INTERSTITIAL LUNG DISEASES - ILD

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DEFINITION OF ILD

- INTERSTITIAL LUNG DISEASES (ILD) ARE

A HUGE HETEROGENEOUS GROUP OF LUNG DISEASES WHOSE

COMMON CHARACTERISTIC IS WIDESPREAD INFILTRATION INTO THE LUNG INTERSTITIUM.

DEFINITION

Interstitial lung disease is a general category that includes many different lung conditions.

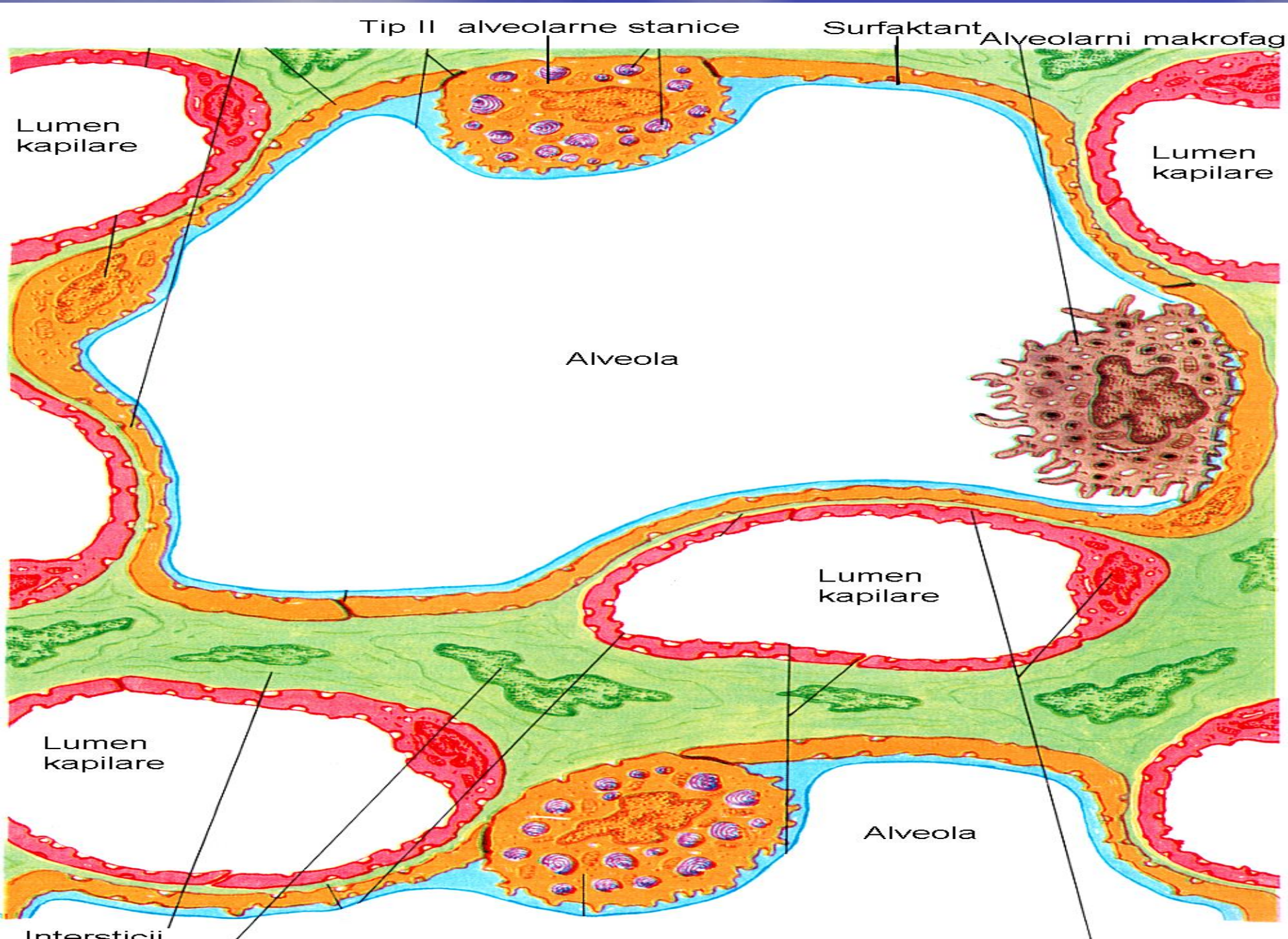
All interstitial lung diseases affect the interstitium (inter-space of the lung)

The interstitium provides support to the lungs' microscopic air sacs (alveoli). Tiny blood vessels travel through the interstitium, allowing gas exchange between blood and the air in the lungs.

Normally, the interstitium is so thin it can't be seen on conventional chest X-ray, but it can be seen on CT- HRCT/MSCT scan.

STRUCTURE OF ALVEOLARCAPILARY MEMBRANE

1. Epithelial cells (pneumocites type 1 and 2)
2. Surfactant substance (factor)
3. Endothelial cells of blood and lymphatic vessells (capillaries)
4. Collagen type 1, collagen type 3, fibronectin, elastic fibers and proteoglycens that are in the interstitial matrix between the alevolar and vessels walls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INFILTRATION of LUNG PARENCHYM CAN BE BY:

- Inflammatory cells
- Malignant cells
- Connective tissue or/and
- Collagen tissue
- Fluid (cardiac edema, toxic edema, etc.
- Blood (traumaof chest, toxic damage of blood vessels, vasculitis)

- A many number of particles (factors) can cause diffused interstitial lung disease such as:

- cigarette smoke
- organic dusts (causing extrinsic allergic alveolitis)
- inorganic dusts (causing pneumoconioses)
- gases or fumes (smog)
- drugs
- radiation
- infection
- other pollution

INHALED IRRITANTS

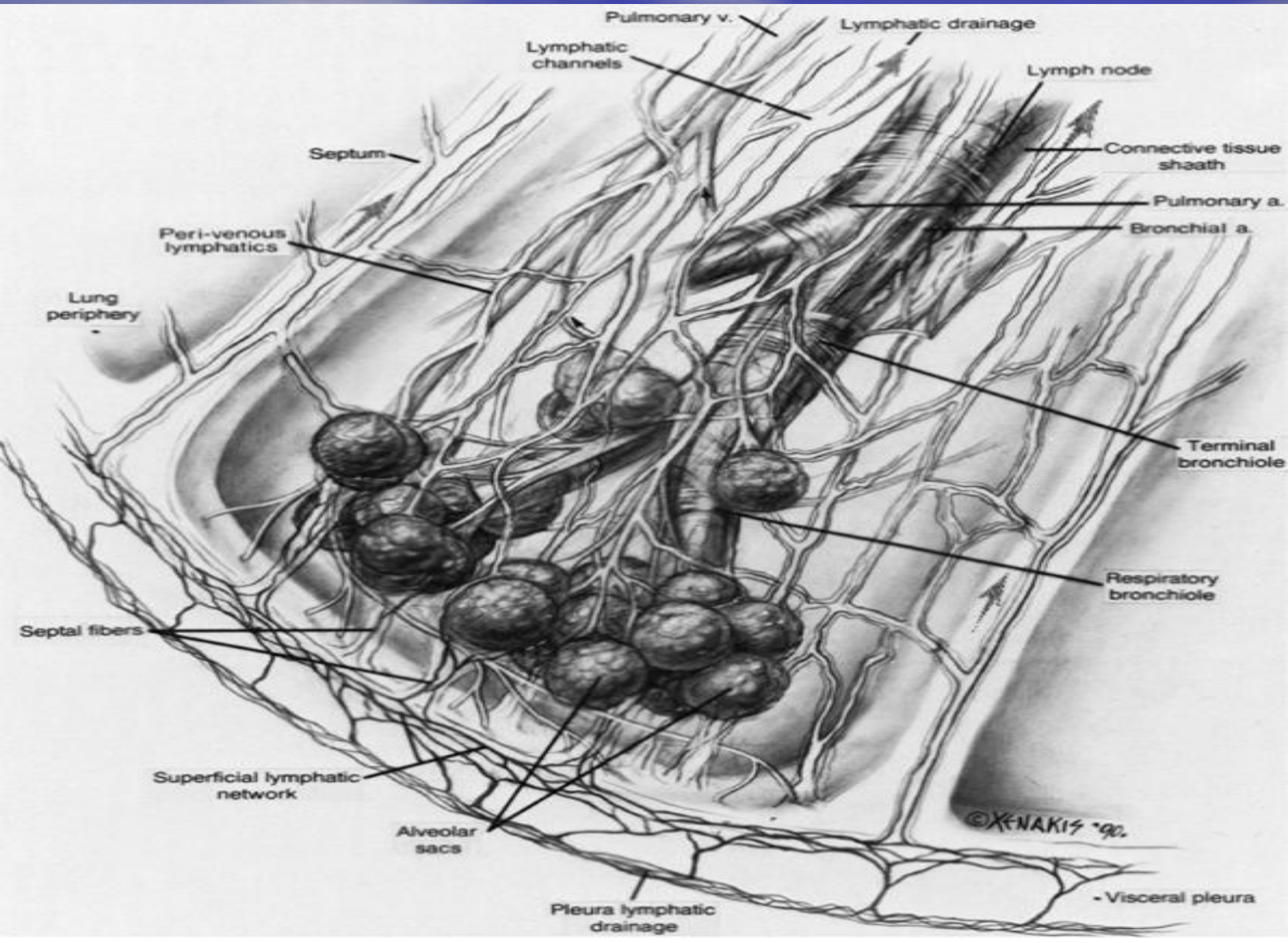
Exposures **at work** or during **hobbies** can also cause some interstitial lung disease. These irritants include:

- Asbestos dust
- Silica dust
- Talc
- Coal dust, or various other metal dusts from working in mining
- Grain dust from farming (“farmer´s lung”)
- Bird,s proteins (such as from exotic birds, chickens or pigeons-”pigeon´s lung”- and other animals)

- All forms of interstitial lung disease cause thickening of the interstitium (interspace of lung). The thickening can be due to inflammation, scarring, or extra cell fluid (edema).
- Some forms of interstitial lung disease are short-lived; others are chronic and irreversible diseases, that last a lifetime.

- Consequence of pathological infiltration of interstitium is:

INTERFERING passage of respiratory gases through alveolar-capilary membrane: O_2 into and $C0_2$ out of arterial blood - -> therefore leads to respiratory failure - respiratory insufficientia (RI).


Pulmonary v.
Lymphatic drainage
Lymphatic channels
Lymph node
Septum
Connective tissue shaath
Pulmonary a.
Bronchial a.
Peri-venous lymphatics
Lung periphery
Terminal bronchiole
Respiratory bronchiole
Septal fibers
Superficial lymphatic network
Alveolar sacs
©XENAKIS '90.
Visceral pleura
Pleura lymphatic drainage

Diagnosis and classification of ILD can be complex, and the combined efforts of clinicians, radiologists, and pathologists can yield an accurate diagnosis.

More than two third (2/3) of these diseases is unknown etiology.

The division of ILD is difficult and complicated, but practical classification for clinicians is:

CLASSIFATION OF THE ILD

1. **Known etiology** (interst. Pneumonia caused by: Mycoplasma, Coxiella p., Chlamydia, Legionella p., TB, pneumoconiosis)

2. **Unknown etiology:** huge group of ILD. More frequent is sarcoidosis and idiopathic pulmonary fibrosis (70%)

1. ILD **with granulomas in the lung** (Sarcoidosis, Wegener g., TB, Brucelosis, etc.)

2. ILD **without granulomas** (IPF, Azbestosis, Eosinoph. p.)

CLASSIFICATION

pathological fin.. In the lung	known etiology	unknown etiology
Interstitial inflammation and fibrosis **without** granulomas	**azbestosis** fungi, gases *Drugs* (antibiotics, citostatics), irradiation, neoplazma (lymphangiosis) **hearth diseases,** aspiration pneumonia	**IPF** Collagen tissue diseases Haemosiderosis, **Goodpasture syndrome** Alveolar pulmonary proteinosis Ankilozni spondylitis Lymphatic infiltration **Eosinophilic plumonary infiltrates**
Interstitional inflammationes **with** granulomas	**Hipersensitiv pneumonitis** **dust:** Beriliosis (cooton) Silicosis (silicium-glass **infection- My.TB** (speciphic granulomas)	**Sarcoidosis** Hystiocitosis X Eosinophyllic granulomas Vasculitis granulomatosus **Wegener gran. - WG** **Churg- Strauss sy.** Alergic granulomatous

FOR DIAGNOSIS IMPORTANT:

- ANAMNESIS (medical history)
- PHYSICAL EXAMINATION OF PATIENT (status praesens)
- RADIOLOGICAL FINDINGS
- PULMONARY FUNCTION TEST
- RESPIRATORY GASES (O_2 and CO_2) IN ARTERIAL BLOOD
- FIBER-BRONCHOSCOPY with TBLB (transbronchial lung biopsy) and BAL
- VATS or open lung biopsy

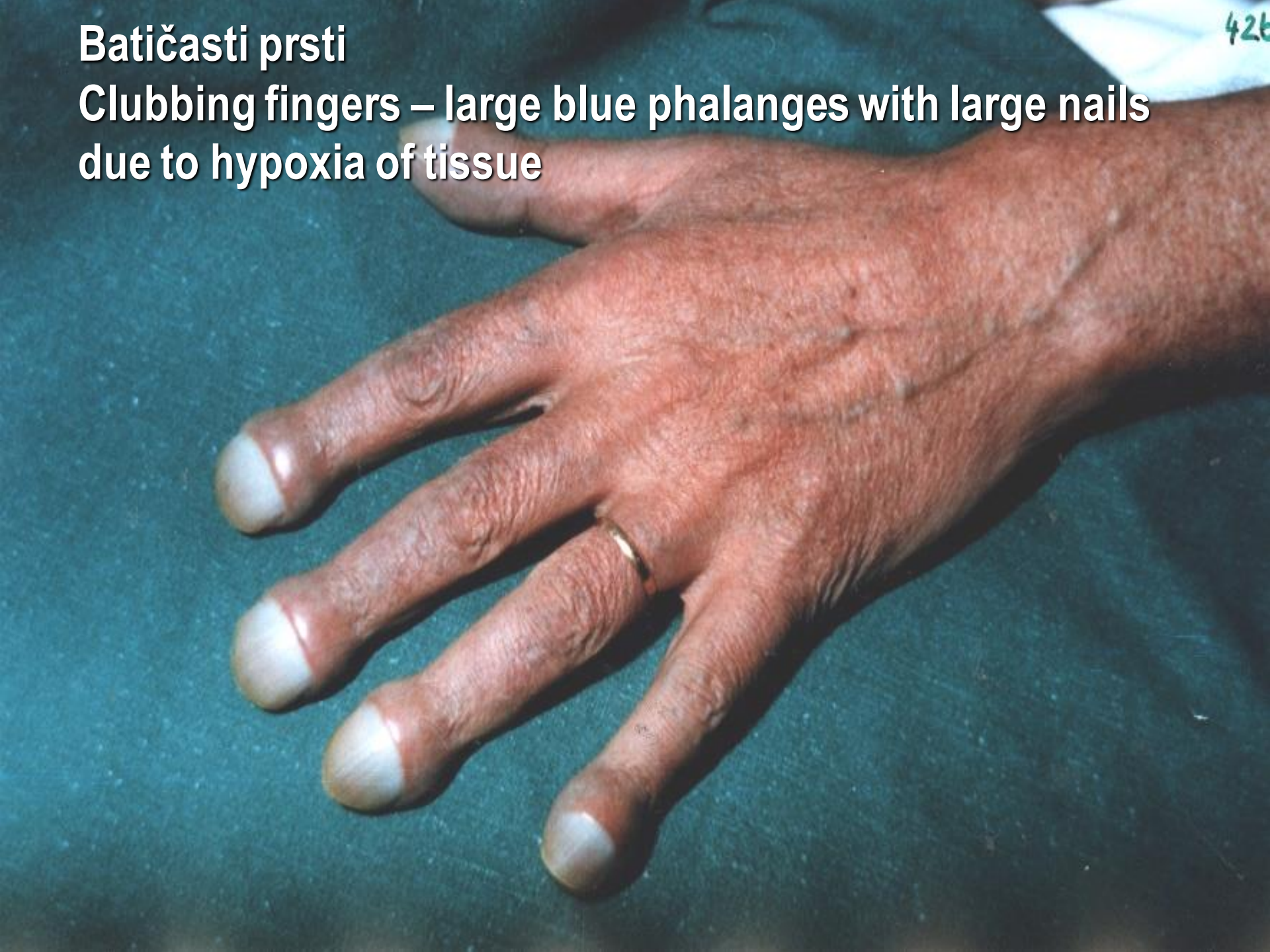
ANAMNESIS (MEDICAL HISTORY)

- We must take previous medical history - previous diseases: collagen tissue dis. (RA, LE, SS), malignant diseases, use of drugs, AIDS, etc.)
- Employment history (shipyard, azbestosis factory, miners,etc.)
- Environmental exposition: organic and inorganic dust, fumes, toxic gases, and other pollution.
- Familly history-anamnesis: TB, sarcoidosis, IPF, RA, LE, SS, and other collagen and familly diseases (genetic inherited diseases)

PHYSICAL EXAMINATION AND SYMPTOMS

Patients complain (komplein) of the following symptoms:

- shortness of breath-Dyspnea-tahypnea, cough, fatigue (fatig), sweating. Cyanosis: peripheral and central
- **LUNG AUSCULTATION-** rales(crackles) at the end of inspirations (crepitations) at both of the lung, rare bronchial rhonchi in the expiration
- In terminal stage of pulmonary fibrosis : “velcrorales”-fine crackles in inspiration - asynchronic sencventional sound in the inspiration. Typical for IPF
- Clubbing fingers


Batičasti prsti
Clubbing fingers – large blue phalanges with large nails due to hypoxia of tissue

- Heart condition
- Perypheral lymphonodes, splenomegalia (spleen), hepatomegalia (liver)
- Heavy breathing with additional respiratory muscles

RADIOLOGICAL EXAMINATION OF THE CHEST

1. **Conventional x-ray image of the chest (P-A and lateral picture)**

2. **MSCT/HRCT scan of the chest: (**multislice spiral CT/high resolution CT)

3. **MSCT angiography of pulmonal arteria – If pulmonary embolia is suspected (especially recurrent PE)**

RADIOLOGICAL FINDING

Practical approach is to divide these into four patterns:

1. Consolidation of the lung parenchym
2. Interstitial infiltration of the lung
3. Nodules or masses in the lung
4. Atelectasis: - collapse a part of the lung due to a decrease in the amount of air in the alveoli resulting in volume loss and increased density.

RADIOLOGIC IMAGE OF LUNG IN ILD

- Diffuse **interstitial infiltration** or **opacification** -**"ground glass"** or/and small **nodules** - They have a perilymphatic and subpleural distribution

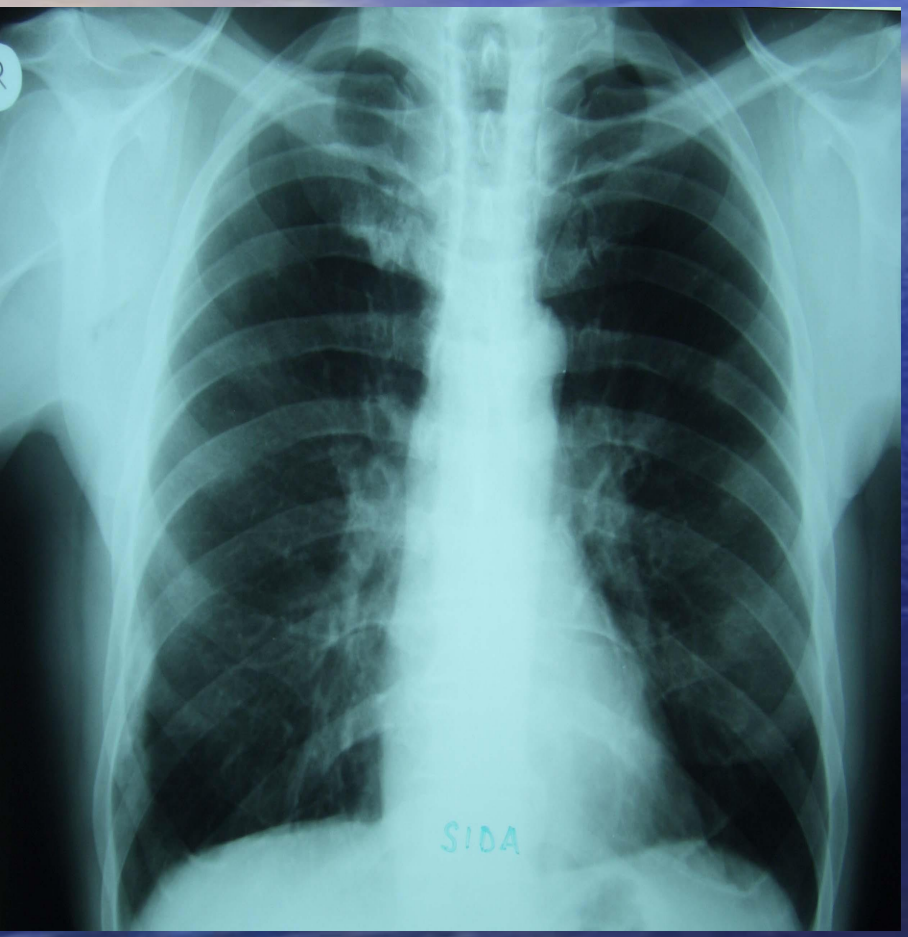
- Infiltrations -Changes in the lung are the most common in the upper and middle parts of the lung

- **Lymphadenopathy :** can be found in left or right hilus or both, and paratracheal, often with calcifications in lymphonodes.

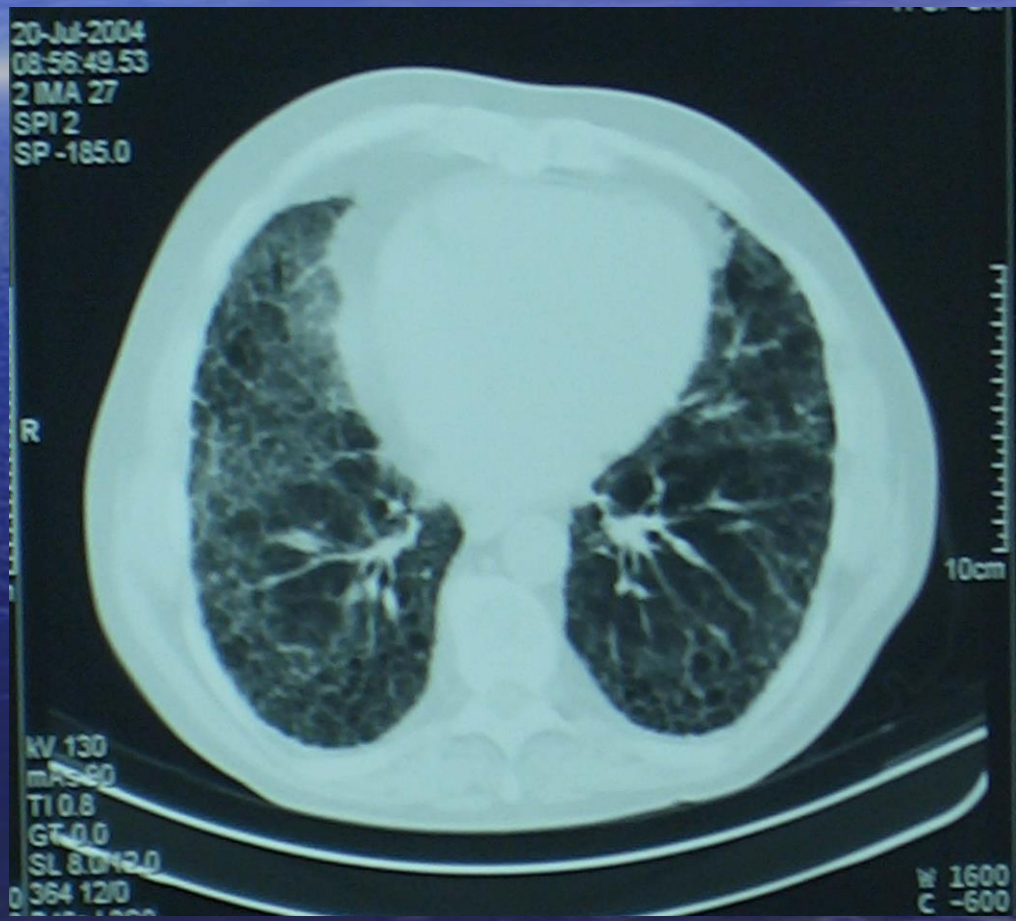
COMPUTOR-TOMOGRAPHY

- **HIGH-RESOLUTION CT-SCAN:** If interstitial lung disease is suspected, based on medical history and conventional x-ray picture, CT scan is used to confirm ILD.
- CT can improve the image of the interstitium, especially with high resolution-CT or multislice-CT scan (MSCT)
- The CT scan increases ability to detect interstitial lung diseases.

X-ray picture

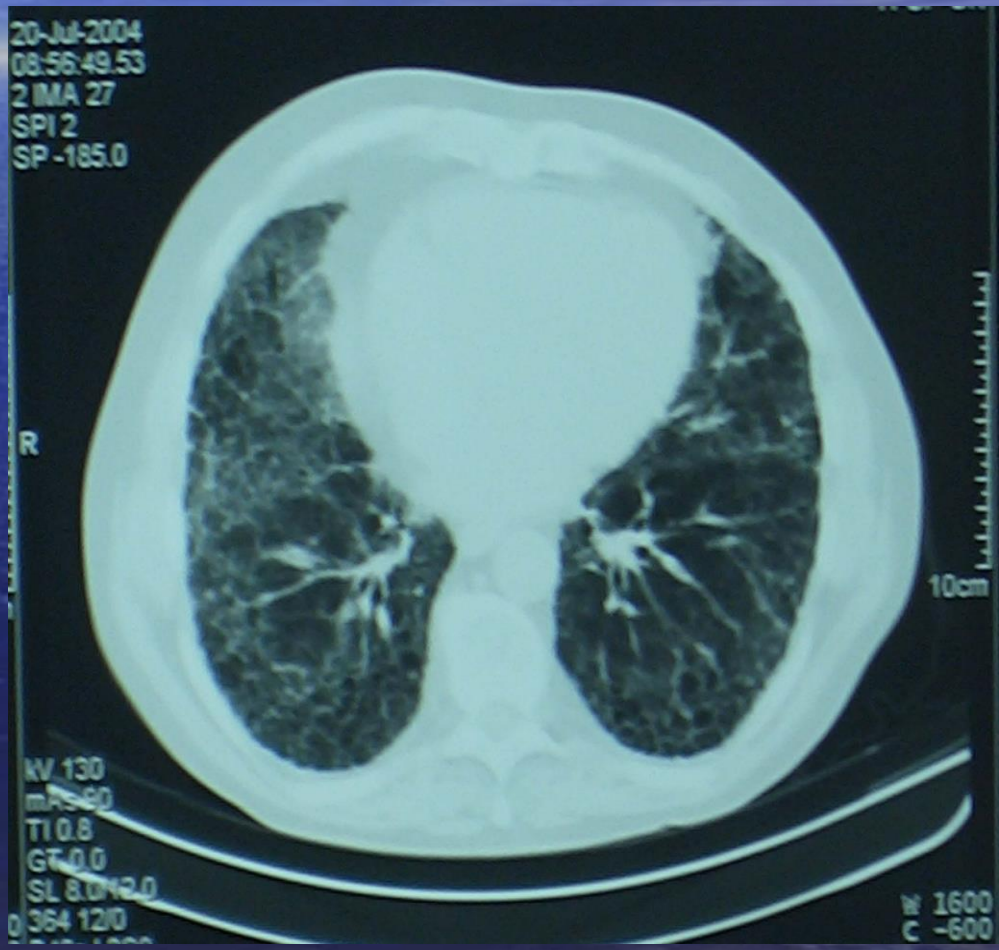


MSCT scan



Computerized tomography (CT) scan.

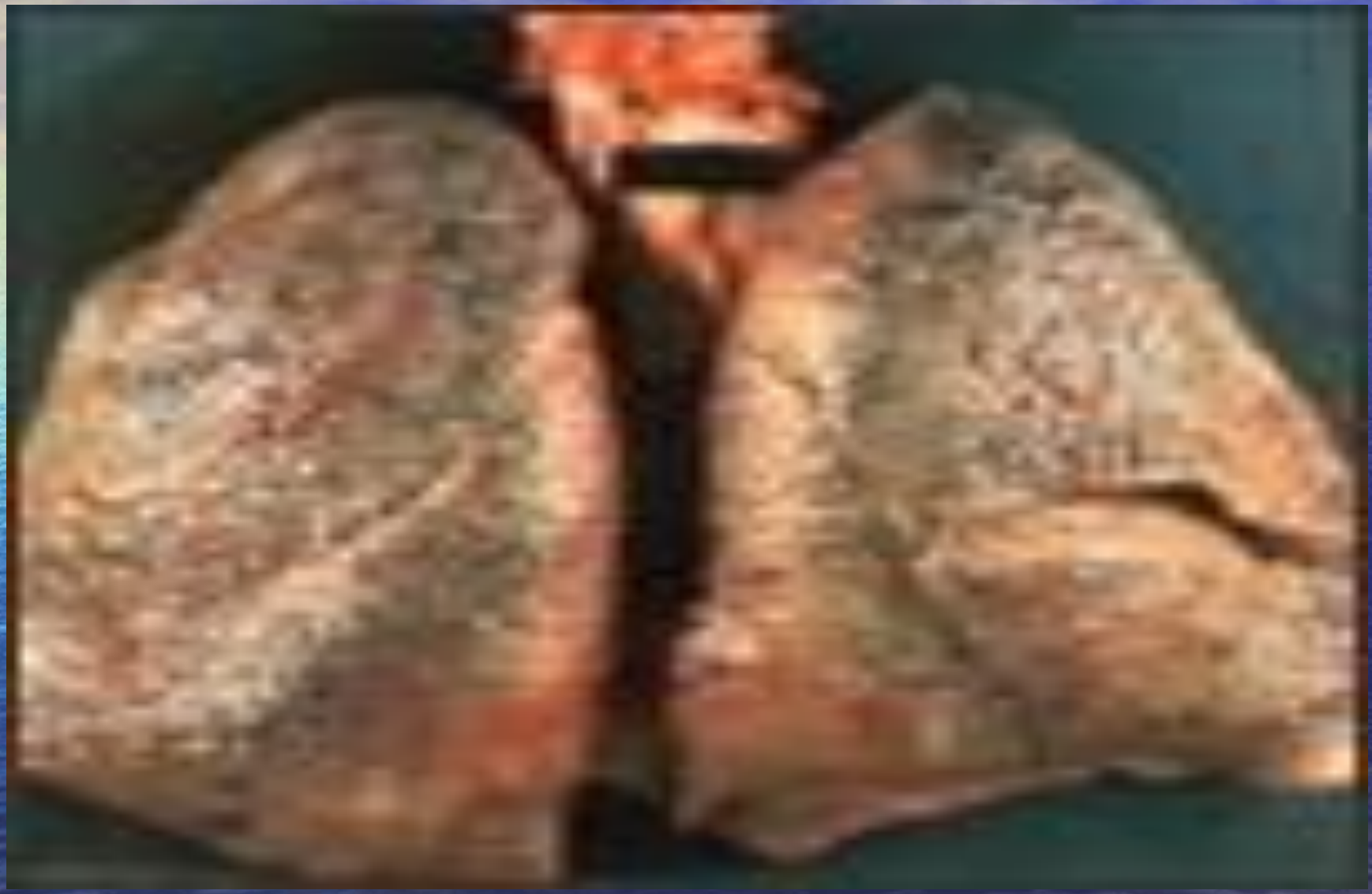
- A high-resolution HRCT or MSCT scan can be particularly helpful in determining the extent of lung damage caused by interstitial lung disease.
- It can show details of the ground-glass opacities and fibrosis, which can be helpful in narrowing down the diagnosis



PULMONARY FUNCTION TESTING

- **RESTRICTIVE VENTILATORY INTERFERENCE, DEFECT** is charecteristic of all ILDs , because the lung have lost elasticity, (lung is solid)
- **REDUCED DIFFUSING CAPACiTY OF CO (DLco/TLco)** - typical for ILD because. Inter-space of lung is infiltrated with various cells, connective and /or collagen tissue, fluid, fibrosis, etc. Alveolar membrane is tight or thickened and with reduced diffusion to exchange of respiratory gases. The result is hypoxemia (respiratory failure).
- **HYPOXEMIA** = (respiratory insuffitientia)

1. In the beginning of disease manifested only in exercise - latent hypoxemia, can be confirmed with 6-MWT
2. In advanced diseases hypoxemia manifested in rest – manifest hypoxemia

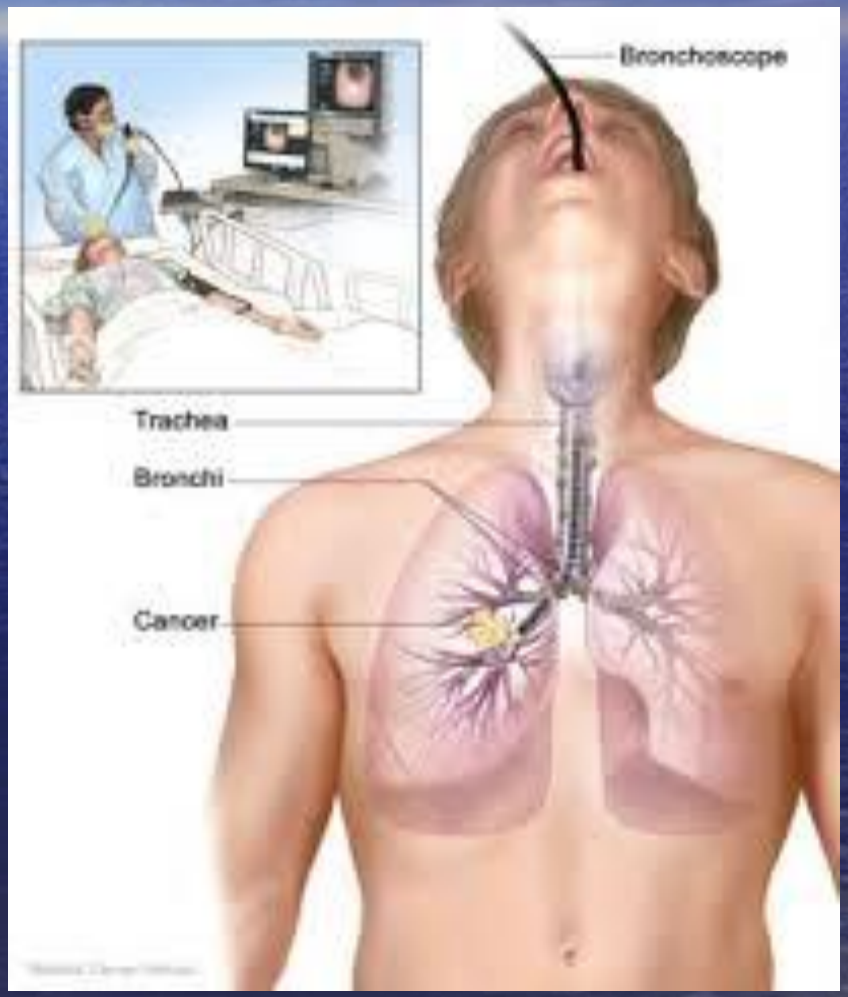


Lung autopsy of coal worker – hard-solid lung without elasticity

BRONCHOSCOPY

— — using a small, flexible bronchoscope that's passed through mouth or nose and enters the lung. With a small forceps take several pieces of tissue for histological examination.

Sometimes samples are too small for an accurate diagnosis of ILD.



DIAGNOSIS OF ILD

BRONCHOALVEOLAR LAVAGE- BAL is a procedure with a flexible-bronchoscope, with which we enter into the lung, and inject distilled water end immediately suctions it out. The solution that's withdrawn contains cells from air sacs.

BAL often may not give enough information to diagnosis of ILD, but it is good for prognosis and monitoring treatment of disease.

HISTOLOGY DIAGNOSIS

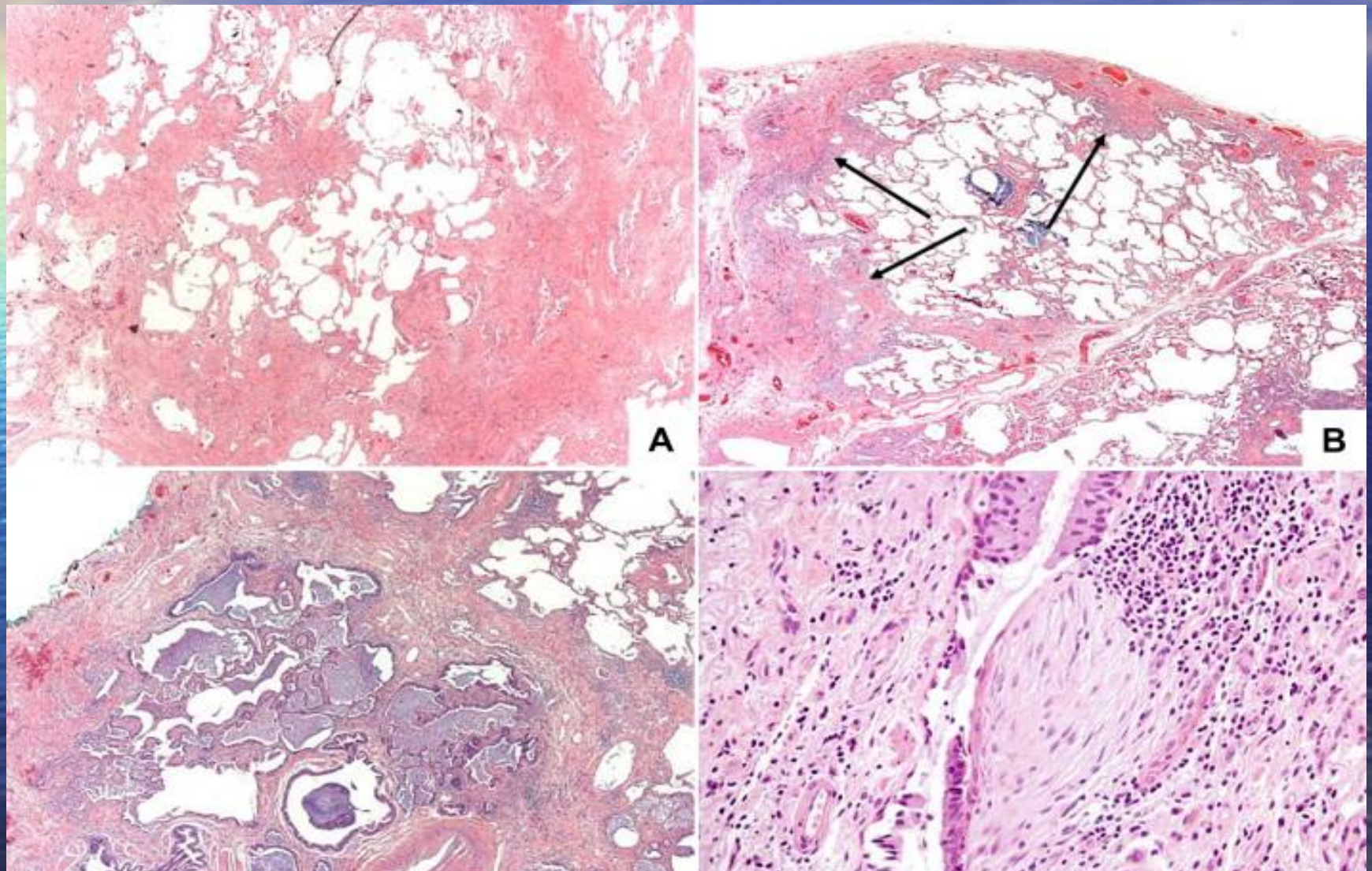
- is very important for accurate dg.

If we do not have a diagnosis with TBLB, we must do:

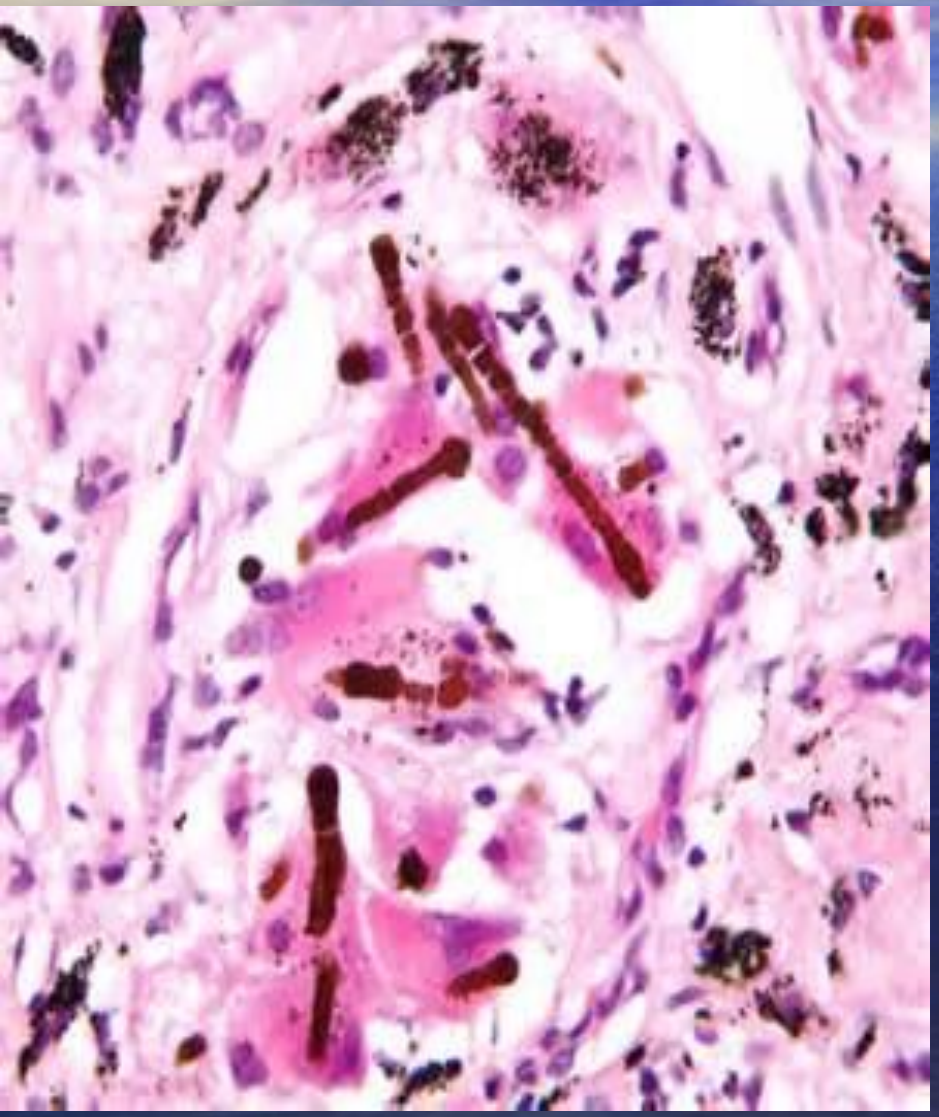
1. **VIDEO-ASSISTED THORACOSCOPIC SURGERY (VATS):** with an instrument passed through the intercostal space to enter the pleural cavity and taken several pieces of lung tissue witch are adequate for pathologic analysis, for accurate diagnosis.

2. **OPEN LUNG BIOPSY (THORACOTOMY)**: In some cases, traditional surgery with a large incision in the chest –

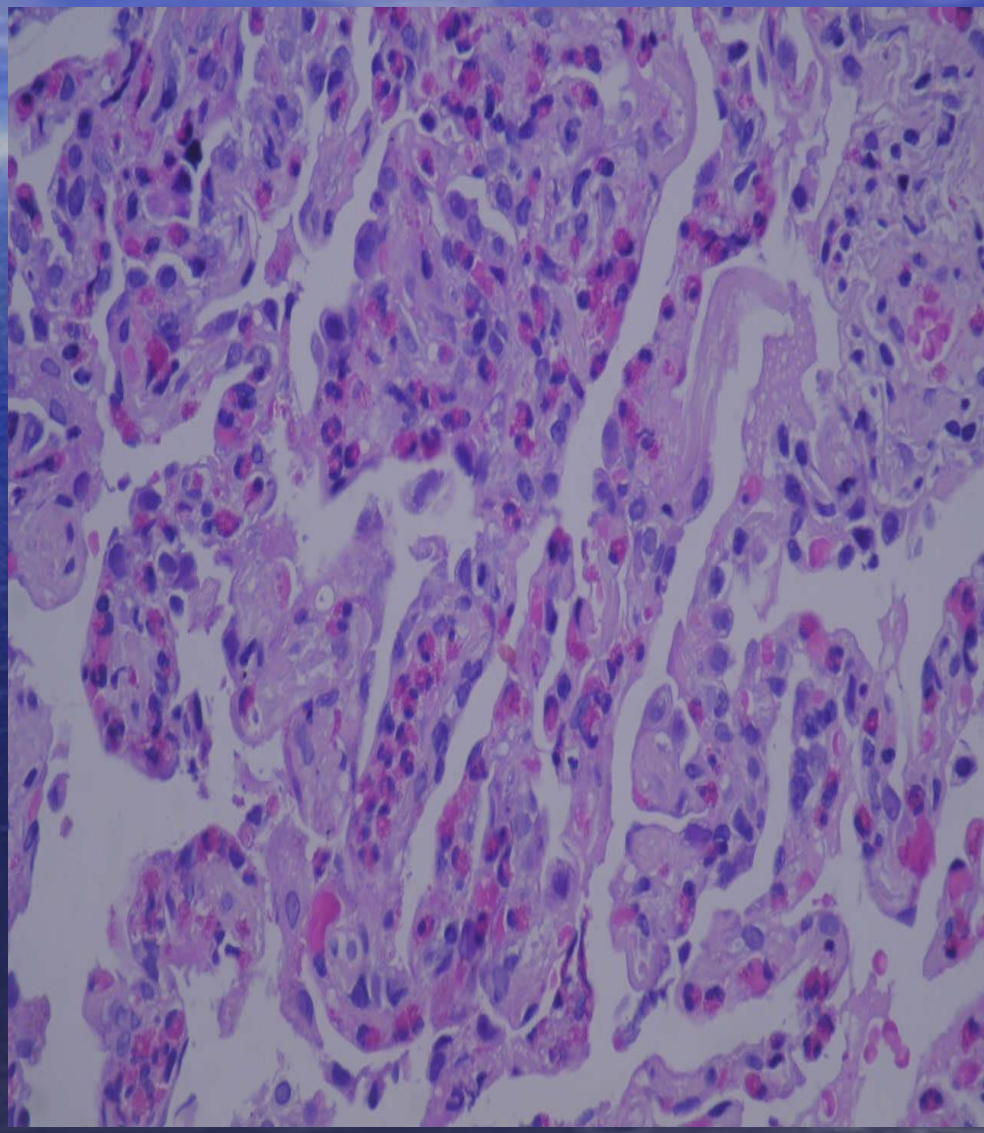
HISTOLOGICAL FINDINGS ON LUNG BIOPSY IN DIFERENT STAGES of ILD



Asbestosis,"asbestos bodies"



Eosinophillic infiltration-CEP
Lung tissuse by TBLB



TREATMENT OF ILD

- Treatments for interstitial lung disease vary according to the type of interstitial lung disease and its cause.

  ANTIBITICS

- BUT-2/3 unknown etiology- because treated them with IMMUNOSUPRESSIVS drugs:

1. CORTICOSTEROIDES (glucocorticoides)
2. CYTOSTATICS - low dose
3. BIOLOGICAL DRUGS: anti -TNF- alfa factor -infliximab,

anti-TGFbeta factor- pirfinidone, nintedanib. Thay are new medication for ILD unknow etiology:

ANTIBIOTICS

- These are effective treatments for most interstitial pneumonias (Mycoplasma, Chlamidia, Coxiella, Legionella, etc).

Azithromycin (Zithromax) and levofloxacin (Levaquin) eliminate the bacteria that cause most interstitial pneumonias.

Viral pneumonias usually resolve on their own.

Fungal pneumonias are rare, but can be treated with antifungal drugs.

CORTICOSTEROIDS:

CORTICOSTEROIDES - CS:

Corticosteroids like prednisone and **methylprednisolone** reduce the activity of the immune system. CS reduces the amount of inflammation in the lungs and the rest of the body.

- ANTIMALARIC: chloroquin
- CYTOSTATICS-low dose:

  - azatyoprin, cyclophosphamid, methotrexat, cyclosporin

OXYGEN: at the terminal phase of disease-in RI

- **Inhaled oxygen:** In patients with low oxygen blood levels due to interstitial lung disease, inhaled oxygen may improve symptoms and improve Q of L.
- Regular use of oxygen might also protect the heart from damage caused by low oxygen levels.
- Transplatation of the lung

IDIOPATHIC INTERSTITIAL PNEUMONIA

1. Acute idiopathic inetrstitial p.: AIP – Hamman-Rich
2. Bronchiolitis obliterans organisation pneum. **(BOOP)**
3. Non-speciphic interstitial pneum.- **NSIP**
4. Lymphocytic interst. pneum. – **LIP**
5. Desquamat interst. pneum.- **DIP**
6. Usual interst. pneum. – **UIP**

BOOP – (COP=old name)

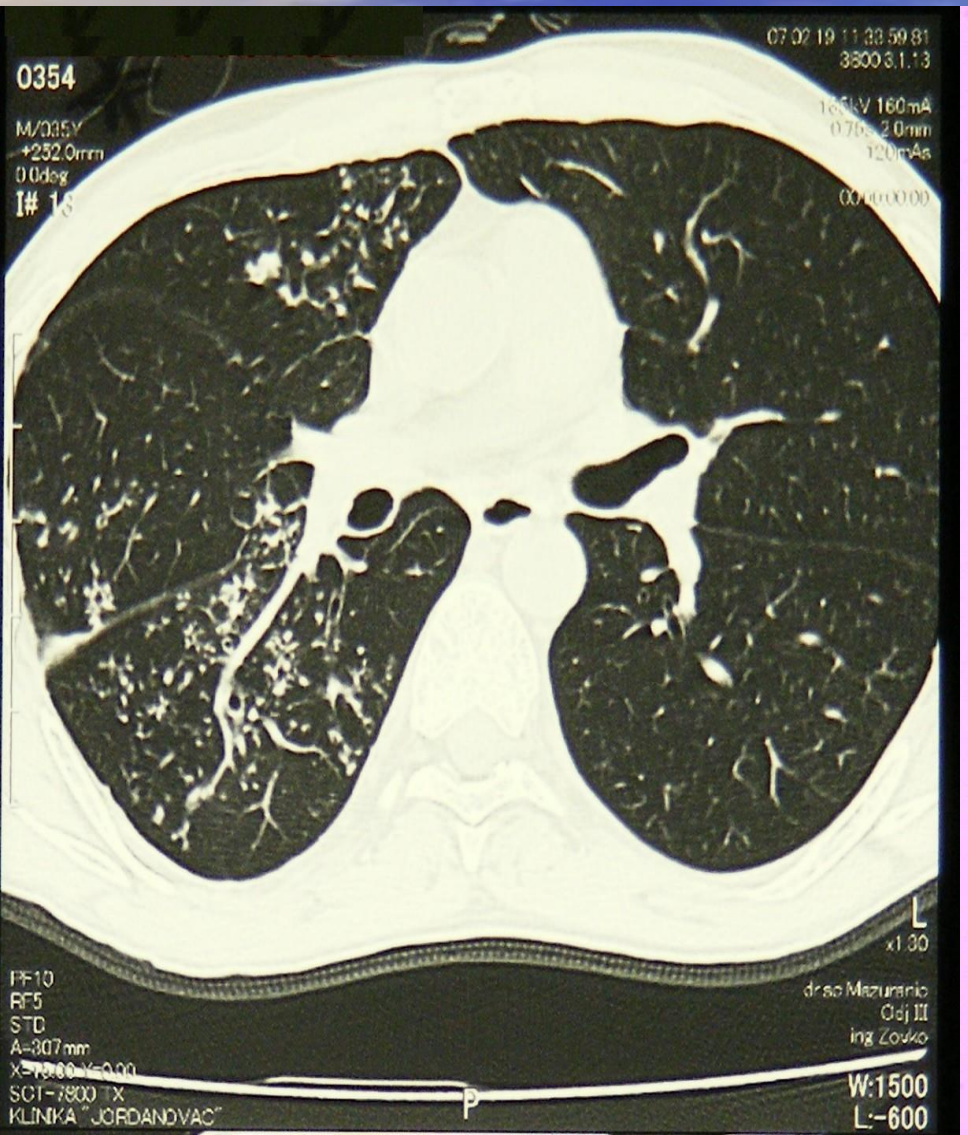
- Bronchiolitis obliterans organisation pneumonia **BOOP**
- Charecteristics: Granulation tissue can be found within the lumen of small airways (alveoli, terminal and respiratory bronchioles)
- BOOP usually found after lung infections caused by atypical bacteria (M. Pneumoniae, C. Pneumoniae, Legionella, etc) and different of viruses
- **Treatment: CS** - in 85% -good prognosis

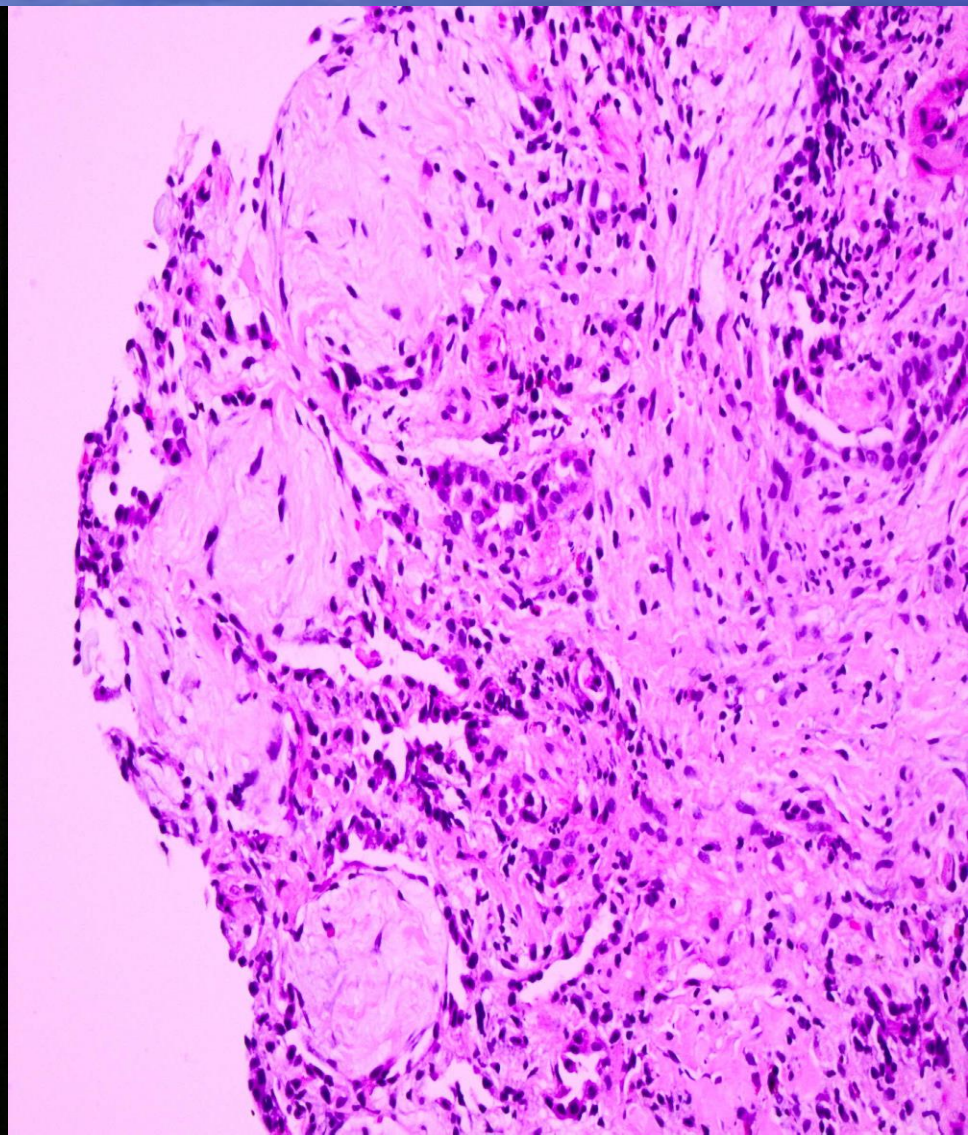
  Quit smoking !

  Often recurrent

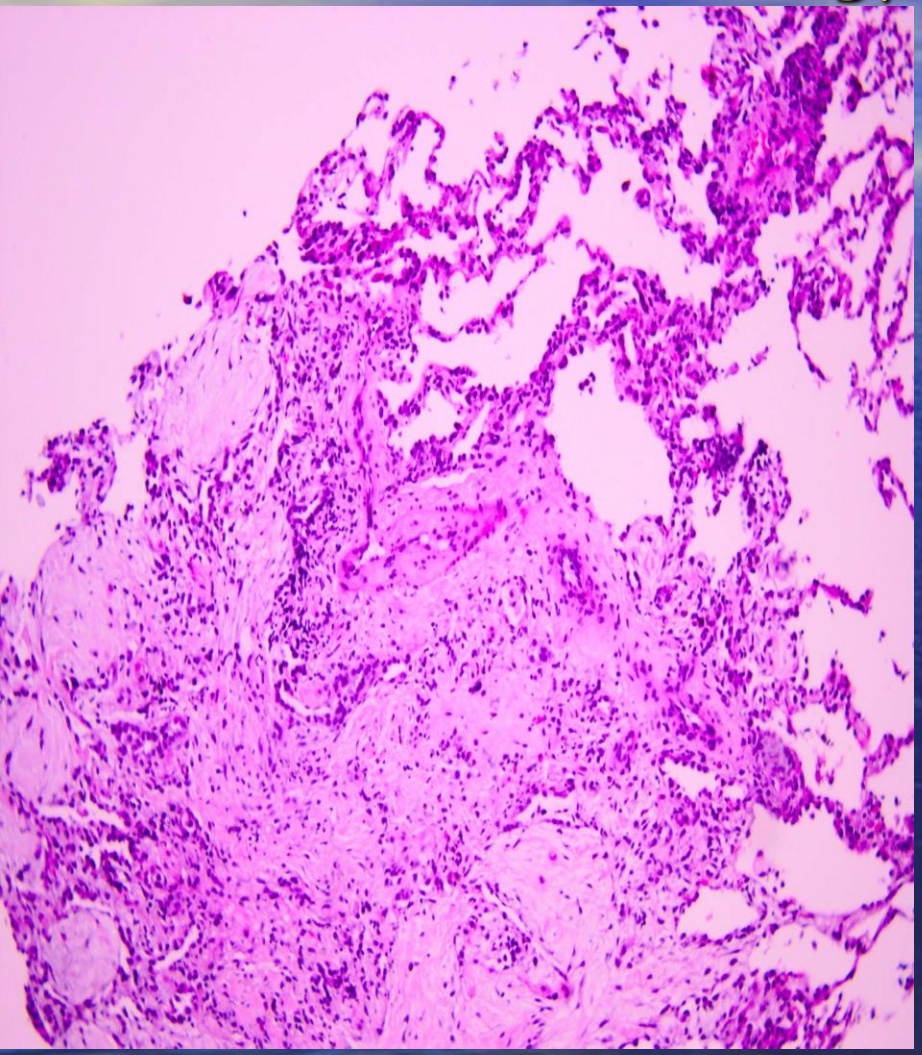
“Tree-in-bud” sample
(“Pupanje drveta”)

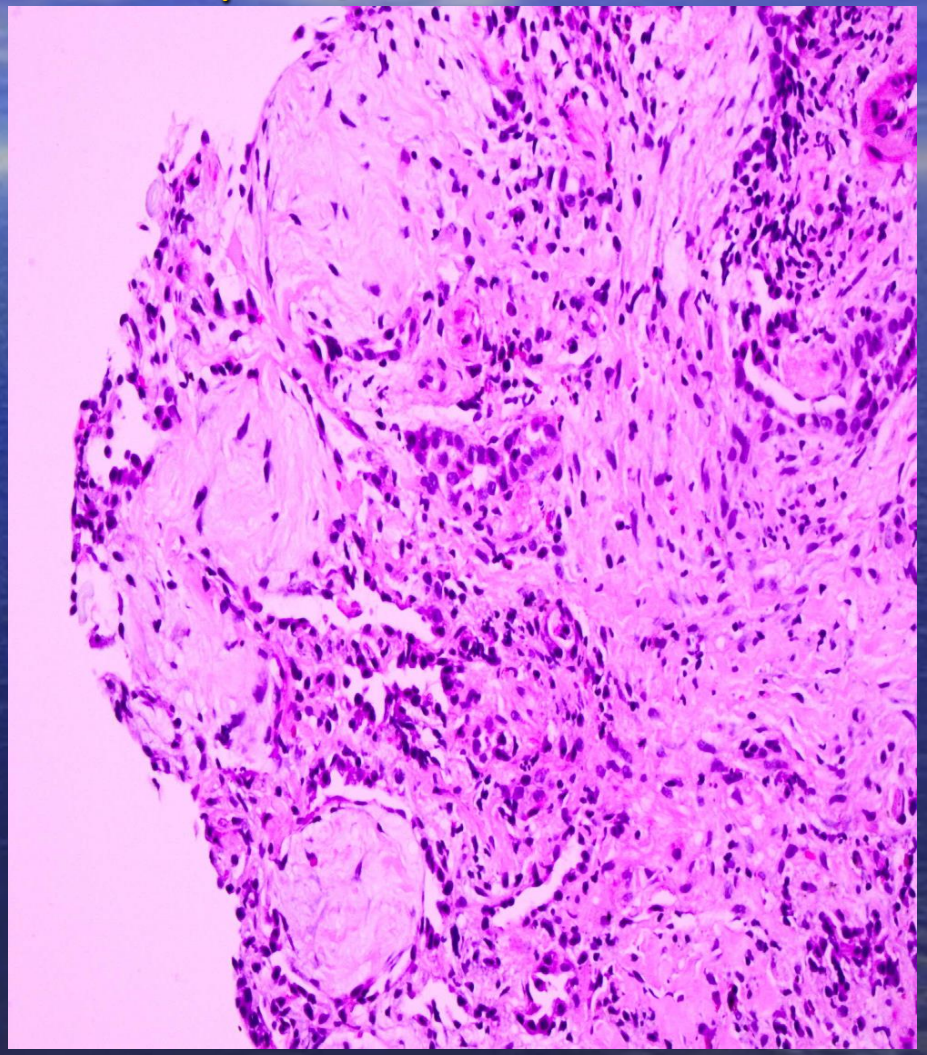
Image of histology of BOOP
lung tissue obtained by biopsy -
granulation tissue in bronchioli





BOOP – pathology findings (histology-KBC Split)





LIP - LYMPHOCYTIC INTERST. PNEUMONIA

- Charecteristic: The accumulation mature lymphocytes in the lung interstitium
- LIP is more common with: AIDS, Sjogren's syndrome, drugs intoxicity, etc

DESQUAMATE INTERSTITIAL PNEUMONIA - DIP

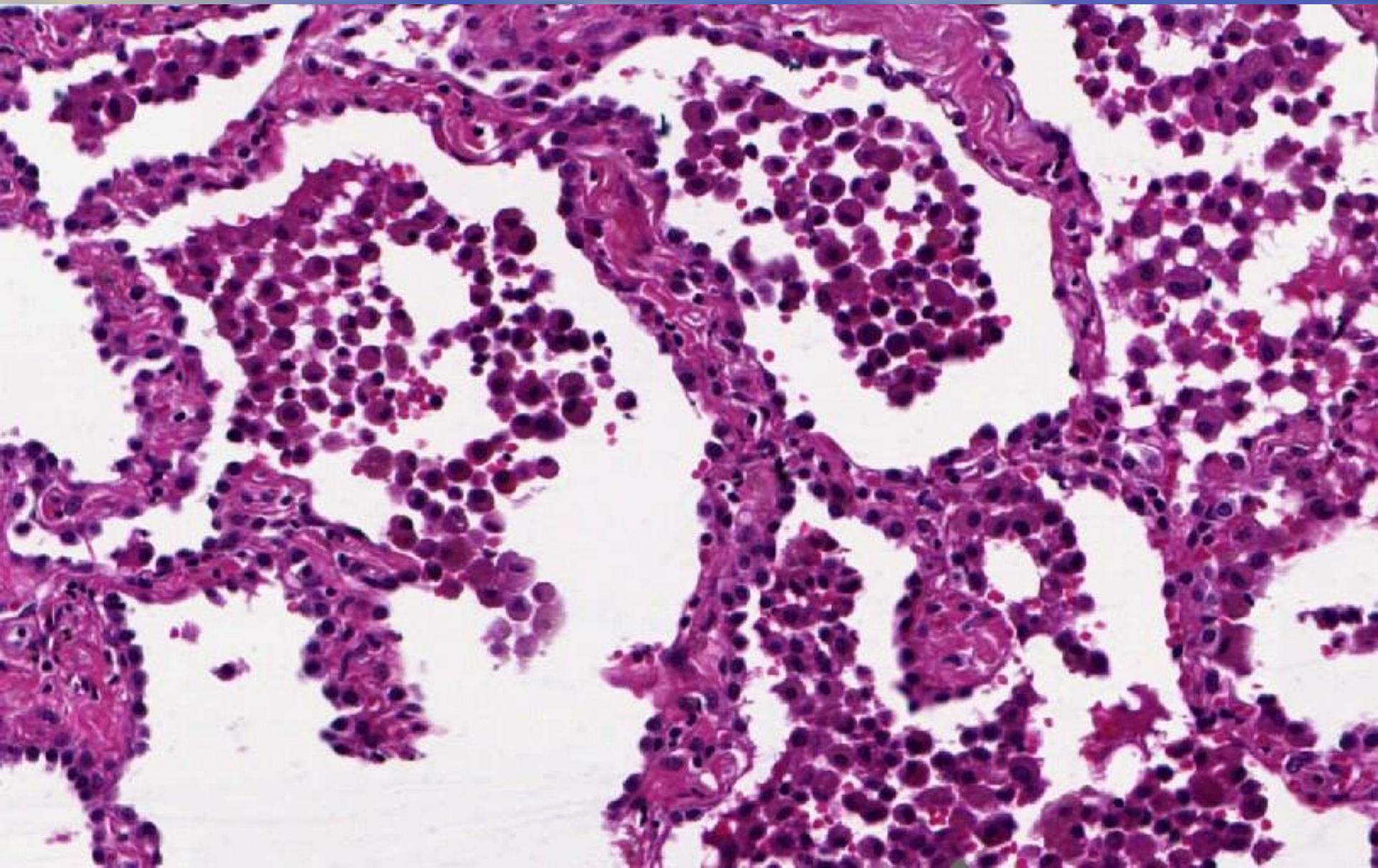
Typical finding: Desquamation of pneumocytes in alveoli and other small airways

- More common in young people

Symptoms:

- Cough
- shortness of breath, fatigue, dyspnea
- CHEST X-RAY: shadows "frosted" glass in the middle and lower lung fields
  Prognosis is good.
- **Th:** corticosteroides (CS)

DIP- patohistological finding



IDIOPATHIC PULMONARY FIBROSIS - IPF

1. **Hamman-Rich:** acute form

2. **IPF:** chronic form

ACUTE IDIOPATHIC PNEUMONIA - HAMMAN RICH

- The disease is very rare, acute, fulminant form of lung damage in healthy persons (darvel).

- Symptoms: fever, dry cough, progressive dyspnoea
- X-ray image of the chest: both sides massive interstitial infiltrates - "ground glasses").

- **Histological finding:** respiratory distress with hyaline membranes on alveoles, hyperplastic and atypical pneumocytes type II.
  Fast onset of ARDS. **Mortality** >70% within 3 months.

IDIOPATHIC PULMONARY FIBROSIS - IPF

IPF is the specific form of non-specific chronic interstitial pneumonia (NSIP), unknown etiology.

IPF - generated sequential acute damage to the lung parenchyma, resulting in the progressive creation of fixed pulmonary fibrosis, which interferes with the normal architecture of the lung and pulmonary function ➔ ultimately leading to pulmonary hypertension and – pulmonary heart (cor pulmonale).

EPIDEMIOLOGY ET ETIOLOGY

- Epidemiology:

PREVALENCE: 20/100000 male and 13.2 female

Prevalence increases at oldest > 65 ys.o.- 168-180/100000 male

Survival: is poor, only from 2 to 5 years since Dg.

- Men affected twice more likely.

PATHOGENESIS:

- The cellular response to the unknown factor in the lung injury is too strong:
- The immune response to the unknown antigen is similar Th_2-type immune response in the lung tissue.

- Interstitial lung tissue in IPF is infiltrated by:

eosinophils cells, neutrophils, mast cells, increased different cytokines –(TNF-α TGF- ß1), IL-4 and IL-13 , other patological susptance.

SYMPTOMS AND SIGNS OF IPF

- **Dry cough** and **progressive dyspnea (dyspnoa)** last **6** months.
- General symptoms: fever, fatigue, sweating, loss of weight

- Clubbing fingers: in 25-50% of patients - (very often)
- Cyanosis

Auscultation : breathing sound is diffused weakened , we can hear crackles in the late inspiratory (crepitations) , than, in late stages of the IPFcan be heard expiratory bronchial noises - sequential bronchial noises –"**verclocarckles**" (like : *the cry of a gull)*

DIAGNOSIS-

- Erythrocyte sedimentation rate (ER) is often accelerated, leukocytosis, hypergammaglobulinemia, elevated LDH, RF, ANA, ANCA

- Pulmonary function-Spirometry: restriction interference ventilation
  Discount DLco
  Discount pO_2, but pCO_2 normal or slightly reduced

- **BAL:** 70-90% neutrophils, eosinophils 40-60%, 10-20% lymphocytes.

IPF

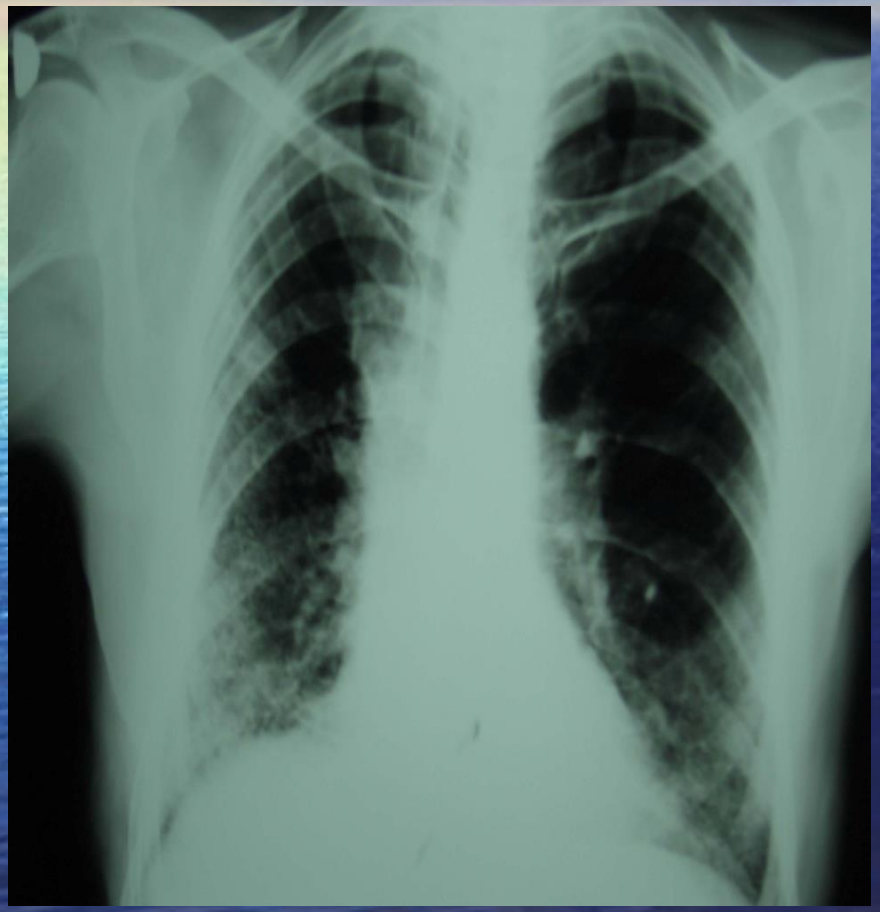
Diagnosis: If a doctor suspects for the IPF, must make TBLB with fiber-bronchoscop.

If it does not get diagnosed with TBLB, patient should be sent to the VATS- is method of choice for histological dg.

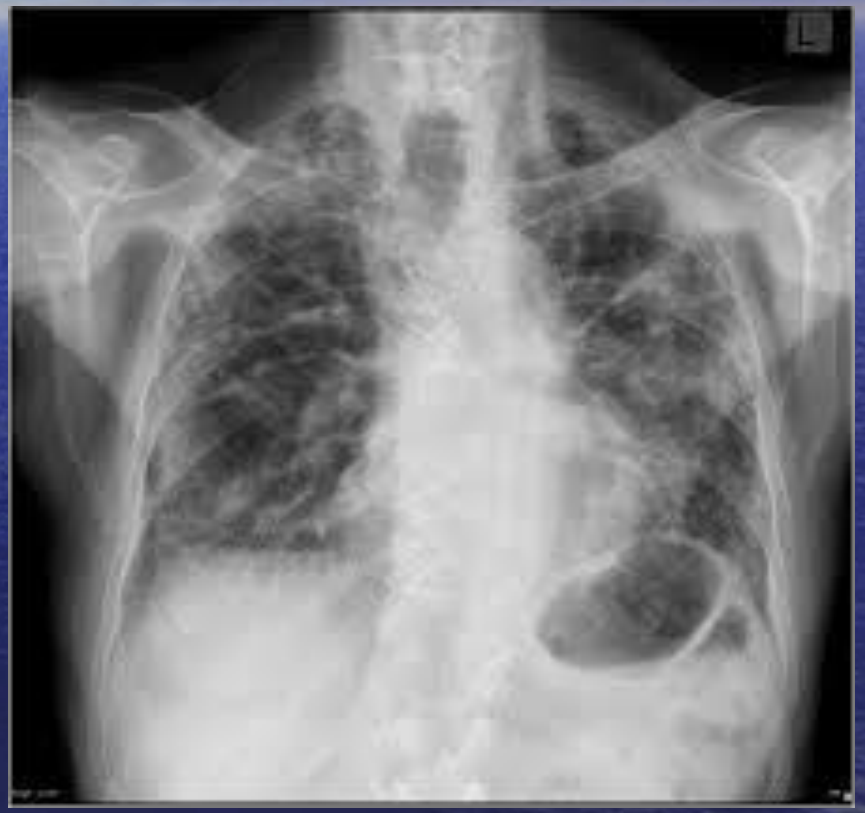
Classic surgical procedure - Open lung biopsy – is rare.

But, **IPF** can be diagnosed only on the basis of HRCT scan of the chest - very typical findings for IPF on HRCT (patognomonic image-finding)

IPF at the time of diagnosis

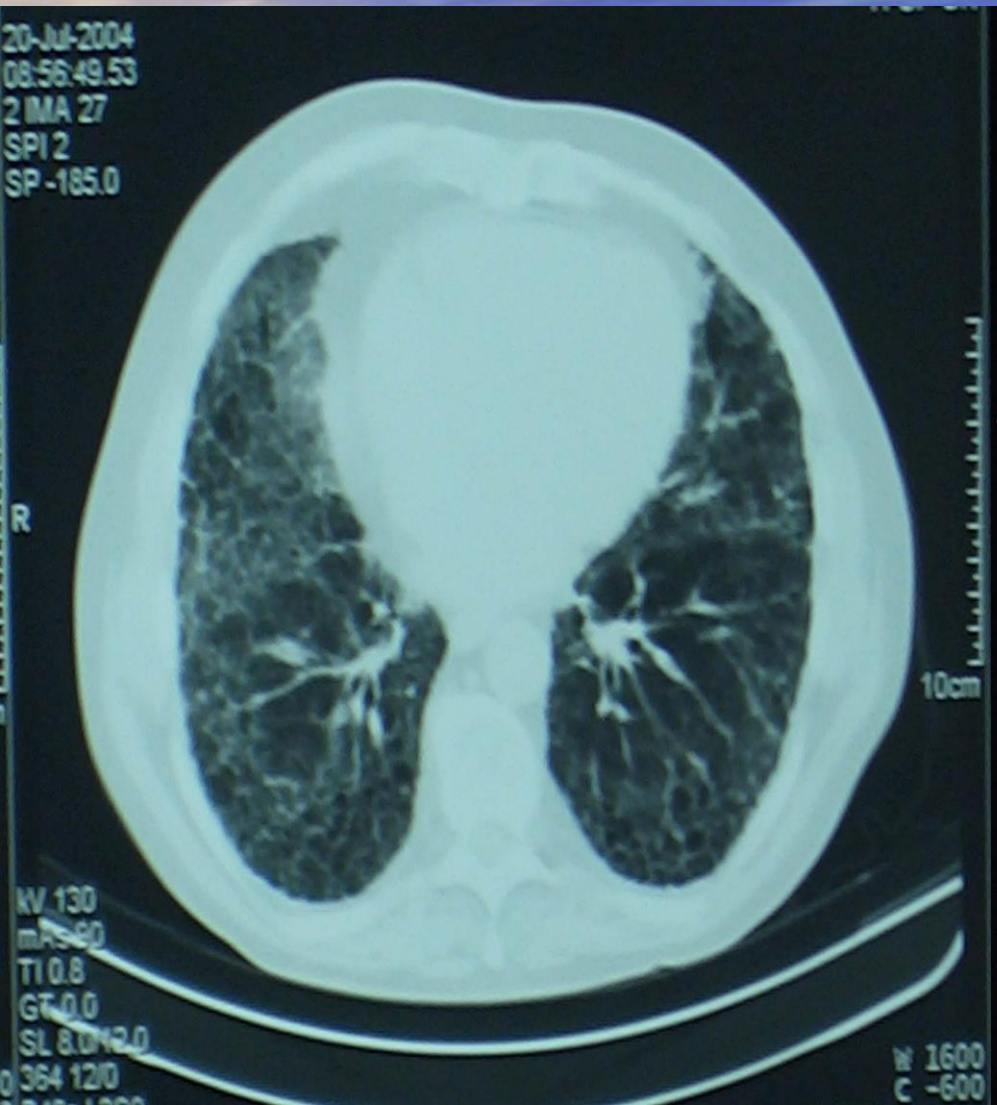


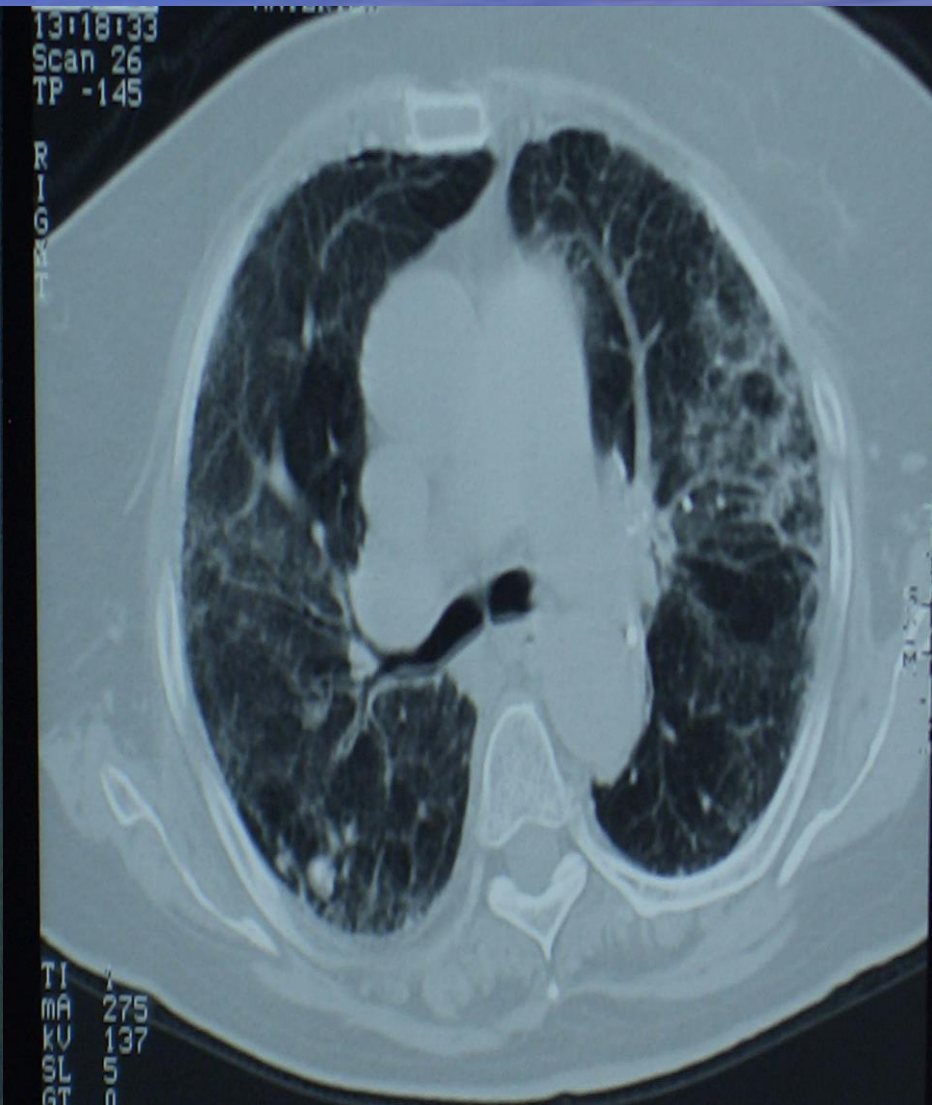
IPF stage IV-the end-final phase



IPF –MSCT scan

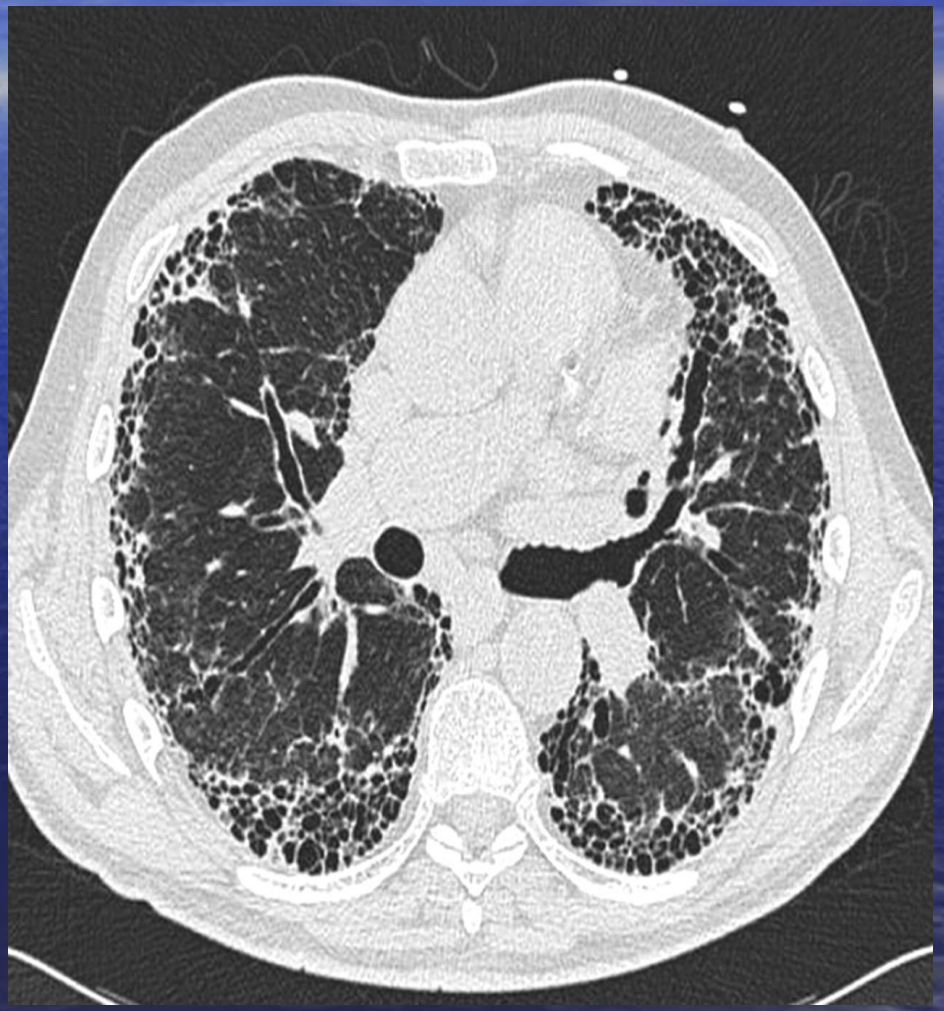
in the begining of IPF and 4 ys after Dg.





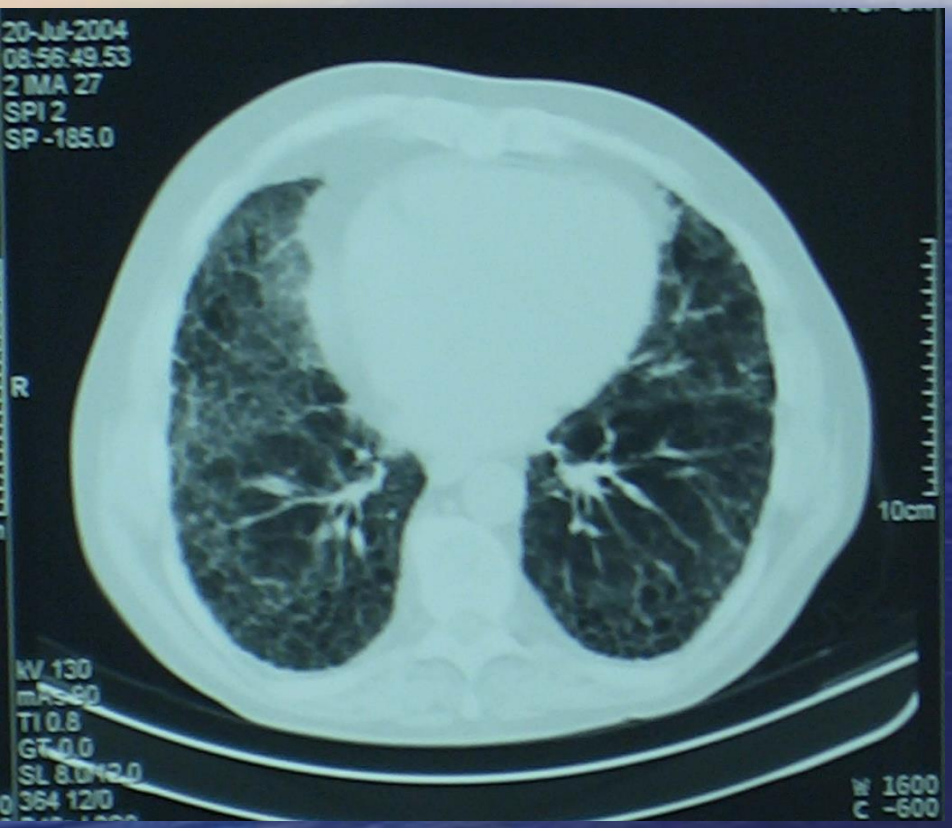
IPF- HRCT THE END STAGE

- Honeycombing consisting of multilayered thick- walled cysts.
- Architectural distortion with traction bronchi and occurrence bronchiectasis due to **fibrosis.**
- Predominance in basal and subpleural region.
- Mild mediastinal lymphadenopathy



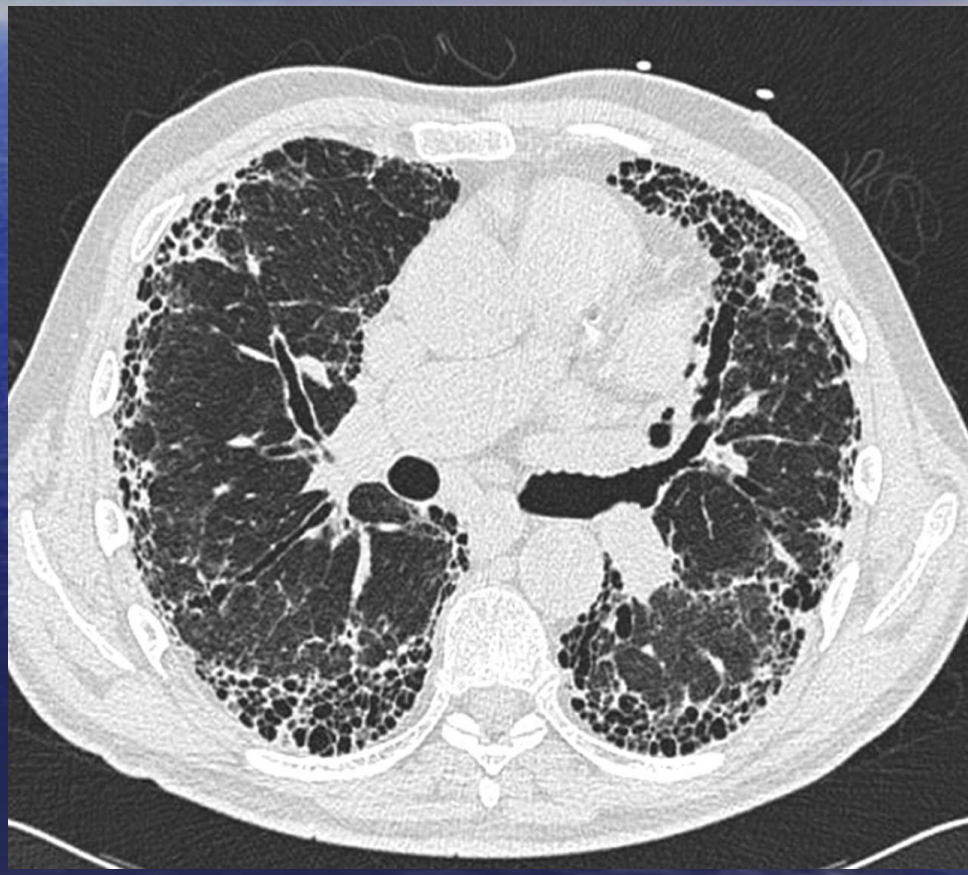
HRCT OF IPF

at time a diagnosis



HRCT OF IPF in the final stage:

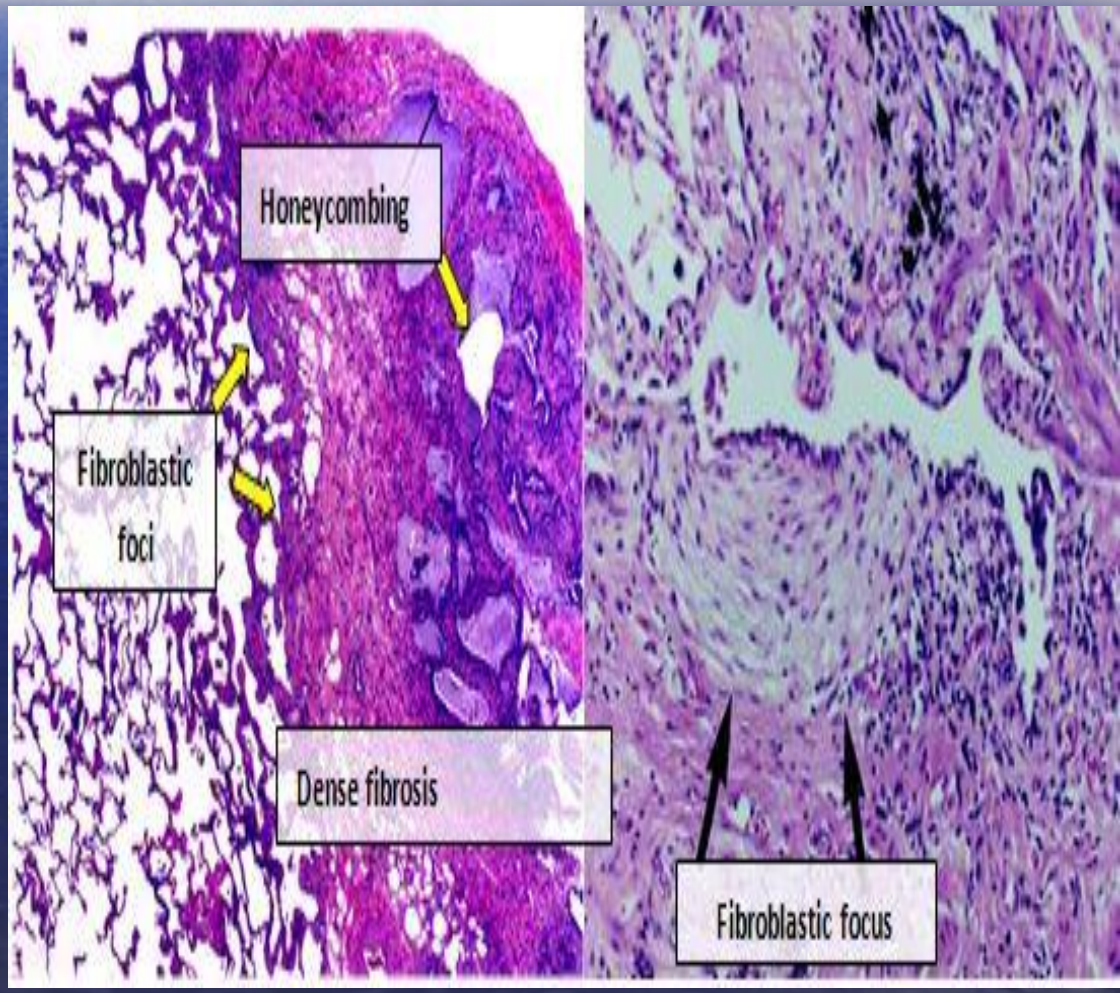
“honeycombing”



HISTOLOGY OF IPF

Proliferative focus and **"Fibroblastic foci"** (focus) are made of **fibroblasts** and **myofibroblasts** .

They are **pathognomonic** finding in the pulmonary interstitium, and very important for diagnosis IPF.



TREATMENT OF IPF

- **CORTICOSTEROIDES - CS** ongoing inflammation in the lungs causes damage and scarring.
- CS like prednisone and methylprednisolone reduce the activity of the immune system (immune reaction).
- **CS (or Glucocorticoides**) with or without cyclophosphamide or azathioprene. (0.5 - 1 mg / kg of metilprednisolone/day OR
- "pulse doses“ of GC 1x weekly)
- Cyclophosphamide
- Azatiprim: reduction after evaluating the success of the 125 mg *Imuran* / day and 20 mg metilprednisolone (GC effectiveness is observed for 6 ie.,
-

EXPECTORANTS

- **N-acetylcysteine (Mucomyst):** is potent antioxidant.
- Benefit of expectorants: coughing out of lung expectoration of mucus, which is rich in elastase that destroy alveoli
- However, it does not improve people's survival

OXYGEN

- **Inhaled oxygen:** In patients with low oxygen blood levels due to interstitial lung disease, inhaled oxygen may improve symptoms.
- Regular use of oxygen also protect the heart from damage caused by low oxygen levels.

NEW DRUGS

- PIRFENIDONE: anti-TGF factor- "Esbriet", and
- NINTEDANIB: "Ofev"

LUNG TRANSPLANT-

- In advanced interstitial lung disease causing severe impairment of health, lung transplant may be the best option for patient. (last hope)

SARCOIDOSIS

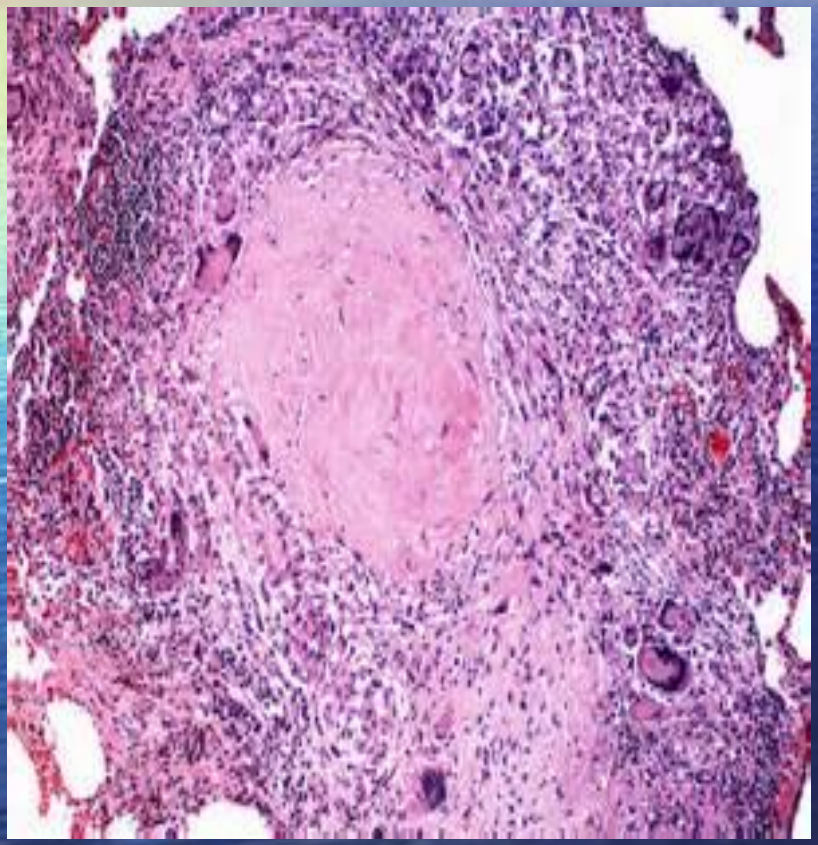
WHAT IS SARCOIDOSIS ?

- Sarcoidosis is a multisystemic granulomatous disorder of unknown etiology.
- **Non-cascating epitheloid immune granulomas** in involved organs and tissue are caracteristic for S.

- The ratio of T-lymphocites-CD4 : CD8 > 3.5 in granulomas. Local immune respons very strong, but peripheral cellular immunity is poor, depression.

- Depression of peripheral cellular immunity- we confirm with **cutaneus tuberculin test: it is negative - PPD**

GRANULOMAS IN S.



Non-cascating epitheloid Immune granuloma

made: epiteloid cells, lymphocites, gigantic cell and plasma cells

EPIDEMIOLOGY

S. occurs worldwide, affecting both sexes, races and age.

- S. commonly affects young and middle age adults, mostly women.
- More than >90% primarly affects the lung and lymphatic system of the body

Prevalence:

Highest prevalence: Scandinawian countries - Denmark , Sweden, Norway.

In USA highest in Afroamericans, 30 - 64/100.000 , and 0.8-10/100000 white people

CRO: 2.4 - 11/ 100000 inhabitants (Split-Dalm. Region 3.1)

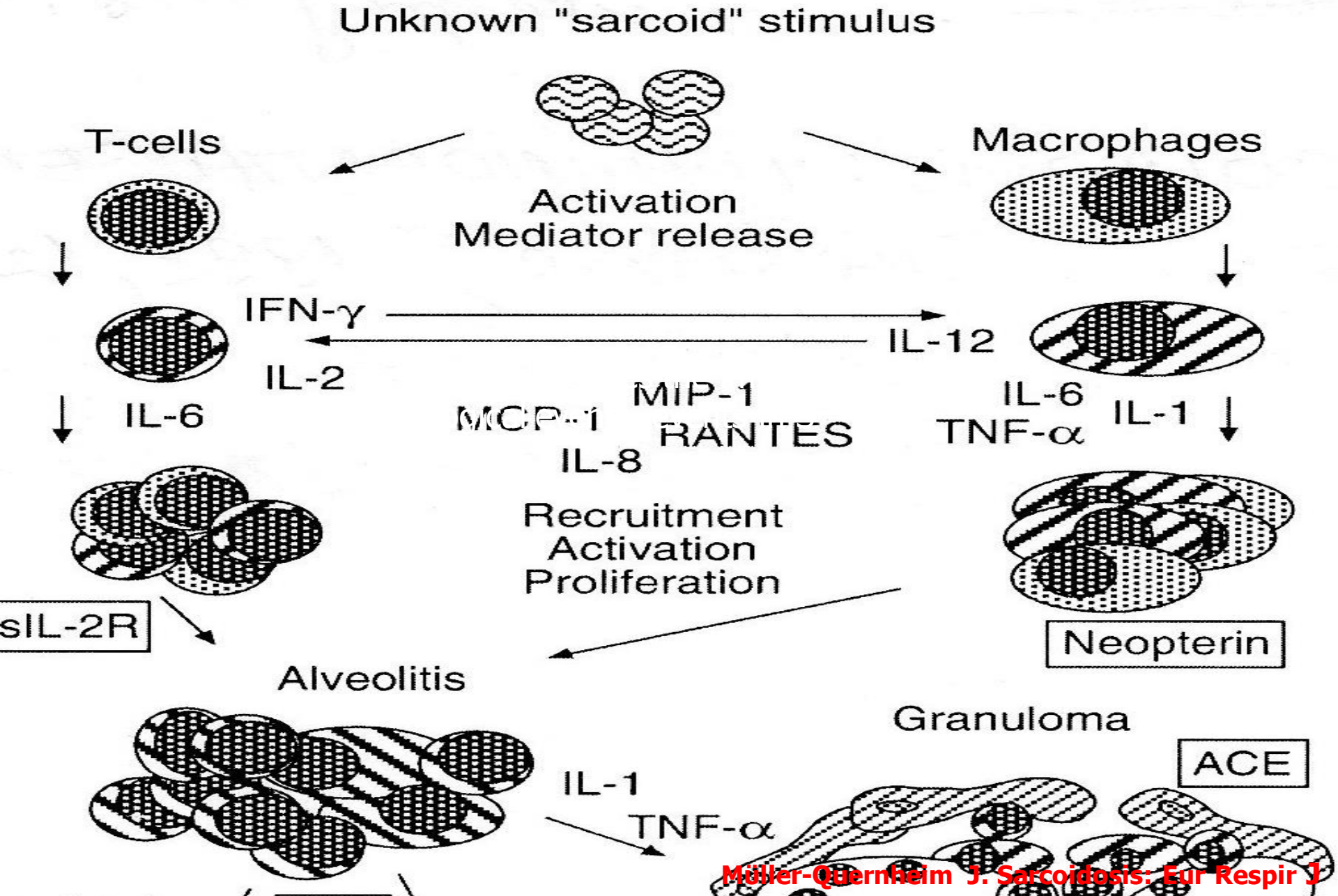
>

PATOGENESIS

- Accumulation of mononuclear cells in the lung occurs “sarcoid alveolitis”, which can be absorbed and disappear spontaneously, if secreted good cytocines (INF-y,TGF,IL-6, IL-18)

- But, if predominate secreted bad cytokines (IL-1,IL-2, IL-8, TNF-α), granulomas that can develops in lung fibrosis.

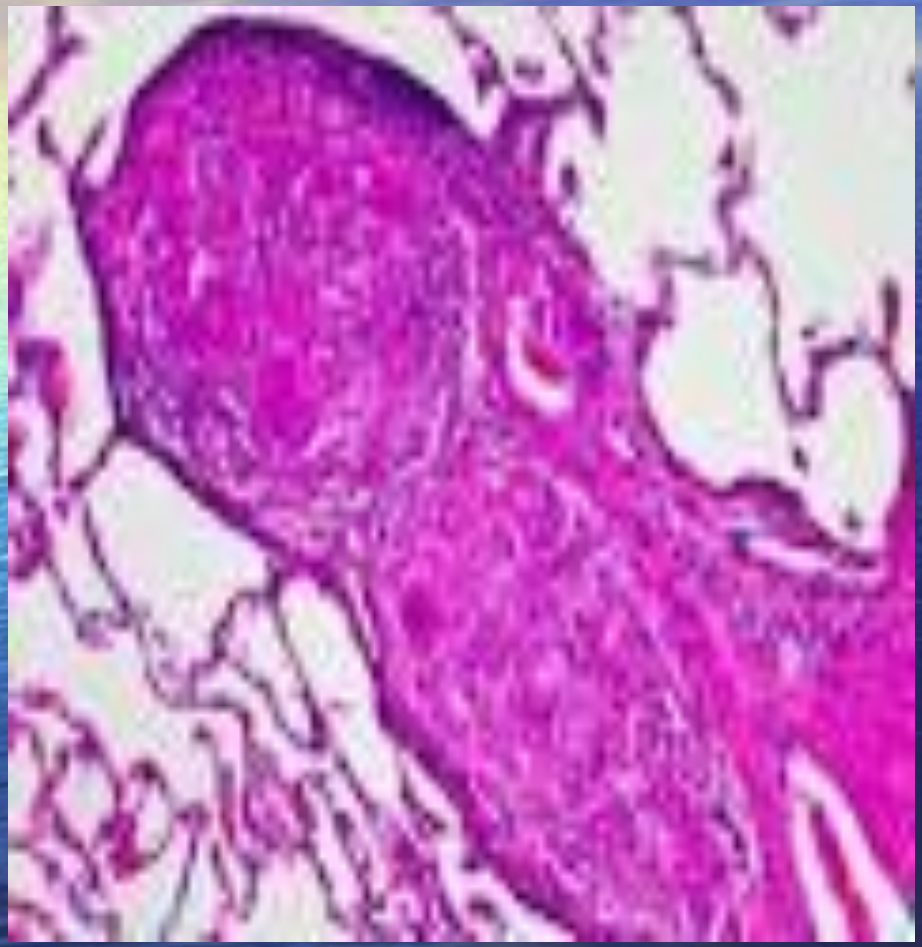
This figure describes the immune pathological development, events in S

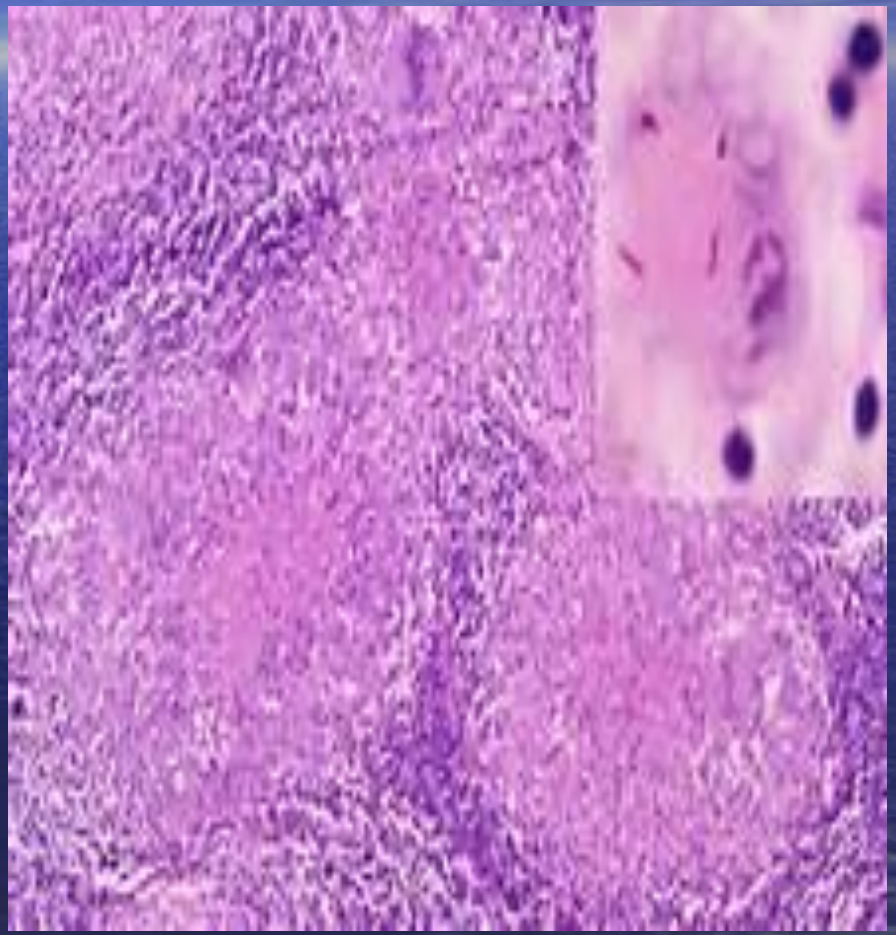


Müller-Quernheim J. Sarcoidosis: Eur Respir J

Histological finding of sarcoidosis : granulomas in sarcoidosis without caseous necrosis and

TB with caseous necrosis





Sarcoid granulomas:

- Epitheloid cells of sarcoid granulomas secrete: angiotensin converting enzyme (ACE - biomarker for Sarcoidosis), lysozyme, collagenase, 1.25 dihidroxicalciferol, that causes abnormal metabolism of vitamin D3

Classification of Sarcoidosis

1. - ACUTE S.

2. – CHRONIC S.

Other division of the S. is
divided by location granulomas in organs, by affected organs

ACUTE S.

Affects predominantly younger people < 40 y. o.

1. **Lofgren syndrome:**

   Symptoms: fever, erythema nodosum (EN-red skin),
   edema of anckles, especially hocks,
   rhinitis, conjunctivitis

   Chest X-ray: Bilateral hilar lymphadenopaty (BHL)

2. **Heerfordt-Waldenstrom syndrome:**

   Symptoms: fever, edema of parotid glands, uveitis,
   paralysis of the facial nerve (n.VII)

CHRONIC SARCOIDOSIS

- Since the beginning the disease has a chronic course, often with relapses and recurrences .
- Primary chronic disease:
  Affects predominantly older people, older than 40 y.o.
- Charecteriscitcs are:

Oligosymptomatic disease

very common skin manifestation

manifestation in the lungs with granulomas and fibrosis

Keratoconjunctivitis

Very rarely spontaneously regression

Prognosis is poor, bad

SYMPTOMS OF CHR. SARCOIDOSIS

- Symptoms depend in which the organ is localized disease

Endothoracal S. is most common – in more than 96% of cases:

non-productive cough, shortness of breath are common symptoms.

Pleura is affected in approximately 3% of cases

- 10% of cases have an unwanted course of the disease (sec. pulmonary fibrosis, PH, chronic pulmonary heart)

- **stage 0:** normal chest radiograph
  - 5-10% of patients at presentation
- **stage I:** hilar or mediastinal nodal enlargement only
  - 45-65% of patients at presentation
  - 60% go onto complete resolution
- **stage II:** nodal enlargement and parenchymal disease
  - 25-30% of patients at presentation
- **stage III:** parenchymal disease only
  - 15% of patients at presentation
- **stage IV:** end-stage lung (pulmonary fibrosis)

ENDOTHORACIC STAGES OF SARCOIDOSIS (based on X-ray image of the chest)

Stage 0 : no change in the chest (extracthoracic S.)

Stage I : Bihillar lymphadenopathy - enlarged hilar and mediastinal lymph- nodes but without infiltrates in the lungs

St. II : BHL with infiltration in the lung

St. III : only interstitial pulmonary infiltration, no enlarged hilar or mediastinal lymphonodes

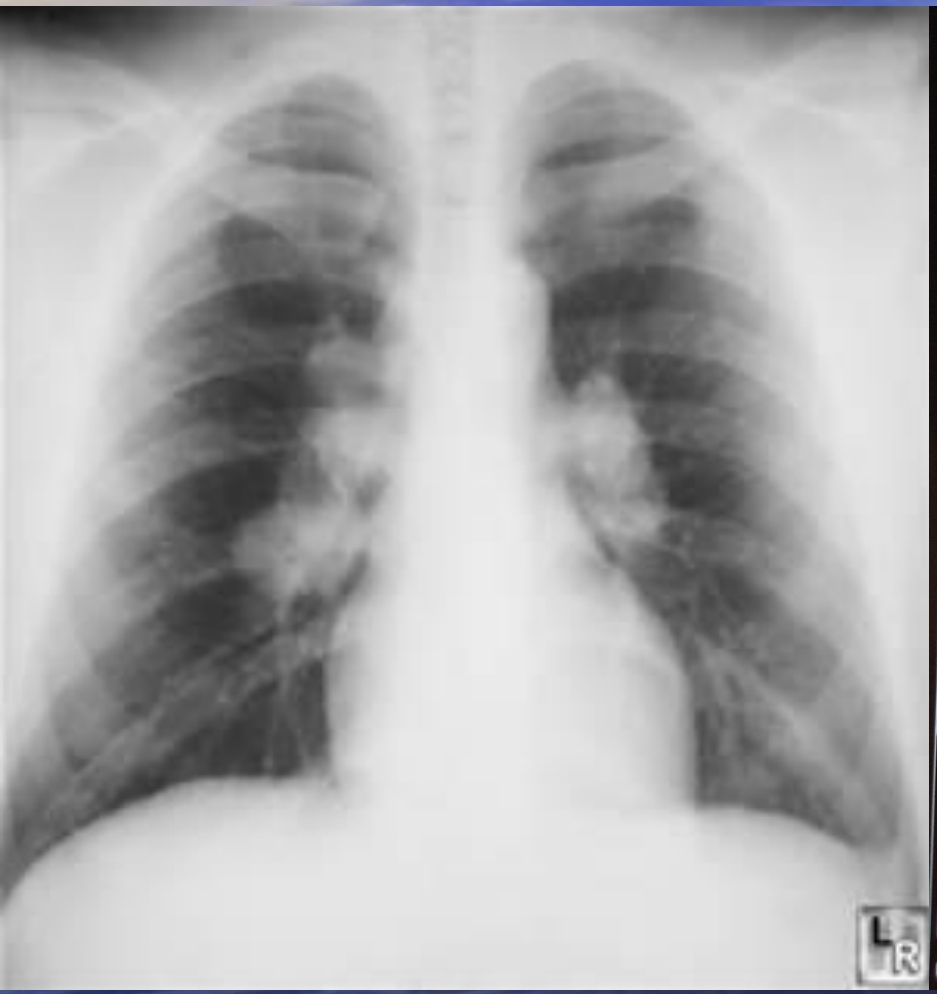
St. IV : only pulmonary fibrosis (chronic S- “the end stage”)

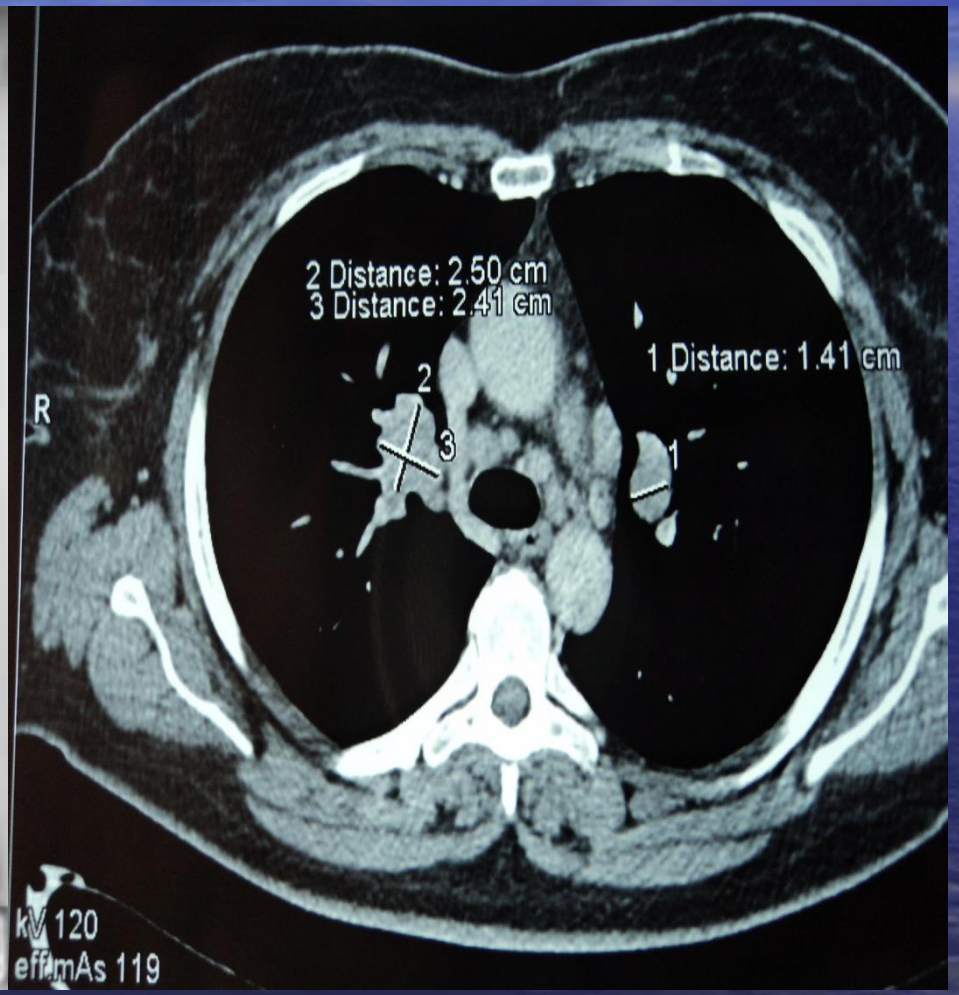
CALSSIFICATION OF ENDOTHORACAL S.

Stage : 0

- Normal x-ray picture of the chest
- This caracteristic for extrathoracic S.

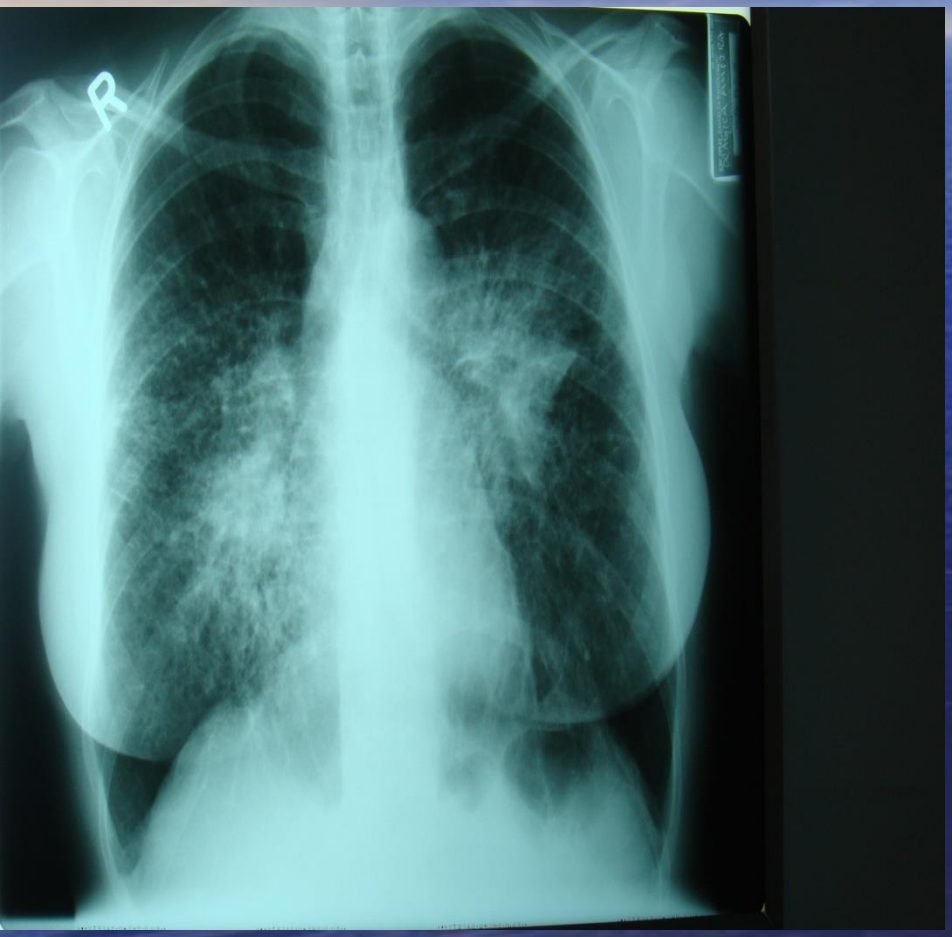
STAGE I. ENDOTHORACIC SA:
-only BHL, without pulmonary infitration

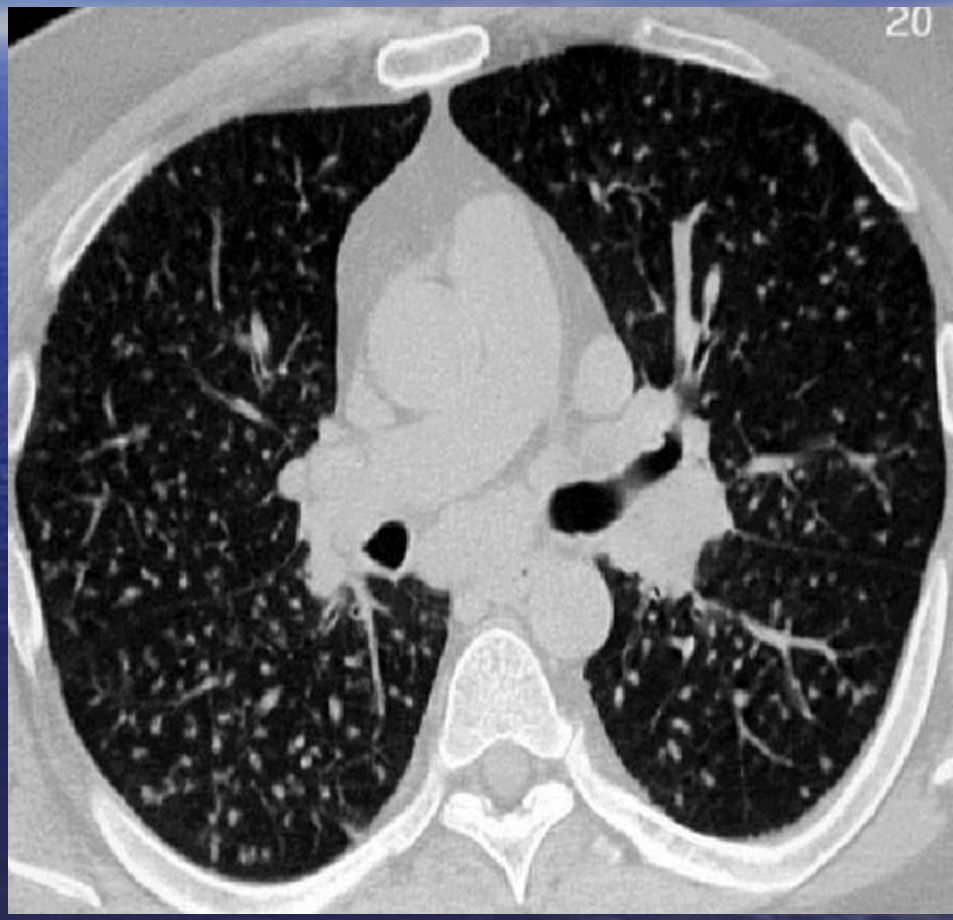




STAGE II. of ENDOTHORACIC S.:

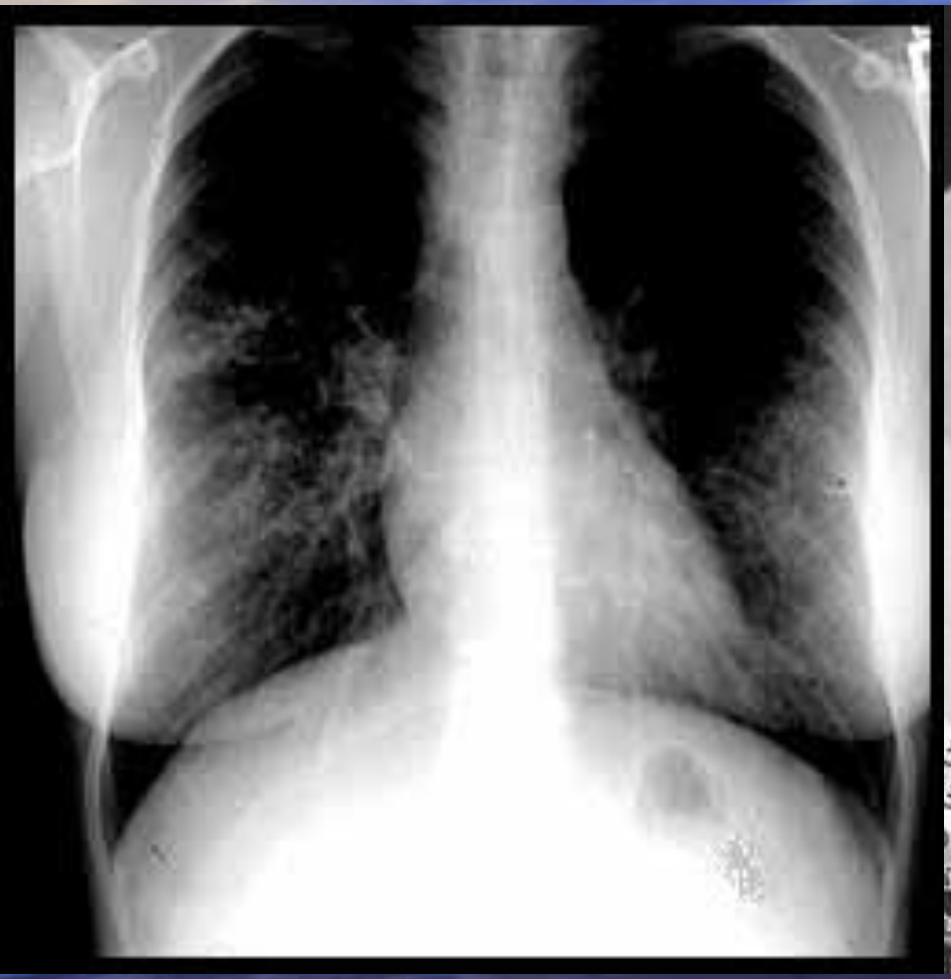
BHL with pulmonray infiltrations

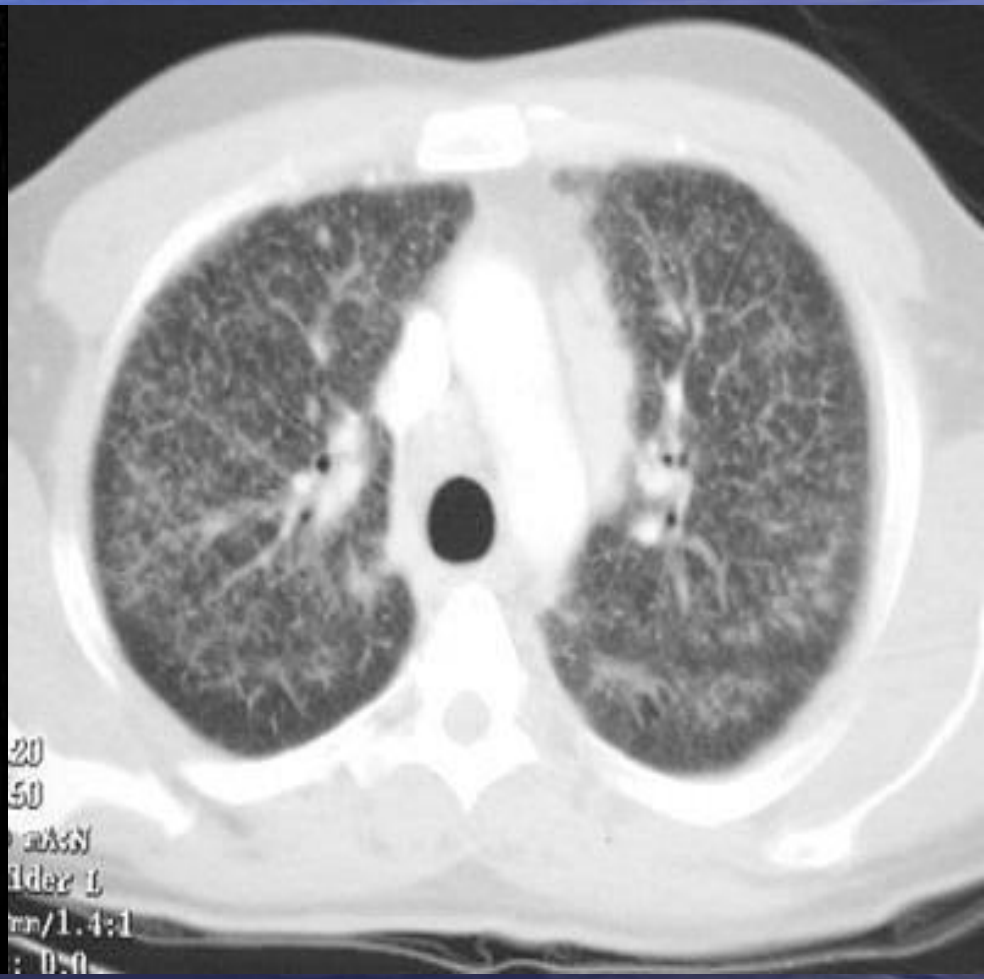




STAGE III. of ENDOTHORACIS S.:

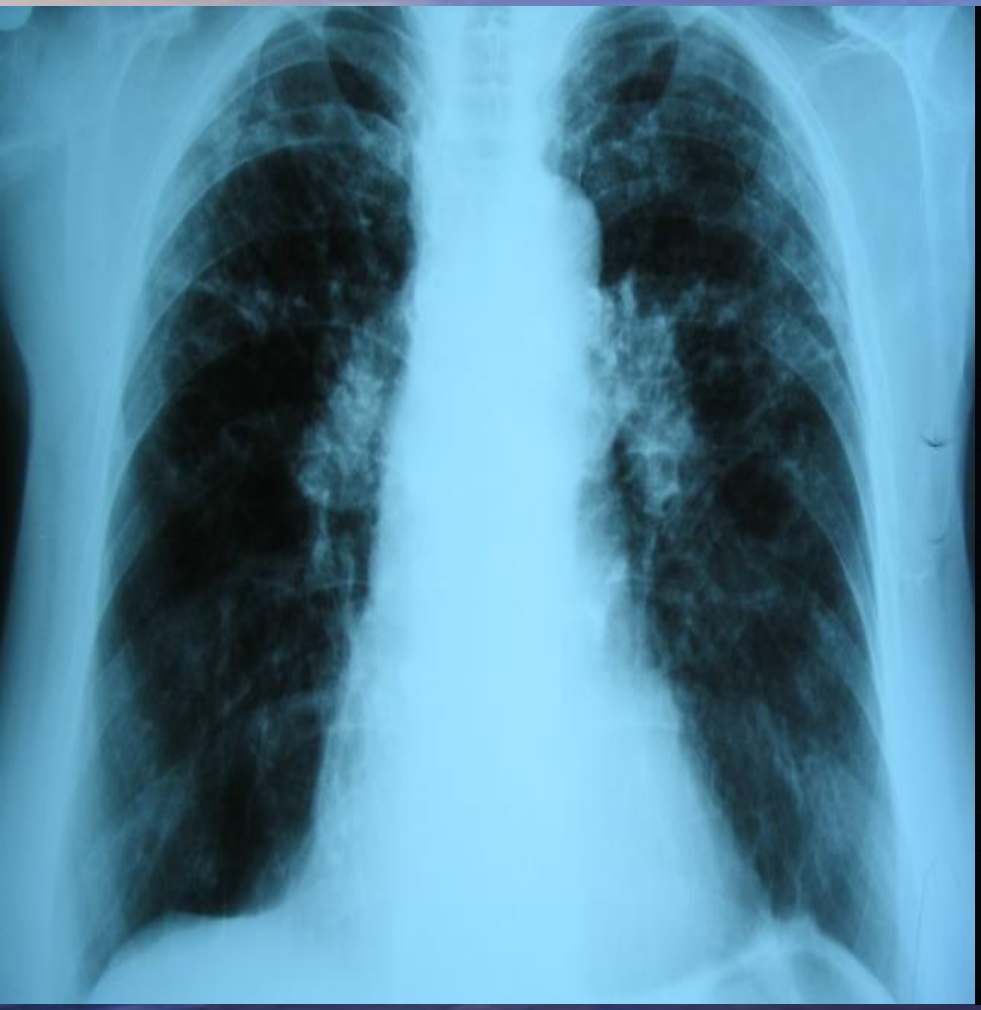
dense pulmonary infiltration without BHL

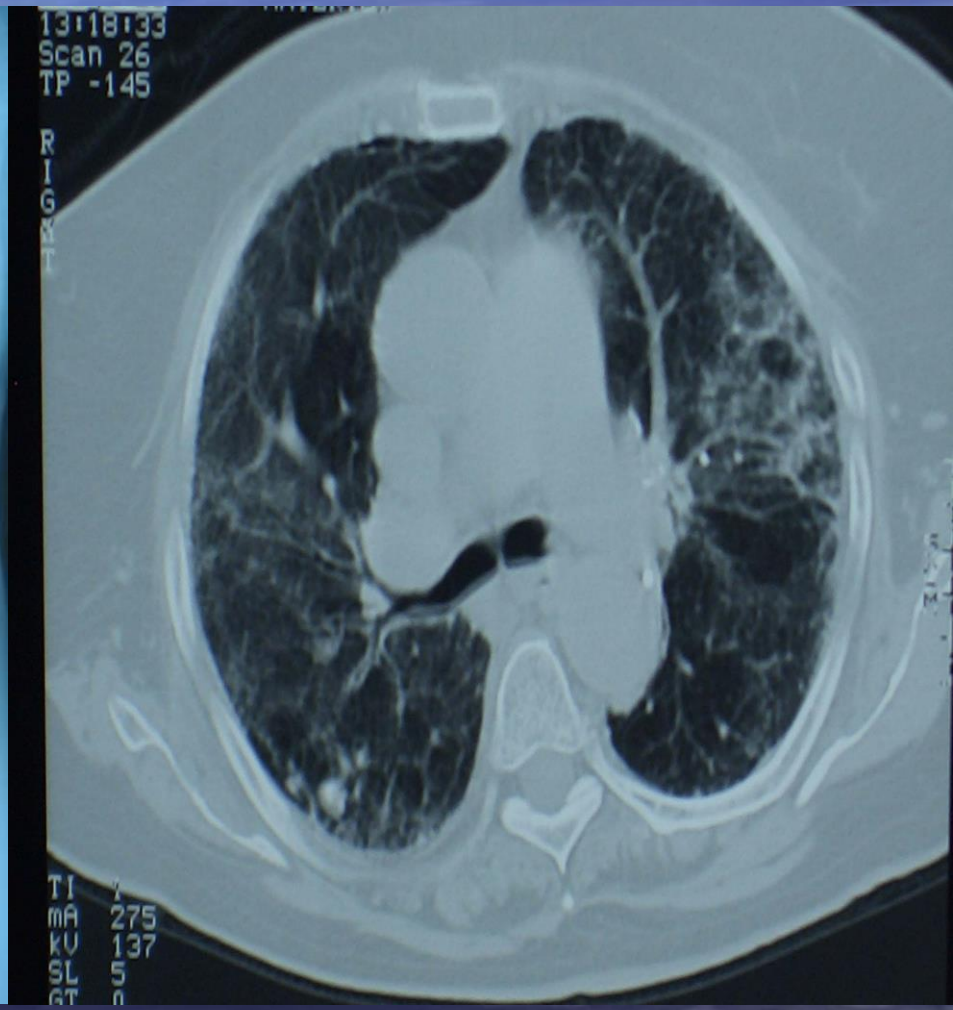




IV. STAGE of ENDOTHORACIC S.:

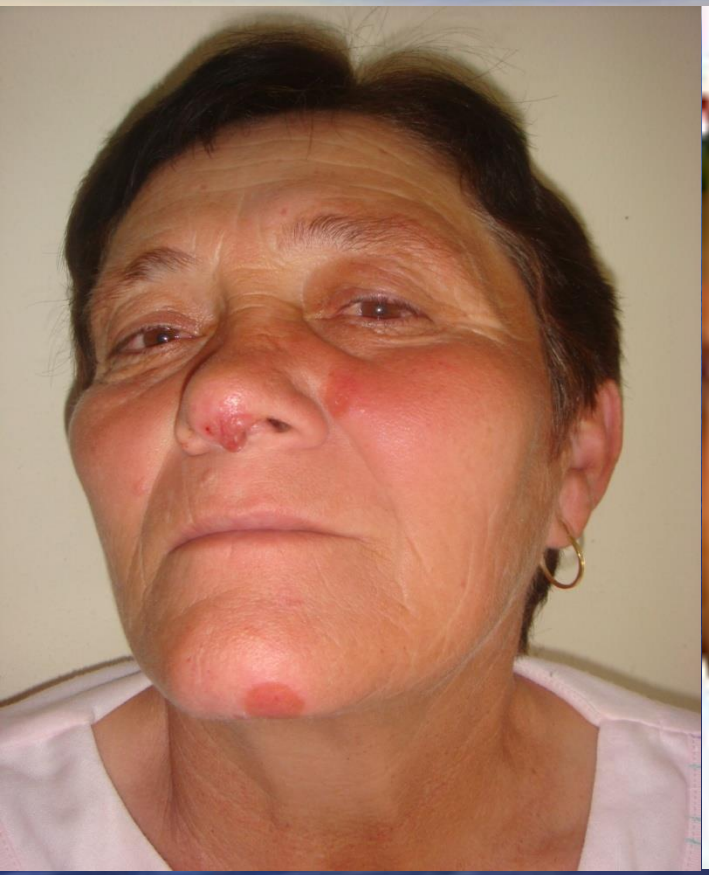
dispersen plulmonary fibrosis, fibrosis BHL , destruction of lung parenchima, bronchiectasis, cystis

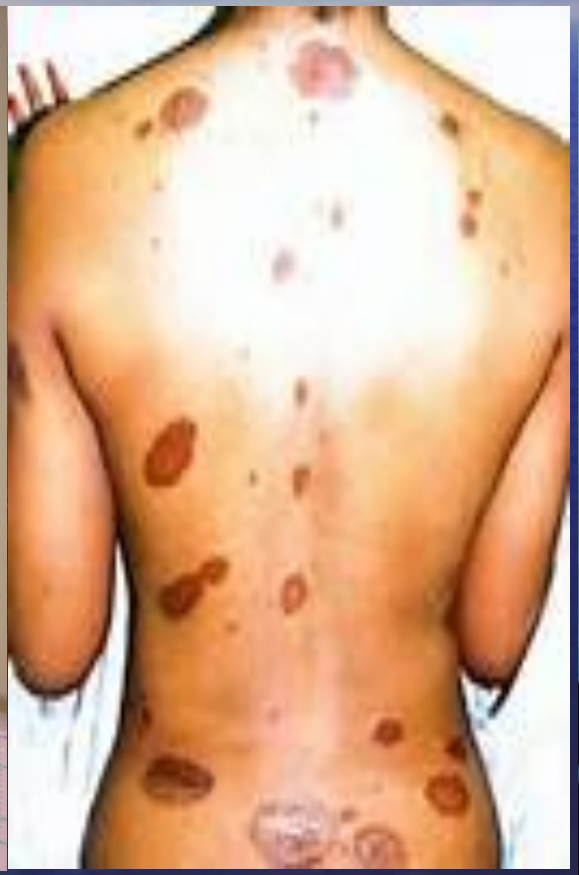


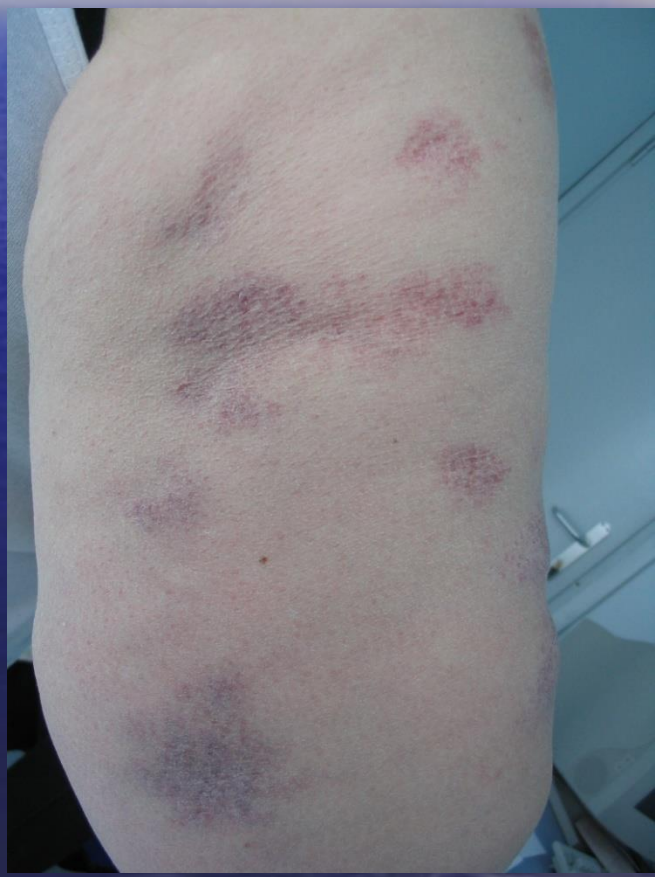


SKIN SARCOIDOSIS – DIFFERENT STAGING

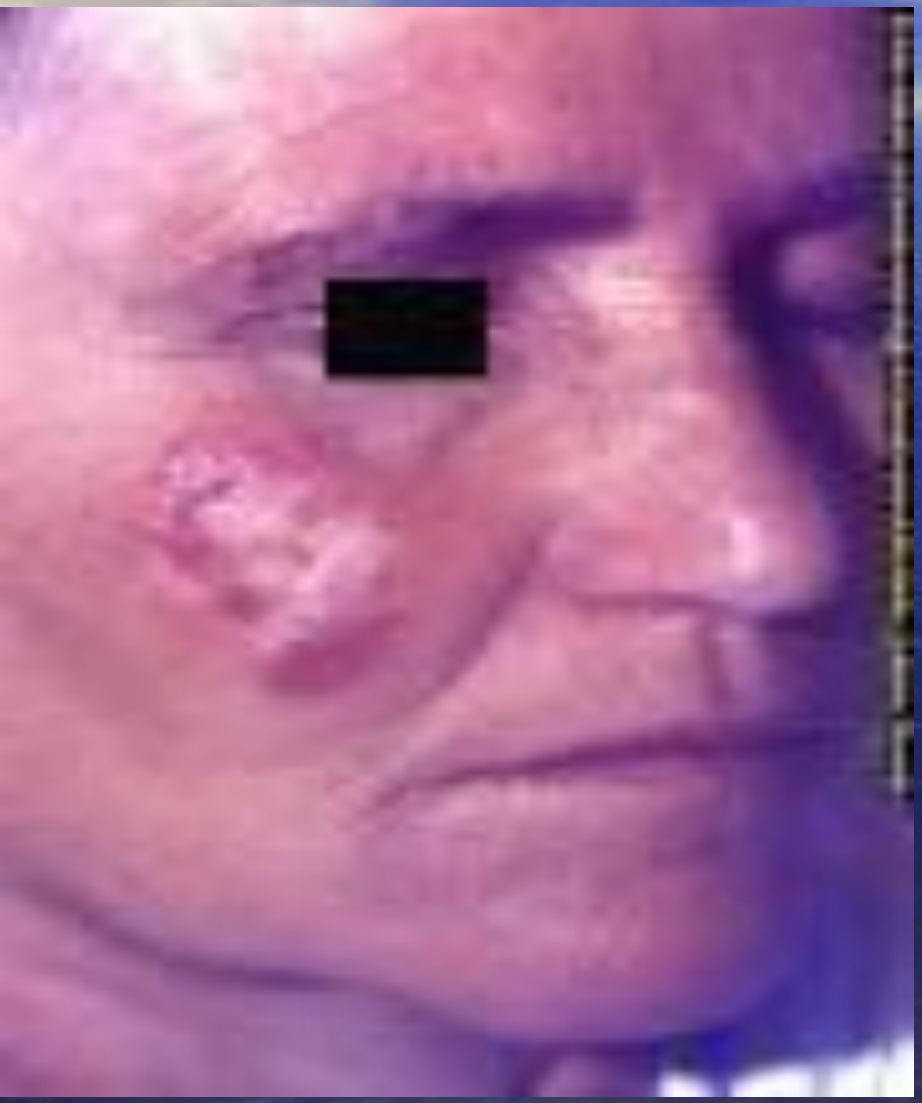
acute porgress chronic phase



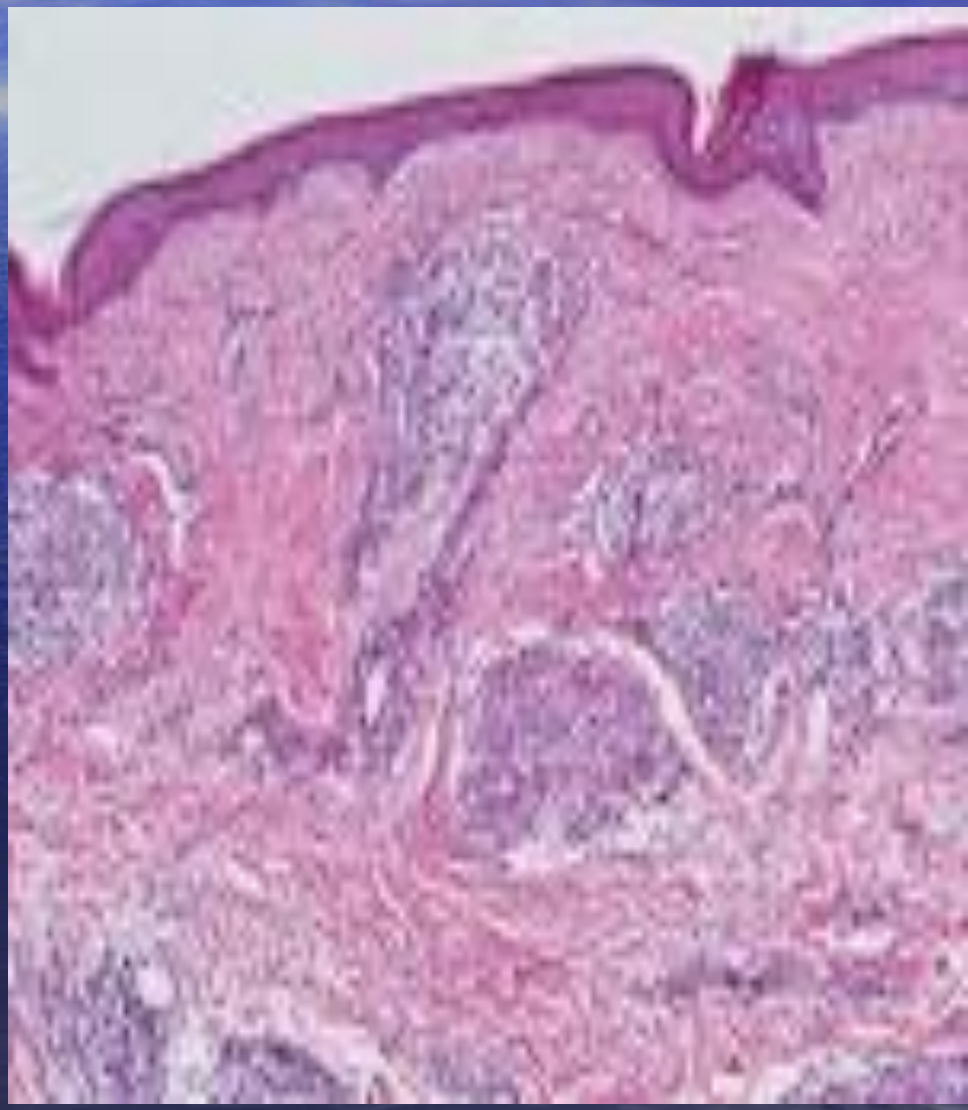




Chronic S. on the face



Histoloogy of the skin



EXTRATHORACIC SARCOIDOSIS

- Liver: positive biopsy is in 52 % ,
  (palpitation liver-hepatomegalia only 10 %).
- Skin: 32 %
- Joints : 25 %
- Peripheral lympho-nodes : 10 %
- Heart: 4 %, probably more, but undiagnosed
- Eyes: 5 %
- Salivary glands: 3 %

DIFFERENTIAL DIAGNOSIS

- TUBERCULOSIS ! (important, because the treatment is opposite to S.)
- Other nonsarcoid granulomatous diseases (WG, Lymphatic granulomat., granulomatosis of foreign body,
- Brucelosis, silicosis, beriliosis, other infectious granulomas
- Malignant granulomatous

TREATMENT OF SARCOIDOSIS

Symptoms often improve without treatment.

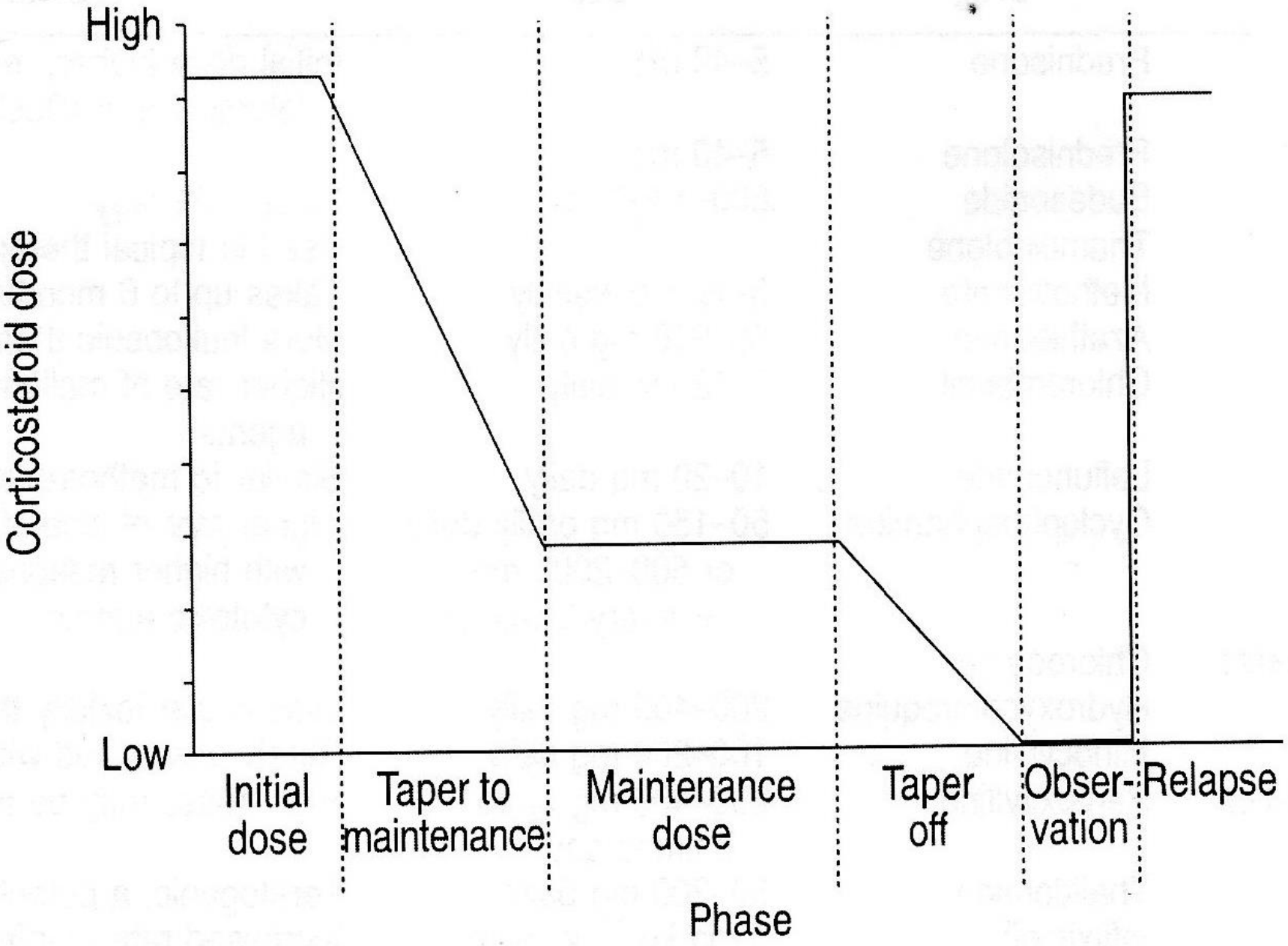
But, if the inflammation is severe: the first line of treatment is

- **Corticosteroid** - to reduce inflammation
- **Immunosuppressive drugs -** to decrease the immune systemic response

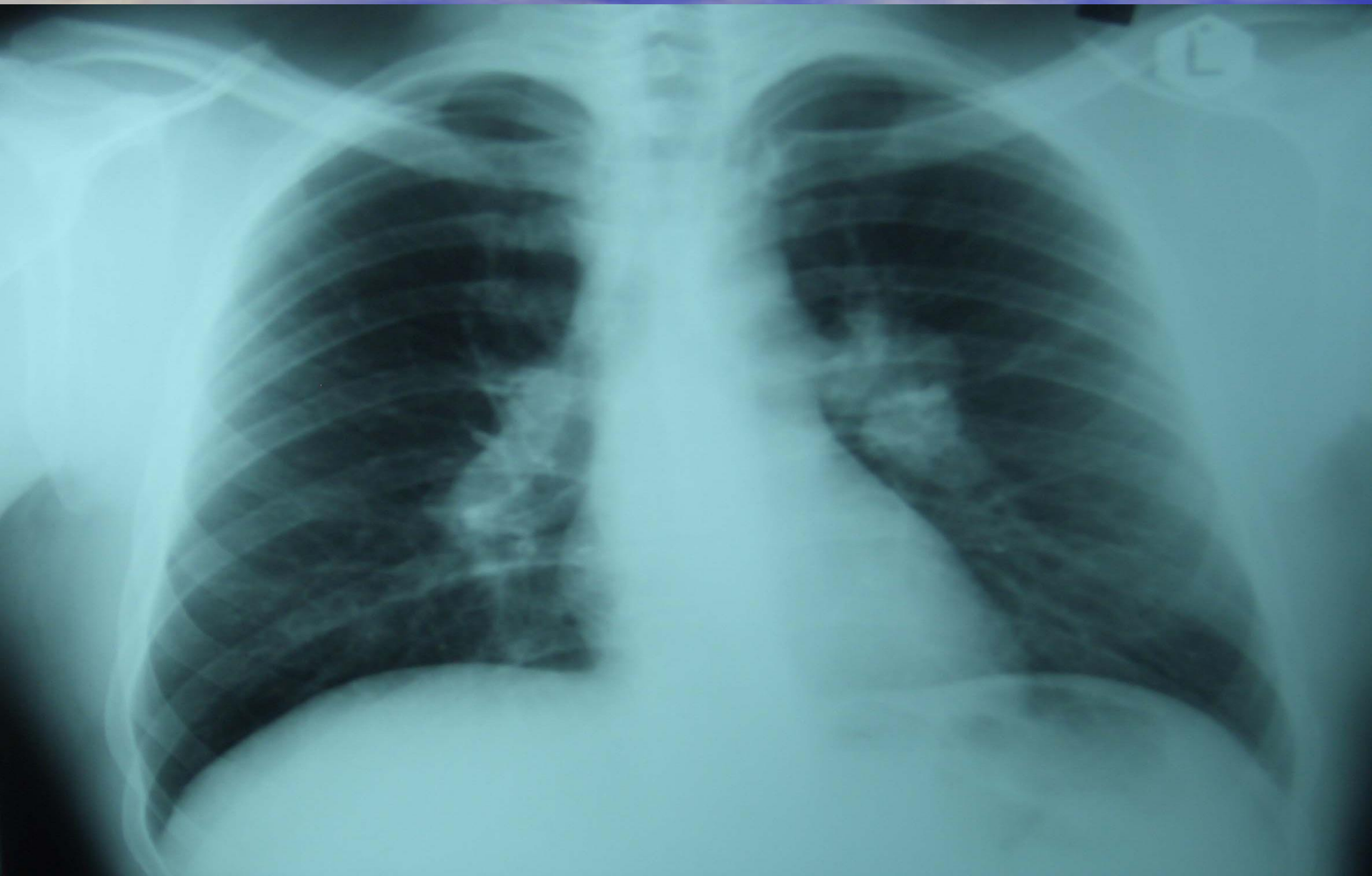
Treatment sarcoidosis with drugs is more likely if the disease affects:

eyes, lungs, heart, nervous system

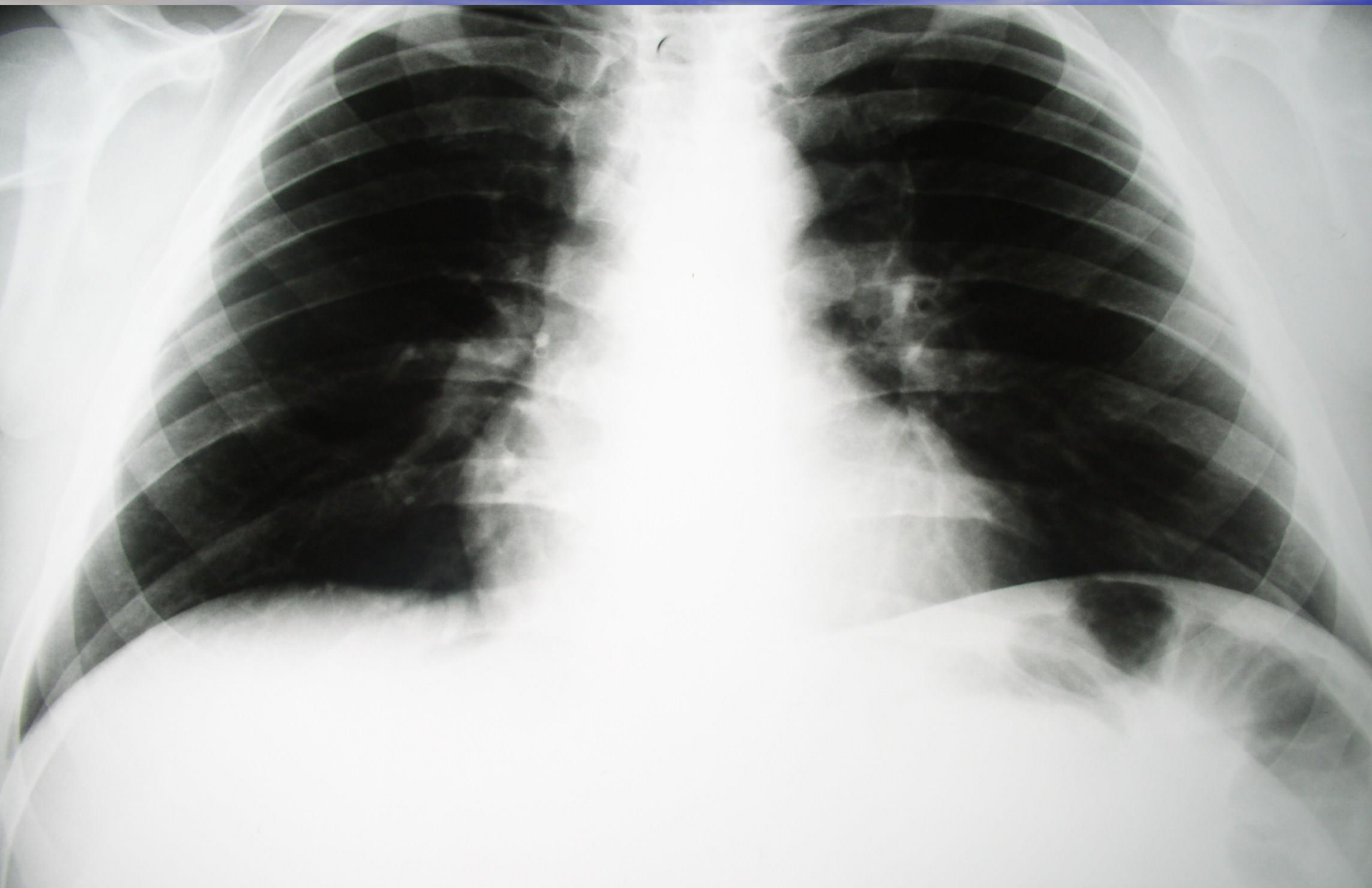
Graf of 6 treatment phases of S. with CS



Sarcoidosis, st. I. before treatment



Sarkoidoza- after 4 mon. treatment



NONCORTICOSTEROID THERAPY

- In steroid-resistant disease, intolerable adverse effects, or patient desire not to take corticosteroids, **administered Non-corticostroid drugs:**
  - **Methotrexate** (MTX) has been a successful alternative to prednisone and is a steroid-sparing agent. For skin sarcoidosis !
  - **Chloroquine** and **hydroxychloroquine** are antimalarial drug
  - **Cyclophosphamide** has been rarely used with modest success a steroid-sparing treatment in refractory sarcoidosis.
  - **Azathioprine** is too second-line therapy, which is best used as a steroid-sparing agent rather than as a single-drug treatment for sarcoidosis.
  - **Chlorambucil**

TREATMENT OF SARCOIDOSIS - NEW DRUGS

Humanized monoclonal antibodies:

anti-TNF-α therapies-Infliximab (remicaid)

- Adalimumab (Humira)
- Subcutaneous delivery
- Usually given with another drugs

INFLIXIMAB (IFX: anti-TNF-α - monoclonal antibody.

IFX (Rmicade) is highly specific for TNF-α.

- **Dose:** ***5 mg/kg***, every 4-6 wks.
- **Use:** Chronic/refractory S. and Corticosteroid resistant S., neurosarcoidosis
- It can be combined th. (CS, MTX, AZT)
- must be cautious with opportunistic infections (especially with TB)

ADALIMUMAB: Humira

WHEN TO START TREATMENT OF SARCOIDOSIS

1. Decline in FVC <15% and/or decline DLCO <20% of the reference values
2. Hypoxemia at time of diagnosis
3. Involvement in Central nervous system
4. Cardiac sarcoidosis
5. Severe skin involvement (lupus pernio)
6. Hypercalcaemia
7. Solid organ lesions with evidence of organ function impairment
8. Spleen enlargement with severe pain

ACTIVITY AND PROGRESSION

- **Factors indicating poor prognosis:**
  - IL-8: potential neutrophil chemnotactic factor - "neutrophilic alveolitis"
  - MIP-1alfa, MCP-1: ongoing inflammation
  - IL-2, IL-12: indicator of poor prognosis
  - IL-8 (TGF): ongoing fibrosis
- **Factors indicating better prognosis:**
  - **IL-18:** induces release of INTERFERON-γ from T-cells, ass. with spontaneous resolution.

ROLE OF TNF-α IN Sarcoidosis

- The chemokine and cytokine pathways that regulate granuloma formation are not well understood, but TNF-α is known to play a key role.
- TNF-α: higher in active S.
- **2 types of TNF-α receptors:**

  - **TNF-α R I** (Chron`s disease, and malignancies), and

  - TNF-α R II- *parameters of activ.and progress. of S.*
- **Chronic Sarcoidosis with high TNF-α-II**: does not respond well to steroids (**TNF –α** decreases sensitivity of monocytes to dexamethasone → ***cortiosteroid resistence).***

- TUBERCULOSIS
  - TB -

WHAT IS TB

- Tuberculosis (TB) is infectious disease,

potentially serious infectious disease that mainly affects lungs.

TB is caused by Mycobacterium tuberculosis-typus humanus-MTB

- MTB are spread from one person to another through tiny droplets released into the air via cough and sneeze.

DIAGNOSIS

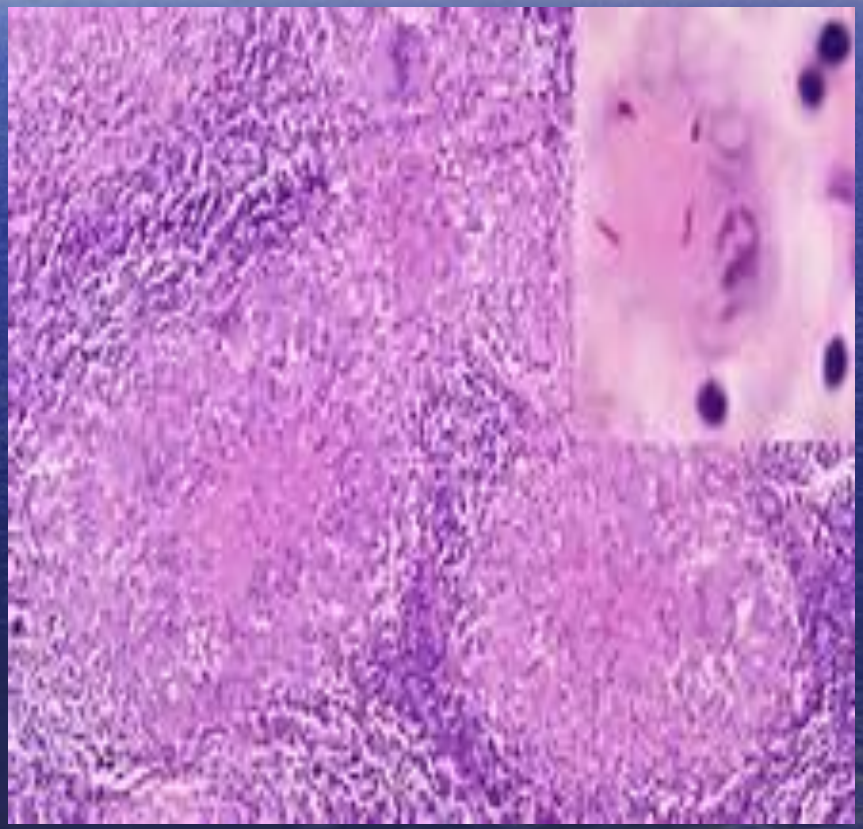
Evidence TB finding Mycobacteria tuberculosis in the diseased –infection materials, most often in sputum or finding of caseous granulomas in affected tissue.

Pulmonary TB is specific pneumonia with caseoting necrosis.

DIAGNOSIS: microscopic findgs

- Specific inflammation with the formation of granuloma with caseous necrosis

- For diagnosis, it is important that the granuloma found caseous necrosis and / or MTB



EPIDEMIOLOGY

- Once rare in developed countries, tuberculosis infections began increasing in 1985, partly because of the emergence of HIV, the virus that causes AIDS. HIV weakens a person's immune system so it can't fight the TB germs.
- Incidence TB in West countries less than 10/100000 habitans
- Incidence in East Europe, Kosovo, BiH is high (30-40), in CRO-Dalmatia: 11-13/100000 persons

CLASSIFICATION TB

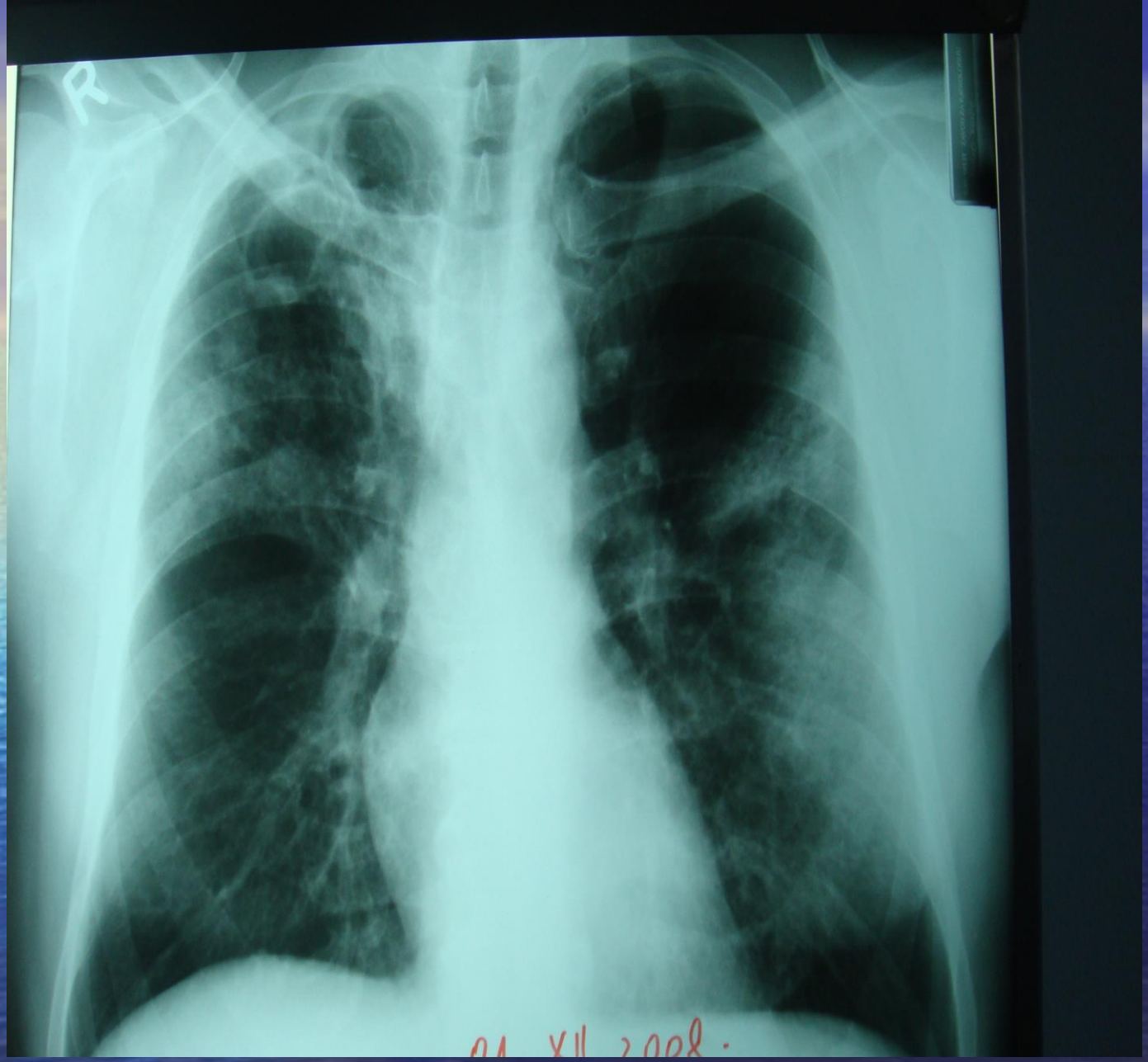
Latent TB. In this condition, there is a TB infection, but the bacteria remain in your body in an inactive state and causes no symptoms. Latent TB, also called **inactive TB or TB infection**, isn't contagious.

Active TB In the first few weeks after infection with the TB bacteria, or it might occur years later.

Acitve TB always manifestation with symptoms of disease

COMMON SYMPTOMS INCLUDE:

- A cough with thick expectoration, cloudy, and sometimes bloody sputum (mucus) -haemoptysis
- Fever, chills, and night sweats.
- Fatigue and weakness.
- Loss of appetite and unexplained weight loss.
- Shortness of breath and chest pain.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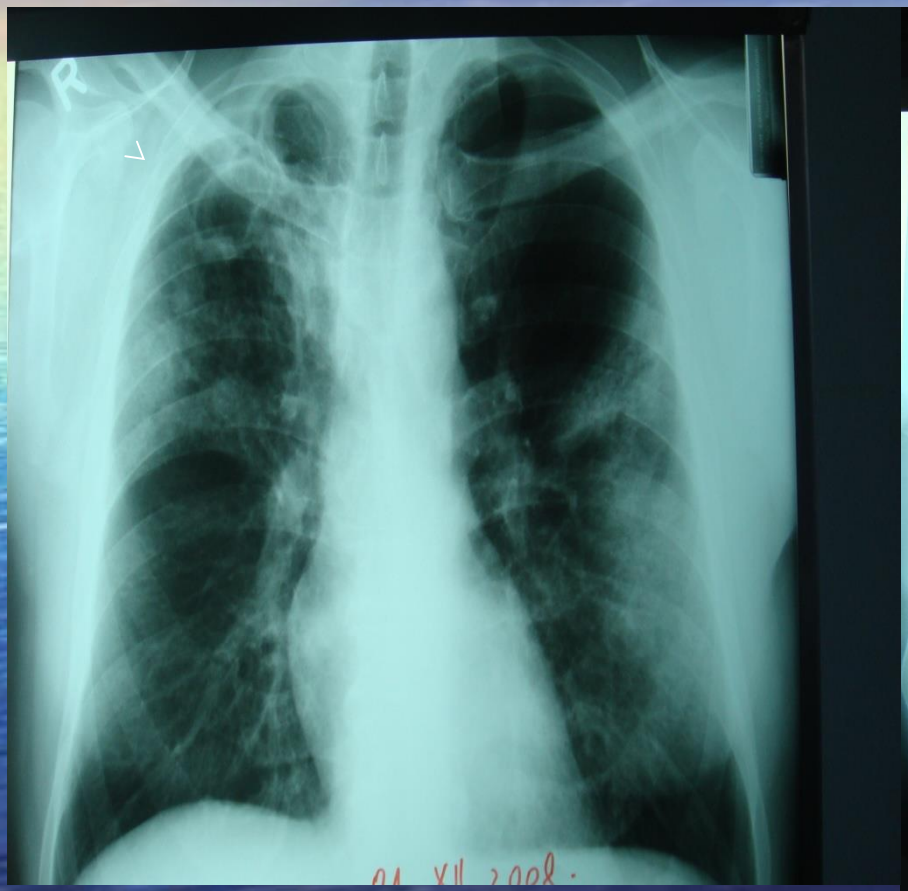
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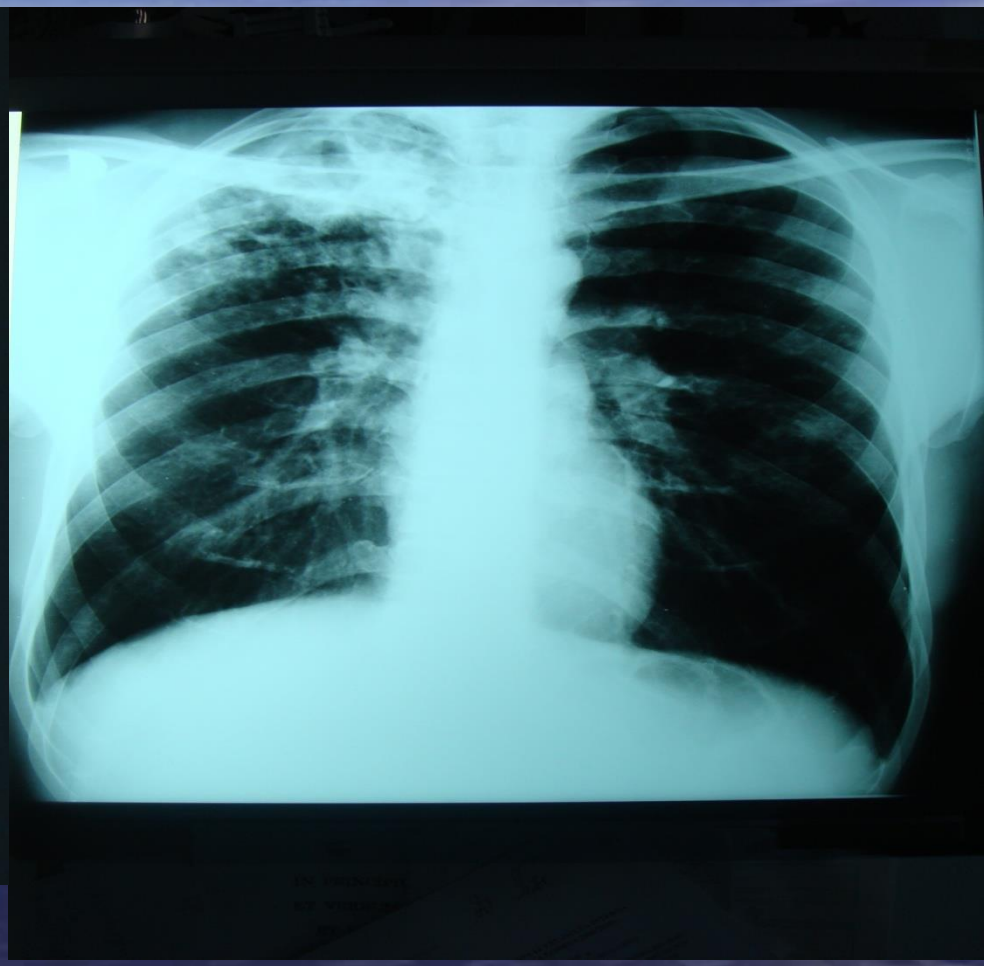
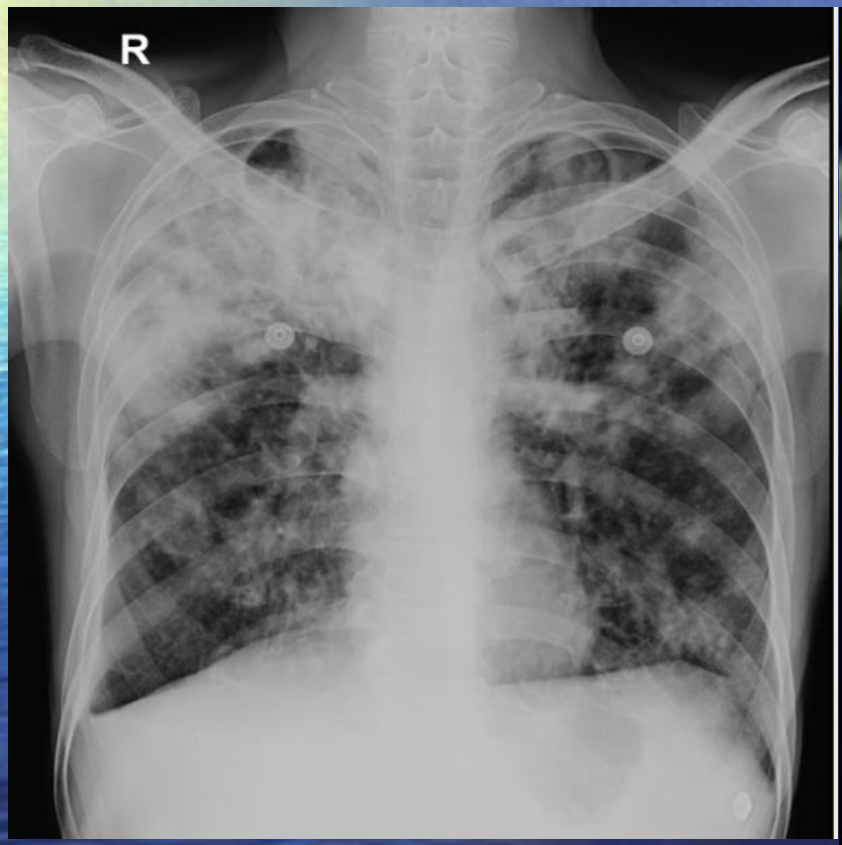
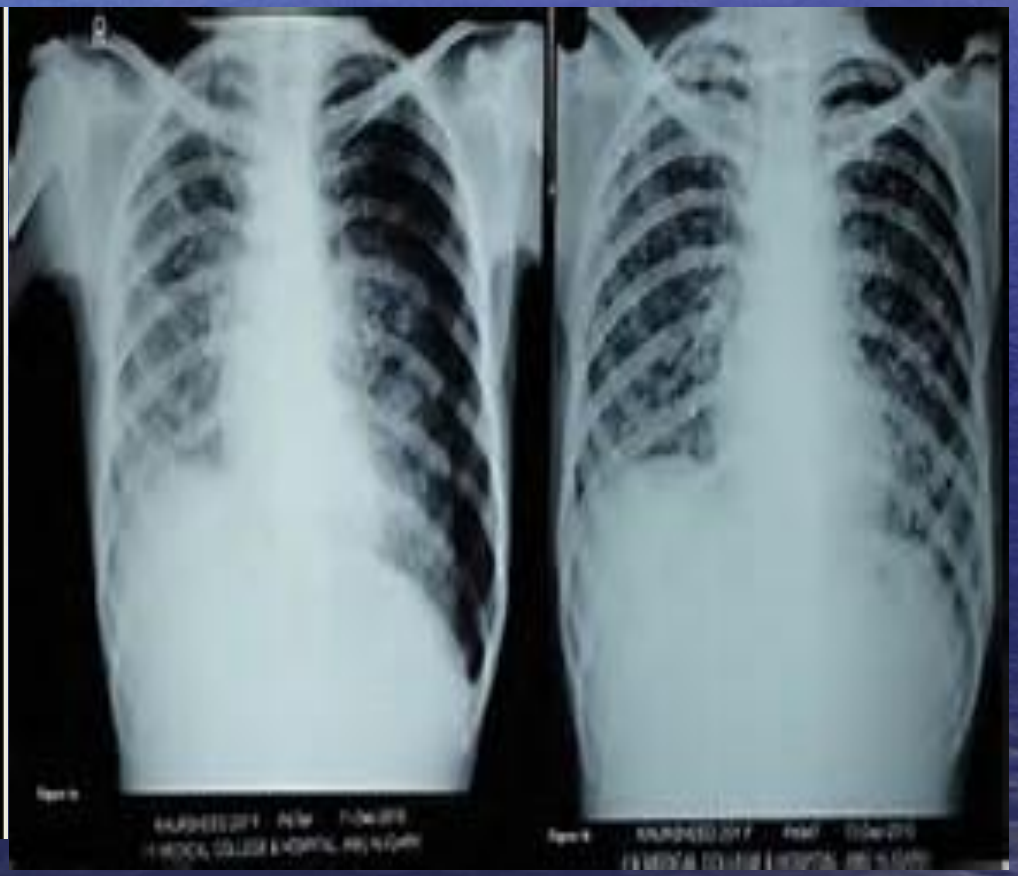


EXTENDED pulmonary tuberculosis





TREATMENT - drugs

Basic of drugs for treatment TB are:

- Isoniazid (INH)
- Rifampincin (RIF; Rifadin),
- Pyrazinamid (RPT; Priftin)
- Ethambutol (EMB)

TREATMENT OF TB

I. INITIAL PHASE - Preferred Regimen

Daily INH, RIF, PZA, and EMB 8 weeks (2 mo)

Alternative regimen: daily INH, RIF, PZA, and EMB 2 weeks, then twice weekly for 6 weeks

II. CONTINUATION PHASE

Daily INH and RIF for 18 weeks (4-6 mo)

Continuation Phase Alternative reg.:Twice-weekly

INH and RIF for 18 weeks

PRINCIPES TREATMENT OF TB THERAPY

1. **Combined** (initial phase 2 months-mos : 3-4 drugs)
2. **Continuous** (4-6 mos .) TB of kidney, lymphonodes, spinal chord, therapy is more than 12)
3. **Controlled** (constant control for regular take medication)

- **DRUGS :** rifampicin (RM) , isoniazid (INH - B6) , ethambutol (ETB) , pyrazinamide (PZY) , and rare streptomycin (STM)

Other Antibiotics : - Quinolones , azithromycin , makorlides,etc

IMPORTANT

- It is very important that people who have been in contact with a tuberculosis patient control immediately and 2x per year for 2 years
- TB is not scary when it is start on time and properly treated.

HVALA NA POZORNOSTI

MODRA ŠPILJA BIŠEVO

KORNELIJA MIŠE


Thank you for your attention!
pO2 7,7 kPa, pCO2 4,1 kPa

GRANULOMATOSIS WEGENEROV (WG)
GOODPASTURE SYNDROME
REUMATHOID ARTRITIS
SYSTEMIC SCLEROSIS
ANKYLOSIS

You will learn and hear about these diseases in other lessons (course-lecture) in Rheumatology

- WEGENER,S GRANULOMATOSIS

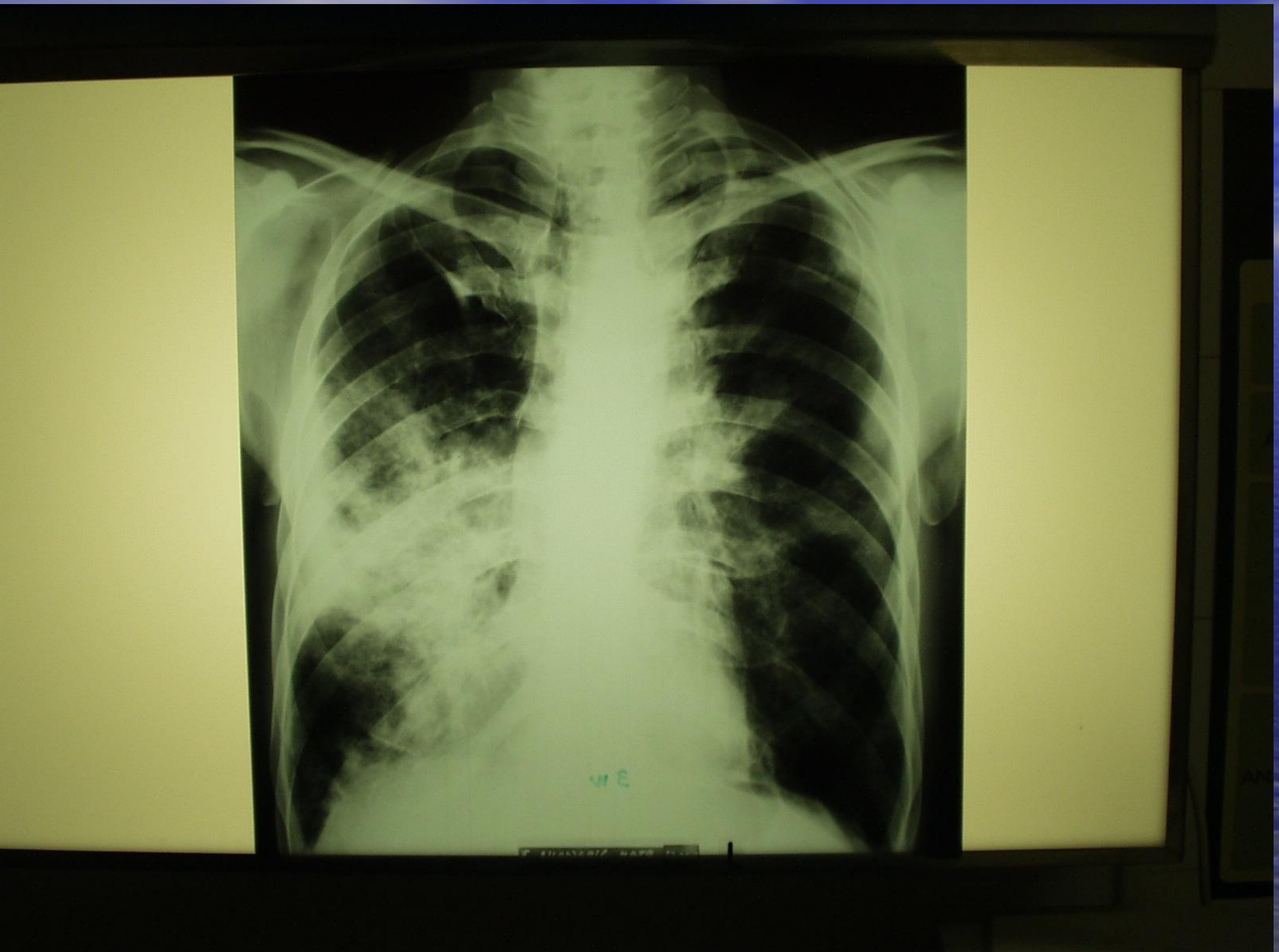
- *Nekrotizirajuća granulomatoza s angiitisom (arteriole i venule)*
- Nepoznata uzroka,javlja se 4/100000 stan.
- Češće mušrakci: 2-3:1
- Lokalizacija: nosna forma, plućna i bubrežna

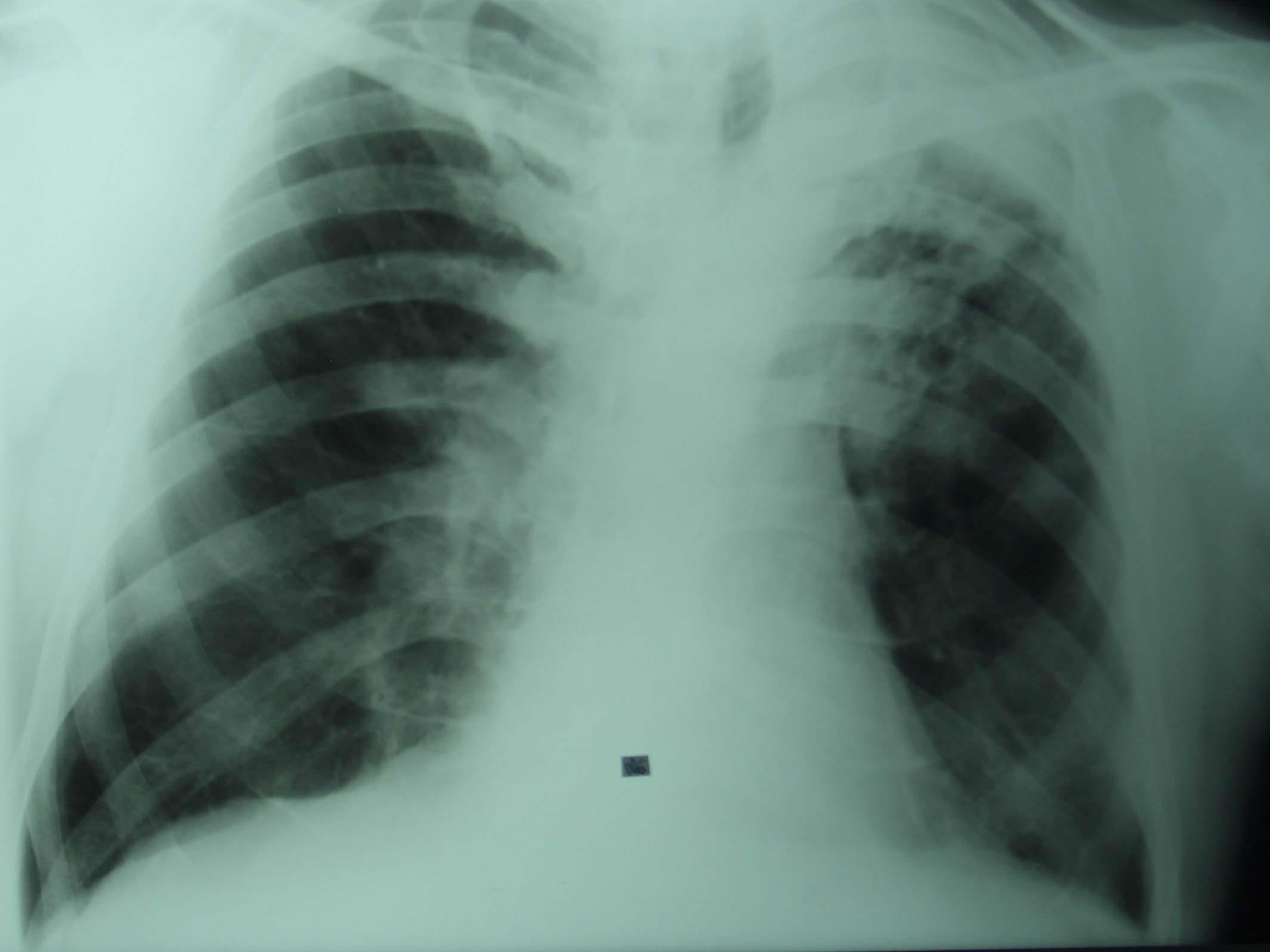
Nosna forma

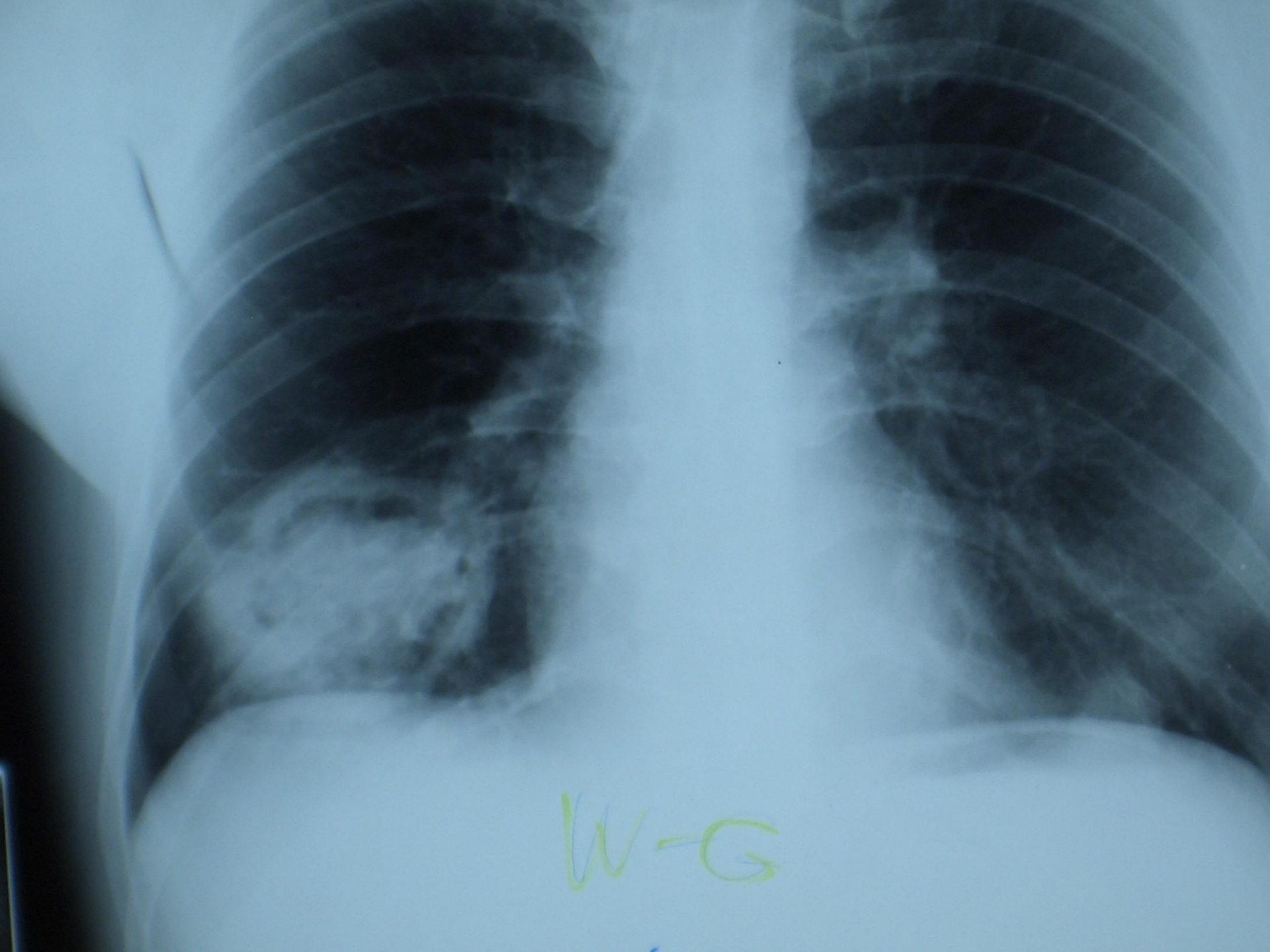
- 75-80%
- Česti sinuitisi, gnojne infekcije, rinitisi, krvarenja iz nosa i neugodan zadah
- Ponekad razorena nosna hrskavica
- Dg.: *biopsija nosne sluznice*

PLUĆNA FORMA (85-90%)

- Vrućica, kašalj, hemoptize, recidivirajuće bakterijske upale, mršavljenje, znojenje
- RDG pluća: okrugli solitarni infiltrati s ili bez raspada (slični TB), ili difuzna zasjenjenja, jedno ili obostrano (krvarenja u alveole)
- Laboratorijski nalazi: *SE visoka, leukocitoza*, CRP, trombocitoza, *c-ANCA poz.*



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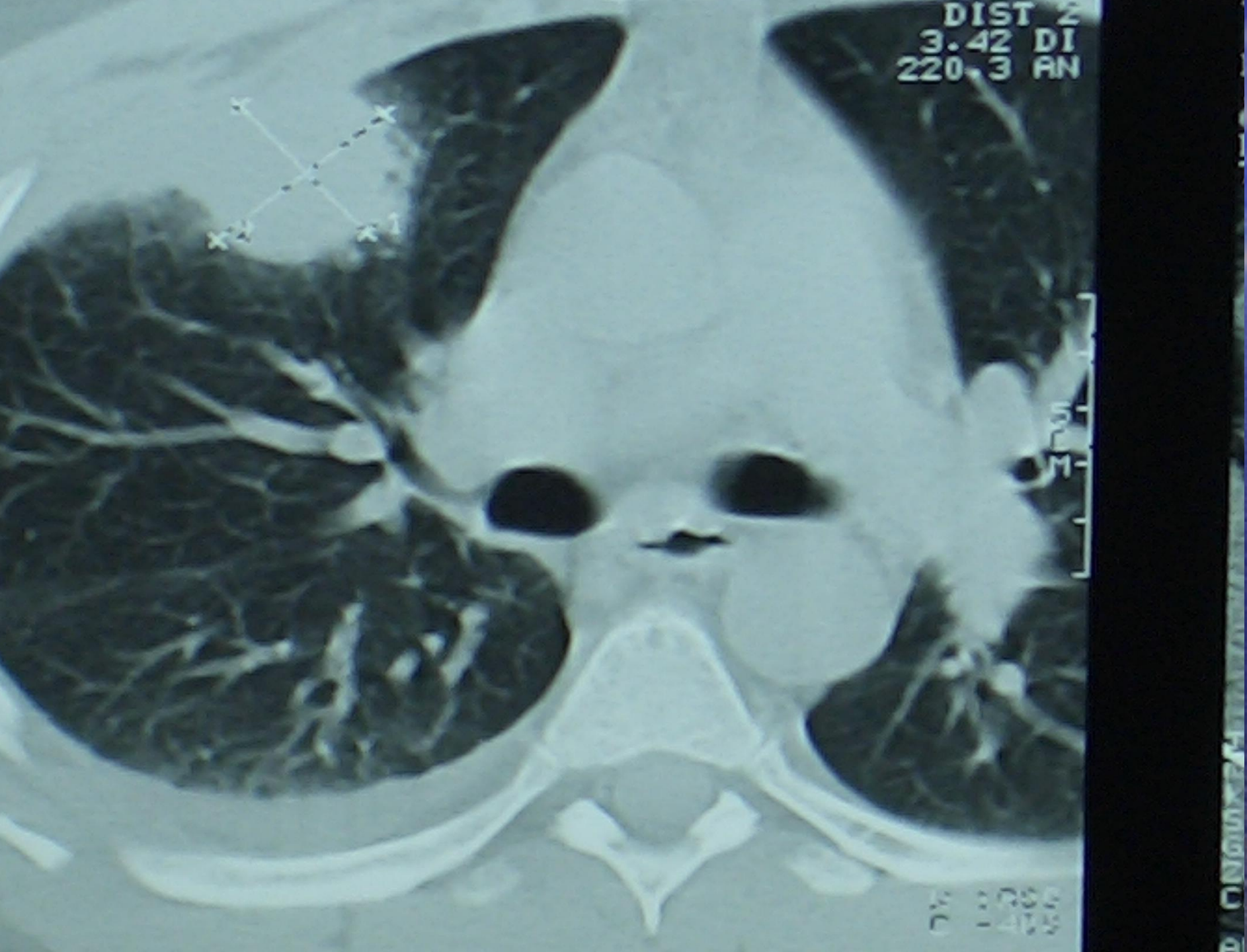
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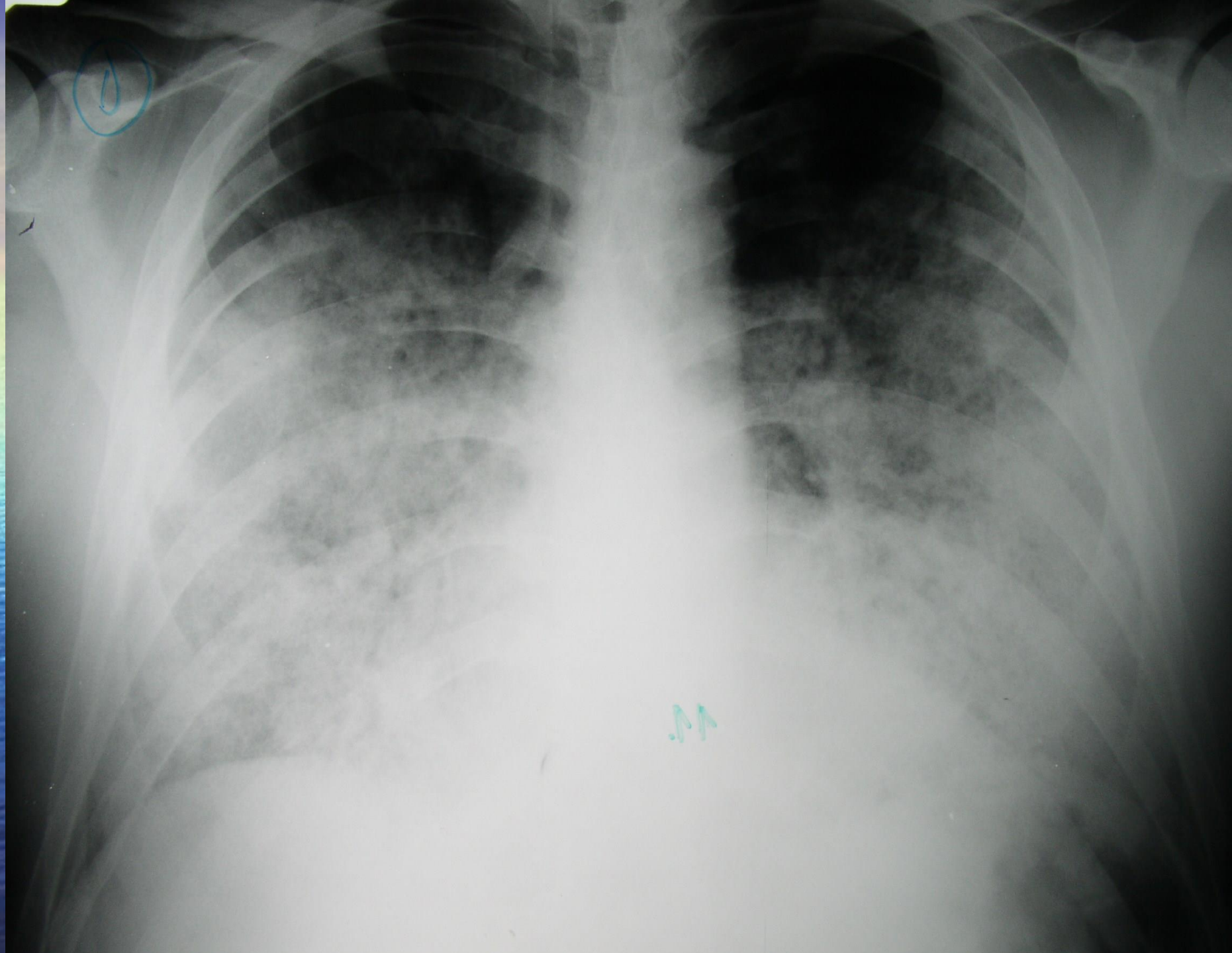


Bubrežni oblik

- Česte infekcije urotrakta
- Eritrociturija
- Povećane vrijednosti kreatinina, ureje
- Oligurija do anurije i bubrežne insuficijencije.

Drugi oblici:

- Kosti - zglobovi : 65-70%
- Uho : 61%
- Oko: 50%
- Živčani sustav: 22%
- Srce: 10%

GOODPASTURE SINDROM

- **Plućna hemoragija**
- **Brzo napredujući glomerulonefritis**
- **Cirkulirajuća antitijela usmjerena na bazalnu membranu glomerula (*anti-GBM)***

- Antitijela su karakteristična, usmjerena su na antigen baz. membrane = *alfa-3 lanac kolagena tipa IV.*
- *Većina bolesnika su pušači – pušenje(organski ugljikovodici) oštećeje endotel bazalne membrane u plućima (omogućuju pristup autoantitijelima). Virusi – mogući uzročnici.*

Patološki nalaz:

- U **plućima** nastaju ponavljajuća krvarenja u međualveolarne prostore (slično kod hemosideroze pl.):
- **Akutna faza:** svježi E, a poslije sidrofagi
- **Kronična faza:** hiperplastični pneumociti, dilatacija i savijenost kapilara, interst. fibroza
- **Bubrezi:** fokalni i prolifer. nekrotizirajući glomerulonefritis

KLINIČKA SLIKA

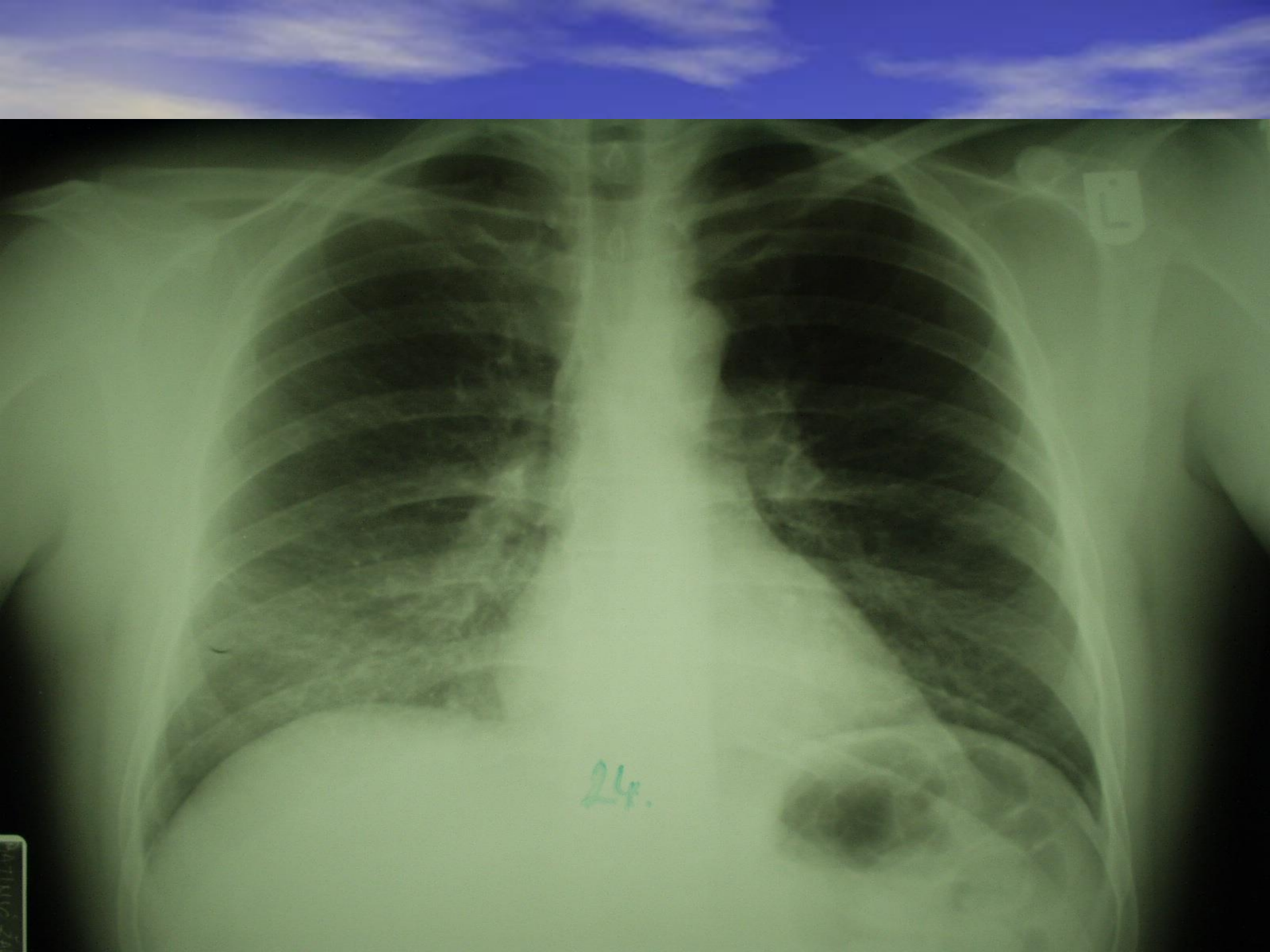
- Kašalj, zaduha, hemoptize: do masivnog kravrenja
- Anemija: nemoć, malaksalost, artralgije, vrućica, hematurija, oligurija, anurije: renalna insuficijencija
- DIJAGNOZA: anti-GBM u 90% sl. poz.
- Biopsija tkiva: imunofluores. dokaz linearnih depozita antitij.na bazalnoj membrani (pluća, bubrezi)

Liječenje:

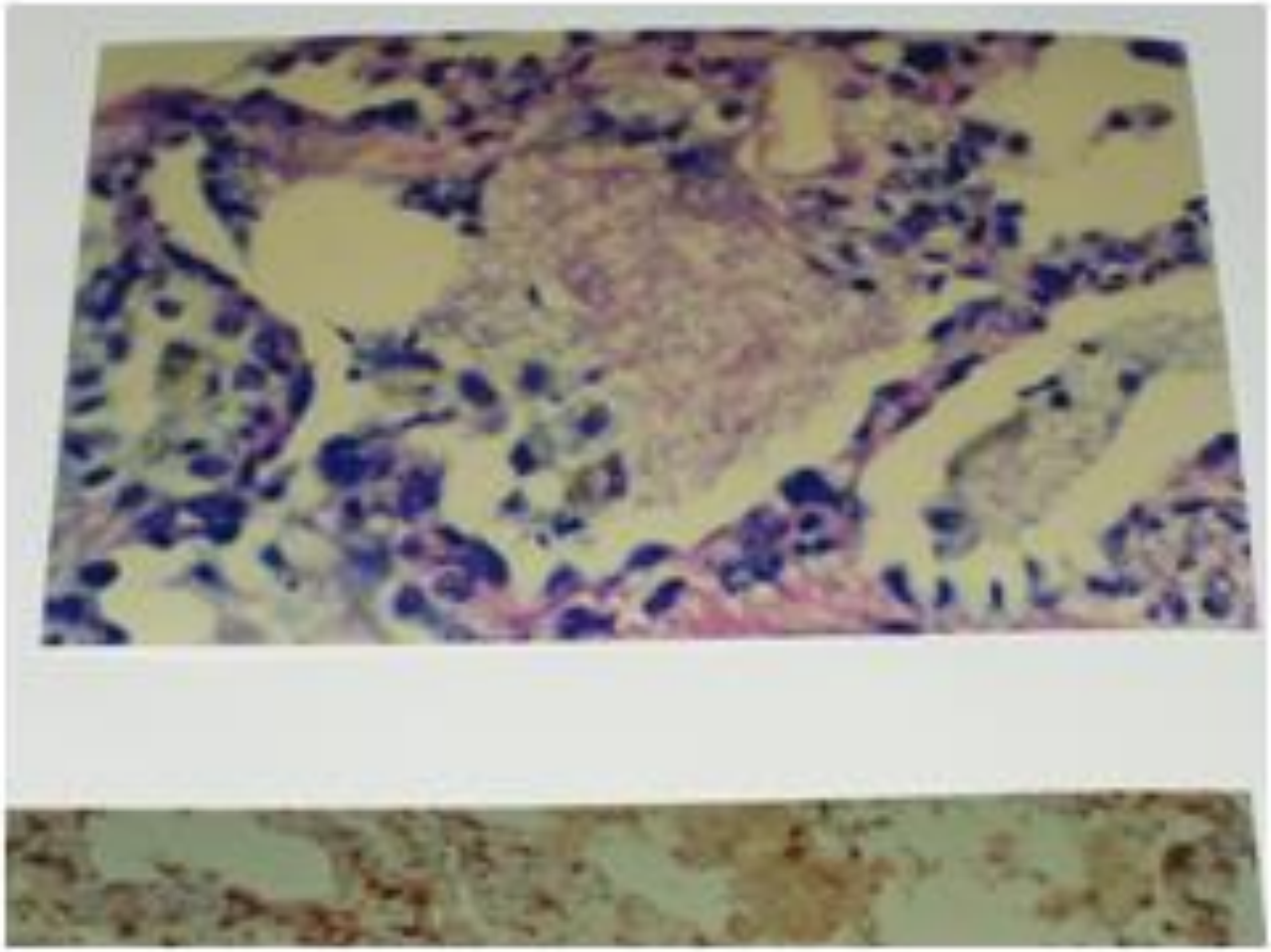
- KS (metilprednisolon) 60 mg/dan
- Ciklofosfamid 3mg/kg /dan
- Azatioprin 1 mg/ dan

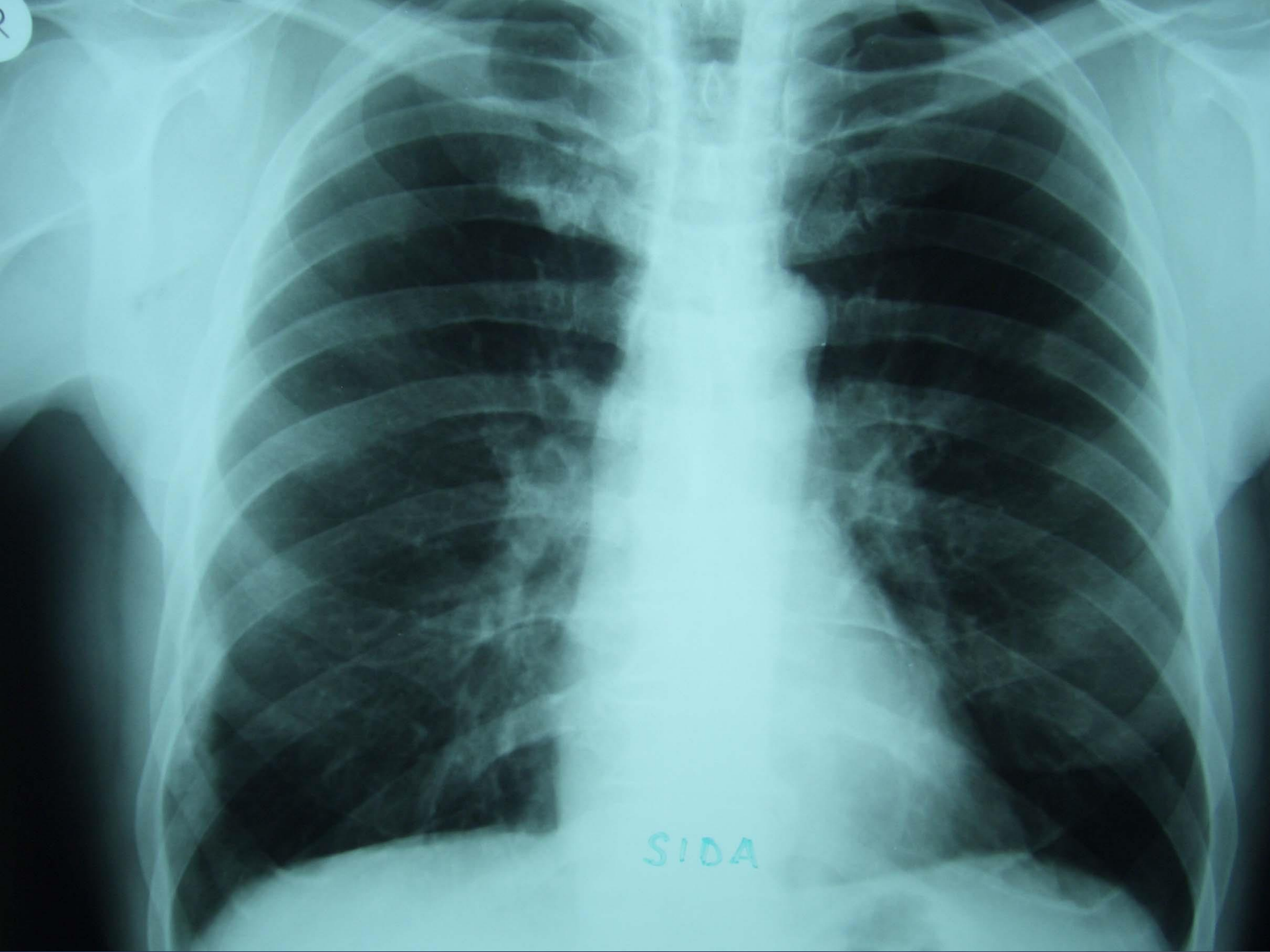
INTERSTICIJSKA PNEUMONIJA

- vrućica (supfebrilna- visoko febr.)
- zaduha, tahipneja,
- suhi kašalj, hemoptize
- znojenje

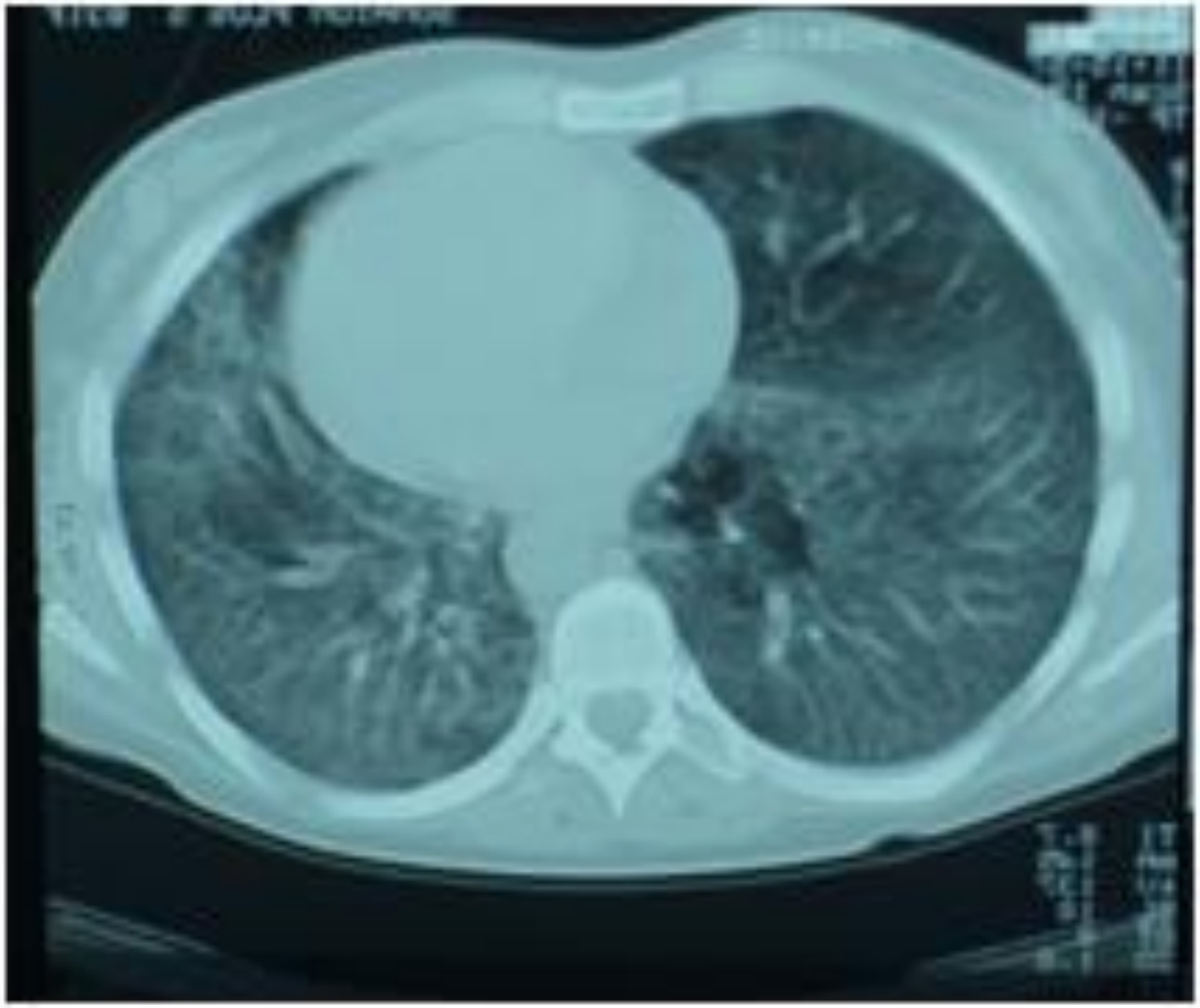

24.

Slika 5.: Patohistološki nalaz plućevine: proširen intersticisjki prostor s gustim infiltratima –mrežicom P. carinii.




SIDA

Slika 8.: CT prsišta u iste bolesnice. Gusta infiltracija plućnog intersticija, "mliječno staklo".



- PLUĆNI EOZINOFILNI INFILTRATI

- Porast broja eozinofila (Eo) u perifernoj krvi i/ili tkivima (10% od ukupnih L)
- Uzroci: alergijske, zarazne, maligne i idiopatske bolesti.

  Lijekovi !

- Najčešće su nepoznatog uzroka.
- Eozinofilopoezu potiču čimbenici rasta Eo: stimulator kolonije granulocita i makrofaga (GM-CSF), IL-3,osobito IL-5.

- Eo u ak. stanju: pojačana im je matabolička aktivnost, citotoksičnost posredovana antitijelima i povećana sinteza leukotriena 4 (LTC4)

- Javlja se najčešće u imunosnim stanjima: *IL-5 stvaraju T-pomagački limf.tip 2, tada i IgE povišen u krvi.*

- Kod nejasnih stanja (neimunoloških), PristIgE nije povišen.

1. **Plućna eozinofilija uzrokovana lijekovima:**

   (ampicilin, cefotaksim,etambutol, penicilin, tetraciklini, sulfonamidi,nesteroidni antireumat.,kaptopril, cimetidin,bleomicin, metotreksat, i dr.).

2. **Lofflerov sindrom:**

   (Ascaris lumbricoides, Toxocara): 9-12 d. nakon ingestije jajašaca askarisa: suhi kašalj, substernalano pečenje.

   RDG pluća: magličasti infiltrati u plućima.

Stolica na parazite: tek 40-60 dana nakon simpt.

Alergijska bronhopulmonalna aspergiloza

Udisanjem spora ubikvitarnih gljivica kod imunokomprom. osoba

- alerg. astmu posredovanu IgE protutij.
- invazivnu aspergilozu
- aspergilom
- alerg. hipersenzitivni pneumonitis
- alerg. bronhopulm. aspergilozu

Simptomi ABPA (Alerg. bronhopulm. aspergiloza)

- Simptomi astme, plućni infiltrati, mukoidne impakcije bronha, eozinofilija u perif. krvi, cilidr. bronhiektazije u gor. režnjevima.

- Bolest u astmatičara i bolesnika s cističnom pl. fibrozom.

Kronična eozinofilna pneumonija – KEP (Carrington)

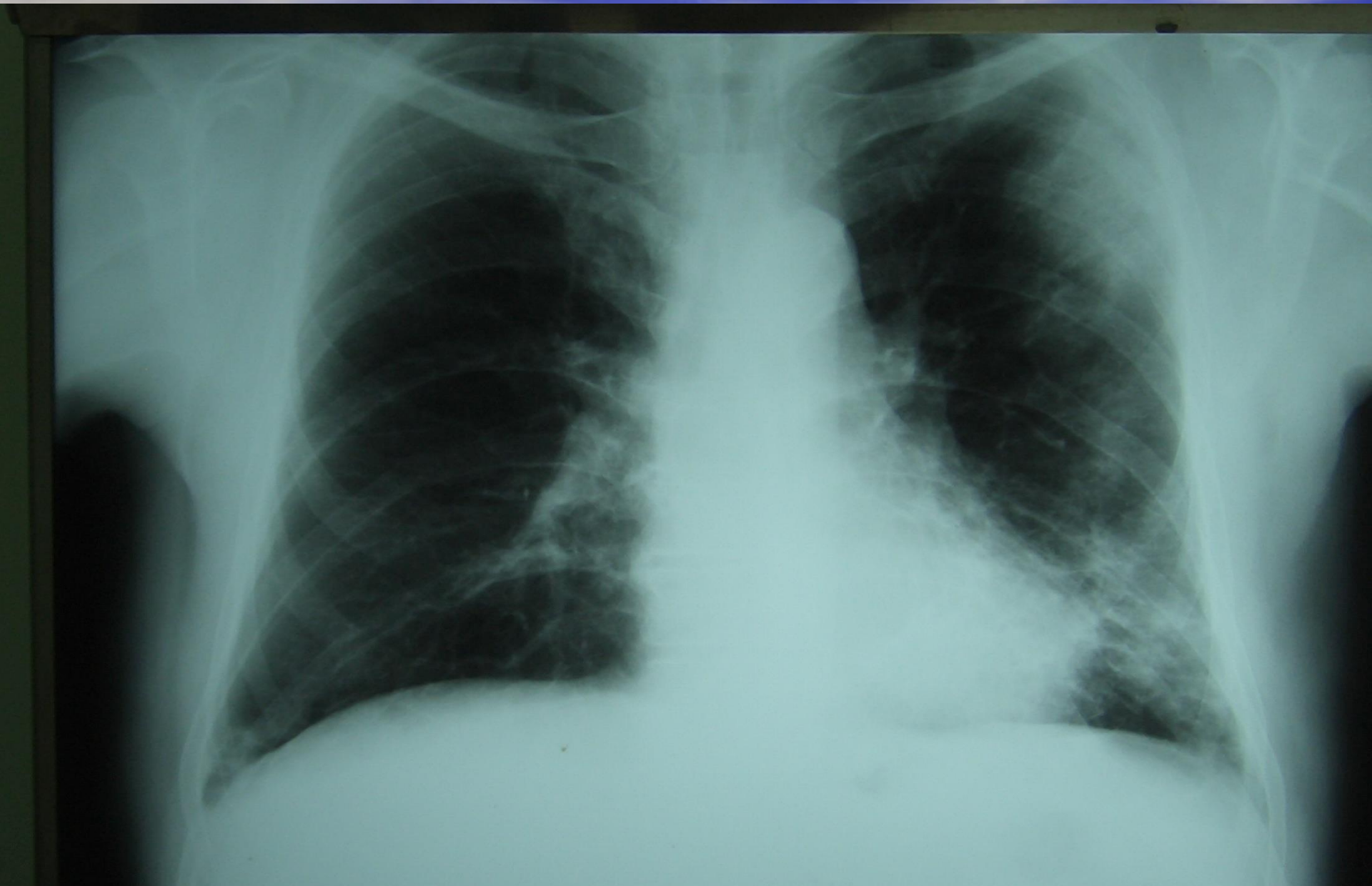
Infiltracija plućnog intersticija s Eo, manje limfocitima i drugim mononukl. upalnim stanicama, makrofagima

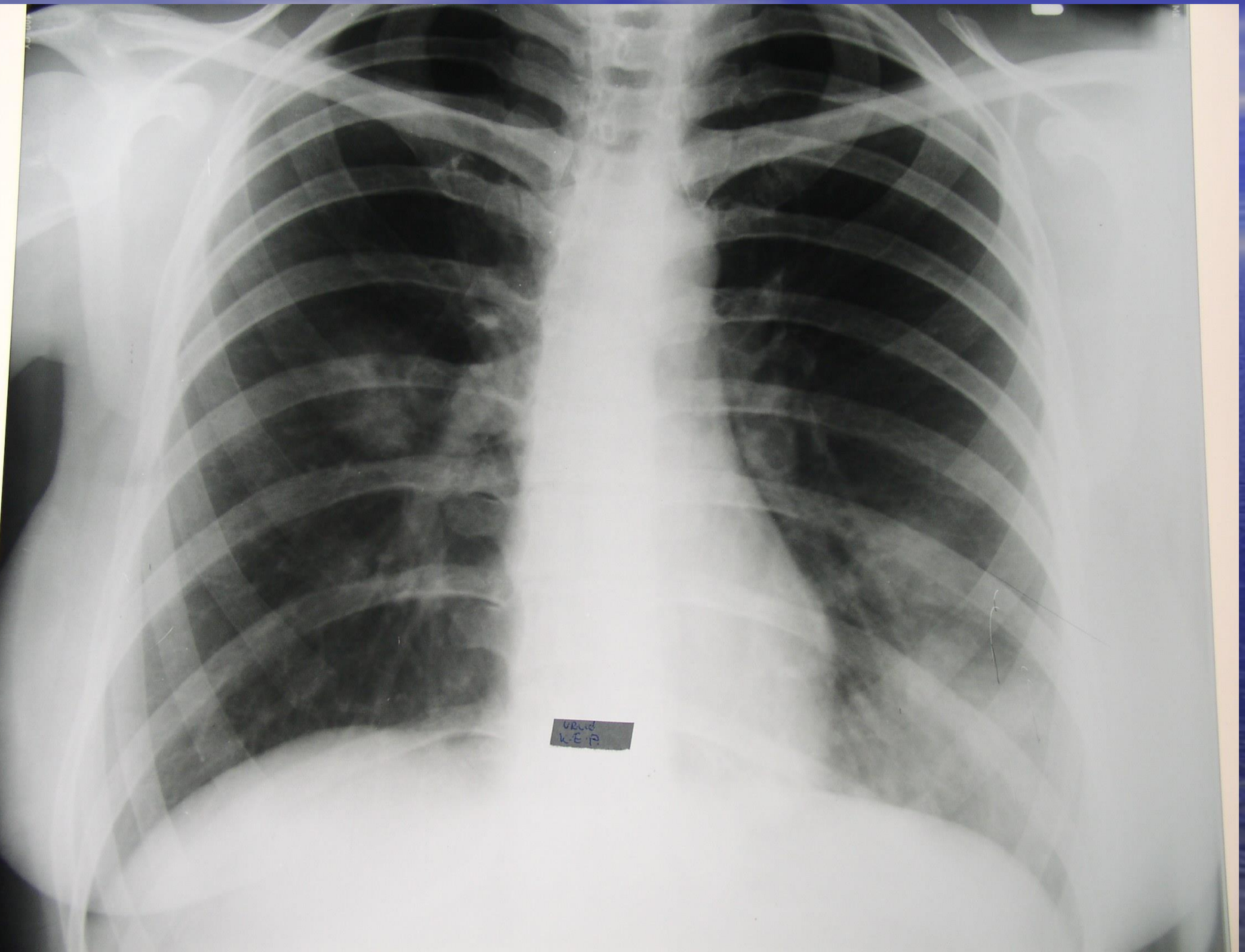
Simptomi: vrućica, znojenje, suhi kašalj, zaduha, mršavljenje, ponekad hemoptize

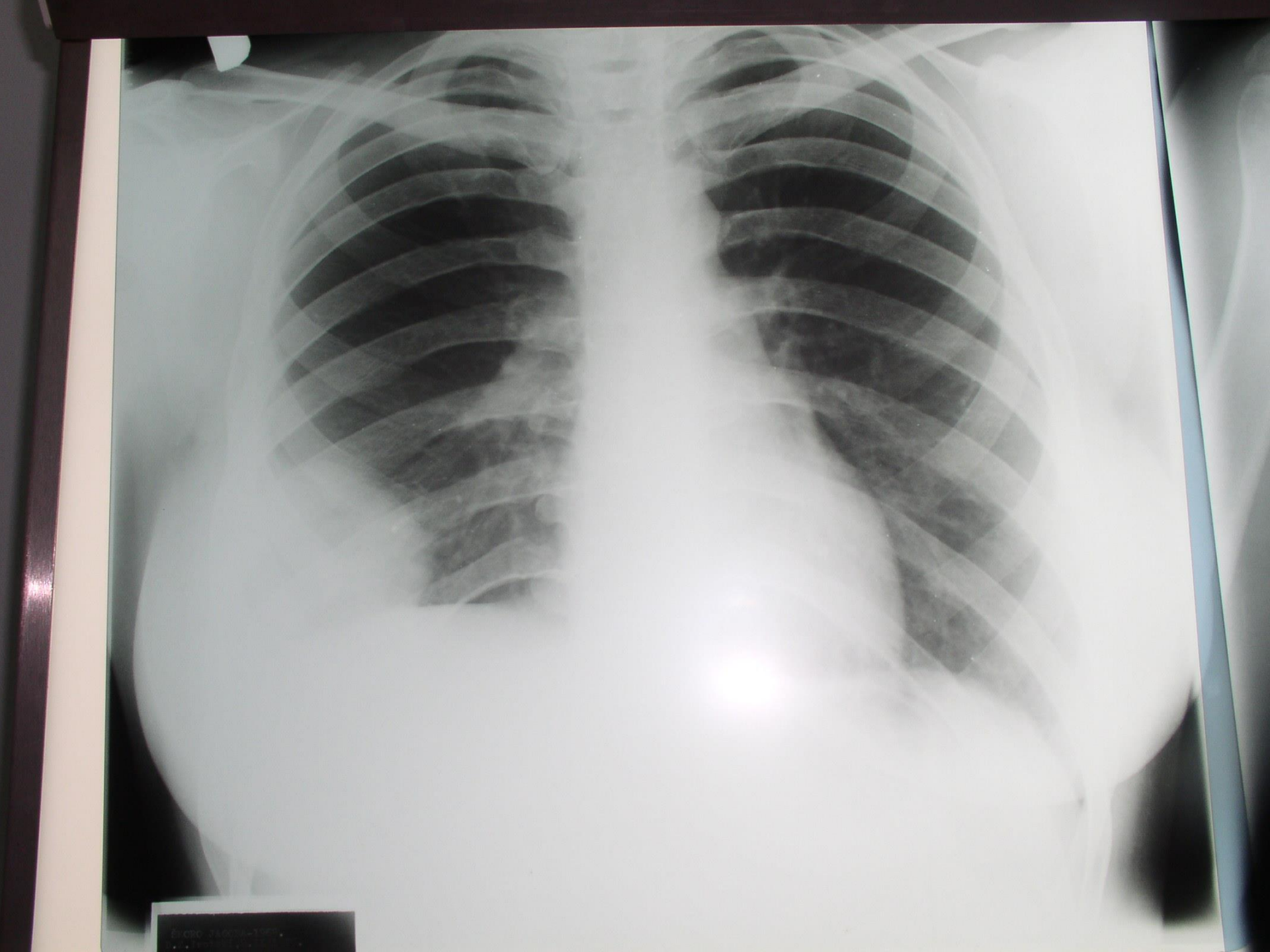
Nepoznate etiologija

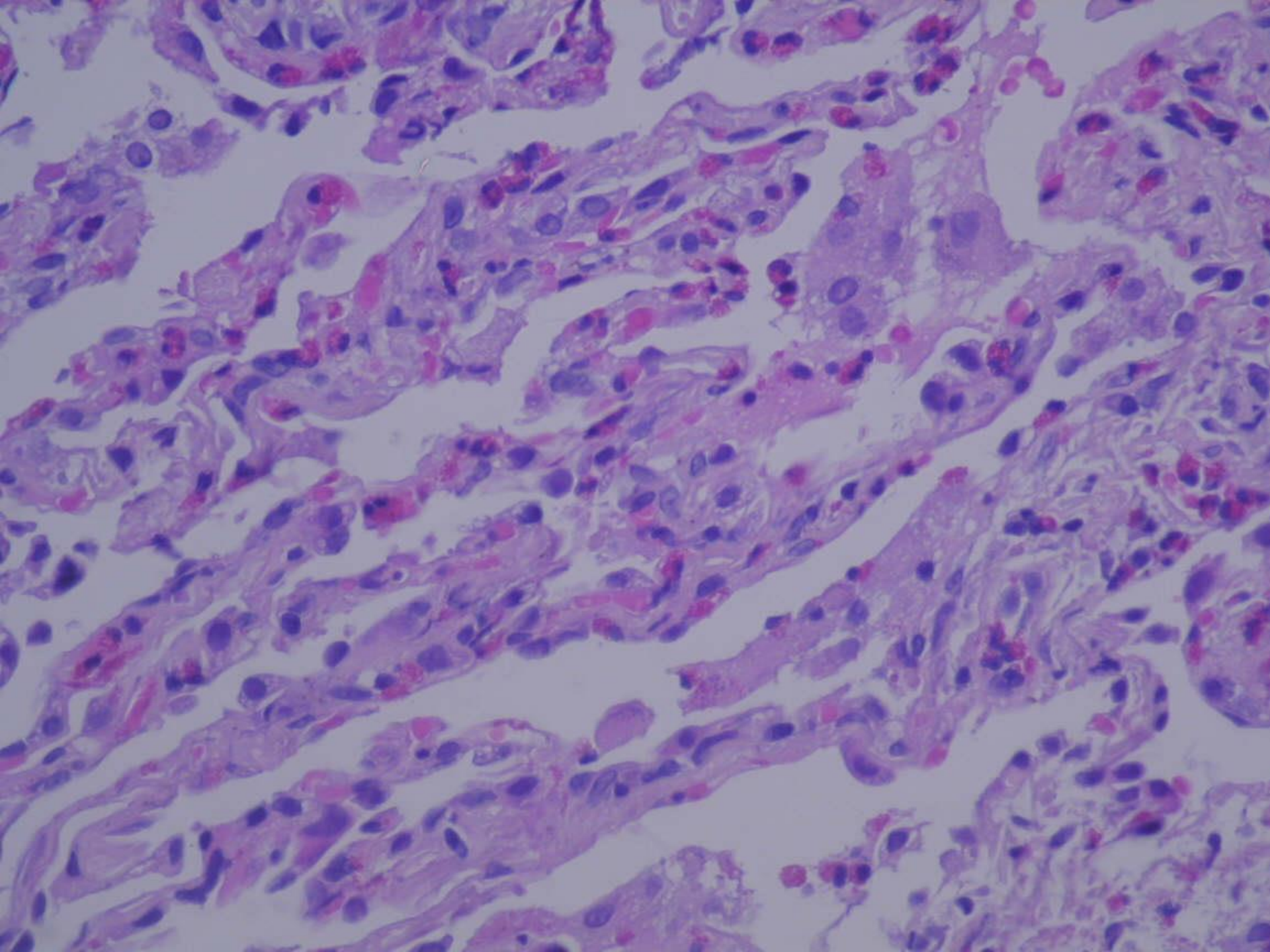
- **Auskultacija pluća:** krepitacije obostrano.
- **RDG pluća:** nježni, trokutasti infiltrati (segm.), često migriraju
- **Laborat. nalazi:** SE jako ubrzana, u perifernoj krvi eozinofilija (često i bez)
- **BAL:** eozinofili
- **DG.:** Biopsija pluća (TBB ili otvorena biopsija: infiltracija alveola eoz.)
- **Terapija:** KS- promtan odgovor na KS.
- Često recidiviraju.

KEP-Carrington









CHURG-STRAUSS SINDROM - CSS

Alergijska granulomatoza povezana s astmom i perifernom eozinofilijom. Nepoznata uzroka, oboljevaju atopičari

KRITERIJI ZA CSS (po ACR)

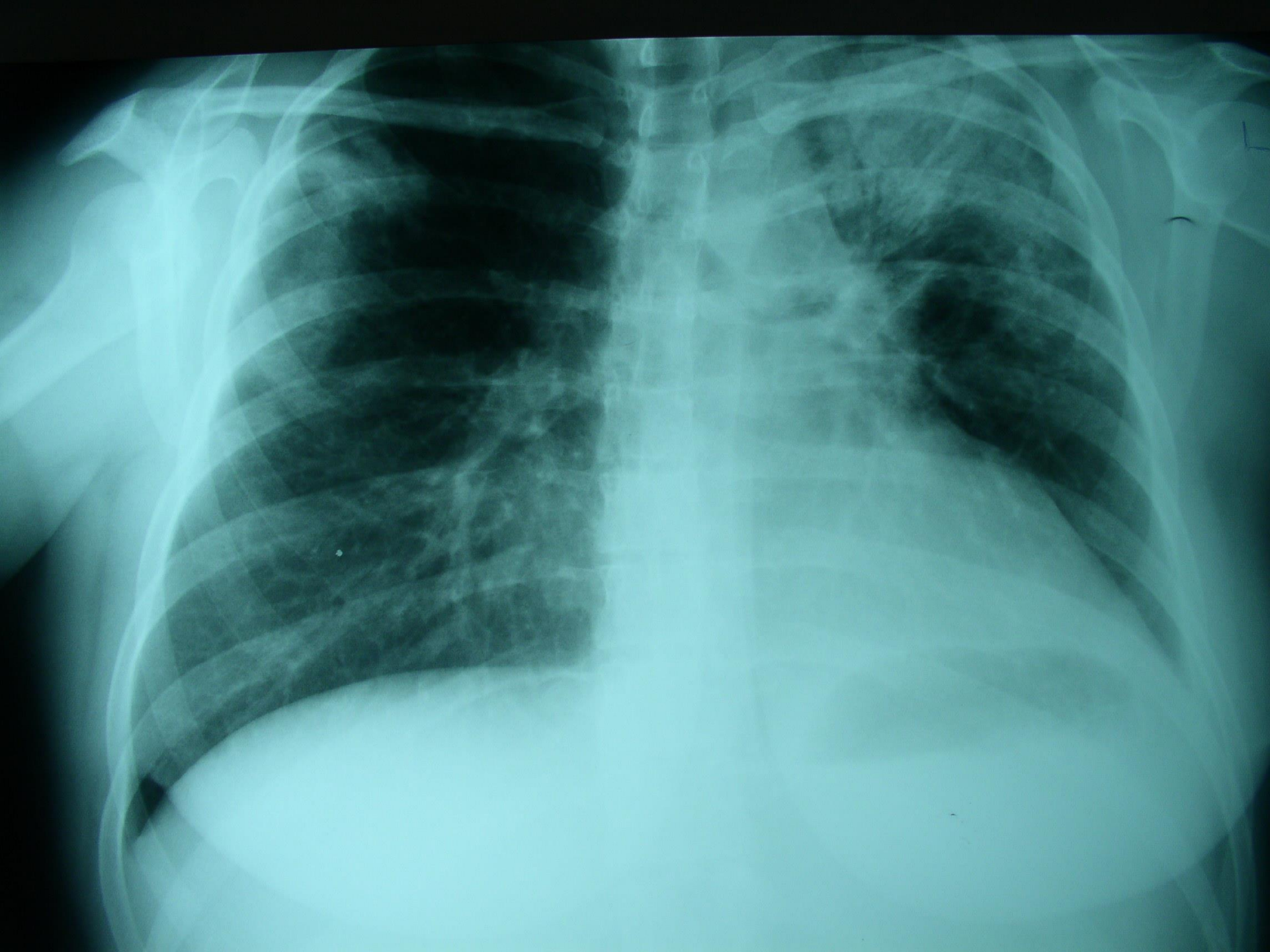
1. Astma (97% sl.)
2. Eozinofilija u perif.krvi (>10%)
3. Alerg.rinitis/paranazalni sinusitis (90%), često s nosnom polipozom (61%)
4. Plućni infiltrati: migrirajući i prolazni
5. Periferna neuropatija-mononeuritis multipleks
6. Patohistološki nalaz: perivaskularni i intravas. eozinofilni infiltrati i granulomi: vaskulitis malih i srednje velikih krv. žila (art. i vena).

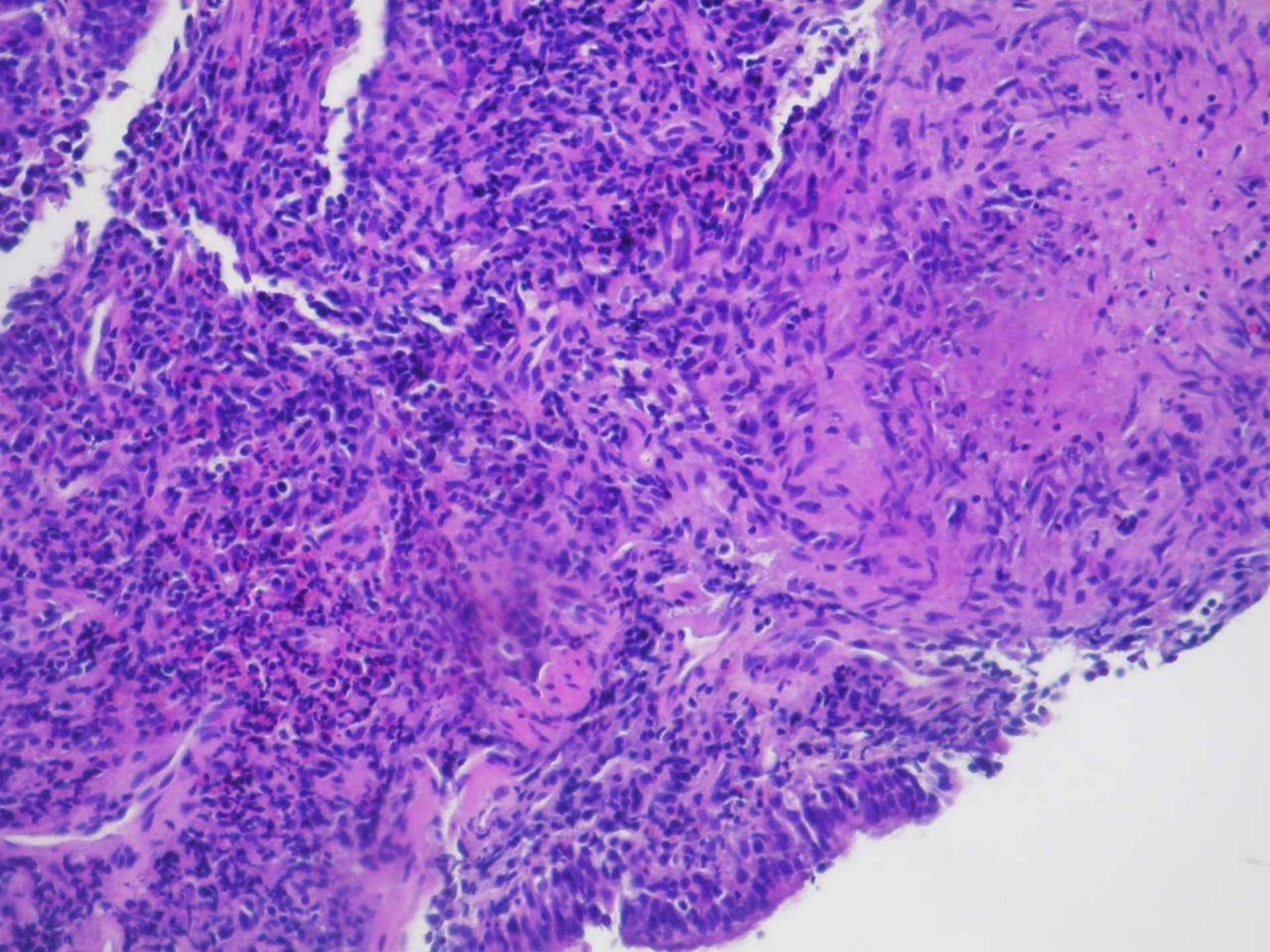
1. **faza:** Sinuitis, rinitis, nosni polipi

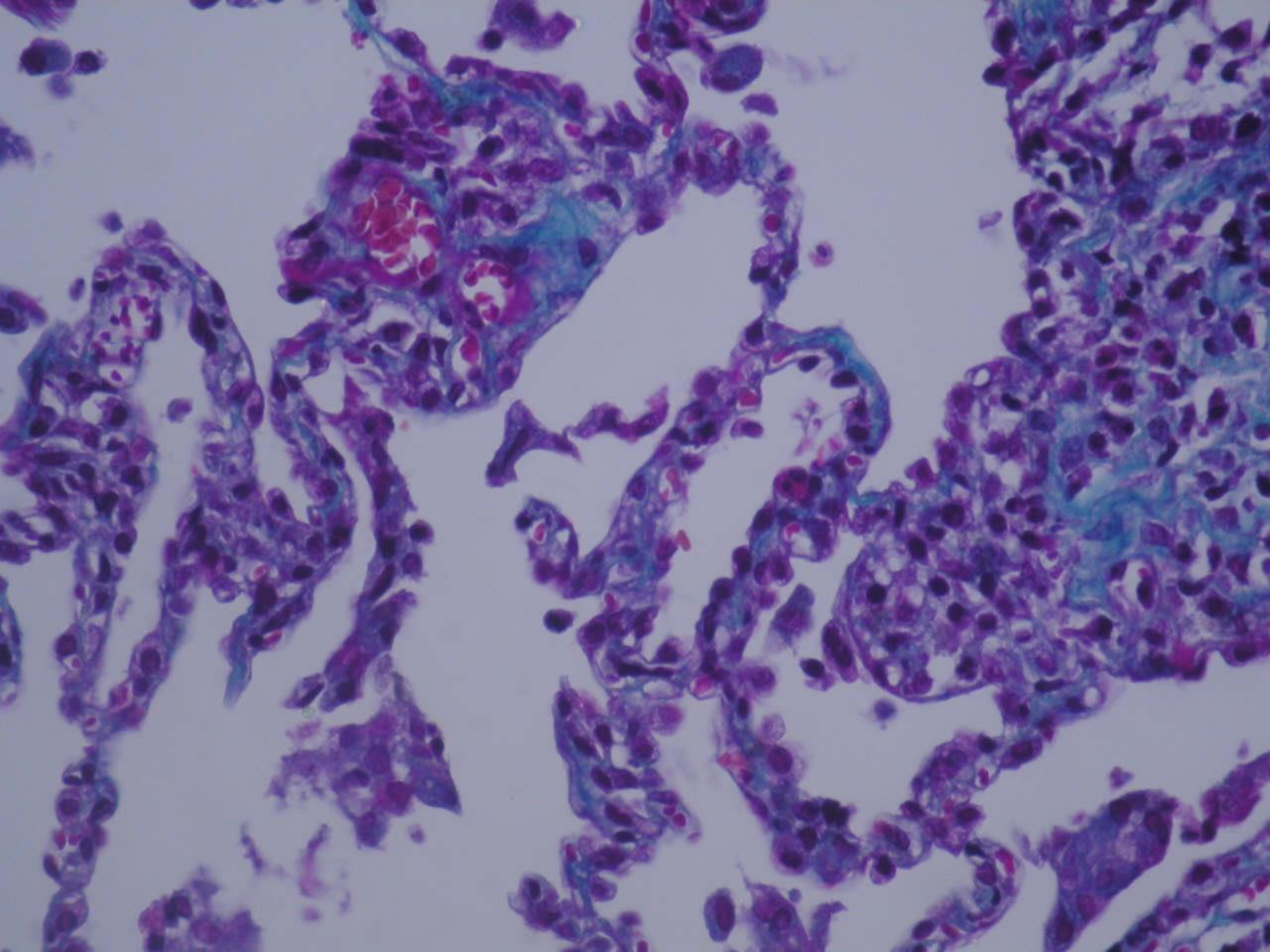
---> **astma. Polineuritis**

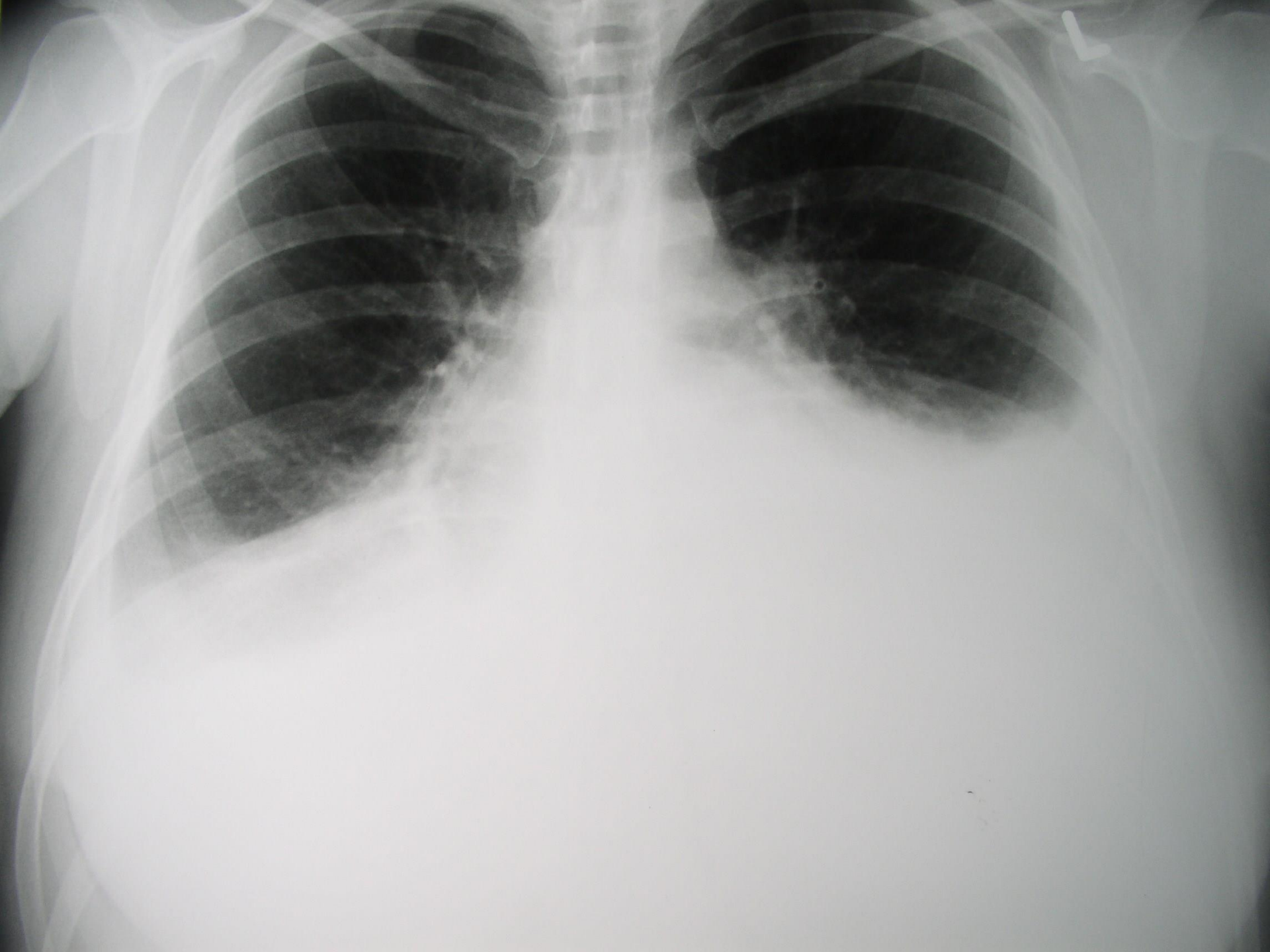
2. **faza:** eozinofilija u perifernoj krvi, eoz. infiltrati pluća, adenopat. medijastinuma, eoz. infiltr. u probavnom sustavu.

3. **faza:** umor, nemoć, mršavljenje, vrućica. Infiltr. u miokrad, koži, perif. živ.sustav-**mononeuritis multiplex**, očni živac, itd.





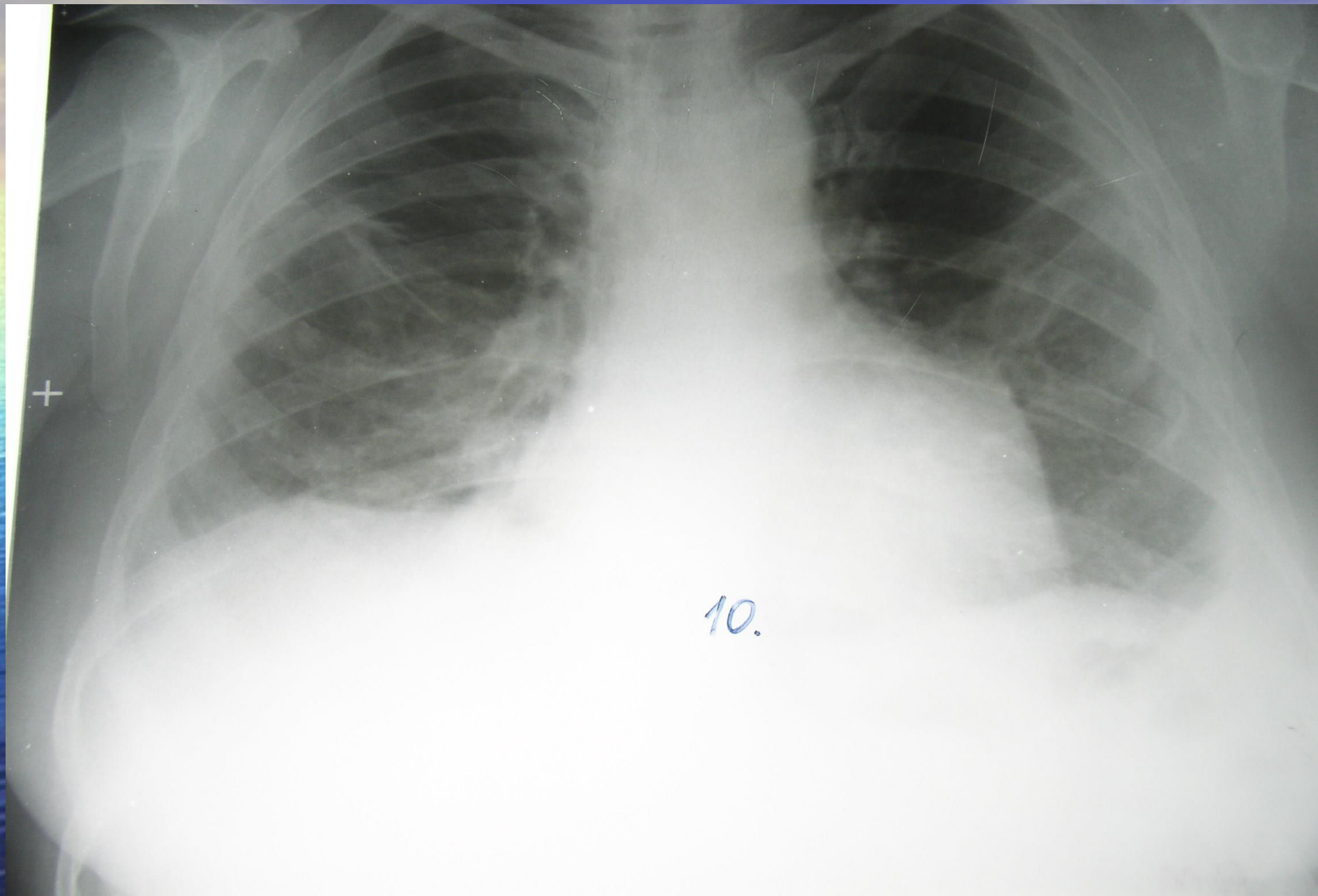


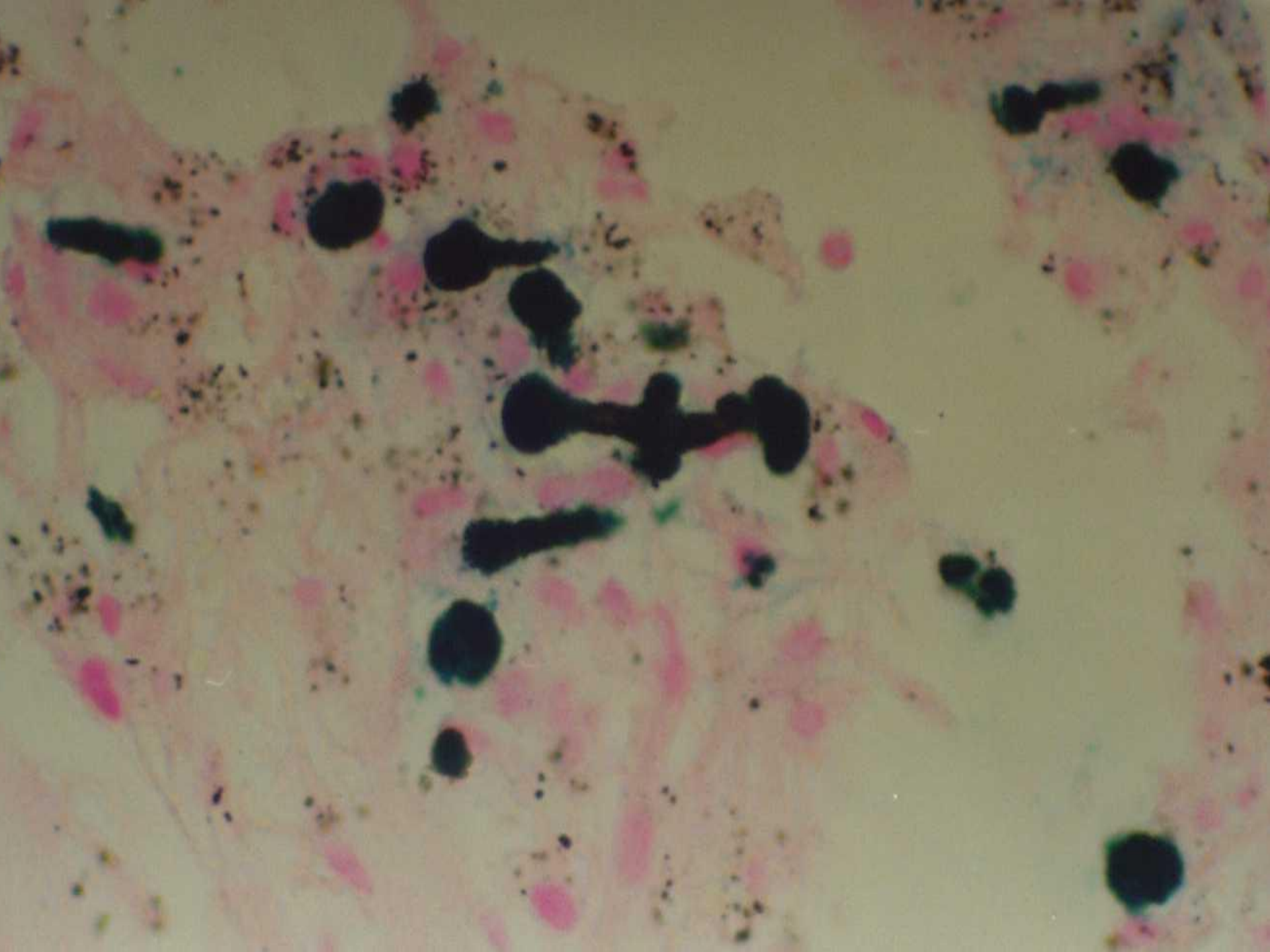


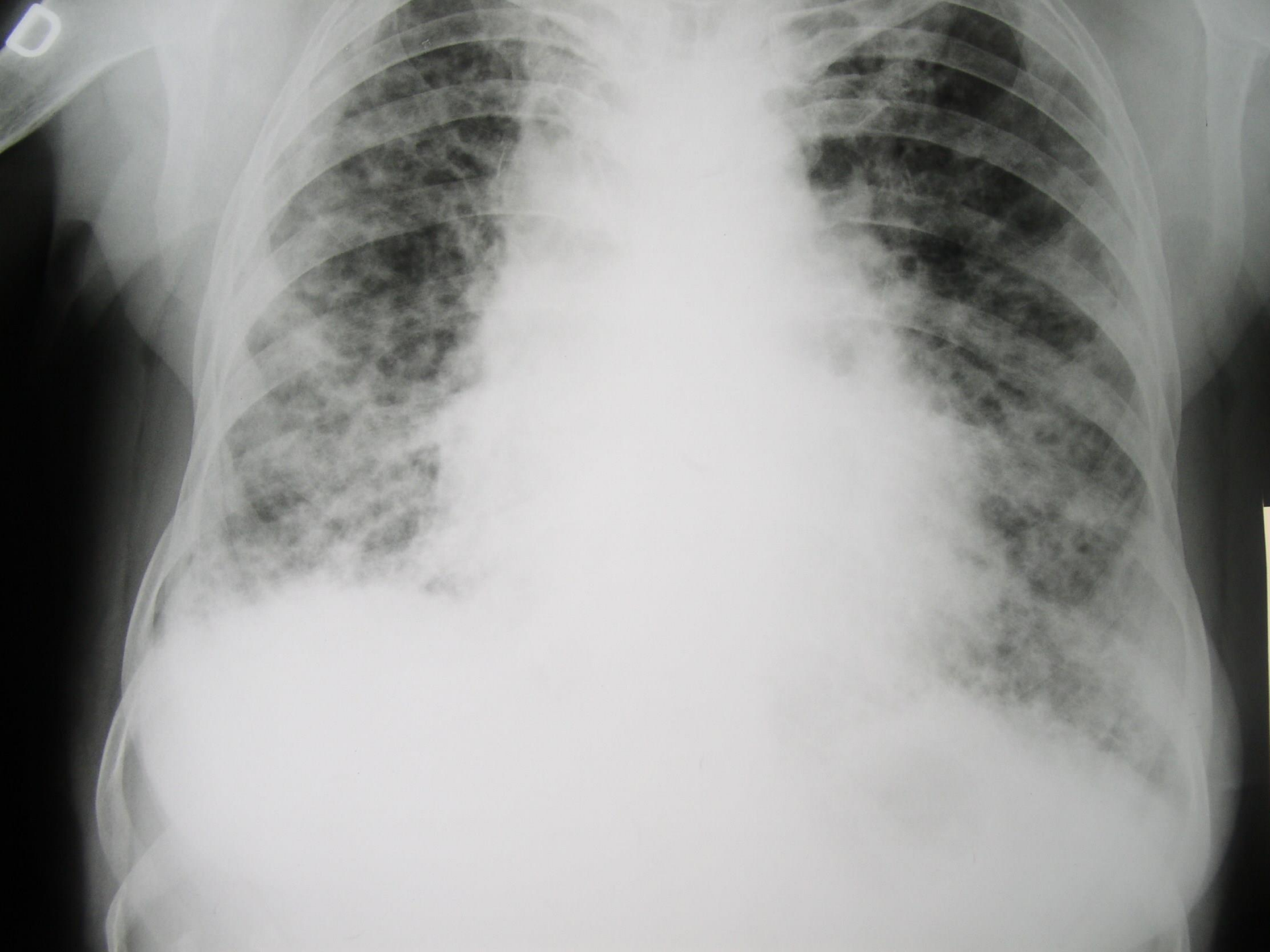
Liječenje:

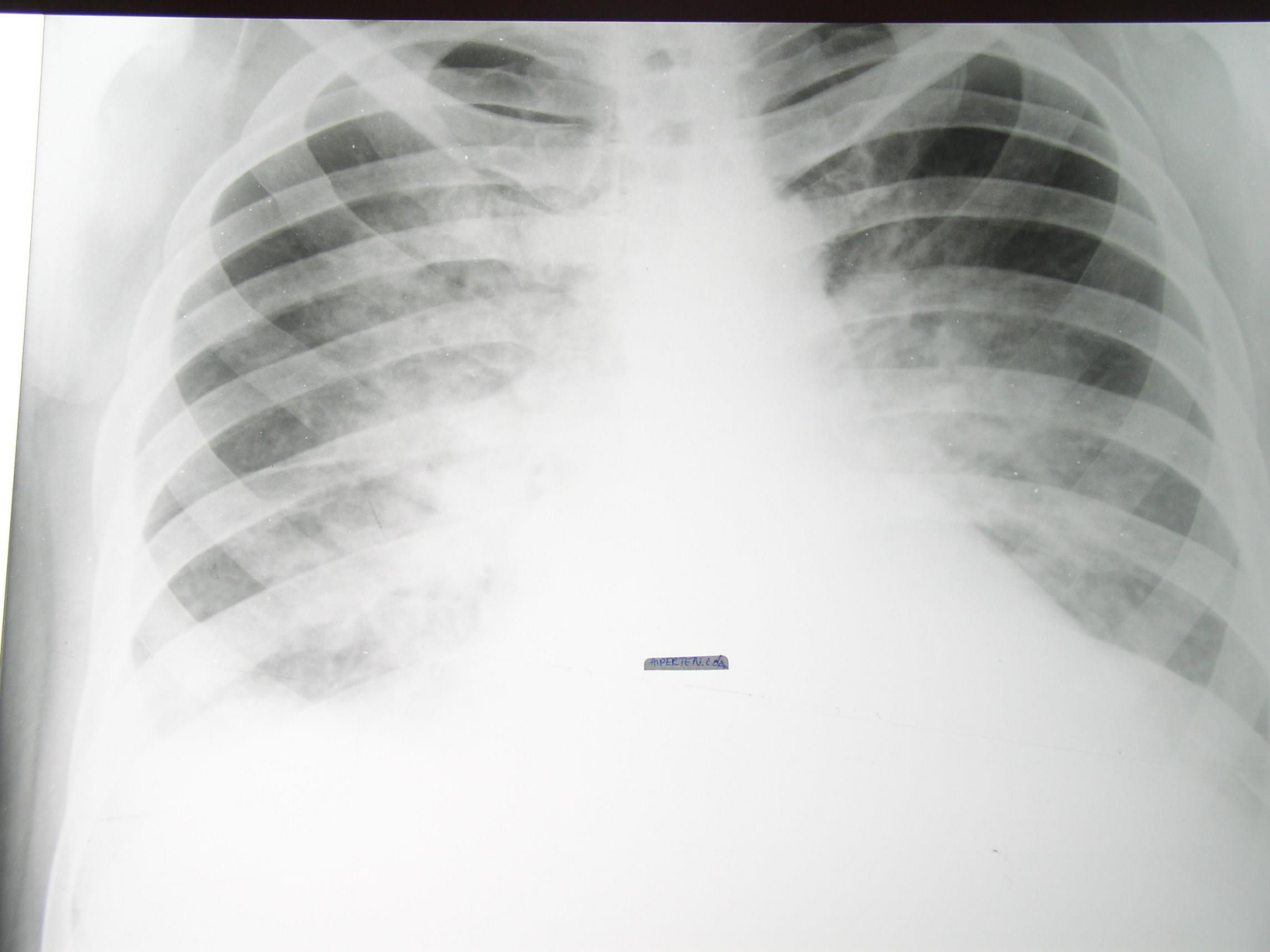
- Kortikosteroidi: metilprednisolon, prednisolon, prednison
- Imunosupresivi: azatioprim, ciklofosfamid, itd.
- Biološki lijekovi (infliximab,adalimumab ?)

Pleuropulmonalna azbestoza









Opstrukcijski nalaz

Kronični opstrukcijski bronhitis

Astma

Cistična fibroza pluća

Obliteracijski bronhiolitis

↓

EKG: znaci opterećenja DK

Bez opstrukcijskog nalaza pluća

RDG pluća: difuzna infiltracija

Auskultacija: krepitacije
Funkcija pluća:
restrikcijske smetnje

FBSK s TBB
ABS: hipokanija s normoksemijom i/ili hipoksemijom
EKG: godinama normalan
UZV srca: obično uredan

sporo nastaje; ovisno o lokalizacijii obimu procesa na kapilarama

↓

INTERSTICIJSKA PLUĆNA FIBROZA

Normalni rdg pluća→HRCT pluća

Oslabljen šum disanja

Restrikcijske smetnje

Kontraindicirana normoksemija ili blaga hipoksemija u mirovanju

EKG: znaci opterećenja DK

UZV srca: pl. hipertenzija

brzo nastaje (mlađi bolesnici)

↓

PRIMARNA PLUĆNA HIPERTENZIJA

HVALA NA POZORNOSTI

KORNELIJA MIŠE


Thank you for your attention!