Covid 19 differential diagnosis

Community-acquired pneumonia

> see our comprehensive coverage of Community-acquired pneumonia

Differentiating signs/symptoms

- Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.

  Differentiating COVID-19 from community-acquired bacterial pneumonia is not usually possible from signs and symptoms. However, patients with bacterial pneumonia are more likely to have rapid development of symptoms and purulent sputum. They are less likely to have myalgia, anosmia, or pleuritic pain. [705]

Differentiating investigations

- Blood or sputum culture or molecular testing: positive for causative organism.

  RT-PCR: negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA (co-infections are possible).

  CT chest: centrilobular nodules, mucoid impactions. [706]

Influenza infection

> see our comprehensive coverage of Influenza infection

Differentiating signs/symptoms

- Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.

  Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.

  Incubation period is shorter. [707] Symptoms typically peak during the first 3 to 7 days of illness with influenza, compared with week 2 or 3 of illness with COVID-19. [708]

  More common in children. [708] Children with COVID-19 tend to be older, and are more likely to have comorbidities, fever, gastrointestinal symptoms, headache, and chest pain compared with those with influenza. [709]

  Fever is less common. Rhinorrhoea, sore throat, myalgia, headache, and dyspnoea are more common. [707] [710] New-onset smell and/or taste disorders were less common in a case-control study. [711]

Differentiating investigations

- Only testing can distinguish between influenza infection and COVID-19 and identify co-infection. When SARS-CoV-2 and influenza viruses are co-circulating, test for both viruses in all hospitalised patients with acute respiratory illness, and only test for influenza virus in outpatients with acute respiratory illness if the results will change clinical management of the patient. [3]

  RT-PCR: positive for influenza A or B viral RNA; negative for SARS-CoV-2 viral RNA (co-infections are possible).

  Chest x-ray: less likely to be abnormal. [707]

  CT chest: there is emerging evidence that CT can be used for differentiating between influenza and COVID-19. COVID-19 patients are more likely to have rounded or linear opacities, crazy-paving sign, vascular enlargement, and interlobular septal thickening, but less likely to have nodules, tree-in-bud sign, bronchiectasis, and pleural effusion. [712] [713]

  Inflammatory markers and coagulation screen: there is emerging evidence that inflammatory markers (lactate dehydrogenase, erythrocyte sedimentation rate, C-reactive protein) and coagulation parameters are not as high in patients with influenza compared with COVID-19. [714]

Common cold

> see our comprehensive coverage of Common cold

Differentiating signs/symptoms

- Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.

  Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, fever is less common, and headache, rhinorrhoea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms. **[710]**

Differentiating investigations

- RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible).

Common cold

> see our comprehensive coverage of Common cold

Differentiating signs/symptoms

- Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.

  Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms. However, fever is less common, and headache, rhinorrhoea, myalgia, and sore throat are more common. Patients may have a greater number of general symptoms. **[710]**

Differentiating investigations

- RT-PCR: positive for causative organism; negative for SARS-CoV-2 viral RNA (co-infections are possible).

Other viral or bacterial respiratory infections

> see our comprehensive coverage of Atypical pneumonia

Differentiating signs/symptoms

- Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.

  Differentiating COVID-19 from community-acquired respiratory tract infections is not possible from signs and symptoms.

  Adenovirus and *Mycoplasma* should be considered in clusters of pneumonia patients, especially in closed settings such as military camps and schools.

Differentiating investigations

- Blood or sputum culture of molecular testing: positive for causative organism.

  RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).

Pneumocystis jirovecii pneumonia

> see our comprehensive coverage of Pneumocystis jirovecii pneumonia

Differentiating signs/symptoms

- Lack of residence in/travel history to an area with ongoing transmission, or lack of close contact with a suspected/confirmed case of COVID-19 in the 14 days prior to symptom onset.

  Differentiating COVID-19 from pneumocystis jirovecii pneumonia is not usually possible from signs and symptoms.

  Patients are usually immunocompromised (e.g., HIV positive) and duration of symptoms may be longer.

Differentiating investigations

- Sputum culture: positive for *Pneumocystis*.

  RT-PCR: negative for SARS-CoV-2 viral RNA (co-infections are possible).

  CT chest: ground-glass opacity is usually more diffusely distributed with a tendency to spare the subpleural regions. [706]

Pulmonary tuberculosis

> see our comprehensive coverage of Pulmonary tuberculosis

Differentiating signs/symptoms

- Consider diagnosis in endemic areas, especially in patients who are immunocompromised.

  History of symptoms is usually longer.

  Presence of night sweats and weight loss may help to differentiate.

Differentiating investigations

- Chest x-ray: fibronodular opacities in upper lobes with or without cavitation; atypical pattern includes opacities in middle or lower lobes, or hilar or paratracheal lymphadenopathy, and/or pleural effusion.

  Sputum acid-fast bacilli smear and sputum culture: positive.

  Molecular testing: positive for *Mycoplasma tuberculosis*.

Febrile neutropenia

› see our comprehensive coverage of Febrile neutropenia

Differentiating signs/symptoms

- Suspect neutropenic sepsis in patients with a history of recent systemic anticancer treatment who present with fever (with or without respiratory symptoms) as this can be rapid and life-threatening. **[716]**

  Symptoms of COVID-19 and neutropenic sepsis may be difficult to differentiate at initial presentation.

Differentiating investigations

- CBC: neutropenia.

  RT-PCR: negative for SARS-CoV-2 viral RNA.

COVID-19 Differential Diagnosis

Groundglass Mimickers	Differential diagnosis	Overlapping diseases
Insufficient inspiration	Cardiogenic edema	Organizing pneumonia
Asthma	Pulmonary infarctions	Influenza pneumonia
Bronchiolitis obliterans	Alveolar hemorrhage	Pneumocystis pneumonia
Hypersensitivity pneumonitis	Eosinophilic pneumon	Adult respiratory distress syndrome
	Drug-induced pneumonitis	
	Radiation pneumonitis	
	Hypersensitivity pneumonitis	
	NSIP	
	Adenocarcinoma	
	Alveolar proteinosis	

The differential diagnosis of COVID-19 can be arbitrary divided into 3 subgroups:

- Groundglass mimickers
  There is no real ground-glass but high density lung as a result of insufficient inspiration or normal lung looking like ground-glass because it is next to hypoperfused black lung due to vasoconstriction
- Differential diagnosis
  Many diseases that may look like COVID-19, but you should be able to find the differences by combinding CT and clinical findings.
- Overlapping diseases
  Diseases of the lung that have the exact pattern as COVID-19. Distinction can only be made with clinical parameters.

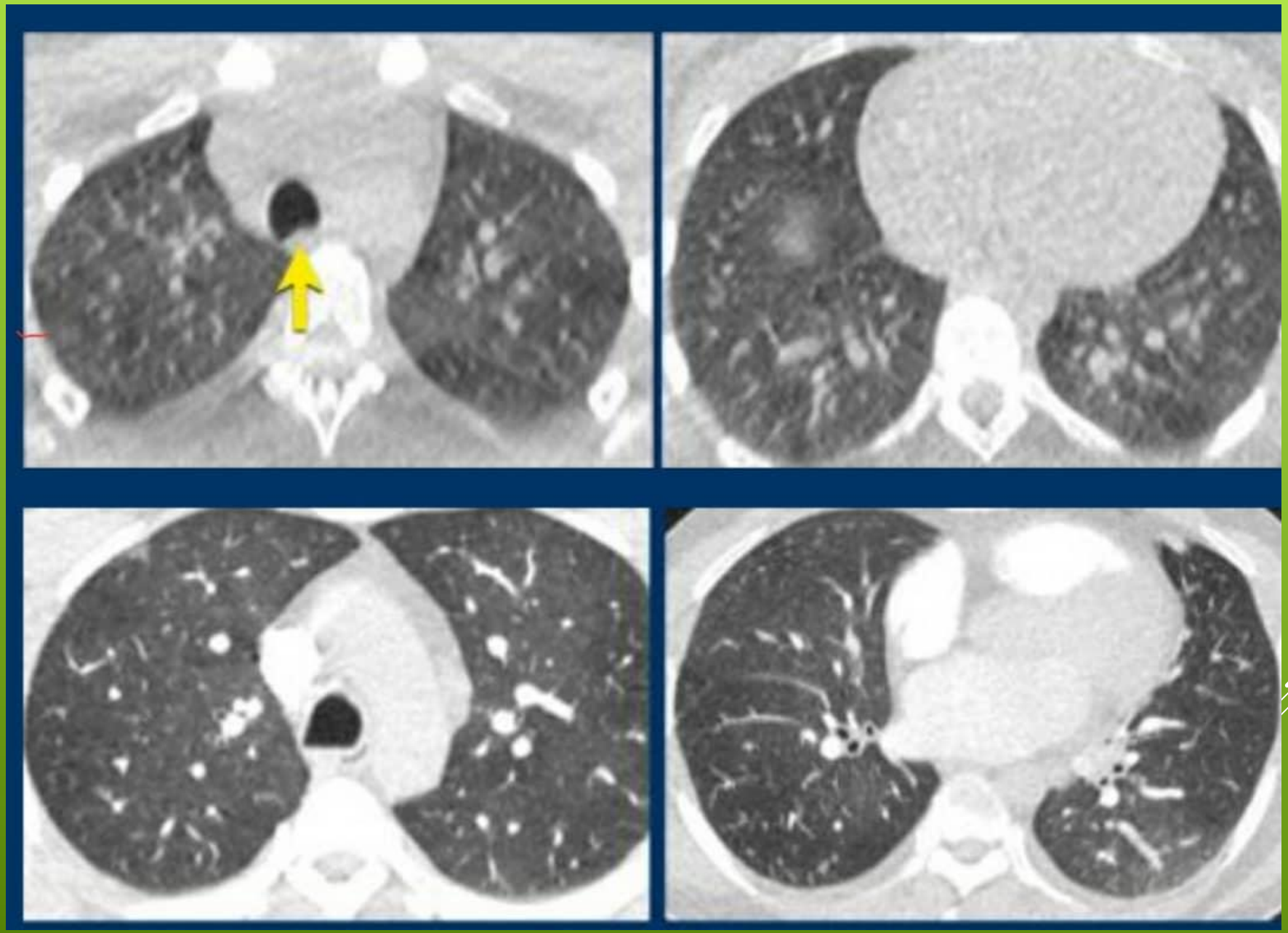
COVID-19 Ground glass mimickers

- **Inadequate inspiration**
- **Mosaic attenuation**
  - hypoperfusion in pulmonary emboli
  - bronchopathy with secondary vasoconstriction in:
    - asthma
    - bronchiolitis obliterans
    - hypersensitivity pneumonitis

Inadequate inspiration

Notice the presence of inward bowing of the posterior membrane, indicative of inadequate inspiration.

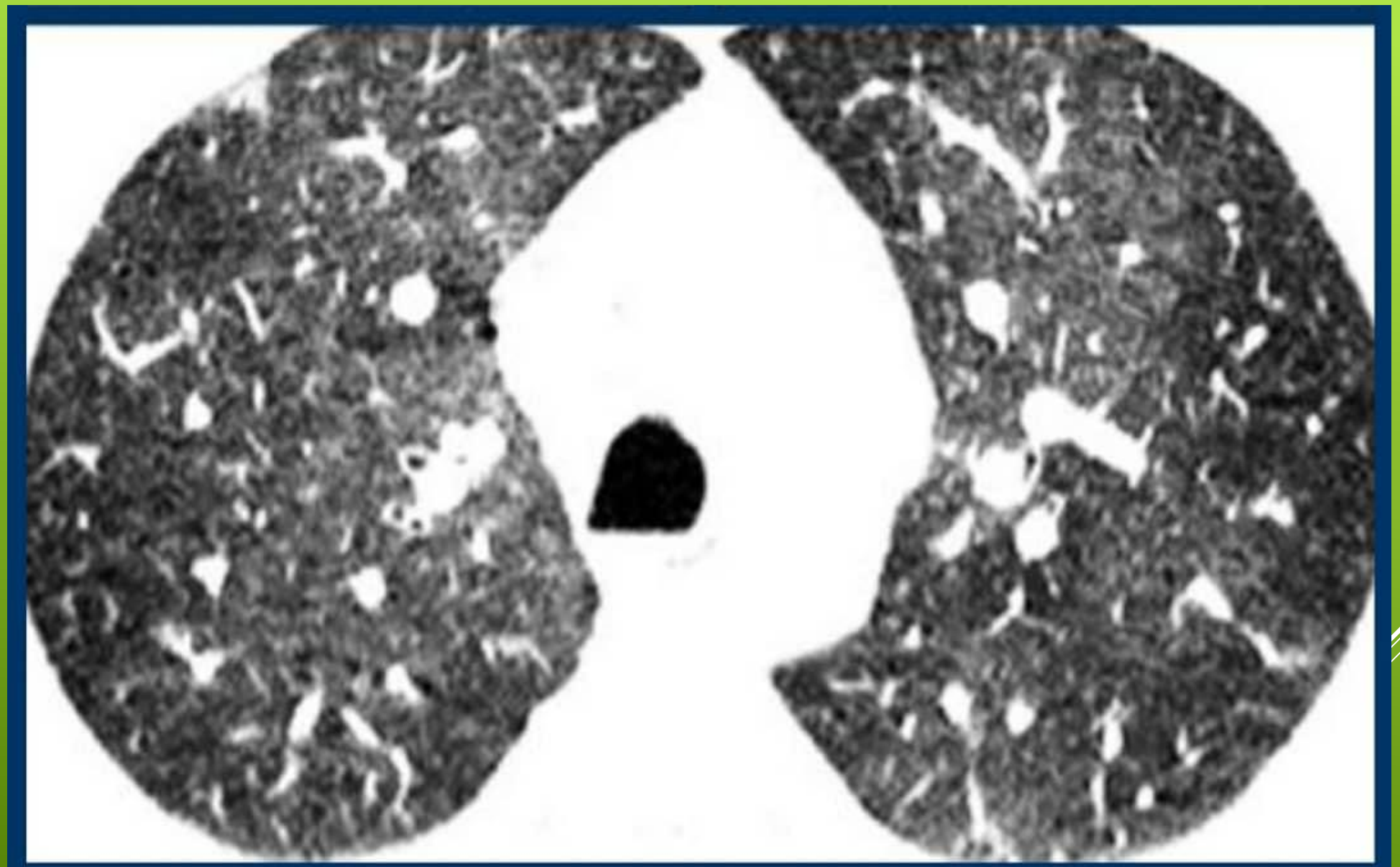
Repeat examination showed normal parenchymal density (not shown).



Mosaic attenuation

Mosaic attenuation of lung parenchyma based on multifocal hypoperfusion or hypoventilation can mimic ground-glass opacities, but is fundamentally distinct.

Here, it is the low density pulmonary parenchyma that is abnormal.
It is caused by bronchopathy with hypoventilation and secondary hypoxic vasoconstriction.
The relatively high density parenchyma is normal.

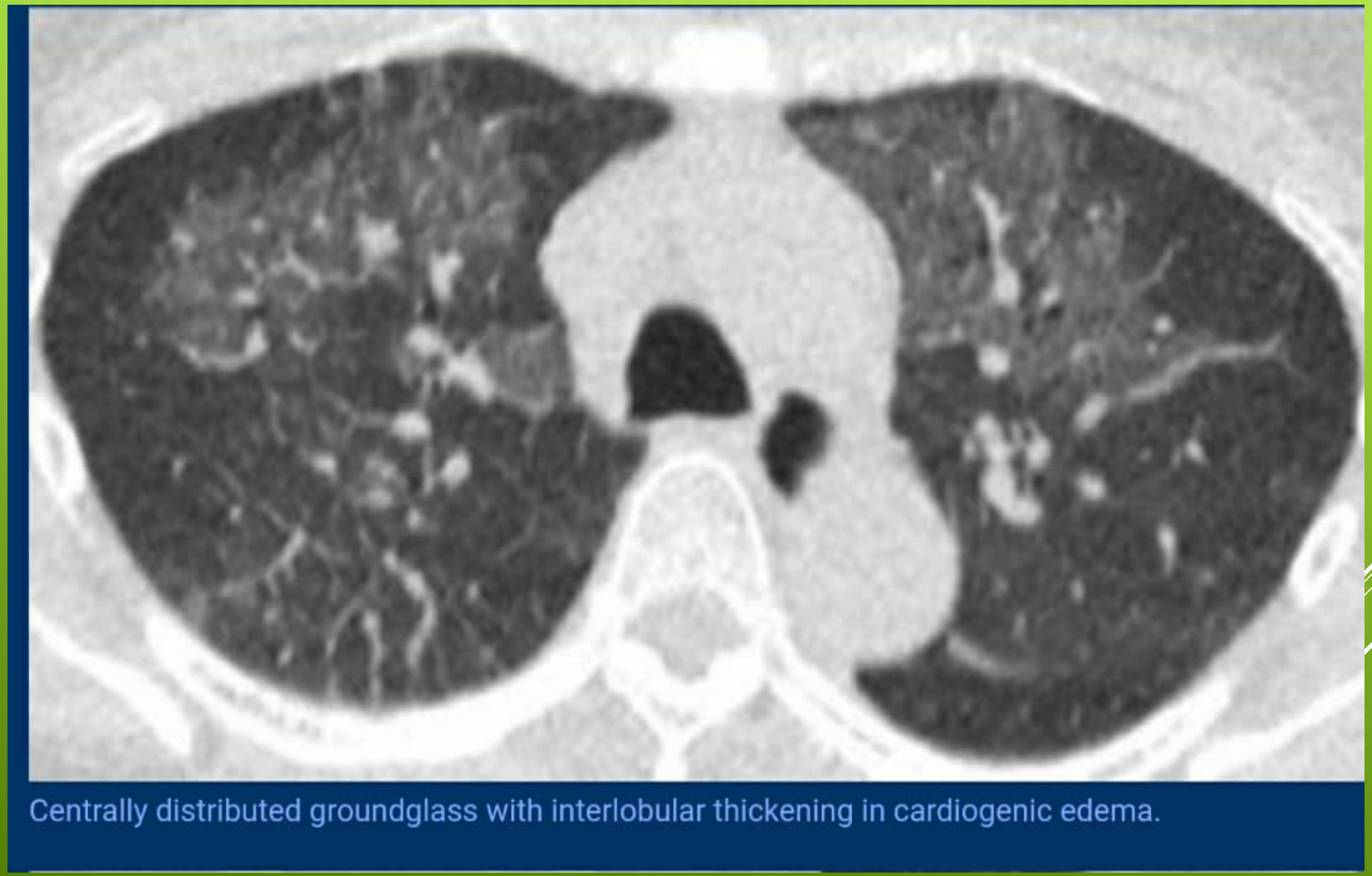


Mosaic attenutaion in a patient with bronchopathy with hypoxic vasconstriction.

Pulmonary cardiogenic edema

Pulmonary cardiogenic edema presents with bilateral ground-glass opacities reflecting extravascular fluid in the alveolar spaces.

These ground-glass opacities are typically more centrally distributed with sparing of the peripheral parenchyma and do not fulfill the complete obligatory COVID-19 feature of location of ground glass close to the pleural surfaces.

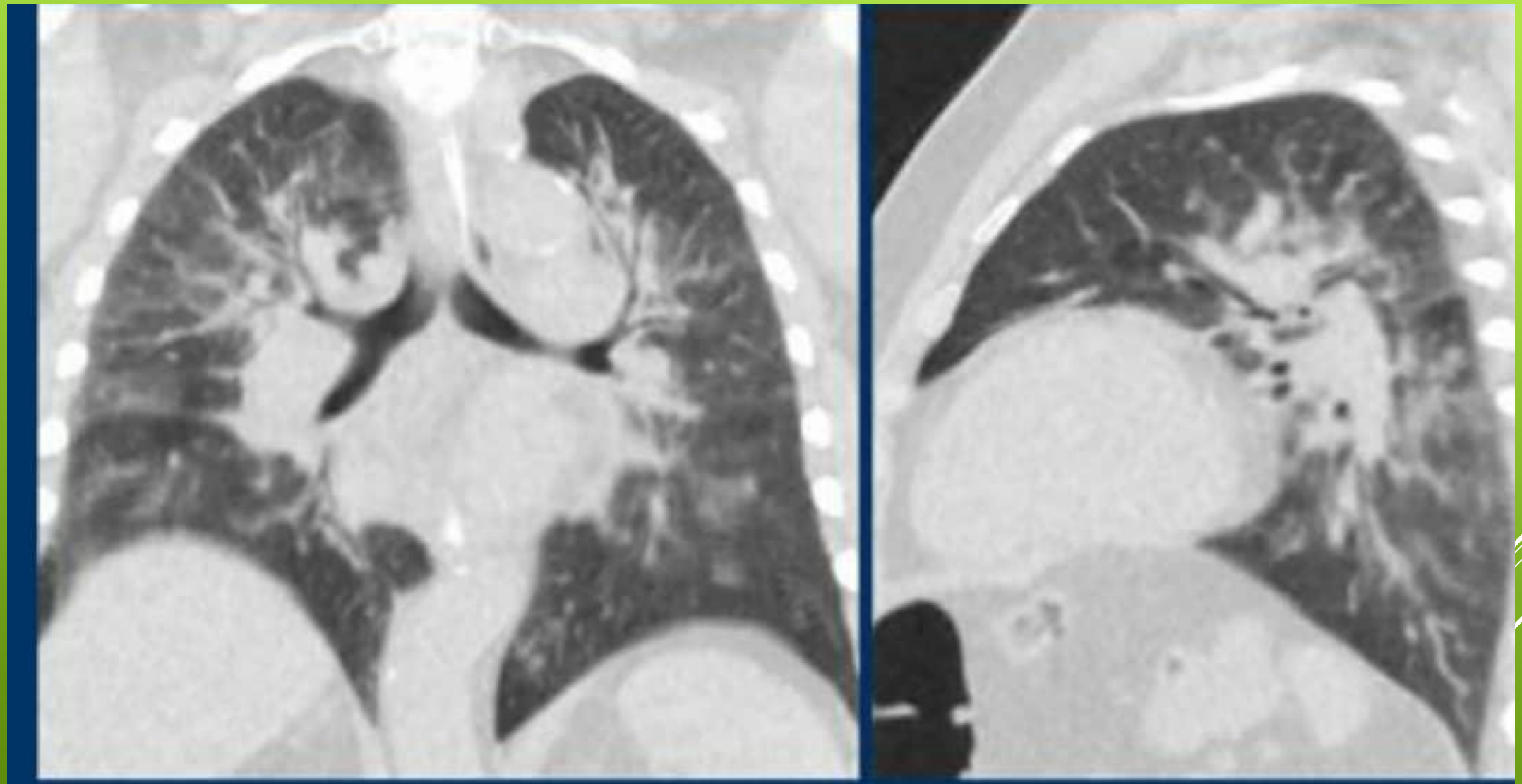


Centrally distributed groundglass with interlobular thickening in cardiogenic edema.

In addition, distribution of edema can be gravity dependent, which can be appreciated on sagittal reconstructions.

Accompanying signs suggestive of cardiogenic edema:

- Interlobular septal thickening
- Diiffuse vascular enlargement
- Lymph node enlargement
- Structural cardiac pathology
- Pleural fluid
- Clinical presentation of the patient



Pulmonary cardiogenic edema with centrally distributed groundglass, diffuse vascular enlargement, lymphnode enlargement and bronchial cuffing.

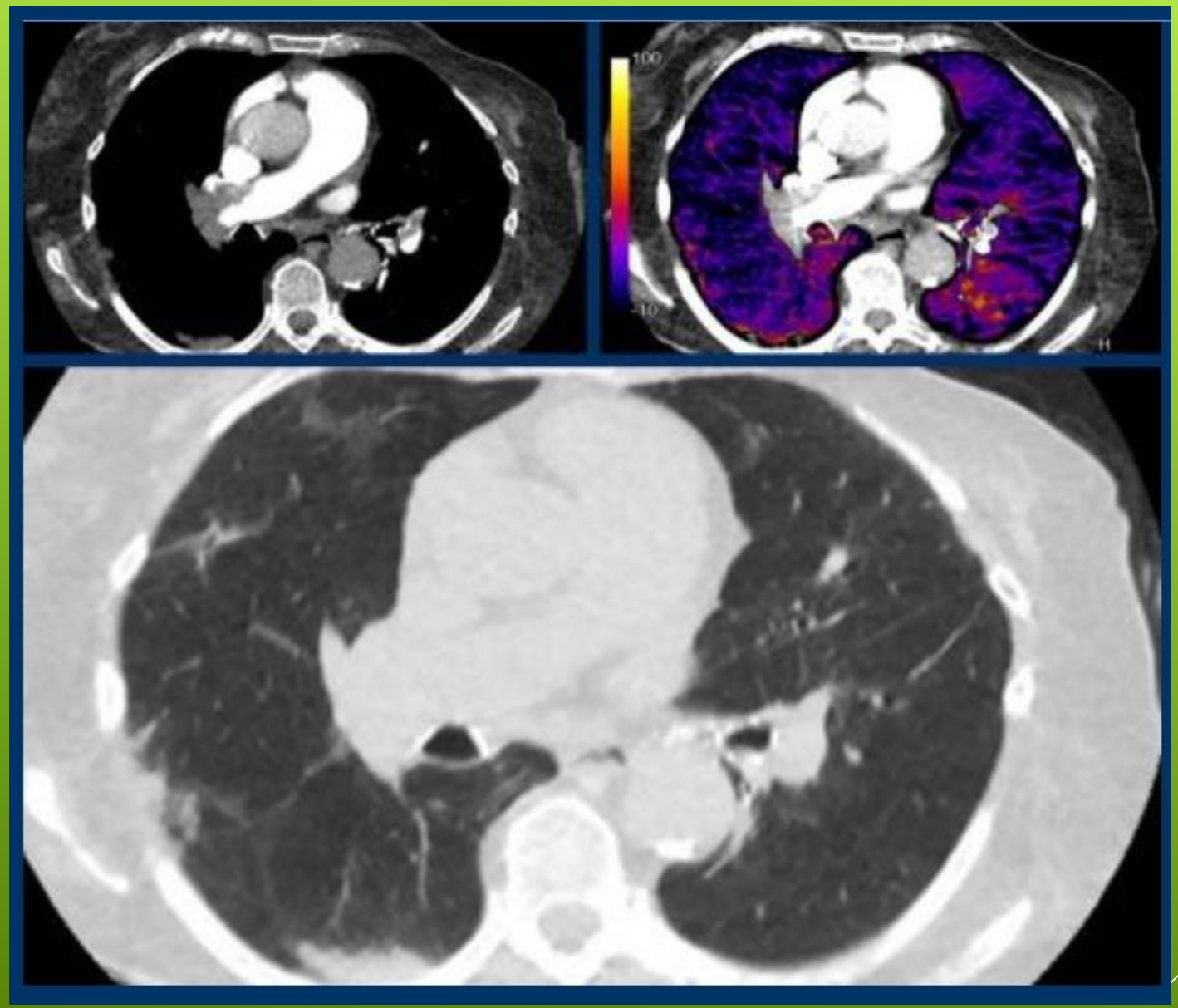
Pulmonary infarctions

Infarctions secondary to pulmonary emboli cause peripheral densities adjacent to the pleural surfaces.

Although these densities in part consist of ground-glass opacities, especially in the early stage, infarctions are frequently more peripheral, triangular and dense.

The images show:

1. Central pulmonary embolism.
2. Corresponding perfusion defects at subtraction iodine mapping.
3. Peripheral, triangular pulmonary opacities in the vascular territories.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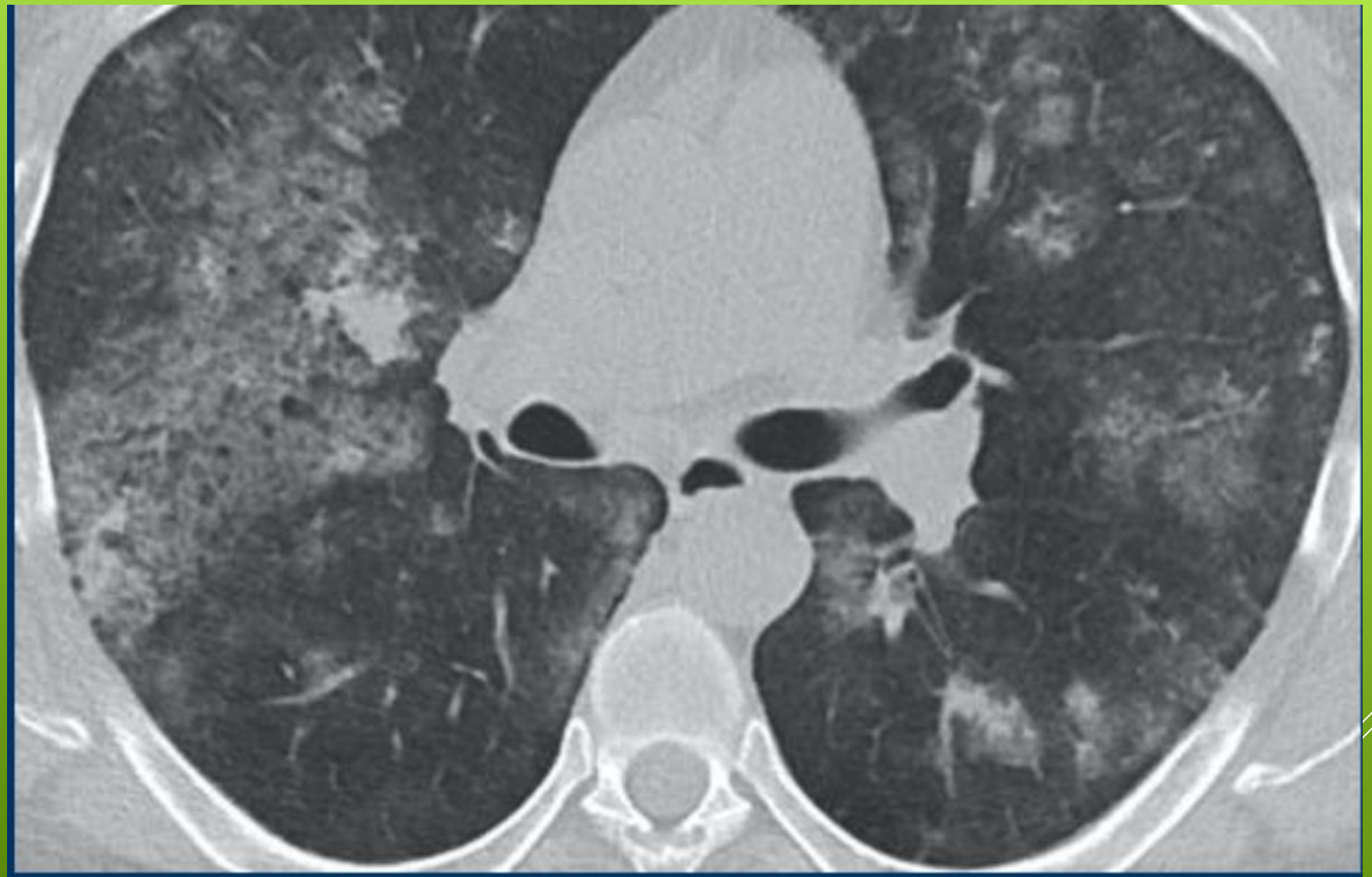
Alveolar hemorrhage

Bilateral and confluent airspace opacities caused by diffuse alveolar hemorrhage such as in e.g. systemic lupus erythomathosus on this image are distributed more along the bronchovascular bundles, and predominantly spare the peripheral pleural surfaces and costophrenic angles.

These opacities should resolve in weeks if bleeding does not recur.

The image shows alveloar hemorrhage with patchy groundglass along the bronchovascular bundles in a patient with secondary vasculitis in systemic lupus erythemathosus.



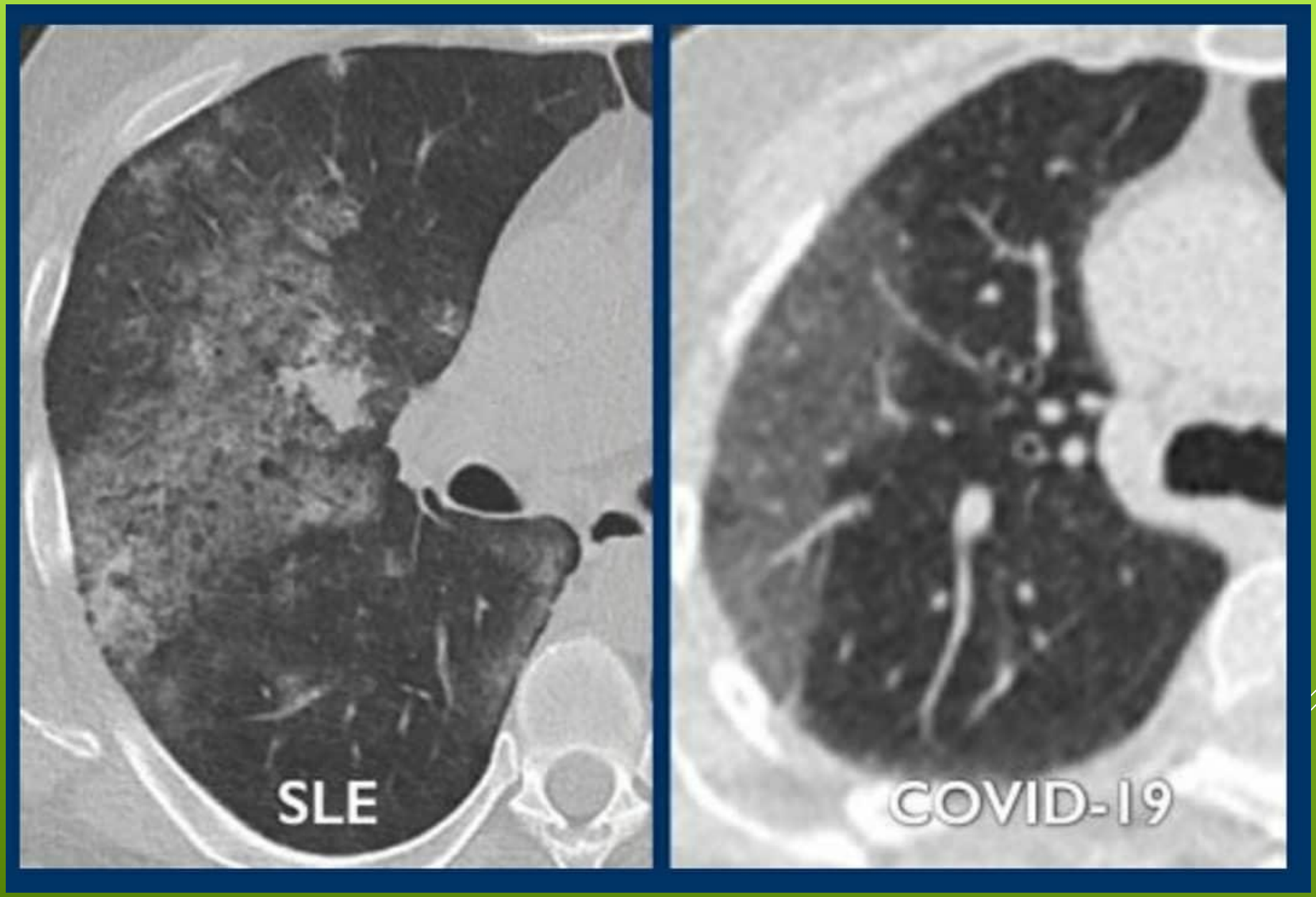
Alveloar hemorrhage in a patient with SLE.

In COVID-19 the groundglass is more peripheral and diffuse.

More chronic or subacute hemorrhage causes crazy paving and fibrosis.

In addition, clinical presentation including fever, cough and leukocytosis are less common in patients with alveolar hemorrhage, although the clinical presentation of diffuse pulmonary hemorrhage remains highly variable.

Only approximately 2/3 of patients have hemoptysis

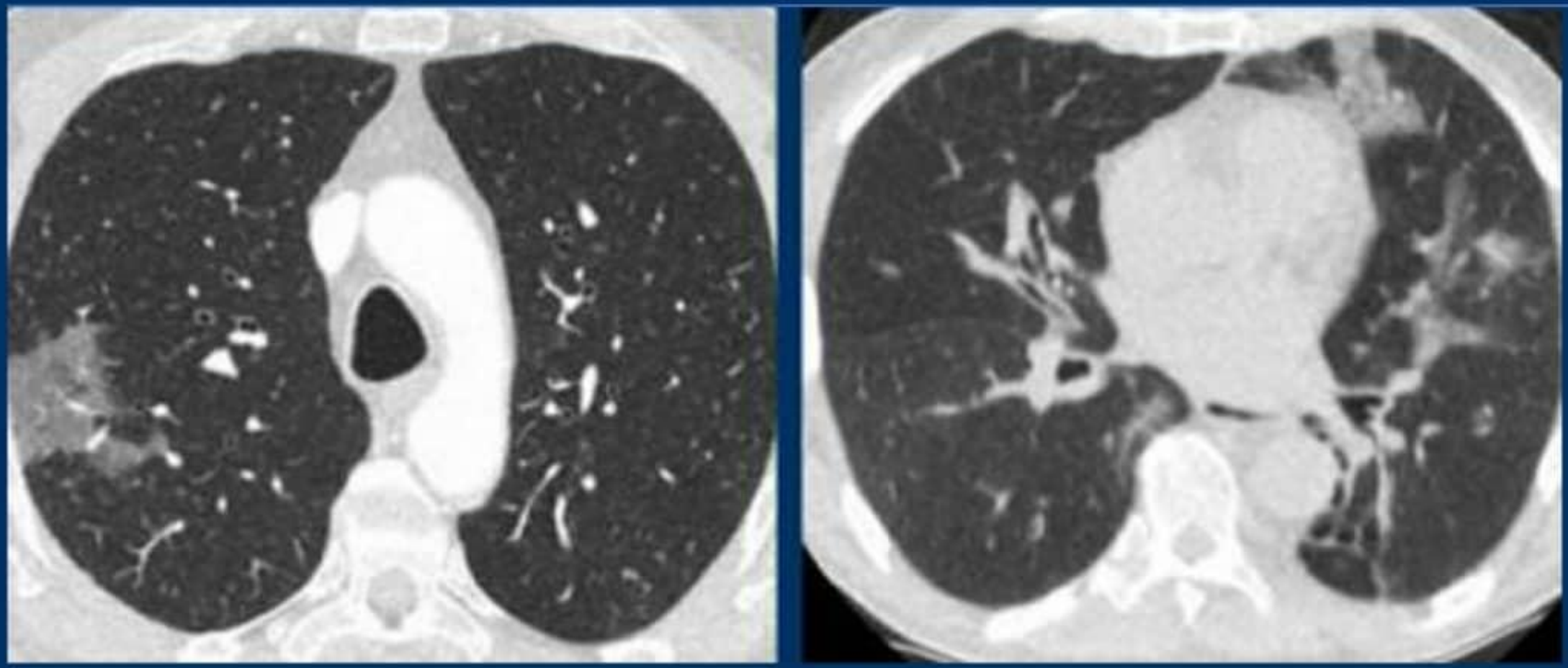

SLE
COVID-19

Eosinophilic pneumonia

Eosinophilic pneumonia can also present with fever and cough just like COVID-19. On CT it presents like COVID-19 with peripheral ground-glass and consolidations, with or without a crazy paving pattern, which makes is very hard to distinghuish from COVID-19 on CT alone.

Differentiation from COVID-19 is possible based on:

- Clinical presentation with slow onset of symptoms
- Association with asthma
- Eosinophilia in bronchioalveolar lavage and blood samples
- Mainly, and more strictly upper lung zone distribution



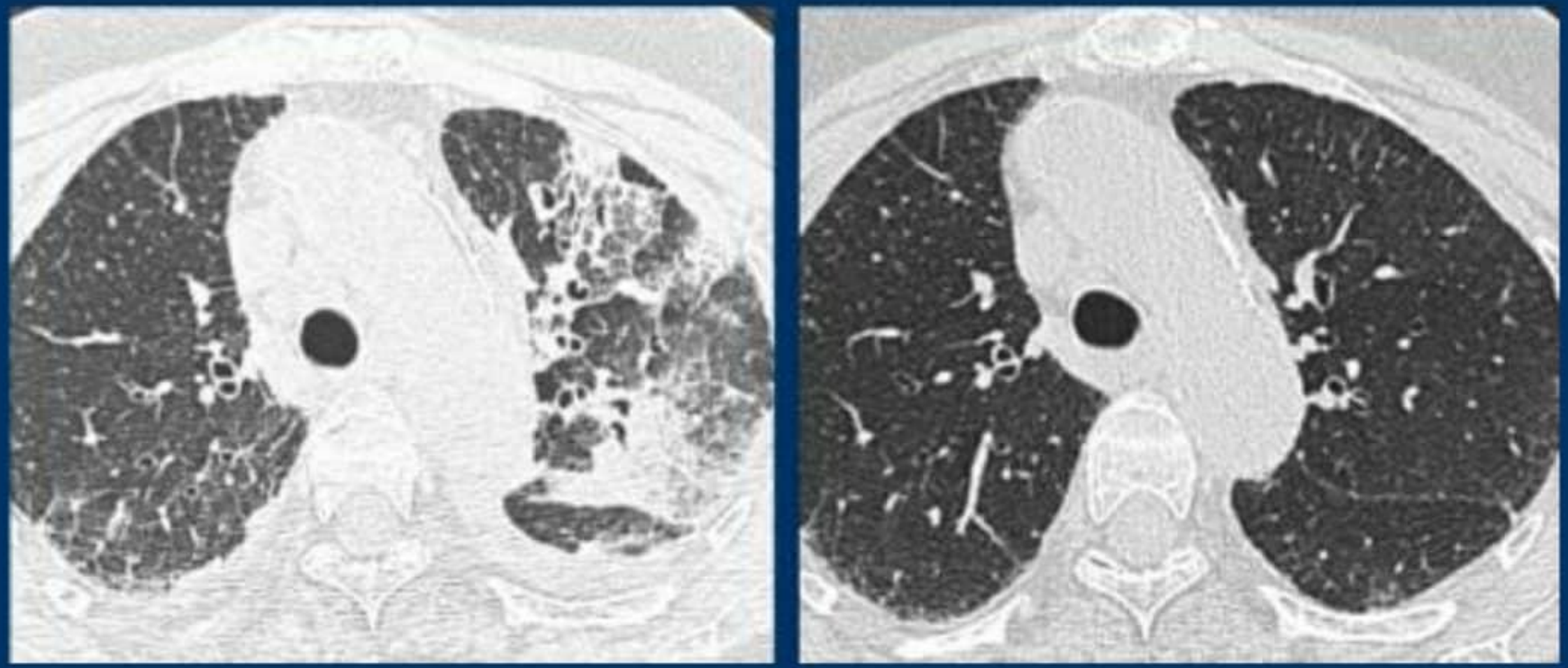
Peripheral groundglass in chronic eosinophilic pneumonia

Drug-induced pneumonitis

Drugs can cause CT patterns similar to confirmatory patterns of COVID-19, including ground glass, peripheral consolidations, crazy paving and organizing pneumonia patterns.

The appropriate clinical setting of potentially pneumotoxic drugs and clear improvement after drug withdrawal (right) helps in suggesting this differential diagnosis.

A list of pneumotoxic drugs and the findings on CT is found on www.pneumotox.com.



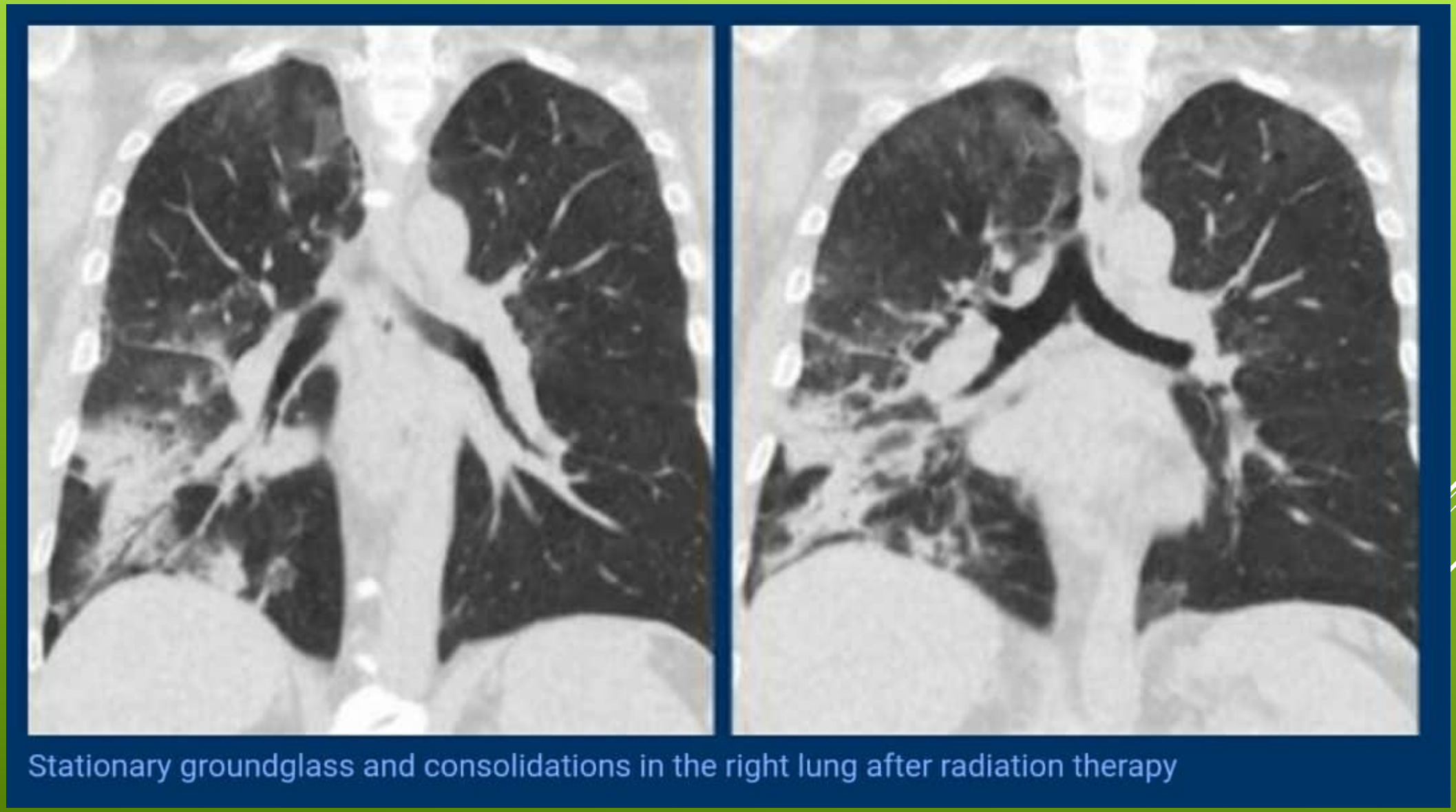
Drug-induced pneunmonitis with groundglass, reticulation, crazy paving and consolidations (left), which resolved after drug withdrawal (right).

Radiation pneumonitis

Inflammatory and fibrotic changes associated with radiotherapy can cause peripheral ground-glass and consolidations in the area of the radiation therapy field.

However, bilateral organizing pneumonia outside the radiation field can also occur, mimicking one of the confirmatory feature of COVID-19.

Correlation with the radiotherapy field and stationary location of abnormalities over time can virtually always confirm radiation pneumonitis.



Stationary groundglass and consolidations in the right lung after radiation therapy

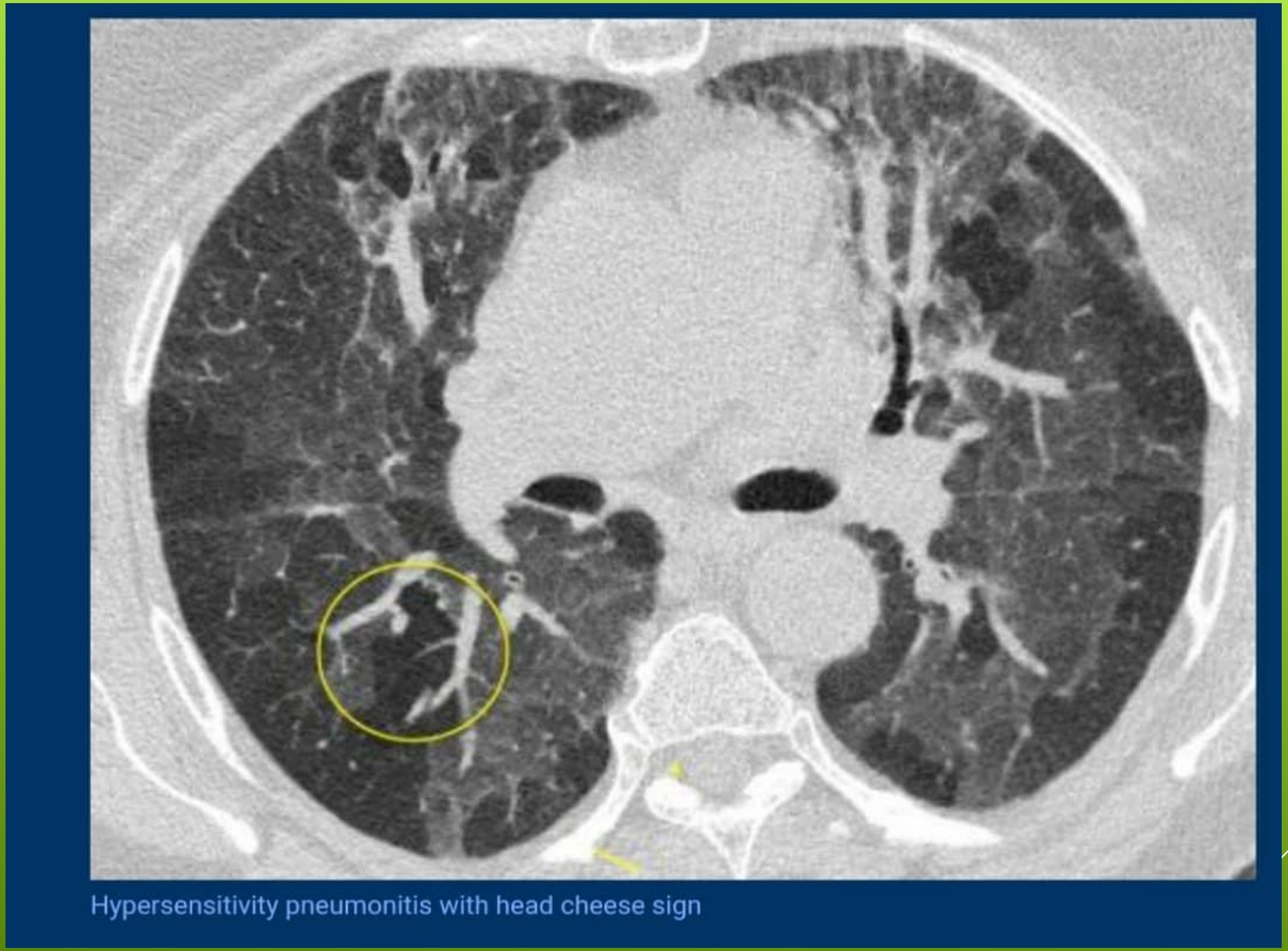
Hypersensitivity pneumonitis

Ground glass opacities in hypersensitivity pneumonitis (HP) are also bilateral, but show a more geographical pattern.

In addition, HP has other features uncommon in COVID-19:

- Centrilobular nodules
- Headcheese sign" with a mixture of lobules with ground glass, normal density parenchyma, and air trapping
- Clinical presentation with a history of exposure to sometimes unknown antigens
- HP patients can develop fibrotic changes in a later stage.

The image shows typical bilateral groundglass opacities in hypersensitivity pneumonitis with head cheese sign: a mixture of ground glass, normal density parenchyma and air trapping (circle).



Hypersensitivity pneumonitis with head cheese sign

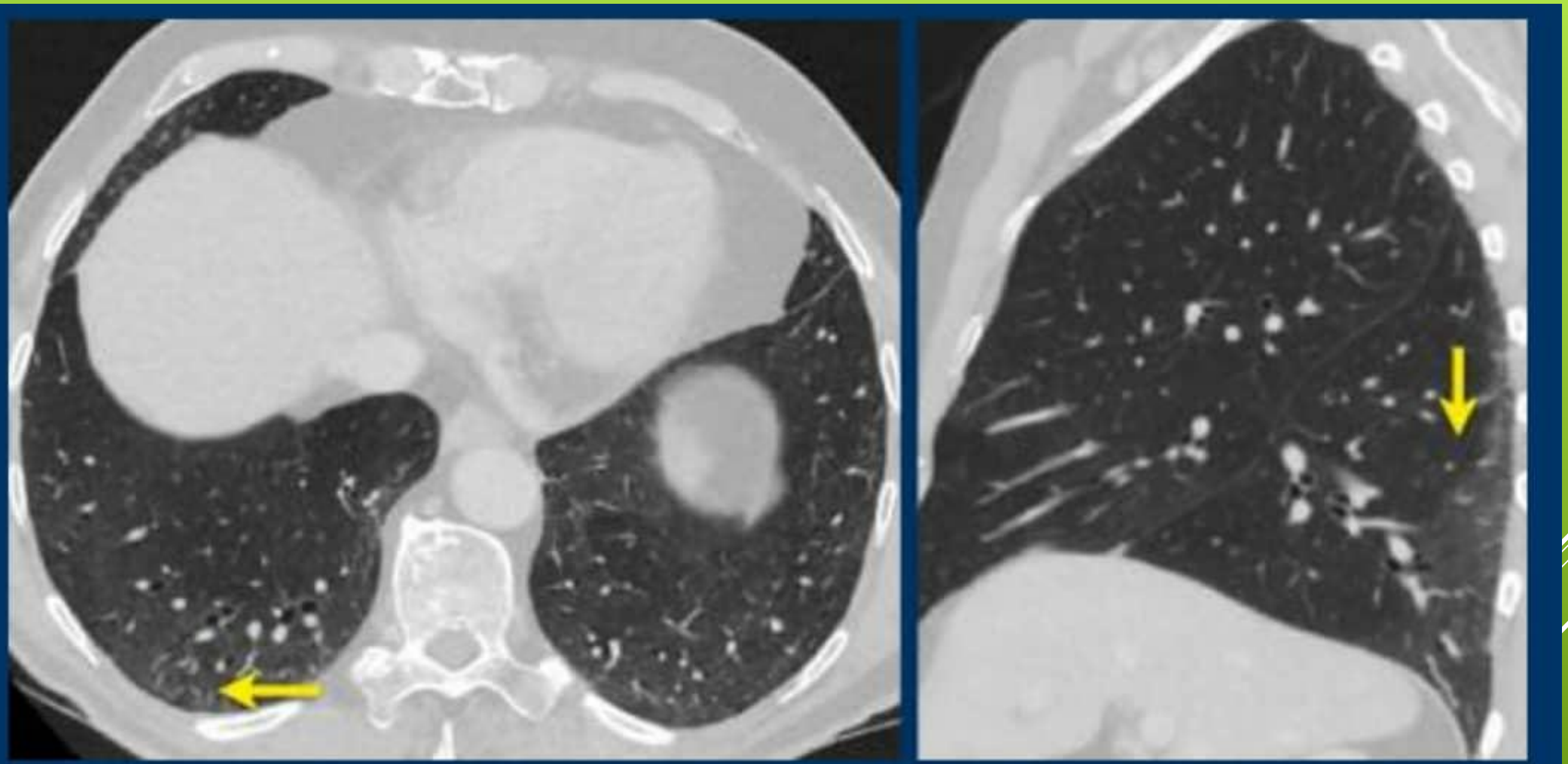
NSIP

Other interstitial lung diseases, such as nonspecific interstitial pneumonia can present with peripheral ground glass opacities, which can simulate COVID-19.

This patient had nonspecific interstitial pneumonia and presented on CT with faint ground glass resembling cellular and, to some extent, fibrotic interstitial disease.

Differentiation from COVID-19:

- The opacities are not demarcated
- No vascular thickening
- Mostly stable over time
- Clinical presentation is distinct from infection.



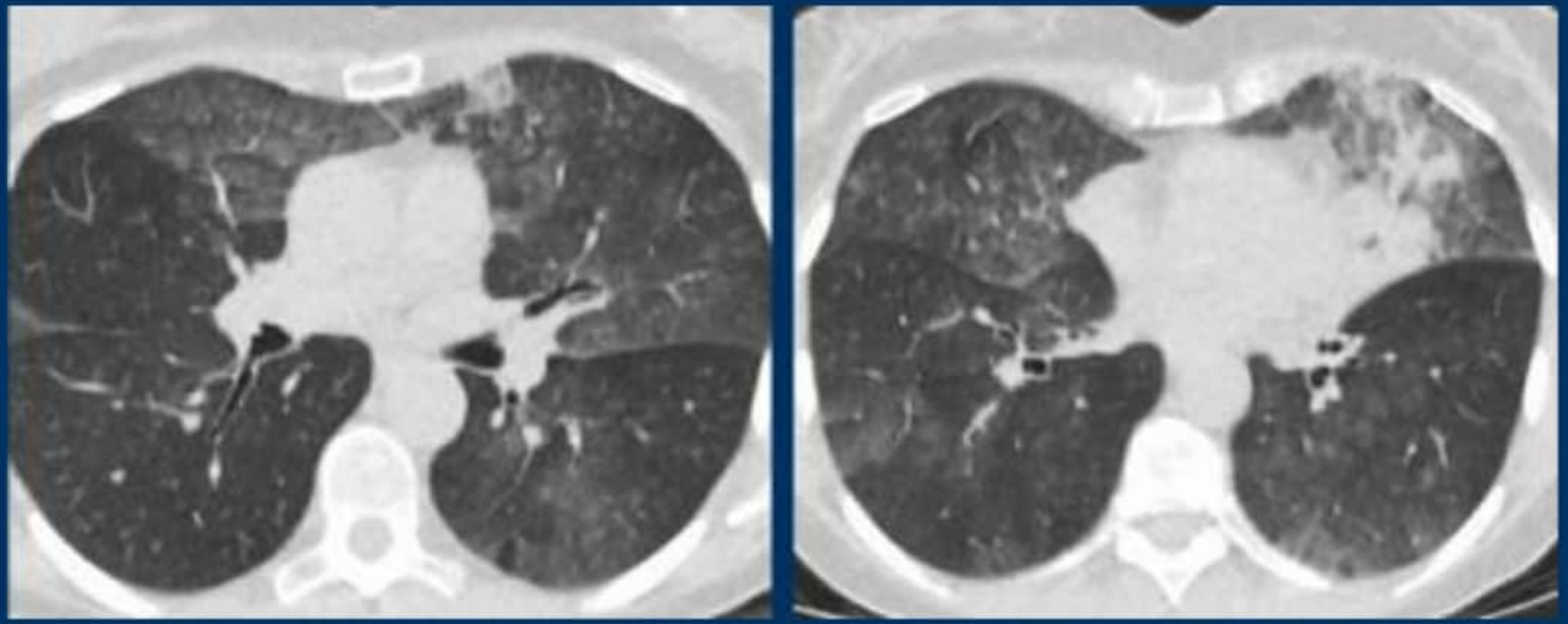
Peripheral, faint groundglass (arrows) in a patient with nonspecific interstitial pneumonia

Adenocarcinoma

Especially adenocarcinoma and its precursors can present with pure ground glass opacities with or without solid components, depending on the degree of invasiveness.

Multifocal adenocarcinoma **in situ** can present as bilateral ground glass opacities, which might look like COVID-19.

Here, distribution is different from COVID-19, with a more geographical and diffuse distribution and no peripheral predominance.

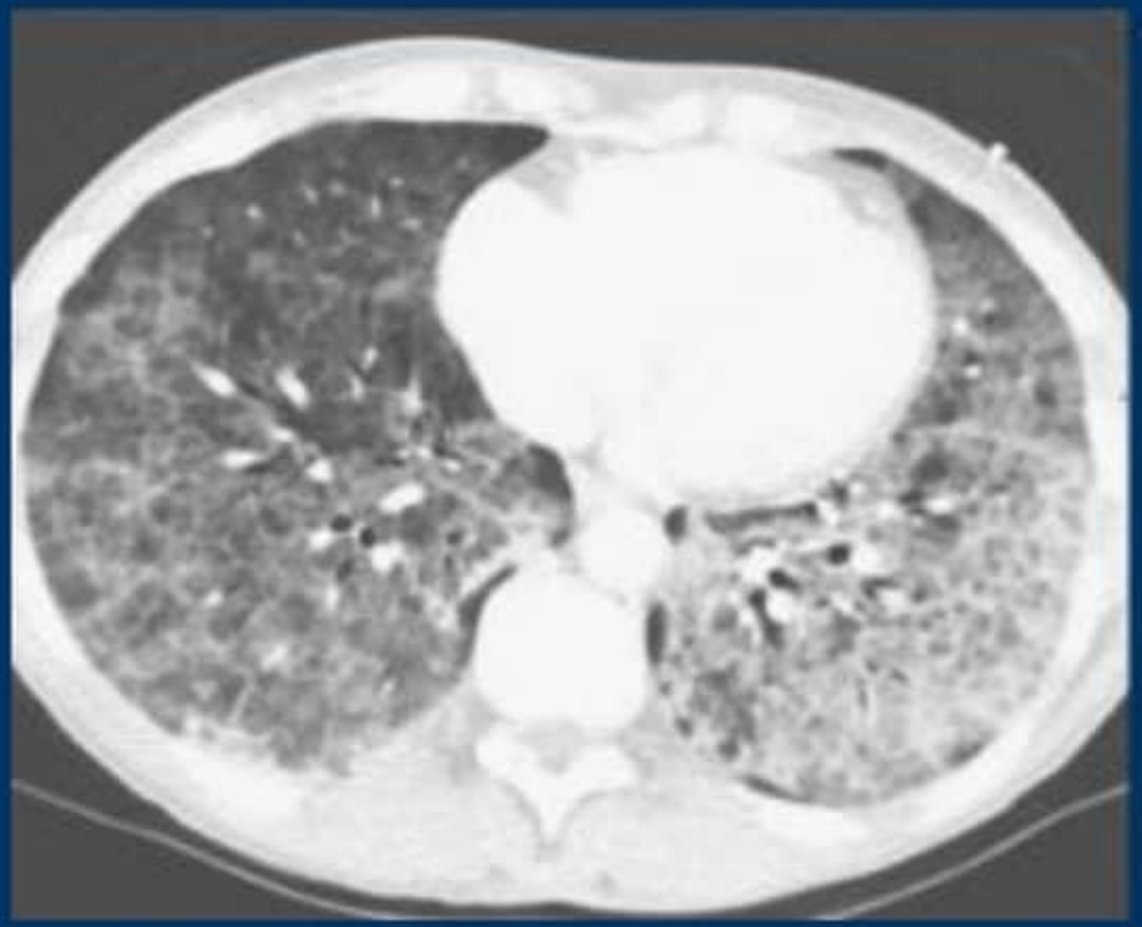


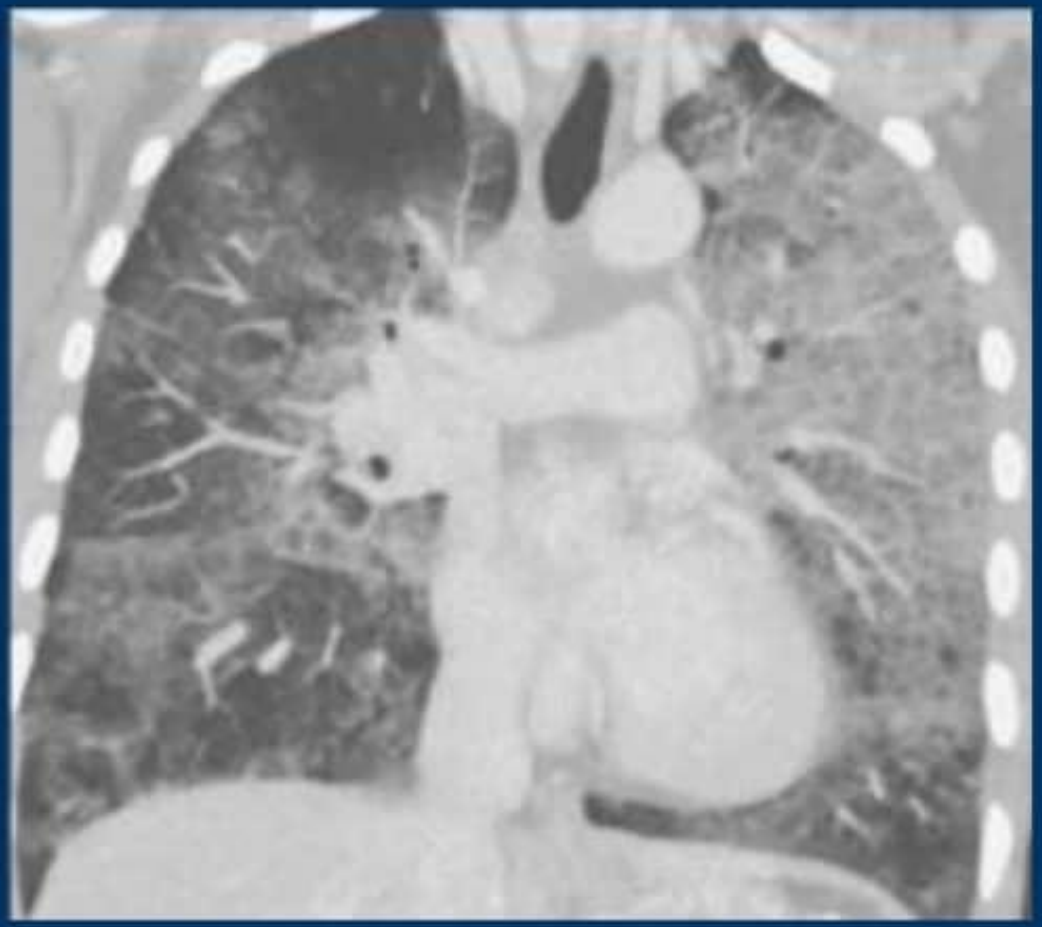
Groundglass and consolidations resembling extensive, bilateral non-mucinous invasive adenocarcinoma and adenocarcinoma in situ.

Alveolar proteinosis

Alveolar proteinosis is a rare condition, frequently associated with elevated lactate dehydrogenase, antibodies against granulocyte-macrophage colony-stimulating factor and broncheoalveolar fluid findings typical for alveolar proteinosis.

Crazy paving in alveolar proteinosis is much more diffuse than in COVID-19, with incidental lobular or geographic sparing, and is frequently disproportional with severity of complaints.





Alveolar proteinosis with diffuse crazy paving

Overlapping diseases

With overlapping diseases we mean diseases of the lung that have the exact pattern as COVID-19.
Distinction can only be made with clinical parameters.

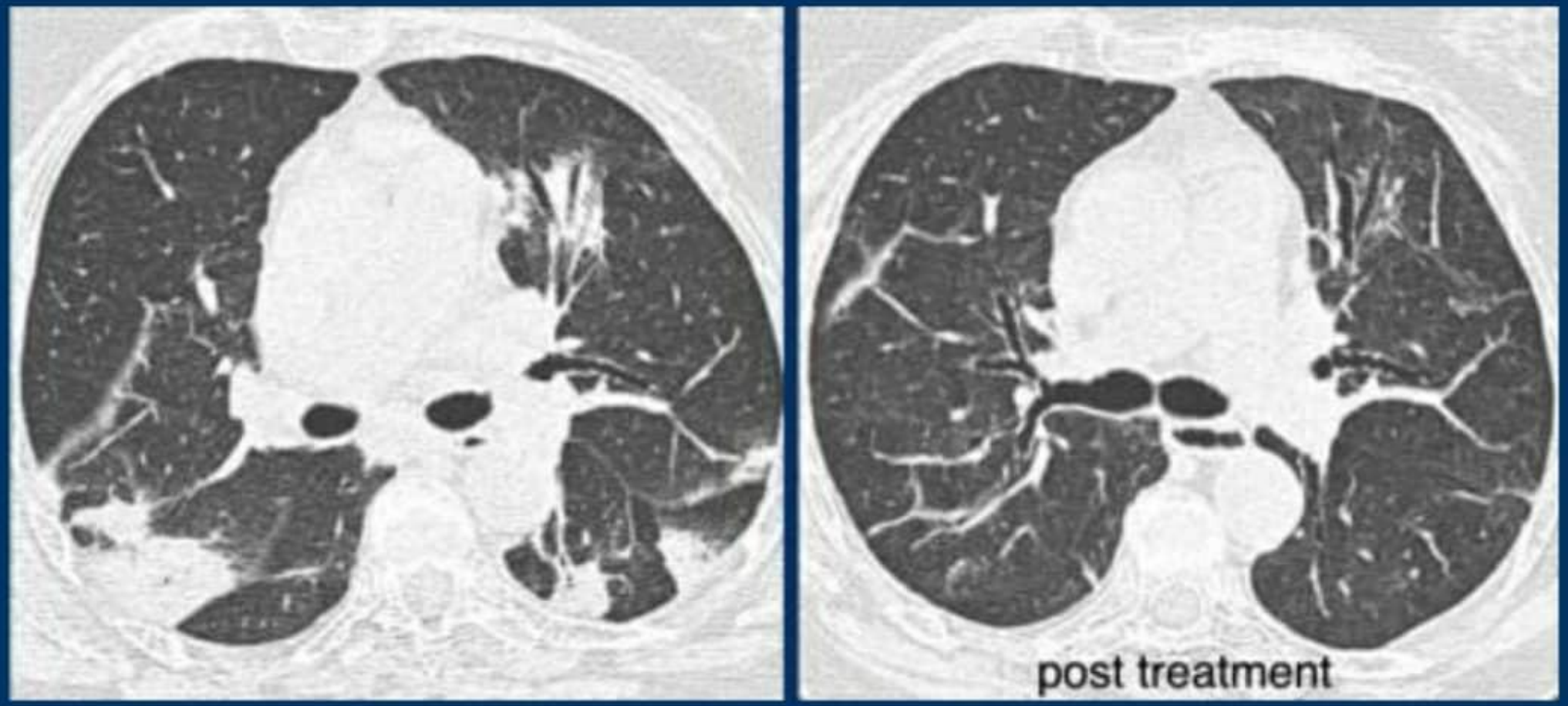
Organizing pneumonia

Patterns compatible with organizing pneumonia commonly occur in COVID-19.

It is regarded as a confirmatory pattern, reflecting a later stage in the temporal evolution of the parenchymal abnormalities.

This pattern in COVID-19 overlaps with organizing pneumonia due to other causes with typical peripheral and central peribronchiolar consolidations and central airway dilatation (figure).

The lung abnormalities decreased after treatment with corticosteroids.



Organizing pneumonia. LEFT typical peripheral and central peribronchiolar consolidations with central airway dilatation. RIGHT post treatment

Influenza pneumonia

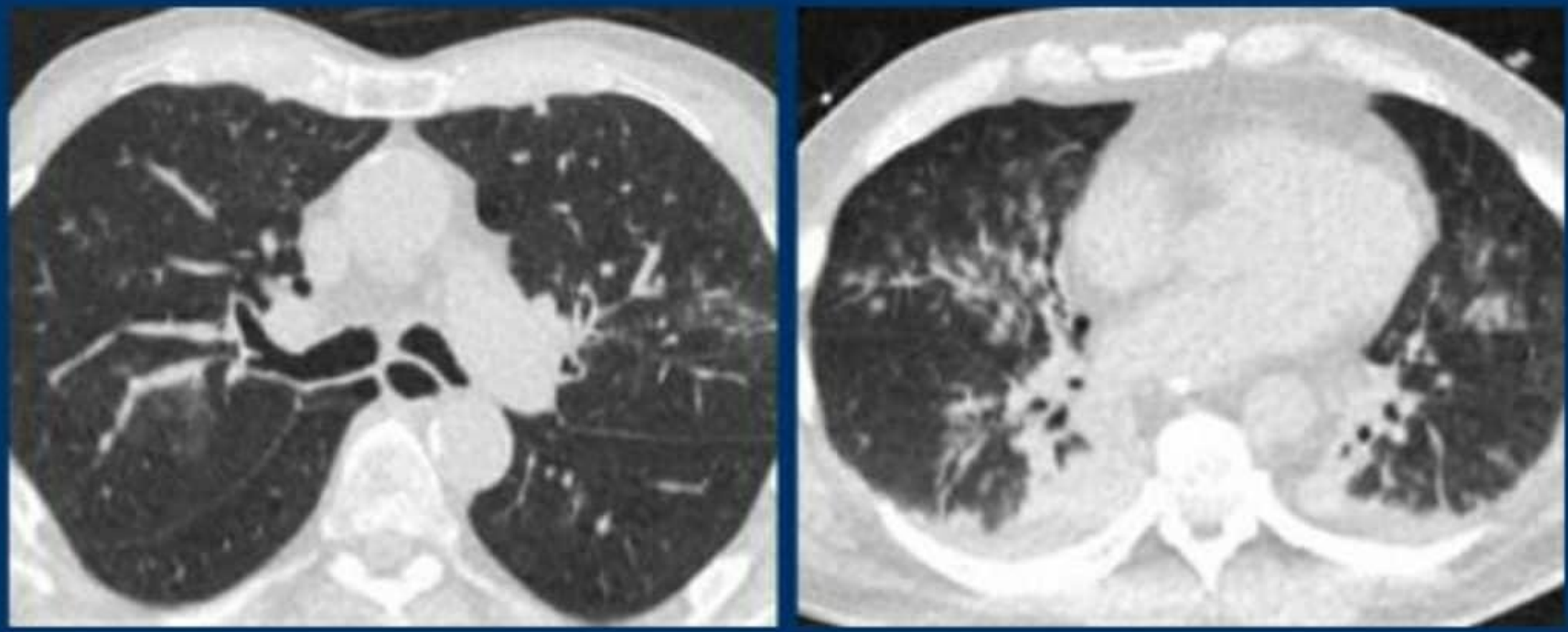
Viral pneumonias show overlapping features on CT.

Influenza virus infection can result in bilateral ground-glass opacities, consolidations and crazy paving that appear similar to COVID-19.

Typical features of influenza are:

- Mucoid airway impaction
- Linear opacities
- Central distribution (as shown in these two cases)

In addition, vessel thickening and upper lobe involvement seem to occur more frequently in the abnormal COVID-19 parenchyma than in other viral pneumonias.



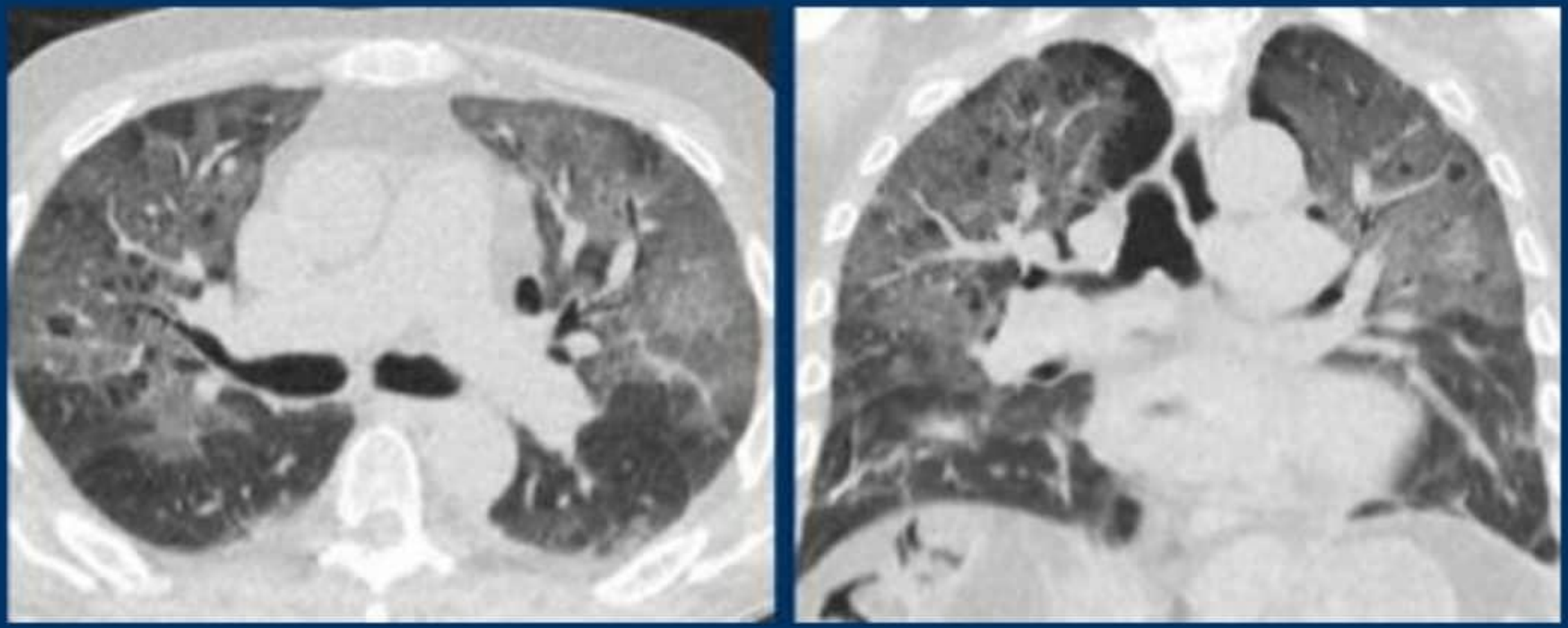
Influenza pneumonia. bilateral groundglass with central distribution and centrilobular groundglass nodules.

Pneumocystis pneumonia

Pneumocystis pneumonia also causes bilateral ground-glass and in later stages consolidations with or without crazy paving.

However, this frequently occurs in a more central distribution than in COVID-19, and only in immunocompromised patients.

PCP is furthermore associated with pulmonary cysts and spontaneous pneumo-thoraces, although pneumothoraces and bullae also present in a small minority of hospitalized COVID-19 patients.



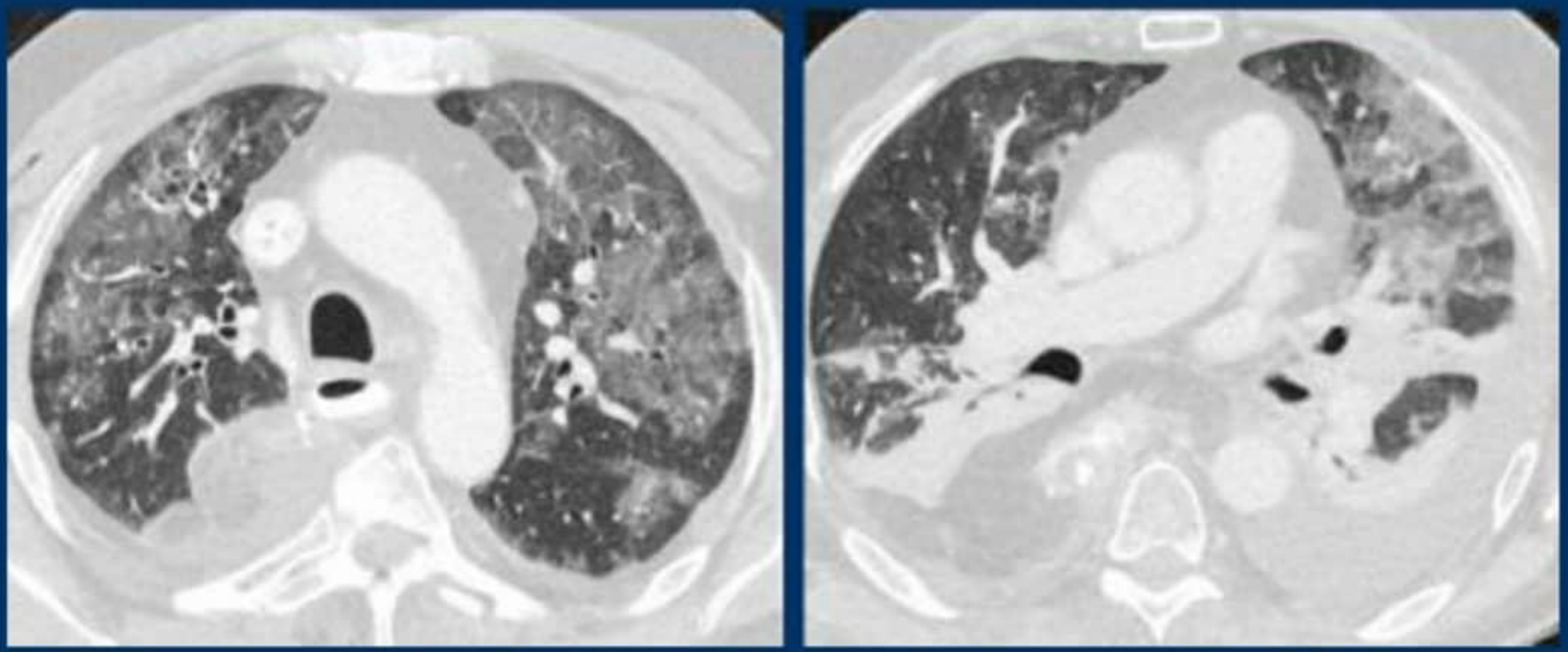
Bilateral groundglass in PCP in an immunocompromised patient.

Adult respiratory distress syndrome

Diffuse alveolar damage can also show peripheral ground-glass, consolidations and crazy paving, which can be similar to the alveolar damage in patients with COVID-19 (left), but also more gravity dependent reflecting permeability edema (right).

ARDS can only occur in the appropriate setting, such as in a postoperative situation or in case of prolonged mechanical ventilation.

However, ARDS can concomitantly occur with COVID-19 in ICU patients.



ARDS. Bilateral, in part gravity dependent groundglass with atelectasis, and pleural fluid in a patient who underwent a gastro-esophageal resection.

THE END