

Pathogenesis of Imaging in COVID-19 (Narrative Review)

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ABSTRACT

The novel coronavirus disease (COVID-19), which was accepted as a pandemic by the World Health Organization (WHO) in 2020, has affected millions of people all over the world and caused deaths. Examining the pathophysiology of radiological lesions is perhaps the key in understanding this endless disease for which early diagnosis is crucial due to its high contagiousness. Considering that individuals with mild or even asymptomatic COVID-19 can significantly increase the transmission in the society, early diagnosis is crucial in the fight against the pandemic. Although RT-PCR is the first method of choice for diagnosis, when the studies are reviewed, imaging methods that provide faster results in diagnosis come to the fore, especially in clinically severe cases, since RT-PCR and lung imaging do not have a clear advantage over each other and even they help in diagnosis. At this point, understanding the pathogenesis of these pathological formations detected on imaging may play a key role in this broad disease. In this article, the background pathophysiology of radiological imaging, which is important to us, clinicians, has been discussed in the light of the current literature review.

INTRODUCTION

The novel coronavirus disease (COVID-19), which first emerged in Wuhan, China in December 2019 and affected the whole world, has been accepted as a pandemic by the World Health Organization (WHO) as of March 2020.^[1] Being highly contagious, COVID-19 causes severe pneumonia that can result in death but may also present with many nonspecific findings such as fever, cough, headache, and malaise.^[2] The standard diagnostic method for COVID-19 is to examine the oropharyngeal swab by reverse transcriptase-polymerase chain reaction (RT-PCR). However, the time required for the RT-PCR test to yield results may delay the diagnosis. In addition, unfortunately, this test may give false negative results in the initial stag-

es of the disease.^[3,4] In the diagnosis of COVID-19 pneumonia, where the symptoms and signs are so nonspecific, the characteristics of specific radiological findings are becoming more and more important every day. Therefore, radiological findings and delineating the pathophysiology underlying these findings may shed light on this dark path for accurate and early diagnosis. Radiological imaging is critical for clinicians in evaluating the diagnosis, severity, and progression of COVID-19. In this article, we examine the pathophysiology underlying the radiological imaging findings frequently detected in COVID-19 from the point of view of the clinician.

Pathophysiology of Lung Injury in COVID-19

Like the MERS and SARS coronaviruses, the SARS-CoV-2

virus binds to the angiotensin-converting enzyme-2 (ACE-2) receptor of the virus spike protein, allowing it to enter the cell. These receptors are usually found in alveolar cells of the lung tissue, underlying the development of respiratory symptoms as the most common manifestation of COVID-19.^[5]

SARS-CoV-2 interacts with any host cell by attaching the viral envelope protein to ACE-2. ACE-2 is profusely expressed in the nose, airways, lung, intestinal epithelium, and cardiovascular cells. In its initial stages, the virus infects the nasal cells and produces a mild inflammatory reaction. The virus then spreads to the respiratory tract when the host's immune response is stronger and the disease becomes clinically apparent.^[6] The disease progression to severe pulmonary damage and acute respiratory distress syndrome (ARDS) is thought to be due to factors that are not clearly understood but include the components of cytotoxicity and lymphopenia, followed by an augmented inflammatory response.^[7,8] Thus, amplified expression of inflammatory indicators such as D-dimer, ferritin and interleukin (IL)-6 has been associated with a poor clinical prognosis.^[9,10]

The clearest explanation to date of the early pathological characteristics of the disease has been reported from two cases in Wuhan, where the incidental infection was recorded in surgical specimens of lung tumors proven to be adenocarcinoma.^[11] One of these patients was an 84-year-old asymptomatic woman who underwent a right middle lobectomy for a lung nodule with ground-glass opacity (GGO) of unknown cause in preoperative imaging. The patient became symptomatic after the surgery and tested/positive for the SARS-CoV-2 virus. Another case was a 73-year-old male patient who underwent a right lower lobectomy for a lung nodule. Peripheral GGO was detected in lung computed tomography (CT) two days after surgery. The COVID-19 test result on the 9th day of the disease was found to be positive. These allowed us to explore areas of focal alveolar damage along with early pathological signs of COVID-19, alveolar edema, and proteinaceous exudates. Significant signs of ongoing repair, including prominent secretions, mononuclear (non-neutrophilic) alveolar inflammation, and a vascular occlusion in the focal regions of the multinucleated giant cells, with accompanying severe pneumocyte hyperplasia, proliferation of interstitial fibroblasts, and interstitial thickening, were seen in particular. In addition, viral inclusions have been suspected in some cells.^[11]

A late sign of severe COVID-19 infection was first defined in a 50-year-old case with ARDS.^[12] The autopsy was carried out on the day 14 of a severe, swiftly deteriorating respiratory illness. The findings demonstrated diffuse alveolar damage with cellular fibromyxoid exudates and hyaline membrane formation, suggestive of ARDS. Lymphocytic predominantly interstitial and airway inflammation was observed. Besides, there were profuse multinucleated syncytial cells and unusually distended pneumocytes in the alveolar spaces, indicating viral cytopathic-like changes.

Currently, post-mortem series of two patients and post-mortem biopsy series from the USA were also published, demonstrating extensive alveolar damage and mononuclear airspace and airway inflammation.^[13,14] In the post-mortem case series, the authors also demonstrated that SARS-CoV-2 viral testing can be done from post-mortem swabs for verification if pre-mortem testing is not available.^[14]

Considering the pathological findings of the disease in the early and late stages, mild mononuclear and giant cell inflammation that starts to occur especially in the alveoli in the early period of COVID-19 becomes exudates with protein and fibrin. This causes focal type-1 pneumocyte damage. Type 2 pneumocyte hyperplasia develops to repair this damage. Later, it creates interstitial fibroblast proliferation, vascular occlusion and local edema. This pathophysiology is reflected in lung CT imaging as peripheral, bilateral GGO, vascular expansion, superimposed reticular thickening (crazy-paving) findings. If this process continues further, diffuse alveolar damage (pneumocyte desquamation) begins to occur. Respectively, cellular fibromyxoid exudates (rich in lymphocytes) exacerbate inflammation and multinucleated syncytial cells form a sort of hyaline membrane formation. Protein and fibrinous exudates also cause interstitial fibrosis and vascular microthrombi. This pathophysiology also appears in lung CT imaging with the findings of consolidation, organized pneumonia, central GGO and peripheral consolidation (reversed-halo sign). Also, recently, there has been a mosaic attenuation due to a 'possible' decrease in regional lung density due to subpleural fibrosis and microthrombosis/microembolism.^[15]

Since the outbreak of the pandemic, in the COVID-19 diagnostic and treatment guidelines, it was suggested for the first time by The National Health Commission to include suspected cases with lung radiological findings compatible with this disease in the scope of "clinical diagnosis".^[16] These imaging findings mainly reflect the inflammatory pathological process of lung tissue examination, proliferation and metamorphism. Although chest radiography (CXR) is considered for diagnosis at the initial stage, radiological diagnosis is mainly performed by CT (especially high-resolution computed tomography [HRCT]), since it cannot provide quality guidance in general and especially in the early stages of the disease.^[17,18] Lung CT examination is the main screening and diagnostic basis for COVID-19 pneumonia. Apart from this, cardiac MRI for cardiovascular complications and comorbid conditions (myopericarditis, etc.), lung ultrasonography for serial and easy follow-up of the patient, and very rarely lung positron emission tomography (PET) can be included in radiological imaging.

Pathophysiology of radiological imaging in COVID-19

I. COVID-19 and chest radiography (X-ray)

In the literature, the role of lung radiography in the diagnosis of COVID-19 pneumonia is 30–60%, and it can be

considered to be very low compared to other methods.^[19] Although normal lung radiography cannot rule out the presence of COVID-19, in the presence of COVID-19, it may be possible to see atypical findings in the lung radiography. Although the success of lung radiography in diagnosing COVID-19 is low, it can be very important in monitoring the course of the disease in positive cases and especially in ARDS cases requiring intensive care.^[20] As the disease progresses, the opacities combine and become more intense on CXR, which may manifest as irregular consolidations, pleural effusion, perihilar and peripheral distributions. These findings are approximately 10–12 days before the day the onset of symptoms. In the light of this knowledge, the American College of Radiology also advocates that the primary imaging method for COVID-19 patients is portable lung radiography.^[20]

2. Pulmonary computed tomography (CT) in COVID-19

Chest radiography findings are normal, but in suspicious cases, non-contrast lung CT can make early diagnosis possible. Thus, the possibility of transmission in the society decreases with early isolation.^[21] Some specific radiological images, such as the presence of infiltrates prevailing bilaterally in the peripheral and basal regions, were shown in the lung CT findings of patients with COVID-19 pneumonia.^[22] With the worldwide increase in the number of cases and better recognition of the radiological findings over time, certain classifications have been made in order to make an accurate and rapid diagnosis and to evaluate the radiological findings with standardization. One of them is the classification in which radiological findings related to COVID-19 are categorized into 4 groups by the British Society of Thoracic Imaging (BSTI), which is frequently used worldwide (Table 1).^[15,23]

Abnormal findings detected in lung CT progress rapidly within an average of 6–13 days from the onset of symptoms. Subsequently, in the more severe stages of the disease, the diffuse reticular pattern emerges as a more dominant finding. In a study evaluating 70 patients who were found to be positive for COVID-19, it is also observed that the presence of residual disease findings due to fibrosis after discharge from the hospital in 66 of the cases.^[24] The COVID-19 pneumonia case series were first published in China, where the disease originated. In a prospective study evaluating 1014 cases, the sensitivity of RT-PCR in detecting the diagnosis of COVID-19 was 60–70%, while the lung CT sensitivity was found to be very high, up to 97%. Although RT-PCR is the gold standard test for diagnosis, lung CT is also thought to be a very powerful alternative as diagnostic imaging with its very high sensitivity.^[25,26]

Frequent computed tomography (CT) images of the lungs in COVID-19 pneumonia

a. Ground-glass opacity (GGO)

Ground-glass opacity is the most frequently described

Table 1. COVID-19 imaging patterns on lung CT with confidence levels described in a guidance document of the BSTI^[23] (adapted from the study of Nagpal et al.^[15])

Disease pattern	Imaging appearance
Typical	Lower lobe and peripheral predominant, bilateral*, multifocal, round, GGO With or without: • Reticular interstitial thickening • Reversed halo sign** • Peripheral consolidation**
Possible	Lower lobe predominant peripheral consolidation with: • Bronchocentric disease • Less GGO • Reversed halo sign**
Uncertain	Typical or probable imaging pattern without clinical suspicion Disease pattern that doesn't fit into typical or possible
Excluded	• Cavitory lesions • Tree-in-bud or centrilobular nodules • Lobar consolidation • Pulmonary fibrosis (improved) • Lymphadenopathy or pleural effusions

BSTI: British Society of Thoracic Imaging; GGO: Ground-glass opacity; CT: Computed tomography. *Provided >1 lesion, can also be one-sided. **Organised pneumonia.

imaging finding in COVID-19 and is characterized by the weakening of bronchovascular structures, especially in CT. Ground-glass opacity is difficult to detect on chest radiography (CXR) in this regard but may be easier to detect whether GGO is associated with reticular interstitial thickening.^[27] Unilateral GGO may be seen in the lower lobes of the lung if the patient is imaged even shortly before the onset of symptoms.^[28] Anyway, imaging findings are usually normal in the beginning and may appear over time. As the disease develops, GGO may vanish or turn into open consolidation by becoming more unified and widespread. In a study conducted in Wuhan, GGO was shown on CT of approximately 60–70% of patients with COVID-19 pneumonia, and the right lower lobe is usually the most frequently affected area. One of the typical imaging findings of COVID-19 infection is accepted as GGO seen bilaterally in a peripheral distribution, especially in the lower lobes. These opacities tend to be morphologically rounded are usually bronchocentric and frequently located in the posterior region.^[29,30]

b. Diffuse consolidation and the presence of air bronchograms (White lung)

As the clinic progresses, extensive damage to the alveoli and mucosal surfaces, consolidation and massive exuda-

tion due to the inflammation storm cause radiologically white lung. Air bronchogram refers to the phenomenon of dendritic low-intensity shadowing of the air-containing bronchus in the consolidation of lung tissue that is more common in advanced disease. The pathological origin is that the pathogen invades epithelial cells, yielding inflammatory thickening and swelling of the bronchial wall, but not obstructing the bronchioles.^[31]

c. Reticular interstitial thickening and paving stone (crazy-paving) sign

Another finding seen in HRCT is the paving stone sign. This appearance occurs in CT because of the thickening between the lobules, the interlobular line, and a ground glass-like opaque plan on the background of interstitial thickening and the irregular shape of these forms.^[32] This pattern is generally observed in the subacute to the chronic phase of the disease and probably symbolizes the aggregation of interstitial inflammatory cells. Pleural effusion is rare in COVID-19, and this helps differentiate the imaging from heart failure. In the later stages of the disease, GGO and consolidations improve, but reticular interstitial opacities may enhance.^[4,32]

d. Reversed halo (Atoll) sign

It is defined as the central GGO surrounded by more intense peripheral consolidation. In its pathophysiology, it is associated with peripheral and central alveolar inflammation and debris in the interstitial tissue and distal airways. This sign can be seen in the advanced stage (due to GGO) and in the recovery phase (because of consolidations of COVID-19).^[33–35]

e. Fibrous lesions

During the repair and improvement of chronic inflammation or hyperplasia of the lung, the fibrous components gradually substitute the normal cellular components and take on a fibrotic appearance in CT. These fibrous lesions may cause damaged bronchi and associated bronchiectasis.^[32–35]

3. Pulmonary and cardiac magnetic resonance imaging (MRI) in COVID-19

SARS-CoV-2 interacts with host cells by binding the envelope protein to ACE-2. ACE-2 is copiously expressed in cardiovascular cells as well as the airways.^[6] It is thought that SARS-CoV-2 may cause direct cardiovascular damage (such as myopericarditis, pericardial effusion) through the same ACE-2 receptor as well as secondary to systemic inflammation.^[5,36] MRI findings of COVID-19 pneumonia appear as regions of abnormally augmented signal intensity in both T1 and T2-weighted sequences, with predominant GGO and consolidative opacities in the basilar and peripheral regions in pathophysiology, similar to lung CT and radiography. In cardiac MRI, it can be very useful in identifying cardiac pathologies associated with COVID-19 such as myocarditis and cardiomyopathy with late gadolinium enhancement in the small, subepicardial, basilar anterolateral wall due to cellular inflammation.^[37,38]

4. Pulmonary 2-fluoro-2-deoxy-D-glucose (FDG) - positron emission tomography/computed tomography (PET/CT) in COVID-19

FDG-PET/CT may have the potential to better comprehend the mechanism of COVID-19. Because FDG, a glucose analog, is a molecular imaging probe used to evaluate tissue glucose metabolism and utilization. PET/CT testing can simultaneously provide metabolic and anatomical information of lesions.^[39] Because FDG accumulates in activated inflammatory cells, including neutrophils and macrophages, FDG-PET/CT may have great potential to diagnose and monitor an inflammatory process-intensive disease such as COVID-19.^[40] In FDG-PET/CT imaging of severe lung injury in COVID-19 pneumonia, lobar large glass opacity findings occur, especially due to moderated FDG uptake, and this image returns to normal as the disease improves.^[41]

5. Lung ultrasonography (US) in COVID-19

Another imaging method whose use has recently increased slightly is LUS. It seems to be a very useful method with the advantage of bedside use, especially in units such as emergency services and intensive care. It has been underlined that LUS has a higher sensitivity in the diagnosis of pneumonia compared to lung radiography.^[42] Common manifestations of the SARS-CoV-2 virus in COVID-19 pneumonia by causing damage to the pleural separation, conducting airways and lung parenchyma include subpleural consolidations, irregular pleural line and white lung images.^[43,44] In patients with COVID-19 pneumonia, LUS reveals a typical pattern of diffuse interstitial lung syndrome characterized by multiple or confluent bilateral B-lines with spared areas, thickening of the pleural line with pleural line irregularity, and peripheral consolidations. LUS has been found to be a promising tool for diagnosing COVID-19 pneumonia, and LUS findings are highly correlated with those of chest CT scan. Compared to CT, LUS has several other advantages such as no radiation exposure, bedside repeatability during follow-up, low cost, and easier application in low-resource settings. Consequently, LUS may reduce the use of conventional diagnostic imaging resources (CT scan and chest X-ray). LUS may help in the early diagnosis, therapeutic decisions, and follow-up monitoring of COVID-19 pneumonia, particularly in the intensive care setting and in children, pregnant women, and patients in areas with high rates of community transmission.^[45] Another recent study examined outpatients with SARS-CoV-2 infection. The fact that LUS findings were also associated with a high prevalence in this group and lung disease resulted in a wide range of LUS severity scores suggested that LUS may not be useful as a risk stratification tool in SARS-CoV-2 in the general outpatient population.^[46] It has even come to the fore that LUS can be effective in detecting even asymptomatic SARS-CoV-2 carriers.^[47] In a study investigating the accuracy of bedside LUS as a rapid and effective assessment tool in suspected Covid-19 cases, it was shown that bedside lung ultrasound can be used to detect the presence of pulmonary involvement in suspected

Covid-19 cases, especially for effective triage of patients in the emergency room.^[46] As a different point from adults, LUS is recommended as a useful tool in the initial therapeutic management, evaluation and monitoring of possible cardiovascular deterioration in children with suspected MIS-C, which is a highly feared picture in the pediatric age group with very high morbidity and mortality.^[49]

As a result, in addition to many positive advantages such as easy to repetition at the bedside, low cost, comfortable use, and not being exposed to radiation, widespread use of LUS will be very important and beneficial in terms of triage optimization. The absence of radiation exposure also makes the US even more attractive to the pediatric patient population.^[42,44]

CONCLUSION

Considering that individuals with mild or even asymptomatic COVID-19 can increase the transmission in the society significantly, it is very important to be able to make an early diagnosis in the fight against the pandemic. Although RT-PCR is the first preferred method for diagnosis, when the studies are reviewed, it has been shown that imaging methods come to the fore and provide faster results. Also, RT-PCR and lung imaging do not have a clear advantage over each other, and even imaging helps in the diagnosis, especially in clinically severe cases. At this point, understanding the pathogenesis of these formations detected in imaging will perhaps play a key role in this endless disease.

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Conflict of Interest

None declared.

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COVID-19'da Görüntülemenin Patogenezi (Derleme)

2020 yılında, Dünya Sağlık Örgütü (DSÖ) tarafından pandemi olarak kabul edilen yeni tip koronavirüs hastalığı (COVID-19) tüm dünyada milyonlarca insanı etkilemiş ve ölümlere neden olmuştur. Radyolojik lezyonların patofizyolojisini incelemek, yüksek bulaşıcılığı nedeniyle erken teşhisin çok önemli olduğu bu uçsuz bucaksız hastalığı anlamak için belki de anahtar rol oynamaktadır. Hafif ve hatta asemptomatik COVID-19'lu bireylerin toplumdaki bulaşmayı önemli ölçüde artırabileceği düşünüldüğünde, pandemiyle mücadelede erken tanı konulabilmesi oldukça önemlidir. Tanıda ilk tercih edilen yöntem RT-PCR olmasına rağmen, çalışmalar gözden geçirildiğinde RT-PCR ve akciğer görüntülemesinin birbirlerine karşı net bir avantajı olmamakla birlikte teşhise yardımcı olmaktadır. Özellikle klinik olarak ağır vakalarda tanıda daha hızlı sonuç veren görüntüleme yöntemleri ön plana çıkmaktadır. Bu noktada, görüntülemede tespit edilen bu patolojik oluşumların patogenezi anlamak, belki de uçsuz bucaksız bu hastalıkta kilit rol oynayacaktır. Bu yazıda biz klinisyenler için önemli olan radyolojik görüntülemenin arka planındaki patofizyolojisi güncel literatür incelemesi ışığında tartışılmıştır.

Anahtar Sözcükler: Akciğer ultrasonografisi; bilgisayarlı tomografi; COVID-19; manyetik rezonans görüntüleme; patogenezi; pozitron emisyon tomografi; radyoloji; X-ışını.