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Seminars in ULTRASOUND CT and MRI

Immune-Mediated Lung Diseases

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Immune-mediated lung diseases are a complex group of diseases characterized by inflammatory cellular infiltration of the lungs which can result in progressive airway remodeling and parenchymal injury. Diseases have variable presentation depending on antigen exposure, patient predisposition, and type of immune response. Early recognition, removal of the inciting antigen, and steroid intervention are important to prevent disease progression. This article will review key clinical, radiologic, and pathologic features of immune-mediated lung diseases.

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Introduction

The airways and lungs are continuously exposed to antigens which are cleared by the host's defense system. The mechanical defense barrier is the first-line of protection—particles >5 μm are trapped in the upper airways by nasal hair, pharyngeal mucosa, and mucin before clearance via ciliary action. Antigens that make it past the mechanical defense barrier are removed by the innate pulmonary immune system which is a complex coordination of different cell types such as leukocytes, phagocytic alveolar macrophages, fibroblasts, epithelial cells, and pneumocytes. Cells secret enzymes, immunoglobulins, fibronectin, lactoferrin, and defensins, which have direct antimicrobial properties and stimulate an immune response with cytokines and chemokines.[1] The lymphatic system also plays an important role, clearing fluid, debris, and white cells. At the level of the secondary pulmonary lobule, lymphatics track along the intralobular and interlobular septa and on a macroscopic scale are concentrated in a peribronchovascular, perifissural, and subpleural distribution.[2]

Some individuals, potentially through genetic predisposition, have a propensity toward a hyperimmune response. Abnormal immune activation is associated with a diverse group of pulmonary pathologies resulting in inflammatory cellular infiltration of the lungs. These immune-mediated lung diseases most notably include diseases of hypersensitivity response and eosinophilia.

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Hypersensitivity Diseases

Normal immune response creates protective immunity against an infectious antigen, but can also produce undesirable tissue damage in response to innocuous antigens. Such injurious reactions are termed "hypersensitivity" reactions. Hypersensitivity can be antibody or cell-mediated, and disease entities include hypersensitivity pneumonitis (HP), asthma, and allergic bronchopulmonary aspergillosis (ABPA).

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is a diffuse parenchymal lung disease characterized by T-cell mediated immune response to an inhaled antigen resulting in bronchiolocentric inflammation. HP is often associated with specific occupational or recreational exposures, prompting delineation of HP subtypes in the literature such as "farmer's lung" or "bird fancier's" which implies distinct disease entities but these reported subtypes are actually the same disease pathology from different triggering antigens. Inhaled culprit antigens must be small enough (<3 μm) to reach the distal bronchioles/alveoli and most often are composed of organic material from fungi, bacteria, protozoa, animal, or insect proteins. In rare instances, HP may be induced by low molecular weight chemical compounds (Table 1). There are also reported cases of drug-induced HP secondary to antineoplastic agents such as paclitaxel and antibiotics such as minocycline.[3-5]

Initial antigen exposure triggers an antibody-driven, type III hypersensitivity response which results in pulmonary neutrophilic infiltration. Continued, repeated exposure triggers a cell-mediated, type IV hypersensitivity response with increased activity and differentiation of CD4 + T-cells resulting

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Table 1 Examples of Hypersensitivity Pneumonitis (HP)

HP Type	Antigen (Source)
Fungal/Bacterial Products	
Farmer's lung	*Saccharopolyspora rectivirgula* (moldy hay)
Hot tub lung	*Mycobacterium avium complex*
Humidifier lung	*Thermoactinomyces* species
Bagassosis	*T. vulgaris* (moldy sugarcane)
Compost lung	*T. vulgaris, Aspergillus* species
Malt-worker's lung	*A. fumigatus* (barley)
Maple bark disease	*Cryptostroma corticale* (maple logs)
Sequoiosis	Multiple fungi (wood dust)
Familial HP	*B. subtilis* (wood dust in walls)
Cheese-washer's disease	*Penicillium* species (cheese casings)
Tobacco worker's disease	*Aspergillus* species (moldy tobacco)
Wine grower's lung	*Botrytis cinerea* (mold on grapes)
Suberosis	Multiple fungi (cork dust)
Japanese summer disease	*Trichosporon cutaneum* (moldy house)
Dry rot lung	*Merulius lacrymans* (rotting wood)
Animal/Insect Products	
Bird-fancier's disease	Bird droppings, feather
Fish meal worker's lung	Fish meal dust
Pituitary snuff taker's lung	Bovine and porcine pituitary proteins
Furrier's lung	Animal pelts
Miller's lung	Wheat weevil insect in dust-contaminated grain
Chemicals	
Epoxy resin lung	Phthalic anhydride (heated epoxy resin)
Pyrethrum pneumonitis	Pyrethrum (insecticide)
Popcorn worker's lung	Microwave popcorn flavoring

in cytokine and protease release which may contribute to lung injury, granuloma formation, and fibrotic response.[6,7] Patients with HP demonstrate alveolar lymphocytosis (>40%) with decreased CD4 + /CD8 + lymphocytic ratio in bronchoalveolar lavage (BAL) specimens.[8] Smokers are less likely to have HP, possibly secondary to an inhibitory effect of nicotine on alveolar macrophages.[9] As not all individuals exposed to an antigen develop HP, there is likely a genetic predisposition toward HP, which is supported by reported associations between major histocompatibility complex polymorphisms and HP.[10,11]

HP is classically categorized as acute, subacute, or chronic based on timeline of presentation. However, this is controversial as there is considerable overlap among the 3 groups, with subacute HP being the most difficult to define as it can share features of both acute and chronic disease. Proposed reclassification schemes include division into 2 clusters—recurrent systemic symptoms vs those with signs of hypoxemia and fibrosis[12]—; descriptive categories of acute episodic disease, insidious onset with superimposed acute attacks, and insidious onset without acute attacks;[13] and dividing into intermittent high-level exposure vs continuous low-level exposure.[14] We propose classifying HP into 3 categories according to degree of antigen load, timeline of antigen exposure, and presence of fibrosis: acute HP, inflammatory HP, and fibrotic HP as described in detail below.

Acute HP is an acute lung injury secondary to massive inhalational antigen exposure over a short time period. Patients present with sudden onset of symptoms such as fever, chills, dyspnea, and cough which peak within 24 hours of exposure.[15] Pathology features include peribronchial neutrophilic infiltration and intra-alveolar fibrin deposition.[16,17] Chest radiograph and CT imaging demonstrate upper lobe predominant, symmetric bilateral ground-glass opacities with or without reticulation/interlobular septal thickening (Fig. 1).[13,18,19] On CT, acute HP has a similar imaging appearance to diffuse alveolar damage given the underlying pathology. This acute lung injury is a relatively rare occurrence as it requires 2 triggers. First, a person must be exposed to a very large dose of inhaled antigen. Second, the person must have a genetic predisposition to develop a hypersensitivity reaction to that specific antigen. Patients are often quite ill and may require intubation due to the severity of lung injury. However, once the diagnosis of a hypersensitivity reaction is made and steroids are administered, most patients recover quickly without long-term sequela.

Inflammatory HP is an inflammatory process secondary to chronic, low-level antigen exposure. Inflammatory HP, similar to the historically described "subacute HP," has an insidious onset over weeks to months or even years following low, intermittent antigen exposure with systemic symptoms such as fatigue, anorexia, and weight loss in addition to cough and dyspnea.[15] Poorly circumscribed, non-necrotizing granulomas centered on the bronchioles form and are characteristic of inflammatory HP, in contradistinction to the well-formed granulomas of sarcoidosis.[16,17] The bronchiolocentric inflammation results in upper lobe predominant, ill-defined centrilobular ground-glass nodules on high-resolution computed tomography (HRCT), usually <5 mm in diameter (Figs. 2 and 3). Lobular, geographic areas of high attenuation and low attenuation (aka mosaic attenuation) is another common HRCT finding with areas of low attenuation corresponding to air trapping[13,18,19] (Fig. 3). Inspiratory and expiratory images should be obtained to demonstrate air trapping. The combination of ground-glass opacities, normal lung, and air trapping is referred to as the "head-cheese" sign which is considered classic, but not specific, for HP.[20] Ancillary findings may include mediastinal lymphadenopathy, which was seen in approximately 30% of patients with farmer's lung.[21]

If there is prolonged low-antigen exposure, inflammatory HP can progress to pulmonary fibrosis. On histopathology, fibrotic HP shows features of usual interstitial pneumonia (UIP) or nonspecific interstitial pneumonia (NSIP) patterns of pulmonary fibrosis often with areas of organizing pneumonia. Unlike idiopathic pulmonary fibrosis, the fibrosis in fibrotic HP is usually upper and mid lung predominant.[16,17] HP is increasingly recognized as a common form of fibrotic interstitial lung disease with a report that up to 50% of

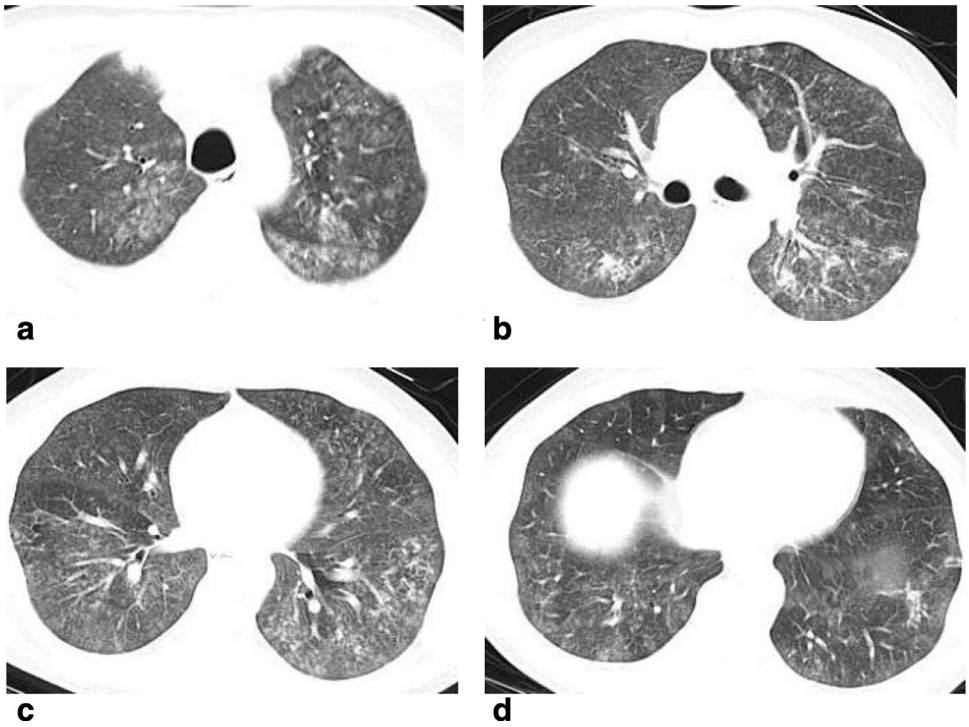

Figure 1 Acute hypersensitivity pneumonitis in a 55-year-old male presenting with shortness of breath and fever a few hours after cleaning a nonventilated attic. (A-D) Sequential axial CT images from the lung apices to bases shows patchy ground-glass opacities and ill-defined nodularity with upper lung predominance. One week following initiation of corticosteroids, CT findings dramatically improved.

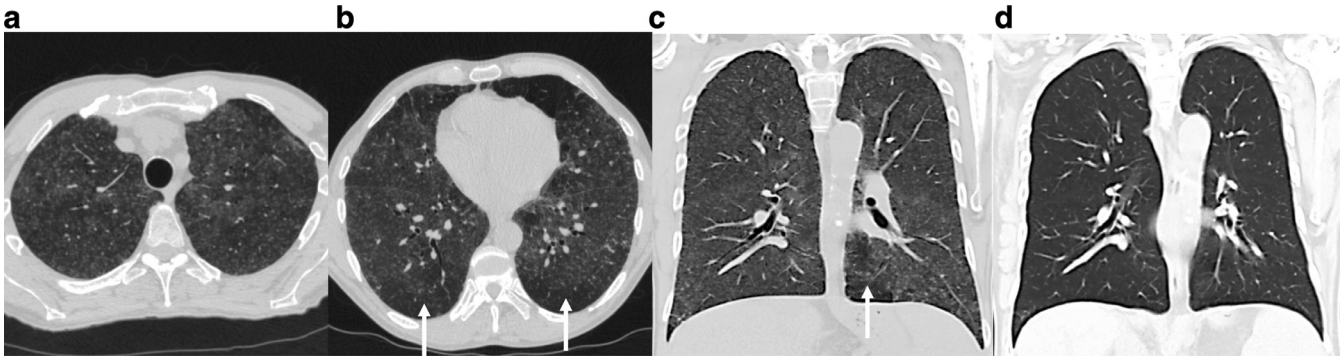

Figure 2 Inflammatory hypersensitivity pneumonitis ("hot tub lung") in a 50-year-old male swimmer. (A, B) Axial CT images through the upper lobes and lung bases demonstrate extensive but upper lobe predominant centrilobular nodules. Note subpleural sparing, compatible with centrilobular distribution, and relative sparing of the costophrenic sulci (arrows). (C) Coronal CT image from the same patient nicely shows the extent of disease with upper lobe predominant centrilobular nodularity and slightly more pronounced ground-glass opacity with areas of relative sparing at the bases (arrow) D. Coronal image at the same level 6 weeks following cessation of exposure and initiation of corticosteroids therapy shows complete resolution of the inflammatory process.

patients previously diagnosed with IPF were subsequently diagnosed as fibrotic HP.[22] HRCT features include reticulation, septal thickening, traction bronchiectasis, and honeycombing (Figs. 4 and 5). Prominent mosaic attenuation is a characteristic feature and helps differentiate HP from other diagnoses with upper lung-predominant pulmonary fibrosis such as sarcoidosis. Superimposed centrilobular ground-glass nodules may be present.[13,18,19] Acute exacerbation of fibrotic HP, analogous to acute exacerbations of UIP and idiopathic pulmonary fibrosis, can occur and is defined as acute worsening hypoxia without a known cause such as pneumonia or drug toxicity.[17]

It is interesting to note that the inflammatory and fibrotic forms of HP are most pronounced in the mid and upper lung zones. However, HP is not the only inhalational injury to follow this distribution. Smoking-related lung diseases such as pulmonary Langerhans cell histiocytosis and respiratory bronchiolitis, in addition to pneumoconioses such as

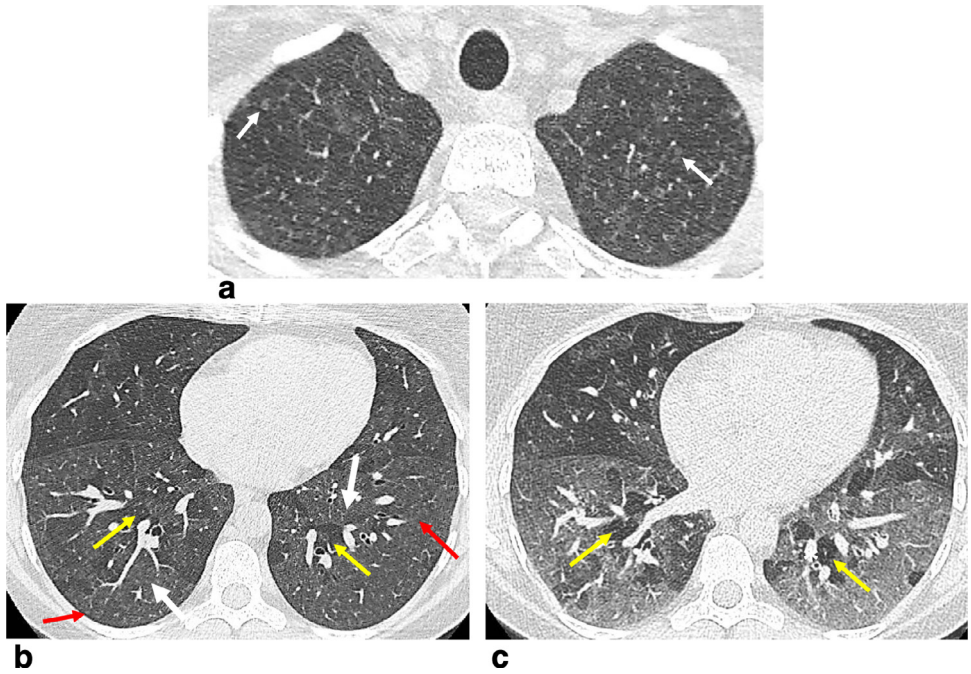

Figure 3 Inflammatory hypersensitivity pneumonitis (HP) in a 45-year-old female owner of 3 pigeons presenting with worsening cough and exertional dyspnea for 2 months. (A) Axial CT through the apices shows numerous ill-defined centrilobular nodules (arrows) and scattered ground-glass opacities. (B) Axial CT image through the mid lung zone shows a decrease in centrilobular nodules but a more pronounced mosaic attenuation with areas of relatively attenuation high (white arrows) directly adjacent to areas of relatively low attenuation (yellow arrows). There are subtle centrilobular nodules within the more dense lung (red arrows) suggesting that it is abnormal. (C) Expiratory imaging at the same level shows that the relatively low-attenuation lung in (B) does not increase in attenuation on expiration (C, yellow arrows) which is diagnostic of air trapping. The more dense lung in (B) diffusely increased in attenuation on expiration. However, the presence of centrilobular nodules in the more dense regions on inspiratory imaging and air trapping within the more lucent lung on expiratory imaging shows that very little of the parenchyma is normal in this case, a common finding in inflammatory HP. (Color version of figure is available online.)

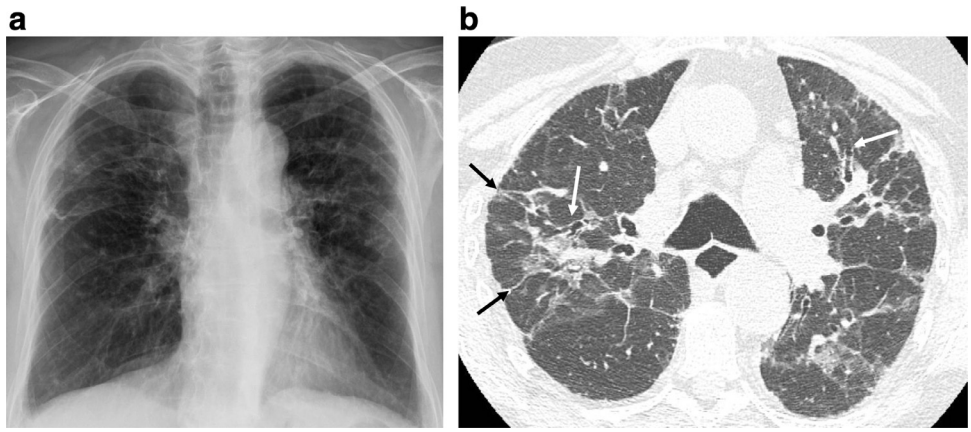

Figure 4 Fibrotic hypersensitivity pneumonitis in 72-year-old female. (A) PA chest radiograph demonstrates upper lung predominant bronchiectasis and reticular opacities. (B) Axial CT image through the upper lobes again shows bronchiectasis with surrounding architectural distortion (white arrows), mosaic attenuation, and peripheral septal thickening (black arrows). (Color version of figure is available online.)

silicosis and coal worker's pneumoconiosis, also share this upper lobe predominance. This distribution is somewhat counterintuitive given that the majority of antigen in nearly all inhalational lung diseases is deposited in the lower lobes given the normal distribution of air flow. To explain this discrepancy between antigen deposition and the site of most severe injury, one must understand the distribution of the lymphatic system in the lungs. Compared to the upper

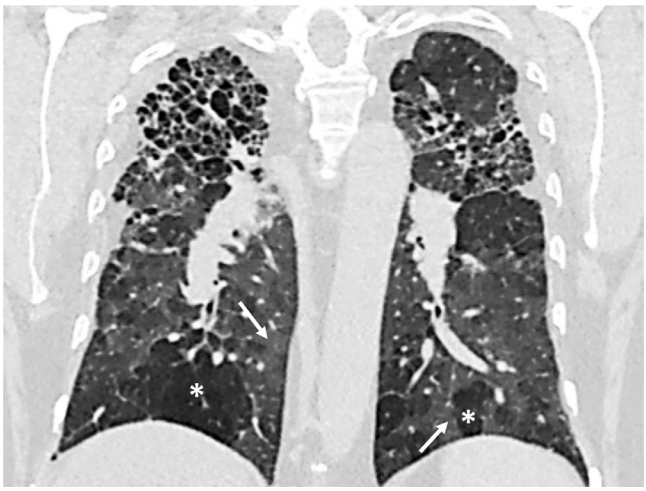

Figure 5 Fibrotic hypersensitivity pneumonitis (HP) in a female patient who owns a parrot. Coronal CT images demonstrate upper lobe predominant fibrosis with traction bronchiectasis and reticulation. In the mid and lower lung zones, there is a prominent mosaic attenuation with areas of low attenuation (asterisks), corresponding to areas of air trapping on expiratory imaging (not shown), and adjacent areas of increased attenuation (white arrows) due to ground-glass opacity. Given the numerous shades of gray, it is difficult to determine which part of the lung is normal. The pattern of fibrosis and mosaic attenuation is highly suggestive of fibrotic HP, even in the absence of centrilobular nodules.

lung zones, the lymphatic system in the lower lung zones is better developed. In addition, motion of the chest wall during respiration, which is more pronounced in the lower lobes, further promotes lymphatic clearance.[23] Therefore, while more antigen is inhaled into the lower lungs, more of this antigen is cleared leading to the upper lobe predominance seen in most inhalation lung diseases.

The mainstays of HP treatment include removal of the causative antigen and corticosteroids.[24] It is important for the radiologist to recognize HP early as he/she may be the first to identify this diagnosis and early initiation of corticosteroids in the inflammatory phase can prevent progression to fibrosis. The presence of pulmonary fibrosis portends poor prognosis[25] with a median survival of 3-5 years.[25-27]

Asthma

Asthma is a chronic inflammatory disease affecting 5%-10% of the population that causes at least partial reversible bronchoconstriction in response to various stimuli such as environmental allergens, cold air, or exercise. Asthma is an umbrella diagnosis that encompasses multiple pathophysiological phenotypes, of which allergic asthma is the most common.[28]

Allergic asthma is a manifestation of an IgE-mediated, type I hypersensitivity response, other examples of which include atopic dermatitis and allergic anaphylaxis. There are 2 phases of the type I hypersensitivity response. In the initial sensitizing stage, the triggering antigen is engulfed by antigen-presenting B-cells and dendritic cells, which then stimulate type-2 helper T (T_H2) cells to produce cytokines such as IL-4 and IL-5. These cytokines in turn stimulate B-cell production of IgE antibodies, mast cell maturation, and eosinophil differentiation. Repeat exposure to an antigen in the late phase of type I hypersensitivity results in antigen crosslinking with sensitized, IgE-coated mast cells, triggering inflammatory cytokine release and lymphocytic infiltration of neutrophils, basophils, and eosinophils.[29] Allergic asthma tends to have childhood-onset and is the most responsive to inhaled corticosteroids. Other less common asthma phenotypes generally have adult-onset, are not driven by the T_H2 inflammatory pathway, and are less responsive to inhaled corticosteroids.[28]

On histology, patients with asthma have bronchial and bronchiolar subepithelial basement membrane thickening, smooth muscle hypertrophy, goblet cell hyperplasia, and mucous gland hyperplasia which together stimulate airway remodeling and increased airway resistance.[30] Large endobronchial and bronchiolar mucous plugs consisting of shed epithelial cells and mucin obstruct the airways.[31] In chronic severe asthma, extensive airway remodeling causes fixed airflow obstruction with reduced responsiveness to inhaled corticosteroids.[32]

Patients with asthma have a variable radiographic and CT imaging appearance depending on disease severity. Bronchial wall thickening is the most common radiographic finding, seen in up to 71% of patients (Fig. 6),[33] and lung hyperexpansion the second most common radiographic finding, seen in up to 24% of patients.[34] Chest radiographs may be normal in mild cases of asthma.

Studies of CT bronchial measurements in asthma patients have demonstrated decreased bronchial lumen area and increased bronchial wall-to-lumen area, correlating with pulmonary function indices[35] and pathology.[36] Additional CT findings include mosaic attenuation with corresponding air trapping on expiratory images (Fig. 7), which is associated with greater disease severity.[37] A separate study found decreased bronchial cross-sectional area and increased air trapping provoked by bronchial challenge, mimicking an acute asthmatic episode.[38] Air trapping physiologically corresponds to the abnormally increased residual volume and total lung capacity found on pulmonary function tests. Bronchiectasis, defined as bronchial cross-sectional area exceeding that of the accompanying pulmonary artery, of varying severity is seen in up to 62% of patients.[39] Additional findings include endobronchial mucous plugging and centrilobular nodularity.[34]

Allergic Bronchopulmonary Aspergillosis

ABPA is an allergic hypersensitive immune response to antigens released by *Aspergillus fumigatus (A. fumigatus)*, which colonizes airways in susceptible individuals such as those

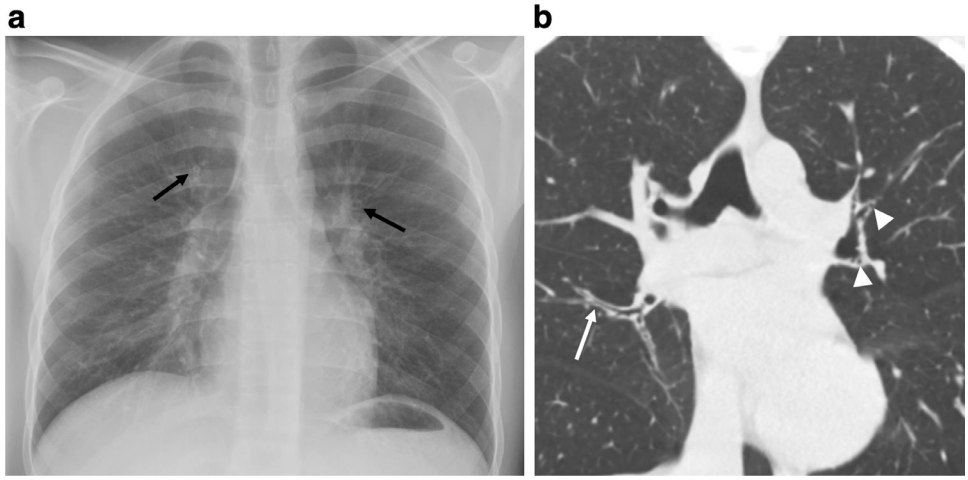

Figure 6 Bronchial wall thickening and bronchial diverticula in asthma. (A) PA chest radiograph of a 19-year-old male with asthma shows circumferential wall thickening of central bronchi (black arrows). (B) Coronal CT of a 37-year-old female with asthma and hypersensitivity pneumonitis demonstrates bronchial wall thickening (white arrow) and small air-containing outpouchings from the left upper and lower lobe bronchi (white arrowheads) compatible with diverticula, which are associated with long-standing obstructive lung disease.

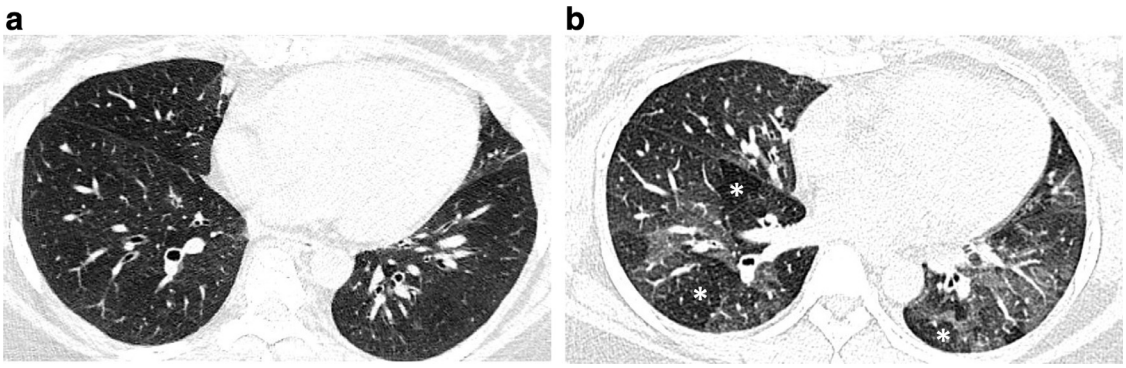

Figure 7 Air trapping in 41-year-old female with asthma. Inspiratory (A) and expiratory (B) axial CT images through the lower lobes demonstrate geographic areas of persistent low parenchymal lung attenuation (asterisks) during expiration, corresponding to areas of air trapping.

with asthma and cystic fibrosis. ABPA is a combination of immediate type I, antibody-mediated type III, and delayed cell-mediated type IV hypersensitivity responses.[40] *A. fumigatus* releases exoproteases and other fungal elements which impair mucociliary clearance, damage the bronchial epithelial layer, stimulate inflammatory antigen-antibody immune complex formation, and trigger eosinophilic lung infiltration.[41] Inflammation causes airway remodeling with progressive central bronchiectasis and large mucous plugs composed of fungal hyphae, fibrin, Curschmann spirals, Charcot-Leyden crystals, necrotic eosinophils, and debris.[42] While this process can lead to extensive damage of the large and small airways, it is important to remember that this airway injury is not secondary to *A. fumigatus* itself but rather the "heavy-handed" immune response to this otherwise relatively innocuous antigen.

Clinical diagnostic criteria for ABPA are as follows: (1) presence of a predisposing condition—either asthma or cystic fibrosis; (2) Aspergillus skin test positivity or elevated *A. fumigatus*-specific serum IgE antibodies; (3) elevated total serum IgE (>1000 IU/ml); (4) and at least 2 of the following—precipitating serum antibodies to *A. fumigatus*, radiographic abnormalities consistent with ABPA, or total eosinophil count >500 cells/μl in glucocorticoid-naïve patients.[43] Elevated *A. fumigatus*-specific serum antibodies has been reported as the most sensitive test for ABPA.[44] Up to 28% and 16% of patients with asthma have Aspergillus hypersensitivity and ABPA, respectively, while approximately 6%-10% of cystic fibrosis have ABPA.[45,46] Clinical manifestations of ABPA include asthma or cystic fibrosis exacerbation, low-grade fever, hemoptysis, and productive cough.[40]

Common radiographic features of ABPA are central bronchiectasis in an upper and mid lung distribution, bronchial wall thickening, mucous plugging, and atelectasis[47,48] (Fig. 8A). HRCT features of ABPA include bronchiectasis which is most severe centrally, and mucous plugging with or without distal atelectasis (Fig. 8B).

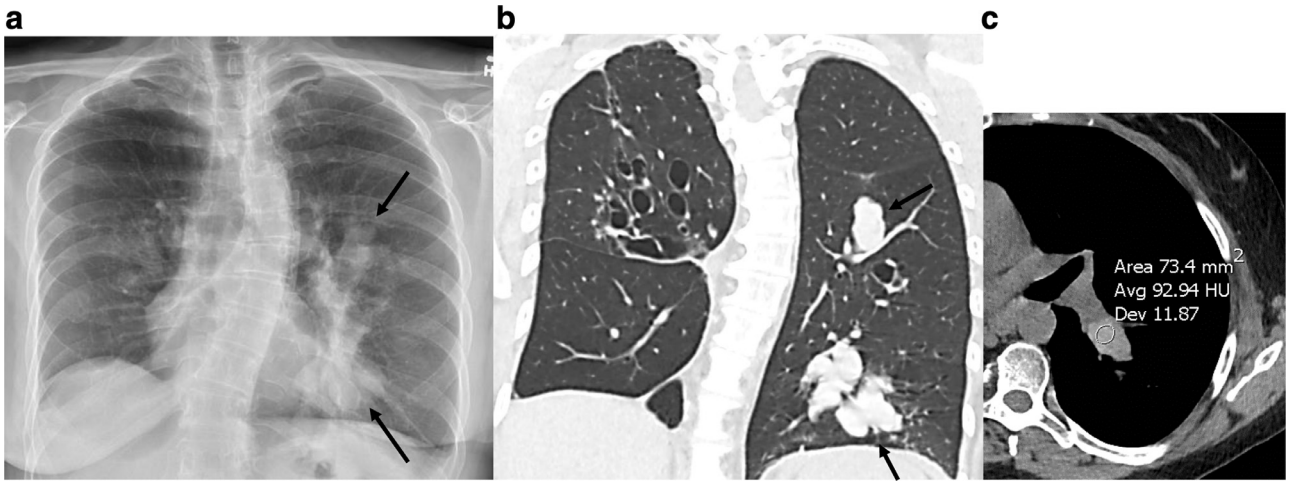

Figure 8 Allergic bronchopulmonary aspergillosis (ABPA) in a 53-year-old female patient. PA chest radiograph (A) and coronal CT (B) demonstrate tubular opacities (arrows) in the left lower lobe corresponding to mucoid impaction within dilated bronchi, compatible with the "finger-in-glove" sign of ABPA. Additional bronchiectasis is seen in the right upper lobe. (C) Axial CT image through the left lower lobe shows high attenuation (93 Hounsfield units) of the endobronchial mucous.

Tubular endobronchial mucous plugs distal to the affected airways classically have a "finger-in-glove" appearance[48-50] (Fig. 8A-B). High-attenuation mucous plugs (>70 Hounsfield units) correlate with serologic parameters of disease severity and has reported high specificity for ABPA[44,51] (Fig. 8C). Less common CT findings include mosaic attenuation indicating air trapping, centrilobular nodularity, mucoceles, endobronchial air-fluid levels, consolidation, and lymphadenopathy.[49] Fibrotic changes are seen in end-stage disease.[49,52]

Although central bronchiectasis is often considered the defining feature of ABPA, the diagnosis of ABPA is primarily a serologic diagnosis. In very early or mild disease with positive serologic markers, HRCT may be normal.[49,53] ABPA is then classified as serologic ABPA (ABPA-S) in which elevated serum antibodies are present but chest radiograph and HRCT are normal, ABPA with central bronchiectasis (ABPA-CB), and ABPA with central bronchiectasis and high-attenuation mucous (ABPA-CB-HAM) with successive categories thought to represent increased immunologic disease severity.[54]

ABPA is highly response to systemic glucocorticoid treatment. Early diagnosis is essential as steroid intervention prevents further airway remodeling and bronchiectasis.[55]

Eosinophilic Lung Diseases

Eosinophilic lung disease encompasses a diverse group of parenchymal lung diseases which share peripheral and/or pulmonary eosinophilia. Diagnosis is based on satisfaction of 1 of 3 criteria: peripheral eosinophilia and chest radiographic abnormalities, pulmonary eosinophilia on open lung biopsy, or elevated BAL eosinophils.[56]

Eosinophils are derived from pluripotent stem cells in the bone marrow and are normally present in the peripheral blood and GI tract, but do not normally reside in the lung, suggesting a pathologic process. Eosinophils are an important immune defense against helminthic parasitic infection, but are abnormally activated by inflammatory and allergic diseases. T_H2 lymphocytes produce IL-3, IL-5, and GM-CSF which stimulate eosinophil differentiation and tissue recruitment. Eosinophils contain granules which characteristically stain pink with acid dyes. Upon activation, eosinophils release these granules containing cationic proteins such as major basic protein, eosinophil derived neurotoxin, cytokines, and chemokines which mediate cell damage.[57]

There are primary and secondary causes of eosinophilic lung disease, of which secondary causes are more common. Secondary causes include infection (parasitic, fungal, bacterial, and viral), drug toxicity, ABPA, connective tissue disease, malignancy (leukemia, lymphoma, myelodysplastic disorders, and lung carcinoma), sarcoidosis, and pulmonary fibrosis.[58] Primary causes are idiopathic (also referred to as "eosinophilic lung disease of unknown cause" in the literature) and are either lung-limited or systemic. Lung-limited eosinophilic lung disease is comprised of simple pulmonary eosinophilia (SPE), acute eosinophilic pneumonia (AEP), and chronic eosinophilic pneumonia (CEP). Systemic etiologies include hypereosinophilic syndrome (HES) and eosinophilic granulomatosis with polyangiitis (EGPA).[58-60]

Simple Pulmonary Eosinophilia

SPE, also known as Loeffler syndrome, was originally described in 1932 as a phenomenon of transient pulmonary opacities in the setting of peripheral eosinophilia.[61] Radiographic opacities are unilateral or bilateral, may migrate, and

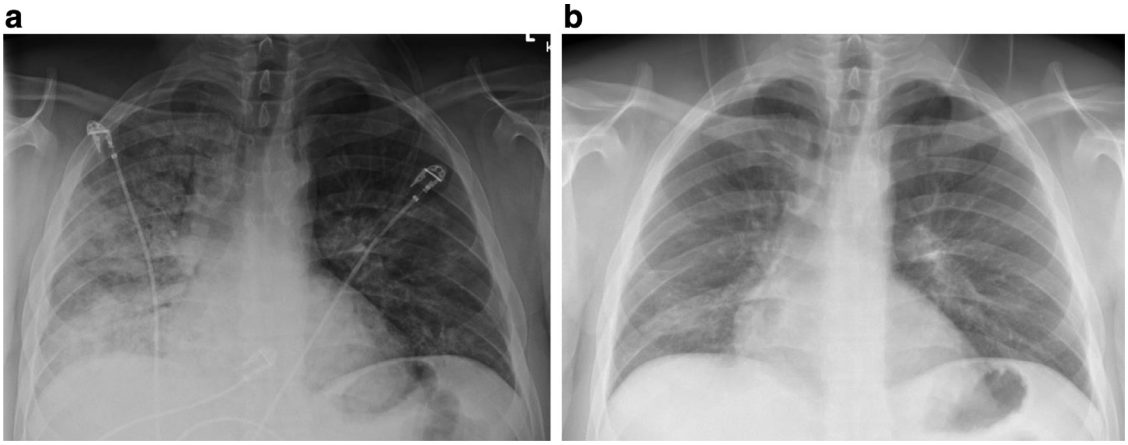

Figure 9 Acute eosinophilic pneumonia (AEP) in a 19-year-old male presenting with 7 days of fever, malaise, shortness of breath and progressive respiratory failure, not clinically improving on antibiotic therapy. (A) On presenting AP chest radiograph (a), there are basal predominant heterogeneous opacities, right greater than left. (B) Twenty-four hours following initiation of intravenous steroids, there is near complete resolution of opacities. Such rapid improvement following steroid therapy is characteristic of AEP.

are patchy in distribution.[61,62] Patients have minimal, if any, symptoms at presentation and radiographic abnormalities usually resolve within 1 month without intervention.[63] HRCT imaging findings include consolidation and ground-glass opacities in a peripheral or random distribution, upper/mid lung zone predominance, ill-defined pulmonary nodularity, and bronchial wall thickening.[60,63] Pathologically, there is alveolar infiltration of eosinophils. The exact etiology of SPE is unknown, but has been associated with the presence of parasites, ABPA, and drug toxicity.[59]

Acute Eosinophilic Pneumonia

AEP is an acute lung injury mediated by bronchoalveolar eosinophilic infiltration. Patients present with cough, hypoxemia, and respiratory failure following an acute febrile illness of 1-5 days without evidence of infection. Patients tend to be younger compared to those with CEP, male, and otherwise healthy.[64,65] Elevated eosinophils on BAL (>25%) is a defining feature, whereas peripheral blood eosinophilia is often not present during the early stages of lung injury.[64-66] On histopathology, AEP mirrors the exudative phase of diffuse alveolar damage, sharing features of epithelial detachment, loss of normal capillary integrity, alveolar edema, fibrinous exudate, and hyaline membrane deposition.[67,68] Lung biopsy with findings of diffuse alveolar damage and pulmonary eosinophilia is highly suggestive of an AEP diagnosis.

There are a number of case reports documenting association between AEP and various exposures including inhalational exposures related to cigarette smoking, recreational drugs, World Trade Center dust, cave exploration, and woodpile moving; drug exposures such as antimicrobials, antidepressants, nonsteroidal anti-inflammatory medications, and chemotherapeutics; and infectious exposures such as parasites, fungi, and viruses including influenza. Association with cigarette smoking is the most well described, including new-onset smoking, increased smoking, change in cigarette brand, and second-hand smoke.[69] An oft-cited example of smoking-related AEP is a case series of 19 Iraqi military personnel with AEP which found that 100% of cases were smokers, of which 78% were new smokers.[66]

Radiographic findings of AEP are bilateral lower lobe predominant opacities with or without septal thickening, and pleural effusions (Figs. 9 and 11).[65,70] Common HRCT findings of AEP are peripheral ill-defined ground-glass opacities and consolidation in a peripheral and random or lower lobe distribution, poorly defined centrilobular nodules, peribronchovascular thickening, and interlobular septal thickening (Figs. 10 and 12). Pleural effusions are present in nearly all patients, and are usually bilateral.[63,65,70,71] Lymphadenopathy has been reported in some case series, although this is not a predominant feature.[63,71] The diagnosis of AEP by imaging alone is extremely difficult as the imaging findings are similar to those seen with pulmonary edema and diffuse alveolar damage given that these are the underlying pathologic findings. Because of this, the diagnosis is not often made until the patient undergoes bronchoscopy or when the peripheral eosinophil count begins to rise around 5-6 days after the onset of symptoms.

AEP is highly steroid-responsive as radiographic abnormalities resolve rapidly, usually within a few days, following initiation of systemic corticosteroids (Figs. 9 and 11).[65] After initial recovery, there is no evidence for relapse, in contradistinction to CEP.[64]

Chronic Eosinophilic Pneumonia

CEP was first described in 1969 as a disease of pulmonary eosinophilic infiltration presenting with systemic and pulmonary symptoms including fever, night sweats, anorexia, dyspnea, and cough.[72] Although AEP and CEP share BAL eosinophilia, CEP has a more insidious onset exceeding 2-4 weeks, peripheral blood eosinophilia, and rarely causes respiratory failure.[73] CEP has a 2-to-1 female predominance, peak incidence in the fifth decade, and is strongly associated

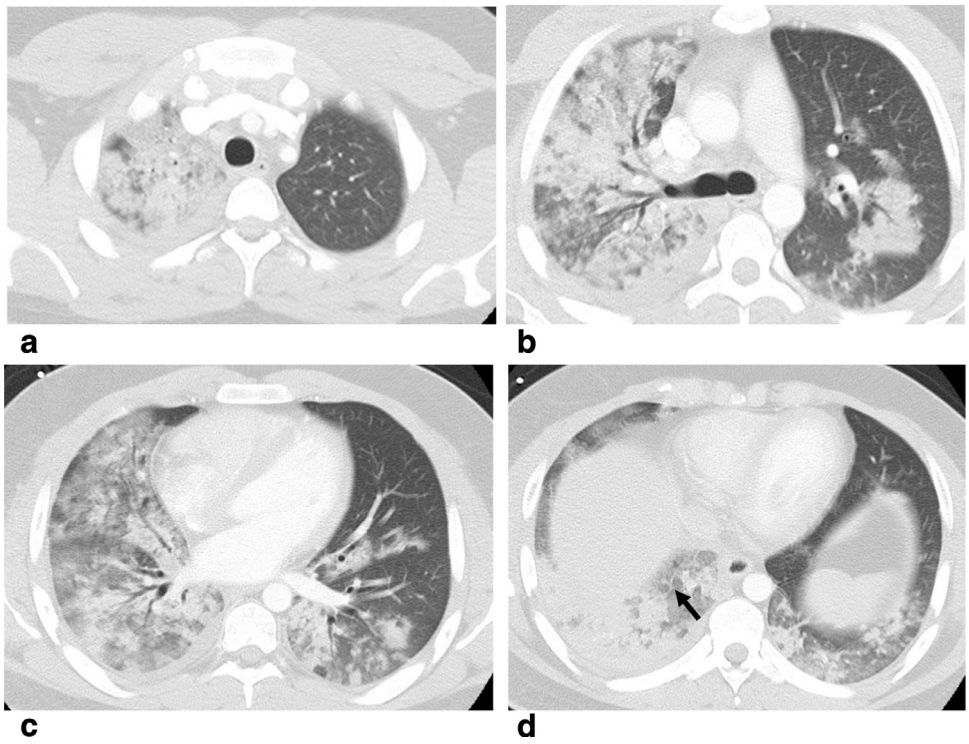

Figure 10 Acute eosinophilic pneumonia, same patient as in Figure 9. (A-D) Sequential axial CT images starting from the lung apices demonstrate mixed consolidative and ground-glass opacities throughout the right lung, left lower lobe, and lingula. Interlobular septal thickening (arrow) and a small right pleural effusion are present.

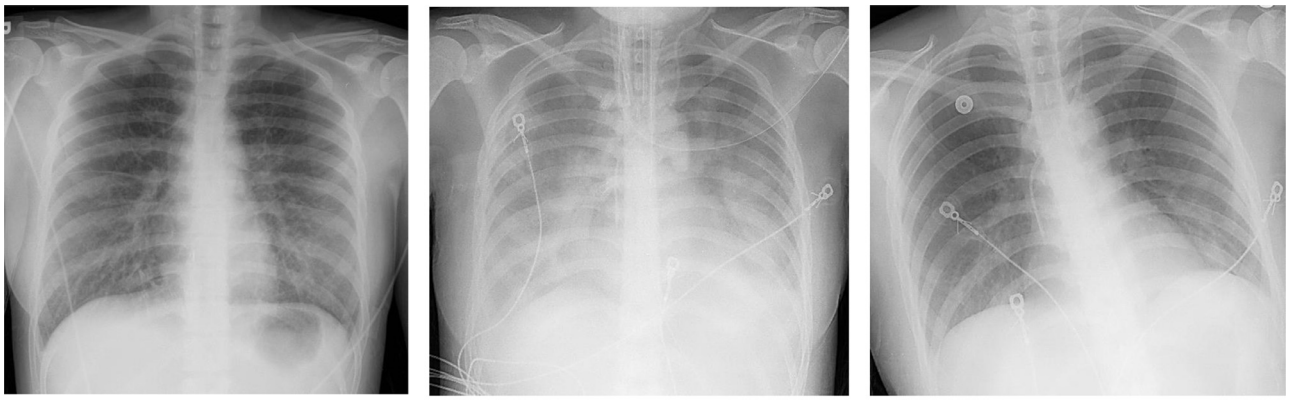

Figure 11 Acute eosinophilic pneumonia in a 20-year-old female presenting with fever and cough who required intubation for hypoxemia shortly after admission. Sequential chest radiographs on presentation (A), 6 days after admission (B), and 9 days after admission (C) show initial rapid progression of basal predominant heterogeneous opacities. Although normal on presentation, blood eosinophils rapidly increased through day 6 prompting bronchoscopy which found 71% eosinophils on bronchoalveolar lavage (BAL) and patient was diagnosed with AEP. Three days after initiation of steroids, parenchymal opacities cleared and patient was extubated (C).

with atopy and asthma, which is present in up to one-half of patients.[74,75] CEP is highly steroid responsive like AEP but there is increased risk for relapse which occurs in approximately 44%-58% of patients, necessitating a longer steroid courses (Fig. 13).[64,76]

Radiographic imaging appearance of CEP has classically been described as the "photographic negative of pulmonary edema," characterized by peripheral opacities in a nonsegmental distribution,[74,75,77,78] although this pattern is seen in less than one-half of CEP cases[75] (Figs. 13 and 15A). HRCT shows bilateral peripheral areas of consolidation and ground-glass opacities in an upper and mid lung zone distribution, mirroring the imaging appearance of organizing pneumonia (Figs. 14-16). Less common imaging features

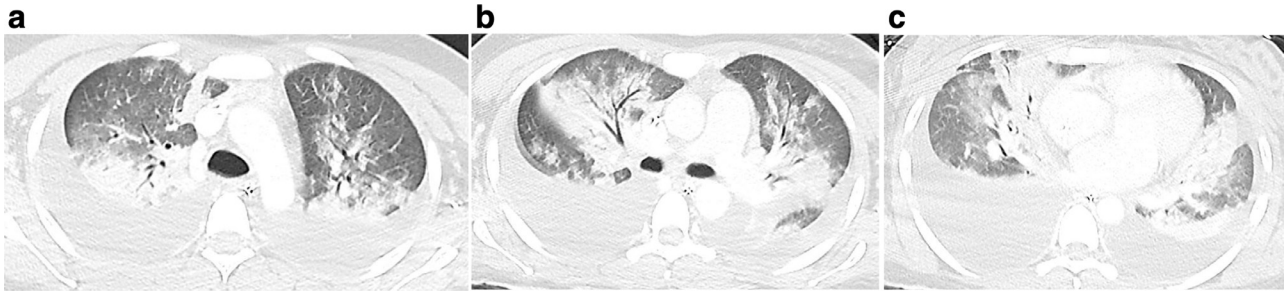

Figure 12 Acute eosinophilic pneumonia, same patient as in Figure 12. (A-C) Axial CT images show multifocal areas of consolidation in a peripheral and peribronchovascular distribution in addition to large right and moderate left pleural effusions. CT performed at similar time point as chest radiograph of Figure 11b.

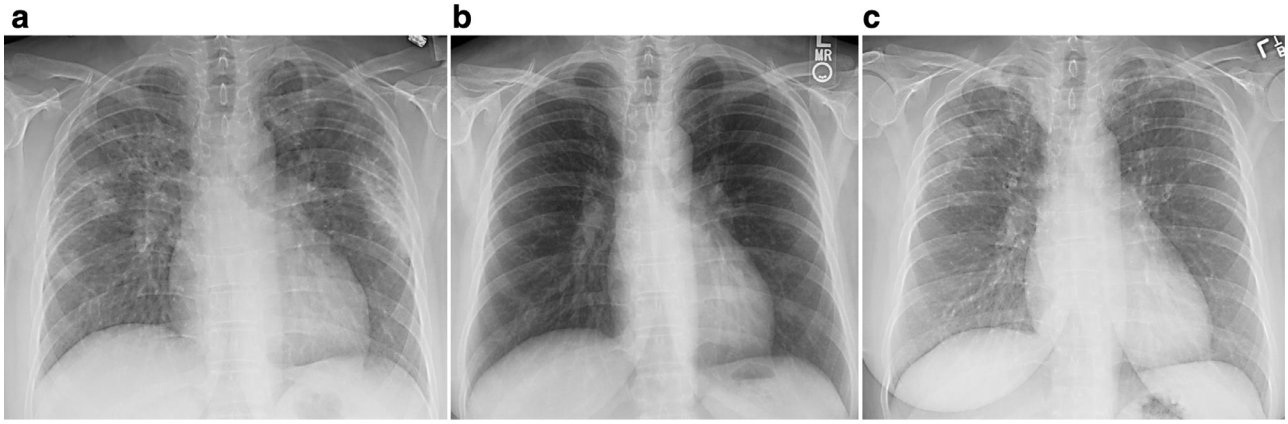

Figure 13 Chronic eosinophilic pneumonia in a 53-year-old female presenting with worsening dyspnea on exertion, dry cough, and involuntary weight loss for 2 months. Both peripheral blood eosinophilia (800/μl) and elevated eosinophils on BAL (40%) were present. (A) On initial chest radiograph, there are patchy peripheral opacities in an upper and mid lung distribution. (B) Two weeks following initiation of oral steroids, the lung abnormalities have cleared. (C) However, 1 year later shortly after tapering off steroids, symptoms recurred with reappearance of parenchymal opacities in a similar distribution as the initial radiograph.

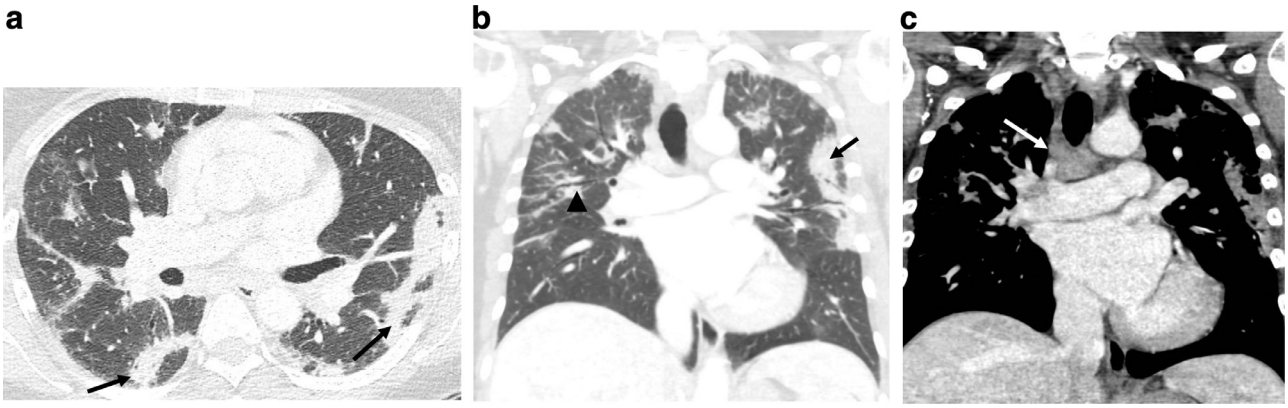

Figure 14 Chronic eosinophilic pneumonia (CEP), same patient as in Figure 13. Axial (A) and coronal (B) CT images demonstrate peripheral (black arrows) and peribronchovascular (black arrowhead) areas of consolidation characteristic of organizing pneumonia (OP), which is the underlying pathologic pattern in this disease process. Given that the eosinophilic infiltration leads to OP, the imaging appearance of CEP and OP are identical and differentiation between the 2 cannot be made with imaging alone in most instances. (C) Coronal image in soft tissue windows shows enlarged mediastinal lymph nodes (white arrow).

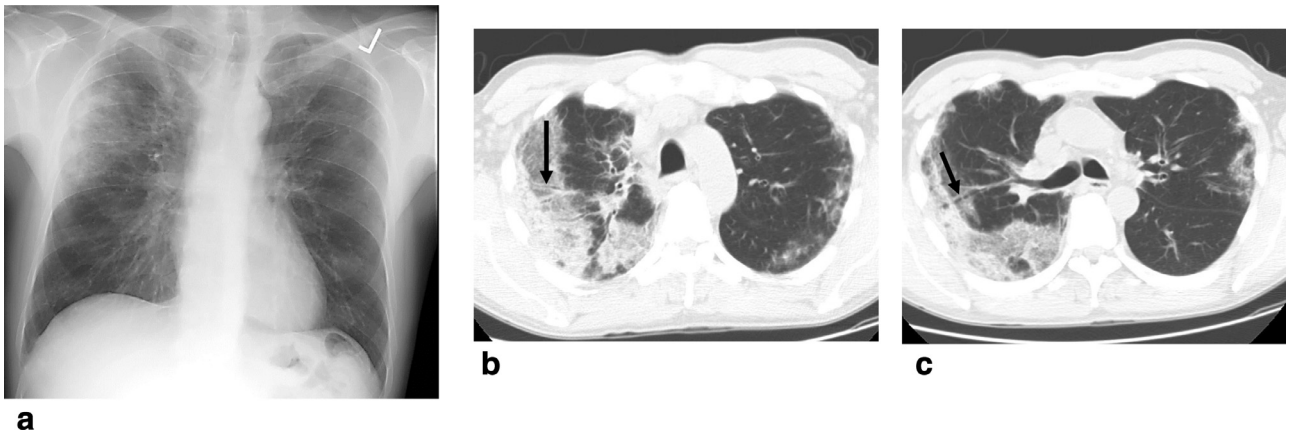

Figure 15 A 66-year-old man with recurrent episodes of chronic eosinophilic pneumonia. (A) PA chest radiograph shows peripheral consolidation in the mid and upper lung zones creating the "reverse imaging pattern of pulmonary edema" appearance. (B, C) Axial CT images through the upper lobes demonstrate upper lobe peripheral consolidation and ground-glass opacity. Areas of traction bronchiectasis are present due to mild underlying fibrosis which can occur with repeated episodes of lung injury.

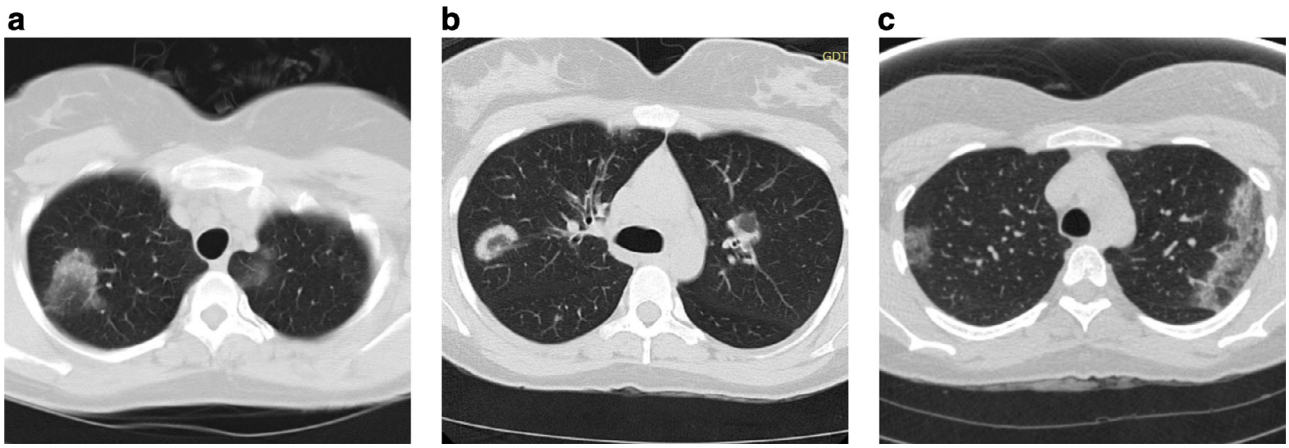

Figure 16 A 30-year-old woman with multiple relapses of chronic eosinophilic pneumonia (CEP). Axial CT images through the upper lobes from February 2012 (A), December 2012 (B), and July 2013 (C) show repeated episodes of peripheral and/or peribronchovascular consolidation due to CEP. The patient was treated with steroids between each episode with a resolution of parenchymal findings. Repeated injury can lead to fibrosis over time.

include pulmonary nodules, reticulation, and pleural effusion.[63] Case series have also reported mediastinal lymphadenopathy and septal thickening.[63,79] In the later clinical stages of CEP, band-like opacities and lobar atelectasis can be seen.[77]

Although CEP may be suspected based on clinical and imaging features, it is difficult to differentiate CEP from organizing pneumonia on imaging and diagnosis often requires BAL with or without lung biopsy. Analogous to how AEP overlaps histologically with diffuse alveolar damage, CEP pathology overlaps with that of organizing pneumonia. On histology, there is eosinophilic and lymphocytic infiltration of the alveolar lumen and interstitium with disruption of the basal lamina, intraluminal fibrosis, and fibrin deposition. Compared to AEP, CEP tends to demonstrate more basal lamina damage and intraluminal fibrosis, potentially related to cytotoxic granule formation and increased fibroblast migration in CEP.[67]

Hypereosinophilic Syndrome

HES encompasses a heterogeneous group of disorders characterized by eosinophilic end-organ damage. Diagnostic criteria include chronic peripheral blood eosinophilia exceeding 1500/μl, absence of an underlying cause of hypereosinophilia, and organ dysfunction secondary to eosinophilic tissue damage.[80,81] Patients tend to be younger with disease onset between 20 and 50 years old, and there is a male predominance.[82,83]

Although any organ can be affected, common sites of disease include lung, skin, heart, and nervous system with cardiac

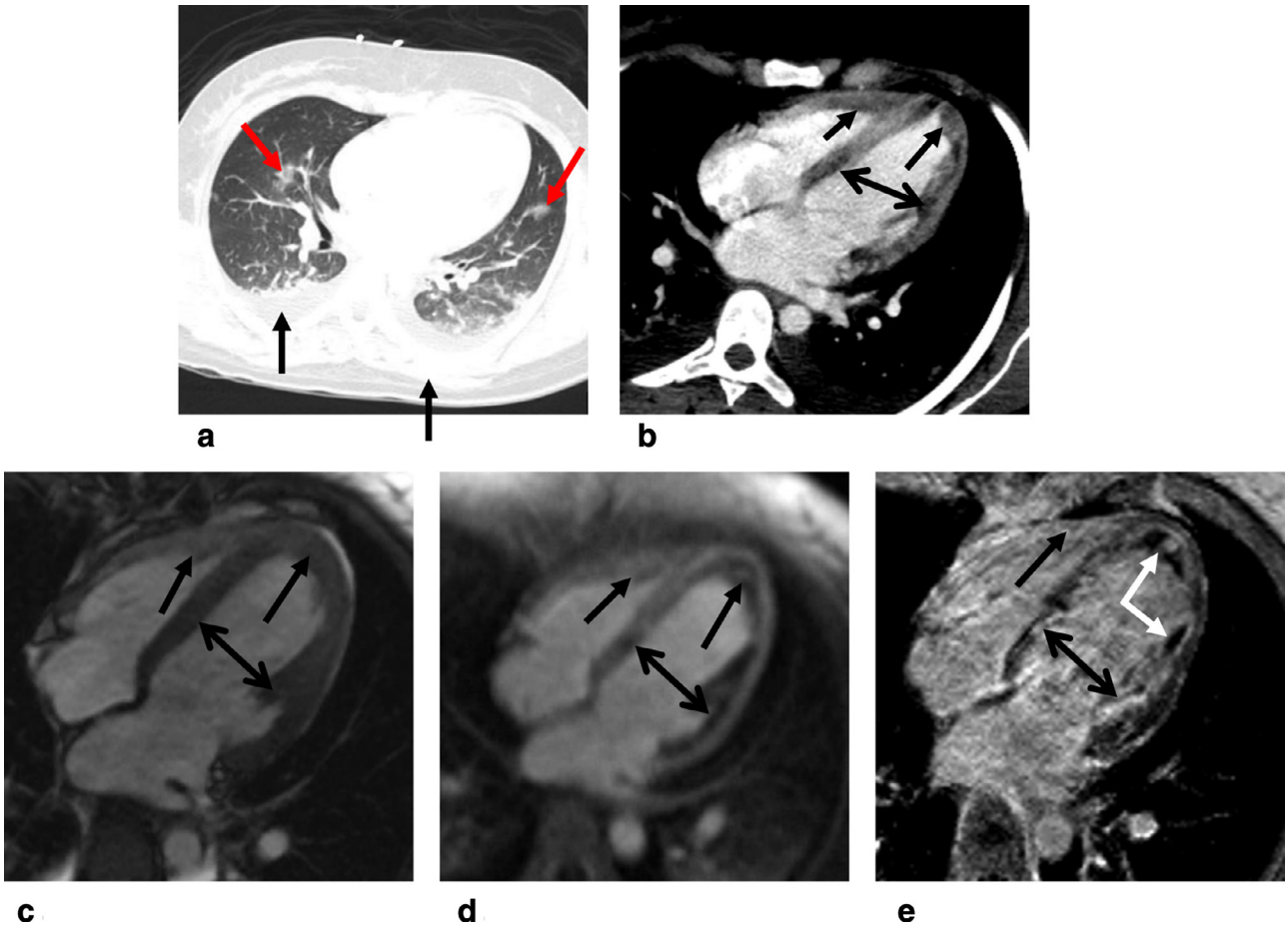

Figure 17 Hypereosinophilic syndrome (HES), acute necrotic stage. A 35-year-old woman who presented to the emergency department with shortness of breath and fever. The patient's white blood cell count was markedly elevated at 62,000/μl with 94% eosinophils. (A) Axial image from a CT pulmonary embolism study shows patchy perivascular ground-glass nodules (red arrows) and bilateral pleural effusions (black arrows). (B) Four-chamber image from the same CT shows multiple areas of subendocardial hypoperfusion (black arrows) throughout the ventricles. The constellation of findings along with the laboratory values suggested the diagnosis of HES with pulmonary and cardiac involvement. (C, D) Four-chamber images from a cardiac MRI performed the next day shows subtle areas of ventricular myocardial thickening on the SSFP image (arrows, C), which correspond to areas of subendocardial hypoperfusion on the first pass perfusion sequence (arrows, D). (E) Four-chamber gadolinium delayed enhancement image shows extensive linear subendocardial delayed enhancement (black arrows). A few areas of low signal (white arrows) corresponded to areas of myocardial necrosis and eosinophilic laden thrombus formation on autopsy. The patient died a few hours after the cardiac MRI.

disease, the primary cause of morbidity and mortality in HES.[82] Pulmonary involvement is seen in approximately 40% of cases, although the majority of pulmonary manifestations are secondary, related to heart failure and pulmonary edema.[82] Imaging features of pulmonary HES are nonspecific. Chest radiographs may be normal or show patchy areas of consolidation with or without pleural effusion. On HRCT, the primary parenchymal abnormality is small pulmonary nodules with ground-glass halos in addition to randomly distributed areas of ground-glass opacities.[63,84] Additional CT findings include bronchovascular thickening and nodal enlargement.[63]

The classic cardiac manifestation of HES is eosinophilic endomyocarditis characterized by cytotoxic eosinophilic infiltration of the endomyocardium which can progress to endomyocardial fibrosis and restrictive cardiomyopathy (aka Loeffler endocarditis). In the acute phase, endocardial necrosis leads to edema and late gadolinium enhancement localized to the subendocardial portion of the ventricles (Fig. 17). Endocardial necrosis promotes thrombus formation along the walls of the ventricle which, along with diffuse subendocardial fibrosis, are the characteristic findings in the thrombotic phase of this disease (Fig. 18). If the patient survives, over time the necrotic endocardium with adherent thrombus is replaced by fibrotic tissue with partially obliterates the ventricular cavity, leading to a restrictive cardiomyopathy (Fig. 19).[85,86]

Eosinophilic Granulomatosis With Polyangiitis

EGPA, formerly known as Churg-Strauss syndrome, is a multisystem, small-vessel vasculitis seen in asthmatic or atopic patients. Diagnostic criteria according to the American College

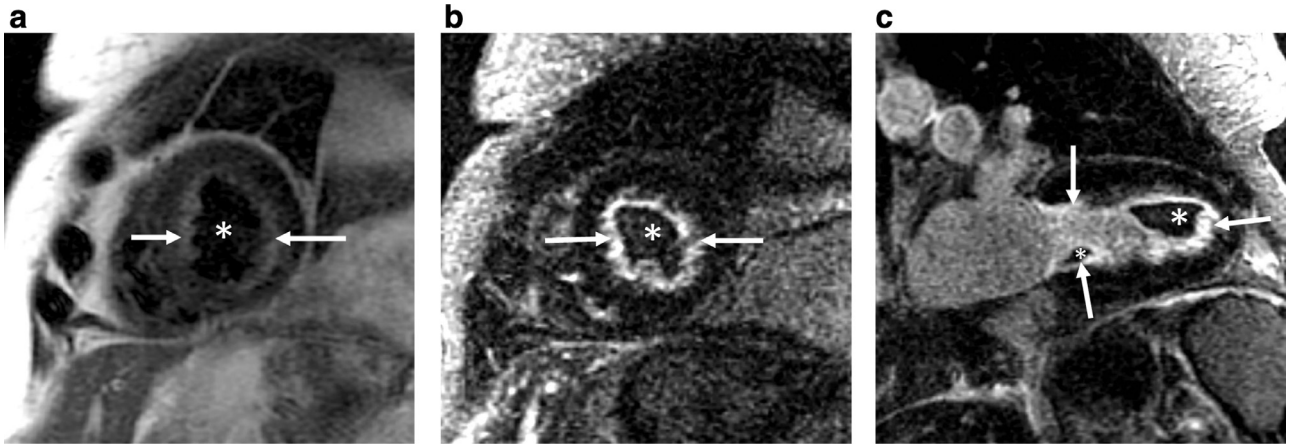

Figure 18 Thrombotic stage of Loeffler's endocarditis in a 28-year-old woman. (A) Short axis T2-weighted image through the left ventricular apex shows thrombus filling the chamber (asterisk) with subendocardial edema (arrows). (B) Corresponding short axis gadolinium delayed enhancement image at a similar level shows the nonenhancing thrombus (asterisk) and circumferential subendocardial delayed enhancement (arrows). (C) Two-chamber gadolinium delayed enhancement image shows diffuse circumferential delayed enhancement throughout the left ventricle (white arrows) with multiple thrombi (asterisks) diagnostic of Loeffler's endocarditis.

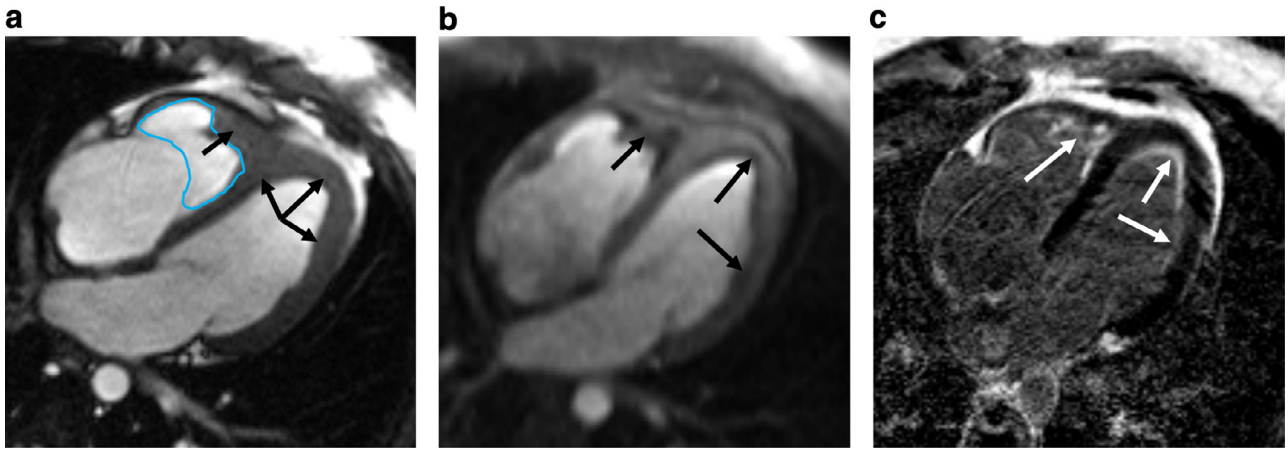

Figure 19 Fibrotic stage of Loeffler's endocarditis in a 31-year-old man with hypereosinophilic syndrome. (A) Four-chamber SSFP image during diastole shows thickening of the bilateral ventricular apices (black arrows). The area of right ventricular chamber is dramatically reduced (blue outline) and the right atrium is dilated. (B, C) First pass perfusion (B) and delayed enhancement (C) images in the same plane show that these areas of thickening correspond to areas of subendocardial hypoperfusion (B, arrows) and fibrosis (C, arrows), respectively. The conglomerate mass of fibrosis in the right ventricular apex leads to a dramatic reduction in size of the cavity and a restrictive cardiomyopathy. (Color version of figure is available online.)

of Radiology include 4 out of 6 criteria: asthma, peripheral eosinophilia >10%, neuropathy, chest radiograph opacities, paranasal sinus abnormality, and biopsy positive for extravascular eosinophils.[87] Clinical, radiographic, and pathologic features of EGPA overlap with other vasculitides such as polyarteritis nodosa and granulomatosis with polyangiitis (aka Wegner's granulomatosis), except EGPA vasculitis is mediated by eosinophils. EGPA usually presents in the fourth or fifth decade preceded by a prodromal phase of several years characterized by the development of asthma and allergic rhinitis. As the disease progresses, patients develop constitutional symptoms such as fever or weight loss in addition to signs of end-organ involvement such as central nervous system, gastrointestinal, and renal disease. Approximately one-third to one-half of patient will be antineutrophil cytoplasmic antibody (ANCA) positive.[88]

Radiographic imaging findings include migratory bilateral nonsegmental consolidation, nodules, bronchial wall thickening, and hyperinflation. On HRCT, there are patchy ground-glass opacities and consolidation with a peripheral, subpleural predominance and lower lobe predilection in addition to bronchial wall thickening, centrilobular nodules, and interlobular septal thickening (Fig. 20).[89,90] Histopathologic findings include eosinophilic granulomas, perivascular edema, and areas of organizing pneumonia.[90]

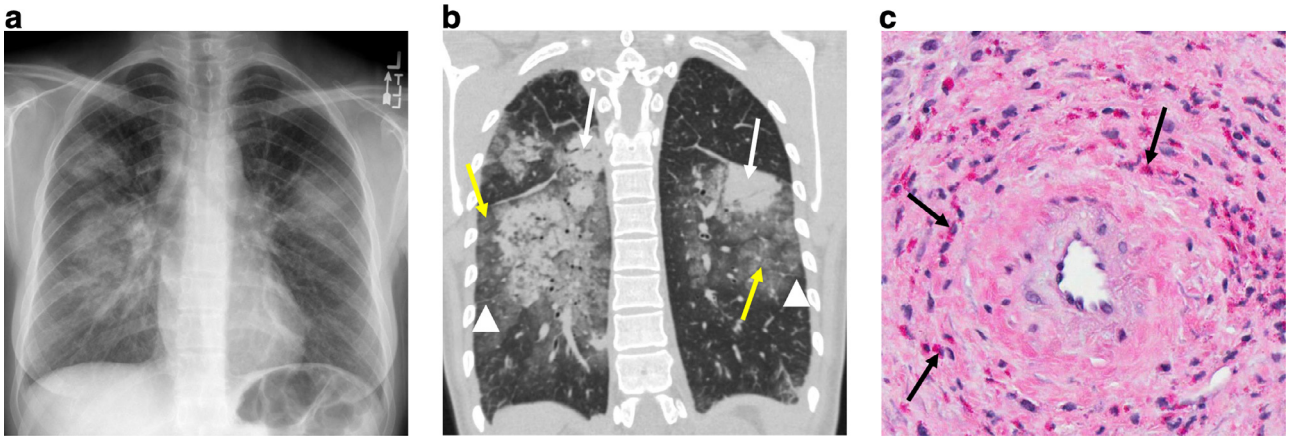

Figure 20 Eosinophilic granulomatosis with polyangiitis (EGPA) in a 41-year-old male with history of asthma and allergic sinusitis presenting with fever, cough, hemoptysis. (A) PA chest radiograph shows multifocal bilateral consolidation with slight peripheral sparing. (B) Corresponding coronal CT image shows bilateral multifocal areas of consolidation (white arrows) with surrounding "fluffy" ground-glass opacity (yellow arrows) and associated septal thickening (white arrowheads). This parenchymal pattern is highly suggestive of pulmonary hemorrhage. (C) Transbronchial biopsy shows numerous eosinophils (black arrows) surrounding a small vessel. In addition, the patient had mild peripheral eosinophilia, p-ANCA positivity, and elevated eosinophils on bronchoalveolar lavage (BAL) confirming the diagnosis of EGPA. (Color version of figure is available online.)

Conclusion

Immune-mediated lung disease encompasses a complex group of diseases with variable presentation depending on antigen exposure, patient predisposition, and type of immune response. Clinical scenario and specific imaging features can be important distinguishing features to aid diagnosis. It is important to recognize the imaging findings of immune-mediated lung disease, as early treatment can prevent disease progression and potentially irreversible pulmonary fibrosis.

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