TREATMENT OF RHEUMATOID LUNG DISEASE

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PLEUROPULMONARY MANIFESTATIONS OF RA

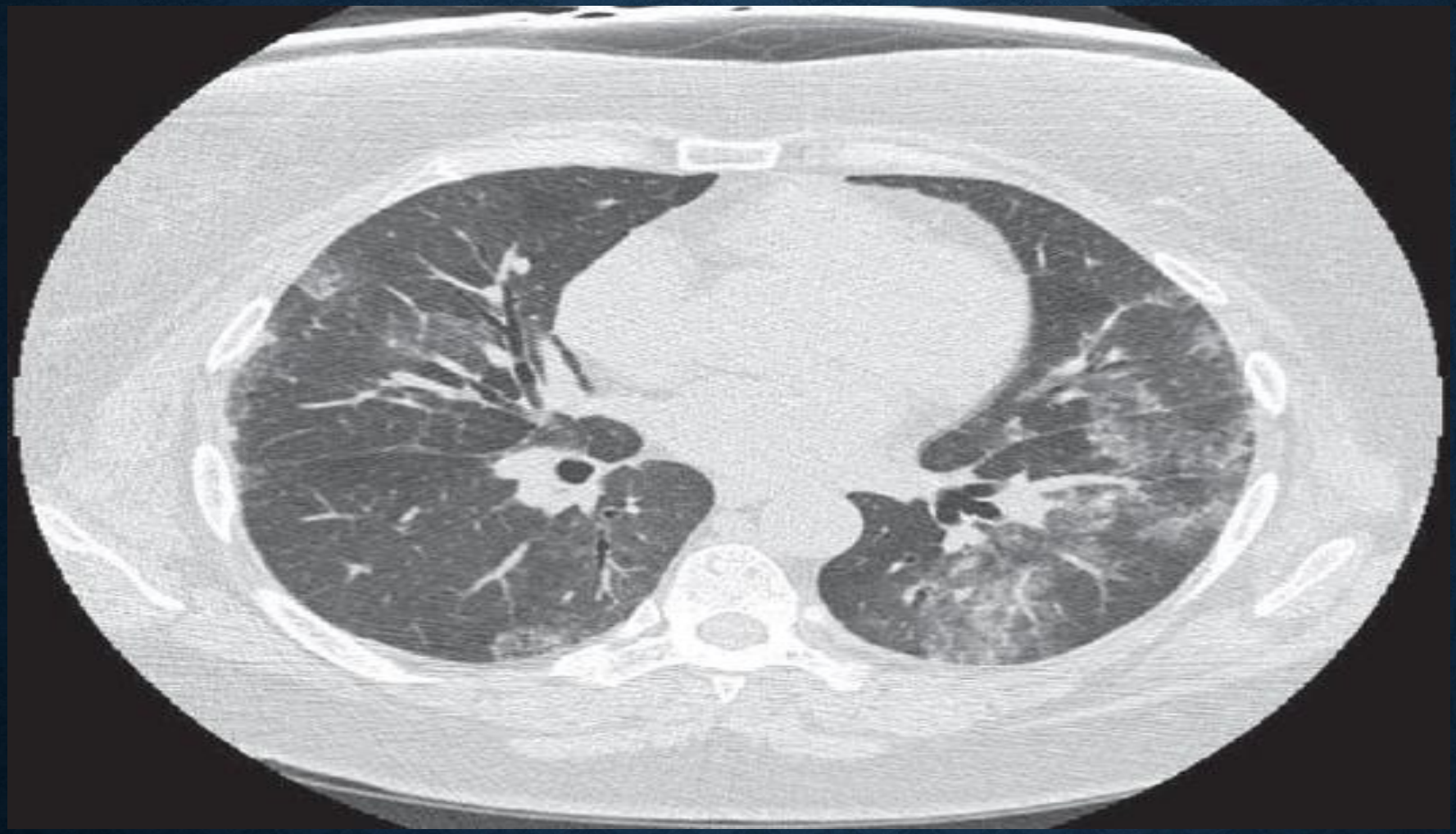
- Rheumatoid-associated parenchymal lung disease including interstitial disease and pulmonary nodules
- Large and small airway obstruction
- Rheumatoid pleural disease
- Drug-related lung disease
- Vascular disease (vasculitis and pulmonary hypertension)
- Comorbid medical conditions (thoracic cage immobility, venous thromboembolism, lung cancer)
- Overlapping clinical syndromes (interstitial lung disease and pleural thickening)
- Pleuropulmonary infection

ILD is the most common pulmonary manifestation of RA

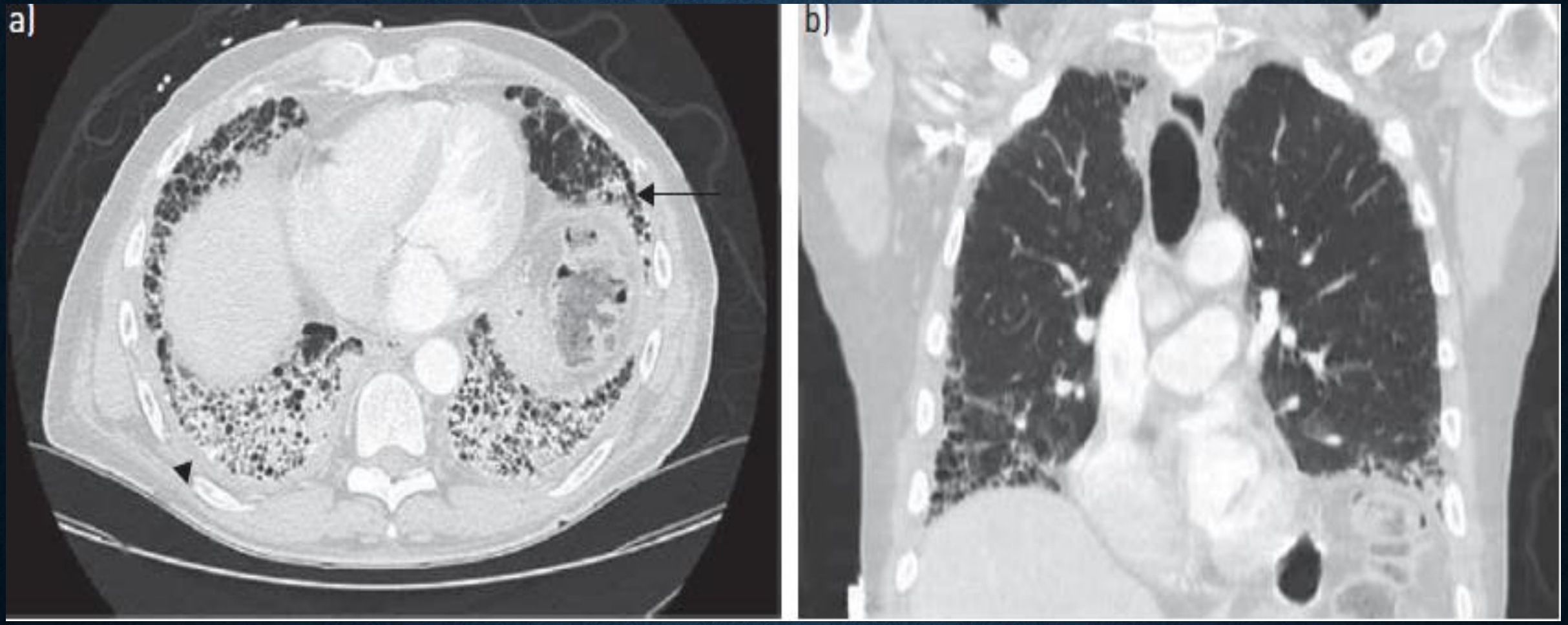
RA-INTERSTITIAL LUNG DISEASE

- Usual interstitial pneumonia (UIP)
- Nonspecific interstitial pneumonia (NSIP)
- Organizing pneumonia (OP)
- Lymphocytic interstitial pneumonia (LIP)
- Desquamative interstitial pneumonia (DIP)
- Acute interstitial pneumonia (AIP) or Diffuse alveolar damage (DAD)
- Idiopathic pleuroparenchymal fibroelastosis (PPFE)

Relevance of determining the subtype in selecting therapy for patients with RA-ILD is still to be determined



NSIP pattern with basal predominant ground-glass opacities and associated subpleural sparing in RA



a) Axial and b) coronal computed tomography scans of usual interstitial pneumonia pattern in a patient with RA. Subpleural and basilar predominant reticulations, minimal ground-glass opacities, honeycombing (arrow) and pleural thickening (arrowhead) are visible, as well as traction bronchiectasis

- **Distinguish between primary and secondary RA-ILD or indirect complications can be challenging**
- Based on :

- Clinician judgment
- Clinical context
- A temporal link of disease development with a particular therapy
- Response to withdrawal of the suspected agent

BIOMARKERS ASSOCIATED WITH RA-ILD

- ACPAs
- Heat shock proteins Abs (Anti-citrullinated Hsp90)
- Krebs von den lungen 6 (KL6 protein)
- Cytokine(anti-interleukin-1-alpha) and metalloproteinase (MMP7)
- surfactant protein D (SP-D)
- platelet-derived growth factor

- **None of these have yet been shown to be of clinical value**

TREATMENT

- ***No randomized placebo-controlled therapeutic trials have been performed to date in RA-ILD***

- ***Conservative therapy:***
- Education, psychosocial support , exercise rehabilitation
- Smoking cessation
- Supplemental oxygen therapy
- annual influenza vaccination and regular pneumococcal vaccination
- Prophylaxis against PCP pneumonia for all patients on immunosuppressive
- The decision to start treatment is influenced by patient age, the worsening of
- symptoms or pulmonary function tests (PFTs) contraindications to pharmacological treatments, multiple comorbidity, or frailty

- In asymptomatic patients with non-progressive ILD, a "wait and see" approach is usually recommended

TREATMENT

- **Immunosuppressive agents:**
- Corticosteroids: first-line therapy,usually 0.5–1 mg/kg prednisolone
- Azathioprine
- Cyclophosphamide
- Mycophenolate mofetil
- Rituximab
- Abatacept: Increasing interest in RA-ILD is emerging in the last years
- Tocilizumab
- Limited reports also exist for treatment with cyclosporine, methotrexate, and TNF alpha inhibitors
- Antifibrotic Agents: Pirfenidone, Tyrosine kinase inhibitors (nintedanib)

- **In RA- ILD: ABA, TCZ, or RTX appear more promising than TNF-i**

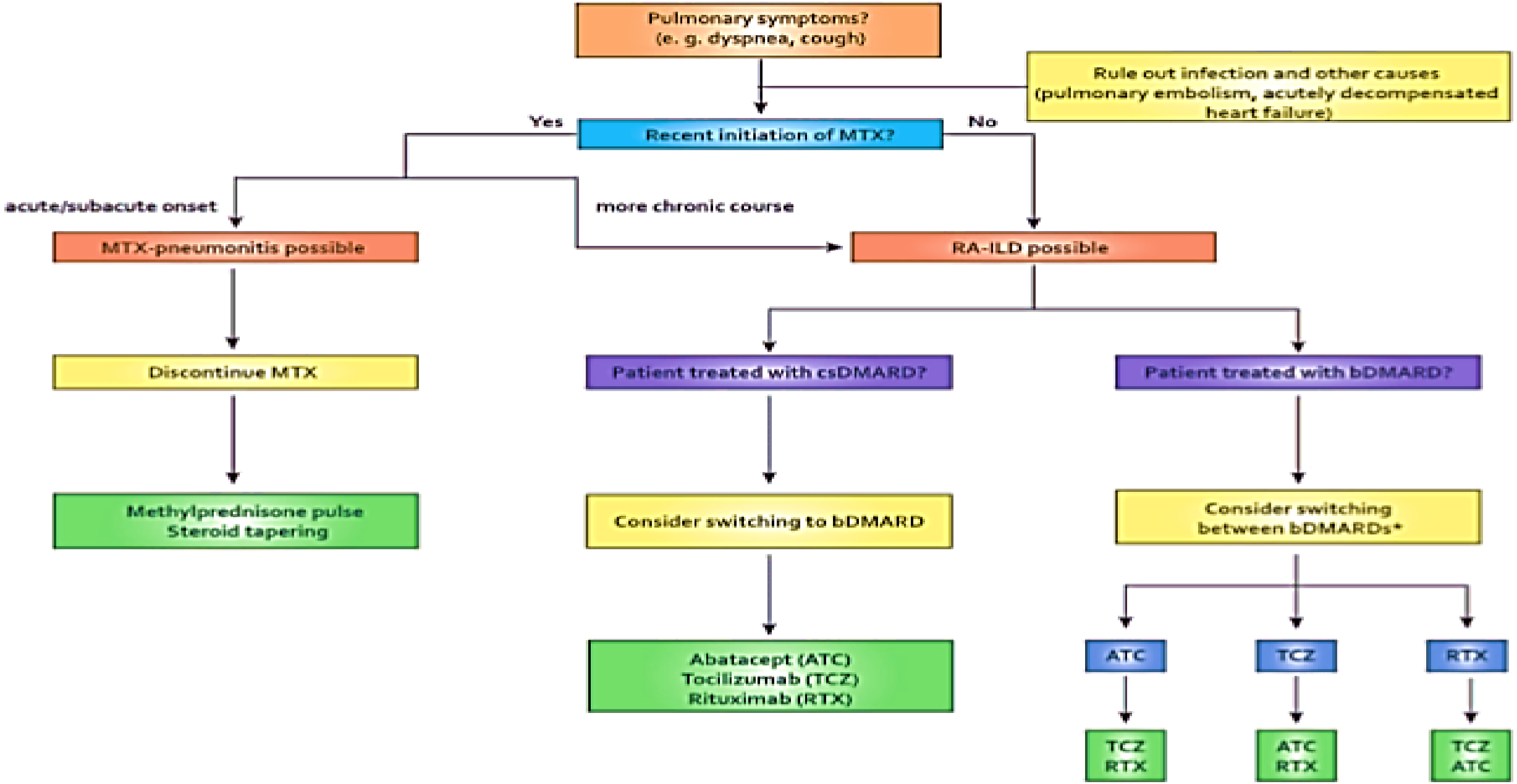
although the evidence base for this remains weak

- The latest ACR and EULAR guidelines do not specifically consider patients with RA-ILD

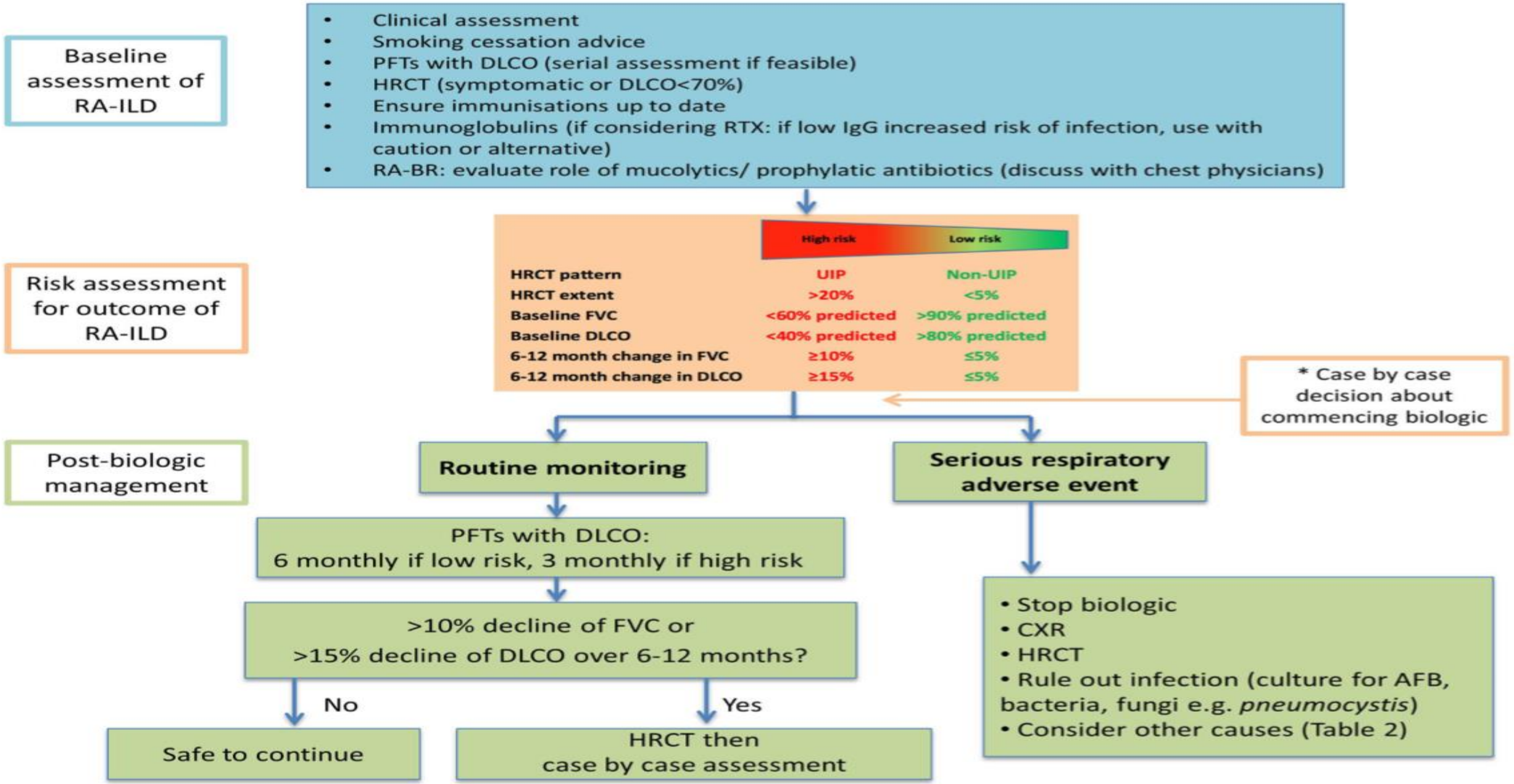
- while the National Institute for Health and Care Excellence (NICE) and Spanish Society of Rheumatology have proposed national recommendations:
- **suggesting the use of abatacept and rituximab in patients with RA-ILD, and advising against the use of TNF inhibitors**

- **Lung transplant:** 5-year survival from 46% to 76%

- **Recent retrospective analyses centered on treatment of RA-ILD with MMF and RTX have shown promising results**



Methotrexate-Associated Pneumonitis and Rheumatoid Arthritis-Interstitial Lung Disease: Current Concepts for the Diagnosis and Treatment, Review ARTICLE , 23 October 2019, George E. Fragoulis,et al



Practical Management of Respiratory Comorbidities in Patients with Rheumatoid Arthritis,James Bluett ,et al, Rheumatol Ther (2017) 4: 309-302

LUNG DISEASE IN THE SETTING OF MTX

- **Acute/subacute HP:** within the first year of treatment .Imaging are nonspecific,BAL and lung biopsy are more helpful in R/O alternative causes (i.e. infection), although the presence of **poorly formed non-necrotising granulomas and scattered eosinophils** may suggest methotrexate-induced HP, as these are not typical findings in RA-ILD

- **Progressive pulmonary fibrosis :**but it is controversial whether this is directly related to methotrexate

- **Acute, severe, life-threatening pneumonitis:** this is difficult to differentiate from RA acute DAD (Rare)

- **Provoking rheumatoid nodule formation**

- **Lymphoproliferative diseases :** With disease regression once MTX is stopped

- Recent studies and meta-analyses suggested that MTX-hypersensitivity pneumonia is less common than previously thought, and interestingly, no episodes of MTX related HP have been recorded in controlled trials after 2001

- **Association between MTX and ILD development has been recently questioned**

- Kiely described data by ERAN and ERAS registries, showing no increased risk of ILD in RA patients treated with MTX; even better, exposure to MTX was associated with a significantly reduced risk of incident RA-ILD

- Finally, Rojas-Serrano has recently observed a longer survival in RA-ILD patients treated with MTX compared to other cDMARDs (2017)

MTX has not been conclusively shown to induce or exacerbate underlying RA-ILD or lead to a greater risk of pulmonary death than patients not taking MTX

SULFASALAZINE

- **Drug reaction with eosinophilia and systemic symptoms (DRESS):**
- pneumonitis, with fever and rash, pulmonary infiltrates , eosinophilia
- Treatment:
- sulfasalazine withdrawal, systemic glucocorticoid therapy is not well-studied
- **NSIP**
- **BOOP**
- **Granulomatous lung disease**
- **Bronchiolitis obliterans**
- **Pleural effusion** (rare)

OBLITERATIVE BRONCHIOLITIS

- a rare, usually fatal, condition characterized by progressive concentric narrowing of membranous bronchioles

- Patients typically present with the rapid onset of dyspnea and cough WITHOUT fever, weight loss, and malaise.

- **Diagnosis:**

Airflow obstruction, normal or reduced diffusing capacity (DLCO), and hypoxemia on testing of pulmonary function and arterial blood gases

normal chest radiograph or hyperinflation

Bronchial wall thickening, centrilobular emphysema, areas of low attenuation with a mosaic pattern, and bronchiectasis may be seen on HRC

OB TREATMENT

- The first step in treatment of RA-associated OB is to stop any medications that are potential culprits (eg, penicillamine, gold, sulfasalazine)

- trial of high dose glucocorticoids (eg, prednisolone 1 to 1.5 mg/kg per day, maximum 100 mg/d)
- The role of immunosuppressive therapy with cyclophosphamide, methotrexate, or a TNF-alpha inhibitor is unclear

- Macrolide antibiotics: trial of erythromycin (200 to 600 mg/day) or another macrolide antibiotic is a reasonable choice

- For patients with respiratory failure due to progressive obliterative bronchiolitis, lung transplantation

LEFLUNOMIDE INDUCED PNEUMONITIS

- This appears to occur especially in japanese and korean patients

- It has been associated with the development and or exacerbation of ILD
- Potentially secondary to an active metabolite that may induce transition of lung epithelial cells to myofibroblasts, a process known as the epithelial-mesenchymal transition

- In treatment, cholestyramine resin (eg, 8 g/day for three days) can be used to hasten elimination

ANTI TNF-ALPHA LUNG INVOLVEMENT

- They may accelerate the progression of ILD and patients can develop pulmonary fibrosis
- Reports of new-onset ILD have been described for all five TNF-inhibitors
- Studies have reported **sarcoid-like granulomatous disease, organizing pneumonia and exacerbation of existing pulmonary infection.**
- Because methotrexate was co-prescribed, it is unclear how many of these cases were real, although most of the cases occurred **within 3 months after starting anti-TNF therapy**, with a high mortality
- **Patients with prior RA-ILD should receive anti-TNF treatment with caution**

RHEUMATOID PULMONARY NODULES

- Usually in patients with longstanding disease and subcutaneous nodules
- Histologically composed of a central fibrinoid necrotic region surrounded by, palisading epithelioid cells, granulation tissue,mononuclear cell infiltrate, and associated vasculitis
- Typically in pleural or subpleural regions, occasionally with cavitation
- Nodules are asymptomatic unless cavitate or rupture then infection, pleural effusion or bronchopleural fistula, pneumothorax, pyopneumothorax may occur
- Uncomplicated nodules may spontaneously regress or improve with standard therapy
- Paradoxically enlarge with methotrexate or leflunamid treatment

PLEURAL INVOLVEMENT

- About 5-21% of patients are symptomatic
- The pleural disease can precede joint disease and is more common in older males and those with rheumatoid nodules

- RA effusions are exudative and sterile, occasionally unilateral, often with low glucose<60 mg/dl and low Ph, wbc<5000/cc, ADA could be positive

- Pathognomonic for rheumatoid effusions are macrophages and multinucleate giant cells, together with granulomatous debris

- Fever and pleuritic chest pain are common, but **cough is absent** unless there is comorbid parenchymal lung diseas

Pleural involvement

- Less commonly, patients with RA and a long-standing pleural effusion may have a **cholesterol effusion** also known as a pseudochylous with (elevated cholesterol level (above 200 mg/dL and sometimes over 1000 mg/d)

PLEURAL BIOPSY INDICATIONS

- persistent, sterile exudative effusion, but without the classic cytologic finding of rheumatoid pleuritic
- cholesterol effusion
- unexpandable lung

TREATMENT OF RHEUMATOID PLEURAL EFFUSION

- usually do not require specific treatment
- When treatment is needed , initial choice is an NSAID, such as indomethacin
- Therapeutic thoracentesis
- In refracrory cases, Intrapleural and systemic glucocorticoid therapy and DMARDs have all been tried with variable success

THANKS FOR YOUR ATTENTION