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Imaging of Hematological Patients in the Era of COVID-19

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Abstract
The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in changes in management and imaging routines for patients with hematological malignancies. Treating physicians had to familiarize themselves with a new disease, with distinct imaging manifestations, sometimes overlapping with other infections prevalent in this patient population. In some aspects, infected hematological patients might exhibit a different disease course, and routine imaging in asymptomatic hematological patients may result in unexpected COVID-19 findings, implying covert infection, that should be further explored. Furthermore, some complications of hematological diseases and treatments may present with findings similar to COVID-19 manifestations, and treating physicians must consider both possibilities in the differential diagnosis. In this review, we aimed to present the influence the COVID-19 pandemic had on hematological malignancy imaging.

Introduction

COVID-19, which was declared a world pandemic by the World Health Organization in the beginning of March 2020, has transformed the lives of millions of people, with repercussions on patients and their caretakers. For patients with hematological diseases, lockdown changed management and imaging routines. Fear of contracting the disease and lockdown orders discouraged some people from unnecessary medical encounters, at least at the initial stages [1, 2]. Caretakers had to familiarize themselves with the characteristics of a new disease, and differential diagnosis for symptoms and imaging findings had to be expanded to include COVID-19 manifestations.

This review will describe common imaging findings of COVID-19 infection (mainly partaining to the alfa and delta variants), clinical COVID-19 presentations specific to hematological patients, and COVID-19-related imaging findings, which mimic typical findings and complications in hematological patients. We also present typical imaging findings after mRNA-based COVID-19 vaccination, which may mimic findings usually more typical for hematological malignancies.

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Main Imaging Findings in COVID-19 Pneumonia

The majority of COVID-19 manifestations are related to the respiratory tract. Chest X-ray could be a triage tool in symptomatic patients [3] with suspected COVID-19 infection, showing multilobular, pulmonary ground-glass opacities (GGOs), and consolidations, especially in bilateral and peripheral lower lobe distribution, consistent with pneumonia [4]. However, these findings are in no way specific for COVID-19, and there is an overlap with other diseases, some common in hematological patients, including other viral infections (including influenza and others); bacterial infections (including atypical pathogens, such as *Mycoplasma pneumoniae*); fungal infections (mainly Pneumocystis jiroveci [PJP]); and other noninfectious diseases [5–7]. In most hospitals, dedicated chest X-ray rooms were used to image suspected COVID-19 patients, with protection measures for the attending stuff. Although it is a powerful, cheap, and available imaging modality, about 30% of COVID-19 patients requiring admission and 20% of hospitalized patients had normal chest X-rays [8].

Chest computed tomography (CT) is more sensitive in detecting the typical COVID-19 pulmonary findings, especially GGOs and reticular infiltrates. Although chest CT was found to be positive in some patients with negative real-time reverse transcription-polymerase chain reaction (RT-PCR), it is not advised as a first-line screening tool in the diagnosis of COVID-19, but reserved for assessment of complications in symptomatic, hospitalized patients, such as patients with suspected pulmonary embolism [3].

Chest CT findings are typically chronologically related to symptom's onset. These include small, subpleural, unilateral, or bilateral GGOs in the lower lobes (peaking on days 12–17 from the patient's symptom onset), turning into a "crazy paving" pattern, which eventually transforms into pulmonary consolidations. These findings typically subside, leaving subpleural parenchymal bands, and finally resolve, usually within 2–3 weeks [9, 10].

Protracted COVID-19 Pneumonia in B Cell-Depleted Patients

B cell-depleted patients may be protected from COVID-19-associated cytokine storm. However, they may have difficulties in viral clearance leading to a protracted pneumonia [11, 12]. Some COVID-19 patients receiving anti-CD20 treatment were described as showing a prolonged course of COVID-19-associated recurring-remitting pneumonia, apparent also on chest imaging 3 [11], 6 [13], and even 12 months [14] after initial COVID-19 symptoms. This was not described in immunocompetent patients, as the acute phase of COVID-19 usually subsides within a few days or weeks after symptoms begin [15, 16]. In our hospital, we encountered a case of a 78-year-old patient, who contracted COVID-19 infection 4 months after cessation of bendamustine-rituximab treatment for splenic marginal zone lymphoma, with repeat hospitalizations due to relapsing, migrating pneumonia, confirmed by CT and positron emission tomography (PET)-CT scans (shown in Fig. 1), lasting 7 months after initial COVID-19 diagnosis.

Challenges in Imaging Patients with Hematological Malignancies during the COVID-19 Pandemic

Patients with hematological malignancies are frequent visitors to the radiology and nuclear medicine departments, as most patients with aggressive lymphomas are staged, evaluated for response, and followed up by PET-CT [17], with frequent visits, as often as every 2 to 3 months during active treatment. Indolent lymphoma patients are usually evaluated by CT, but can also be referred to PET-CT when transformation to aggressive disease is suspected. Some patients with multiple myeloma are staged or followed up by CT, magnetic resonance imaging (MRI), or PET-CT, as well as some leukemia patients assessed for extramedullary diseases [18]. Moreover, these patients can be referred for imaging when complications are suspected. Since these visits are deemed critical for patient management, they were not rescheduled during COVID-19 outbreaks. As a result, some asymptomatic patients were diagnosed with COVID-19 following routine imaging.

PET-CT Unit Performance during Lockdown

Most guidelines for performing PET-CT during the pandemic stated that 18-fluorodeoxyglucose (FDG) PET-CT for staging or therapy response assessment should not be postponed in patients without known active COVID-19 infection [19]. In fact, the workload in nuclear medicine departments was less affected by the initial worldwide lockdown (between March and May 2020) than other imaging modalities, with rebound resurgence in scan numbers in the following months [20]. A study conducted in 7 US medical centers found that PET-CT specifically was consistently the least impacted imaging

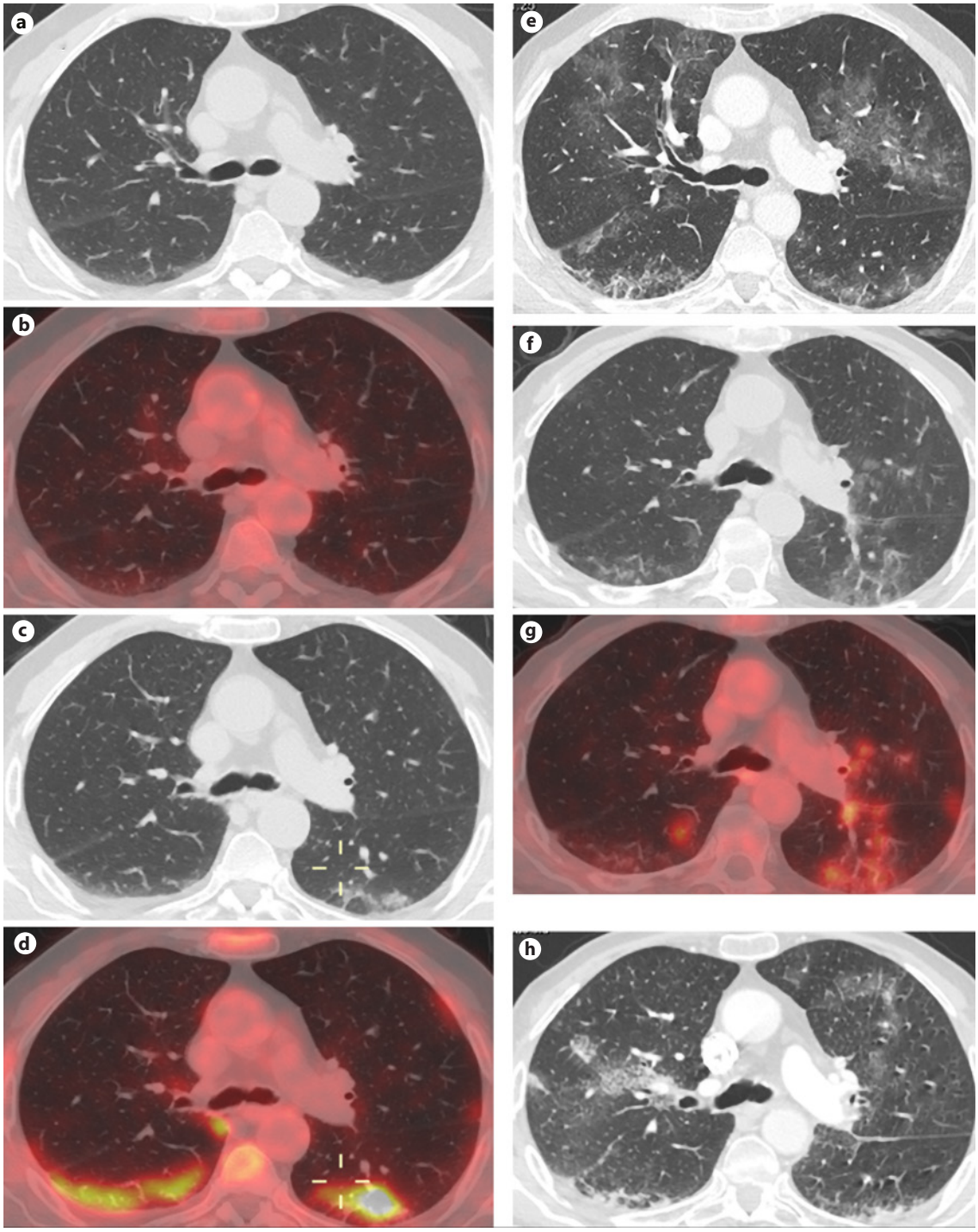

Fig. 1. A 78-year-old patient, who contracted COVID-19 4 months after BR treatment cessation for follicular lymphoma. Relapsing remitting episodes of fever and pneumonia, tests negative for other pathogens. **a**, **b** Before COVID-19 infection. No pulmonary findings. **c**, **d** One week after symptoms onset. High FDG uptake in lower lobes peripheral pulmonary infiltrates. **e** One month after primary COVID infection. Recurring, migrating GGOs. **f**, **g** Three months after primary infection. Mild FDG uptake in peripheral lower lobes reticular infiltrates. **h** Seven months after primary COVID infection. New GGOs in upper lobes and subpleural reticular infiltrates in lower lobes. BR, bendamustin-rituximab.

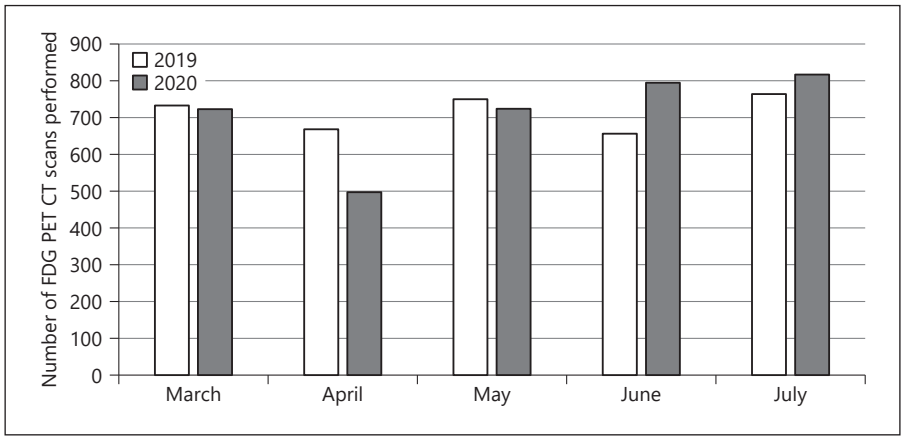

Fig. 2. Matched FDG-PET-CT scan number between lockdown and comparable period the prior year in a single tertiary hospital. While a small drop in scan numbers was noted in the first two lockdown months in 2020, there was a rebound effect in the following months.

modality, with a drop of 16% in patient output, more pronounced in centers located at pandemic outbreak locations [21]. In our tertiary hospital, there was no change in number of FDG-PET-CT performed at the beginning of lockdown in March 2020, a minimal reduction in April compared to the previous year, and a later rebound in June and July 2020 (shown in Fig. 2). There was no effective change in annual scan numbers.

Incidental COVID-19 Diagnosis in Asymptomatic Patients Performing PET-CT

PET-CT in not the optimal first-line imaging modality used in COVID-19 patients, due to its high radiation exposure, lower availability, long acquisition time (raising the risk of disease spread) [22], and high cost. Unlike X-ray or CT suites, which could be dedicated to biohazard patients, most facilities cannot afford to dedicate a PET-CT scanner solely for COVID-19 patients, and the room and equipment must be decontaminated after scanning a known COVID-19 patient [23, 24].

However, asymptomatic patients with hematological malignancies undergoing frequent and routine PET-CT, may exhibit pulmonary findings consistent with previously unknown COVID-19 infection. Such findings can also be spotted in known, convalescing patients, usually lasting up to 2 weeks after symptoms onset. These findings usually include characteristic multiple peripheral GGOs with high uptake of the radioactive glucose analogue FDG [25], portraying anaerobic glycolysis taking place in neutrophils [26]. Higher maximal standard uptake values were noted at earlier stages of COVID-19 pneumonia infiltrates [27], with complete resolution of pulmonary findings and uptake within 4 weeks of symptom onset [28].

Reactive mediastinal and supraclavicular lymph node uptake was frequently detected in active COVID-19 patients [25, 28–32], occurring in normal-sized lymph nodes, which may therefore be left unnoted on regular chest CT scans [33]. Other nonpulmonary COVID-19 FDG-PET-CT findings include reduced metabolic activity in the frontal cortex of the brain (consistent with anosmia symptoms) [34] and increase in FDG uptake in the parotid/salivary glands [35].

COVID-19 Imaging Mimickers of Common Hematological Findings

Some imaging findings in active COVID-19 patients, convalescing COVID-19 patients, and subjects receiving anti-COVID-19 vaccinations, resemble imaging findings usually encountered in hematological patients. Recognizing them in these patients with known COVID-19 or in times of outbreak could broaden the differential diagnosis and reduce imaging misinterpretation.

As the sensitivity of chest CT may be greater than that of RT-PCR in diagnosing early COVID-19 (98% vs. 71%, respectively) [36], a suspicious CT scan with negative RT-PCR does not exclude COVID-19 infection, rendering the differentiation more difficult. It should be noted that COVID-19 pneumonia often has the same features on chest CT in immunosuppressed and nonimmunosuppressed patients [37].

Drug Toxicity Associated Pneumonitis versus COVID-19 Pneumonia

Bilateral, multifocal, peripheral, and patchy GGOs, with mild FDG uptake, which are typical pulmonary find-

ings in COVID-19 patients, are also typical findings in pulmonary drug toxicities, and the differentiation is difficult in hematological patients receiving chemotherapy or anti-CD20 medications in times of COVID-19 outbreaks. Karasu et al. [38] described 2 patients with drug-related pulmonary infiltrates resembling COVID-19 pneumonia, with resolution of findings after drug withdrawal and steroid treatment. Dai et al. [39] described a patient with dyspnea and pneumonitis while treated with anti-PD-1 therapy, with persistently negative RT-PCR and good response to steroids and antibiotics.

However, patients presenting with fever, conjunctivitis, or gastrointestinal symptoms accompanying the pulmonary infiltrates are more likely to suffer from COVID-19 and not drug toxicity [40]. Headaches and sore throat, which are typical in COVID-19 infection, are possibly additional partitioning symptoms.

Atypical Pneumonia versus COVID-19 Pneumonia

COVID-19-related lymphopenia, prolonged intensive care hospitalization, and steroid treatment can render COVID-19 patients more prone to atypical, opportunistic infections, which are usually commonly seen only in immunocompromised patient.

Differentiating between pulmonary findings in COVID-19 and other entities common in hemato-oncological patients, such as aspiration pneumonia, tuberculosis, nocardiosis, and pulmonary Langerhans cell histiocytosis is beyond the scope of this review, but has been discussed elsewhere [41]. Interestingly, Giannakis et al. [42] found that thoracic radiologists were able to differentiate COVID-19 pneumonia from atypical pneumonias (influenza virus, parainfluenza virus, respiratory syncytial virus, cytomegalovirus, herpes simplex virus type 1, *M. pneumoniae*, *Legionella pneumophila*, and PJP) on chest CT scans with high overall accuracy (88%) and specificity (90%), but somewhat lower sensitivity (79%), especially in the non GGOs stages (probably because GGOs are also commonly encountered in PJP, herpes simplex virus type 1, and cytomegalovirus).

Increased Bone Marrow and Spleen Uptake

A pitfall in active COVID-19 infection includes diffusely increased bone marrow and spleen FDG uptake, which could mimic or obscure bone marrow involvement in hematological diseases [28, 32]. Interestingly, the spleen was also found to increase in size in the week following COVID-19 onset. Tahtbasi et al. [43] compared splenic indexes and splenic volume at COVID-19 infection presentation and in the following week, in 160 clinically deteriorating COVID-19 patients and found increase in spleen size, correlating with COVID-19 pneumonia severity. Both these findings may overlap disease relapse in patients with hematological malignancies and should be taken into account in the presence of PET-CT scan during active COVID-19.

Several case reports described splenic infarction incidentally detected on CT of nonhematological COVID-19 patients, probably related to their prothrombotic state [44–46]. In 1 study, 3 out of 209 critical care COVID-19 patients exhibited splenic infarct on imaging [47]. However, the incidence of this finding in noncritical care patients is unknown. As hematological patients with splenomegaly, splenic involvement, sickle cell traits, [48] or prothrombotic states are prone to splenic infarctions, this pitfall should also be recognized.

Other COVID-19 Complications Mimicking Hematological Complications

COVID-19-associated mucormycosis [49, 50] was also described as a rare complication of critically ill COVID-19 patients, especially in India. Maini et al. [51] reported a case of mucormycosis established by MRI in a recovering COVID-19 patient with chemosis and left ocular pain. In addition, COVID-19-associated pulmonary aspergillosis has been described in an incidence ranging between 3 and 20% among critically ill COVID-19 patients, mainly immunocompetent [52]. Of course, similar infections are seen in patients with hematological malignancies, and such an overlap should be taken into account when encountering these patients. Typhlitis, a life-threatening necrotizing enterocolitis usually described in neutropenic patient, was also described in a patient without prior hematological malignancy with COVID-19-associated pancytopenia [53].

Vaccination-Associated Lymphadenopathy

With the widespread emergence of the novel mRNA vaccinations, multiple vaccinated subjects presented with enlarged and sometimes painful lymph nodes in the vaccinated arm draining basin [54], which posed a diagnostic dilemma, especially in woman with known or suspected breast cancer, in melanoma patients of the thorax, head, and neck or arms, and in hemato-oncological diseases involving lymph nodes. Although FDG avid lymphadenopathy secondary to vaccinations has been described in 5–29% of patients after influenza vaccination [55, 56], it usually exhibited only mild FDG uptake and lasted for no more than 14–49 days [56, 57].

In the case of mRNA vaccinations against COVID-19, these seem to trigger a more extensive regional immune

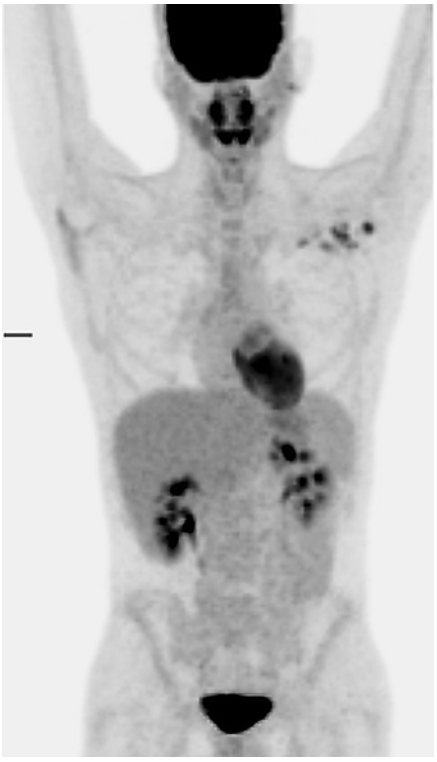

Fig. 3. A 21-year-old patient, follow-up scan 2 years after treatment for follicular lymphoma. Scan performed 4 days after left arm mRNA vaccination for COVID-19, showing avid left axillary lymphadenopathy. Under observation, the lymphadenopathy resolved.

response than reported for the influenza vaccine. Among vaccinated people, 14–66% of patients undergoing FDG-PET-CT after anti-COVID-19 vaccination had avid axillary lymphadenopathy ipsilateral to the injection site [58–61], as shown in Figure 3, with higher FDG uptake, and a prolonged response, reported to last even 10 weeks after the injection [62].

Knowledge of recent vaccination history can limit the rate of misdiagnosing these lymph nodes as pathological. Clinical and imaging follow-up will show resolution of lymphadenopathy. In highly controversial cases, a biopsy can be performed. Of note, immunosuppressed and hematological patients were significantly less prone to increased axillary lymph node uptake than the rest of the population [60].

Vaccine-Induced Immune Thrombotic Thrombocytopenia

A rare complication of COVID-19 vaccines, namely those applying the adenovirus-vector technique (e.g., AstraZeneca's and Johnson & Johnson's COVID-19 vaccines), is vaccine-induced thrombotic thrombocytopenia (VITT), which was identified within 6 weeks of the vaccines' initial rollout [63]. VITT is characterized by thrombotic events occurring in various sites, including cerebral sinus vein thrombosis [64], pulmonary embolism, leg deep-vein thrombosis, and other less common sites (e.g., portal vein, splenic vein, and others). These usually present within 5–30 days after being vaccinated with an adenoviral-vectored COVID-19 vaccine and are more common in younger and female vaccine recipients. VITT's pathophysiology is not yet completely clear but has been suggested to be related to antigenic complexed formed between vaccine components and platelet factor 4, therefore creating an anti-platelet factor 4 response [65]. Laboratory findings in classic VITT can include thrombocytopenia, elevated D-dimer levels, and decreased fibrinogen levels. When a thrombotic event is suspected in a patient who was recently vaccinated with one of the culprit vaccines, urgent targeted imaging is advised. Imaging options include compression ultrasound for suspected deep-vein thrombosis, pulmonary artery CT for suspected pulmonary embolism, and CT or MRI venography for any other site of suspected thrombosis.

Conclusion

The COVID-19 pandemic poses new challenges for patients with hematological malignancies and their treating physicians. With gained experience, having overcome the initial pandemic waves, we should be familiar with the typical imaging findings of COVID-19, diagnose previously unsuspected COVID-19 infections, recognize typical incidental imaging findings and acknowledge that some of the complications, previously more specific to hematological patients, can also represent COVID-19 (or COVID-19 vaccination) manifestations.

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Statement of Ethics

The patient in Figure 1 was part of a study reviewed and approved by the Sheba Medical Center Institutional Review Board, approval number 8176-21-SMC, informed consent was waived.

The patient in Figure 3 was part of a study reviewed and approved by the Sheba Medical Center Institutional Review Board, approval number 8802-21-SMC, informed consent was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: Y.E. and N.T. Clinical data collection: Y.E. and A.A. Script preparation and revisions: Y.E., N.T., M.K., and A.A.

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