



Computed Tomography of Chest in Non-Infectious Granulomatous Lung Diseases: A Pictorial Essay

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Abstract

Non-infectious granulomatous lung diseases represent a group of disorders with relatively non-specific clinical history and imaging findings. Following pathologies are enlisted, (1) Inflammatory: sarcoidosis and necrotizing sarcoid granulomatosis (NSG); (2) Pulmonary lymphoid lesions: lymphomatoid granulomatosis (LYG) and granulomatous-lymphocytic interstitial lung disease (GLILD); (3) Aspiration/exposure: aspiration pneumonia, talcosis, berylliosis, and hypersensitivity pneumonitis (HP); (4) Vasculitis: granulomatosis with polyangiitis and eosinophilic GPA (EGPA) (formerly called as Churg-Strauss syndrome); and (5) Collagen vascular disorders: rheumatoid lung nodules. Role of radiologist is to narrow the diagnosis combining the imaging findings with clinical findings thus following a multidisciplinary approach.

Keywords

- ▶ ground glass opacity
- ▶ halo sign
- ▶ reverse atoll sign
- ▶ cysts

Introduction

Noninfectious granulomatous lung diseases represent a group of disorders characterized by pulmonary opacities with associated granulomatous inflammation, a relatively nonspecific finding encountered by the pathologists. Most of the lung diseases have an overlapping clinical picture and present a diagnostic challenge because of nonspecific imaging findings.

Patients with noninfectious granulomatous lung disease may initially be identified based on pulmonary symptoms or chest radiographic abnormalities. A variety of noninfectious pulmonary disorders may be associated with occasional granulomatous lesions: (1) inflammatory: sarcoidosis and necrotizing sarcoid granulomatosis (NSG); (2) pulmonary lymphoid lesions: lymphomatoid granulomatosis (LYG) and granulomatous-lymphocytic interstitial lung disease (GLILD); (3) aspiration/exposure: aspiration pneumonia, talcosis, berylliosis, and hypersensitivity pneumonitis (HP); (4) vasculitis: granulomatosis with polyangiitis (GPA) (formerly Wegener's granulomatosis) and eosinophilic GPA (EGPA) (formerly called as Churg-Strauss syndrome); and (5) collagen vascular disorders: rheumatoid lung nodules.^{1–3}

Herein, we describe, illustrate, and discuss the imaging features of common and uncommon noninfectious granulomatous lung diseases to suggest a specific diagnosis or to substantially narrow down the differential diagnosis using the imaging appearance and anatomic location of the lesion.

We the radiologists have a role in identifying these granulomatous disease processes that can be diagnosed confidently on the basis of imaging and the clinical context, which obviates the need for biopsy. The approach to the patient must rely on correlating imaging, clinical, laboratory, and pathologic findings in a multidisciplinary fashion (▶ **Table 1**).

The checklist for noninfectious granulomatous lung disease must include distribution, additional findings of nodules, consolidation, cavitation, airway involvement, vessel wall involvement, pleural effusion, and lymphadenopathy.

Sarcoidosis

Sarcoidosis is a disease of unknown etiology and can affect any system in our body. It can affect patients of any age or sex, it usually affects adults less than 40 years, and the incidence is high in the third decade of life. Involvement of the lung and

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Table 1 Categorization of the noninfectious granulomatous lung diseases

Noninfectious lung diseases	
Inflammatory	Sarcoidosis
	Necrotizing sarcoid granulomatosis
	Bronchocentric granulomatosis
Exposure/Toxins	Hypersensitivity pneumonitis
	Drugs
	Talc
	Metals
Vasculitis	Granulomatosis polyangiitis
	Eosinophilic granulomatosis with polyangiitis
Autoimmune	Rheumatoid arthritis
Malignancy	Lymphomatoid granulomatosis
Others	Pulmonary Langerhans cell histiocytosis (LCH)
	Granulocyte lymphocytic interstitial lung disease

Note: European Respiratory Review.⁴

mediastinal lymph nodes is the most common presentation and is responsible for majority of morbidity and mortality associated with the disease. Demonstration of noncaseating granulomas on pathology along with clinical and radiological findings is used for diagnosing the disease. The clinical symptoms include weight loss, general malaise, fatigue, and less frequently, fever. The clinical course varies. A restrictive ventilatory defect with decreased volumes and decreased carbon monoxide diffusing capacity is seen with pulmonary function tests. Around two-thirds of patients usually remain stable or experience a remission within a decade of diagnosis, with few or no consequences thereafter. However, around 20% of patients go onto develop chronic disease leading to fibrosis. Recurrence after a remission lasting 1 year or more is usually uncommon (< 5% of patients), but recurrent disease can develop at any age. Less than 5% of the patients die of sarcoidosis; death from sarcoidosis is most commonly the result of extensive, irreversible lung fibrosis with respiratory failure or cardiac or neurologic involvement.⁵⁻⁷

Noncaseous granulomas composed of a central core of histiocytes, multinucleated giant cells, and epithelioid cells, surrounded by plasma cells, lymphocytes, and varying number of fibroblasts and collagen in the periphery is the one of the histologic hallmarks of sarcoidosis. The giant cells frequently have cytoplasmic inclusions like asteroid bodies and Schaumann bodies. The central portion of a granuloma consists mainly of lymphocytes that express CD4 protein, whereas lymphocytes that express CD8 are found in the peripheral zone of the granuloma. Dense bands of mast cells, fibroblasts, proteoglycans, and collagen can encase the granuloma and lead to fibrosis, end-organ damage with irreversible disruption of organ function. Fibrotic changes usually

begin at the periphery of a granuloma and then extend to the center of granuloma, leading to complete hyalinization, fibrosis, or both. Granulomas sometimes can exhibit focal coagulative necrosis, and it has been suggested that NSG can be a variant of sarcoidosis.⁸⁻¹⁰

Imaging plays a pivotal role in the diagnosis and follow-up. Although chest radiography is the initial imaging modality utilized, it has several limitations that include limited resolution for the detection of parenchymal abnormalities and mediastinal lymphadenopathy.

The disease was staged with the Siltzbach classification into the following five stages¹¹:

- Stage 0: normal chest radiography;
- Stage 1: mediastinal lymphadenopathy;
- Stage 2: lymphadenopathy with parenchymal lung disease;
- Stage 3: parenchymal lesions only; and
- Stage 4: with end-stage fibrosis.

Radiographic Features

One of the most salient features is bilateral hilar lymphadenopathy (BHL), which is generally symmetrical and noncompressive.

Different patterns of lymphadenopathy include^{12,13}:

- Garland triad or 1–2–3 sign—pattern of lymph node enlargement which include right paratracheal and bilateral hilar lymph nodes. Aortopulmonary and left paratracheal nodes can also be frequently enlarged, but harder to identify.
- Nodes can be large, but generally do not abut the cardiac silhouette, as in lymphoma, in which nodes can be continuous with the pericardial outline.

In patients with thoracic lymphadenopathy, BHL is the most common and is seen in over 95% of cases, often associated with enlarged right paratracheal and aortopulmonary lymph nodes. Anterior mediastinal, subcarinal, and posterior mediastinal lymph nodal involvement is less common. The lone presence of paratracheal, subcarinal, or mediastinal lymph nodes without evidence of BHL is exceptional, and should raise the possibility of an alternative diagnosis (i.e., infection, lymphoma, bronchogenic, or extrathoracic malignancy). The lymph node size can vary from minimal to massive and tends to be largest at the time of presentation, with gradual diminution over a period of time, in a majority of cases, to complete regression within 2 years. When initially unilateral, sarcoidosis lymph nodes tend to become bilateral within a period of around 3 months. In long-standing cases of sarcoidosis, calcification is seen on chest radiography in more than 20% of cases after 10 years of the disease, occurring in most instances during the second or third decade after onset.

Pulmonary infiltrates are noted in nearly 25 to 50% of sarcoidosis patients. Bilateral and symmetrical distribution with a frank predilection for mid/upper lung zones is seen. The pattern is usually micronodular or reticulo-micronodular. When present, fibrotic changes are variably marked on chest radiography with evidence of volume loss with hilar upward retraction, architectural distortion, masses, coarse linear bands, and bullae in advanced disease.¹¹

One of the characteristic features of sarcoidosis includes the presence of small nodules and nodular thickening along the

lymphatics in the bronchovascular sheath. Most of the sarcoid granulomas can resolve spontaneously; however, they can also progress to severe fibrosis. Although they are microscopic in size, the lesions often coalesce to macroscopic nodules. As seen on high-resolution computed tomography (HRCT), the nodules can be as small as a few millimeters and tend to be sharply defined despite the small size. Due to its perilymphatic distribution, HRCT images usually demonstrate the presence of multiple small nodules that predominate in the peribronchovascular interstitium, interlobar fissures, and interlobular septae. The nodules may be distributed throughout bilateral lung parenchyma, a predominance for the upper lobe.^{14–16} Sarcoidosis can present with perilymphatic micronodules, random micronodules, larger nodules, or masses surrounded by satellite nodules (“galaxy” sign). Air trapping can sometimes be seen with sarcoidosis and should not be confused with HP.¹⁷

Airspace or alveolar opacification can be seen in few of the patients with sarcoidosis. It is generally bilaterally symmetric predominantly involving the peribronchovascular regions of the upper and middle zones. These central regions of consolidation may contain air bronchograms and commonly have ill-defined margins. Airspace consolidation in sarcoidosis represents the confluence of micronodules (acinar and interstitial) that compress the surrounding alveoli or encroach onto the alveolar spaces. These coalescent nodules typically appear on radiograph as multiple radiographic opacities often larger than 5 mm, a pattern referred to as the alveolar or acinar form of sarcoidosis, which can mimic pneumonia, tuberculosis, or bronchiolitis obliterans organizing pneumonia^{18,19} (→ **Figs. 1–4**).

Necrotizing Sarcoid Granulomatosis

Liebow et al made reference to a sarcoid-like granulomatosis with features of vasculitis and necrosis and coined this term, NSG.²⁰ Most believe that this is a variant of sarcoidosis; however, its classification remains in doubt given its overlapping features with HP, GPA, and EGPA.

Extrapulmonary manifestations are common. Lack of renal and upper airway involvement helps to differentiate necrotizing sarcoid from GPA. Antineutrophil cytoplasmic antibody (ANCA) levels generally are normal, allowing differentiation from vasculitis.

Pulmonary necrotizing granuloma covers a group of entities that can result in granuloma formation associated with necrosis. On pathologic examination necrotizing granuloma consists of aggregates of macrophages transformed into epithelium like cells surrounded by mononuclear leukocytes with surrounding area of necrosis.

CT studies show mediastinal and hilar lymphadenopathy. As seen with sarcoidosis, it tends to manifest as nodules or mass-like areas of consolidation. Cavitation sometimes can help in differentiating NSG from sarcoidosis. Pleural effusions can also be seen in some patients.^{21,22}

Hypersensitivity Pneumonitis

HP is an inflammatory response due to an inhaled antigen or chemical that is characterized in part (at pathologic exami-

nation) by noncaseating granulomas. Some of the common subtypes of HP include hot tub lung, farmer’s lung, and bird fancier’s lung. Diagnosis is usually challenging, because the offending antigen is found in less than 50% of the cases. Acute, subacute, and chronic subtypes of HP have been described in the literature. The definition varies according to different authors. The lack of a clinical consensus for separating these forms of HP resulted in some authors suggesting the use of alternative classification based on the imaging into two types that include^{23–25}:

- Nonfibrotic HP.
- Fibrotic HP.

Previously, HP was classified into²⁶:

- acute,
- subacute, and
- chronic.

Inhalation of the etiologic agent can occur at home, work, or at places of recreation. In general, among those exposed to an allergen, only 5 to 15% go onto develop HP. However, frequency of the disease can be much higher. In the original report of maple bark disease, for example, 30% of the people working directly with the material were seen to be affected. Heredity can be important; with some families having a greater predisposition than others. Also, significant is tobacco use: Most of the patients with HP are nonsmokers, a substantially higher proportion than that seen in unaffected populations with similar antigen contact. However, in smokers, the disease is associated with a higher mortality.^{27–29}

The onset of symptoms can be acute (weeks to months) and insidious (month-to-years of gradual worsening symptoms). Common symptoms include cough with dyspnea and with less common symptoms being malaise, weight loss, fever, chest tightness, and wheezing. Clinical examination may demonstrate mid-inspiratory squeaks with clubbing of the fingers. Pulmonary function tests show a restriction pattern with decreased diffusing capacity.^{24,30}

he histopathologic hallmark includes chronic inflammation of the bronchi and peribronchiolar tissue, often with poorly defined giant cells and granulomas in the alveoli or interstitium. Fibrosis and emphysema can develop in the later stages.

Most of the cases, whether acute or insidious, have the following four histologic features in variable combinations²⁴:

- Cellular bronchiolitis.
- Diffuse chronic interstitial inflammatory infiltrates: mainly consist of plasma cells and lymphocytes but can include eosinophils, mast cells, and neutrophils.
- Interstitial nonnecrotizing (noncaseating) granulomas that are poorly circumscribed: consisting of plasma cells, lymphocytes, and epithelioid histiocytes, with or without giant cells.
- Individual giant cells in the interstitium or alveoli.

Smoking is protective against HP, presumably because of the inhibitory action of nicotine on lymphocyte proliferation and function and macrophage activation. However, when the smokers develop HP, it has worse prognosis with a fibrosing disease.²⁹



Fig. 1 (A and B) Axial plain and postcontrast images show heterogeneously enhancing bilateral hilar lymphadenopathy. (C and D) Axial high-resolution computed tomography (HRCT) images show mild bronchial prominence with surrounding varying sized nodules.

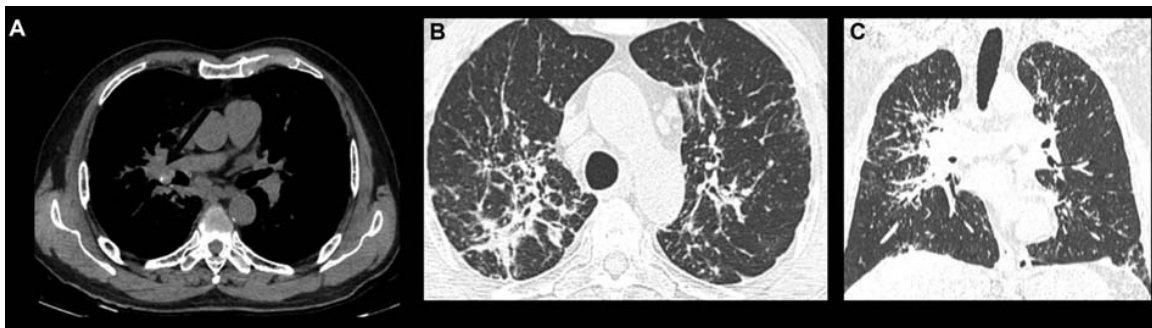


Fig. 2 (A) Axial images show enlarged right hilar lymph node with foci of calcification within. (B and C) High-resolution computed tomography (HRCT) axial and coronal images reveal multiple tiny peribronchovascular, perifissural, and subpleural nodules in bilateral lung parenchyma with peribronchial cuffing of the bronchi and bronchioles.

Imaging: Abnormal chest radiographic findings can include²⁴:

- Numerous poorly defined small (< 5 mm) opacities scattered throughout bilateral lung parenchyma, sometimes with sparing of the apices and bases.
- Airspace disease: usually seen as ground-glass opacities which can be patchy or diffuse resembling pulmonary edema or, rarely, as an area of consolidation.
- A pattern of fine reticulation can also occur.
- Zonal distribution is variable from individual to individual and may show temporal variation within the same individual.

Radiographic features in the later stages when fibrosis develops:

- Reticular pattern and honeycombing, more severe in the upper lobes than in the lower ones.
- Volume loss.
- Cardiomegaly.

In patients, in whom the disease has not progressed to fibrosis, centrilobular ground-glass nodules/opacities and/or lobular air trapping are the predominant features; the latter is best seen on expiratory examination. The combination of ground-glass opacities and areas of air trapping interspersed

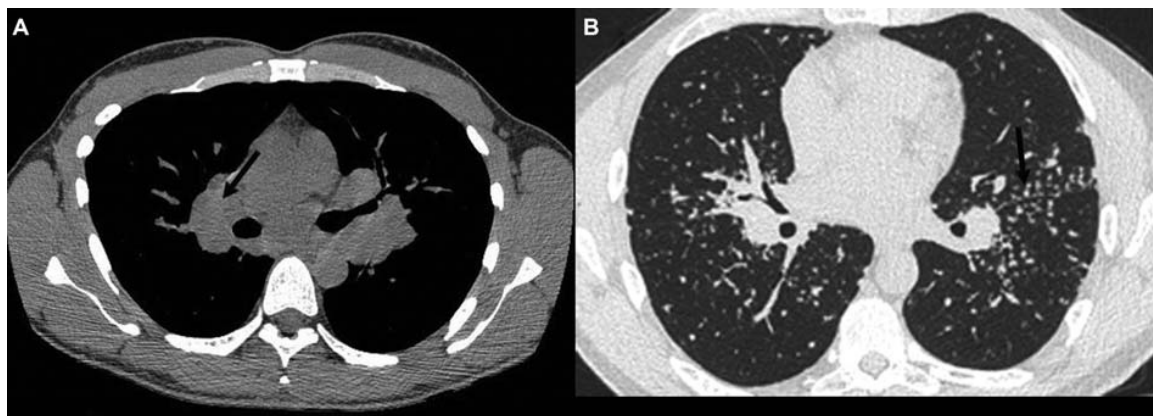


Fig. 3 (A) Noncontrast computed tomography (NCCT) axial image showing bilateral symmetrical hilar lymphadenopathy. (B) High-resolution computed tomography (HRCT) axial image showing micronodules with a perilymphatic distribution including spreading along the fissures.

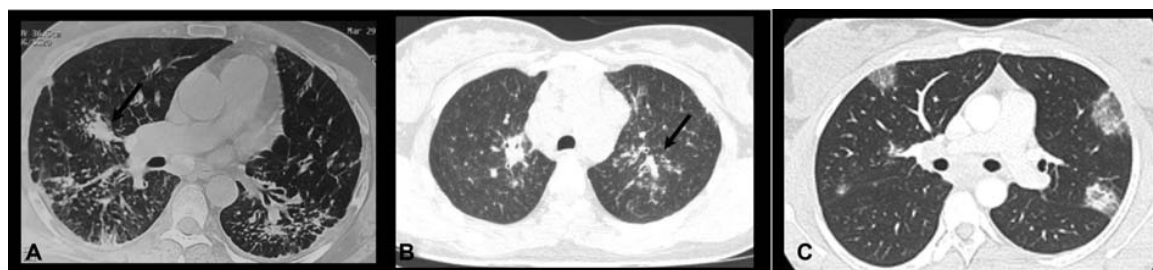


Fig. 4 (A) The "sarcoid galaxy" sign (irregular nodule resulting of the confluence of numerous micronodules). (B) The "sarcoid cluster" sign (clusters of micronodules without confluence). (C) The "reversed halo" sign (ring of micronodules surrounding central ground-glass opacity, which is a very rare finding in sarcoidosis).

with normal lung on CT has been described as the "head cheese" sign.

Bronchiolar wall thickening also can occur. Lung cysts if found occasionally are due to partial obstruction of bronchioles. Occasionally with an insidious onset of disease, focal consolidation can be seen, representing organizing pneumonia or a superimposed unrelated process like aspiration or infectious pneumonia. Mediastinal lymphadenopathy can be seen, but less common. Pulmonary arteries are occasionally enlarged, reflecting pulmonary arterial hypertension. In some patients, particularly the ones with farmer's lung or bird fancier's disease, widespread centrilobular emphysema develops, even in those who are lifelong nonsmokers.³¹⁻³³

When the disease progresses to fibrosis, the imaging pattern can be extremely variable, and can mimic general features of both usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). Changes of architectural distortion, honeycombing, and traction bronchiectasis can be seen. Fibrotic changes in unusual, particularly upper lobe should raise the suspicion for chronic HP. Air trapping involving three or more lobes is also suggestive of HP²³ (► Figs. 5-8).

Talcosis

The intravenous abuse of oral medication can cause pulmonary talcosis.³⁴ In oral medications, talc acts as a filler and



Fig. 5 Frontal radiograph of the chest shows: Multiple tiny nodular radioopacities involving bilateral lung zones.

lubricant. When the drug is crushed, melted, dissolved in water, and then intravenously injected, tiny particles of talc get lodged in the pulmonary vasculature. These particles

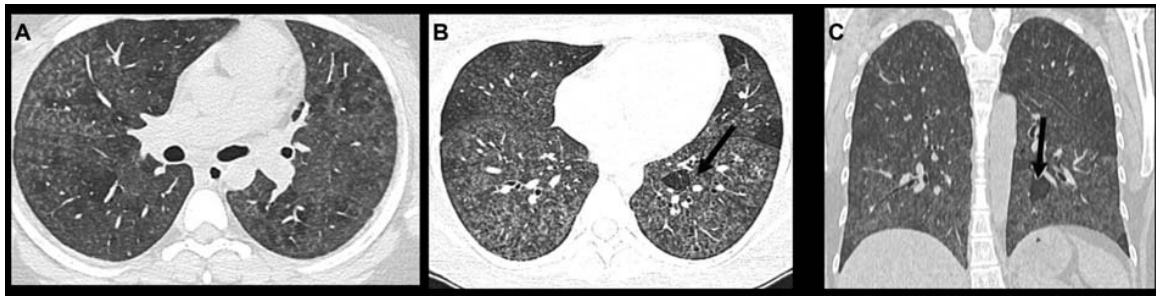


Fig. 6 (A–C) High-resolution computed tomography (HRCT) axial and coronal images showing multiple tiny ground-glass density nodules with areas of air trapping: arrows—representing nonfibrotic type of hypersensitivity pneumonitis.

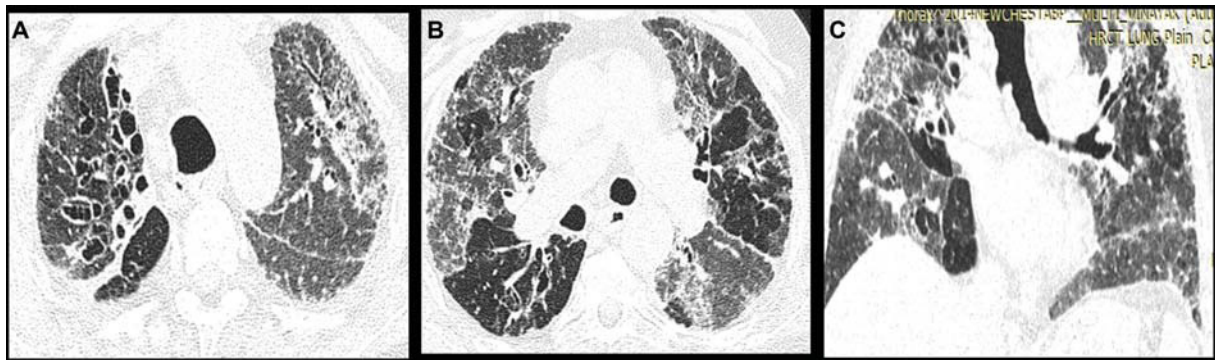


Fig. 7 (A–C) High-resolution computed tomography (HRCT) axial and coronal images show extensive reticular pattern, traction bronchiectasis, and honeycombing, representing fibrotic type of hypersensitivity pneumonitis.

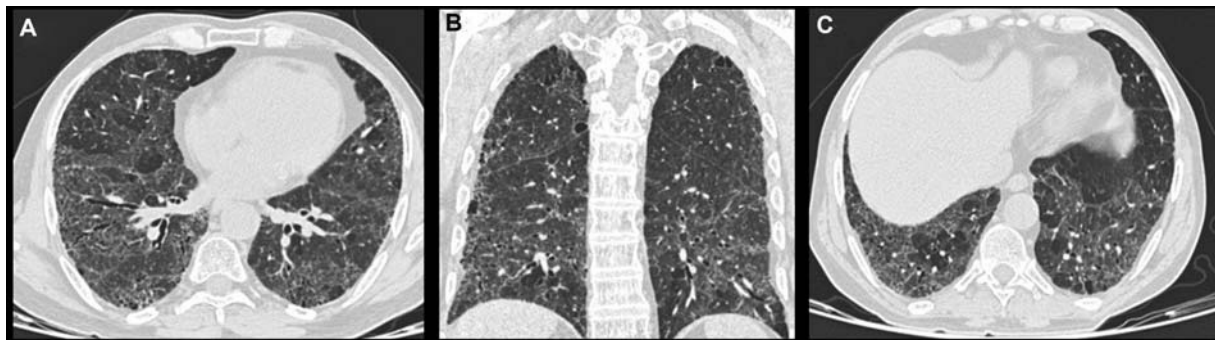


Fig. 8 (A–C) Head cheese pattern—Three density pattern showing areas of ground-glass opacity (GGO) and mosaic attenuation with interspersed normal lung parenchyma.

than migrate to the interstitium, where they induce a foreign body granulomatous reaction. This anatomic deposition manifests as the typical centrilobular pattern. Pulmonary hypertension may also develop with the talc particles obstructing the pulmonary capillary bed. The foreign body reaction can be confirmed by identifying these birefringent talc crystals in the granulomas under polarized light.

Intravenous drug abusers who develop talcosis present with progressive dyspnea and symptoms of chronic obstructive pulmonary disease.^{35,36}

Chest radiography is usually insensitive but can show a diffuse micronodular pattern. In talcosis due to injected material, CT shows innumerable submillimeter micronodules showing a centrilobular pattern. Occasionally, the nodules show high attenuation. Conglomerate masses are

uncommon and are related to inhalation of the talc particles. In inhalational exposure, the involved areas contain foci of high attenuation resembling calcium.^{37–39}

Granulomatous Polyangiitis

Granulomatous polyangiitis also known as Wegener's granulomatosis is characterized by a chronic granulomatous necrotizing vasculitis predominantly involving the small and medium-sized vessels and is named after a German pathologist, Dr. Friedrich Wegener.⁴⁰

It is usually seen in whites and can affect both the sexes equally. It can develop at any age; however, the mean age at diagnosis is around 40 years. The upper respiratory tract is seen to be affected in almost all the cases and the lungs and

kidneys are seen involved in 90 and 80% of patients, respectively.⁴¹ Other organs that are less commonly affected include the central and peripheral nervous system, spleen, and large joints.

Patients present with cough, hemoptysis, or dyspnea. Elevation of serum c-antineutrophil antibodies against protease 3 in cytoplasmic granules titers is frequently seen and is used to assess disease activity.³ For diagnosis, the reference standard is biopsy. Nonspecific glomerulonephritis can be seen on renal biopsy. Lung biopsy can show granulomatous necrotizing small vessel vasculitis.⁴²

The 1990, the American College of Rheumatology (ACR) criteria requires at least two of the four (specificity 92% and sensitivity 88.2%)⁴³:

- Positive biopsy for granulomatous vasculitis.
- Urinary sediment with red blood cells.
- Oral or nasal inflammation.
- Abnormal chest radiograph.

According to Chapel Hill Consensus Conference on Nomenclature of Systemic Vasculitis (1992), establishing the diagnosis requires documentation of granulomatous inflammation involving the respiratory tract and vasculitis of small to medium-sized vessels.⁴⁴

If diagnosis does not fulfill the criteria of the ACR, then Watts and Robson⁴⁵ have proposed an alternative. Diagnosis can be made if:

- A. histologic results are compatible with the guidelines of the Chapel Hill Consensus Conference for granulomatous polyangiitis;
 - B. histologic results are compatible with microscopic polyangiitis, and patient has surrogate markers of granulomatous polyangiitis;
- or
- C. there are no histologic results, but there are positive surrogate markers and serologic results for myeloperoxidase, antiprotease 3 and ANCA.

CT is the mainstay in evaluating patients with GPA who have suspected thoracic involvement.⁴⁶ The classic triad of organ involvement consists of:

- lungs,
- upper respiratory tract or sinuses, and
- kidneys.

Treatment includes immunosuppressant therapy. Remission rates are as high as approximately 90%, but relapses can occur. Resolution of imaging findings may lag behind improvement of clinical manifestations.³

Thoracic manifestations on imaging: The most common radiologic features of Wegener granulomatosis include pulmonary nodules and masses and are seen in up to 70% of the patients either at presentation or during the disease course. Waxing and waning pulmonary nodules and masses are a characteristic feature of the disease. Lesions can be single or multiple (usually less than 10 lesions) and can vary in size from few millimeters to as large as over 10 cm. When

multiple, the nodules have a random distribution. However, subpleural, peribronchovascular, angiocentric, and less commonly centrilobular distributions have been seen.⁴⁷ A centrilobular distribution can mimic infection like tuberculosis, HP, or acute bronchiolitis.⁴⁸ Central cavitation occurs in most of the cases and is more common with larger nodules (larger than 2 cm). The walls of the cavity may be irregular and thick or smooth and thin.

There can be a surrounding ground-glass halo ("CT halo" sign) or reverse halo ("atoll" sign), with radiating linear scarring, and pleural tags being some of the other ancillary findings that, if present, may help distinguish Wegener granulomatosis from other conditions. The halo sign is the result of surrounding parenchymal hemorrhage.⁴⁹ The atoll sign, can also be seen in Wegener granulomatosis,⁵⁰ and usually reflects an organizing pneumonia reaction in the periphery of focal hemorrhage.⁴⁸ Spiculations, radiating linear scarring, and tags to the adjacent pleural surfaces are prominent features of nodules and masses secondary to Wegener granulomatosis. These features are not usually seen in other causes of peripheral masses such as septic emboli, acute pulmonary infarcts, or hematogenous metastases.⁵¹

Diffuse ground-glass opacity and consolidation occur in up to 50% of patients and can result from pulmonary hemorrhage or infection. When they occur in isolation, infection is the most common initial diagnosis, and Wegener granulomatosis is considered only after failure of antibiotic therapy.⁵²

Although consolidation and ground-glass opacity may be quite variable, bilateral perihilar, and peribronchovascular distributions are the most common. Like the pulmonary nodules and masses, ground-glass opacities and consolidations may also wax and wane over the period of time regardless of therapy. Consolidations are generally dense and may contain air bronchogram.^{53,54}

Ground-glass opacity can result either from alveolar hemorrhage or intra-alveolar debris. Ground-glass opacity in association with a mosaic pattern can result from arteriolar involvement. Fewer than 10% patients have extensive ground-glass opacity with subpleural sparing, findings that are suggestive of diffuse alveolar hemorrhage. Areas of diffuse hemorrhage can coalesce to form denser areas of hemorrhagic consolidation. Alveolar hemorrhage is generally acute and can be fatal if untreated. However, treatment can cause complete resolution, and in some cases, resolution may occur spontaneously.^{48,55}

Airway involvement occurs as a late complication. Patients present with progressive stridor and respiratory difficulty. The distribution can be focal or diffuse; with the subglottic trachea being most commonly involved. Concentric wall thickening can cause airway stenosis. Mucosal ulceration can result in hemoptysis. Virtual bronchoscopy is useful to further characterize bronchial stenoses. Airway involvement can mimic tracheobronchial tumors such as adenoid cystic carcinoma as well as tracheal amyloidosis and stenosis from prolonged intubation or infection like tuberculosis⁵⁶⁻⁶⁰ (–Figs. 9–11).

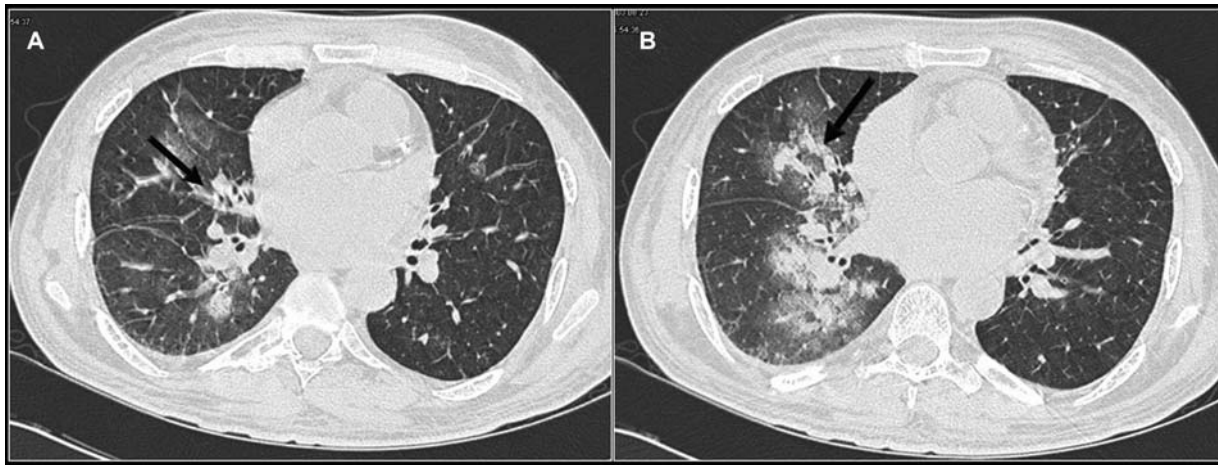


Fig. 9 (A and B) Axial high-resolution computed tomography (HRCT) images reveal, multiple peribronchovascular irregular nodules with few of them coalescing to form consolidations.

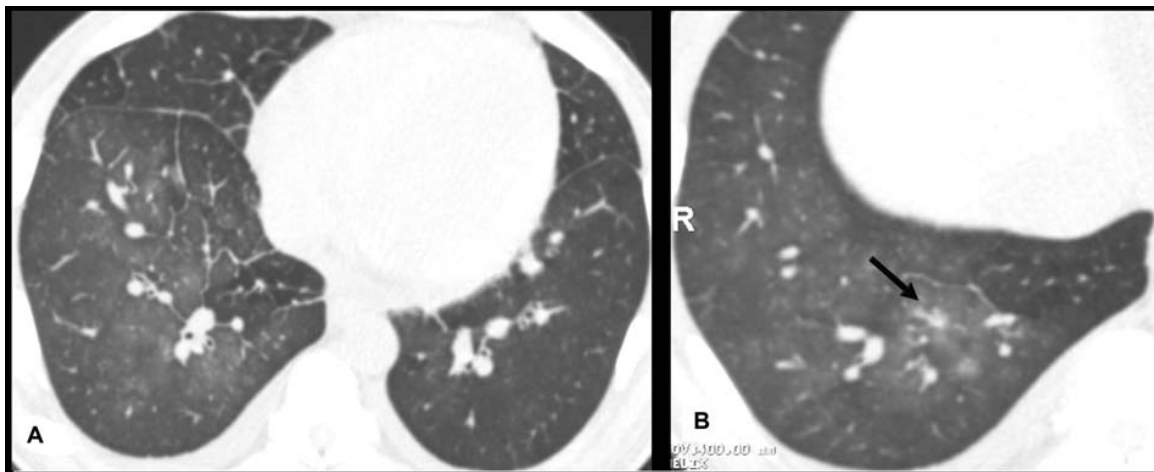


Fig. 10 A 32 years old female proteinase 3 (PR-3) antibodies positive. (A and B) Axial lung window settings reveal multiple ill-defined nodules of ground-glass attenuation in right lower lobe.

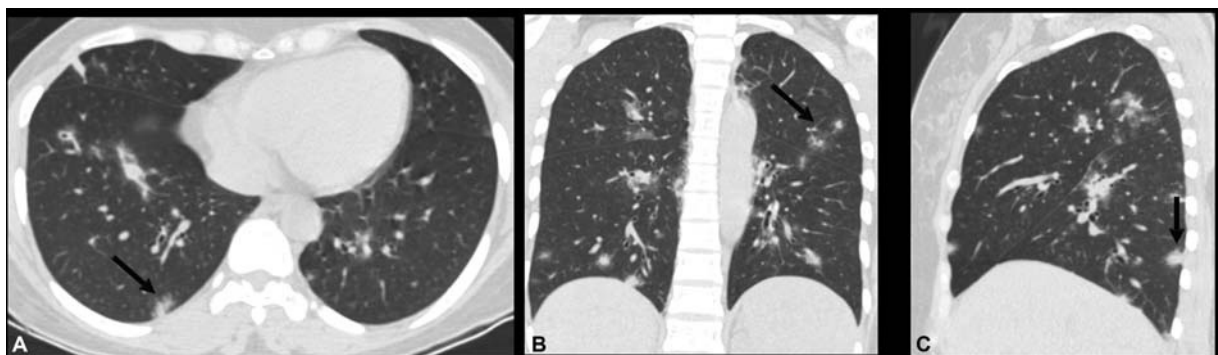


Fig. 11 A 38-year-old female patient with history of fever and breathlessness since 2 weeks. Perinuclear antineutrophil cytoplasmic antibody (p-ANCA) positive. (A–C) High-resolution computed tomography (HRCT) axial, coronal, and sagittal images reveal multiple varying sized nodules randomly distributed throughout the lungs in peribronchovascular and subpleural location, with few of them showing surrounding ground-glass opacities (GGOs).

Eosinophilic Granulomatosis with Polyangiitis

Churg-Strauss syndrome, also known as EGPA, is a rare small-vessel vasculitis associated with ANCA and hypereosinophilic syndromes, characterized by peripheral eosinophilia, tissue eosinophilia, disseminated necrotizing vasculitis, extravascular granulomas, and asthma.

The 1990 ACR criteria requires a positive biopsy and at least four of the six criteria given below⁴³:

- Asthma: seen in almost all the patients.
- Blood eosinophilia (> 10% of the total white blood cell count): seen in almost all the patients.
- Transient pulmonary infiltrates.
- Paranasal sinus abnormalities: plain or radiographic abnormality.
- Mononeuropathy or polyneuropathy.
- Presence of extravascular eosinophils on a biopsy specimen.

Chest radiography findings are nonspecific in EGPA. Bilateral, nonsegmental, multifocal, and typically peripheral consolidation is the most common radiographic abnormality.⁶¹ Pleural effusion can be seen in up to 50% of cases and is usually secondary to eosinophilic cardiomyopathy or pleuritis.⁶² CT is better for characterization of the parenchymal findings of EGPA. In one of the retrospective studies,⁶¹ CT showed pulmonary parenchymal abnormalities with a bronchiolocentric pattern in around 76% of the patients and with an airspace pattern in approximately 40% of patients.

Parenchymal opacities show a mixture of necrotizing granulomas, eosinophilic pneumonia, and granulomatous vasculitis. Small nodules is usually due to eosinophilic bronchiolitis and peribronchiolar vasculitis, while bronchial wall thickening is related to airway wall lymphocytic and eosinophilic infiltration.⁶³ Mediastinal lymphadenopathy is

uncommon.⁶⁴ Patients are more prone to thromboembolic phenomena especially pulmonary embolism because of the eosinophilia.⁶⁵ Cavitory lesions are uncommon in EGPA, as opposed to in GPA, where they are common.⁶⁶ Cavitation is rare and if present possibility of other coexisting pathology should be considered (–Fig. 12).

Necrobiotic Nodules

Rheumatoid pulmonary nodules are well-described extra-articular manifestation of rheumatoid disease, occurring most commonly in cigarette smokers with clinical and radiographic evidence of rheumatoid arthritis (RA).⁶⁷ Lung involvement is seen in approximately 30 to 40% of cases.⁶⁸

Necrobiotic nodules histologically consist of a core of fibrinoid necrosis and an aggregate of numerous epithelioid histiocytes arranged in indistinct nodules with an infiltrate of plasma cells, lymphocytes, and multinucleated giant cells. Features are that of a granuloma.⁴³ Methotrexate is implicated in increased incidence of necrobiotic nodules due to activation of adenosine A1 receptors with consequent cellular fusion into multinucleated giant cells.

Necrobiotic nodules commonly are seen in the upper and middle zones; can be either single or multiple. Usually, they are multiple and pleural based, and can vary in size from few millimeters to as large as 7 cm. They can resolve spontaneously, wax and wane in concert with the disease activity, or may antedate arthritis.⁶⁹ Nodules are usually asymptomatic and require no treatment unless they become/attain a large size or become infected or cavitated. Most of the rheumatoid pulmonary nodules will cavitate and can be associated with pneumothorax, pleural effusion, or pyopneumothorax.⁷⁰ The majority of spontaneous pneumothoraces are associated with subpleural necrobiotic pulmonary nodules.⁷¹

The major patterns of ILD that are associated with RA are UIP, organizing pneumonia, and diffuse alveolar damage.⁷²

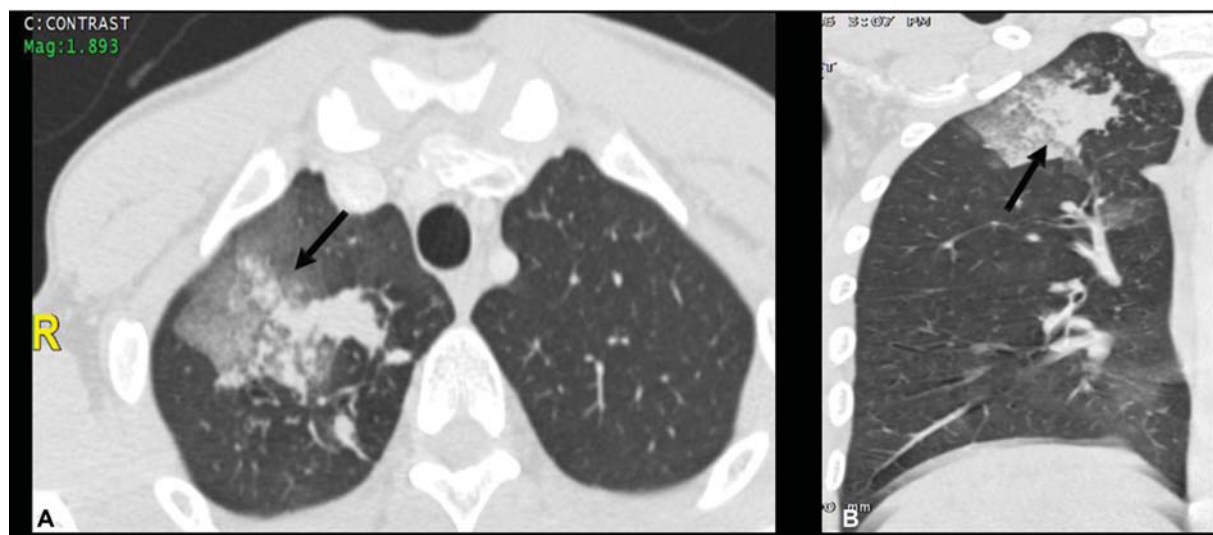


Fig. 12 (A and B) Axial and sagittal high-resolution computed tomography (HRCT) images reveal consolidation with surrounding ground-glass opacities and areas of interlobular septal thickening.



Fig. 13 (A) Frontal radiograph of the chest shows multiple sub-cm sized well-defined radioopacities involving bilateral lung zones, more in lower lung zones. (B and C) Axial and coronal high-resolution computed tomography (HRCT) images show multiple well-defined randomly distributed cavitating nodules involving bilateral lung parenchyma—necrobiotic nodules.

While NSIP radiographic and histological pattern is the most common in the connective tissue disease as a whole, in RA UIP is the most common pattern seen.

In Caplan syndrome, multiple necrobiotic nodules develop in patients with coal worker pneumoconiosis. Tree-in-bud opacities or large cavitating masses should raise the concern for an atypical infection (► **Fig. 13**).

Lymphomatoid Granulomatosis

LYG is a very rare B cell extranodal lymphoproliferative disorder. It is associated with angiocentric and angiodestructive accumulation of atypical B cell lymphocytes infected by Epstein-Barr virus and reactive T cell lymphocytes. Lymphoid cells accumulate in the affected tissues in the form of infiltrative nodular lesions.^{73,74} LYG is related to immune system of the host. Although most of them do not have a preexisting immunodeficiency, evidence of immune dysregulation can be seen in most of the patients. Patients can have a history of autoimmune illnesses, recurrent infections, and lymphoproliferative disorders or can be on immunosuppressive treatment.⁷³ It is generally seen in males between the third and fifth decades of life, although patients of any age group can be affected.⁷⁴ Constitutional symptoms such as malaise, weight loss, and fever can be present in most patients.

Lungs are almost always involved, usually in the form of multiple bilateral pulmonary nodules of varying in a bronchovascular distribution, mainly in middle and lower lung fields. Cavitation caused by necrosis can be seen in some cases. Unilateral or bilateral multiple lung nodules with a basal predominance is the most common radiologic feature. The lesions tend to progress rapidly, coalesce, and cavitate. Nodules can disappear or migrate spontaneously, and a “revers halo sign” is frequently seen.⁷⁵ Pleural effusion can be present.

Marked accumulations of fluorodeoxyglucose are seen. There is no hilar lymphadenopathy since LYG is an extranodal lymphoproliferative disorder.^{73,74} Occasionally, involvement of the pulmonary artery wall can be seen and manifest as wall thickening or an intraluminal filling defect in the pulmonary artery. Vascular findings are almost always seen in combination with parenchymal involvement.

Pulmonary Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is an abnormal nonmalignant proliferation of monoclonal Langerhans cells in one or multiple organ systems. Although the etiology of LCH is unclear, some of the theories include viral infection, antigen exposure, and somatic mutation.⁷⁶

Pulmonary LCH refers to PLCH that is isolated to the respiratory system. It is found almost exclusively in cigarette smokers, which supports the theory of antigen exposure, since cigarette smoke contains thousands of known antigens. PLCH is seen in third to fourth decade. Gender predominance has been debated in past articles.^{77,78}

Patients often present with dyspnea, cough, and fatigue, although they may present with chest pain due to a pneumothorax. Respiratory examination is usually normal or nonspecific. Wheezing, rales, or decreased breath sounds can be, however, present. Obstructive, restrictive, or mixed pattern can be seen in pulmonary function tests. A decrease in carbon monoxide diffusing capacity is present in most of the patients.⁷⁶

PLCH is suspected on the basis of history and chest radiograph and is confirmed by imaging and bronchoscopy with biopsy and bronchoalveolar lavage. Pulmonary function test findings are normal, restrictive, obstructive, or mixed depending on when the test is done during the course of the disease. Most commonly, the diffusing capacity for carbon monoxide is reduced and exercise is impaired.

When imaging and pulmonary function tests are inconclusive, bronchoscopy and biopsy are indicated. Finding > 5% of CD1a cells in bronchoalveolar lavage fluid is suggestive of the disease. Proliferation of Langerhans cells with occasional clustering of eosinophils in the midst of cellular and fibrotic nodules that may take on a stellate configuration can be seen on biopsy. Immunohistochemical staining is positive for S-100 protein, CD1a, and human leukocyte antigen-DR antigens.

The radiologic findings of pulmonary depend on the stage of the disease at diagnosis. Bilateral and mostly symmetric upper lobe-predominant disease with sparing of the costophrenic angles is seen on chest radiography. In early stages diffuse ill-defined bilateral nodules will be seen. Because the disease has an inhalational component, the middle and

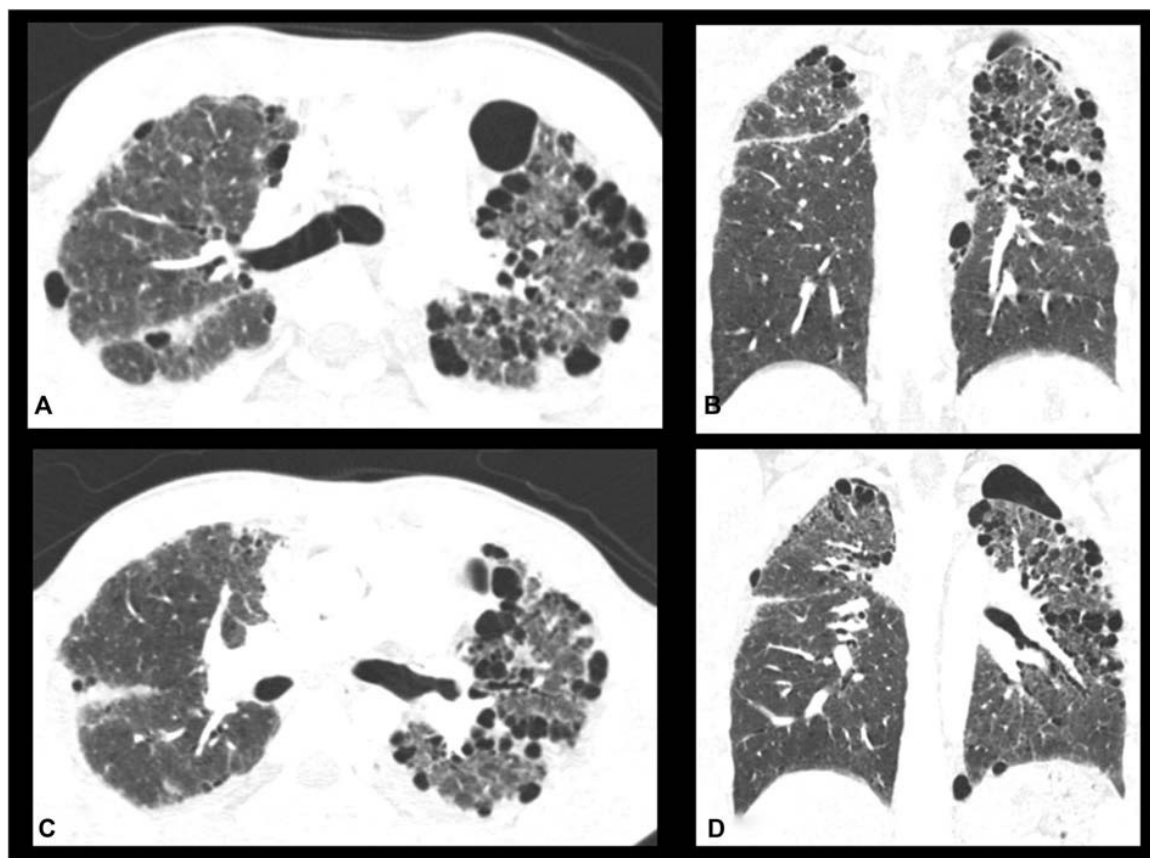


Fig. 14 (A–D) Numerous varying sized cysts in bilateral upper lobes with sparing of costophrenic (CP) angle—pulmonary Langerhans cell histiocytosis (PLCH).

upper lung zones are involved than the lung bases. These nodules undergo cystic degeneration as the disease progresses, and so a reticular pattern begins to appear on chest radiographs.⁷⁵ Fibrotic changes appear over a period of time with changes of honeycombing.⁷⁶ Coexistent emphysema can also be seen. The diagnosis can be easily made with by showing both ill-defined nodules and cysts in a patient who is heavy smoker. However, the diagnostic accuracy falls short when only nodules or cysts alone are present. Most of these cases are confirmed with lung biopsy.⁷⁵

The differential diagnosis of primarily cystic lung disease includes predominantly cystic PLCH, emphysema, lymphangiomyomatosis, and bronchiectasis. The cysts in LCH are often variable in size and wall thickness (bizarre pattern). The early involvement of distal bronchioles often leads to an obstructive pattern of lung disease on chest radiographs, a finding that translates into normal or increased lung volumes despite the fibrosing nature of the disease. The cysts of lymphangiomyomatosis occur diffusely throughout the lungs and affect women almost exclusively. The cystic cavities of emphysema are foci of destroyed parenchyma and do not have definable walls. The cyst-like bronchial dilatation seen in bronchiectasis can be distinguished by the communicating branching pattern.⁷⁶

Patients with PLCH have uncertain clinical courses. Up to one-half will show clinical and radiographic stability, while

up to 25% will show spontaneous regression. The remaining have a continued cystic replacement of parenchyma that may progress to end-stage lung disease. Adults have an overall long-term survival compared with those without the disease.⁷⁶ Mortality is most likely due to respiratory failure or pulmonary hypertension. Although there exists a strong association with cigarette smoking, there is no known link between relapse of disease and continuation of smoking or between regression of disease and cessation of smoking⁷⁸ (► Fig. 14).

Granulomatous and Lymphocytic Interstitial Lung Disease

GLILD is a recently described granulomatous lung disease which is almost always associated with common variable immunodeficiency (CVID). CVID represents a group of heterogeneous primary immunodeficiencies which is characterized by a dysregulated impaired immune response. It is also associated with noninfectious autoimmune and lymphoproliferative complications in addition to an increased susceptibility to infection. Pulmonary involvement is common, and patients can develop an ILD called GLILD.

Radiologically, patients with CVID present with recurrent infections which on imaging are seen as consolidation, bronchiectasis, atelectasis, or air trapping. On the other hand, GLILD

has different distinct imaging features and present with thoracoabdominal lymphadenopathy and soft tissue density and ground-glass micronodules. Mid and lower zone predominance of the nodules is seen which is a helpful feature to distinguish this entity from sarcoid. Patients with GLILD generally have splenomegaly. Bronchiectasis is less common in GLILD than in CVID. It can be differentiated from lymphoma on the basis of low or absent immunoglobulins.^{79,80}

Conclusion

Granulomatous lung disease, includes infectious and noninfectious diseases, former being more common and in our country that being tuberculosis. It is important to understand that not all granulomatous lung diseases are infective. Therefore, a knowledge of noninfectious granulomatous lung disease is important and diagnosing the same will help in initiating serological tests, treatment options, and aid in deciding the mode and target for biopsy if needed. A multidisciplinary approach always helps to narrow down the diagnosis.

Conflict of Interest
None declared.

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