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Multimodality Imaging of COVID-19 and its complications: A comprehensive review for the treating physicians

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ABSTRACT

Coronavirus disease 2019 (COVID-19) primarily affects the lungs with clinical presentation ranging from asymptomatic condition to severe and sometimes fatal disease. Imaging plays an important role in diagnosis and management of Coronavirus disease 2019 (COVID-19) and it's associated complications. Chest radiograph (CXR) is the first imaging modality for routine screening of COVID-19 suspects and for all symptomatic RT-PCR positive COVID-19 patients. Computed tomography (CT) of Chest plays a pivotal role in the diagnosis, triage, prognostication and follow-up of COVID-19 patients. However, chest CT should be done only when it is expected to change patient management and not routinely, as the CT findings are not pathognomonic of COVID-19 pneumonia and closely resemble other viral pneumonias. CT also helps in diagnosing various complications of COVID-19 like thrombo-embolism and mucormycosis. Doppler Ultrasound (USG), CT Angiography/Venography and MR Angiograpy/Venography are the primary imaging modalities for diagnosis of arterial and venous thrombosis and thrombo-embolism in these patients. The widespread and irrational use of Chest CT during the second wave of COVID-19 pandemic in India placed an increased logistic and economic burden on the society and led to unwarranted increased radiation exposure in these patients. Also self-medication and use of high doses of corticosteroids for treatment led to significant increase in Rhino-orbito-cerebral mucormycosis in these patients. Knowledge of the role of various imaging modalities and key diagnostic findings of COVID-19 is essential for the treating physicians to optimize patient care.

Keywords: COVID-19, CXR, Chest CT, Radiation risks, Mucormycosis

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which emerged in Wuhan, China towards the end of 2019 and spread unabated across the globe, is a highly contagious viral disease caused by severe acute respiratory syndrome Coronavirus 2 (SARS-COV-2)[1]. Although, the disease primarily affects the lungs with clinical presentation ranging from asymptomatic, through symptomatic to critically ill, other multi-systemic manifestations of this disease are being more commonly recognized. The common symptoms of COVID-19 include fever, cough, anosmia, sore throat and dyspnea [2]. As there is no definite treatment for COVID-19 till date, the control of disease relies mainly on early diagnosis and quarantine of the infected individuals. Reverse transcription – polymerase chain reaction (RT-PCR) of nasal and pharyngeal swabs is the current reference standard test for diagnosing it. However,

owing to various limitations like improper sample collection, insufficient viral load, transportation and performance of diagnostic kit, the sensitivity of RT-PCR varies from 60-71%. [3,4] The rapid antigen-antibody test and chest radiographs (CXR) have even lower sensitivity. Computed Tomography (CT) of Chest having a sensitivity of upto 98 %, is an excellent modality to conclusively confirm or refute lung involvement. Although, these CT findings are not diagnostic of COVID-19 and closely resemble other viral pneumonias, Chest CT still plays a pivotal role in diagnosis, triage, prognostication and follow-up of these patients. The widespread and irrational use of Chest CT during the second wave of COVID-19 pandemic in India placed an increased logistic and economic burden on the society and led to unwarranted increased radiation exposure in these patients. Also self-medication and use of high dose of corticosteroids for treating COVID-19 pneumonia has led to significant increase in Rhino-orbito-cerebral mucormycosis (black fungus) in these patients. Uncontrolled diabetes, high ferritin levels and endothelial damage due to COVID-19 predisposes to mucormycosis. The current review discusses the indications and role of various imaging modalities in the diagnosis and management of COVID-19 and also highlights the key radiologic findings of COVID-19 pneumonia and it's related complications.

Indications and Role of Chest Radiographs (CXR):

CXR is typically the first-line imaging modality for routine screening of all COVID-19 suspects and for all symptomatic RT-PCR positive patients. It is also indicated for disease monitoring based on patient's clinical status. It's obvious advantages include it's low cost and easy availability. Various CXR patterns of COVID-19 pneumonia have been described. [5] The "reverse batwing appearance" which was pathognomonic of Eosinophilic pneumonia in the pre-COVID era, is one of the most specific pattern of COVID-19 pneumonia. Other patterns include bilateral lower zone consolidation, peribronchial and multifocal consolidation, mass-like opacities and acute respiratory distress syndrome (ARDS) pattern. Pleural effusions, lung cavitations and pneumothorax are rare findings and should raise suspicion of other potential causes.

Indications and Role of Ultrasound (USG):

Pulmonary USG plays a complementary role to CXR in evaluation of critically ill patients with COVID-19. The common findings of lung involvement are presence of B-lines, irregular thickened pleura and subpleural consolidations. Abdominal USG is an excellent modality for evaluating abdominal organs. Acalcular cholecystitis and biliary stasis has been reported in COVID-19 patients. Lower and upper extremity Doppler USG is first-line imaging modality for diagnosis of peripheral venous and arterial thrombosis.

Indications and Role of Chest CT:

Chest CT for Routine Screening and COVID-19 Suspects

All the National and International radiology organizations unanimously recommend not to use chest CT for routine screening of COVID-19. [6-8] This is due to the fact that CT findings of COVID-19 are not diagnostic and 15-50% of COVID-19 patients have a normal chest CT early in course of disease. [9-10] Also there is a risk of infection from surface contamination and/or aerosolization while performing CT scan of these patients. However, Chest CT is useful in COVID-19 suspects who have typical respiratory symptoms of COVID-19, RT-PCR is negative (due to technical errors, low viral load or mutant variants) and chest radiograph is normal or indeterminate. In these COVID-19 suspects, typical CT findings of COVID-19 and "COVID-19 Reporting and Data System" (CO-RADS) [11] category 4/5 allows presumptive diagnosis of COVID-19 pneumonia. Diagnostic accuracy of Chest CT in this clinical scenario can be further increased when CT interpretation is done along with various blood indices and serum markers that are likely to be altered in COVID-19, like lymphopenia, increased neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), D-dimer, Lactate dehydrogenase (LDH), Ferritin, Fibrinogen and Interleukin-6 (1L-6). Detection of RT-PCR negative COVID-19 patients by CT Chest helps not only to start treatment early but also prevents them from being super-spreaders due to isolation/quarantine recommendations. CT Chest may also be advised for routine screening before emergency surgeries and high aerosol generating procedures in case the RT-PCR results are not available in time.

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Chest CT in RT-PCR Positive COVID-19 Patients

Chest CT should not be done routinely in RT-PCR positive COVID-19 patients. It is indicated only in moderate to severe symptomatic patients when it is expected to change patient management (breathlessness, falling oxygen saturation). Chest CT plays a pivotal role in staging, prognostication, management and follow-up of moderate to severe symptomatic patients. In elderly patients (> 65 years) and in patients with associated co-morbidities it helps in triaging the need for hospitalization. Chest CT also helps in evaluation of COVID-19 patients who show sudden clinical deterioration either due to disease progression or secondary cardio-pulmonary complications. High resolution CT (HRCT) has a sensitivity of 98% in diagnosing COVID-19 pneumonia. The HRCT findings can be divided into four stages. These include an early stage (0-4 days) from onset of symptoms, intermediate stage (5-8 days), peak stage (9-13 days) and resolution stage (>14 days). The early stage is characterized by presence of ground-glass opacities (GGO's) usually bilateral and in multilobar distribution. Other HRCT features of COVID-19 pneumonia include consolidations with basal and peripheral predominance, crazy-paving pattern, sub-pleural linear opacities, parenchymal bands, halo sign, reverse-halo sign (Atoll sign), organizing pneumonia pattern and ARDS pattern. [12-15] Pulmonary vascular abnormalities such as vessel enlargement in lung periphery (vascular tree-in-bud) and regional mosaic perfusion patterns are also commonly seen in COVID-19 pneumonia. However, these CT findings are not pathognomonic of COVID-19 pneumonia and closely resemble other viral pneumonias like Influenza, H1N1, Adenovirus and Rhinovirus. [16-18] Other imaging differential diagnosis include Eosinophilic pneumonia, Cryptogenic organizing pneumonia, acute exacerbation of Interstitial lung disease (ILD), IgG4 disease, Chemotherapy related lung toxicity, Pneumocystis jirovecii pneumonia (AIDS patients) and Primary pulmonary proteinosis. Pleural effusion, cavitation, nodules, tree-in-bud opacities and lymphadenopathy have not been reported in COVID-19 pneumonia and are useful in differentiating it from other conditions. In an attempt to make interpretation of Chest CT findings easy, a COVID-19 Reporting and Data System (CO-RADS) [11] was introduced with level of suspicion ranging from very low (CO-RADS 1) to very high (CO-RADS 5). Chest CT helps in staging COVID-19 pneumonia into mild, moderate and severe disease based on a visual 25- point CT scoring system [19] which assigns a score of 0 to 5 to each of the 5 lobes of lung based on extent of lung involvement (<5% -1; 6-25% -2; 26-50% -3; 51-75% -4 & >75% -5). Although not a perfect scoring system, CT score of >18 has been shown to be associated with worse outcome (CT score <7: mild). Certain imaging features like bilaterality, crazy-paving and pulmonary vascular changes indicate poor short-term prognosis. [20] An additional benefit of Chest CT in COVID-19 is that it diagnosis concurrent pulmonary diseases like Emphysema, ILD and Tuberculosis (TB). This is especially important as it may alter the patient treatment considering the fact that corticosteroids and tocilizumab can flare up tuberculosis. Underlying Emphysema and ILD lead to atypical CT features in COVID-19 pneumonia. In cases of underlying ILD and paraseptal emphysema, the typical subpleural distribution of COVID-19 pneumonia may be absent. The GGO's and consolidations superimposed on emphysema background leads to a "bubble-like" appearance which could be misinterpreted as lung cysts or cavitation and thus can lead to erroneous ruling out of COVID-19. Chest CT is also beneficial in monitoring post-COVID-19 lung fibrosis especially in patients with persistent hypoxia. [21] While architectural distortion, honey-combing and traction bronchiectasis occurs in some patients, complete resolution of fibrosis has been observed in many patients on follow-up chest CT. [22] However, despite normal CT chest, many patients experience breathlessness for several months post-COVID-19. Xenon-MRI of lungs in these patients show reduced alveolar capillary permeability.

Indications and role of imaging in diagnosis of various complications of COVID-19:

Contrast-enhanced CT scan plays an important role in diagnosis of vascular, neurological and other complications of COVID-19. While CT-Pulmonary Angiography is useful in diagnosing pulmonary embolism, CT-Venography and CT-Arteriography helps in evaluation of venous and arterial thrombosis in these patients. CT scan is also useful for diagnosing Pulmonary and Rhino-sino-orbital-Cerebral mucormycosis. Mass-like consolidaton, multiple nodules frequently with cavitation, reverse-

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halo sign, consolidations directly crossing the fissures and pleural effusions are suggestive of pulmonary mucormycosis. As these findings are also seen in Invasive Aspergillosis, biopsy/fine needle aspiration is the gold standard for diagnosis of mucormycosis. CT scanning of paranasal sinuses (PNS) can help diagnose Rhino-sino-orbital mucormycosis. Opacification of affected sinuses with hyperdense areas within and adjacent soft tissue thickening with or without bony erosions are noted in these patients. Contrast-enhanced Magnetic Resonance Imaging (CEMRI) is superior to CT scan for demonstrating soft tissue and intracranial extension. Non-enhancing turbinate, the "black turbinate sign", is highly suggestive of angioinvasive fungal sinusitis including mucormycosis. [23]

Imaging helps diagnose various neurological complications of COVID-19 such as stroke, hemorrhage or venous sinus thrombosis. MRI Brain is more sensitive than CT scan and demonstrates microhemorrhages, white matter signal abnormalities and lepto-meningeal contrast enhancement. The white matter signal abnormalities may be due to viral encephalitis, post-infectious demyelination, post-hypoxic leuko-encephalopathy, metabolic encephalopathy or posterior reversible encephalopathy syndrome (PRES). CT or MR Venography can be used, if necessary, to confirm venous sinus thrombosis.

Imaging also helps in detection of various cardiovascular complications of COVID-19. Although CXR, Chest CT and Echocardiography can be used to evaluate cardiac complications, myocardial injury is best evaluated using Cardiac MRI. The MRI features of myocarditis include wall motion abnormalities and late Gadolinium enhancement in a non-ischemic pattern. In children who develop pediatric multisystem inflammatory syndrome (PMIS), Echocardiography reveals myocarditis, pancarditis, dilated cardiomyopathy and pericardial effusions. Coronary artery aneurysms are best detected on Cardiac CT.

Imaging manifestations of COVID-19 that may overlap with Cancer Imaging:

Certain imaging features associated with COVID-19 may impact Cancer imaging, staging and treatment. This is especially important as cancer patients are more prone to COVID-19 infection and many of them may be asymptomatic. Cancer patients who are asymptomatic for COVID-19 may show CT/18-FDG-PET scan findings mimicking lung metastasis or therapy-associated pneumonitis. Hence, when CT/18-FDG-PET scan findings in a known cancer patients show COVID-19 appearance, appropriate evaluation for COVID-19 should be considered.

Imaging manifestation of Post-COVID-19 Vaccination:

Mammography, MRI breast, Chest CT and PET-CT may show unilateral axillary adenopathy on ipsilateral side upto 6 weeks post-COVID-19 vaccination. No further evaluation is required in these cases. Axillary USG may be recommended if clinical concern persists even after 6 weeks post-vaccination.

Radiation with CT scanning and patient safety:

Since, its inception in 1970's CT scan has revolutionized diagnostic imaging and hence decision making by the treating doctors. [24] At the same time, radiation exposure from CT Scanning and subsequent risk of developing cancer has received much attention. However, most of the data on radiation risk comes from Japanese atomic bomb survivor cohort and is based on "Linear No-Threshold (LNT) model. [25] According to this model, the radiation-induced cancer risk is uniform across all doses. The main problem with LNT model is that it does not take into account the fact that the body responds to radiation induced cell level changes by DNA repair and apoptosis. As such the LNT model has now been replaced by "Threshold Model" which suggests that there is a threshold below which radiation dose does not increase cancer risk and that the risk increases only after cumulative dose of 100 mSv or more is reached. [26] Epidemiological evidence suggests that low dose radiation exposure may actually lead to a decreased cancer incidence, indicating possible radiation "hormesis". [27] This is probably due to the beneficial effects from activation of body's immune response. Pediatric patients have been believed to be at a higher lifetime risk of developing radiation associated cancer as they are assumed to be more radiosensitive. [28] Also, for any given CT examination, the dose delivered to children is higher than adults. However, more recent studies in pediatric population which adjusted for various factors did not demonstrate any significant excess cancer risk. [29,30] Thus based on the current literature, the radiation

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risks for carcinogenesis are grossly exaggerated. The effective dose from chest CT scanning is 8mSv which although is 400 times that of a chest radiograph (0.02mSv), and 2.6 times that of annual natural background radiation (3mSv), still falls in "Low Dose" (10-100 mSv) radiation range. Also, it is important to understand that potential carcinogenesis is a "stochastic effect" which means that prior radiation exposure has no bearing on the risk of developing cancer due to CT scanning in future.

Role of Cutaneous and Ocular Manifestations of COVID-19:

A number of cutaneous and ocular manifestations like vesicular eruptions, maculo-papular lesions, urticaria, livedo reticularis, pseudo-chilblain (COVID toes), and conjunctival chemosis have been reported in COVID-19 patients. These manifestations especially COVID toes and conjunctival chemosis can be used as markers of COVID-19 suspects. One or several hyperintense nodules of posterior pole of globe have been noted in Ocular MRI of hospitalized COVID-19 patients. Also, the development of necrotic eschar in a moderate to severely ill COVID-19 patient should alert the treating physician that the patient may have developed cutaneous mucormycosis.

Conclusion:

Although COVID-19 primarily affects the respiratory system, other multi-systemic manifestations are being commonly recognized. Imaging plays a significant role in the diagnosis and management of the disease and it's associated complications. Knowledge of various imaging modalities and key diagnostic findings of COVID-19 is essential for the treating physician to optimize patient care.

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