Evil Humors: Thoracic Manifestations of Immunoglobulin-Related Disease

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Introduction

Disorders of humoral immunity result in a variety of clinically significant immunoglobulin (Ig)-related diseases.

Ig-related diseases are systemic disorders that have characteristic serologic profiles and thoracic imaging findings.

These are broadly categorized into disorders of overproduction, underproduction, and specific antibody-related conditions.
Learning Objectives

Review antibody (Ig)-mediated immunity, autoimmunity, and specific Ig functions.

Identify Ig-related diseases including clinical manifestations, serologic profiles, and characteristic radiographic and CT findings.

Demonstrate how familiarity with Ig-related diseases informs imaging findings and narrows differential diagnosis.

- Review of normal humoral immunity and immunoglobulin function
- Immunoglobulin-related diseases
  - Overproduction (e.g., hypersensitivity reactions, plasma cell disorders)
  - Underproduction (immunodeficiencies)
The primary role of antibodies is protection against infectious agents and their products.

Igs are glycoproteins composed of light (LC) and heavy (HC) chain polypeptides.
- LC and HCs have constant and variable regions
  - Variable regions responsible for antigen binding
  - Constant regions responsible for biologic function
- Types: IgA, IgD (uncertain function), IgE, IgG, IgM

Function:
1) Neutralize toxins and viruses
2) Opsonize microorganism/pathogen
   - Opsonization – antibody binding marks a pathogen for ingestion and destruction
   - Ig interacts directly with phagocyte or activates complement

Autoimmunity – immune reaction to host tissue/antigen
- Most autoimmune disorders are antibody-mediated
- Some overlap between hypersensitivity reactions and antibody-mediated autoimmune disorders

Figures from: Humoral Immunity Review of Medical Microbiology and Immunology, 13e, 2014
<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Function</th>
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<tbody>
<tr>
<td>IgA</td>
<td>Main Ig in secretions (colostrum, respiratory, GI/GU secretions)</td>
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<td></td>
<td>Prevents pathogen attachment to mucous membranes</td>
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<td></td>
<td>Structure: Monomer (serum) or dimer (secretory)</td>
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<td>IgE</td>
<td>Immediate hypersensitivity (mediates anaphylaxis)</td>
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<td>Main host defense against parasites (particularly helminths – e.g. <em>Strongyloides</em>, <em>Trichinella</em>, <em>Ascaris</em>)</td>
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<td>Trace amounts in normal serum; increased in individuals with allergic reactivity</td>
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<tr>
<td>IgG</td>
<td>Predominant Ig in secondary response</td>
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<tr>
<td></td>
<td>Opsonizes, can activate complement; important in bacterial and viral infection</td>
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<tr>
<td></td>
<td>Structure: Divalent monomer with 2 LC and 2 HCs; 4 subclasses IgG1-IgG4</td>
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<tr>
<td>IgM</td>
<td>Predominant Ig in primary response</td>
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<td></td>
<td>Agglutination, complement activation; important in bacterial and viral infection</td>
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<tr>
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<td>Structure: Monomer (B-cell surface Ig) or pentamer (serum)</td>
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Adapted from: *Humoral Immunity; Review of Medical Microbiology and Immunology*, 13e, 2014
Overproduction

IgE-related
- Hypersensitivity/Eosinophilic Lung Disease

IgG-related
- Specific Ig-Mediated
- ANCA-associated vasculitides
- IgG4

Mixed Ig-Mediated
- Amyloid
- Plasma Cell Disorder
Allergic Bronchopulmonary Aspergillosis (ABPA)

**Background:** Hypersensitivity reactions (types I and III) to *Aspergillus fumigatus*

**Clinical:** History of asthma or cystic fibrosis. Variable – fever, cough, dyspnea, wheezing, hemoptysis

**CXR:** Central bronchial opacities, finger-in-glove opacities (mucoid impaction), tram-tracking (bronchial wall thickening) nodules, atelectasis

**CT:** Central bronchiectasis, high attenuation mucus plugging within dilated airways, centrilobular nodules and tree-in-bud opacities, mild mosaic attenuation, variable atelectasis

**Serology:** Increased IgE, IgG against *A. fumigatus*, eosinophilia
IgE-related: ABPA

Figure: ABPA in a patient with asthma. A. Soft tissue images show high attenuation mucoid impaction in dilated central airways (arrow). B. Lung images show central bronchiectasis (arrow), mild mosaic attenuation (arrow), and variable tree-in-bud opacities (arrow). C & D. Additional examples of central bronchiectasis, and mucoid impaction.

KEYS:
- Central bronchiectasis, mucoid impaction – “finger in glove” sign
- High attenuation mucoid impaction virtually pathognomonic for ABPA
- Increased IgE, IgG against A. fumigatus
Parasitic Infections

**Background:** IgE is the main host defense against parasitic infection

**Clinical:** Result of direct parasitic invasion or secondary allergic reaction to that pathogen

Specific parasitic infection depends on endemic pathogens within a particular geographic region

**CXR and CT:** Nonspecific, pathogen dependent. Ranges from edema pattern to nodular and mass-like areas of consolidation, acute and chronic eosinophilic pneumonia

**Serology:** Increased IgE, eosinophilia

**Figure:** Eosinophilic pneumonia and elevated IgE in a patient with strongyloidiasis. Multiple peripheral regions of nodular consolidation with associated GGO. (Image courtesy of J. David Godwin MD, Seattle, WA)
Chronic Eosinophilic Pneumonia

**Background:** Idiopathic, may be hypersensitivity mediated

**Clinical:** Female > male. History of asthma in 50%. Insidious onset of fever, malaise, weight loss, dyspnea, cough, wheeze. Rapid response to steroid therapy

**CXR:** Peripheral upper lobe predominate consolidation

**CT:** Typically bilateral, peripheral upper lobe predominate consolidation and GGO, nodular consolidation. Waxing and waning consolidation, recurs in similar location and distribution

**Serology:** Peripheral eosinophilia, ↑ IgE (in 2/3)

**Figure:** Chronic eosinophilic pneumonia in a patient with history of asthma, ABPA, and elevated IgE. Peripheral upper lobe predominate consolidation with associated GGO (arrow), central bronchiectasis (arrow), and mucoid impaction (arrow).
**IgE-related: Eosinophilic Lung Disease**

**“Crack Lung”**

**Background:** Acute pulmonary syndrome secondary to freebase inhalation of crack cocaine

**Clinical:** Fever, hypoxia, hemoptysis, respiratory failure

**CXR:** Perihilar consolidation and GGO in a diffuse alveolar damage pattern

**CT:** Perihilar consolidation, GGO, interlobular septal thickening

**Histology:** BAL with increased IgE and eosinophils

**Figure:** Acute lung injury in a patient following freebase cocaine inhalation. Perihilar consolidation and GGO. (Image courtesy of Daniel Vargas MD, Denver, CO)
Churg-Strauss Syndrome (CSS)

**Background:** Rare, systemic small and medium vessel vasculitis, extravascular granulomas, eosinophilia

**Clinical:** Almost exclusively in asthmatics, pulmonary involvement most common, may have cardiac involvement (13-47%)

Three phases: 1) prodromal (asthma or allergic rhinitis), 2) peripheral eosinophilia, 3) vasculitic (may be life threatening)

**Diagnosis:** Vasculitis + at least 4 of the following: asthma, eosinophilia, mono or polyneuropathy, non-fixed pulmonary opacities, sinus abnormality, extravascular eosinophils

**CXR:** Peripheral transient patchy consolidation

**CT:** Transient or migratory peripheral/subpleural ground-glass and nodular consolidation, small centrilobular nodules, GGO, bronchial wall thickening, consolidation, air-trapping/mosaic attenuation, interlobular septal thickening

**Serology:** perinuclear-ANCA (IgG), increased IgE (variable), eosinophilia

**IgG-related: Specific Antibody Mediated**

IgG, IgA, IgE, IgM

- IgA
- IgE ↑ p-ANCA
- IgG
- IgM
Figure: CSS in a patient with asthma, increased IgE, and + p-ANCA. A. Patchy peripheral upper lobe consolidation. B. Coronal reformatted CT images show peripheral ground-glass opacity and consolidation (arrow) and mosaic attenuation (arrow). C. GGO with ground-glass nodules, interlobular septal thickening (arrow).

KEYS:
- Asthma history
- Transient peripheral consolidation
- + p-ANCA
- ↑ IgE
Granulomatosis with Polyangiitis

**Background**: Rare, multisystem small and medium vessel vasculitis

**Clinical Triad**: 1) upper airway involvement (sinusitis, otitis), 2) lower airway involvement (e.g. cough, chest pain, hemoptysis, stridor), 3) glomerulonephritis

**CXR**: Common: nodules and consolidation of varying sizes and cavitation, Uncommon: mediastinal or hilar lymphadenopathy, pleural effusion. Subglottic airway stenosis, atelectasis

**CT**: Lung: nodules or masses of variable sizes. Nodules usually randomly distributed. GGO (represents hemorrhage). “CT halo” sign – hemorrhage surrounding nodule. “Atoll” – organizing PNA surrounding focal hemorrhage

Tracheobronchial: Smooth or nodular focal/segmental circumferential wall thickening. Involvement of the posterior membrane

**Serology**: Circulating antineutrophil cytoplasmic antibodies (IgG), typically against proteinase 3 and myeloperoxidase

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**IgG-related: Specific Antibody Mediated**

*Image: Patient with + c-ANCA, dyspnea, and hemoptysis. CXR with multiple cavitary nodules and mass-like consolidation.*
**IgG-related: Granulomatosis with Polyangiitis**

**Figure:** Patient with + c-ANCA, dyspnea, and hemoptysis.  
A. Coronal CT image shows multiple random lung nodules and mass-like consolidation with associated cavitation (arrow).  
B. Right middle lobe consolidation with adjacent GGO and interlobular septal thickening (arrow).  
C. Additional cavitary lung nodules.  
D. Left lung nodule. “Atoll” sign in the right middle lobe (arrow).

**KEYS:**
- Triad: sinus, lung, & renal disease
- + c-ANCA
- Cavitary lung nodules and masses
- Circumferential focal/segmental tracheobronchial wall thickening
Myasthenia Gravis (MG)

Background: Disorder of the neuromuscular junction characterized by variable and fluctuating muscular weakness and fatigability

Ig-mediated response against the postsynaptic acetylcholine receptor or acetylcholine receptor related proteins

Clinical: Ocular, bulbar, proximal limb weakness and fatigability

CXR: May be normal, anterior mediastinal mass

CT: Thymic enlargement or focal mass representing lymphoid hyperplasia or thymoma, respectively. Thymoma is typically a circumscribed round or ovoid anterior mediastinal soft tissue mass. Local invasion or pleural dissemination occur with invasive thymoma

Serology: Anti-acetylcholine receptor (AchR) or acetylcholine receptor related protein (IgG)
IgG-related: Myasthenia Gravis

Figure: Examples of thymoma and thymic hyperplasia in patients with (MG).

A. Circumscribed lobular anterior mediastinal mass and associated left sided “hilum overlay” sign (arrow). B. Contrast-enhanced CT confirms the smooth, well-defined, lobular anterior mediastinal soft tissue mass, typical of thymoma (arrow). C & D. Additional examples of thymic lymphoid hyperplasia associated with MG (arrow) and cystic thymoma (arrow), respectively.

KEYS:

- Neuromuscular junction disorder
- Associated with thymoma or thymic hyperplasia
- Anti-acetylcholine receptor or acetylcholine receptor related protein (IgG-mediated)
**Graves Disease (GD)**

**Background:** Autoimmune thyroid disease characterized by thyroid stimulating hormone (TSH) autoantibody

**Clinical:** Hyperthyroidism (weight loss, tremulousness, atrial fibrillation, etc.), goiter, orbitopathy, and dermatopathy (myxedema)

Autoantibodies activate the TSH receptor leading to thyroid hormone synthesis and gland enlargement

**CXR:** Goiter with possible mass effect on trachea

**CT:** Diffuse thyroid gland enlargement (goiter), diffuse thymic enlargement by lymphoid hyperplasia may also be seen

**Serology:** TSH receptor antibody AKA thyroid stimulating immunoglobulin (TSI) (IgG)

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64 yo male with GD presenting with atrial fibrillation. A. Thyroid uptake scan shows uniform thyroid uptake elevated at 72.9%.
Figure: 64-year-old man with GD presenting with atrial fibrillation. B. CT images from 6 months prior show hazy soft tissue infiltration of the anterior mediastinal fat (arrow). C & D. CT images at the time of the thyroid scan show a lobular soft tissue mass in the anterior mediastinum representing thymic hyperplasia (arrows).

KEYS:
➢ Thyroid stimulating immunoglobulin (TSI)

➢ Diffuse thyroid enlargement, elevated uptake, may see associated thymoma or thymic hyperplasia
**Goodpasture Disease**

**Background:** Anti-glomerular basement membrane disease

**Clinical:** Typically present with respiratory symptoms – dyspnea, hemoptysis

Triad: 1) anti-glomerular basement membrane Ig, 2) diffuse alveolar hemorrhage, 3) glomerulonephritis

**CXR:** Extensive bilateral patchy opacities

**CT:** Combined ground-glass opacity and consolidation, perihilar distribution, affects lower and middle lung zones

**Serology:** Anti-glomerular basement membrane (GBM) (IgG)

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**IgG Related: Specific Antibody Mediated**

*Figure: Patient with Goodpasture disease + anti-GBM Ig.* Extensive patchy ground-glass opacity consistent with hemorrhage.
Autoimmune Pulmonary Alveolar Proteinosis (PAP)

**Background:** Rare syndrome characterized by intra-alveolar accumulation of surfactant lipids and proteins

Granulocyte macrophage colony-stimulating factor (GM-CSF) autoantibodies neutralize the effects of GM-CSF and impair surfactant clearance and neutrophil function

**Clinical:** Commonly progressive dyspnea, dry cough. Other s/sx: fatigue, weight loss, low grade fever, chest pain, hemoptysis. Association with cigarette smoking

**CXR:** Symmetric central lung opacities – GGO, reticulation, nodules, consolidation; relative sparing of apices and costophrenic sulci

**CT:** Extensive geographic ground-glass opacity with superimposed septal thickening in a “crazy paving” pattern; consolidation

**Serology:** ↑ Lactate dehydrogenase, anti-GM-CSF IgG

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**IgG-related: Specific Antibody Mediated**

Figure: PAP in a young adult male with progressive dyspnea and anti-GM-CSF Ab. CXR with diffuse opacity and reticulation sparing the costophrenic sulci.
IgG-related: Autoimmune PAP

Figure: PAP in a young adult male with progressive dyspnea and autoantibodies against granulocyte macrophage colony stimulating factor (anti-GM-CSF). CT images show extensive geographic ground-glass opacity with superimposed septal thickening in a “crazy paving” pattern.

KEYS:
- “Crazy-paving” pattern
- Anti-GM-CSF antibodies
- Association with cigarette smoking
Amyloidosis

Background: Heterogeneous disorders characterized by deposition of extracellular protein

Majority are amyloid light chain (AL) or amyloid A chain (AA) amyloidosis. AL – monoclonal Ig (e.g. multiple myeloma or MGUS). AA – result of chronic disease

Clinical: Cardiac > tracheobronchial > lung > lymph nodes > pleura. Gradual onset of airway related symptoms. Symptoms depend of site of airway involvement – large, medium, or small airways. May have cough, dyspnea, wheezing, hoarseness, obstructive symptoms, or recurrent infection. Green birefringence with Congo red stain

CXR: Tracheobronchial thickening +/- Ca++, nodules +/- Ca++, lymphadenopathy

CT: Airway nodular soft tissue thickening +/- Ca++. Lung nodules (20% Ca++). Mediastinal and hilar lymphadenopathy, “egg shell” calcification

Serology: Increased total protein, IgG > IgM > IgA

Figure. Patient with thoracic amyloidosis. A. Contrast-enhanced CT shows exuberant paratracheal and aortopulmonary lymphadenopathy with calcification (arrow).
Figure. Two patients with thoracic amyloidosis. B. Soft tissue CT images show diffuse nodular soft tissue thickening of the tracheobronchial tree with scattered calcification (arrow). C. Nodular soft tissue thickening of the main bronchi (arrow) and left lower lobe nodular consolidation (arrow).

KEYS:
- Green birefringence with Congo red stain is pathognomonic for amyloidosis
- Circumferential nodular airway soft tissue thickening and lymphadenopathy with “eggshell” Ca++
- IgG > IgM > IgA
Multiple Myeloma/Plasmacytoma

**Background:** Neoplastic disorder resulting in proliferation of monoclonal plasma cells and monoclonal Ig production

**Clinical:** Single mass or diffuse marrow involvement resulting in anemia, bone pain, renal dysfunction, weakness/fatigue, hypercalcemia, weight loss. Secondary immunodeficiency due to B-cell suppression

**Diagnosis:** 1) serum or urinary monoclonal protein, 2) clonal cells in bone marrow or plasmacytoma, 3) end organ damage (CRAB – ↑calcium, renal failure, anemia, bone – lytic lesions)

**CXR:** Lytic bone lesions (destructive rib lesion) or chest wall soft tissue mass

**CT:** Similar to radiographs. Lytic bone lesions or chest wall soft tissue mass. May see soft tissue nodules in extramedullary plasmacytoma

**Serology:** Increased total protein, IgG > IgM > IgA

**Figure:** 55-year-old female with extramedullary plasmacytomas. CT shows multiple nodules (arrows) corresponding to biopsy proven plasmacytoma. (Image courtesy of Howard Mann MD, Salt Lake City, UT)
IgG4 related disease

**Background:** Multisystem IgG4 related sclerosing disease. Infiltration by IgG4 positive plasma cells leading to fibrosis.

**Clinical:** Initially described in the context of autoimmune pancreatitis. Also affects the biliary tree, kidneys, retroperitoneum, mesentery, lacrimal and salivary glands, lungs, GI tract, lymph nodes, vessels. Responds to steroid therapy.

Lung involvement in ~13% of those with autoimmune pancreatitis. Sclerosing process involving the pulmonary interstitium.

Four major types: 1) solid nodular, 2) round-shaped GGO, 3) alveolar interstitial, 4) bronchovascular. May mimic lung cancer.

**CXR:** Nodules, mass-like consolidation or linear opacities.

**CT:** GGO most common. Bronchovascular bundle thickening, interlobular septal thickening. May be solitary large nodule or mass or multiple small nodules. Mediastinal lymphadenopathy.

**Serology:** Elevated IgG and IgG4.

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**Figure:** 51 yo man with IgG4-related disease. CT shows multiple small nodules (arrow) and a mass-like region of solid nodular left lower lobe consolidation (arrow). (Images courtesy of Arlene Sirajuddin MD, Tucson, AZ)
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<tr>
<th>Specific Antibody Mediated Disorder</th>
<th>Immunoglobulin</th>
<th>Key Features</th>
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| Churg-Strauss Syndrome             | p-ANCA +, IgE | Small and medium vessel vasculitis  
Asthma  
Transient, migratory, peripheral nodular consolidation |
| Granulomatosis with Polyangiitis   | c-ANCA +      | Triad: sinus, lung, renal disease  
Cavitary lung nodules and masses  
Circumferential focal/segmental tracheobronchial wall thickening |
| Myasthenia Gravis                 | Anti-AchR or AchRRP | Neuromuscular junction disorder  
Associated with thymoma or thymic hyperplasia |
| Graves Disease                    | TSI           | Diffuse thyroid enlargement, elevated thyroid uptake  
May see associated thymoma or thymic hyperplasia |
| Goodpasture Disease               | Anti-GBM      | Triad: anti-GBM Ig, diffuse alveolar hemorrhage, glomerulonephritis |
| Autoimmune pulmonary alveolar proteinosis | Anti-GM-CSF | Association with cigarette smoking  
“Crazy paving” pattern on HRCT |
Underproduction

- Common variable immunodeficiency disease
- Ig subtype deficiency
  - IgA-related
  - IgG-related
Common Variable Immunodeficiency (CVID)

**Background:** Most common symptomatic 1° immunodeficiency in adults

**Clinical:** Variable, typically recurrent infection. Onset late childhood or early adulthood. ↑ susceptibility to encapsulated bacteria. ↑ lymphoproliferative disorders including lymphoma

10-20% develop granulomatous lymphocytic interstitial lung disease (GLILD)
- Noninfectious sequela of CVID with associated splenomegaly, diffuse adenopathy
- ↑ mortality, ↑ risk of lymphoma
- Histology: LIP, follicular bronchiolitis, granulomas

**CXR:** Multifocal consolidation, lower zone predominant bronchiectasis, fibrosis (chronic)

**CT:** Multifocal segmental or lobar consolidation (acute), cystic or cylindrical bronchiectasis, lymphoid interstitial pneumonia, organizing pneumonia, lower zone fibrosis (chronic)

**Serology:** ↓ all Ig subtypes

**Figure:** 36 yo male with CVID and recurrent pneumonias. CXR shows lower zone predominant, multifocal segmental and nodular consolidation.
Figure: 36-year-old man with CVID and recurrent pneumonias. A & B. Multifocal segmental and nodular consolidation indicating acute infection (arrows). Scattered cystic bronchiectasis and intermittent mucus plugging. C & D. Lower lung zone nodular and branching opacities and bronchiectasis (arrows) are due to recurrent infection.

KEYS
- All Ig subtypes
- Most common symptomatic deficiency in adults with recurrent infections, ↑ susceptibility to encapsulated bacteria
- Bronchiectasis, multifocal consolidation, mucus plugging
- 10-20% develop GLILD, ↑ mortality
**Background:** Heterogeneous conditions defined by specific Ig subtype deficiency

**Clinical:** Infectious and noninfectious disorders. Increased susceptibility to infection (recurrent) including encapsulated bacteria.

Airways are commonly involved: bronchial wall thickening, bronchiectasis, mucoid impaction, air-trapping. Develop diffuse lung disease over time.

IgA deficiency most common immune deficiency. Common immunologic variant, ranging from asymptomatic to recurrent infections.

**CXR:** Bronchiectasis, consolidation, linear opacities

**CT:** Bronchiectasis, bronchial wall thickening, consolidation. Chronic: organizing pneumonia pattern, peripheral consolidation, “atoll” sign, lower lobe predominate

**Serology:** Depends on the Ig subtype involved
Figure: 34-year-old female with recurrent infections. A. Frontal radiograph shows coarse linear opacities and consolidation in the right middle, left upper, and lower lobes with lower lobe predominant bronchiectasis. B. CT images confirm peribronchovascular nodules with tree-in-bud opacities (arrow). C. Left lower lobe bronchiectasis (arrow), mucus plugging, and peribronchovascular consolidation.
Immune Deficiency: IgG3-deficiency and Hypogammaglobulinemia

Figure: Two patients with Ig deficiency.
A & B. IgG3-deficiency.
Bronchiectasis (arrow) and tree-in-bud opacities (arrow) in a patient with recurrent infection.
C & D. IgG-hypogammaglobulinemia.
Left upper lobe tree-in-bud opacity (arrow) and lower lobe bronchiectasis (arrows) due to recurrent infection.

KEYS
- Specific Ig subtypes
- Bronchiectasis, multifocal consolidation, mucus plugging are hallmarks
Immunoglobulins play an important role in protection against infection.

Ig-related diseases represent a heterogeneous group of disorders that can be broadly grouped into overproduction and underproduction states, and these diseases have characteristic thoracic imaging findings.

A wide variety of systemic diseases ranging from allergic to infectious to autoimmune to neoplastic etiologies result in Ig-overproduction.

The commonest findings in Ig-immunodeficiency states are related to infection – consolidation (acutely) and bronchiectasis with organizing pneumonia pattern over time.

Familiarity with these specific entities and their characteristic biochemical/serologic profiles can be useful to radiologists and referring clinicians to establish definitive diagnoses.