HYPERSENSITIVITY PNEUMONITIS

A *preventable* fibrosis

MOSAVIR ANSARIE

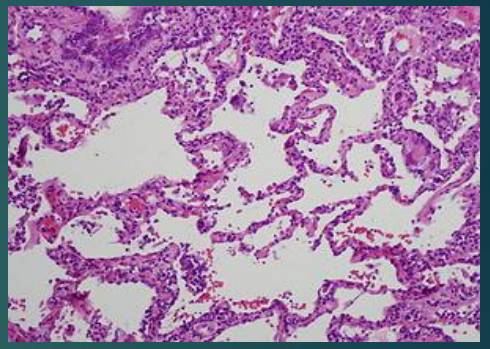
MB., FCCP

INTERSTITIAL LUNG DISEASES

A heterogeneous group of non infectious, non malignant diffuse parenchymal disorders of the lower respiratory tract affecting the alveolar wall structure and often as well small airways and blood vessels of the lung parenchyma

What is Hypersensitivity Pneumonitis?

Hypersensitivity pneumonitis (HP) is a pulmonary disease with symptoms of dyspnea and cough resulting from the inhalation of an antigen to which the subject has been previously sensitized.



Epidemiology

- HP represents 4% to 15% of all interstitial diseases.
- It is estimated that 0.5% to 3% of farmer will develop HP.
- The difficulties in establishing the incidence and prevalence of HP are further complicated by geographic variables, including climatic conditions & in the case of farmers lung agricultural practices.

Etiology

- There is increasing evidence that although HP is caused by specific antigens, a trigger factor may be needed to induce the disease.

TABLE 1. ETIOLOGIC AGENTS OF HYPERSENSITIVITY PNEUMONITIS

Disease	Antigen	Source
Fungal and bacterial		
Farmer's lung	*Saccharopolyspora rectivirgula*	Moldy hay, grain, silage
Ventilation pneumonitis; humidifier lung; air conditioner lung	*Thermoactinomyces vulgaris, Thermoactinomyces sacchari, Thermoactinomyces candidus, Klebsiella oxytoca*	Contaminated forced-air systems; water reservoirs
Bagassosis	*T. vulgaris*	Moldy sugarcane (i.e., bagasse)
Mushroom worker's lung	*T. sacchari*	Moldy mushroom compost
Enoki mushroom worker's lung (Japan)	*Penicillium citrinum*	Moldy mushroom compost
Suberosis	*Thermoactinomyces viridis, Aspergillus fumigatus, Penicillium frequentans, Penicillium glabrum*	Moldy cork
Detergent lung; washing powder lung	*Bacillus subtilis* enzymes	Detergents (during processing or use)
Malt worker's lung	*Aspergillus fumigatus, Aspergillus clavatus*	Moldy barley
Sequoiosis	*Graphium, Pullularia, and Trichoderma* spp., *Aureobasidium pullulans*	Moldy wood dust
Maple bark stripper's lung	*Cryptostroma corticale*	Moldy maple bark
Cheese washer's lung	*Penicillium casei, A. clavatus*	Moldy cheese
Woodworker's lung	*Alternaria* spp., wood dust	Oak, cedar, and mahogany dust, pine and spruce pulp
Hardwood worker's lung	*Paecilomyces*	Kiln-dried wood
Paprika slicer's lung	*Mucor stolonifer*	Moldy paprika pods
Sauna taker's lung	*Aureobasidium* spp., other sources	Contaminated sauna water
Familial HP	*B. subtilis*	Contaminated wood dust in walls
Wood trimmer's lung	*Rhizopus* spp., *Mucor* spp.	Contaminated wood trimmings
Composter's lung	*T. vulgaris, Aspergillus*	Compost
Basement shower HP	*Epicoccum nigrum*	Mold on unventilated shower
Hot tub lung	*Mycobacterium avium complex*	Hot tub mists; mold on ceiling
Wine maker's lung	*Botrytis cinerea*	Mold on grapes
Woodsman's disease	*Penicillium* spp.	Oak and maple trees
Thatched roof lung	*Saccharomonospora viridis*	Dead grasses and leaves
Tobacco grower's lung	*Aspergillus* spp.	Tobacco plants
Potato riddler's lung	*Thermophilic actinomycetes, S. rectivirgula, T. vulgaris, Aspergillus* spp.	Moldy hay around potatoes
Summer-type pneumonitis	*Trichosporon cutaneum*	Contaminated old houses
Dry rot lung	*Merulius lacrymans*	Rotten wood
Stipatosis	*Aspergillus fumigatus; T. actinomycetes*	Esparto dust
Machine operator's lung	*Mycobacterium immunogenum; Pseudomonas fluorescens*	Aerosolized metalworking fluid
Residential provoked pneumonitis Amebae	*Aureobasidium pullulans*	Residential exposure
Humidifier lung	*Naegleria gruberi, Acanthamoeba polyphaga, Acanthamoeba castellani, Bacillus* sp., others	Contaminated water from home humidifier, ultrasonic misting fountains
Shower curtain disease	*Phoma violacea*	Moldy shower curtain
Animal proteins		
Pigeon breeder's or pigeon fancier's disease	Avian droppings, feathers, serum	Parakeets, budgerigars, pigeons, chickens, turkeys
Pituitary snuff taker's lung	Pituitary snuff	Bovine and porcine pituitary proteins
Fish meal worker's lung	Fish meal	Fish meal dust
Bat lung	Bat serum protein	Bat droppings
Furrier's lung	Animal fur dust	Animal pelts
Animal handler's lung; laboratory worker's lung	Rats, gerbils	Urine, serum, pelts, proteins
Insect proteins		
Miller's lung	*Sitophilus granarius* (i.e., wheat weevil)	Dust-contaminated grain
Lycoperdonosis	Puffball spores	Lycoperdon puffballs

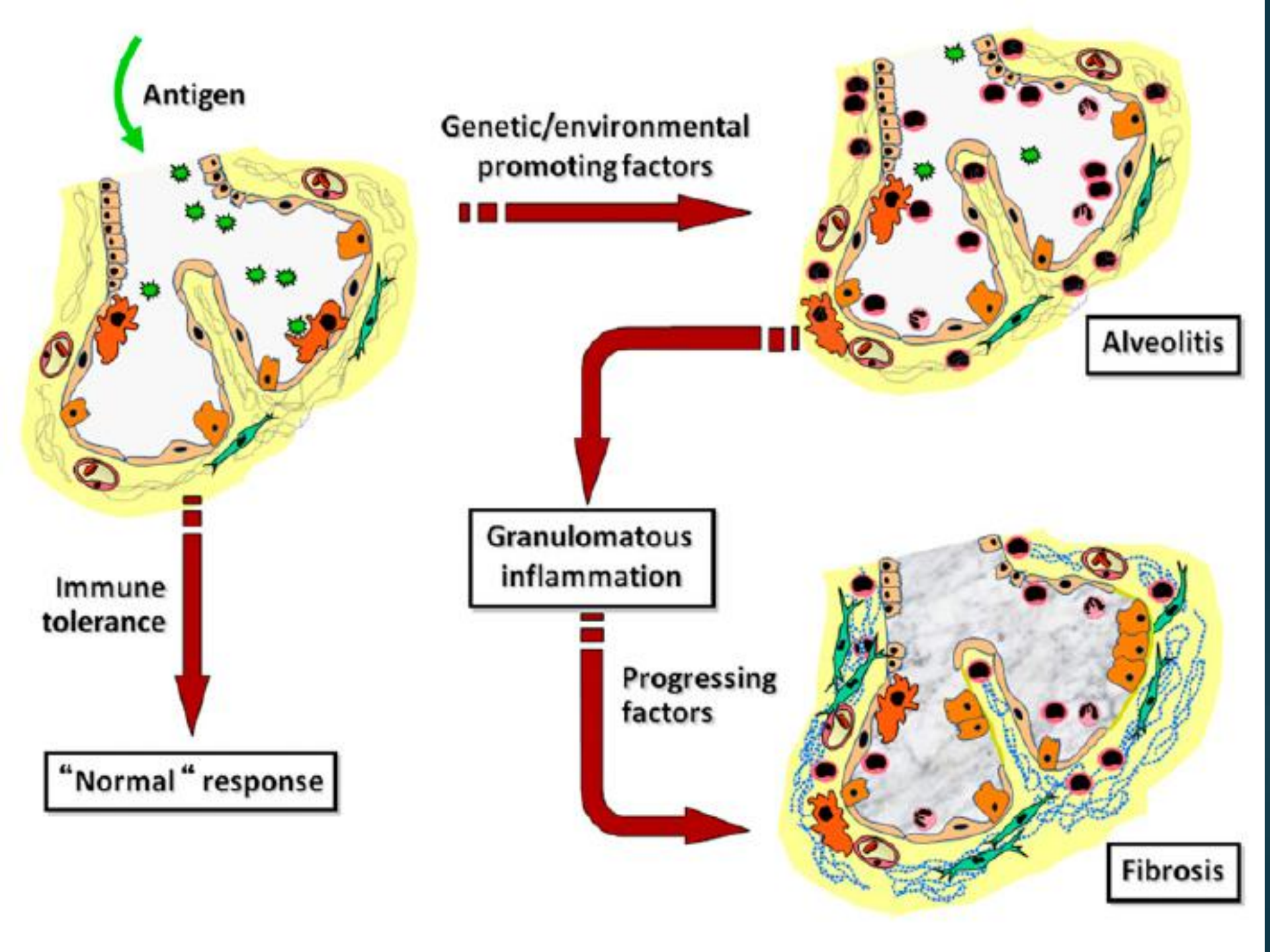
Etiology (summary)

Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Bird proteins	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

Pathophysiology

- Most exposed individuals develop an immune tolerance, and the antigen inhalation may result at most in a mild increase of local lymphocytes, *without clinical consequences*.

- The coexistence of genetic or environmental promoting factors provokes the development of an exaggerated immune reaction that results in marked lung inflammation.


Antigen
Genetic/environmental promoting factors
Alveolitis
Granulomatous inflammation
Immune tolerance
Progressing factors
"Normal" response
Fibrosis

Pathophysiology (continued)

- Lung cellular influx and inflammatory responses are initiated via immune cell receptors called toll-like receptors ***TLRs*** are expressed on immune cells and recognize most antigens, be they viral, bacterial, or other.

Pathophysiology (continued)

- In HP, when specific TLRs are activated, they react through an intracellular pathway, known as the MyD88 pathway, to release many proinflamatory cytokines and mediators.

- Studies suggest that TLRs and the MyD88 pathway could be attractive targets for future therapy of HP.

Classification

- Clinical presentations of HP have classically been defined as
  - acute,
  - subacute
  - chronic

Acute HP

- Characterized by an influenza-like syndrome
- Occurring a few hours after a (usually) substantial exposure
- Symptoms gradually decrease over hours/days but often recur with reexposure
- Acute episodes can be indistinguishable from an acute respiratory infection caused by viral or mycoplasmal agents

Subacute HP

- Characterized by an insidious onset of dyspnea, fatigue, and cough
- Symptoms develop over weeks to a few months
- In general, subacute HP is a progressive disease, with coughing and dyspnea becoming persistent.

Chronic HP

- Unrecognized and untreated acute/subacute episodes may evolve to chronic HP.
- Present as a slowly progressive (insidious) chronic respiratory disease
- Characterized by progressive dyspnea, cough, fatigue, malaise, and weight loss.
- This presentation is common in patients with bird antigen exposure.

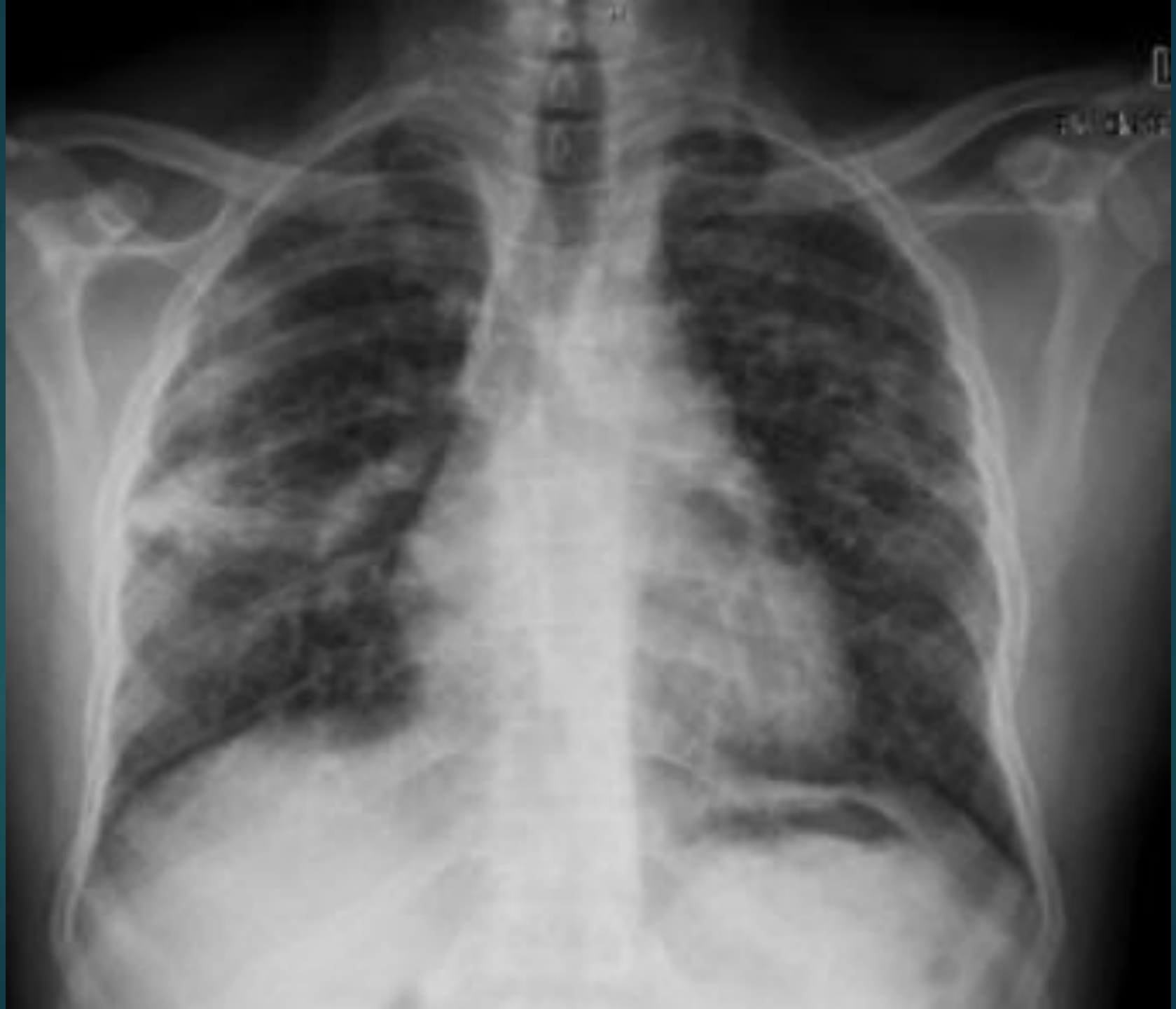
Diagnostic Dilemma

PFTs

- Pulmonary function tests have no discriminative properties in differentiating HP from other interstitial lung diseases.
- The typical physiological profile of acute HP is a restrictive pattern with low DLCO
- The importance of pulmonary function tests is to determine the severity of the physiologic impairment at diagnosis and during follow-up
- The results of pulmonary function tests may also guide therapy by helping the clinician to select those for whom a treatment with corticosteroids may be justified

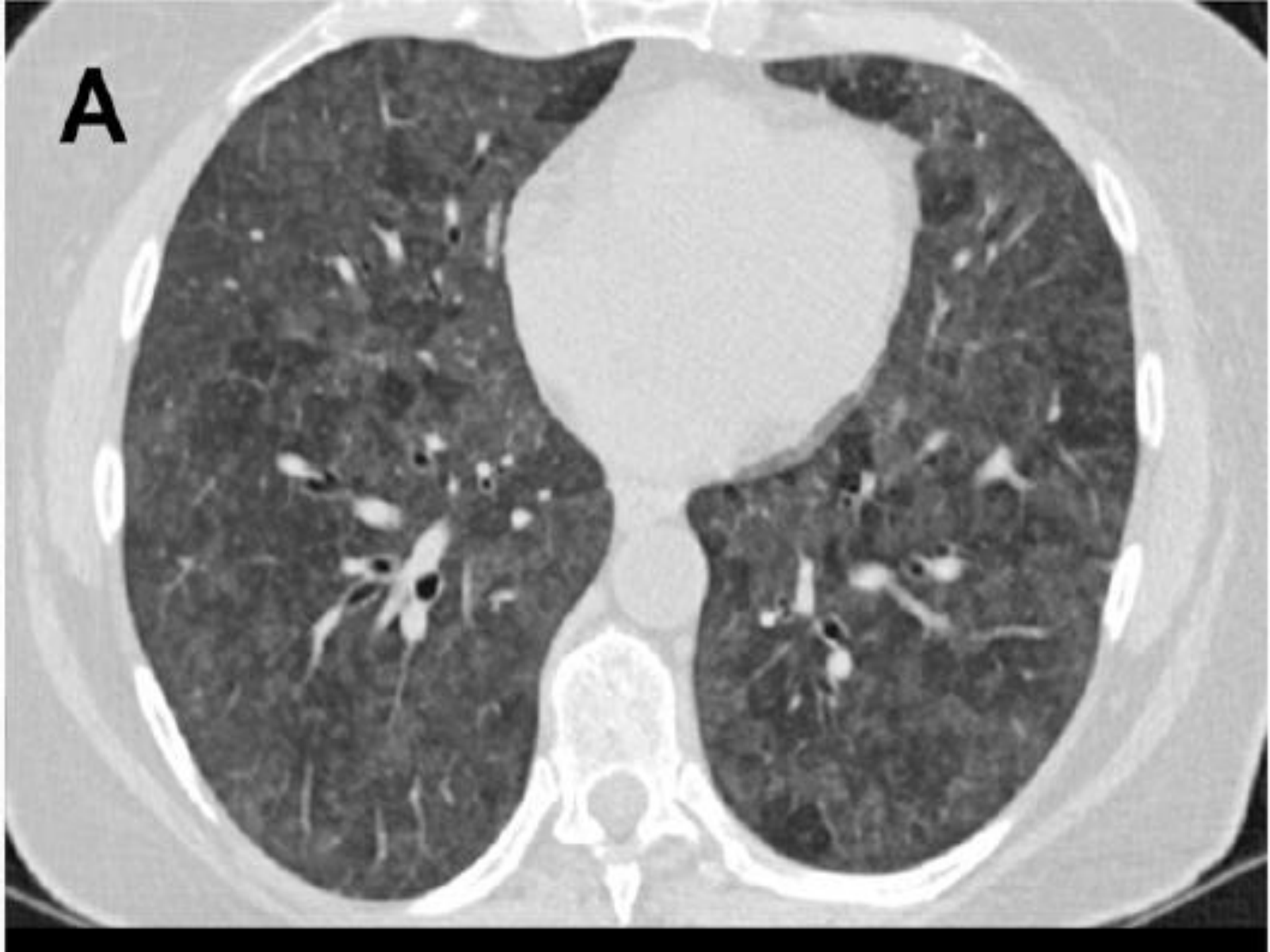
Chest X-Ray

- The first objective of chest x-ray is not to rule in HP but rather to rule out other diseases for the patient's illness.
- In acute HP, one expects to find groundglass infiltrates, nodular and/or striated patchy opacities
- The distribution of these infiltrates is usually diffuse but often sparing the bases in the subacute form



HRCT
Acute HP

- HRCT may be normal in patients with symptomatic acute HP.
- When abnormal, the predominant findings are ground-glass opacities or poorly defined small nodules.
- Diffuse areas of dense air-space consolidation may be associated with groundglass opacities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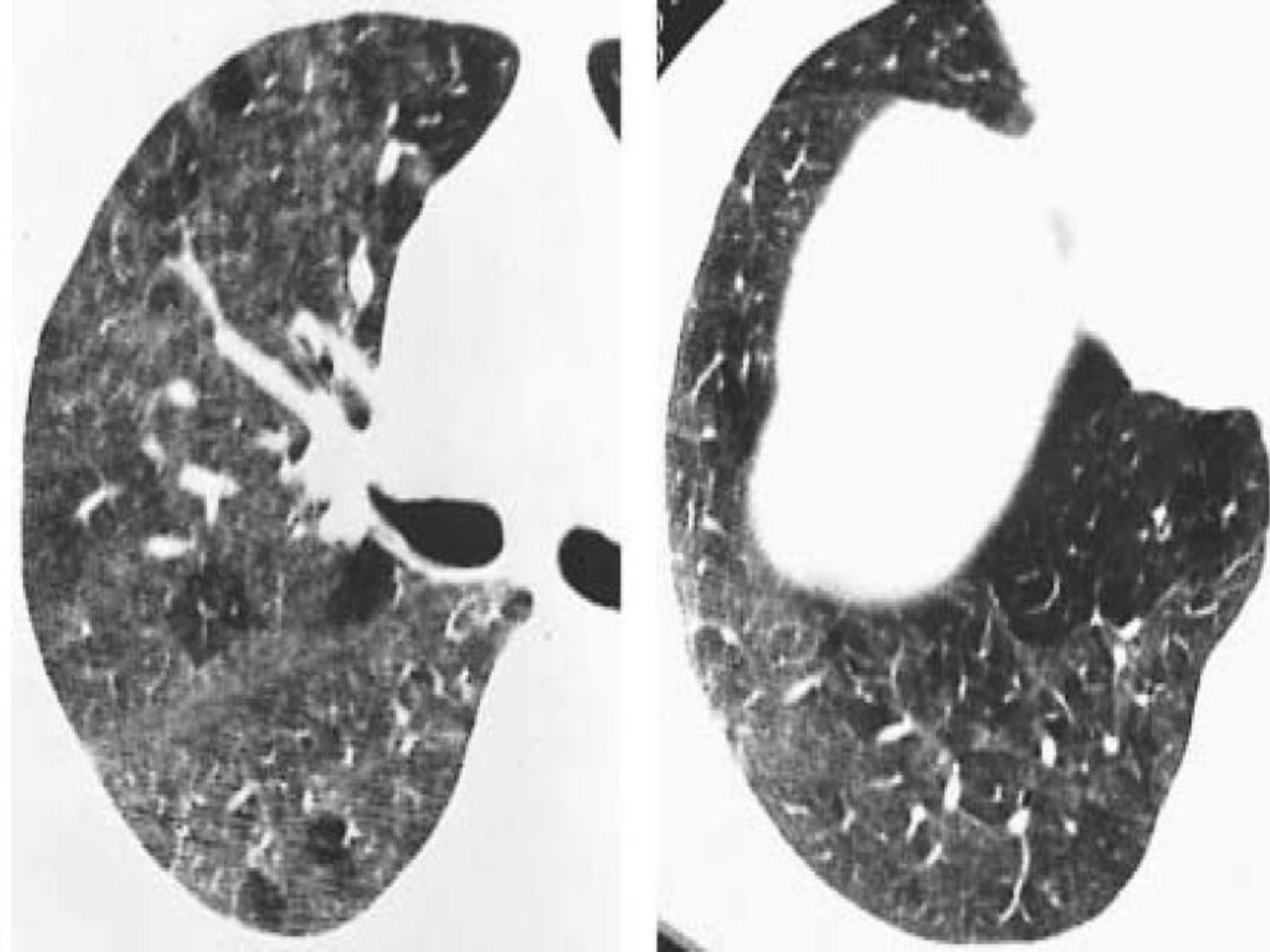
HRCT
Subacute HP

- Ground-glass opacities or poorly defined small nodules are commonly found in subacute HP
- In addition, mosaic perfusion is observed in patients with extensive bronchiolar obstruction

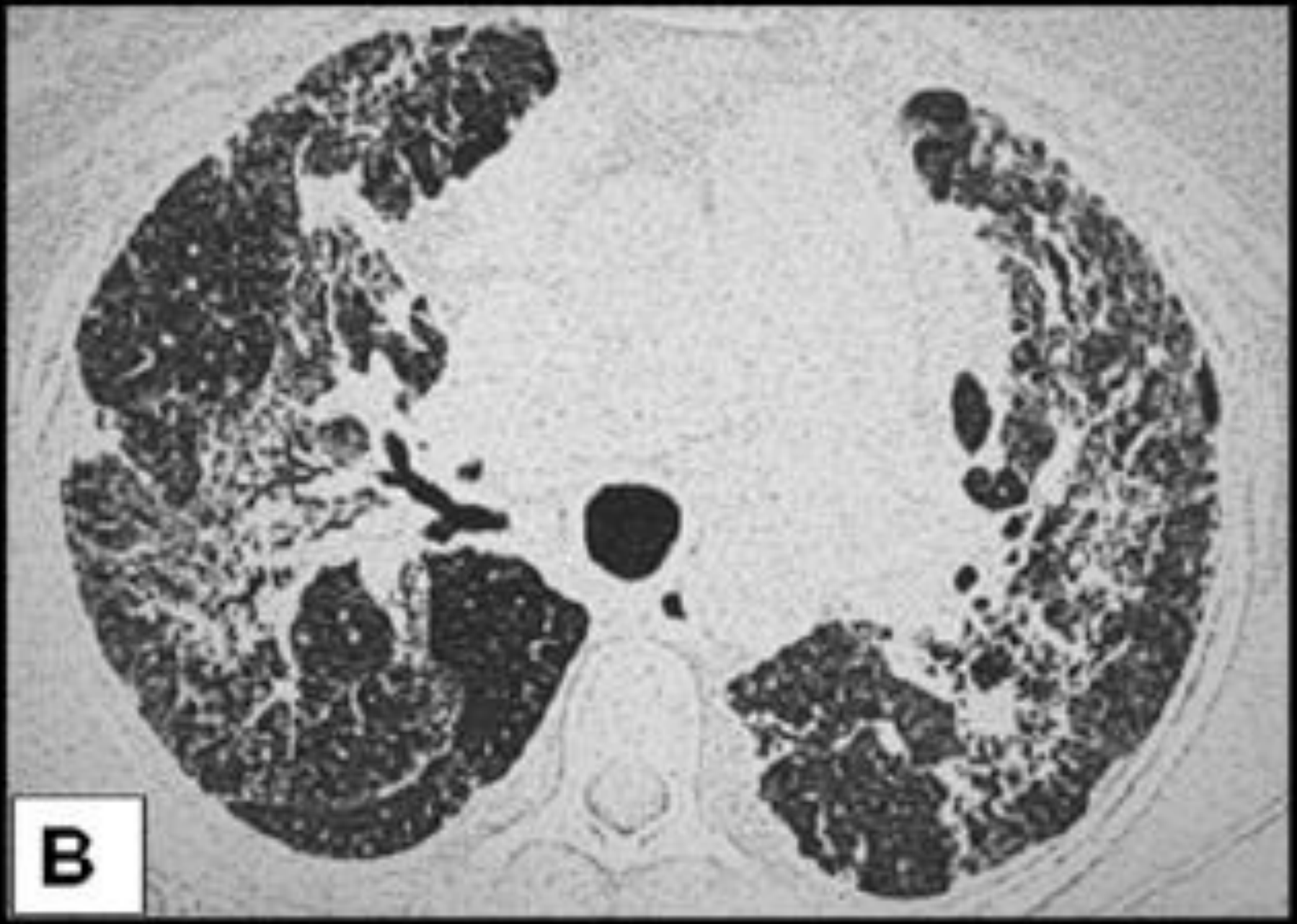


HRCT
Chronic HP

Combination of:

- reticular
- ground-glass
- centrilobular nodular opacities
- associated with signs of “fibrosis”

(i.e., interlobular septal thickening, lobar volume loss, traction bronchiectasis, and honeycombing)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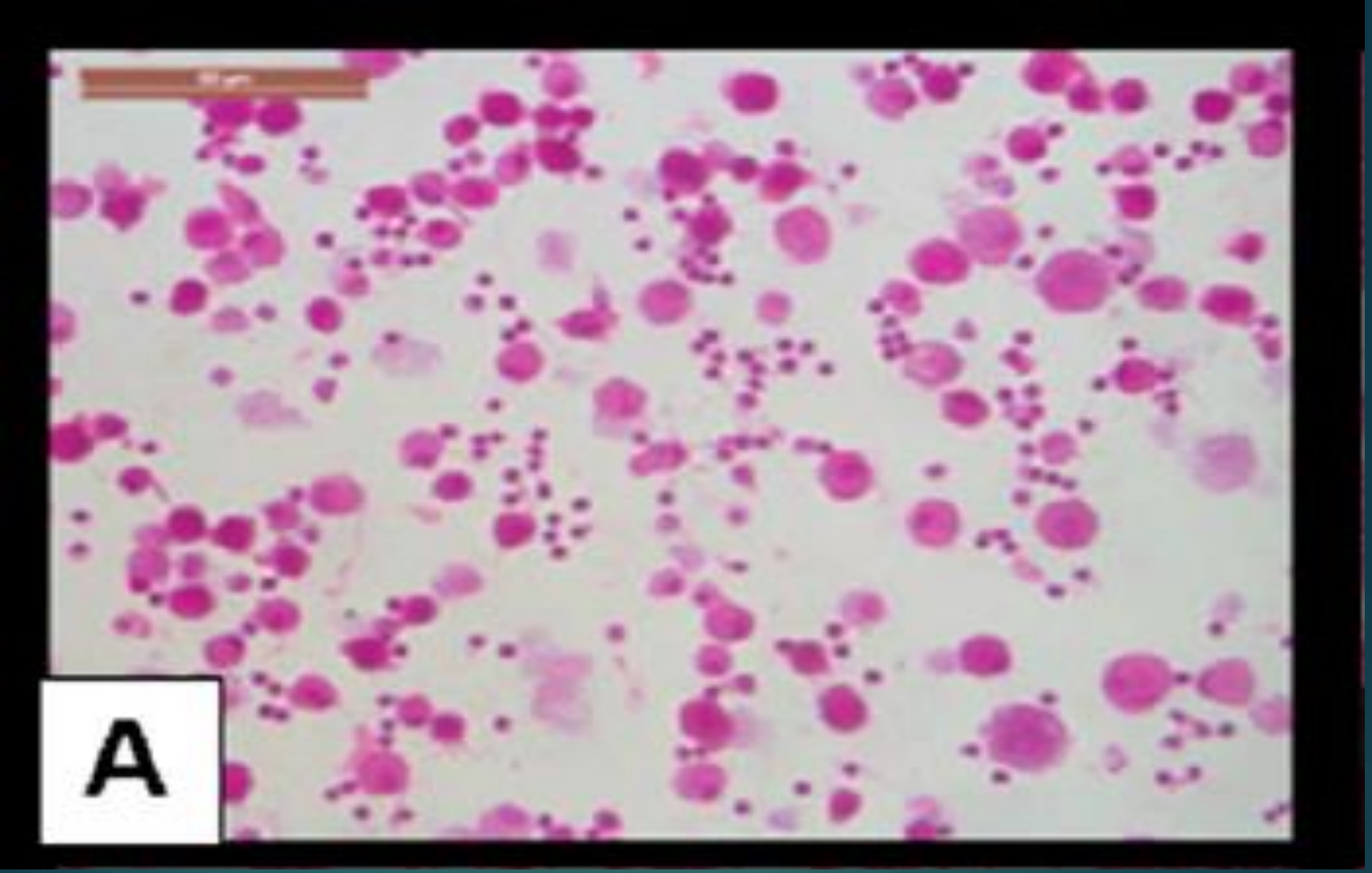
BronchoAlveolarLavage (BAL)

- Forms a supportive element
- An increase in the total cell count with a remarkable elevation in the percentage of T lymphocytes, often over 50%, characterizes HP
- However, in patients with HP who are smokers or have chronic, fibrotic parenchymal abnormalities, the BAL lymphocyte count is lower



Bronchoalveolar lavage of a patient with subacute hypersensitivity pneumonitis (HP) showing a marked increase in lymphocytes

Antibodies

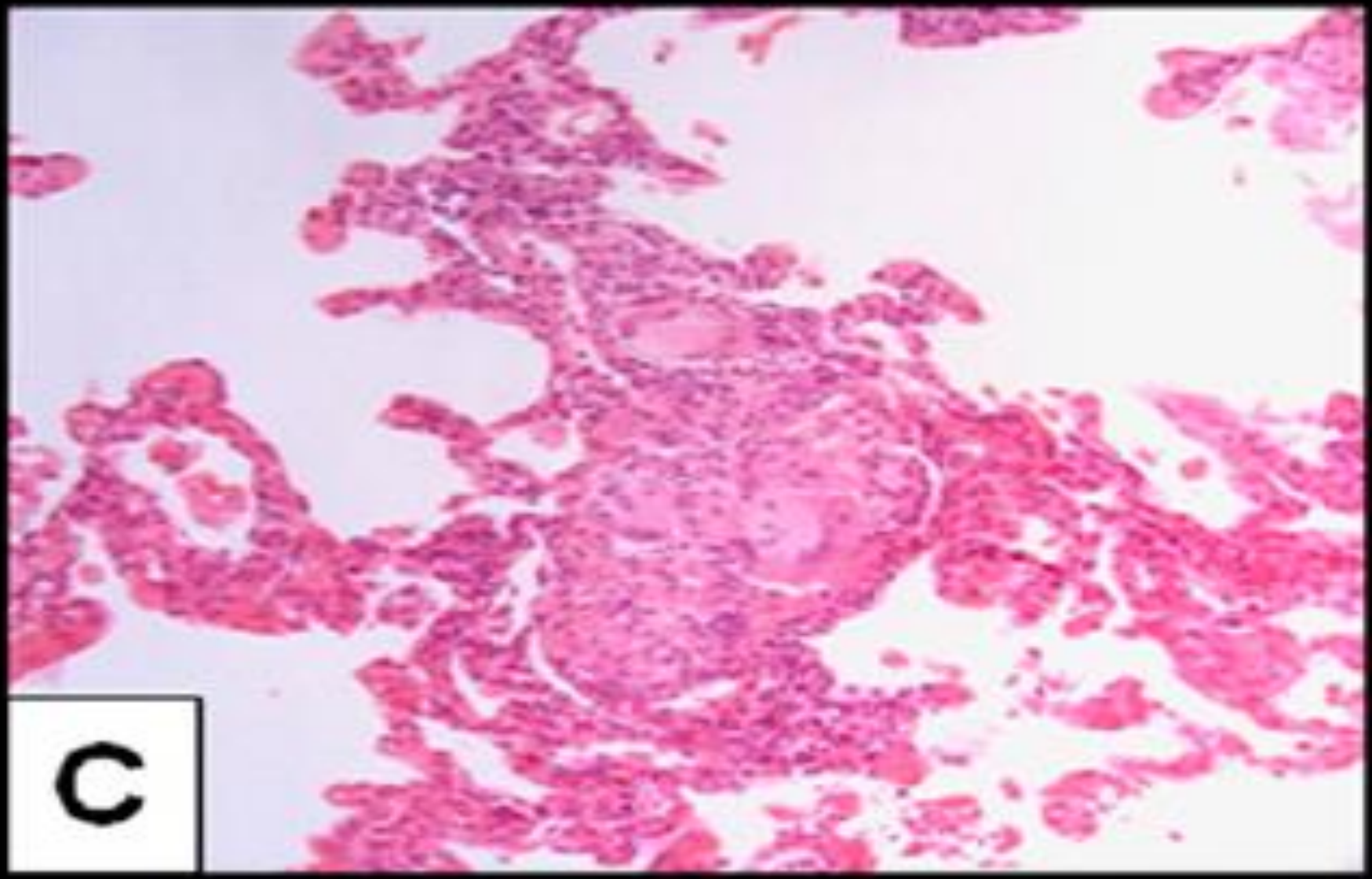
- Specific antibodies analysis can be useful as supportive evidence
- Antigens available for testing in most centers included pigeon and parakeet sera, dove feather antigen, Aspergillus sp, Penicillium, Saccharopolyspora rectivirgula, and Thermoactinomyces viridans
- The selection of antigens to be tested often needs to be determined locally according to the prevalent antigens

Biopsy

- Patients with acute HP rarely undergo biopsy.
- Acute HP shows interstitial inflammation in a peribronchiolar pattern, loose histiocytic aggregates, prominent increase of interstitial neutrophils, and fibrin deposition

Biopsy (continued)

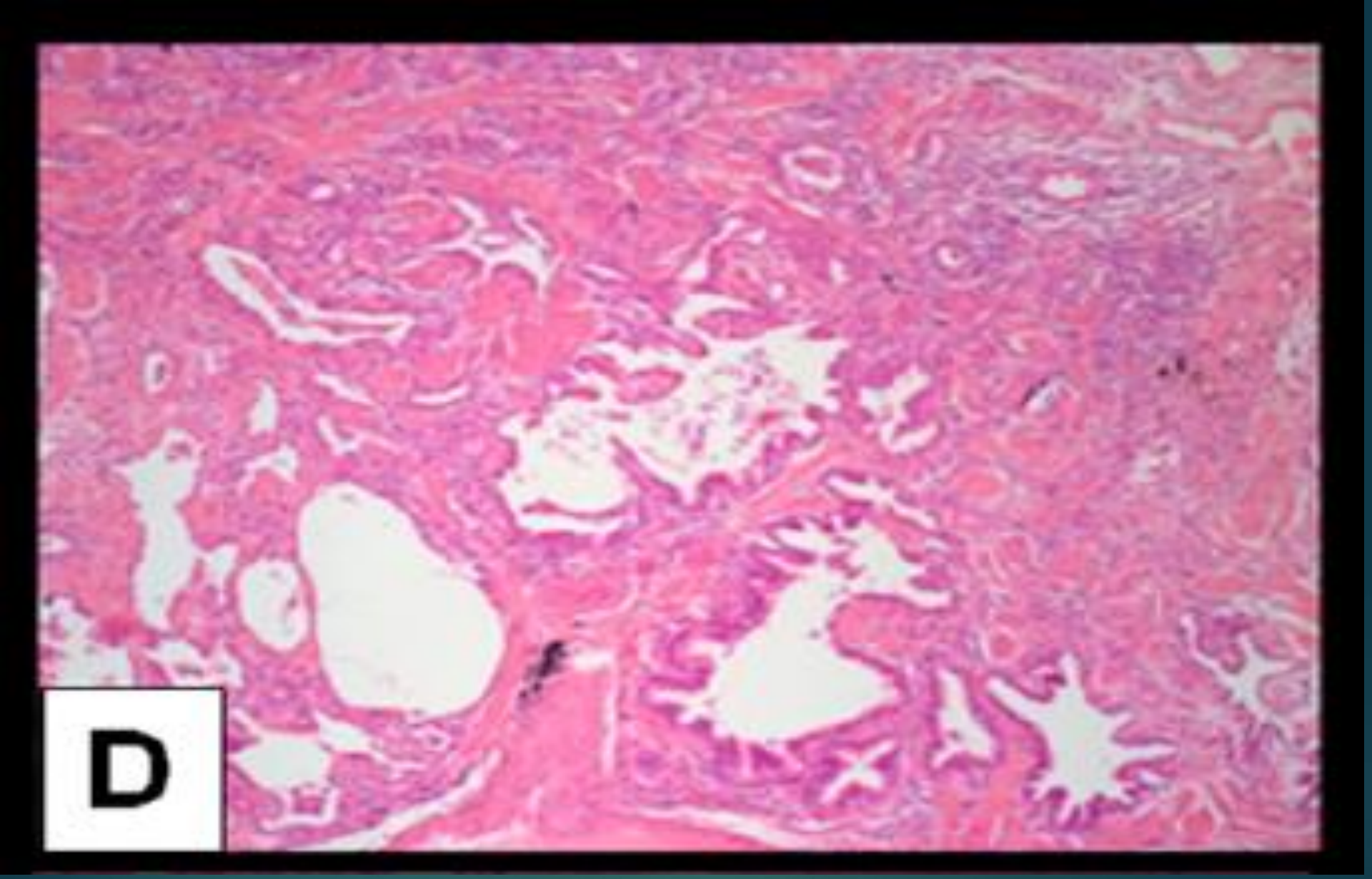
- Subacute HP, independent of the etiologic agent, is characterized by a granulomatous interstitial bronchiolocentric pneumonitis. The inflammation is composed mainly of lymphocytes, with fewer plasma cells and histiocytes, and only occasional eosinophils and neutrophils.



High magnification photomicrograph of a typical interstitial HP granuloma

Biopsy (continued)

- Chronic HP presents with fibrotic changes and architectural distortion superimposed on subacute changes



Chronic HP: Photomicrograph (H&E) of surgical lung biopsy showing fibrosis, architectural remodeling in peribronchiolar pattern.

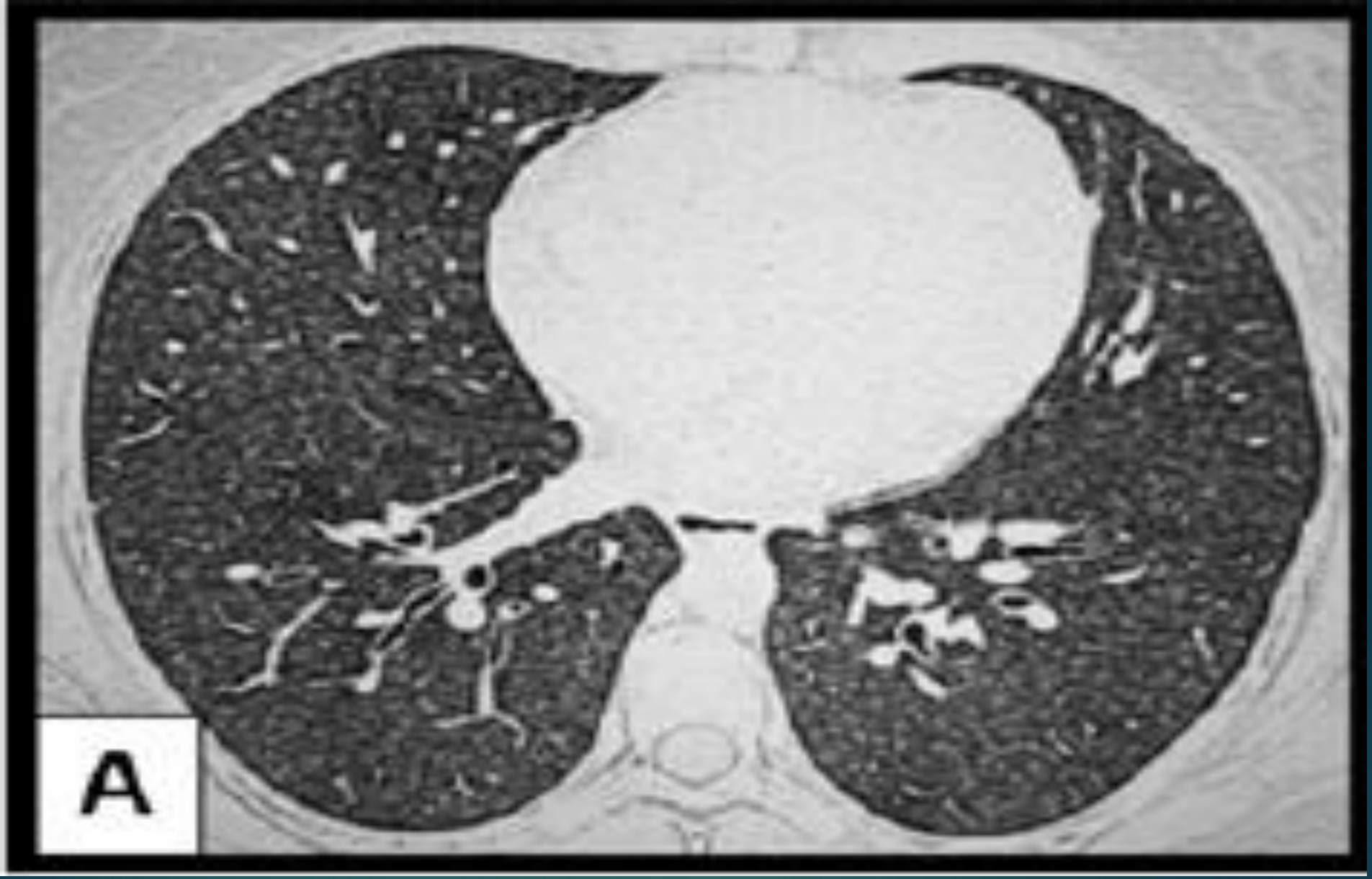
	Time Frame	Clinical Features	HRCT Findings	Immuno-Pathology	Prognosis
Acute	4-48 h r	Fever, chills Cough, hypoxemia, aches	Ground-glass infiltrates	Alveolitis, immune complex	Good
Subacute	Weeks to 4 mo	Dyspnea, cough, episodic flares	Micro-nodules air trapping	Granulomas, bronchiolitis	Good
Chronic	4 mo to years	Dyspnea, cough, fatigue, weight loss	Fibrosis +/- honeycombing, emphysema	Lymphocytic infiltration and fibrosis, neutrophil-mediated destruction	Poor

HRCT, High-resolution computed tomogography (CT scan) 2

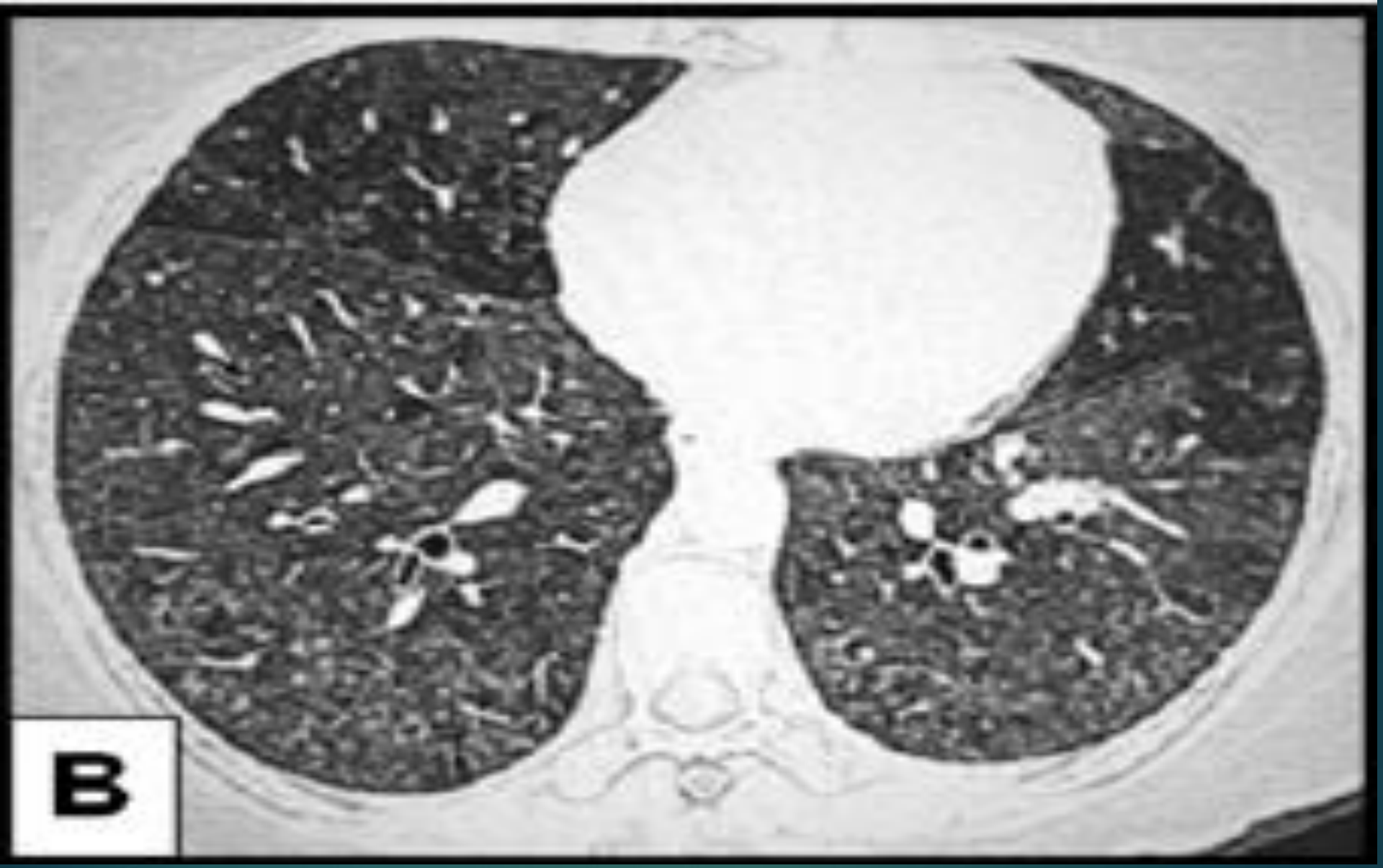
Avian Antigen Exposure

TABLE 2. DIFFERENCES IN CLINICAL, PHYSIOLOGIC, RADIOLOGIC, BRONCHOALVEOLAR LAVAGE, HISTOLOGIC, AND PROGNOSTIC FEATURES BETWEEN MICROORGANISMS AND SOLUBLE AVIAN PROTEINS EXPOSURES

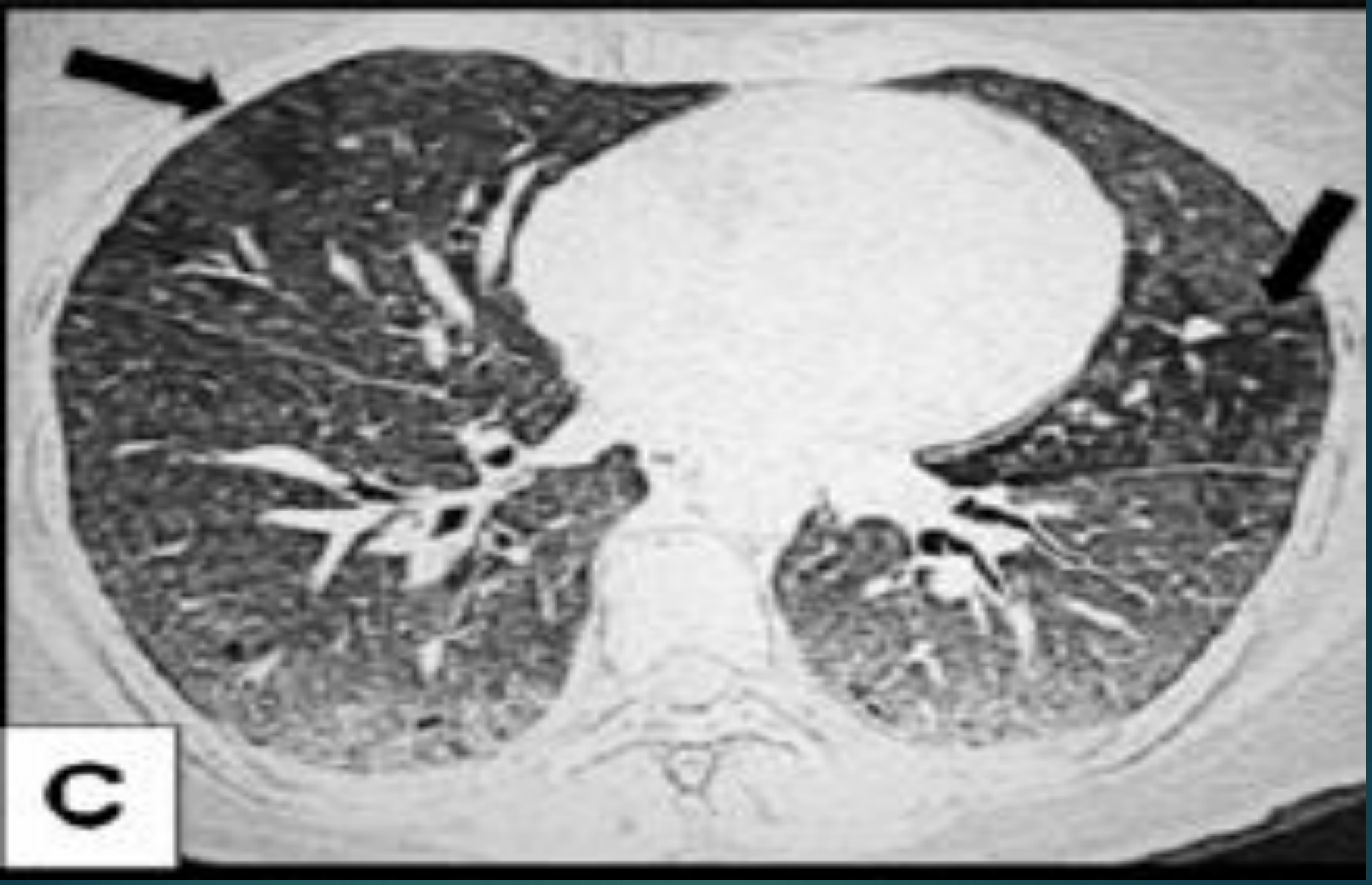
Antigen	Microorganisms: Thermophilic Actinomycetes, Fungi (e.g., Farmer's Lung; Water Damage)	Soluble Avian Proteins (e.g., BFL)
Exposure	Usually short and massive: ~ 750,000 actinomycetes spores per min	Recurrent: breed dozens of pigeons in a loft. Insidious: prolonged and low level (i.e., few birds in the domestic environment or down products)
Clinical behavior	Primarily acute/subacute: higher frequency of fever and recurrent episodes More recurrent systemic symptoms (chills, body aches)	Recurrent BFL: cough and mild exertional dyspnea, low-grade fever Insidious BFL: progressive dyspnea; clubbing
Lung function tests	Mild restrictive abnormalities that resolve Airflow obstruction (usually mild) seen in chronic disease	Restrictive pattern Hypoxemia at rest or exercise common
Lung imaging studies	Chest X-ray: frequently normal HRCT: ground glass opacities, predominating in the lower lobes, fine nodular shadowing Most frequent long-term sequelae: mild emphysema often sparing the upper parts of the lung	Chest X-ray: frequently abnormal HRCT: irregular reticular opacities, traction bronchiectasis and honeycombing superimposed to subacute changes (e.g., ground-glass opacities or nodules)
BAL	Neutrophilia Lymphocytosis (> 50%) with decreased CD4/CD8 ratio (< 1)	Eosinophilia or neutrophilia Lymphocytosis (< 50%) with increased (> 1.0) CD4/CD8 ratio
Lung biopsy	Small, poorly-formed noncaseating granulomas located near bronchioles Peripheral airways: proliferative bronchiolitis obliterans, characterized by fibroblast proliferation, and an organizing intraluminal exudate that occludes bronchioles from within	Ill-formed granulomas (may be difficult to identify) Fibrotic pattern: NSIP-pattern or UIP-like pattern. Peripheral airways: constrictive bronchiolitis
Outcome	Usually resolves Chronic exposure may lead to chronic bronchitis or emphysema	Poor, often progress to fibrosis



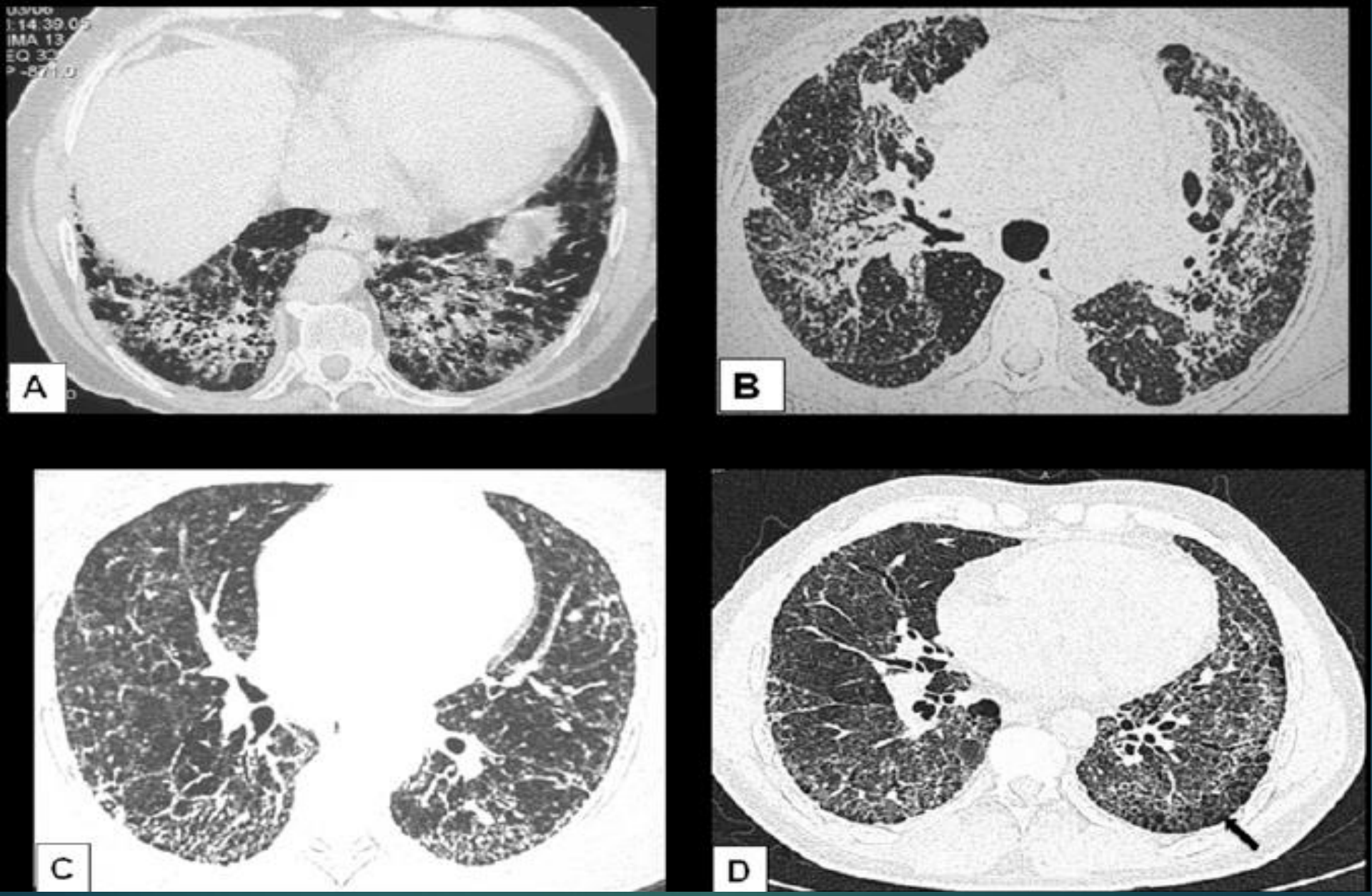
A 40-year-old woman exposed to birds. High-resolution computed tomography (HRCT) scan obtained through lower lungs shows numerous ill-defined nodules.



A 53-year-old woman exposed to birds. HRCT images show patchy ground-glass opacities, ill-defined nodules, and patchy areas of mosaic perfusion

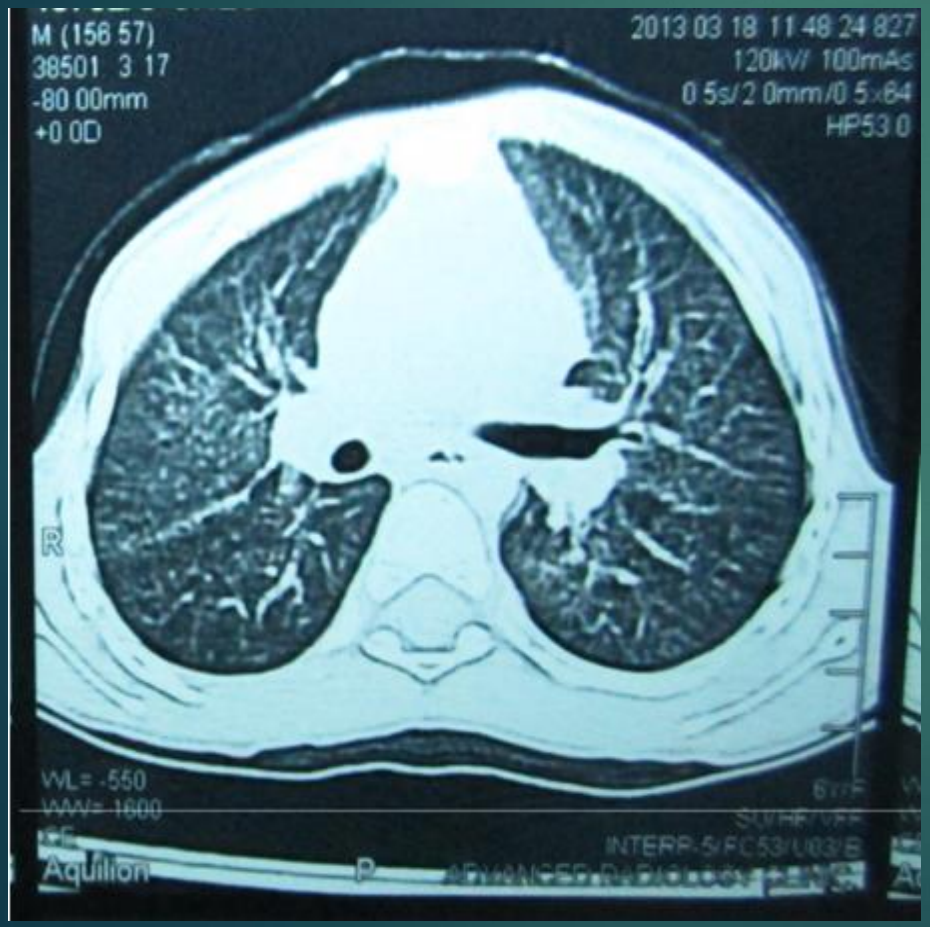


Same patient as in B. Expiratory image demonstrating the prominence of the attenuation differences supporting the presence of air trapping

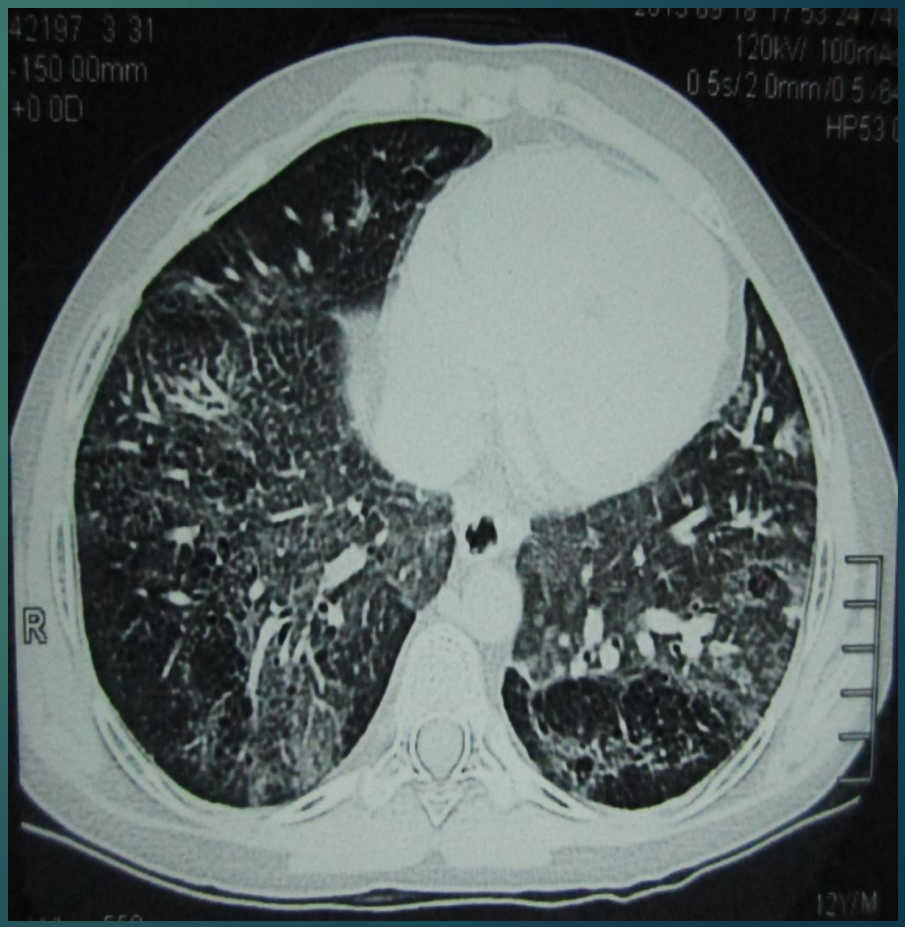


Chronic HP. Irreversible architectural distortion simulating the UIP like pattern

Avian antigen exposure in a 6 year old girl leading to development of subacute HP - demonstrating as ground glass opacity with nodules and air trapping on HRCT chest



Avian antigen exposure in a <u>11 year old boy</u> leading to development of Chronic HP - demonstrating as ground glass opacities with mosaic pattern and fibrosis on HRCT chest



Management

- Prevention
- Treatment

Prevention

- In high-risk environments (such as farming activities), education may prevent respiratory problems
- Improvements in work conditions and reduction in occupational exposure
- Major preventive measures (for e.g. mask wearing, increasing ventilation etc) should be recommended for primary and secondary prevention
- Also, it is important to minimize microbial or avian-antigen exposure by having a clean environment at home

Treatment

- Early diagnosis and antigen avoidance are key actions in the management of HP.
- Systemic corticosteroids represent the only recognized pharmacologic treatment for HP.
- corticosteroids hasten the recovery from the acute stage of HP, but have no beneficial effect on long-term prognosis
- The use of inhaled steroids is anecdotal. The treatment of chronic or residual disease is supportive.

Prognosis

- In general, patients with acute disease, if correctly and timely diagnosed and treated, have a good prognosis, and patients usually improve.

Prognosis (continued)

- By contrast, patients with subacute/chronic HP (in particular those with bird fancier's disease) often progress to irreversible pulmonary fibrosis and may die within a few years after diagnosis.

- Pulmonary hypertension occurs in approximately 20% of patients with chronic HP and is associated with a greater risk of death.


Set the birds free to fly
Their abode is the sky
JAZAK'ALLAH