Imaging Spectrum of Allergic Lung Disease: Hypersensitivity Reactions on the Lung Parenchyma

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Summary of Content

1. Types & pathogenesis of hypersensitivity reactions
2. Hypersensitivity pneumonitis
3. Eosinophilic lung diseases
   1) Idiopathic eosinophilic lung diseases
   2) Eosinophilic lung diseases with known causes
4. Asthma
5. Pulmonary manifestations of other allergic diseases
Hypersensitivity diseases have been grouped into 4 major categories based upon their underlying causes:

- Immediate (type I) hypersensitivity
- Antibody-mediated (type II) hypersensitivity
- Immune complex-mediated (type III) hypersensitivity
- Cell-mediated (type IV) hypersensitivity
Extrinsic allergic alveolitis

- Caused by the inhalation of antigens contained in a variety of organic dusts
  - Farmer’s lung (thermophilic actinomycetes)
  - Bird fancier's lung (bird proteins)
  - Mushroom worker’s lung (thermophilic actinomycetes)
  - Malt worker’s lung (Aspergillus spp.)
  - Maple bark disease (Cryptostroma spp.), etc.
- Responsible antigen cannot be determined in about 50%

Clinical issues

- Acute exposure → fever, chilling, dry cough, dyspnea
- Long-term exposure → progressive shortness of breath
- Recurrent acute episodes with recurrent exposure
- Decrease incidence in tabacco smokers
2. Hypersensitivity Pneumonitis (HP)

- **Acute HP**
  - Exposure to large amounts of antigen in susceptible patients → acute lung injury
  - Alveolar filling by a neutrophilic inflammatory exudate and pulmonary edema or hemorrhage due to diffuse alveolar damage

- Imaging findings
  - Small, ill-defined, centrilobular nodules
  - Bilateral air-space consolidation
  - Predominantly in the mid and lower lung zones
Fig 1. Acute HP in a 53-year-old female with dyspnea after swimming a few hours later. (A) Chest radiograph obtained a few hours after symptom onset demonstrates subtle ground-glass opacity and small nodules in both lungs. (B) Chest radiograph 5 days later shows nearly total resolution of previous lesions in both lungs. (C) Initial CT obtained 4 hours later to initial chest radiography shows ill-defined centrilobular nodules in both lungs.
2. Hypersensitivity Pneumonitis (HP)

- **Subacute HP**
  - Type III & IV hypersensitivity
  - Continued exposure → progressive symptoms over weeks or months
  - Findings of subacute HP usually resolve within weeks to month if the exposure to the antigen is ended or the patient is treated

- Imaging findings
  - Patchy ground-glass opacity (GGO) (75-90%); *headcheese sign* (GGO + mosaic perfusion)
  - Small ill-defined centrilobular nodules of GGO
  - Diffuse or most marked in the mid or lower lung zones
  - Mosaic perfusion on inspiration & air trapping on expiration
  - Areas of consolidation or large nodular opacities due to organizing pneumonia
  - Thin-walled lung cysts (10%), usually ≤ 5 cysts, randomly distribute
Fig 2. Subacute HP in a 70-year-old female with cough and dyspnea. (A, B, C) Axial HRCT images demonstrate diffuse GGO with ill-defined centrilobular nodular opacities in both lungs, combined multifocal areas low density show mosaic attenuation.
2. Hypersensitivity Pneumonitis (HP)

- **Chronic HP**
  - Presence of fibrosis, months or years after the initial exposure
  
  - Imaging findings
    - Irregular reticular opacities; traction bronchiectasis; honeycombing
    - Predominant in the mid or lower lung zones; relative sparing of the lung bases
    - May be parahilar, peribronchovascular, or peripheral distribution
    - Patchy distribution is common
  
    - Superimposed findings of subacute HP
      - patchy bilateral (90%), small ill-defined nodules (60%)
      - areas of reduced lung attenuation due to mosaic perfusion, and air trapping
2. Hypersensitivity Pneumonitis (HP)

- Acute exacerbation of chronic HP
  - Similar HRCT findings to IPF
    - Extensive bilateral ground glass opacities with underlying fibrosis

Fig 3. Acute exacerbation of chronic HP in a 65-year-old female with dyspnea.
(A, B) Initial axial HRCT images demonstrate extensive bilateral GGO in both lungs, especially both upper lobes, with underlying traction bronchiectasis, reticular opacities, and areas of low attenuation in both lungs.
(C, D) Follow up CT scans after 8 years show decreased extent of previous diffuse GGO but residual or some progression of findings of fibrosis.
3. Eosinophilic Lung Disease

- A group of entities characterized by an abundant accumulation of eosinophils in the pulmonary interstitium and air spaces

- Diagnostic criteria
  - Radiographic or CT findings of lung disease in association with peripheral eosinophilia
  - Biopsy-confirmed lung tissue eosinophilia
  - Increased eosinophils at bronchoalveolar lavage
3-1) Idiopathic Eosinophilic Lung Disease

- Simple pulmonary eosinophilia (SPE; Löffler’s syndrome)
  - Characterized by migratory focal areas of consolidation visible on chest radiographs, blood eosinophilia, and resolution within 1 month
  - Clinical manifestations
    - Cough, mild shortness of breath
    - History of asthma or atopy often present
  - Imaging findings
    - Patchy transient & migratory areas of consolidation or GGO that usually clear spontaneously within month
    - Single or multiple; usually ill-defined margins
    - Bronchial wall thickening
    - Predominantly peripheral distribution
Fig 4. Simple pulmonary eosinophilia in a 64-year-old female with chest discomfort. 
(A, B) Initial axial HRCT images show multiple nodular consolidations with subtle GGO halo in upper lobe predominance in both lungs. Blood eosinophil count was 1790/μℓ. 
(C, D) Follow up CT scans after 1 month reveal resolution of previous nodular consolidations in both lungs.
3-1) Idiopathic Eosinophilic Lung Disease

- **Acute eosinophilic pneumonia (AEP)**
  - Diagnosis based on
    - Clinical findings of acute respiratory failure
    - Presence of markedly elevated numbers of eosinophils in BAL fluid
    - Prompt response to steroids
  
  - **Tobacco** smoke, a trigger for AEP, especially in new-onset smokers

- Good prognosis, with no residual disability

- Imaging findings: similar to pulmonary edema
  - Consolidation, often peripheral and patchy in distribution (90%)
  - Bilateral GGO, smooth interlobular septal thickening, pleural effusion
  - Crazy-paving appearance
Fig 6. Acute eosinophilic pneumonia in a 20-year-old male with dyspnea and chilling. He started smoking 3 weeks ago.

(A) Chest radiograph demonstrates increased interstitial opacities in both lung fields, which mimicking bilateral pulmonary edema.

(B-D) Axial HRCT images show smooth interlobular septal thickening with ill-defined nodular consolidation and GGO.
Chronic eosinophilic pneumonia (CEP)
- Characterized by extensive infiltration of the alveoli and interstitium by a mixed inflammatory infiltrate consisting primarily of eosinophils

- Clinical manifestations
  - Fever, cough, weight loss, malaise, shortness of breath
  - Often severe symptom; last 3 months or more

- Imaging findings
  - Consolidation, often peripheral and patchy in distribution (90%)
  - Patchy or peripheral GGO (80%), sometimes associated with crazy-paving
  - Linear or band-like opacities, usually seen during resolution (5%)
  - An upper lobe predominance abnormalities
  - Remain unchanged for weeks or months unless steroid therapy is given
Fig 5. Chronic eosinophilic pneumonia in a 46-year-old male with cough and dyspnea. Blood eosinophil count was 4049/μl.

(A) Chest radiograph shows ill-defined patchy increased opacity in both upper lung zones with peripheral predominancy.

(B-D) Axial HRCT images demonstrate patchy areas of consolidation and GGO with band-like opacities in both lungs, predominantly in both upper lobes and peripheral location.
3-1) Idiopathic Eosinophilic Lung Disease

Hypereosinophilic syndrome (HES)

- Characterized by blood eosinophilia (>1.5x10^9/L) present persistently for at least 6 months, associated with multiorgan tissue infiltration by mature eosinophils
  - Pulmonary and pleural involvement in 40%
  - Cough, wheezing, dyspnea
  - Poor prognosis (only 50% respond to steroid)

- Imaging findings
  - Non-specific findings on simple radiograph
  - Transient hazy GGO or areas of consolidation
  - Bilateral pulmonary nodules
    - ≤ 1cm in diameter, mainly in peripheral lung regions; may show halo sign
  - Cardiac involvement → cardiomegaly, pulmonary edema, pleural effusion
Fig 7. Hypereosinophilic syndrome in a 84-year-old male with dyspnea for several months. Blood eosinophil count was 5444/μl.

(A) Chest radiograph reveals multiple small nodular opacities in both lungs, especially both upper lung zones subpleural areas. Several diseases including sarcoidosis and pneumoconiosis are considered as differential diagnoses.

(B-D) Axial HRCT images show small, randomly distributed nodules, predominantly in subpleural locations.

(E) On mediastinal window setting CT image, small amount of pericardial effusion (arrow) is noted.
3-1) Idiopathic Eosinophilic Lung Disease

- **Churg-Strauss syndrome (CSS)**
  - Multisystem disorder characterized by the presence of
    - Necrotizing vasculitis
    - Extravascular granuloma formation
    - Eosinophilic infiltration of various organs
  - Clinical issues
    - Usually middle-aged patients; average onset 40-50 years
    - P-ANCA (+); “ANCA-associated small vessel vasculitis”
    - Cough, hemoptysis; skin rash, diarrhea, neuropathy, heart failure
    - Usually respond well to treatment with steroids; without treatment, may die within months
    - Associated renal failure associated with poor prognosis

P-ANCA = Perinuclear Anti-Neutrophil Cytoplasmic Antibodies
Churg-Strauss syndrome (CSS)

- Imaging findings
  - Transient multifocal areas of consolidation indistinguishable from SPE or CEP
  - Consolidation or GGO (60%); **peripheral** distribution, patchy, or geographic
  - Nodules or masses (20%), 0.5 ~ 3.5 cm in diameter, which may appear centrilobular or may contain air bronchograms
  - Bronchial wall thickening or bronchiectasis (35%)
  - Interlobular septal thickening due to pulmonary edema (5%)
  - Mediastinal lymphadenopathy, pleural/pericardial effusion
  - Enlarged, irregular, and stellate-shaped arteries
  - Cardiac involvement → cardiomegaly, congestive heart failure

3-1) Idiopathic Eosinophilic Lung Disease
**CSS diagnostic criteria** - four or more of the following six findings are present;
- Asthma
- Blood eosinophilia > 10%
- Neuropathy
- Migratory or transient pulmonary opacities visible radiographically
- Sinus abnormalities
- Extravascular eosinophilia on biopsy

Fig 8. Churg-Strauss syndrome in a 47-year-old man with cough, weight loss (5kg/15days), asthma history, paranasal sinusitis and peripheral eosinophilia (10.8%, 2659/μl).

(A, B, C) Axial HRCT images with lung window setting demonstrate multiple ill-defined centrilobular nodules, bronchial wall thickening, prominent interlobular septal thickenings, combined with multifocal patchy consolidations and GGO in both lungs, especially peripheral locations.

(D, E, F) Contrast-enhanced axial CT images with mediastinal window setting show diffuse bilateral enlarged lymph nodes with homogeneous attenuation in both mediastinal, hilar and interlobar areas.
3-2) Eosinophilic Lung Disease with Known Causes

- **Drug-related disease**
  - Antibiotics, NSAIDs, cytotoxic drugs
  - Similar imaging findings, from SPE to AEP

- **Parasitic infestations**
  - Most commonly, findings similar to SPE
    - Consolidation, GGO, centrilobular nodules, septal lines
    - Roundworms such as *Ascaris lumbricoides*, *Toxocara*, *Ancylostoma*, and *Strongyloides stercoralis*
    - Tropical pulmonary eosinophilia by *Wuchereria bancrofti* and *Brugia malayi* in India, Africa, South America, and Southeast Asia
    - Lung fluke, *Paragonimus westermani* in the Far East
      - Patchy lung consolidation, cystic lesions filled with air or fluid, pneumothorax, and pleural effusion
  - Non-specific symptoms; fever, weight loss, dyspnea, hemoptysis

NSAID = nonsteroidal antiinflammatory drug
Fig 9. A 56-year-old female with incidental abnormal findings on chest radiograph. (A) Chest radiograph demonstrates thick-walled cavitary lesion in right upper lung zone. (B-D) Axial HRCT images show thick-walled cavitary lesion with peripheral GGO halo and small satellite nodules in right upper lobe. Video-assisted thoracoscopic lobectomy was conducted and chronic granulomatous inflammation with parasitic eggs, which was compatible with paragonimiasis, was confirmed on pathologic review.
3-2) Eosinophilic Lung Disease with Known Causes

- Allergic bronchopulmonary aspergillosis (ABPA)
  - Hypersensitivity reaction (Type I & III) to Aspergillus organisms

- 5 essential diagnostic criteria
  - Asthma
  - Specific serum antibodies (IgE and IgG) to Aspergillus
  - Proximal (central) bronchiectasis
  - Elevated IgE (>1000 ng/mL)
  - Reactive skin test

- Additional criteria
  - Blood eosinophilia
  - Serum precipitins to Aspergillus antigen
  - Pulmonary infiltrates on chest radiographs

Ig = Immunoglobulin
3-2) Eosinophilic Lung Disease with Known Causes

- **Allergic bronchopulmonary aspergillosis (ABPA)**
  - Imaging findings
    - Consolidation, resembling eosinophilic pneumonia
    - Central bronchiectasis, upper lobe or widespread
    - Mucus plugging; “finger/hand in glove”; high density (>100HU)
    - Tree-in-bud appearance
    - Peripheral consolidation or diffuse GGO
    - Mosaic perfusion; air trapping on expiration
    - Upper lobe predominance common
Fig 10. ABPA in a 56-year-old male with incidental abnormal findings on chest radiograph. Peripheral eosinophilia (7.0%, 439/μl) and the presence of IgG antibody to Aspergillus were confirmed on laboratory study.

(A) Chest radiograph demonstrates tubular consolidation with finger-in-glove appearance in right upper lung zone.

(B,C) Axial HRCT images reveal central bronchiectasis with mucus plugging in right upper lobe. There are also several small centrilobular nodules.

(D,E) On mediastinal window setting CT images, mucus retention shows hyperattenuation without significant enhancement.
3-2) Eosinophilic Lung Disease with Known Causes

**Bronchocentric granulomatosis (BG)**

- Necrotizing granulomatous inflammation centered around bronchioles and small bronchi
- Commonly associated with Aspergillus, mycobacterial infection or non-infectious inflammatory diseases such as rheumatoid arthritis

- **Clinical issues**
  - Usually **young**; 1/3 have history of **asthma**
  - Peripheral eosinophilia in 50%

- **Imaging findings**
  - Spiculated mass lesion or lobar consolidation with associated mild volume loss
  - Mucoid impaction
  - Abnormalities predominantly in the upper lobes

BG in a 25-year-old asthmatic man with 13% peripheral eosinophilia. Transverse thin-section (2.5-mm collimation) CT scan obtained at the level of the left atrium shows a lobulated soft-tissue mass (arrow) with obstruction of the lingular segmental bronchus.

*Courtesy to Dr. Jeong YJ, Pusan National University Hospital*
4. Asthma

- Type I hypersensitivity
  - Characterized by airway inflammation, which is largely reversible
    - Bronchial and bronchiolar wall thickening caused by inflammation, infiltration by eosinophils, smooth muscle hyperplasia, and edema, and excess mucus production
    - Bronchiectasis; long-standing asthma

- Imaging findings
  - Often normal or subtle; increased lung volume or hyperlucency
  - Mild bronchial wall thickening or dilatation
  - Mucus plugs or tree-in-bud (20%)
  - Mosaic perfusion (20-30%); air trapping on expiration (50%)
Fig 11. A 41-year-old woman with dyspnea. The patient was diagnosed as bronchial asthma. 
(A) Chest radiograph reveals non-specific abnormal findings, however, subtle increase in lung volume is suspicious considering her history of asthma. 
(B,C) Axial and coronal HRCT images show mild bronchiectasis and bronchial wall thickening in central bronchus with multifocal mucus plugging.
5. Pulmonary Manifestations of Other Allergic Diseases

- **Steven-Johns syndrome**
  - An acute self-limited eruption of the skin and mucus membranes
  - represents a hypersensitivity reaction to various agents
  - Although rare, pulmonary complications do occur
  - **Constrictive bronchiolitis**
    - a mosaic pattern with GGOs, mild central bronchiectasis and multiple nodular (probably reflecting centrilobular prominence) and linear branching densities

High-resolution computed tomography scan of the lower lobes showing a mosaic pattern with ground-glass opacifications, central bronchiectasis, multiple centrilobular nodules and linear branching densities.

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In conclusion

- **Allergic lung diseases** include various disease entities with overlapping radiologic manifestations and a wide range of clinical presentations.

- Integration of laboratory, imaging, and clinical findings is essential in making the correct diagnosis of this complex group of disorders.
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