

Non infectious granulomatosis lung disease

Granulomatosis with polyangiitis GPA (Wegener's granulomatosis):

- Systemic vasculitis affecting both the upper and lower airways & usually without eosinophilia & predominantly affects small vessels
- Categorized in ANCA-associated vasculitis(along with EPGA & MPA)
- Proteinase 3 (PR3)-ANCA(C-ANCA) is positive > 90% of extended GPA & 75% in limited GPA without renal involvement
- Typical histological findings for GPA: necrotizing granulomas accompanied by necrotizing vasculitis.

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Eosinophilic granulomatosis with polyangiitis EGPA(Churg–Strauss syndrome)

- Necrotizing granulomatous inflammation with marked eosinophil infiltration in respiratory tract, with necrotizing vasculitis predominantly affecting small-to-medium size vessels, & associated with asthma and eosinophilia.
- Predominant HRCT features include ground-glass opacities (39%), bronchial wall thickening (32%), consolidation (28%) and micronodules (<3 mm) (24%).
- ANCAs are positive 30% to 60% of patients. The majority of ANCA-positive EPGA are MPO-ANCA (P-ANCA).
- BAL cell differentials show a mean eosinophilia of 33%.

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Rheumatoid nodules:

- Rheumatoid nodules are necrotizing granulomas observed in 20% of patients with RA.
- They are usually located subcutaneously but may also occur in lungs as subpleural necrobiotic nodules, either multiple or solitary, with an incidence of <1%.
- Although vasculitis can be found, necrotizing vasculitis is absent.

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Hypersensitivity pneumonitis

- Complex syndrome resulting from repeated inhalation of organic substances.
- Causative particles include fungal (e.g. *Aspergillus* and *Penicillium* species), bacterial, protozoal, animal (mostly bird) & insect proteins, and low-molecular-weight chemical compounds (e.g. isocyanates, zinc, inks and dyes).
- HP presents as acute, subacute or chronic clinical form & overlap is possible.

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Hypersensitivity pneumonitis

- Clinical presentation of HP influenced by several factors including nature & amount of inhaled antigen, intensity and frequency of exposure, and the host immune response.
- The histological triad of HP includes peribronchiolar chronic inflammation, poorly formed small interstitial non-necrotizing granulomas (smaller than those of sarcoidosis) and foci of organizing pneumonia.
- Cigarette smoking seems to be protective against development of HP.

TABLE 2 Predictors of hypersensitivity pneumonitis

Variable	OR (95% CI)
Exposure to a known offending antigen	38.8 (11.6–129.6)
Positive precipitating antibodies	5.3 (2.7–10.4)
Recurrent episodes of symptoms	3.3 (1.5–7.5)
Inspiratory crackles	4.5 (1.8–11.7)
Symptoms 4–8 h after exposure	7.2 (1.8–28.6)
Weight loss	2.0 (1.8–28.6)

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[Hypersensitivity pneumonitis](#)

- HRCT findings
- In acute HP: NL or may shows patchy or diffuse ground-glass attenuation and/or centrilobular poorly defined small nodules, mosaic perfusion .
- In subacute HP: patchy air-trapping areas on expiratory scans often in lobular distribution & poorly defined small nodules in centrilobular distribution.
- In chronic HP, prominent findings on HRCT are signs of lung fibrosis combined with
- ground-glass attenuation, centrilobular small nodules and traction bronchiectasis.

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[Hypersensitivity pneumonitis](#)

- An increase in total cell count with a remarkable increment of lymphocytes (usually >50%) is characteristic for HP.
- Low CD4+ /CD8+ ratio with mean values of 0.5–1.5

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[Hypersensitivity pneumonitis](#)

- Sarcoidosis can be differentiated from chronic HP by different distribution of micronodules(peri lymphatic/subpleural/along fissures in sarcoidosis versus centrilobular in HP) & by lack of mosaic perfusion in sarcoidosis.
- Lymphocyte subsets of HLA-DR+ CD8+ T-cells & NK T-cells in BAL may differentiate HP from sarcoidosis.

Granulomatosis with polyangiitis	Rhinitis, otitis Cough Stridor Obstruction Dyspnoea	↑ Cytoplasmic ANCA	Nodules/granulomas Cavities Pleural effusions Lymphadenopathy	Necrotising granulomas Necrotising vasculitis
Eosinophilic granulomatosis with polyangiitis	Asthma Vasculitis Cutaneous, intestinal, cardiac granulomas	↑ Perinuclear ANCA Eosinophilia	Nodules/granulomas GGOs Bronchial wall thickening Consolidations	Necrotising granulomatous inflammation Eosinophilic infiltration
Hypersensitivity pneumonitis	Acute onset (fever, cough, tachydyspnea) Subacute/chronic (productive cough, fatigue, malaise, chronic cyanosis)	↑ Specific IgGs against organic compounds	Centrilobular GGOs Nodular opacities air-trapping Mosaic attenuation Septal thickening Bronchiectasis Honeycombing	Poorly-formed non-caseating granulomas Bronchiolitis with lymphocytic infiltration Fibrotic nonspecific interstitial inflammation Lymphocytic infiltrates Poorly-formed granulomas

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Drug-induced granulomatous lung disease :

- Granulomas of drug-induced ILD are typically non-necrotizing.
- Depending on immune status of patients, special stains & molecular analyses are necessary to differentiate drug-induced ILD from mycobacteria, PCP or other infections.
- Causative of drugs (MTX, interferon, BCG, infliximab, etanercept, leflunomide, mesalamine and sirolimus) .

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Hot tub lung

- Syndrome that combines features of HP and M. avium complex infection resulting from exposure to contaminated hot tubs.
- HRCT shows ground-glass attenuation and scattered small nodules.
- Pathological findings are similar to typical HP, but pneumonia tends to be less prominent & usually non-necrotizing granulomas are well formed, frequently distributed within airway lumen rather than in peribronchiolar interstitium.
- Cultures & history of exposure are necessary for diagnosis.

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Berylliosis

- Granulomatous reaction in lung to inhaled beryllium.
- Clinical, radiological & histopathological findings mimic sarcoidosis, with lymphangitic distribution & hilar lymph node involvement.
- Histopathology shows interstitial inflammation which rather resembles HP.
- History of exposure to beryllium and a positive beryllium lymphocyte transformation test are crucial for the accurate diagnosis of berylliosis.

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Talc-induced granulomatosis

- Drug abusers, especially of cocaine and crack, can develop a broad spectrum of acute & chronic lung diseases.
- Method of administration (oral, nasal or intravenous), dose size, frequency of exposure and presence of associated substances are associated with different lung manifestations.
- Talc is most frequently used carrier substance for oral medications.
- If such medications applied IV by drug abusers, typical pathological findings are perivascular location of foreign body-containing granulomas.

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Inflammatory bowel disease :

- Characterized by non-necrotizing granulomas of the gastrointestinal tract.
- Extraintestinal manifestations occur in 21–36% of patients, pulmonary granulomatous manifestations are extremely rare
- Chronic bronchiolitis with non-necrotizing granulomas without the lymphangitic pattern has been reported
- BAL may show lymphocytosis but, pathological and/or microscopic findings alone cannot discriminate pulmonary involvement of IBD from other granulomatous lung diseases.

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Pulmonary Langerhans cell histiocytosis

- Rare lung disease of unknown cause, primarily affecting young adults.
- Smoking appears to be one of important etiological factors.
- Symptom: nonproductive cough, dyspnea, fatigue, chest pain, weight loss & fever.

HRCT: multiple cysts & nodules with a middle- to upper-lobe predominance.

Histopathology: accumulation of activated Langerhans cells in granulomas accompanied by eosinophils and lymphocytes.

BAL: presence of CD1a+ and/or CD207 (>5% of total cells)

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Granulomatous–lymphocytic interstitial lung disease (GLILD)

- CVID is primary immunodeficiency characterized by B-lymphocyte dysfunction & hypogammaglobulinaemia.
- Patients with CVID frequently demonstrate recurrent respiratory tract infections.
- Granulomatous & lymphoproliferative inflammation sometimes affects small airways & pulmonary interstitium, this is termed GLILD.
- The incidence of GLILD in CVID ranges from 8% to 22%.
- Impaired T-cell function & impaired antigen handling are possible mechanism of GLILD

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Granulomatous–lymphocytic interstitial lung disease (GLILD)

- Symptom: dyspnea, splenomegaly, lymphadenopathy and/or liver disease in context of multisystem granulomatous/inflammatory involvement.
- PFT: restrictive pattern with a low diffusing capacity of lung for carbon monoxide.
- Bronchoscopic examination for bacterial & mycobacterial culture is necessary in Dx work-up for GLILD.
- HRCT: solid nodules (<3cm), semi-solid nodules, pure ground-glass opacities, patchy consolidations, reticular densities, enlarged hilar and/or mediastinal lymph

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Granulomatous–lymphocytic interstitial lung disease (GLILD)

- Pathological examinations: immunostaining for CD3, CD4, CD8 and CD20 are recommended, and also evaluating clonality to exclude lymphoma.
- The presences of granulomatous inflammation, peribronchiolar lymphoid proliferation, interstitial lymphoid proliferation and CD4+ cell predominance are suggestive of GLILD.

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Aspiration pneumonia

- Aspiration of a variety of substances, including oropharyngeal bacteria, foreign bodies & gastric contents, leads to an aspiration pneumonia.
- Typical pathological findings include acute necrotizing bronchopneumonia accompanied by foreign body granulomas or multinucleated giant cells containing aspirated foreign material.

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Malignant tumors

- Some malignant tumors can trigger significant granulomatous reaction, (Hodgkin's lymphomas, non-Hodgkin disease and carcinomas).
- It is hypothesized that tumor cell antigens could triggers for immune reaction associated with the sarcoid-like granulomas, and distinction of the two disorders is often difficult.
- However, unlike sarcoidosis, B-cell positive granulomas have been found in malignant tumors and drug-induced sarcoid like reactions, and this feature could be useful to differentiate between the two conditions.

TABLE 1 Immunodeficiencies and autoinflammatory disorders associated with pulmonary granulomatosis

Condition	Exemplary clinical features	Exemplary laboratory features	Radiologic presentation	Histology
CVID	Recurrent bronchopulmonary infections Lymphoproliferation	Hypogammaglobulinaemia	GLILD Small and large nodules Round infiltrates (“reversed halo” or “atoll” signs) GGOs (mainly in the lower lobes) Lymphadenopathy	Interstitial pneumonitis Follicular bronchiolitis Non-caseating granulomas Lymphoid infiltration
LRBA/CTLA-4 deficiency	Autoimmunopathies (lymphoproliferation, enteropathy, cytopenias) Respiratory infections CNS involvement	Hypogammaglobulinaemia Cytopenias Functional T-cell defects	See CVID	See CVID
CGD	Recurrent infections Skin and organ abscesses	Reduced “respiratory burst”	Infiltrates Abscesses Pneumatocoeles Bronchiectasis obliterative bronchiolitis Chronic fibrosis	Changes associated with inflammatory infiltrates, abscesses and fibrosis Non-caseating granulomas
STAT3 loss of function (AD HIES)	Dermatitis, skin abscesses Tooth retention Coarse facial features Bronchopulmonary infections	↑ IgE (>2.000 units·mL ⁻¹) ↓ Th17 cells ↓ Memory B cells ↓ Production of inflammatory cytokines (IL-17/IL-22)	Abscesses Pneumatocoeles Chronic pneumothorax Granulomas	Changes associated with inflammatory infiltrates, abscesses and fibrosis Non-caseating granulomas

STAT3 gain of function	Autoimmunopathies (cytopenias, lymphoproliferation, enteropathy, diabetes)	Cytopenias Hyperglycaemia Impaired T-cell signalling	Lymphocytic interstitial pneumonitis Granulomas Cryptogenic organising pneumonia	Lymphocytic interstitial pneumonia Non-necrotising granulomas Fibrosis
MSMD	Mycobacterial infections Infection by intracellular pathogens Chronic mucocutaneous candidiasis	Reduced IFN- γ production	Focal infiltration of upper lobes, middle lobes, or lingula Pulmonary granulomas as in mycobacterial infection Cavernas Lymphadenopathy	Necrotising granulomas in <i>Mycobacterium tuberculosis</i> Varying histology in non- <i>M. tuberculosis</i> mycobacteria (necrotising and non-necrotising) Random or bronchocentric location of granulomas
Blau syndrome/early onset sarcoidosis	Classical triad (granulomatous polyarthritis, dermatitis, uveitis) 50% fever, lymphadenopathy, vasculitis	$\uparrow$ Inflammatory cytokines $\uparrow$ ACE, sCD25, neopterin BAL (lymphocytosis, CD4:CD8 ratio >3.5:1)	GGOs Micronodules Granulomas	Non-necrotising granulomas
NOD2-associated autoinflammatory disease	Recurrent fever Weight loss Non-erosive arthritis Granulomatous dermatitis Granulomatous colitis	Anaemia Leukocytosis Elevated inflammatory cytokines	GGOs Micronodules Granulomas	Non-necrotising granulomas

Diagnostic algorithm of granulomatous lung diseases



