. Serological antibody tests are currently under development, but not yet available for clinical application. Therefore, for now, detection of viral RNA can be considered the gold standard for diagnosis in early stages of disease. However, false-negative test results occur, when the virus spreads to the lungs and virus replication in the throat is reduced consecutively leading to different viral loads at different anatomical sites. Other reasons may be mutation rates, timing of testing, and different validation procedures across different laboratories. Therefore, diagnosis also includes exposure history and presence of clinical symptoms. In addition, especially in patients with progressive symptoms and pre-existing lung diseases, additional chest ima-

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ging may be performed, including thoracic computed tomography (CT). Typically, COVID-19 presents with ground-glass opacities (GGOs) and/or bilateral pulmonary consolidations in multiple (sub)segmental regions [2, 4]. In early stages, primary CT findings are commonly limited to peripheral GGOs and bronchovascular thickening (▶ **Fig. 1A**). Progression of the disease is typically characterized by lesion spread to the center of the lungs and consolidation (▶ **Fig. 1B**). While signs such as interlobular septal thickening and crazy paving [4–6] may also be found in COVID-19 infection, typical features found in other pulmonary infection (e. g. lymphadenopathy, pulmonary nodules, pleural effusions and lung cavitation) are commonly not been found [7]. Overall, CT findings are similar to those of viral pneumonia caused by Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV-1 [8].

So far, the role of Nuclear Medicine in managing COVID-19 is unclear. Even though management of COVID-19 can be considered a multi-disciplinary approach, involving medical specialties such as Infectious Disease, Internal Medicine, Respiratory Medicine, Intensive Care Medicine, and Radiology, the role of a specialized medical field such as Nuclear Medicine in direct management of COVID-19 seems to be rather limited at first glance.

^{18}F-FDG-PET/CT to visualize COVID-19

As imaging method, ^{18}F-FDG-PET/CT plays an important role in assessing infectious and inflammatory lung diseases, including detection of involved lung segments, estimating the extent of the lung involvement, monitoring progression and treatment responses as well as in follow-up [9].

Qin et al. recently reported a series of four ^{18}F-FDG-PET/CT scans of patients highly suspected for COVID-19 [10]. It is important to note, that in three out of these four patients, SARS-CoV-2 nucleic acid testing was not performed and in one of these patients, PCR for detection of SARS-CoV-2 was negative, which represents a major limitation of this case series. However, even though molecular confirmation of SARS-CoV-2 infection is lacking in the presented cases, the authors state that COVID-19 was diagnosed based on clinical presentation, laboratory findings and imaging characteristics. In this case series, all patients presented with peripheral GGOs and/or consolidative opacities in one or several pulmonary lobes. On ^{18}F-FDG-PET imaging, all of these lesions were reported to show high tracer uptake (SUV$_{max}$ 1.8–12.2), reflecting a significant inflammatory burden on COVID-19. In addition, in three out of four patients, FDG-positive mediastinal lymph nodes were observed.

Zou et al. recently reported a ^{18}F-FDG-PET/CT case of a PCR-confirmed COVID-19 patient [11]. FDG-uptake was observed in GGOs with areas of focal consolidation in the right lung (SUV$_{max}$ 4.9) as well as in right paratracheal and right hilar lymph nodes. Notably, indications for bone marrow involvements were seen, too. Czernin et al. recently published a ^{18}F-FDG-PET/CT scan of a 53-year old patient with a neuroendocrine tumor of the pancreas, who was referred for restaging [12]. At the time, the PET scan was performed, the patient was completely asymptomatic. On the PET scan, a new hypermetabolic region in the right upper and lower lobe (SUV$_{max}$ 5.5) was observed, which was in topographic correlation to predominantly peripheral and subpleurally located GGOs with beginning, partly round shaped consolidations. The findings were attributed to an atypical inflammation, later, COVID-19 infection was confirmed.

Discussion

Even though reports of nuclear medicine diagnostics performed in COVID-19 patients are sparse, the first available case reports indicate usefulness of ^{18}F-FDG-PET/CT to visualize inflamed/infected lung areas in COVID-19. Das and colleagues report a patient with MERS-CoV infection who developed pneumonia with severe radiographic deterioration pattern, showing multiple FDG-avid areas on ^{18}F-FDG-PET/CT corresponding with nodules and cavities [13]. Chefer et al. visualized the immune response to MERS-CoV 5 days after viral challenge with ^{18}F-FDG-PET/CT in a nonhuman primate model, showing FDG-avid mediastinal and axillary lymph nodes [14]. Interestingly, no changes on CT imaging or body temperature, body weight, and blood glucose concentrations were observed after viral exposure. However, FDG-uptake in lymph nodes at day 5 after viral exposure was accompanied by a slight increase (within the normal range) in circulating monocytes. As monocytes play an important role in the immune response to viral infections, the reported correlation between FDG-uptake in lung-draining lymph nodes and monocyte count is not surprising. In that respect, it would be interesting to assess the composition of the pulmonary manifestations of COVID-19 with immune PET imaging to characterize, which immune cell subsets are involved. Wilks et al. recently performed PET imaging using ^{89}Zr-labebed Feraheme, an FDA-approved iron oxide nanoparticle, in non-human primates to visualize resident macrophages and monocyte trafficking [15]. They report, that areas of acute inflammation and their draining lymph nodes could be visualized clearly up to 14 days post injection.

In line with the findings presented by Chefer et al. are the results of Wallace and colleagues, who performed ^{18}F-FDG-PET/CT imaging of activated lymphoid tissues during simian-human immunodeficiency virus infection in rhesus macaques and report that FDG-uptake in lymph nodes can preceed fulminant viral replication [16]. Chefer et al. also conclude, that ^{18}F-FDG-PET is able to detect even subtle changes in host immune response to contain a subclinical MERS-CoV infection. For COVID-19 management, these observations could suggest that ^{18}F-FDG-PET/CT imaging might play a role in early stages of the disease, when clinical symptoms are unspecific and differential diagnosis is challenging. With increasing number of infected people, nuclear medicine physicians may also be confronted with PET and CT signs of COVID-19 as incidental findings in patients referred for other clinical questions, especially as findings can occur in completely asymptomatic patients as shown in ▶ **Fig. 1A** or as reported by Czernin et al. [12]. Therefore, it is important to be alerted and report these signs to the referring physicians.

Another potential application of ^{18}F-FDG-PET/CT in COVID-19 could be the monitoring of treatment response and help in predicting the recovery time. The data provided by Qin et al. suggest a trend that higher FDG-uptake in the SARS-CoV-2 induced pul-

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monary lesions may be correlated with longer healing times as one patient with a SUV$_{max}$ of 4.6 recovers approximately 17 days after onset of symptoms, while another patient with a SUV$_{max}$ of 12.2 recovers more than 26 days after appearance of first symptoms [10]. The patient described by Zou et al. has a SUV$_{max}$ of 4.9 in a pulmonary lesion and recovered 15 days after first symptoms occurred [11]. However, these obviously are just case observations, which need to be properly characterized in larger patient cohorts before conclusions can be drawn. To evaluate the potential predictive capability of PET for outcome, quantitative parameters could be correlated with time on ventilation or death.

In addition, ^{18}F-FDG-PET/CT imaging may also be of value to evaluate changes in FDG-uptake pattern elsewhere in the patient's body. It is known that, as COVID-19 progresses, damage to other organs such as the gastrointestinal tract, heart, kidneys or bone marrow can occur [17]. Interestingly, Chefer et al. observed increased FDG-uptake in the bone marrow after MERS-CoV challenge [14] and Zou et al. report bone marrow uptake in one COVID-19 patient [11]. Potentially, PET could be used in COVID-19 as a whole-body non-invasive readout to assess chronical and concomitant organ damage. For instance, after myocardial infarction, concomitant heart-brain inflammation could be observed using ^{18}F-GE180, targeting the mitochondrial translocator protein (TSPO) [18]. If COVID-19 also causes substantial harm in other organs in a chronic setting, PET may be able to analyze these organs as well.

Apart from the few ^{18}F-FDG-PET/CT images of COVID-19 patients published so far, which do suggest a certain correlation between morphologic findings on CT and FDG-uptake, no larger data sets to answer this question are available, yet. It would be interesting to evaluate, whether FDG-uptake increases as the disease progresses and as centralization of lesions on CT occurs. Bellani and colleagues assessed the magnitude and regional distribution of inflammatory metabolic activity in the lungs of patients with ARDS using ^{18}F-FDG-PET/CT [19]. In 7 out of 10 examined patients, highest FDG-uptake was observed in the pulmonary areas with the highest density. Three patients however showed higher FDG uptake in poorly aerated regions as compared to non-aerated regions, suggesting that aerated regions may be considerably infiltrated with inflammatory cells.

In 2008, Rodrigues et al. published a small case series of eight patients after thoracic trauma and pulmonary contusion to evaluate whether FDG-uptake predicts the development of ARDS. 50 % of these patients developed ARDS 1–3 days after PET was performed [20]. Three of the four subjects who developed ARDS showed diffuse FDG uptake throughout the entire lungs, while those who did not develop ARDS showed significant FDG uptake only in areas of focal lung opacity (non or poorly aerated lung units) on CT. As successful management of ARDS often requires quick treatment adjustments, ^{18}F-FDG-PET/CT might be of value in helping predict whether/when the disease progresses to ARDS, allowing clinicians to adapt/intensify treatments in a timely manner.

Conclusion

Taken together, although ^{18}F-FDG PET/CT may not be routinely used in COVID-19 management, especially not in an emergency setting, first data indicate that this imaging modality could play a complementary role in COVID-19 management. ^{18}F-FDG PET/CT may reflect changes in FDG-avidity in pulmonary lesions as well as in other organs during the course of COVID-19, potentially clarifying differential diagnosis, estimating the extent of organ involvement and characterizing treatment response during follow-up. However, the findings so far should be evaluated systematically in larger patient cohorts to allow reliable conclusions.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

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