Manuscript type: Review

Review of the Chest CT Differential Diagnosis of Ground-Glass Opacities in the COVID Era

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Conflicts of interest are listed at the end of this article.

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Learning Objectives:
After reading the article and taking the test, the reader will be able to:
- Identify the multivariate context of appropriate use of imaging in COVID-19 pneumonia
- Specify the limitations of imaging in the diagnosis of COVID-19 pneumonia
- Describe the findings and differentiating features of other lung conditions that can be frequently mistaken for COVID-19 pneumonia

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Essentials:
- Typical CT imaging findings of COVID-19 pneumonia have a wide differential diagnosis.
- The probability that CT findings of any kind represent COVID-19 is highly dependent on the prevalence of SARS-CoV-2 viral infection in the community.
- Careful image analysis can aid in differentiating COVID-19 from other conditions with similar imaging features.

Summary Statement:

Chest CT findings in COVID-19 pneumonia are variable but can be bilateral, lower lobe, and extend to the pleural surfaces. These features can be helpful in distinguishing COVID-19 pneumonia from other causes of lung pathology.

Abbreviations:

AIP - Acute interstitial pneumonia
COP - Cryptogenic organizing pneumonia
GGOs - Ground glass opacities
DAH - Diffuse alveolar hemorrhage
DIP - Desquamative interstitial pneumonitis
HP - Hypersensitivity Pneumonitis
NSIP - Non-Specific Interstitial Pneumonia
PJP - Pneumocystis jirovecii Pneumonia
PAP - Pulmonary alveolar proteinosis
WBC - White Blood Cell Count
RT-PCR - Reverse Transcriptase-Polymerase chain reaction

Abstract

Coronavirus disease 2019 (COVID-19), a recently emerged lower respiratory tract illness, has quickly become a pandemic. The purpose of this review is to discuss and differentiate COVID-19 typical imaging findings from other diseases, which can appear similar in the first instance. The typical CT findings of COVID-19 are bilateral and peripheral predominant ground glass opacities. As per the Fleischner Society consensus statement, CT is appropriate in certain scenarios, including patients who are at risk for and/or develop clinical worsening. The probability, that CT findings represent COVID-19, however, depends largely on the pre-test probability of infection, which is in turn defined by community prevalence of infection. When the community prevalence of COVID-19 is low, a large gap exists between positive predictive values of chest CT vs. RT-PCR. This implies that with usage of Chest CT there are a large number of false positive results. Imaging differentiation is important, for management and isolation purposes, and for appropriate disposition of CT false positive patients. We will discuss differential pathology with close imaging resemblance to typical CT imaging features of COVID-19, and, highlight CT features that may help in differentiation from other conditions.

Introduction

An acute lower respiratory tract infection caused by the novel Coronavirus (nCoV-2019) was first reported in China in December 2019 (1, 2). The clinical spectrum of disease with nCoV-2019 infection (COVID-19) is variable and ranges from an asymptomatic infection, mild upper respiratory tract illness to severe viral pneumonia with respiratory failure and occasionally death (2). While the case fatality ratio has been as high as 15%, the incidence of critical illness has been reported to be 7-26% (3). Patient factors that have been associated with a higher incidence of critical illness and death include male sex, age > 60 years, obesity, diabetes, hypertension, cardiopulmonary comorbidities, higher values of D-dimer and IL-6. (3).

At the time of writing this article, more than 8 million cases and 450,000 deaths worldwide have been reported. The COVID-19 pandemic has resulted in an unprecedented healthcare crisis with immense strain on healthcare resources and disruptions in both routine and emergency health care delivery (4). The lack of adequate diagnostic testing has resulted in suboptimal early detection and containment of this infection, which has contributed to rapid and widespread transmission by undetected individuals with mild or no symptoms (5). The primary diagnostic test, reverse transcriptase-polymerase chain reaction (RT-PCR) assay for COVID-19, has variable sensitivity ranging from 37-71% (5) depending on the rate of viral expression at the time of collection and the site of specimen collection (6). Obstacles to the use of RT-PCR testing include shortage of kits and extended processing period.

Chest CT in COVID-19 pneumonia demonstrates bilateral, peripheral and basal predominant ground glass opacities (GGOs) and/or consolidation in nearly 85% of patients with superimposed irregular lines and interfaces; the imaging findings peak at 9-13 days post-infection (7,8) [Figure 1]. Subsequently, a mixed pattern evolves with crazy paving, architectural distortion and perilobular abnormalities superimposed on GGOs with slow resolution (7) [Figure 1]. Importantly, CT may be normal in an infected patient, particularly early in the disease (8). Atypical Chest CT findings include upper lobe or peribronchovascular distribution of GGOs, cavitation, tree in bud nodules, lymphadenopathy, and pleural thickening (9). Tables 1 and 2 summarize common and uncommon findings of COVID-19 (10-21). It is vitally important to

remember that the CT imaging appearance is dependent on when CT is performed during the patient's time course of this disease.

Patients may also develop cardiac involvement with COVID-19. Risk factors for developing cardiovascular disease include advancing age, impaired immune system, or elevated levels of Angiotensin-converting enzyme 2 (ACE2) and has prognostic implications (22). Studies have reported incidence of myocardial injury with troponin elevation in 7-17% of hospitalized patients and 22-31% of patients admitted to the intensive care unit (8, 9, 23, 24). Cardiac involvement manifests as myocarditis, pericarditis and heart failure, with corresponding imaging findings on chest x-ray, CT and MRI (25, 26, 27). The pathophysiology includes virus infiltration, cardiac stress and inflammation (25, 26). The left ventricular ejection fraction may be preserved or reduced. Acute coronary syndromes have been reported with a proposed mechanism of increased thrombotic activity (25).

The Fleischner consensus statement on the role of chest imaging in COVID-19 is written with a multivariate perspective of disease severity, pre-test probability, risk factors for and/or evidence of disease progression and availability of diagnostic testing (5). As per the consensus statement, CT is appropriate in establishing baseline pulmonary status and identifying underlying cardiopulmonary abnormalities in patients with moderate to severe disease. CT can help triage resources towards patients at risk of disease progression and may identify a cause in case of clinical worsening. CT may also identify an alternate diagnosis (5). CT findings concerning for COVID-19 may be found incidentally in asymptomatic patients in the setting of known community transmission. Aymptomatic carriers of COVID-19 may comprise 17.9-33.3% of infected cases (28, 29). Such patients need to be directed towards RT-PCR testing.

In a resource constrained environment with high community burden of disease and rapid point of care (PoC) testing either unavailable or negative, CT has been used to rapidly triage patients into non COVID-19, possible or most likely COVID-19 (Table 3). Given the presence of CT abnormalities, the probability that the CT findings represent COVID-19 depends largely on the pre-test probability of infection, which is defined by community prevalence of infection and modified by individual factors such as exposure history (5, 30). If the disease prevalence is high, even atypical presentations are likely to represent COVID-19. On the other hand, if the disease

prevalence is low, CT findings that are other otherwise quite typical of COVID-19 may be caused by another disease (30). The positive and negative predictive values (PPV and NPV), which are calculated using disease prevalence in the community, are useful to consider in comparison to sensitivity and specificity, which can only be used when the true COVID-19 status is already known. Therefore, CT diagnosis is not used in isolation without acknowledging the prevalence of disease in the community. As expected, the metrics of diagnostic performance for chest CT (PPV, NPV, sensitivity and specificity) are strictly valid only for the study population from which they are obtained (30).

Kim et al performed a meta-analysis to assess diagnostic performance of CT and RT-PCR (31). For Chest CT the PPV ranged from 1.5% to 30.7% and NPV ranged from 95.4% to 99.8%. For RT-PCR, the PPV ranged from 47.3% to 96.4% and NPV ranged from 96.8% to 99.9%. They report a pooled sensitivity of 94% (95% CI: 91%, 96%; I^2=95%) for Chest CT and 89% (95% CI: 81%, 94%; I^2 =90%) for RT-PCR. The pooled specificity of Chest CT was 35% (95% CI: 26%, 50%). They found that, given the low specificity of CT, a large gap existed between PPV of chest CT vs RT-PCR in low-prevalence areas, specifically if the disease prevalence was less than 10% (31). These results imply that use of Chest CT may result in a large number of false positive results that may lead to further diagnostic testing, greater medical cost and workload and patient anxiety. Patients with suspected COVID-19 on chest CT may be placed in dedicated COVID-19 rule out units and may experience delay in care or intervention. Thus attempts at differentiation of chest CT abnormalities is important for management and isolation of patients with high clinical suspicion as well as for appropriate disposition of patients where disease prevalence or pre-test probability is low.

Given the lack of specificity of chest CT findings for COVID-19, the purpose of this review is to address the range of pulmonary disease processes that can mimic the CT appearance of COVID-19 pneumonia.

INFECTIONS

Bacterial pneumonias:

Bacterial pneumonia is commonly encountered in clinical practice. Pneumonia is the eighth leading cause of death, and the number one cause of death from infectious disease, in the United States. Bacterial pneumonias are classified into three main groups: Community acquired pneumonia (CAP), Aspiration and Nosocomial or hospital acquired pneumonia. Patients typically present with fever, chills, or cough. Chest radiography is the most commonly used imaging tool in pneumonias. CT should be used in unresolved cases or when complications are suspected. The usual pattern of CAP is that of lobar consolidation. The radiographic patterns of Nosocomial pneumonia are very variable, most commonly showing patchy consolidation, and are associated with cavitation and pleural effusion (32) [Figure 2]. Patients typically have a high white cell count unless they are neutropenic or immunocompromised.

In contrast to COVID-19, bacterial pneumonia characteristically produces focal segmental or lobar pulmonary opacities without lower lung predominance. Complications or associated findings such as cavitation, lung abscess, lymphadenopathy, parapneumonic effusions and empyema, when present, are useful imaging differentiating features, as they are not seen in COVID-19 unless the patients are superinfected with bacterial pneumonia (8).

Viral pneumonias:

Viruses are the most common causes of respiratory tract infections and are seen more commonly in children, the elderly and the immunocompromised (33, 34). The most common pathogen causing viral pneumonia in both, immunocompetent and immunocompromised, is Influenza virus (33). The clinical signs and symptoms of viral pneumonia are often diverse and depend on host immune status (34). The spectrum of CT findings encountered in various pulmonary viral diseases encompasses four main categories: (a) GGO and consolidation; (b) nodules, micronodules, and tree-in-bud opacities; (c) interlobular septal thickening; and (d) bronchial and/or bronchiolar wall thickening (35) [Figure 3]. Lymphadenopathy and pleural effusions may also be present (36). Some of the viral pneumonias can present with significant ground glass opacity and include Cytomegalovirus (CMV), Adenovirus, Herpes Simplex Virus (HSV),

Varicella zoster, Measles, Human meta-pneumovirus (HMPV) and Influenza (33, 37). Percentage area of lung involvement with GGOs with different viruses has been extensively described. GGOs can be seen in 50-75% with Adenovirus, over 75% with CMV and HSV and 10-25% in HMPV and measles (33).

Out of the 4 patterns of viral disease, described above, the pattern that can be confused with COVID-19 is GGO as the predominant finding. Therefore, in our discussion we will focus on viruses that demonstrate predominantly this CT finding.

The viral infections most often described to have features that resemble COVID-19, include Influenza, CMV, and other coronaviruses (38-41). As for differentiation from Influenza, as per Liu, et al though peripheral GGOs and consolidation are seen in both these entities, round opacities and septal thickening are more common in COVID-19. Conversely, nodules, tree in bud opacities and pleural effusion are more common in Influenza (38).

Li et al, explored differences in CT features of COVID-19 versus other Coronaviridae, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). They report that GGO, consolidation, septal thickening and air bronchogram sign were similar in COVID-19, SARS and MERS, while, reversed halo sign and pulmonary nodules associated with COVID-19 have not been previously described with SARS and MERS. Lung abnormalities in SARS are more commonly reported to be unifocal (40).

CMV, a cause of severe lung infection in immunocompromised patients, such as those with HIV and organ transplant recipients, can result in widespread GGOs. The clinical context and timing since transplant is best distinguishing feature (33).

HMPV is predominantly seen in stem cell transplant patients and those with hematological malignancies. HPIV occurs in approximately 21% of the intensive care unit patients, and bacterial coinfection is a known association (42). HMPV pneumonia shows multifocal patchy consolidation with GGO on CT. Centrilobular nodules and bronchial wall thickening, seen in 25% are useful differentiating features (43).

Overall, according to Bai et al, compared to non-COVID-19 viral pneumonia, parenchymal opacities in COVID-19 pneumonia were more likely to be peripheral (80% vs. 57%), and have GGO (91% vs. 68%), fine reticular opacity (56% vs. 22%) and vascular thickening (11% vs. 1%). COVID-19 patients were less likely to have central and peripheral distribution (14% vs. 35%), air bronchograms (14% vs. 23%), pleural thickening (15% vs. 33%), pleural effusion (4 vs. 39%) and lymphadenopathy (2.7% vs. 10.2%) (17).

Pneumocystis pneumonia:

Pneumocystis jirovecii (PJP) is a common opportunistic infection that causes pneumonia in immunocompromised patients and, rarely, in immunocompetent individuals. It typically occurs with CD4 counts <200 cells/mm (44). The presentation of PJP in a patient with HIV infection is typically subacute, characterized by a slow onset of dry cough and dyspnea. PJP in patients without HIV infection presents as an acute illness associated with severe hypoxia and results in rapid respiratory deterioration and respiratory failure (45). The radiographic findings of PJP are nonspecific, and in as many as a third of infected patients, they may be normal (46).The most common high-resolution CT (HRCT) finding of PJP is diffuse GGO, which is often greater in extent in patients without HIV infection (45). With more advanced disease, crazy paving pattern, consolidation, nodules and cysts can also develop. Lung consolidation is more common in patients without HIV infection (47) [Figure 4].

Unlike COVID-19, PJP predominantly affects immunosuppressed patients. Although there may be widespread GGO in PJP, in contrast to COVID-19 pneumonia, it is upper lobe predominant. Nodules, cysts, and spontaneous pneumothorax can also develop.

INTERSTITIAL LUNG DISEASES

Nonspecific interstitial pneumonia:

Nonspecific interstitial pneumonia (NSIP) is a common interstitial lung disease (ILD) associated with a number of conditions such as connective tissue disorders, i.e., Systemic Sclerosis, Sjögren's syndrome, polymyositis, dermatomyositis and systemic lupus erythematosus (SLE). Additionally it can be related to autoimmune diseases such as rheumatoid arthritis, primary

biliary cirrhosis, graft versus host disease or drug induced (48, 49). NSIP typically presents in middle age patients, with a higher predilection in women. The symptoms are non-specific and include chronic dyspnea and cough without sputum production. Pulmonary function tests show a restrictive pattern of decreased lung function and reduced gas exchange capacity. HRCT of the chest demonstrates predominantly basilar perivascular GGOs in the earlier stages of the disease, known as cellular NSIP. As the disease progresses fibrotic changes develop in the form of traction bronchiectasis, volume loss, architectural distortion and subpleural irregular reticular opacity [Figure 5]. A hallmark feature of NSIP on HRCT chest is subpleural sparing, however, it is only seen in a few cases (50). Microcystic honeycombing maybe seen with NSIP, where there are subpleural cystic spaces measuring less than 4 mm.

In comparison to COVID-19, the symptoms of NSIP are insidious in onset. There is known association with connective tissue disorders or other predisposing condition. Subpleural sparing, when present is considered specific for NSIP. Stigmata of fibrosis (traction bronchiectasis, architectural distortion and honeycombing) may be seen. If rapidly developing airspace consolidation or ground glass abnormality is seen in an acutely ill patient with NSIP, one should consider the possibility of an acute exacerbation (51).

Desquamative interstitial pneumonia:

Desquamative interstitial pneumonia is a relatively rare ILD seen more commonly in men. It can also be related to marijuana smoke inhalation, infections such as HIV, toxins or occupational exposure such as asbestos (52, 53, and 54). Patients are predominantly middle aged with progressively worsening shortness of breath and chronic cough. Majority of them are smokers. HRCT demonstrates predominantly peripheral and lower lobe GGOs [Figure 6]. Some cases may demonstrate fine linear or reticular opacities, in the peripheral and basal lung zones (55).

The strong association of DIP with smoking is a useful differentiating feature. Small cystic spaces may develop within the areas of GGO, not usually seen with COVID-19 (56).

Organizing pneumonia:

Patients with organizing pneumonia (OP) present with a relatively short history of breathlessness. Additionally they have non-productive cough, weight loss, malaise and fever. OP may have unilateral or bilateral lung involvement and has myriad pulmonary manifestations. The most frequent features on HRCT include bilateral, multifocal, patchy consolidations (present in up to 90% of cases) and ground-glass abnormalities (57) [Figure 7]. Less commonly bronchovascular nodules and bronchial wall thickening can be seen. The reverse halo sign also called atoll sign is considered a hallmark feature, however is seen in only 20% of patients (58). A perilobular pattern is seen in over half of the patients. It appears as polygonal mainly subpleural opacities surrounded by aerated lung (59). The lung manifestations of OP that resemble COVID-19 disease include lower lobe, subpleural and peribronchovascular predominant GGOs and opacities with reverse-halo appearance. The former opacities are migratory in 11-24% (60).

Presence of predisposing conditions can suggest OP. In contrast to COVID-19, pulmonary opacities are often migratory. Perilobular thickening, if present is another helpful differentiating feature. Patients typically respond to steroids.

EXPOSURES

Inhalational:

Hypersensitivity pneumonitis:

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis (EAA), is also known as bird fanciers disease, farmer's lung and hot tub lung, based on the inciting agent. The disease is divided into acute, subacute and chronic type based on timing since presentation. Each of these stages has their own distinctive appearance on HRCT and patients may present with some degree of overlap between stages (61). In the acute phase patients typically present with fever, cough, dyspnea of short duration and myalgia, while they present with weight loss, fatigue, exertional dyspnea, cough possibly with clear sputum in the chronic stages. There are subtle to more diffuse GGOs in the acute phase, which may mimic pulmonary edema (62). The subacute stage is seen weeks to months after the first exposure to allergen. There are distinct tiny centrilobular pulmonary nodules, measuring less than 6 mm. There may be accompanying GGOs. In the fibrotic stage there is bilateral predominantly perihilar fibrosis with mid zone predominance. The

distinct feature of HP is mosaic attenuation of the lungs. This pattern represents geographical areas of high attenuation interspersed with areas of low attenuation due to air trapping (Headcheese sign) [Figure 8]. Rarely, lung cysts may be present, related to small airways disease (63).

Although widespread GGO with HP, can appear similar to COVID-19 pneumonia, other findings such as poorly defined centrilobular GGO, mosaic attenuation, and air trapping on expiratory images can help distinguish the two conditions (Figure 8). In late HP, mid to upper lung zone fibrosis may be present.

Electronic Cigarette or Vaping Product Use Lung Injury (EVALI):

The Center of Disease Control (CDC) identified an outbreak of a respiratory illness in patients with history of vaping in 2019. The entity which is mainly identified in younger patients was named EVALI, given its association with use of e-cigarettes (64). EVALI clinically manifests as an acute viral illness with nearly all patients reporting respiratory symptoms, 75% report also had gastrointestinal symptoms while 85% reported constitutional symptoms (65). It is a diagnosis of exclusion. Most patients improve on supportive treatment, although a small percent succumb to the illness (66). At HRCT, patients demonstrate bilateral and symmetric diffuse hazy ground glass opacities with subpleural sparing without zonal predominance [Figure 9]. Upper lung zone predominant centrilobular nodules may also be present. Later in the disease process there is evidence of organization with architectural distortion and stigmata of fibrosis (64).

Most patients report their last episode of vaping the week before symptom onset. In contrast to COVID-19, the GGOs in EVALI are most pronounced centrally with conspicuous subpleural sparing. Any of the lung zones may be involved. Presence of upper lobe predominant centrilobular nodules is another useful differentiating feature.

Drug toxicity:

There is a growing list of drugs leading to pulmonary adverse effects with recent addition of immunotherapy related medications to the list. The characteristic feature of drug induced pneumonitis is the onset of symptoms such as dry cough and breathlessness following the use of

a new medication. Drug induced pneumonitis usually occurs while the patient is taking the drug rather than after withdrawal. There are varied manifestations, including diffuse GGOs, depending on the inciting drug. The on-line website and mobile app Pneumotox is very useful to help sort out the number of drugs that can be associated with lung pathology (67). We have discussed the imaging appearance and differentiating features of ILD above, which are common drug related findings in the lungs. This section will focus on Immune checkpoint inhibitors as pneumonitis related to these drugs bears close resemblance to COVID-19. Drug-related pneumonitis is observed in 3-6% of patients with non-small cell lung cancer (NSCLC) who are on immunotherapy (68, 69). Four CT patterns have been reported: Cryptogenic organizing pneumonia (COP), NSIP, HP and acute interstitial pneumonia (AIP) [Figure 10].

Diagnosis of drug-induced lung disease is based on definite temporal relation between drug intake and development of respiratory symptoms or imaging abnormality. The relationship may be difficult to establish when lung disease develops after drug withdrawal. Drug-withdrawal generally results in improvement.

MISCELLANEOUS

Pulmonary edema:

Pulmonary edema is the abnormal accumulation of fluid in the extravascular compartments of the lung, and, may be classified as increased hydrostatic pressure edema seen in heart failure, permeability edema with diffuse alveolar damage (DAD) as seen in ARDS, permeability edema without DAD which can be seen with administration of various drugs, and ingestion of toxins, or mixed edema seen in patients with stroke, status epilepticus and subarachnoid hemorrhage (70). Symptoms include acute breathlessness, cough, wheezing, orthopnea and paroxysmal nocturnal dyspnea. Findings of interstitial pulmonary edema are GGO, bronchovascular and interlobular septal thickening (71). Alveolar edema manifests as airspace consolidation in addition to the above findings. Pleural effusions are a frequent accompanying finding in cardiogenic pulmonary edema (72) [Figure 11].

History of an acute cardiac event or of progressive symptoms of heart failure suggests this diagnosis over COVID-19. The distribution of GGO's (usually central or gravity-dependent),

lymphadenopathy, and pleural effusions, in hydrostatic pulmonary edema, are useful differentiating features. There may be indicators of cardiac disease on imaging, including coronary artery calcifications, cardiomegaly and evidence of prior coronary intervention.

As previously mentioned, patients may develop pulmonary edema from COVID-19 related cardiac involvement [Figure 12] (73).

Aspiration:

Aspiration pneumonia occurs due to an insult from entry of a foreign substance into the respiratory tract which could be solid or liquid. Lung damage is mainly the result of pulmonary infection from aspiration of colonized oropharyngeal secretions. Risk factors include alcohol intoxication, general anesthesia, loss of consciousness, structural abnormalities of the pharynx and esophagus, and neuromuscular disorders (74). Clinical features range from no symptoms to severe distress with respiratory failure. Symptom onset may be acute or sub-acute. Acute chemical pneumonitis is characterized by a sudden onset of dyspnea, hypoxemia, tachycardia, and diffuse wheezes or crackles (75).

Aspiration can lead to the development of lobar or segmental pneumonia, bronchopneumonia, lung abscess, and empyema. In recumbent patients, the posterior segment of the upper lobes and the superior segment of the lower lobes are most commonly involved. Aspiration is more likely to involve bilateral basal segments, middle lobe, and lingula when it occurs while the patient is upright (76). A chest radiograph may be negative early in the course of aspiration pneumonia. Komiya et al described that GGOs, centrilobular nodules, consolidation and atelectasis are frequently noted CT findings with aspiration (77). Chronic aspiration results in bronchiectasis and tree-in-bud opacities (74).

There are similarities in the imaging appearance of aspiration and COVID-19 pneumonia due to involvement of peripheral portions of lungs with mixed density parenchymal opacity. The presence of centrilobular nodules, dependent tree-in-bud nodularity, and, when present, complications such as lung abscess, empyema or visible aspirated material are helpful differentiating features. Additionally, imaging findings of predisposing conditions may be present, e.g., dilated esophagus, neuromuscular disorders and anatomic abnormality, such as tracheo-esophageal fistula and head and neck malignancy (78).

Diffuse alveolar hemorrhage:

Diffuse alveolar hemorrhage (DAH) occurs due to passage of blood into the alveoli. It can be seen in coagulation disorders, antiphospholipid antibody syndrome, connective tissue diseases, vasculitides, medications, inhaled toxins, pulmonary hemosiderosis and pulmonary veno-occlusive disorders. Patients with DAH may present with hemoptysis and/or anemia on laboratory testing. A third of patients may not have hemoptysis. BAL is usually required to confirm the diagnosis and rule out other causes for the opacities on imaging. Imaging findings depend upon the chronicity of the process. Initially DAH may present with GGOs. After two to three days intralobular and smooth interlobular septal thickening superimpose on areas of GGOs and may sometimes give rise to a crazy-paving pattern (79) [Figure 13]. In the chronic stages, the GGOs typically recede and there maybe residual centrilobular nodules.

There is often history of hemoptysis and a new drop in hemoglobin which favors this diagnosis. DAH is frequently associated with connective tissue disease and renal disease. BAL shows sequentially increasing RBC counts. The GGOs in DAH, unlike COVID-19 do not have a specific pattern, otherwise, imaging findings of DAH are very similar to COVID-19 and differentiation may only be possible based on clinical history, comparison with any available prior imaging, and BAL or viral testing.

Pulmonary alveolar proteinosis:

Pulmonary alveolar proteinosis (PAP) is characterized by periodic acid Schiff stain positive material within the alveoli. It maybe idiopathic in origin, related to hematological malignancies, seen in immunosuppressed patients or inhalational lung disease. Typically patients are asymptomatic or present with minimal dyspnea. Their CT chest findings are out of proportion to their clinical symptoms. LDH may be elevated. PAP presents with smooth interlobular septal thickening with GGOs in both lungs giving the characteristic "crazy paving" appearance of the lungs (80) [Figure 14]. Crazy-paving in PAP is widespread with sharply marginated areas of lobular sparing.

Strong association with smoking and patient presentation with non-specific symptoms and slow development of exercise intolerance guide towards PAP. Unlike COVID-19, there is no zonal

predilection. Patients may recall a history of similar episode in the past and improvement with BAL [Figure 15].

Eosinophilic Pneumonia:

Patients often have asthma and slow onset of fever and respiratory symptoms. The imaging appearance of this condition is classically known as 'photographic negative of pulmonary edema' as the opacities are distinctly peripheral (81). The parenchymal abnormality consists of consolidation and GGO with an upper-lung predominance. Crazy-paving may be present.

Indolent clinical presentation is indolent and middle or upper zone predilection and non-segmental involvement are useful differentiating features.

Conclusion:

The typical chest CT imaging features of COVID-19 pneumonia have low specificity due to their overlap with a number of other conditions. This review has focused on highlighting these differences with imaging examples. It is important to note that when the prevalence of COVID-19 is high, even atypical imaging features are more likely to be COVID-19. Although definitive diagnosis cannot be made based on CT imaging features alone, the use of a combination of clinical and imaging findings can substantially improve the accuracy of diagnosis.

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FIGURES

a   b   c

d   e   f
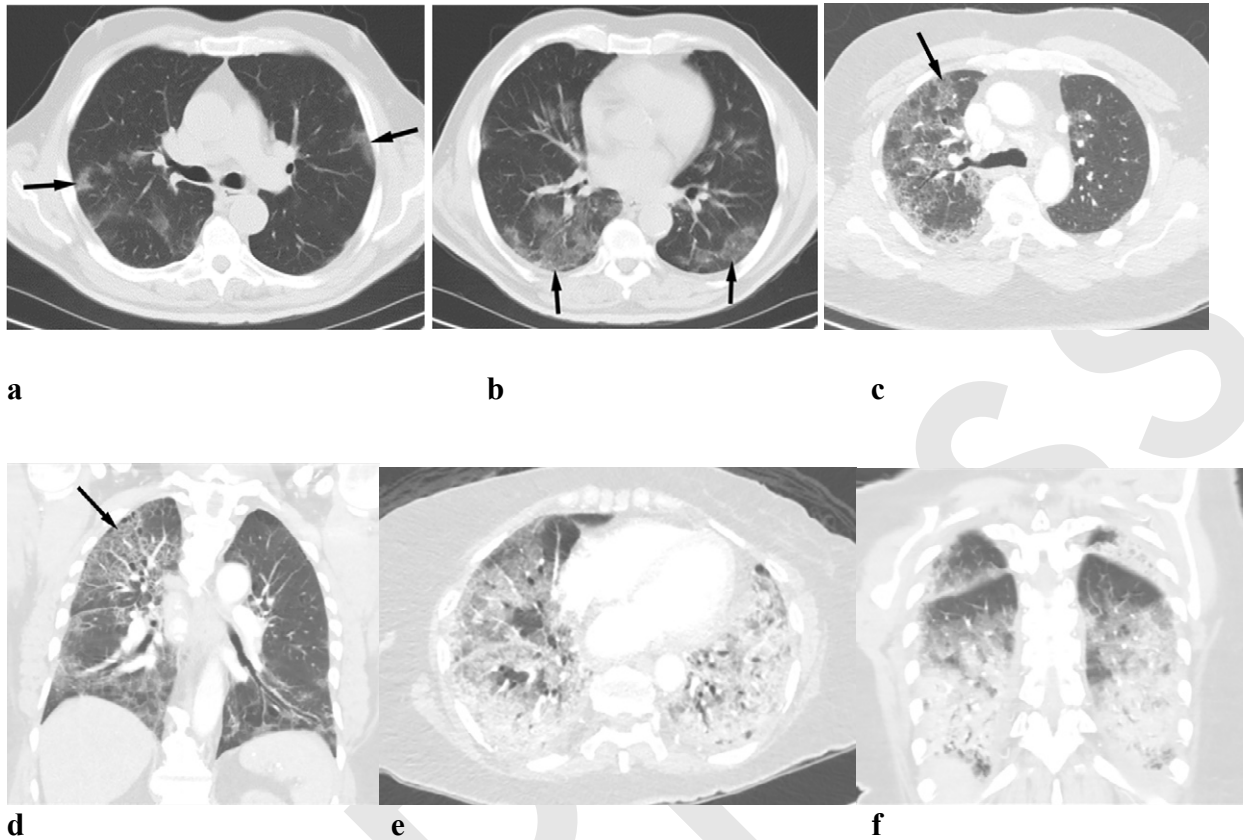
Figure 1. (a,b) COVID 19 pneumonia: A 77-year old male patient presented with low grade fever and shortness of breath since 1 week. Chest CT shows hazy opacities in both lungs predominantly peripheral in distribution (arrows). These are the typical features of the disease that have been reported with COVID -19 infection. **(c,d)** COVID crazy paving: The patient is a 58 year old male presents with lightheadedness. CXR and CT chest supported viral pneumonia diagnosis. His COVID testing was positive. CT shows crazy paving pattern (arrow). **(e,f)** COVID consolidation: 86 year old female with past medical history of hypertension, hyperlipidemia and type 2 diabetes presented with generalized weakness and cough. The patient was found to be positive for COVID. The patient passed away 9 days after admission. Chest CT shows widespread alveolar consolidation with typical radiological findings of ARDS.
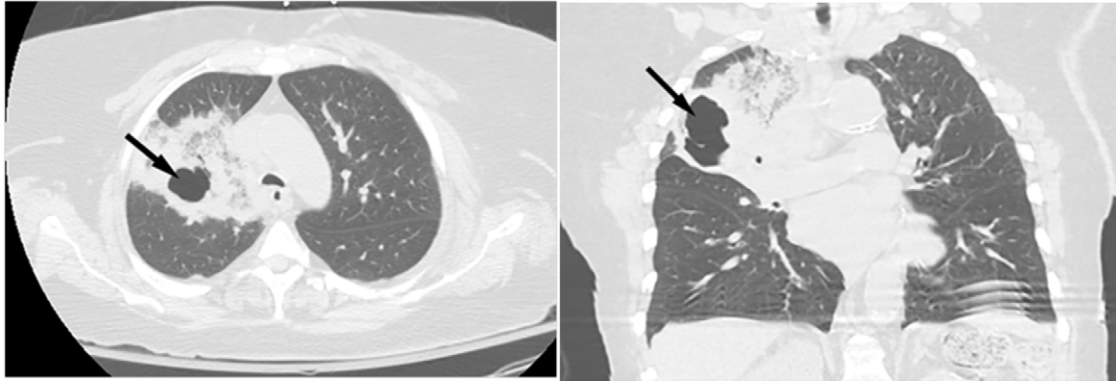
Figure 2. (a,b) Bacterial pneumonia: A 64 year old female patient presented with significant shortness of breath. The patient was noted to have bacteremia secondary to pseudomonas. Chest CT shows mixed ground glass opacities and consolidation in the right upper lobe with cavitation (arrows).
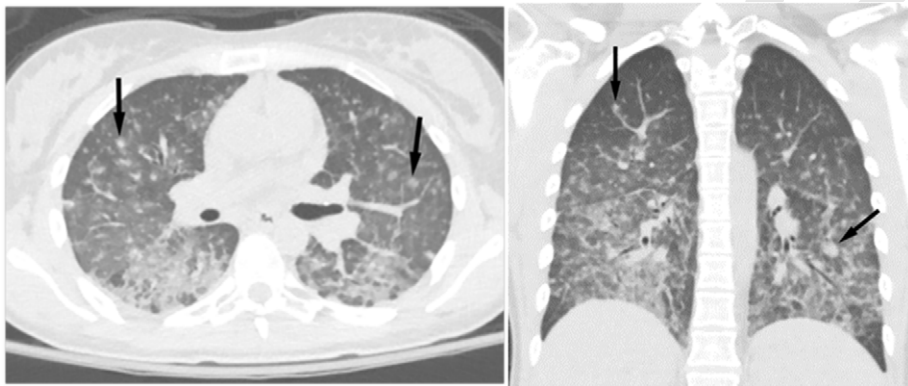

Figure 3. (a,b) CMV pneumonia: 31 year old female with a past medical history of Type 1 Diabetes mellitus complicated by end stage renal disease, s/p kidney/pancreas transplant presents with 2 days of right lower quadrant abdominal pain associated with nausea/vomiting. Upon further work-up, patient was found to have CMV viremia. CT demonstrates diffuse randomly distributed small pulmonary nodules (arrows), many of them are ill-defined and distributed in the secondary pulmonary lobules, and also in the perilymphatic regions.
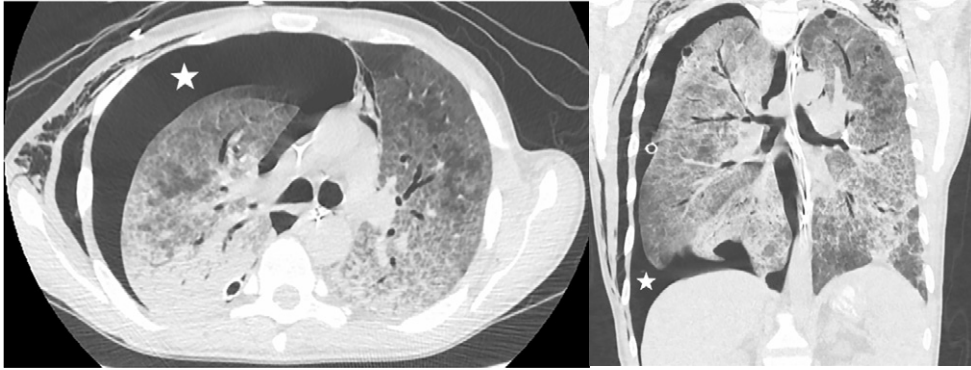
a   **b**

Figure 4a, 4b - Pneumocystis carinii pneumonia: 32 yr old male with AIDS and a CD4 of 7 presented with respiratory arrest. CT demonstrates a moderate right pneumothorax (asterisk) and widespread ground glass and air space opacities.

Figure 5 - Nonspecific interstitial pneumonitis: CT shows subpleural interstitial prominence, most predominant in both lower lobes with associated traction bronchiectasis.
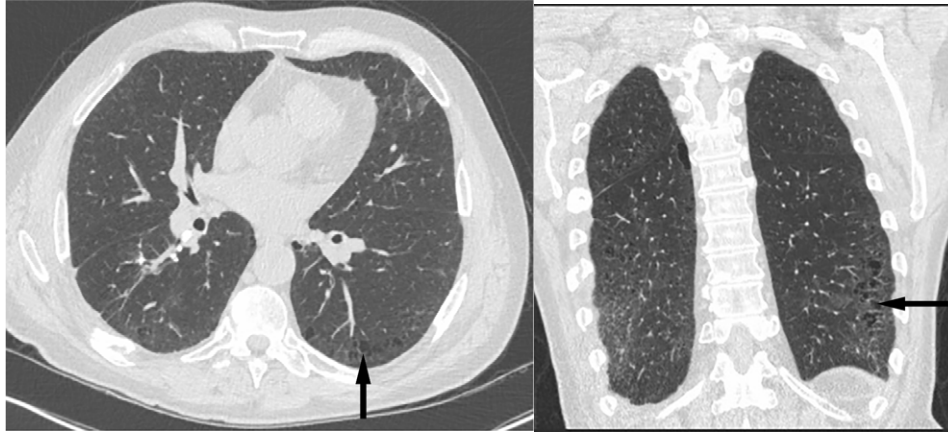
Figure 6a, 6b - Desquamative interstitial pneumonitis: 54 year old male patient with long smoking history presented with declining pulmonary function. CT chest showed irregular linear opacities and small cysts in both lower lobes. Lung biopsy confirmed desquamative interstitial pneumonitis.
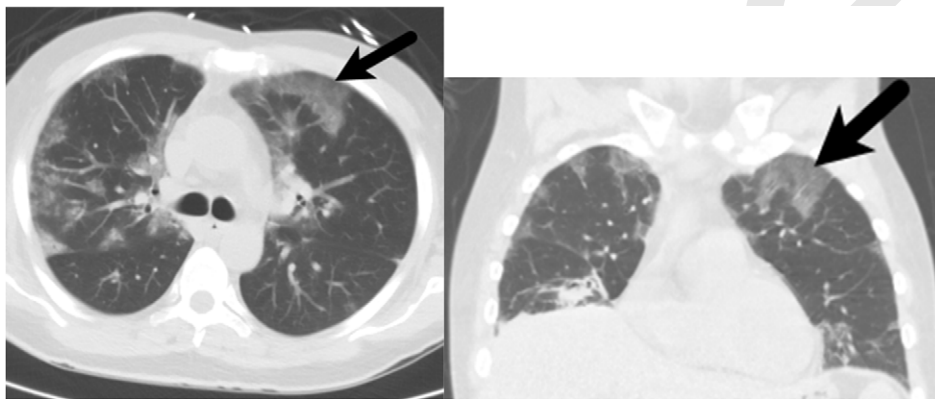

Figures 7a, 7b - Organizing Pneumonia: 43-year-old, Caucasian male with a history of follicular lymphoma, status post chemotherapy. He was admitted for respiratory failure. Lung biopsy yielded organizing pneumonia. He did well on steroids and was discharged.
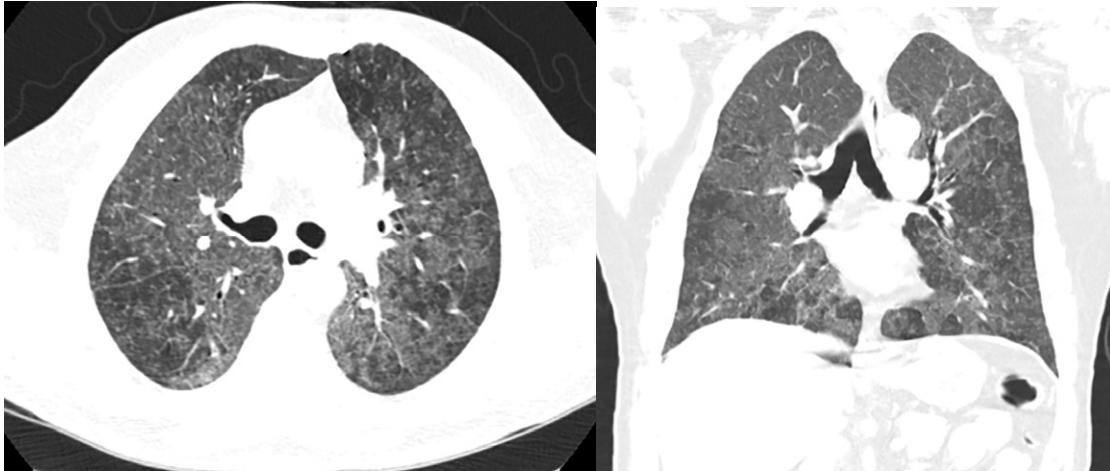
a   **b**

Figure 8a, 8b - Hypersensitivity pneumonitis: 28-year-old female presented with chronic cough associated with shortness of breath dyspnea on exertion. She lives at home where her sister has an African gray parrot. CT shows widespread ground-glass opacities. There is hypoattenuation and hypovascularity of scattered secondary lobules (head cheese sign). Her clinical symptoms worsened and she was diagnosed with hypersensitivity pneumonitis.
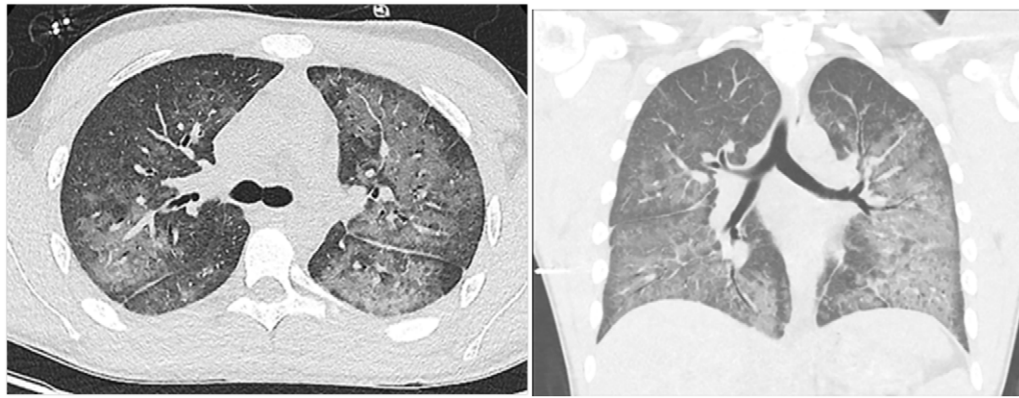
a   **b**

Figure 9a, 9b - E-cigarette or vaping product use associated lung injury: 18 year old male with a history of vaping presented with fever, leukocytosis and pleuritic chest pain. Chest radiograph demonstrates lower lobe predominant air space opacities. CT chest shows multiple perihilar and lower lobe predominant ground glass opacities.
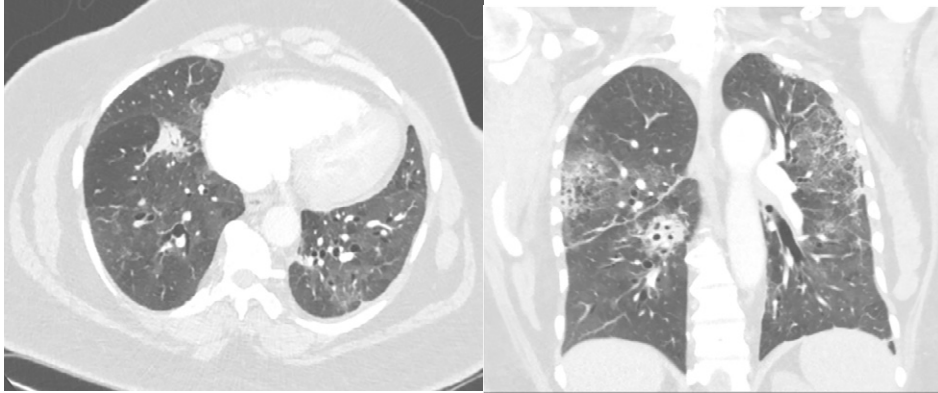
Figure 10a, 10b - Drug induced pneumonitis: 61 year old woman with history of stage IIIA non-small cell lung cancer s/p chemoradiation followed by immunotherapy (durvalumab). Her course was complicated by pneumonitis. The patient improved with steroid treatment.
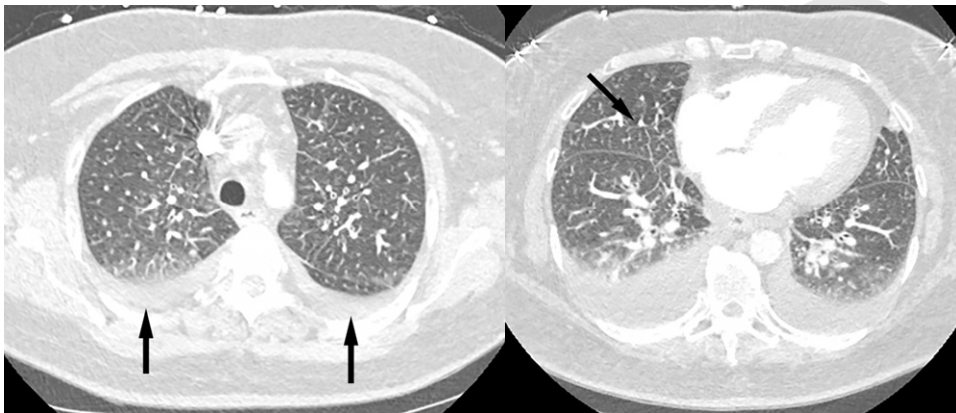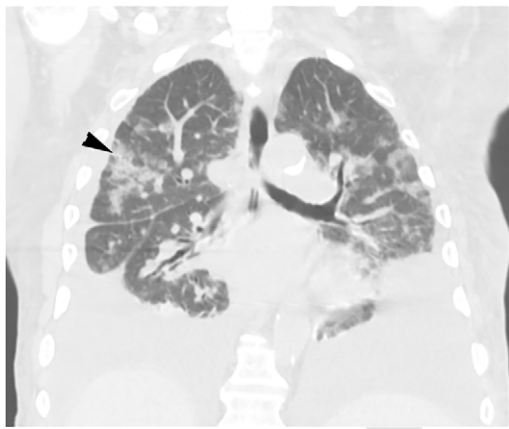

Figure 11a, 11b - Pulmonary edema: A 67 year old female with cardiac history notable for congestive heart failure, coronary artery disease, aortic stenosis and past myocardial infarction presented with dizziness. CT performed to rule out pulmonary embolism demonstrates bilateral pleural effusions and pulmonary interstitial edema (arrows).
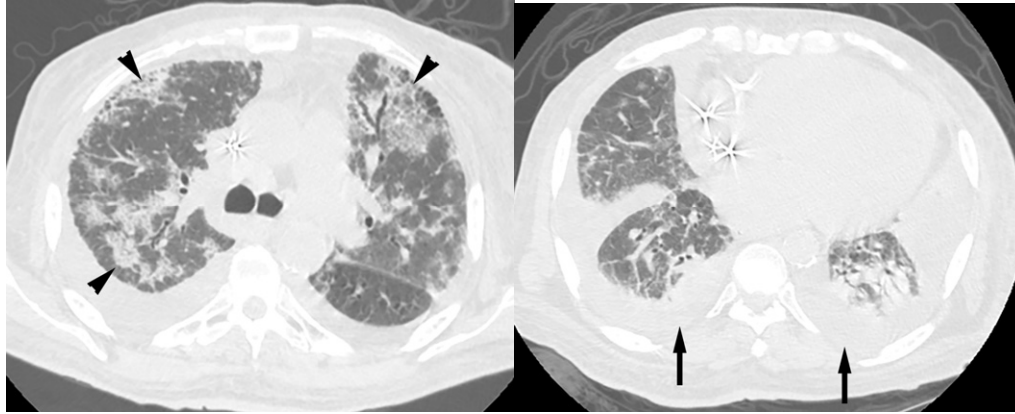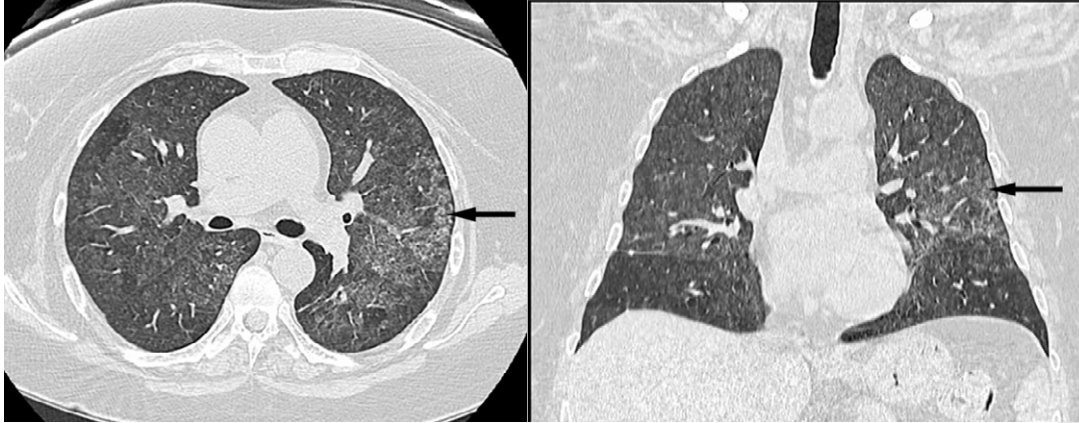
Figure 12a-c -COVID with coexisting heart failure: A 69 year old male presented with acute on chronic CHF with ejection fraction of 28%. The patient tested positive for COVID-19. Note patchy peripherally distributed GGO's (arrowheads). The patient also has moderate bilateral pleural effusions (arrows).

Figure 13 (a, b) Diffuse alveolar hemorrhage: 47 yr old female w recurring hemoptysis. CT demonstrates widespread ground glass opacities in both lungs (arrow).
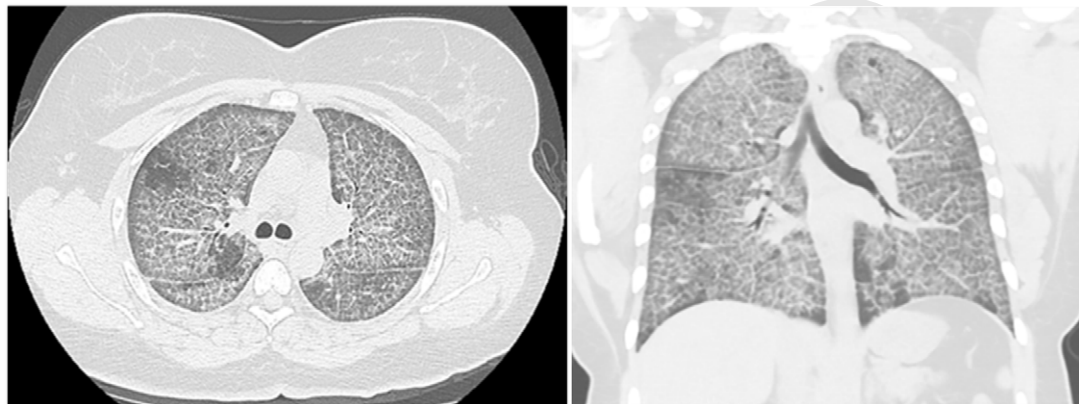
Figure 14 (a, b) Pulmonary alveolar proteinosis: 41 year old female who approximately 6 months ago presented with shortness of breath and a dry cough. A CT scan showed extensive crazy paving appearance of the lung parenchyma, ground-glass opacities with septal thickening. The patient underwent bronchoscopy with biopsy. Findings of bronchoscopy were consistent with pulmonary alveolar proteinosis.
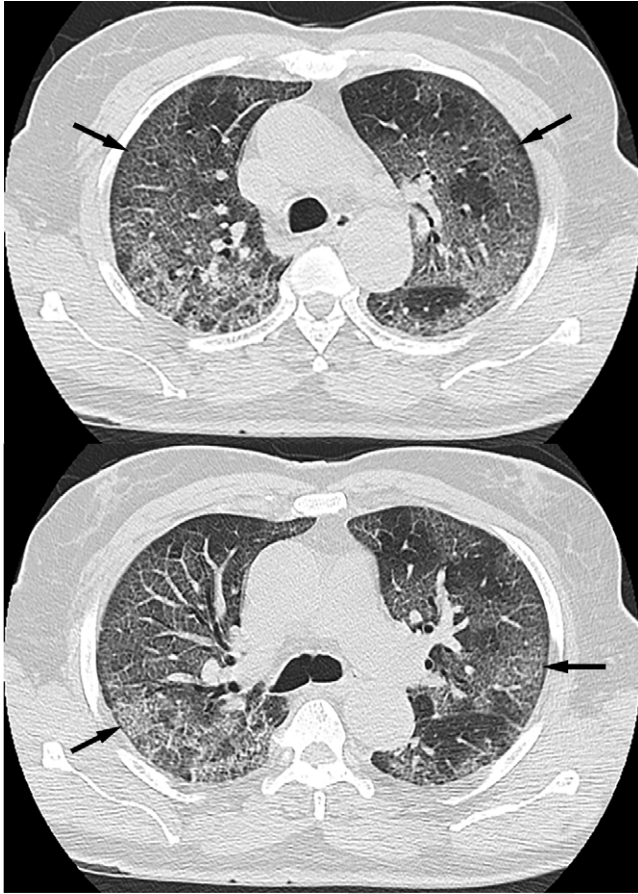
Figure 15 (a,b) COVID mimicking PAP with crazy paving appearance: A 77 year old male was admitted for fever and cough. CT chest axial lung windows demonstrates crazy paving appearance (arrows) mimicking pulmonary alveolar proteinosis. The patient's PCR was positive for COVID-19.

Table 1: Common chest CT findings for COVID-19 pneumonia and their original publications

CT Finding	Number of patients in study	Percentage (95% CI)	Reference First author's last name (Ref)
Ground glass opacity	80 101 393	91 86 88	Wu et al (10) Zhao et al (11) Salehi et al (12)
Consolidation	80 51 82	63 55 63	Wu et al (10) Song et al (1) Pan et al (13)
Lower lobes/ posterior	55 51 62	55 81 77	Zhao et al (11) Salehi et al (12) Zhou et al (14)
Peripheral distribution	101 108 121	87 90 76	Zhao et al (11) Han et al (15) Salehi et al (12)
Bilateral	83 497 121	82 88 60	Zhao et al (11) Salehi et al (12) Bernheim et al (16)

Table 2: Uncommon CT findings in isolated COVID-19 pneumonia

CT Finding	Number of patients in study	Percentage (95% CI)	Reference First author (Ref)
Unilateral	219 58 145	19 59 19	Bai et al (17) Meng et al (18) Chen et al (19)
Central	101 108 219	1 2 1	Zhao et al (11) Han et al (15) Bai et al (17)
Nodules	101 219 51	23 32 22	Zhao et al (11) Bai et al (17) Li et al (20)
Crazy paving pattern	21 121 219	19 6 5	Chung et al (21) Bernheim et al (16) Bai et al (17)
Reverse halo sign	121 219 51	2 5 4	Bernheim et al (16) Bai et al (17) Li et al (20)

Table 3: Differential diagnosis of CT ground glass opacities in the COVID-19 era

Diagnosis	Association	Location of Parenchymal abnormality	Small nodules	Cavitation	Subpleural sparing	Lymphadeno-pathy	Pleural effusion	Other findings
COVID-19	Signs and symptoms of infection, loss of sense of taste or smell, leukopenia, lymphopenia	Bilateral, basal and subpleural predominant	-	-	-	-	-	
Pulmonary edema	History of heart disease	Perihilar	-	-	-	++	+	Imaging findings of heart disease - cardiomegaly, Coronary calcifications
Bacterial pneumonias	Signs and symptoms of infection	No specific	-	+	-	++	+	
Viral pneumonias	Signs and symptoms of infection; some patients may be immunosuppressed	No specific	-	-	-	+	+/-	No specific differentiating features
Aspiration	Dilated Esophagus Neuromuscular disorders Anatomical abnormality, e.g., tracheo-esophageal fistula, head and neck malignancy etc.	Dependent	Dependent centrilobular and Tree-in-bud ++	+/-	-	+/-	+/-	Air-way opacification
Pneumocystis carinii pneumonia	Immunosuppression CD4 <200	Upper	-	-	-	-	-	Cysts +/- Spontaneous pneumothorax possible
Nonspecific Interstitial pneumonitis	Connective tissue disorder or other predisposing condition	Subpleural Lower lung zone predominant Subpleural sparing	-	-	++	+/-	-	Features of fibrosis-traction bronchiectasis, architectural distortion Honeycombing +/-
Cryptogenic organizing pneumonia	Predisposing conditions +/-	Subpleural, peri-bronchovascular	-	-	-	-	-	Perilobular thickening Migratory opacities Prior episodes
Hypersensitivity pneumonitis	Exposure history in 70%	Upper lung zone predominant	Upper lung zone predominant centrilobular ground glass nodules	-	-	-	-	Air trapping on expiratory CT images Mosaic attenuation Upper and/or mid lung predominant fibrosis +/-
Drug induced toxicity	History of recent drug exposure	No zonal distribution	-	-	-	-	-	No specific differentiating imaging features
Desquamative interstitial pneumonia	Smoking history (in 90%)	Lower lung zone	-	-	-	-	-	Small cystic spaces +/-.
Diffuse alveolar hemorrhage	History of hemoptysis Renal disease Other systemic illness	No specific	-	-	-	-	-	H/o prior episodes may be present Migratory opacities
Pulmonary alveolar proteinosis	Tobacco use Subacute symptom onset H/o prior episodes	No specific	-	-	-	-	-	Pronounced crazy-paving pattern often with lobular or geographic sparing.
e-cigarette or vaping product use associated lung injury	History of vaping (New or increased use history may be helpful)	No specific	Centrilobular and upper lung zone predominant nodularity	-	++	-	-	Subpleural sparing
Chronic Eosinophilic Pneumonia	Asthma Subacute presentation	Upper lung zone	-	-	-	-	-	Crazy paving +/-