Pulmonary Manifestations of Common Variable Immunodeficiency

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Abstract

Common variable immunodeficiency (CVID) is a primary immunodeficiency characterized by B and T cell abnormalities. CVID is associated with recurrent respiratory tract infections, and can result in chronic lung disease. CVID-associated lung diseases occur along a spectrum, ranging from infection to malignancy.

The purpose of this exhibit is to describe the clinical, radiologic, and pathologic findings of CVID-associated lung disease. Additionally, the impact of these findings on prognosis and treatment will be addressed. The following CVID-associated lung diseases will be discussed:

- Bronchiectasis/Airways disease
  - Mucoid impaction
  - Centrilobular nodularity
- Interstitial Lung Disease
  - Lymphocytic interstitial pneumonia
  - Follicular bronchiolitis
  - Granulomatous-lymphocytic interstitial lung disease
- Lymphoma/MALToma
- Kabuki Syndrome

CVID is associated with chronic lung disease, ranging from benign airways disease to malignancy. Appropriate identification of these diseases allows for better prognostication and direction of therapy.

Common Variable Immunodeficiency

- Common variable immunodeficiency (CVID) is the most common immune deficiency.
- Characterized by both B-cell and T-cell abnormalities.
- Patients often have a history of recurrent infections, autoimmunity, and chronic lung disease.

Diagnostic Criteria for CVID
Age greater than 4 years
Low serum IgG levels (generally <400 mg/dL)
Low serum IgA and/or low IgM levels
Poor or absent response to immunization
Absence of any other immunodeficiency state

Common Variable Immunodeficiency

- CVID is a heterogeneous disease without clear etiology.
- Polygenic disorder, with multiple genes implicated in its pathogenesis.
- Characterized by both infectious and non-infectious pulmonary diseases.

Infectious Complications (often recurrent)

- Pneumonia
- Otitis media
- Sinusitis
- Conjunctivitis
- Gastrointestinal infections

Non-infectious Complications

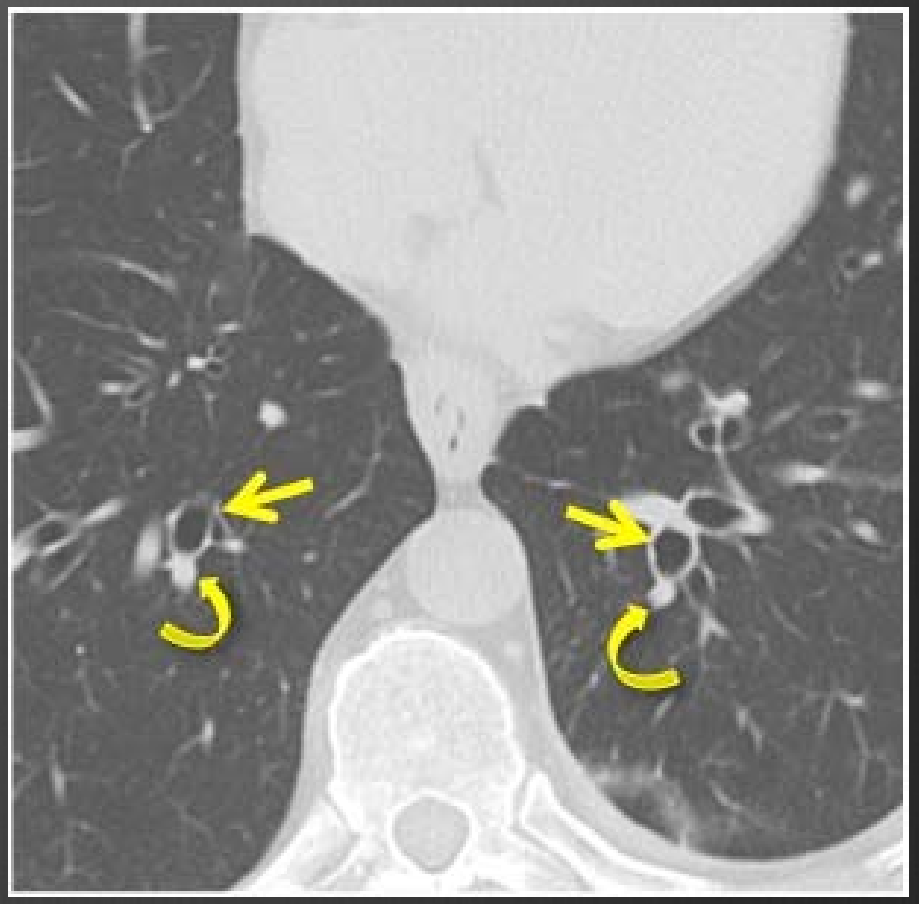
- Lymphocytic interstitial pneumonia
- Follicular bronchiolitis
- Granulomatous-lymphocytic interstitial lung disease
- Autoimmune hemolytic anemia
- Lymphoid hyperplasia/Lymphoma
- Immune thrombocytopenia
- Enteropathy

Treatment of CVID

- Immunoglobulin replacement therapy is the mainstay of therapy, decreasing the number of serious infections and improving quality of life.
- However, IgG levels do not directly correlate with survival and development of chronic lung disease, and IgG supplementation does not reliably prevent silent progression of lung disease.
- IgG levels are not the only contributor to development of infection or chronic lung disease.

Bronchiectasis

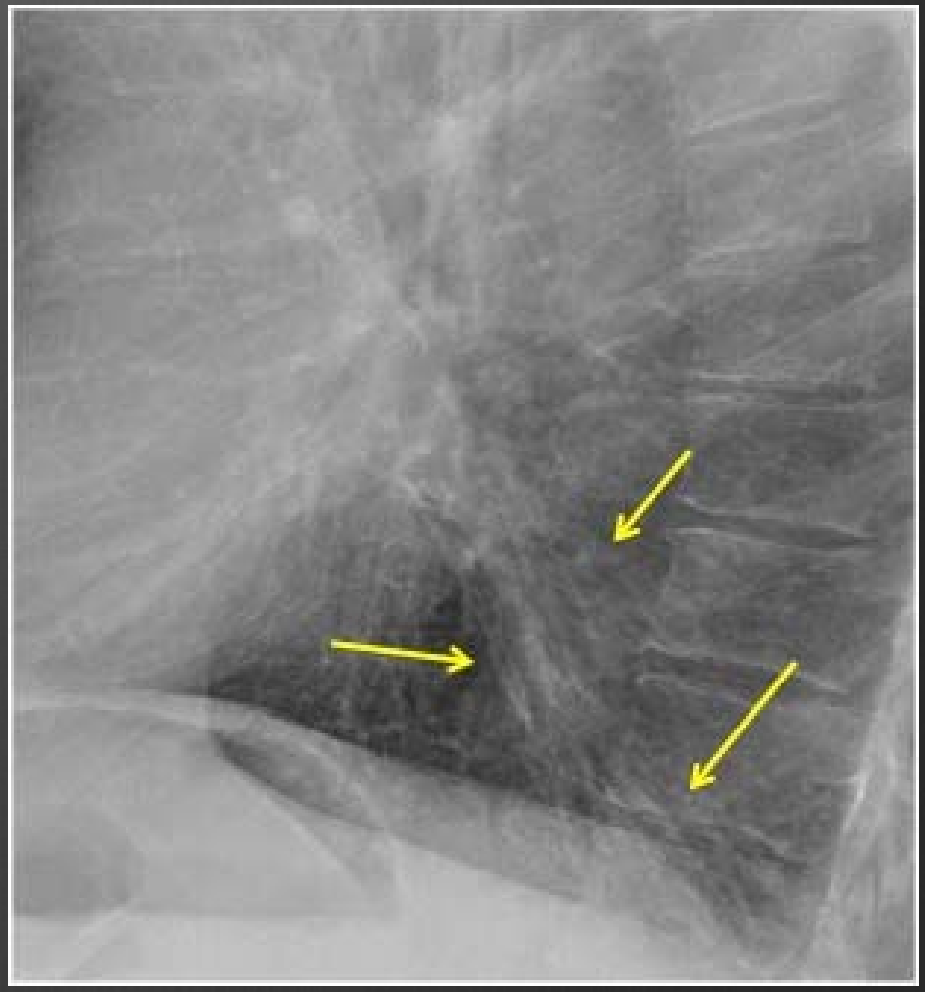
- Defined by airway diameter greater than adjacent pulmonary artery diameter.
- Most common radiologic abnormality in CVID (25-73% of cases), usually occurring in the lower lobes.
- May be associated with mucous plugging and tree-in-bud nodules.



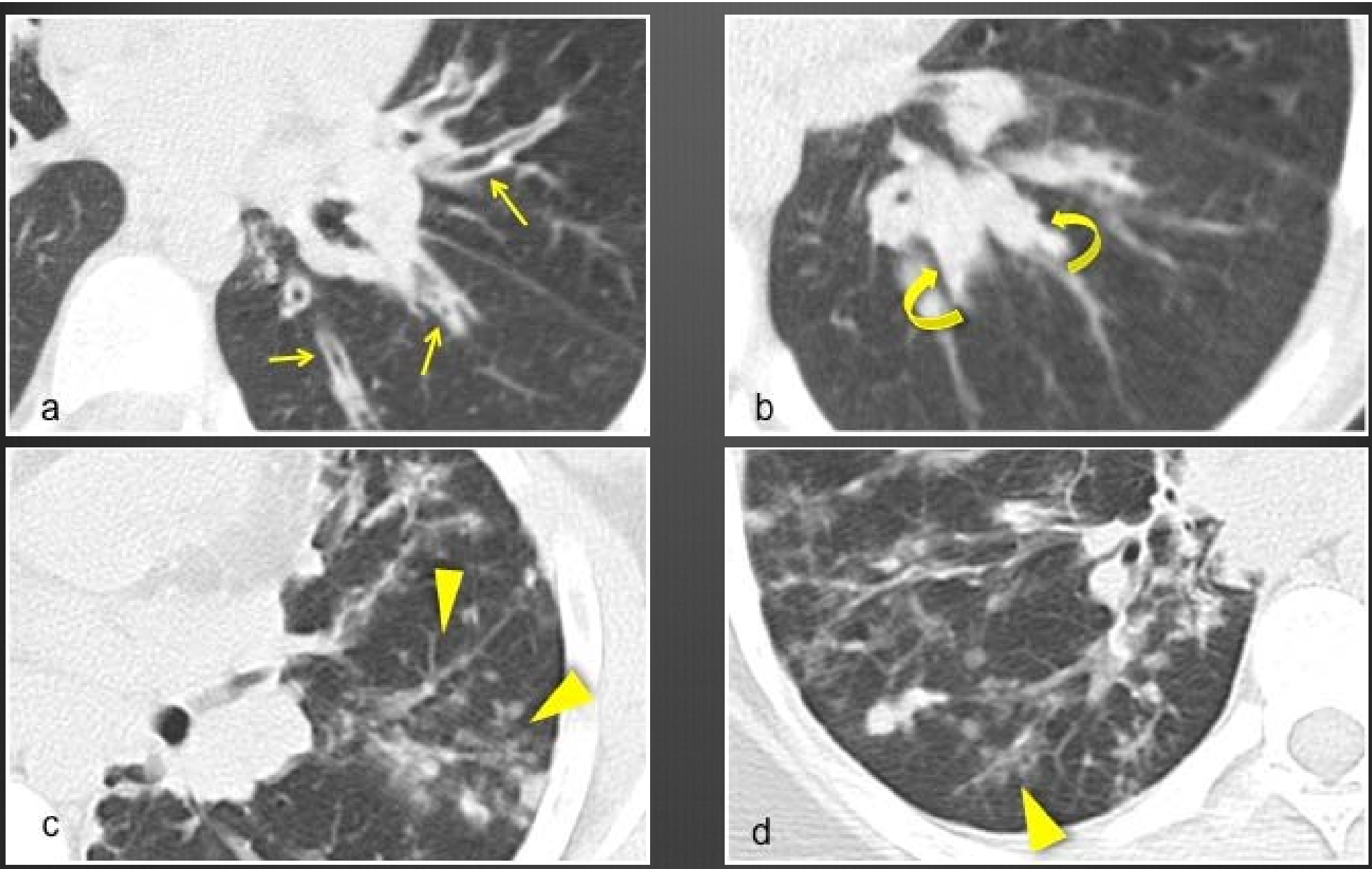
Axial non-contrast CT image of the lung bases in a patient with CVID. The airways in the lung bases (straight arrows) are larger in diameter than the adjacent pulmonary arteries (curved arrows).

Bronchiectasis

- Bronchiectasis is related to history of recurrent infections.
- Bronchiectasis is rare in young patients. Prevalence increases over time, correlating to number of infections.
- However, presence of bronchiectasis does not correlate with IgG levels.



Lateral chest radiograph in a patient with CVID demonstrating lower lung bronchiectasis (arrows).



(a) Axial non-contrast CT image of a patient with CVID and extensive bronchial wall thickening in the lower lungs (arrows). (b) Axial CT image of a different patient with CVID and basilar mucous plugging (curved arrows).

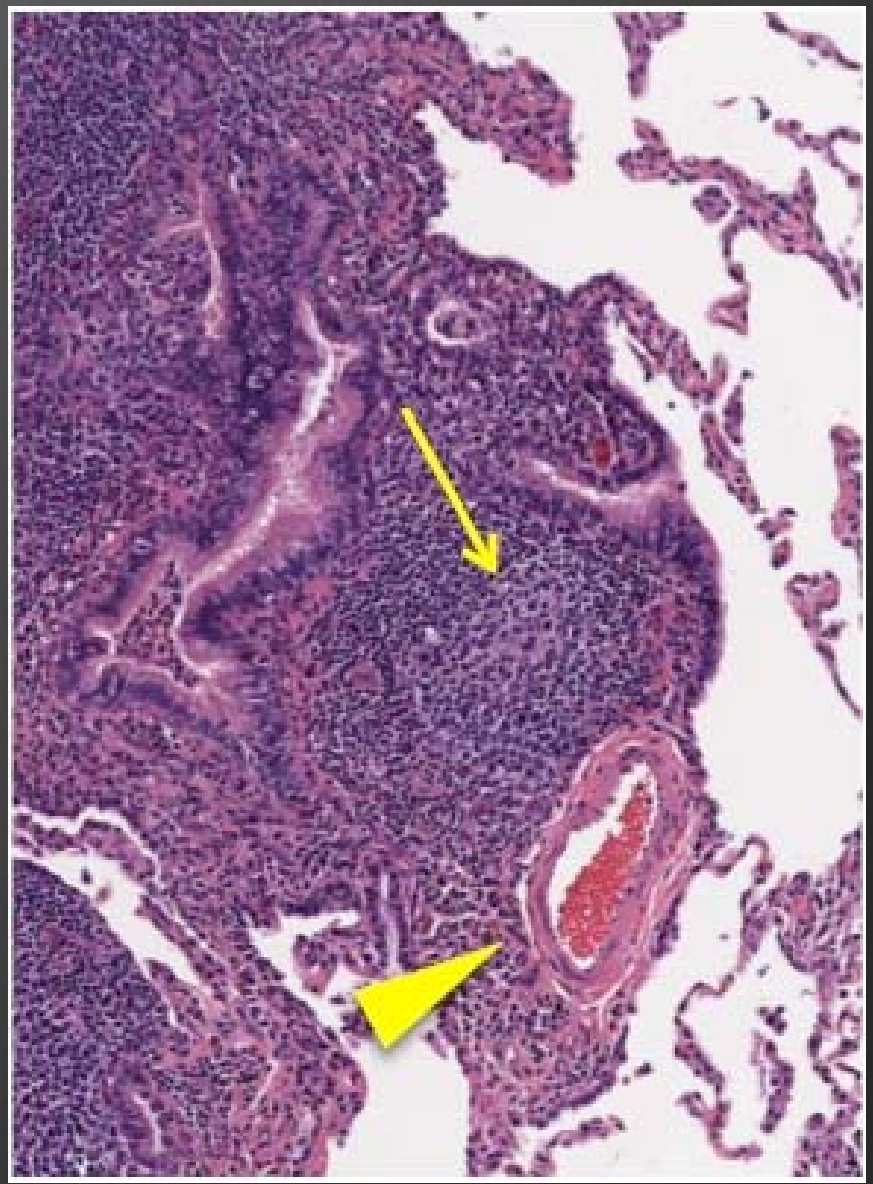
(c, d) Axial CT images of another patient with CVID, with parenchymal nodularity, some of which is in a tree-in-bud distribution (arrowheads).

Interstitial Lung Disease in CVID

- Pathogenesis is unknown, but has been linked to HHV-8, T-cell dysfunction, and immune complex formation.
- Histopathologic patterns of interstitial lung disease (ILD) in CVID commonly include follicular bronchiolitis (FB), lymphocytic interstitial pneumonia (LIP), organizing pneumonia (OP) and granulomatous-lymphocytic interstitial lung disease (GLILD).

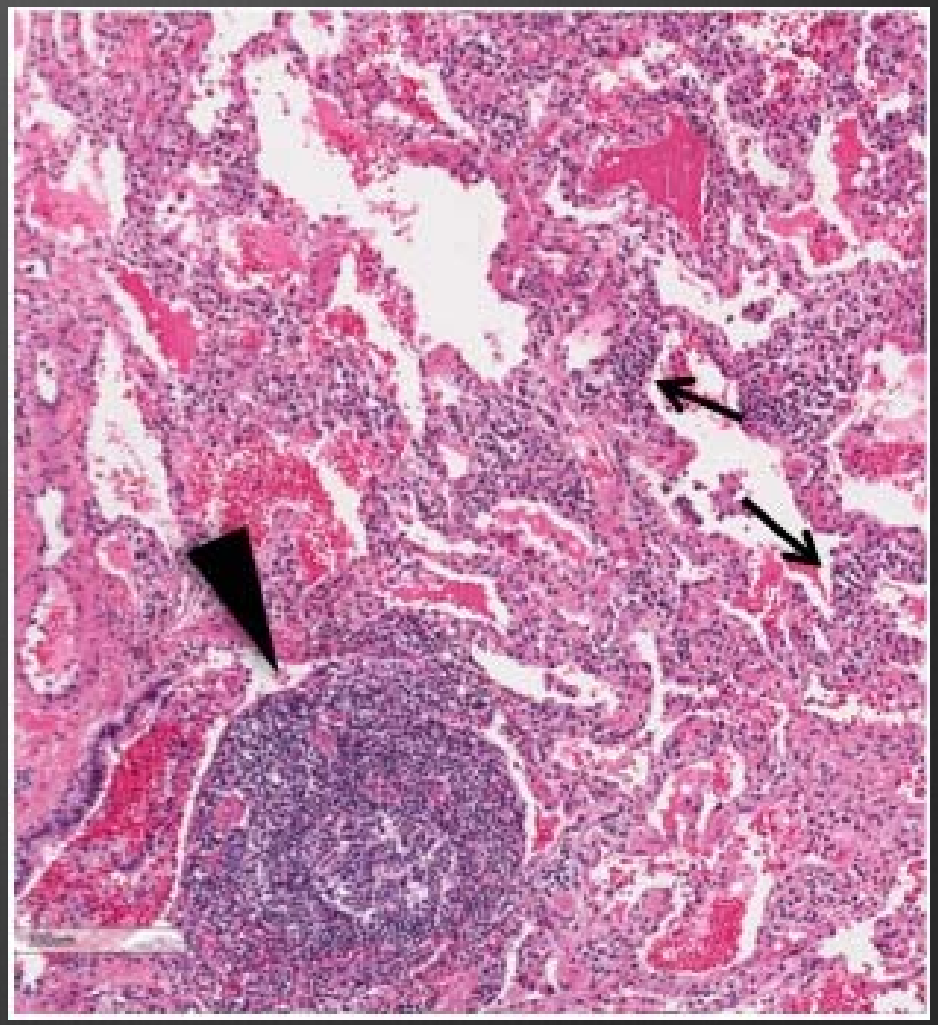
Follicular Bronchiolitis

- Diffuse lung disease characterized by peribronchial ground-glass and centrilobular nodules.
- May see radiologic overlap with LIP.
- Histopathologically, characterized by lymphoid follicles with germinal centers (arrow) in the bronchovascular bundles (arrowhead).



Lymphocytic Interstitial Pneumonia

- Interstitial lung disease characterized by lower-lung predominant cysts and ground glass.
- Also associated with Sjogren syndrome and HIV infection.
- Histopathologically characterized by lymphocytic infiltration resulting in alveolar septal thickening (arrows). Lymphoid follicle (arrowhead) is compatible with lymphoid hyperplasia.

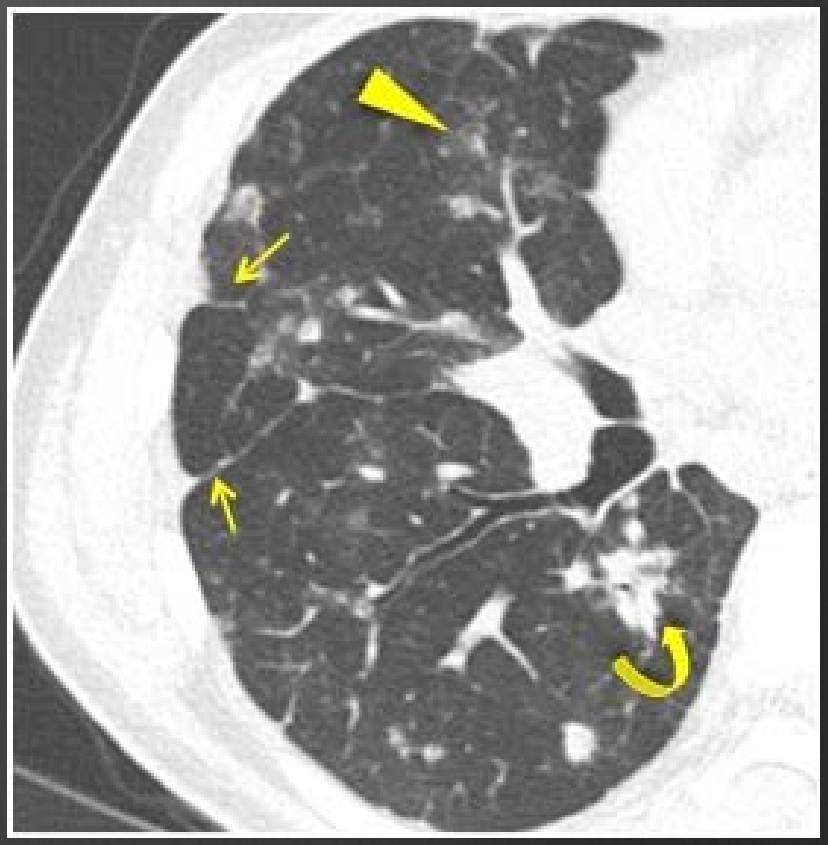


Granulomatous Lymphocytic Interstitial Lung Disease (GLILD)

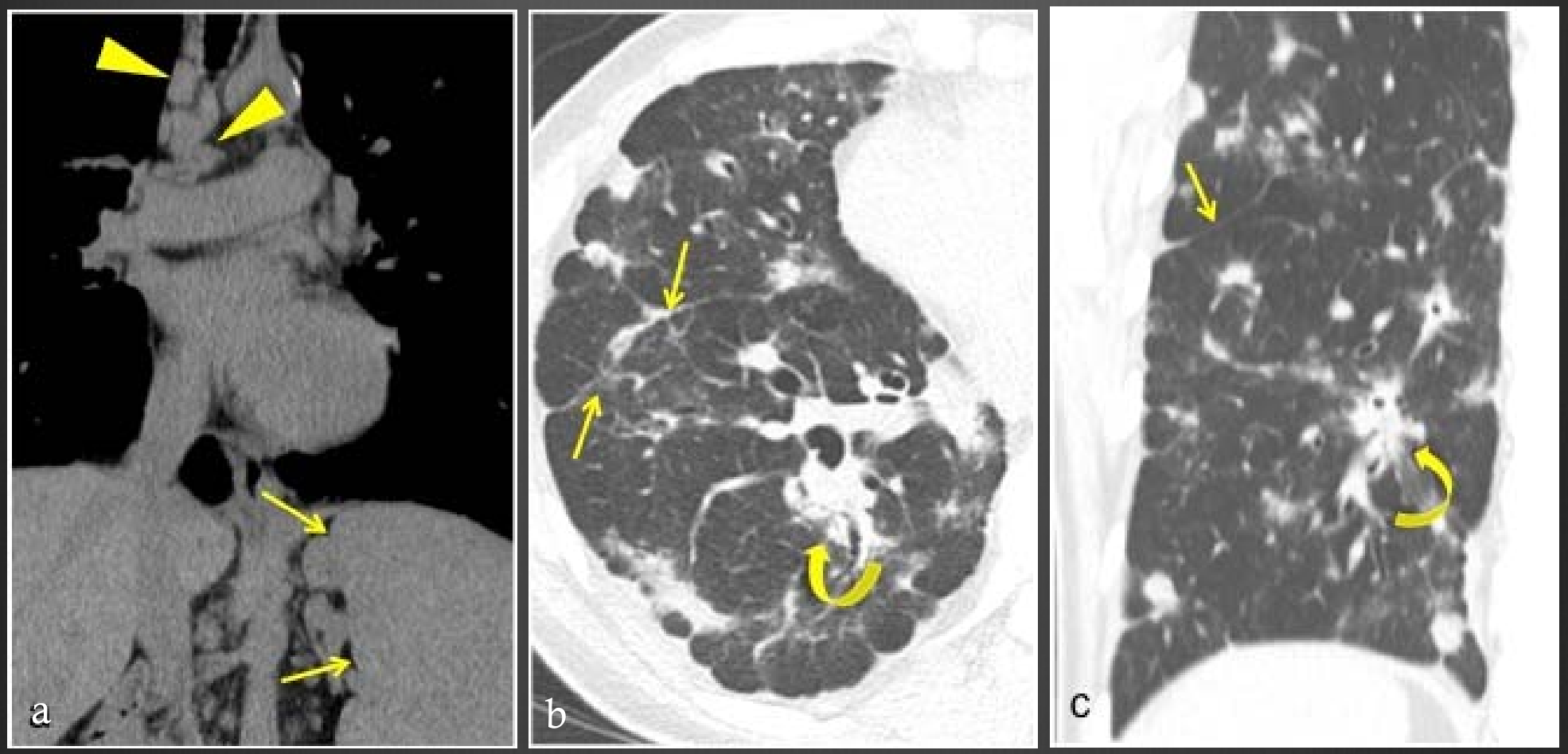
- GLILD is a unique entity, occurring only in the setting of CVID and CVID-like illnesses.
- Characterized by mixed restrictive/obstructive physiology.
- Associated with a poorer prognosis than CVID without GLILD.
- Granulomatous component has non-necrotizing granulomas.
- May have histologic features of:
  - LIP
  - FB
  - Organizing pneumonia
  - NSIP
  - Lymphocyte hyperplasia
  - MALToma

GLILD - Radiology

- Characterized uniquely by a combination of ground glass and consolidative opacities with septal thickening, nodularity, and adenopathy. Splenomegaly is also commonly present and may suggest the diagnosis of GLILD.
- Usually lower lung predominant and peribronchovascular in distribution.
- Radiologic findings may wax and wane over time, and may progress to fibrosis.



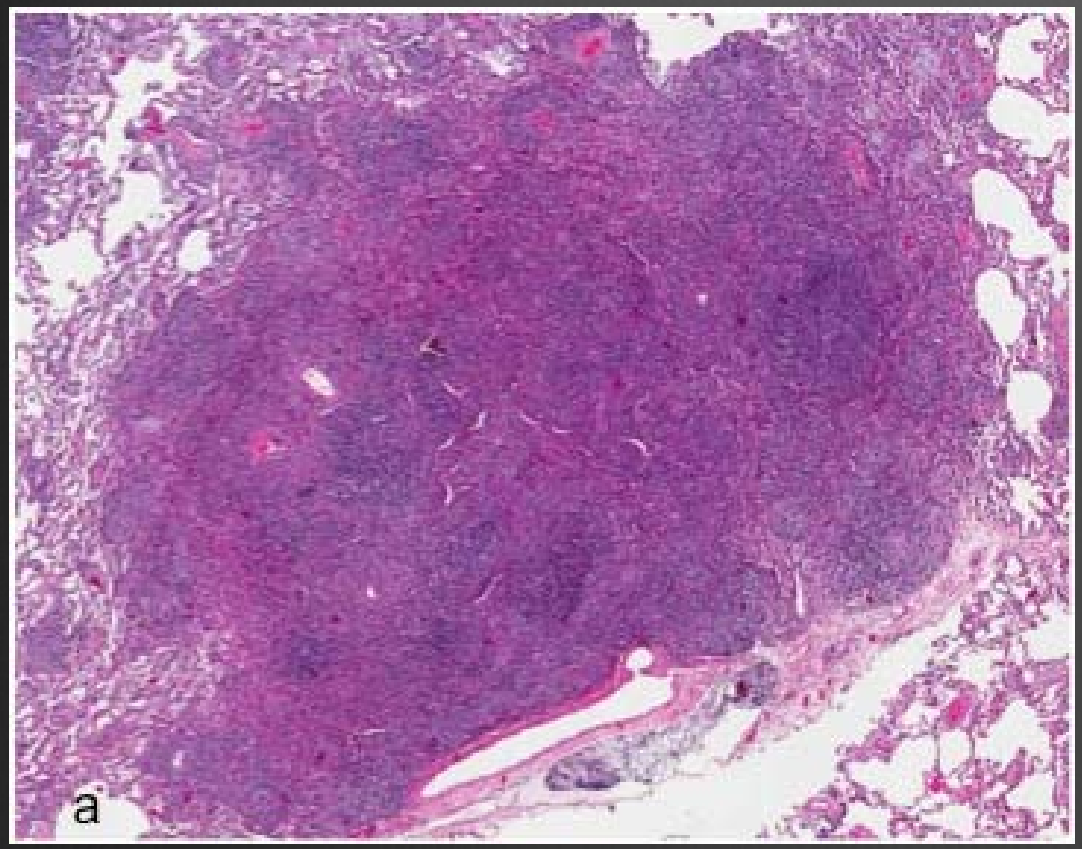
Axial non-contrast CT image of a patient with CVID complicated by GLILD. Note the septal thickening (straight arrows), ground glass (arrowhead), and consolidative opacities (curved arrow).



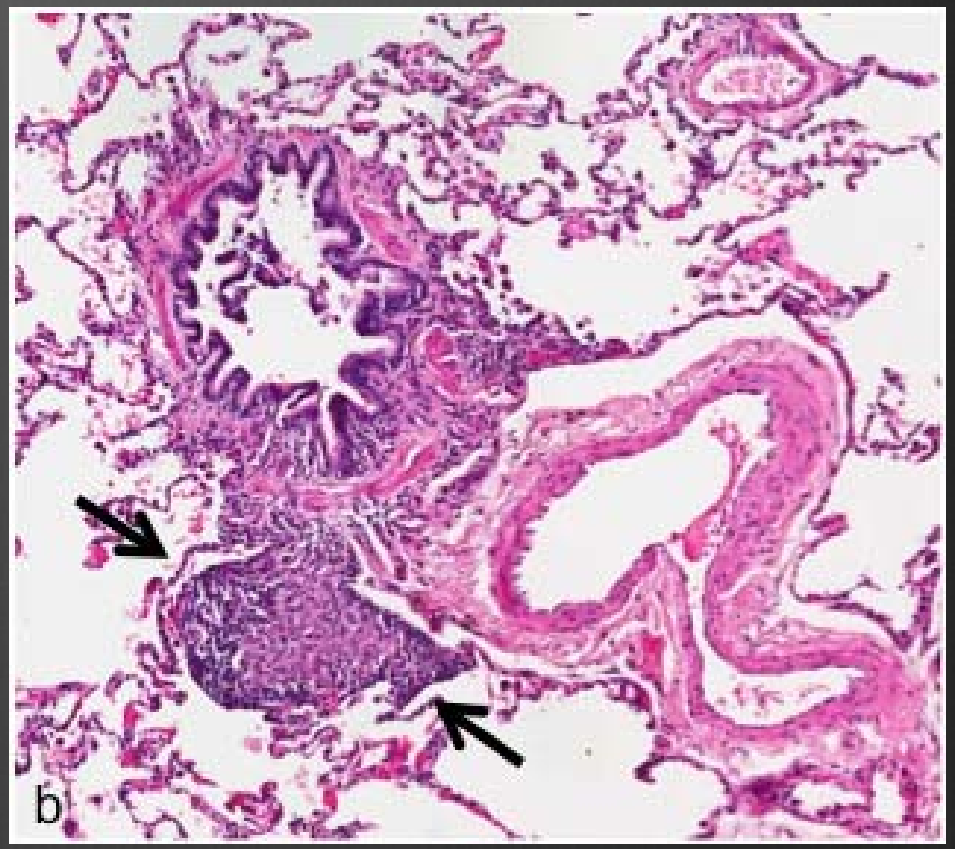
Multiple non-contrast axial images of a patient with CVID and GLILD.

(a) Soft tissue windows demonstrate mediastinal lymphadenopathy (arrowheads) and splenomegaly (arrows).
(b, c) Lung windows demonstrate septal thickening (straight arrows) and consolidative opacities in a peribronchovascular distribution (curved arrows).

GLILD - Pathology

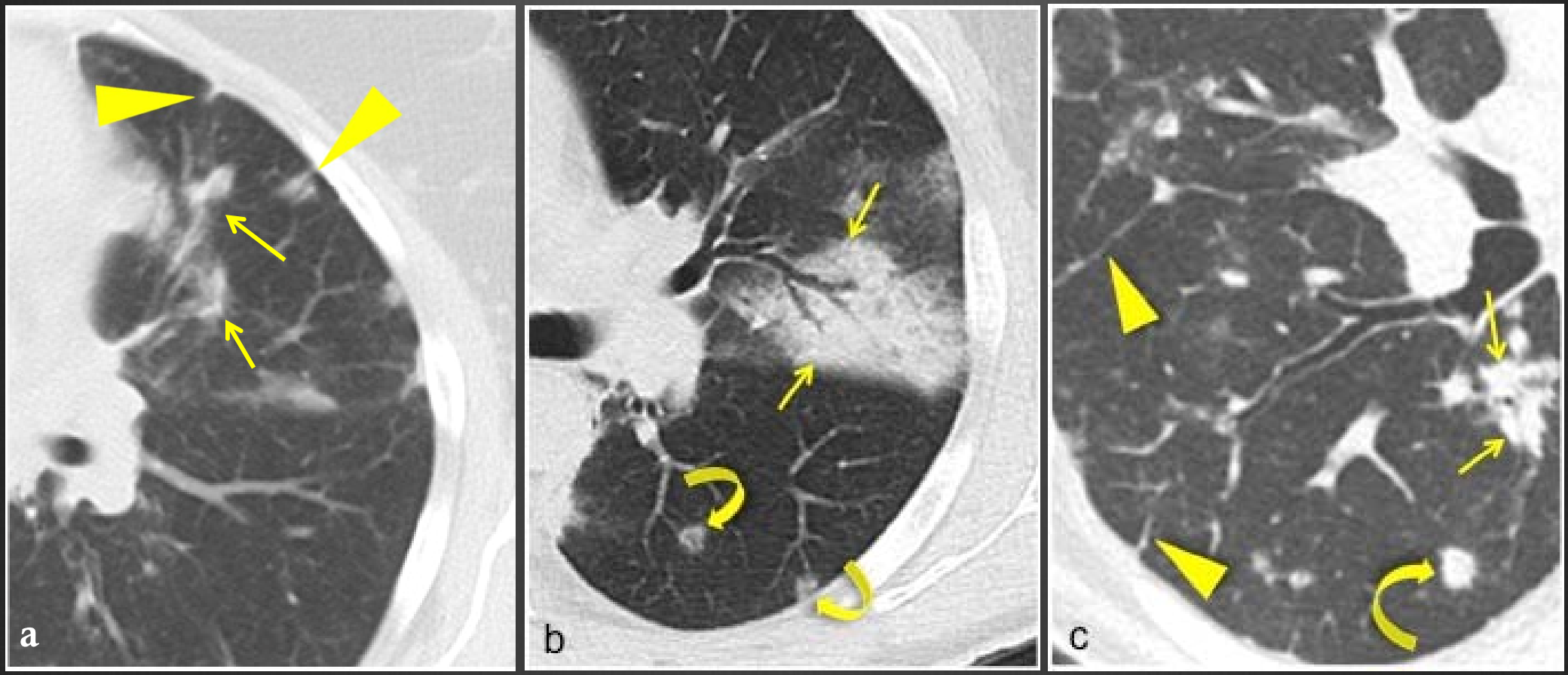


(a) GLILD is characterized by nodular areas of dense lymphoid hyperplasia. However, despite the density of the lymphocytic infiltrate, the underlying architecture is preserved.



(b) Granulomatous infiltration has a variable appearance. Here, a non-necrotizing granuloma (arrow) is immediately adjacent to the bronchovascular bundle.

Radiologic similarities of ILD in CVID



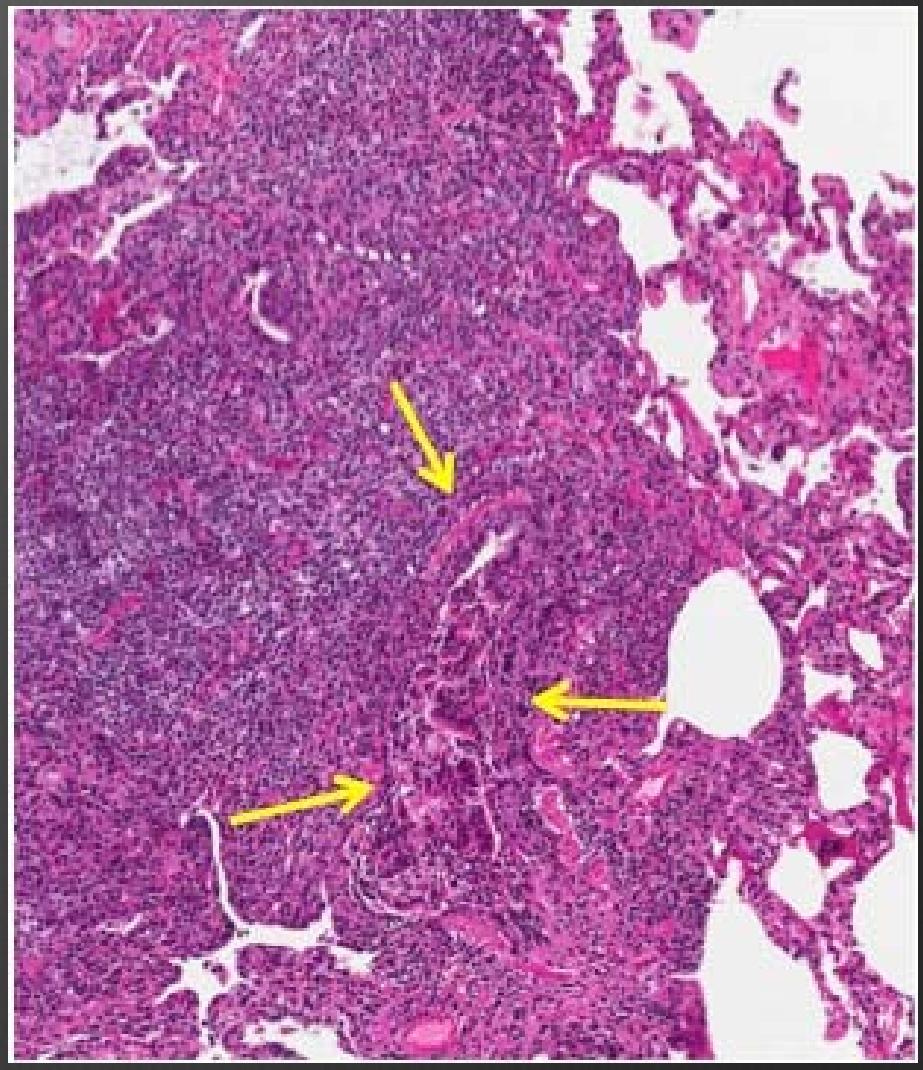
(a) Axial noncontrast CT in pathologically proven LIP in the setting of CVID. Note the septal thickening (arrowheads) and peribronchial opacities (arrows).

(b) Pathologically proven organizing pneumonia with pre-existing CVID. Findings include parenchymal nodules (curved arrows) and consolidation (straight arrows).

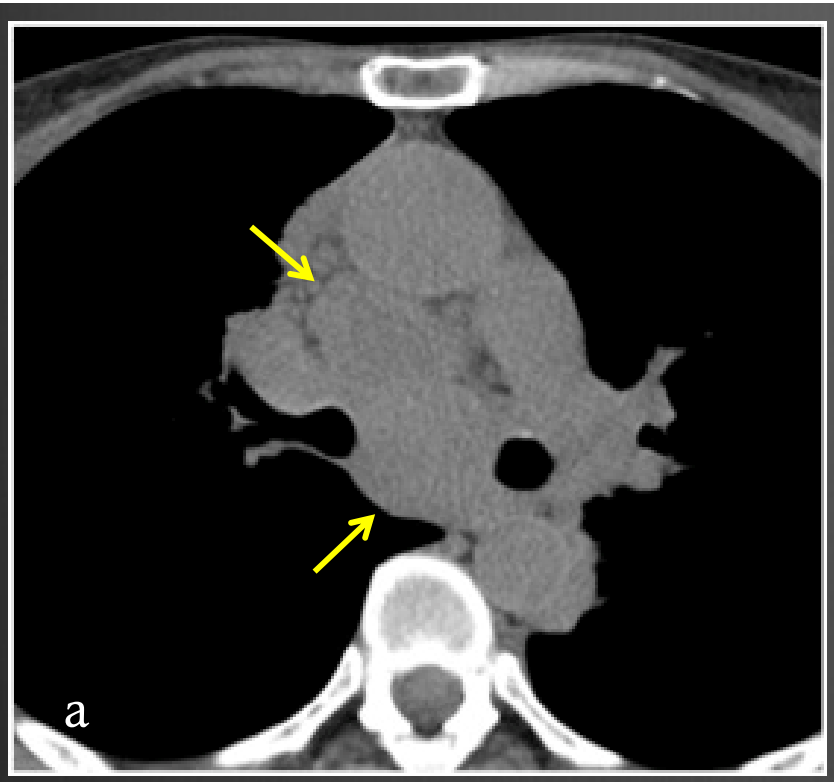
(c) Axial CT of GLILD in the setting of CVID. Characteristic findings include septal thickening (arrowheads), nodules (curved arrow) and peribronchovascular consolidation (straight arrows).

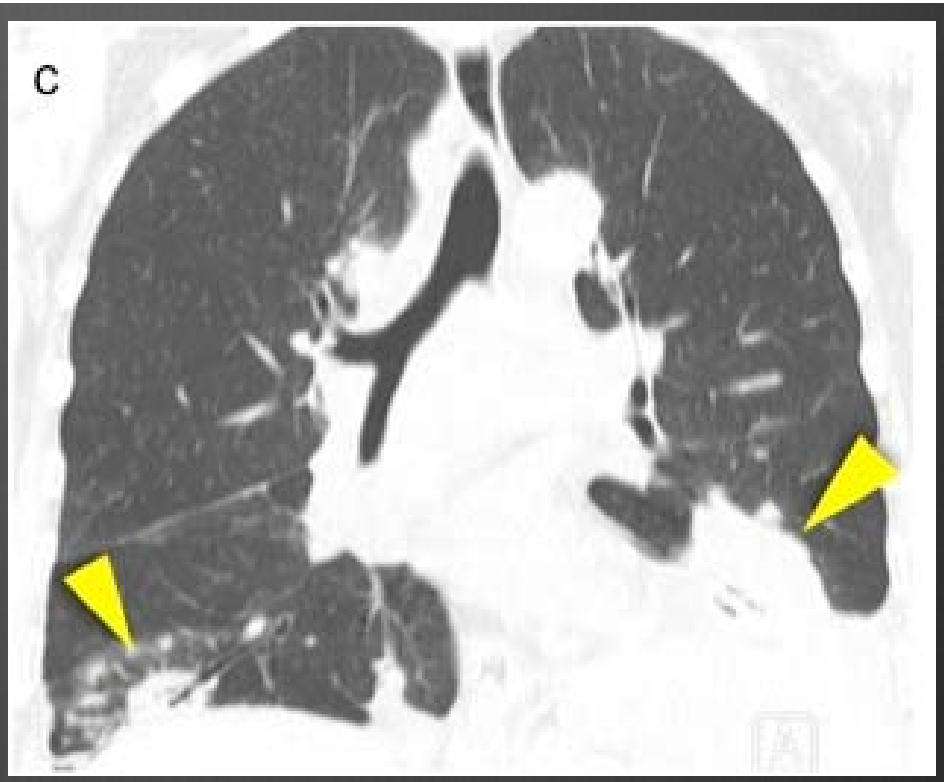
Lymphoproliferative Disease in CVID

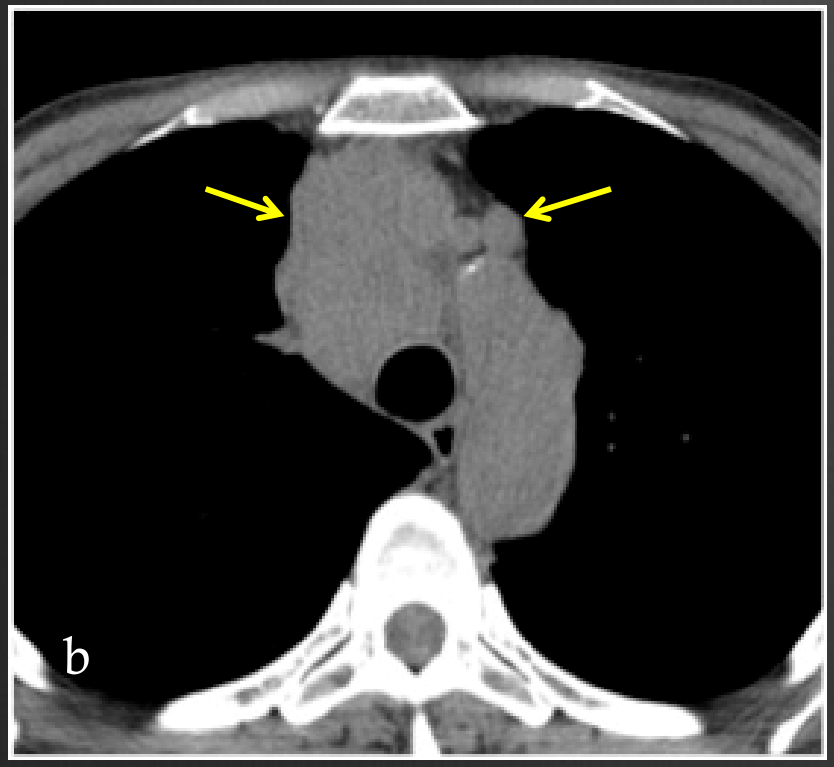
- CVID is associated with an increased risk of lymphoma, up to 30x greater than the general population.
- Most commonly is non-Hodgkin lymphoma, B-cell subtype. In the setting of CVID, lymphoma has a propensity to be extra-nodal and associated with mucosal tissues.
- MALT (mucosa-associated lymphoid tissue) lymphoma or MALToma, is a subset of B-cell non-Hodgkin lymphoma.



Lymphocytic infiltration in pulmonary MALToma effaces the normal architecture, destroying the bronchiole (arrows).







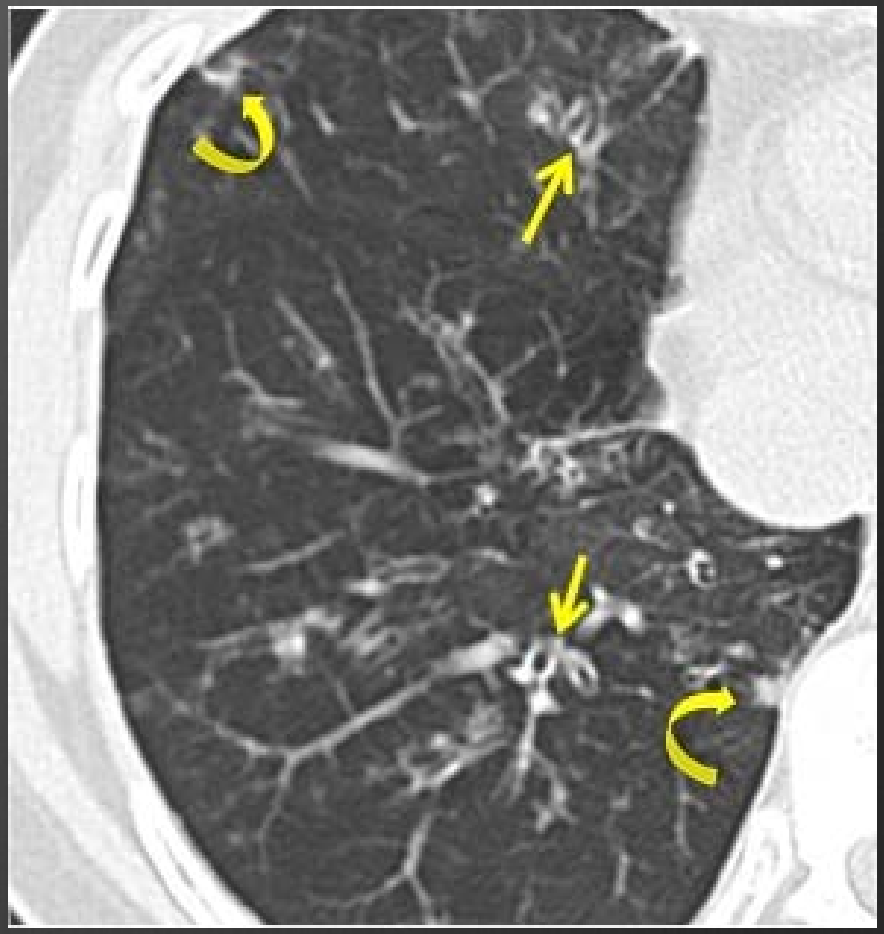
Multiple non-contrast images of a patient with CVID complicated by lymphoma, demonstrating:

(a, b) Extensive, conglomerate mediastinal adenopathy (arrows).

(c) Multifocal, pulmonary masses (arrowheads) with surrounding satellite nodularity.

MALToma

- MALToma has been associated with multiple organ systems including the lung, gastrointestinal system, salivary glands and orbits.
- In the setting of CVID, MALToma has most commonly been reported in the lung.



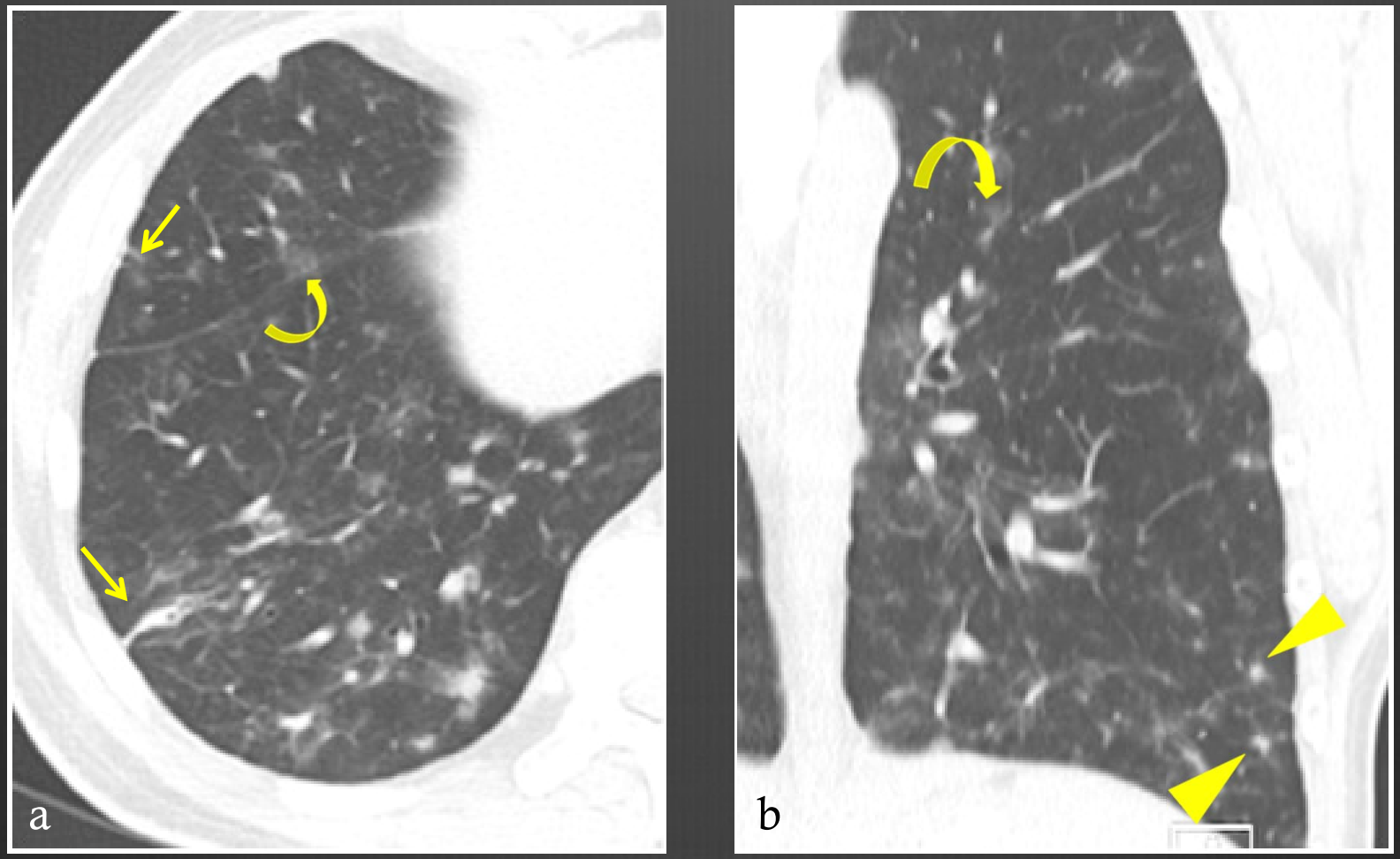
Axial non-contrast CT image of a patient with CVID complicated by pulmonary MALToma. CT findings include peribronchovascular thickening (straight arrows) and nodularity (curved arrows).

Kabuki Syndrome

- Rare genetic disorder with characteristic facial features, CVID-like immunodeficiency, and developmental delay.
- First described in 1981.
- Also known as Niikawa-Kuroki Syndrome.
- Kabuki Syndrome is commonly associated with low immunoglobulin levels (84% of patients), with CVID-like features.
- Given overlap with CVID in immunologic features, Kabuki syndrome is also associated with chronic lung disease, including GLILD.

Features of Kabuki Syndrome

Facial features	Neurologic	Musculoskeletal	Cardiovascular	Immune dysfunction
Long palpebral fissures	Developmental delay	Vertebral anomalies	Coarctation	Hypogammaglobulinemia
Thick eyelashes	Seizures	Joint hyperflexibility		Recurrent otitis media
Cleft palate		Growth delay/short stature		Autoimmunity
Large ears				
Arched eyebrows				



(a) Axial and (b) coronal non-contrast CT images of GLILD in a patient with Kabuki syndrome. CT findings include septal thickening (straight arrows), nodules (arrowheads) and areas of groundglass abnormality (curved arrows).

Summary

- CVID is a complex immune deficiency associated with recurrent infections, chronic lung disease, and autoimmunity.
- Chronic lung disease can be divided into airways disease, interstitial lung disease and GLILD, and lymphoma/MALToma.
- Kabuki syndrome is a rare disorder associated with a CVID-like immunodeficiency. Patients with Kabuki syndrome may develop chronic lung disease similar to CVID, including GLILD.
- Knowledge of and appropriate identification of these lung diseases can aid in prognostication and direction of therapy.

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