PNEUMOMEDICINA 2022

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La sarcoidosi: luci ed ombre

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Sarcoidosis

- is a multisystem disorder of unknown cause
- affects young and middle-aged adults
- the diagnosis is established when **clinicoradiological findings are supported by histological evidence** of noncaseating epithelioid cell granulomas
- Clinical manifestations of sarcoidosis are often nonspecific

- is a multisystem disorder of unknown cause
- affects young and middle-aged adults
- the diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas

- is a rare disease
- prevalence is variable (1.33/100000 in European population, 47/100000 in African-American population and 64/100000 in Scandinavian population)
- **epidemiology of sarcoidosis in Italy is unknown**

Am J Respir Crit Care Med. 1999;160:736–755.
European Respiratory Monograph 32, 2005. p. 13–22.

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis and Detection of Sarcoidosis

An Official American Thoracic Society Clinical Practice Guideline

Elliott D. Crouser*, Lisa A. Maier*, Kevin C. Wilson*, Catherine A. Bonham, Adam S. Morgenthau, Karen C. Patterson, Eric Abston, Richard C. Bernstein, Ron Blankstein, Edward S. Chen, Daniel A. Culver, Wonder Drake, Marjolein Drent, Alicia K. Gerke, Michael Ghobrial, Praveen Govender, Nabeel Hamzeh, W. Ennis James, Marc A. Judson, Liz Kellermeyer, Shandra Knight, Laura L. Koth, Venerino Poletti, Subha V. Raman, Melissa H. Tukey, Gloria E. Westney, and Robert P. Baughman; on behalf of the American Thoracic Society Assembly on Clinical Problems

This official clinical practice guideline was approved by the American Thoracic Society February 2020

Sarcoidosis

The diagnosis of sarcoidosis **is not standardized**, but is based on **three major criteria**:

- a compatible clinical presentation
- the finding of nonnecrotizing granulomatous inflammation in one or more tissue samples (not always required), and
- the exclusion of alternative causes of granulomatous disease.

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Sarcoidosis – Clinical presentation

The clinical presentation of sarcoidosis exhibits **a spectrum of manifestations** ranging from the **asymptomatic state** (50% for pulmonary sarcoidosis) to that of **progressive and relapsing disease** (progressive pulmonary fibrosis or cardiac involvement, including sudden cardiac death (arrhythmias) or congestive heart failure (myocarditis).

The global health implications of sarcoidosis remain unknown, but new evidence indicates that the disease is much more prevalent than previously estimated

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Sarcoidosis – Clinical presentation

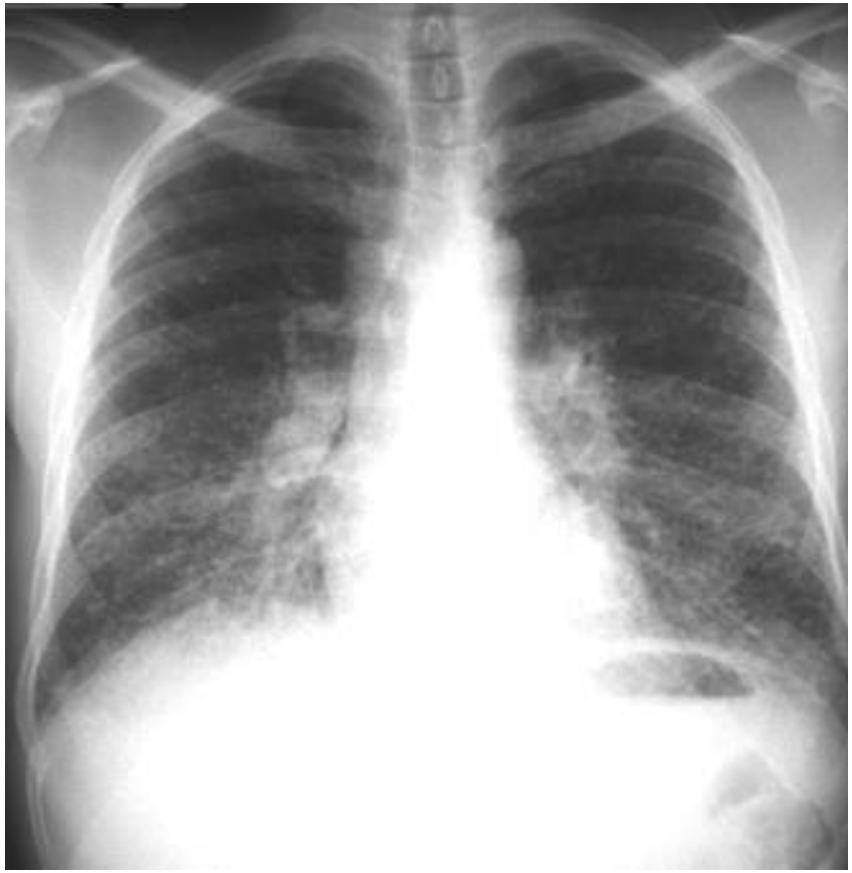
Whereas many sarcoidosis cases are a **diagnostic dilemma**, certain clinical features of sarcoidosis are considered so highly specific for the disease that they have been deemed diagnostic.

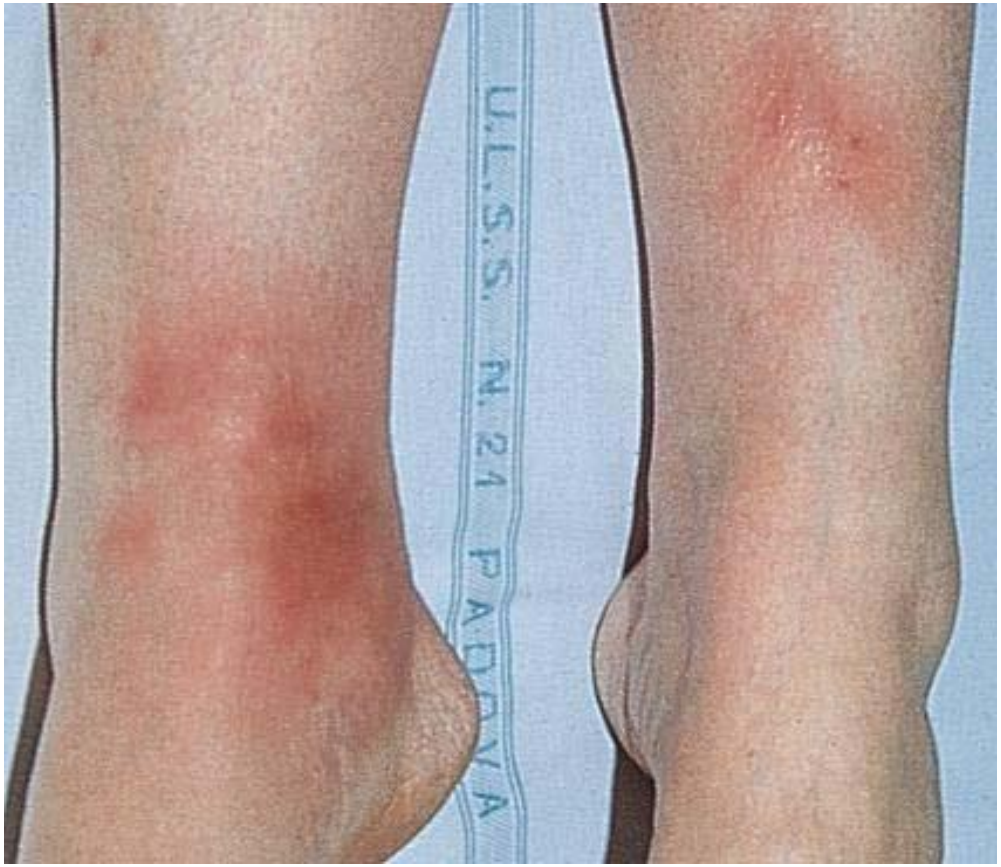
These include

Löfgren’s syndrome,
lupus pernio and
Heerfordt’s syndrome.

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

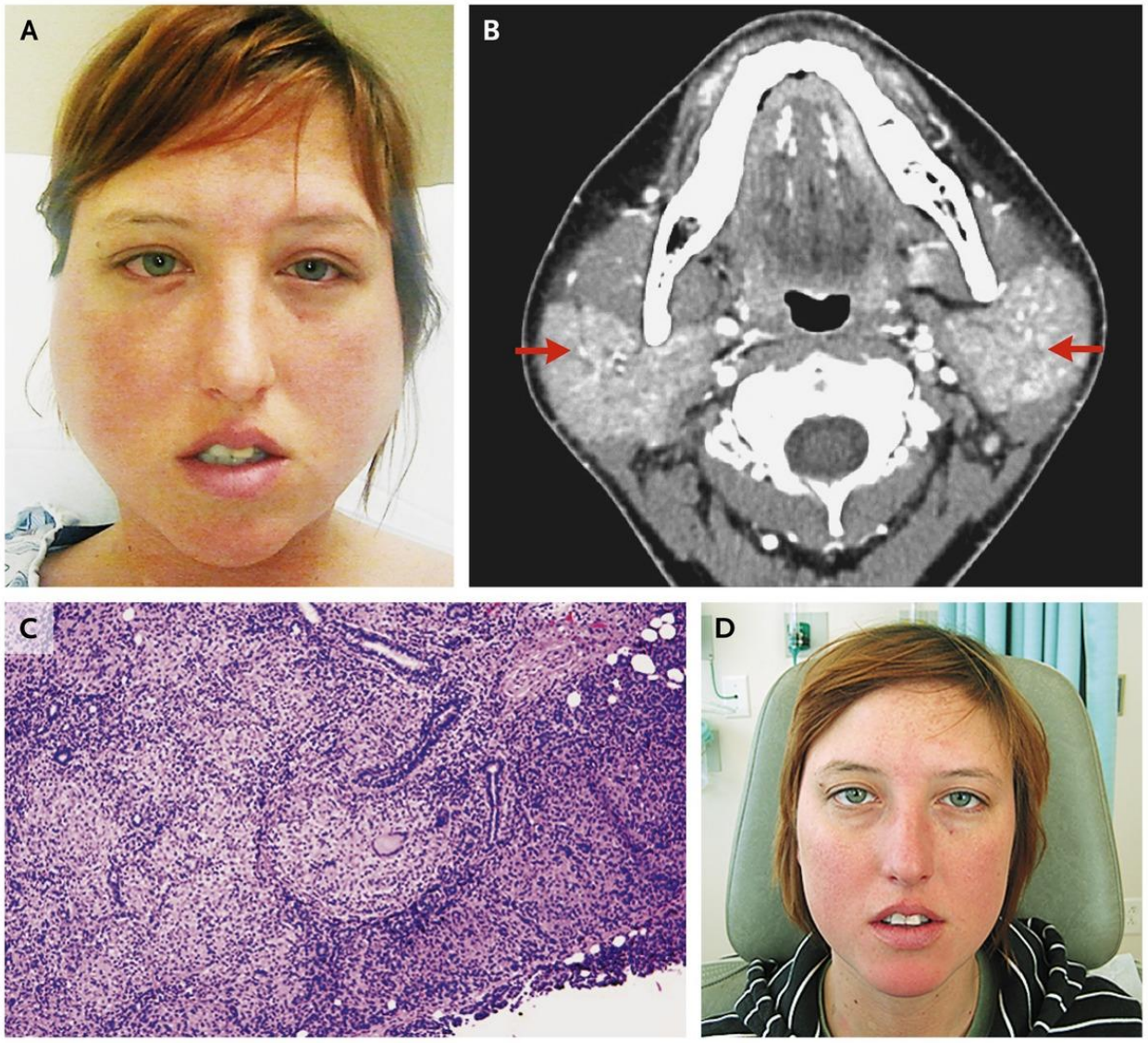
Löfgren's syndrome





Erythema nodosum, bilateral hilar adenopathy, fever, arthralgia

Heerfordt's syndrome

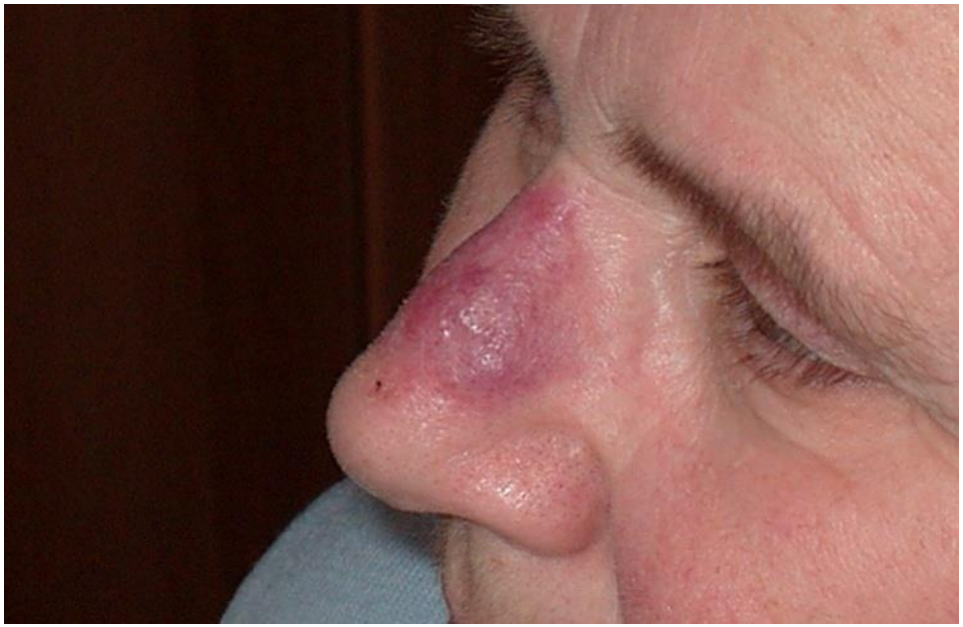


Facial nerve palsy, enlargement of parotid glands, fever, arthralgia

Pulmonary radiography revealed bihilar lymphadenopathy

Dua A, Manadan A. N Engl J Med 2013;369:458-458.

Lupus pernio



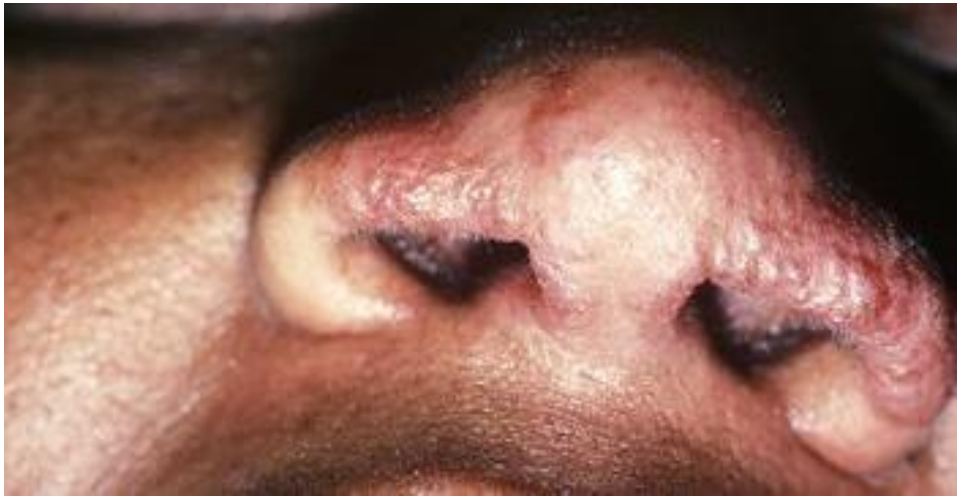


Table 1. Clinical Features Supportive of a Diagnosis of Sarcoidosis

	Highly Probable	Probable
History	Löfgren's syndrome*	Seventh cranial nerve paralysis Treatment-responsive renal failure Treatment-responsive CM or AVNB Spontaneous/inducible VT with no risk factors
Physical	Lupus pernio Uveitis Optic neuritis Erythema nodosum	Maculopapular, erythematous, or violaceous skin lesions Subcutaneous nodules Scleritis Retinitis Lacrimal gland swelling Granulomatous lesions on direct laryngoscopy Symmetrical parotid enlargement Hepato-/splenomegaly
Imaging	Bilateral hilar adenopathy (CXR, CT, and PET) Perilymphatic nodules (chest CT) Gadolinium enhancement on MRI (CNS) Osteolysis, cysts/punched-out lesion, trabecular pattern bone (X-ray, CT, and MRI) Parotid uptake (gallium and PET)	Upper lobe or diffuse infiltrates (CXR, CT, and PET) Peribronchial thickening (CT) Two or more enlarged extra thoracic nodes (CT, MRI, and PET) Increased inflammatory activity in heart (MRI, PET, and gallium) Imaging showing enlargement or nodules in liver or spleen (CT, PET, and MRI) Inflammatory lesions in bone (gallium, PET, and MRI)
Other testing	Hypercalcemia or hypercalciuria with abnormal vitamin D metabolism†	Reduced LVEF with no risk factors (echo and MRI) Elevated ACE level test‡ Nephrolithiasis with calcium stone, no vitamin D testing BAL lymphocytosis or elevated CD4:CD8 ratio Alkaline phosphatase greater than three times the upper limit of normal New-onset, third-degree AV block in young or middle-aged adults

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

- constitutional symptoms (fever, fatigue, malaise, weight loss) 33%
- **lung 90%**
- lymphoid system 33%
- heart 5%
- liver 50-80%
- skin 25%
- ocular lesion 11-83% (26% in recent guidelines)
- Neurosarcoidosis < 10%
- Musculoskeletal system 25-39%

Sarcoidosis – Clinical presentation

Panel 2: **Specific extrapulmonary manifestations associated with sex or ethnic origin**

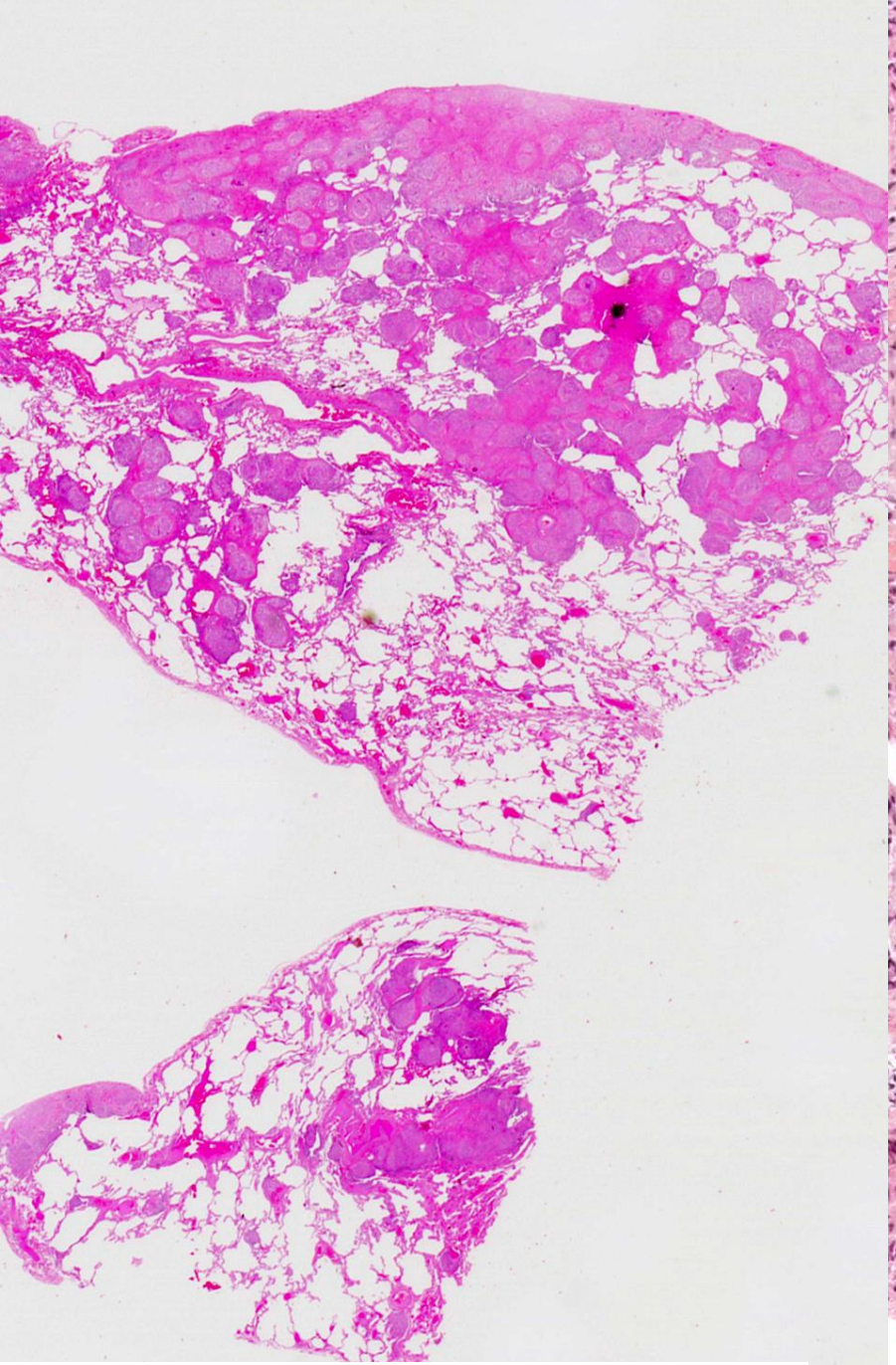
	Women	Men	Scandinavian	Italian	Japanese	African-American/ West Indies
Erythema nodosum	Yes	..	Yes	..	..	..
Lupus pernio	..	..	..	..	..	Yes
Eye	Yes	..	..	..	Yes	Yes
Cardiac	..	..	..	..	Yes	..
Liver	..	..	..	..	..	Yes
Bone marrow	..	...	..	..	..	Yes
Hypercalcaemia	..	Yes	..	Yes	..	..

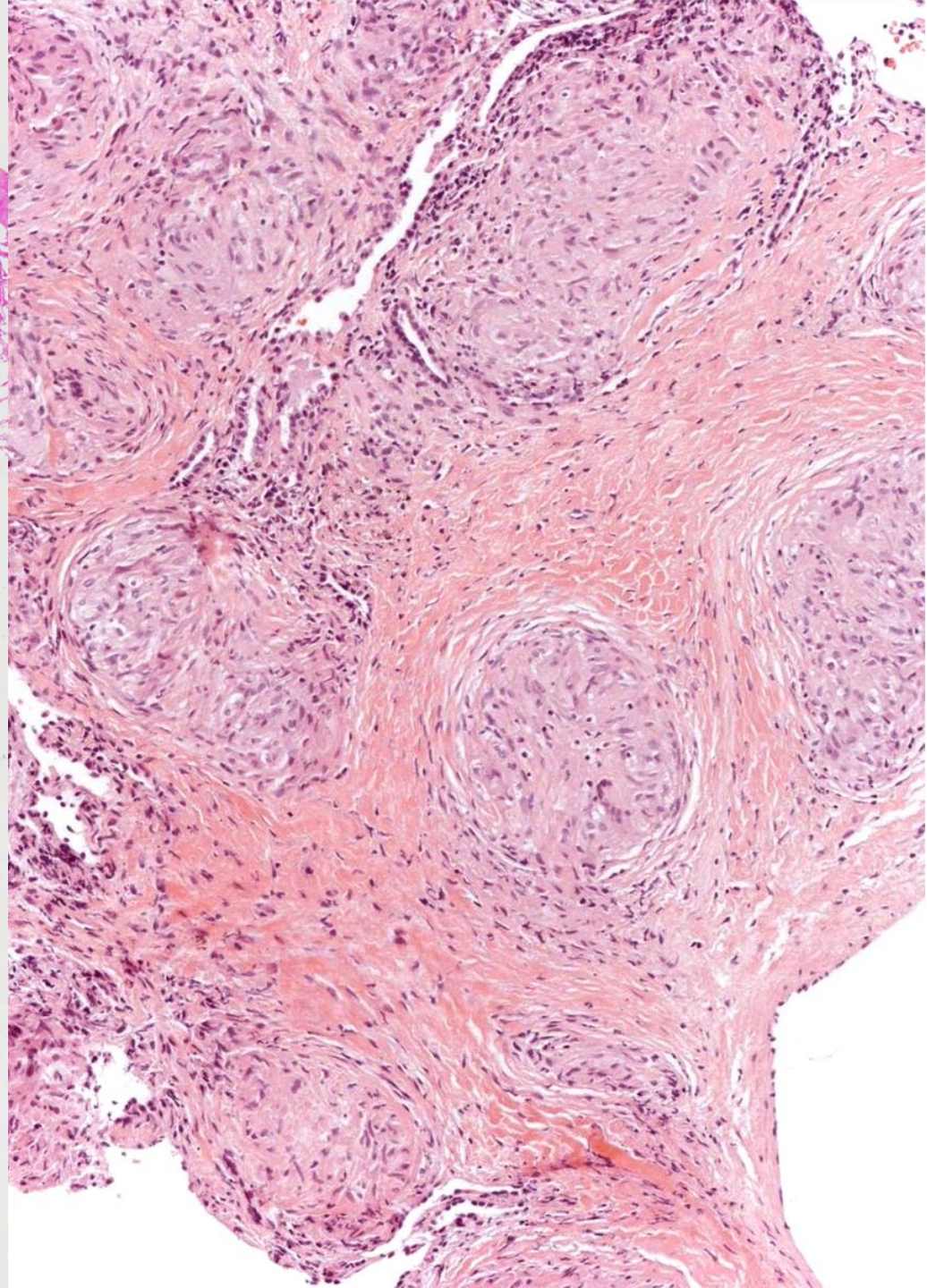
Sarcoidosis – Histopatholohy

Given that the clinical manifestations of sarcoidosis **are often nonspecific**, histological evaluation of tissue granulomas is **often required to establish the diagnosis**.

Sarcoidosis granulomas are most often nonnecrotic; however, variants of sarcoidosis, particularly the nodular pulmonary sarcoidosis phenotype, can present with a mixture of necrotic and nonnecrotic granulomas

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51





Courtesy: Dr. Cavazza (Reggio Emilia)

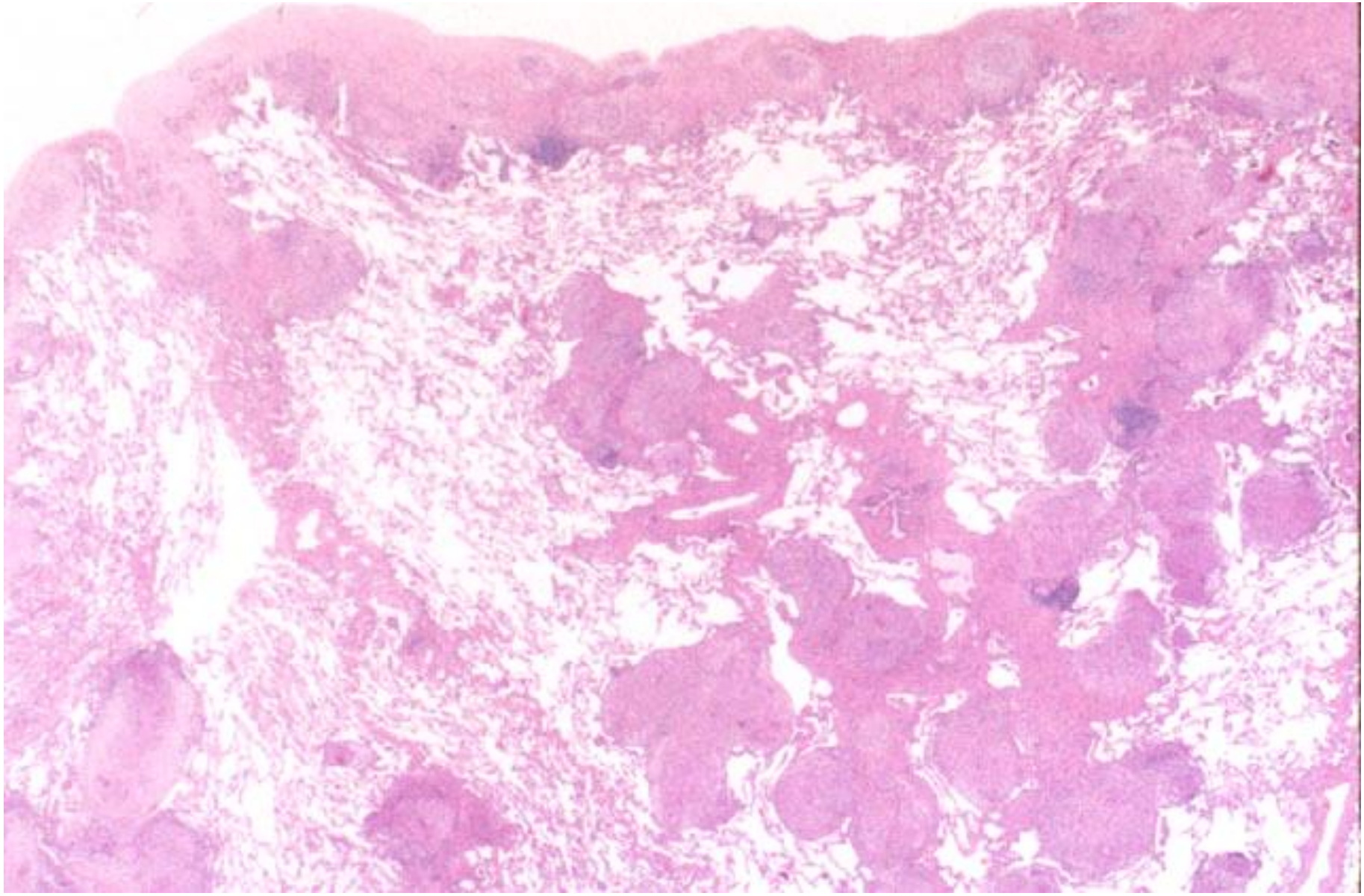


Table 2. Key Pathological Features of Sarcoidosis

Favors Sarcoidosis	Against Sarcoidosis
Granuloma presence	
Numerous	Few
Absent but with nodular hyalinized fibrosis representing healed granulomas (scattered multinucleated giant cells may be detectable)	Absent
Granuloma morphology	
Compact, tightly formed collections of large "epithelioid" histiocytes and multinucleated giant cells. Granulomas tend to stay discrete	Loosely organized collections of mononuclear phagocytes/ multinucleated giant cells
Nonnecrotic or focal and usually minimal ischemic necrosis	• Extensive necrosis • Dirty necrosis (containing nuclear debris) • Palisading granulomas
Fibrosis beginning at the granuloma periphery with extension centrally into the granuloma, with or without calcification	
Lesion location	
Perilymphatic; around bronchovascular bundles and fibrous septa containing pulmonary veins, and near visceral pleura	• Lack of lymphangitic distribution • Intraalveolar granulomas
In necrotizing sarcoid angiitis and granulomatosis: granulomatous angiitis with invasion of vascular walls	
Accompanying histology	
Sparse surrounding lymphocytic infiltrate	• Robust surrounding inflammatory infiltrate (including lymphocytes, neutrophils, eosinophils, and plasma cells) • Secondary lymphoid follicles
Microorganism stains and cultures	
Negative	Positive
Multidisciplinary clinical features	
Intra- and extrathoracic involvement	Extrathoracic involvement only

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Sarcoid-like histopathology

- Sarcoid-like reactions to tumor should be considered in patients with granulomatous adenopathy who are suspected of having malignancy or in those with a recent or concomitant history of neoplasm
- Sarcoid-like histopathologic changes can be seen in lymph nodes from patients with:
  - neoplastic diseases such as Hodgkin disease and other lymphoproliferative disorders,
  - germ cell testicular tumors,
  - breast cancer,
  - renal cell carcinoma,
  - leiomyosarcoma,
  - ovarian mucinous cystadenoma

Brincker H. Sarcoidosis 1989; 6:31

Question 1: Should Lymph Node Sampling Be Performed in a Patient Presenting with Asymptomatic Bilateral Hilar Lymphadenopathy?

- Isolated involvement of mediastinal and hilar lymph nodes **is a common presentation of sarcoidosis**
- Patients generally have self-limited disease, and do not require treatment

- The committee concluded that the decision to biopsy asymptomatic patients with bilateral hilar adenopathy should be made on a case-by-case basis.

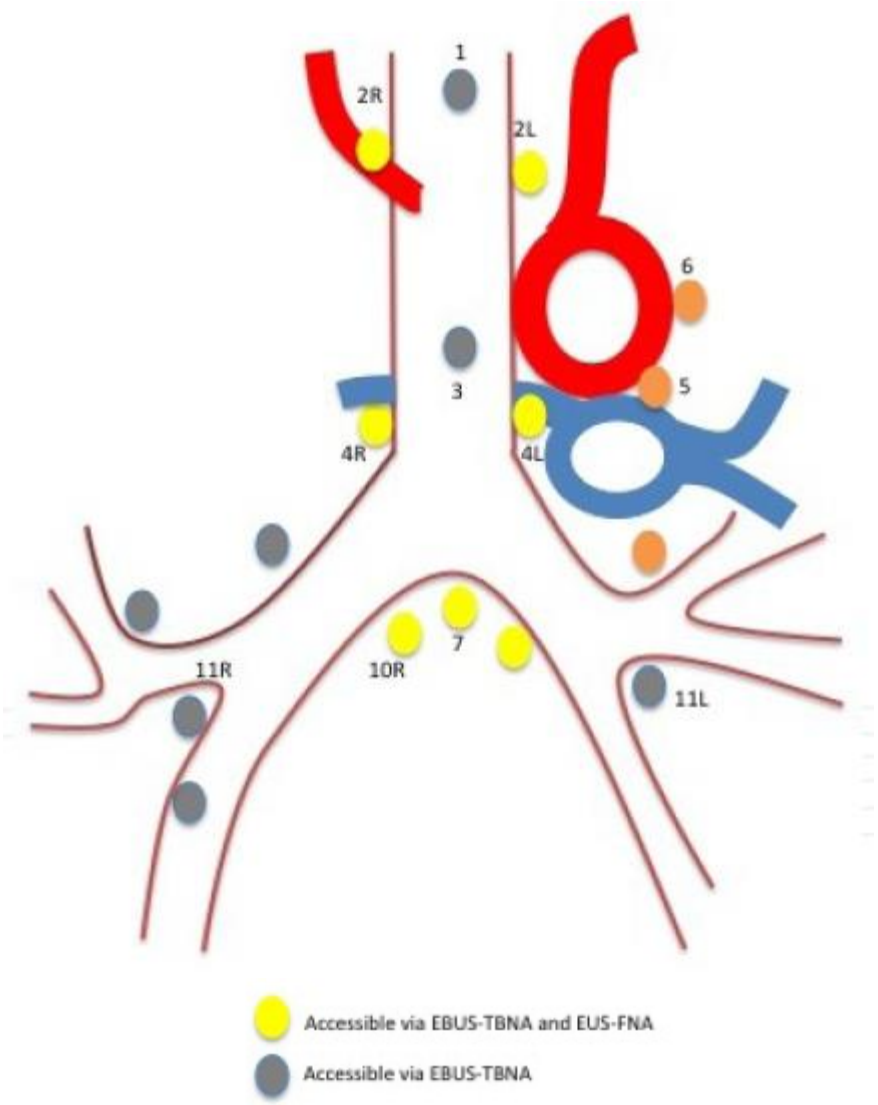
Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Question 2: Should patients with suspected sarcoidosis and mediastinal and/or hilar lymphadenopathy, for whom it has been determined that tissue sampling is necessary, undergo EBUS-guided lymph node sampling or mediastinoscopy as the initial mediastinal and/or hilar lymph node sampling procedure?

- We suggest EBUS-guided lymph node sampling, rather than mediastinoscopy, as the initial mediastinal and/or hilar lymph node sampling procedure (conditional recommendation, very low-quality evidence).

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

TBNA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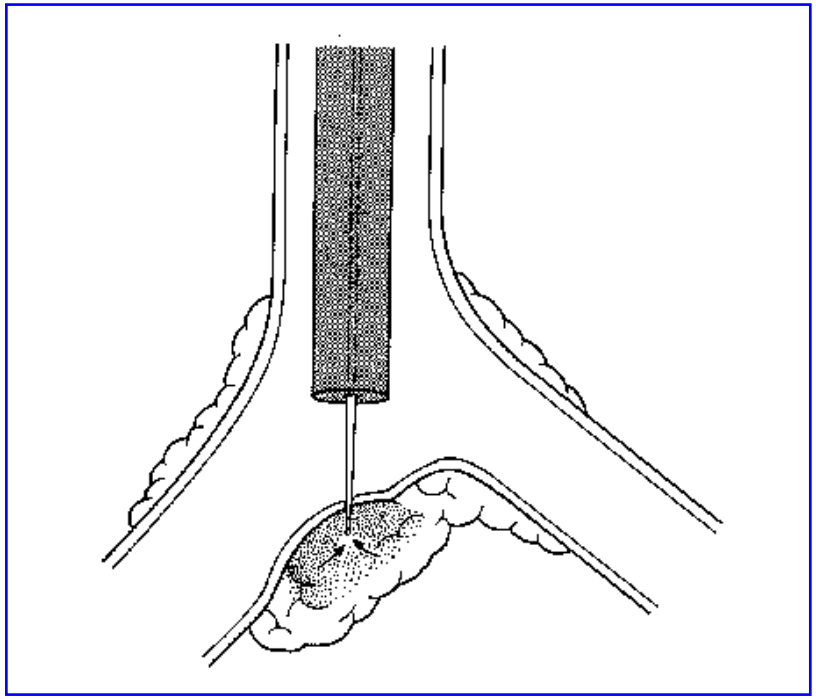

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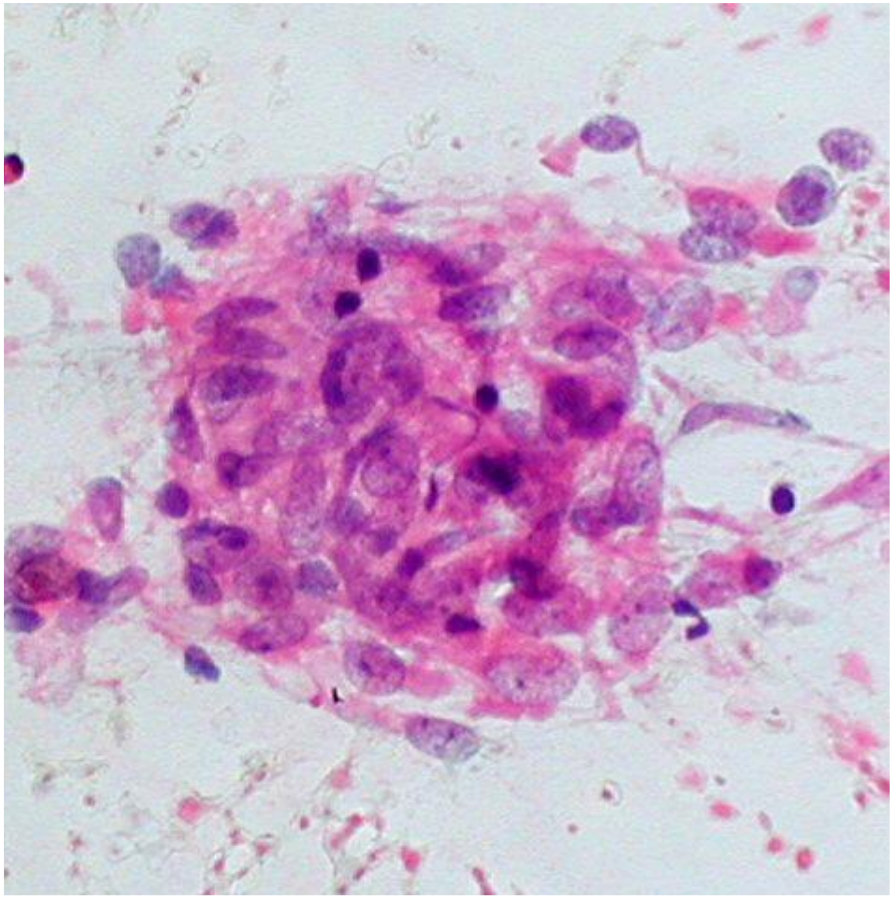
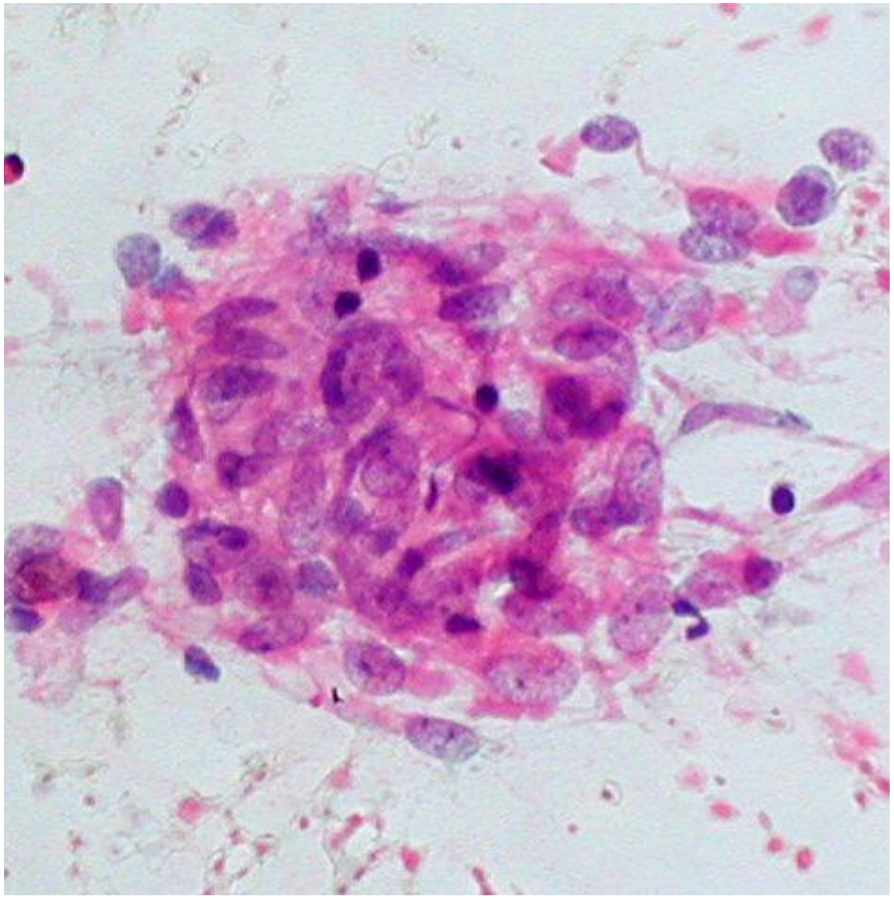


Sensibilità:

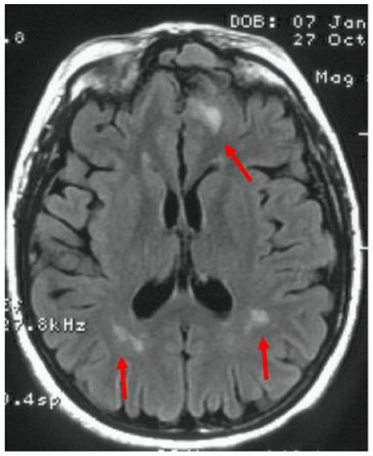
- Stadio I 82.3 %
- Stadio II 46.6 %

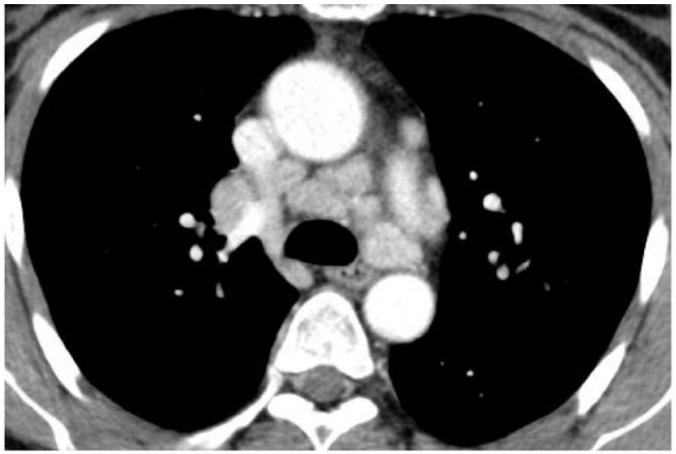
Trisolini R et al. Sarcoidosis 2004; 21: 147

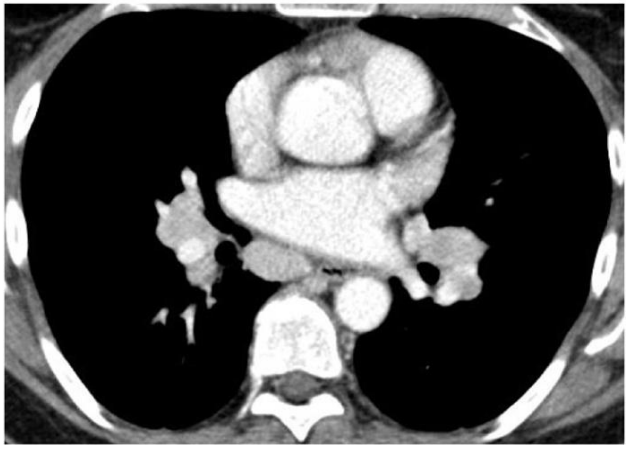
EBUS

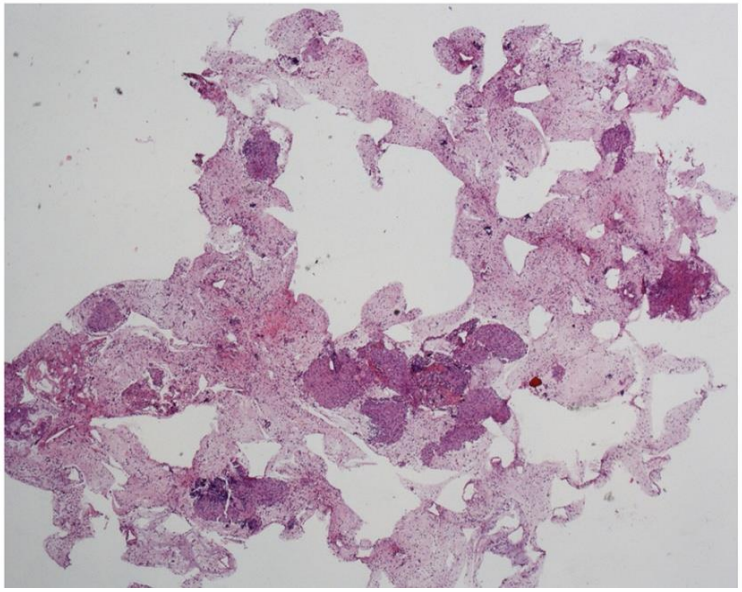


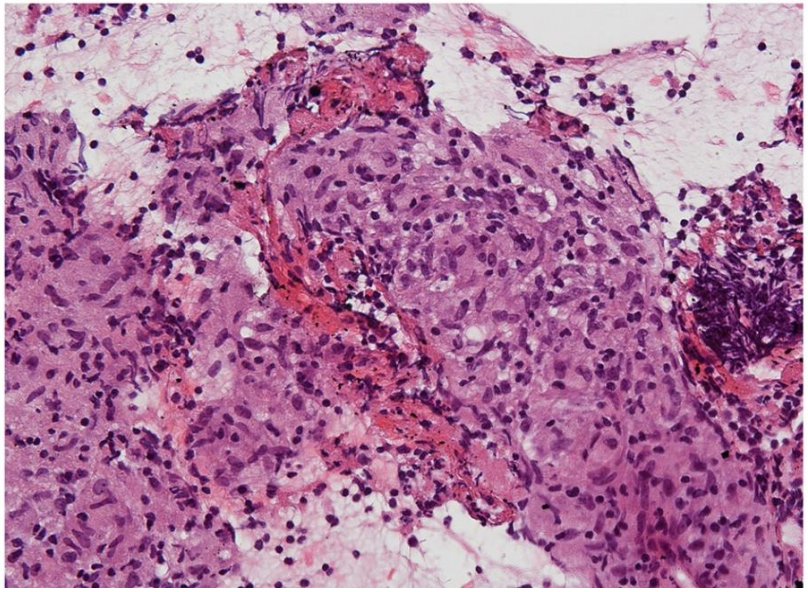
Diagnostic yield of approximately 80 to 90% in patients with mediastinal adenopathy and a clinical suspicion of sarcoidosis





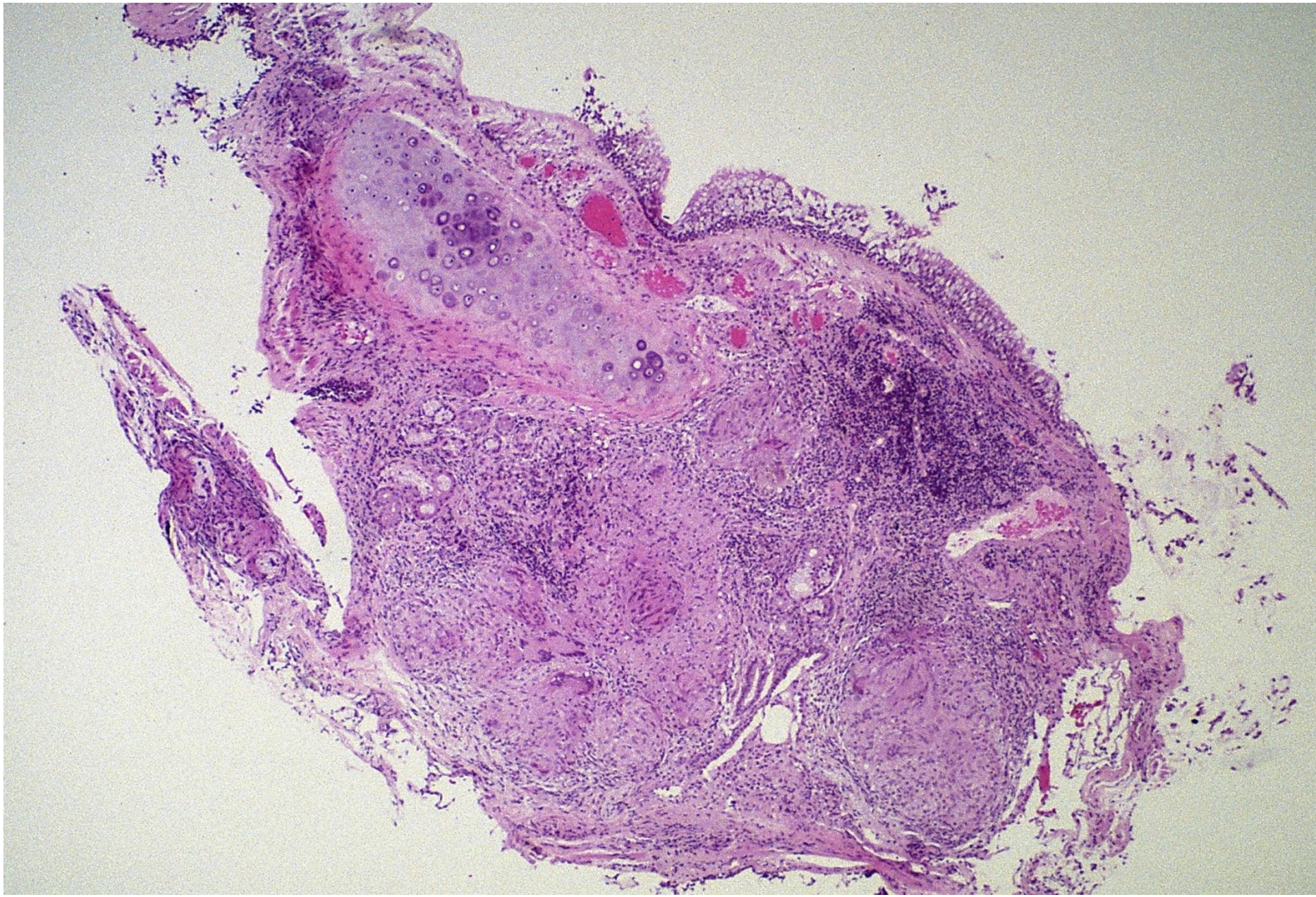




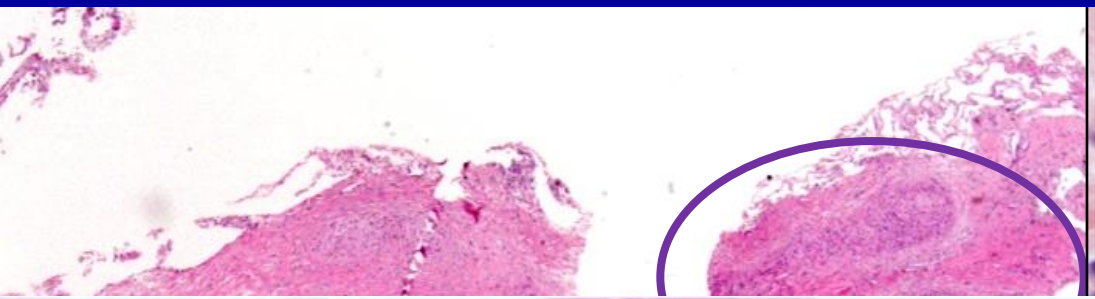


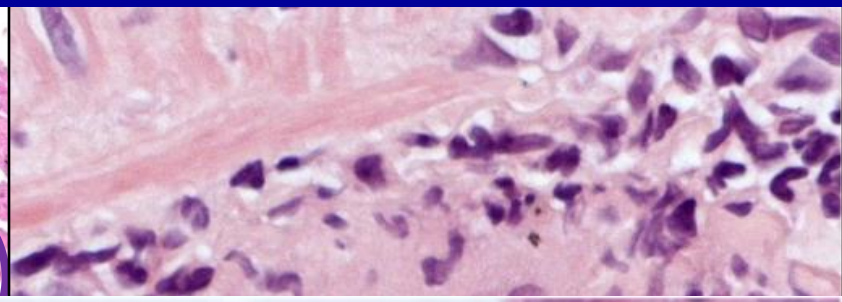
Respirology, 2019; 24 (6): 531-542

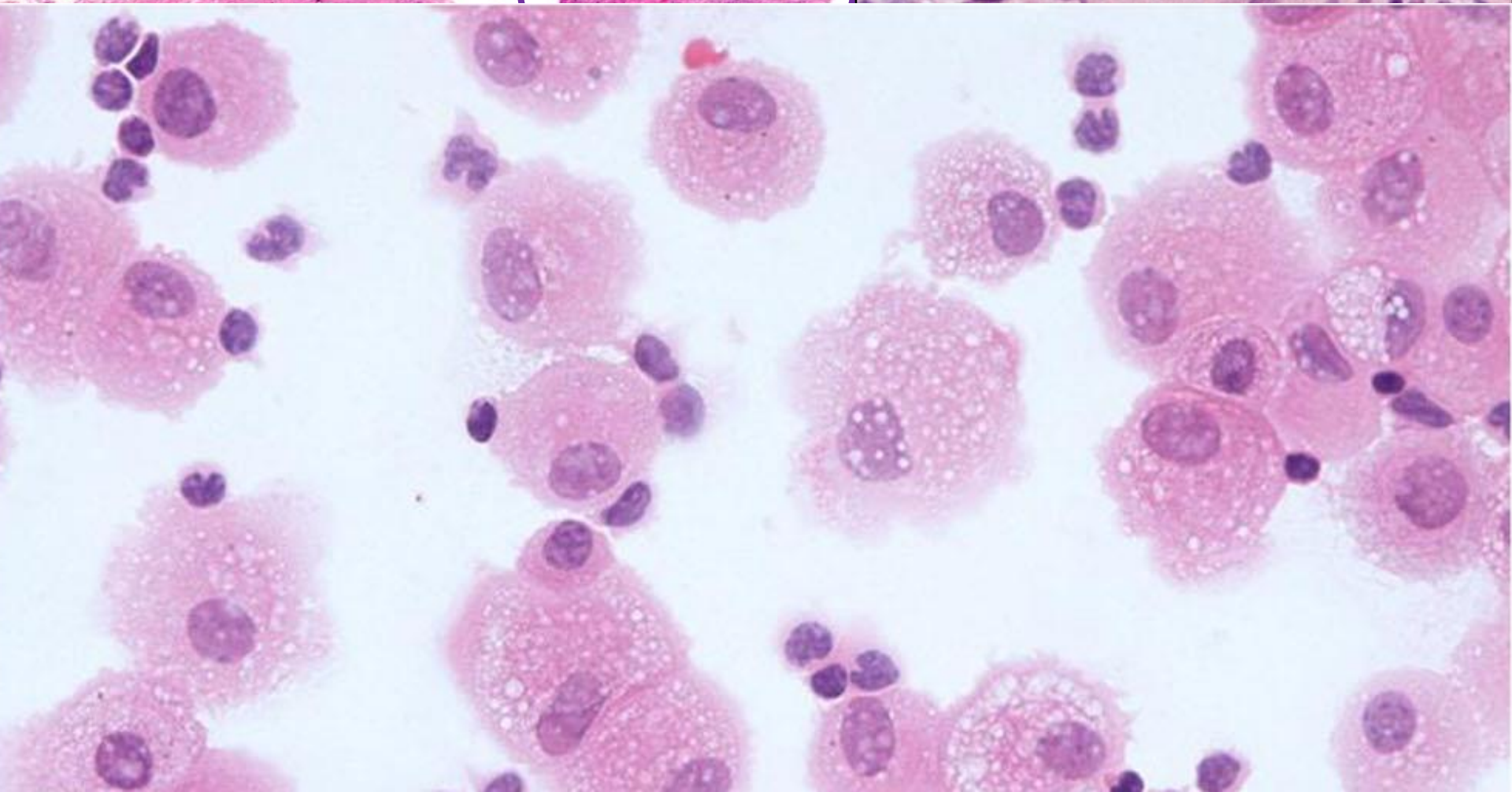
Bronchial biopsy 38-85%

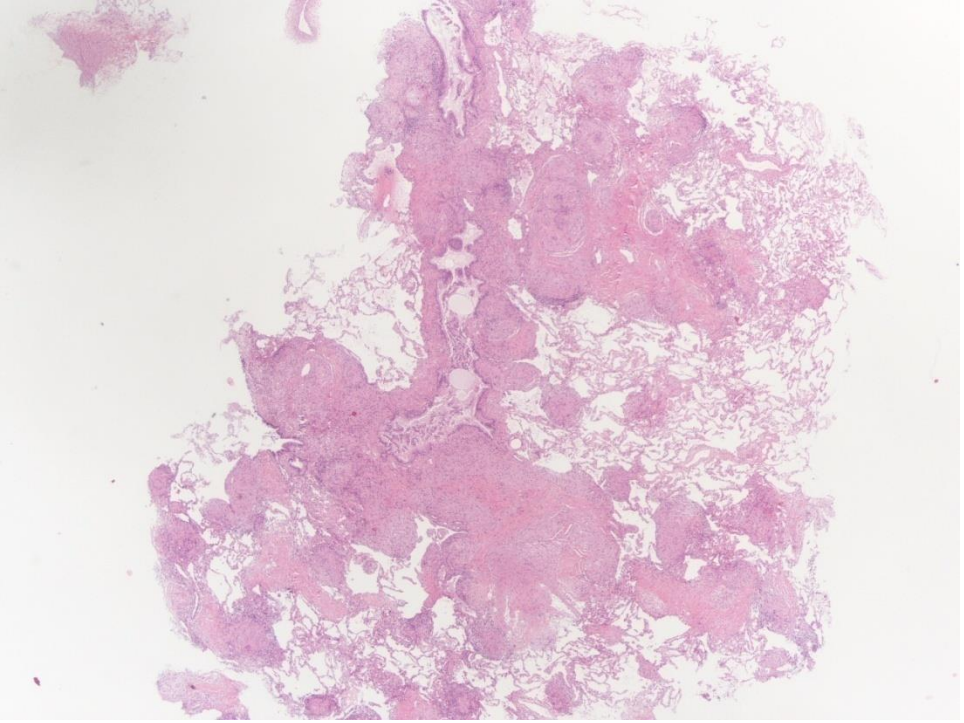


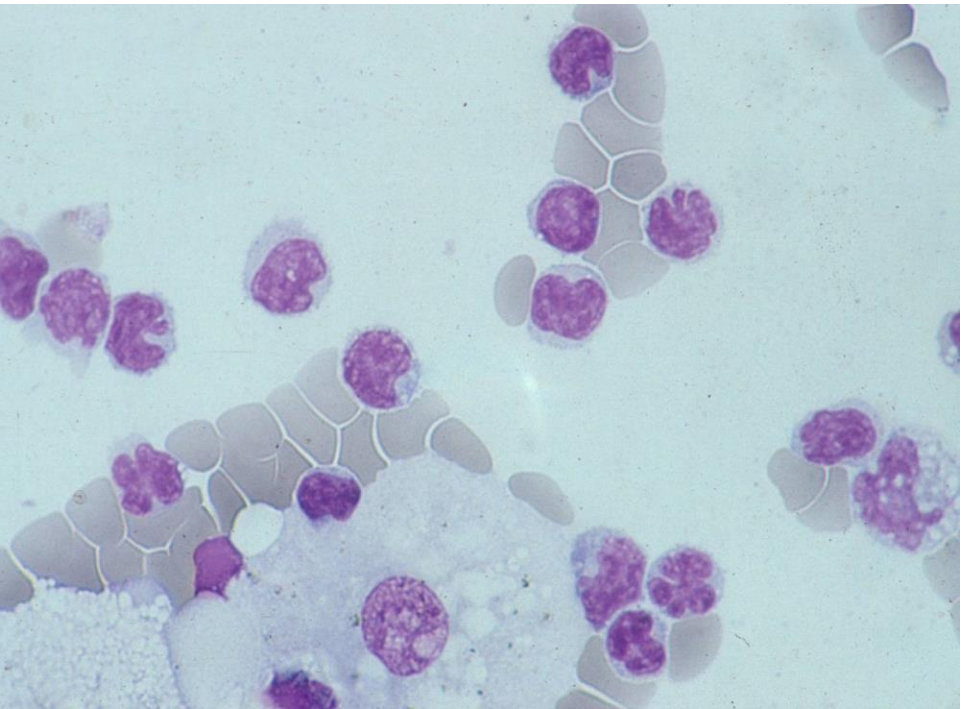
Sarcoidosi su tbb

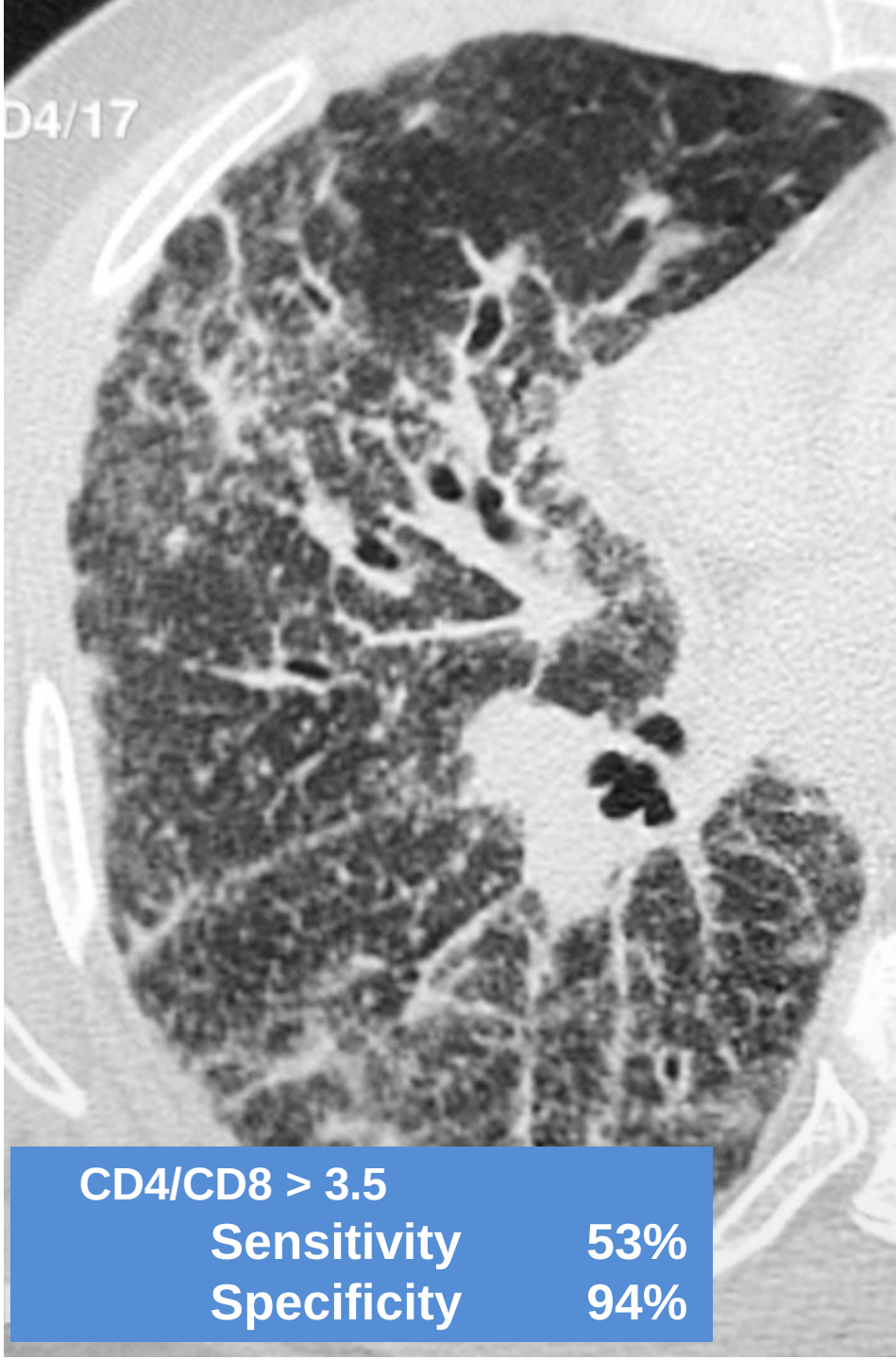








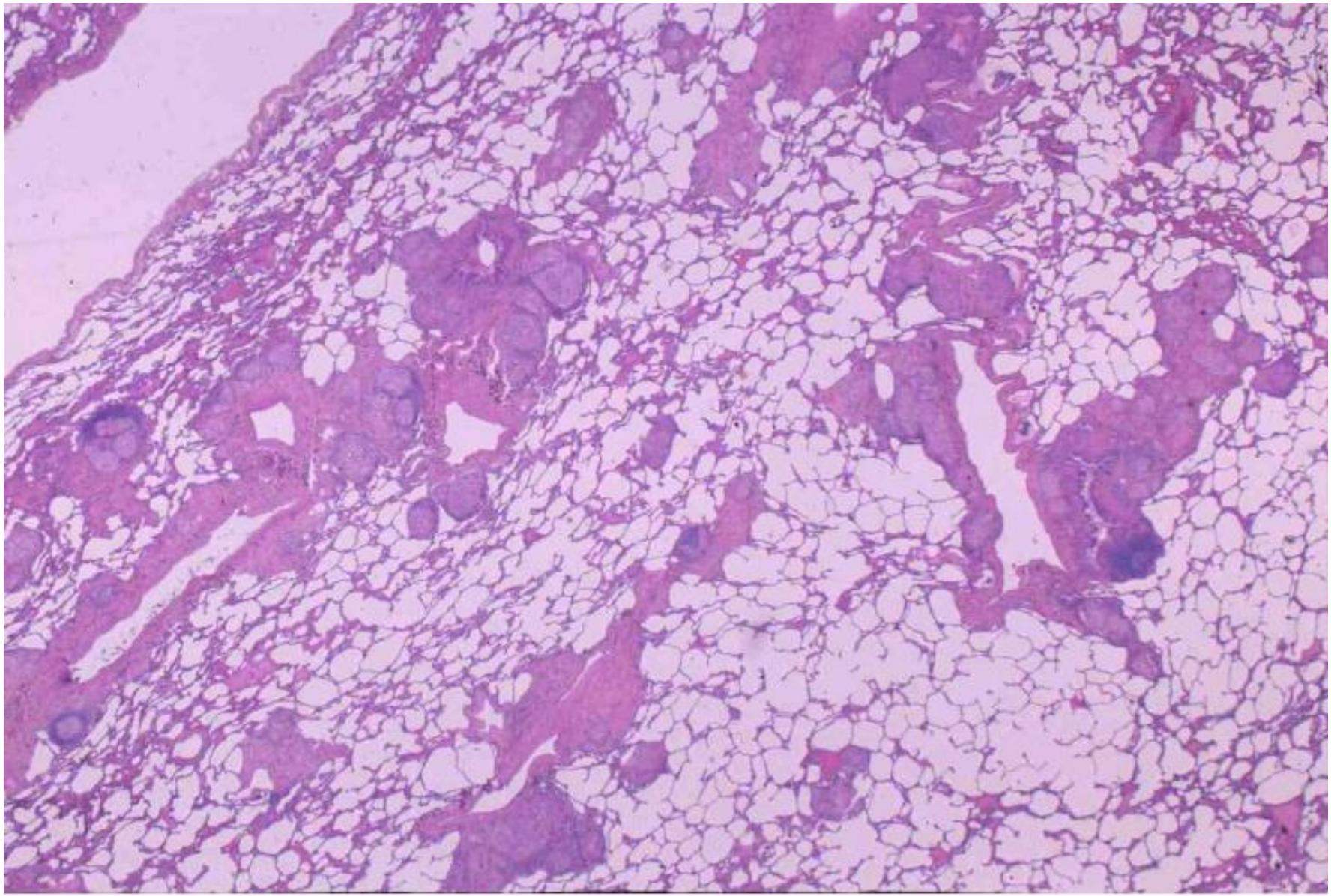


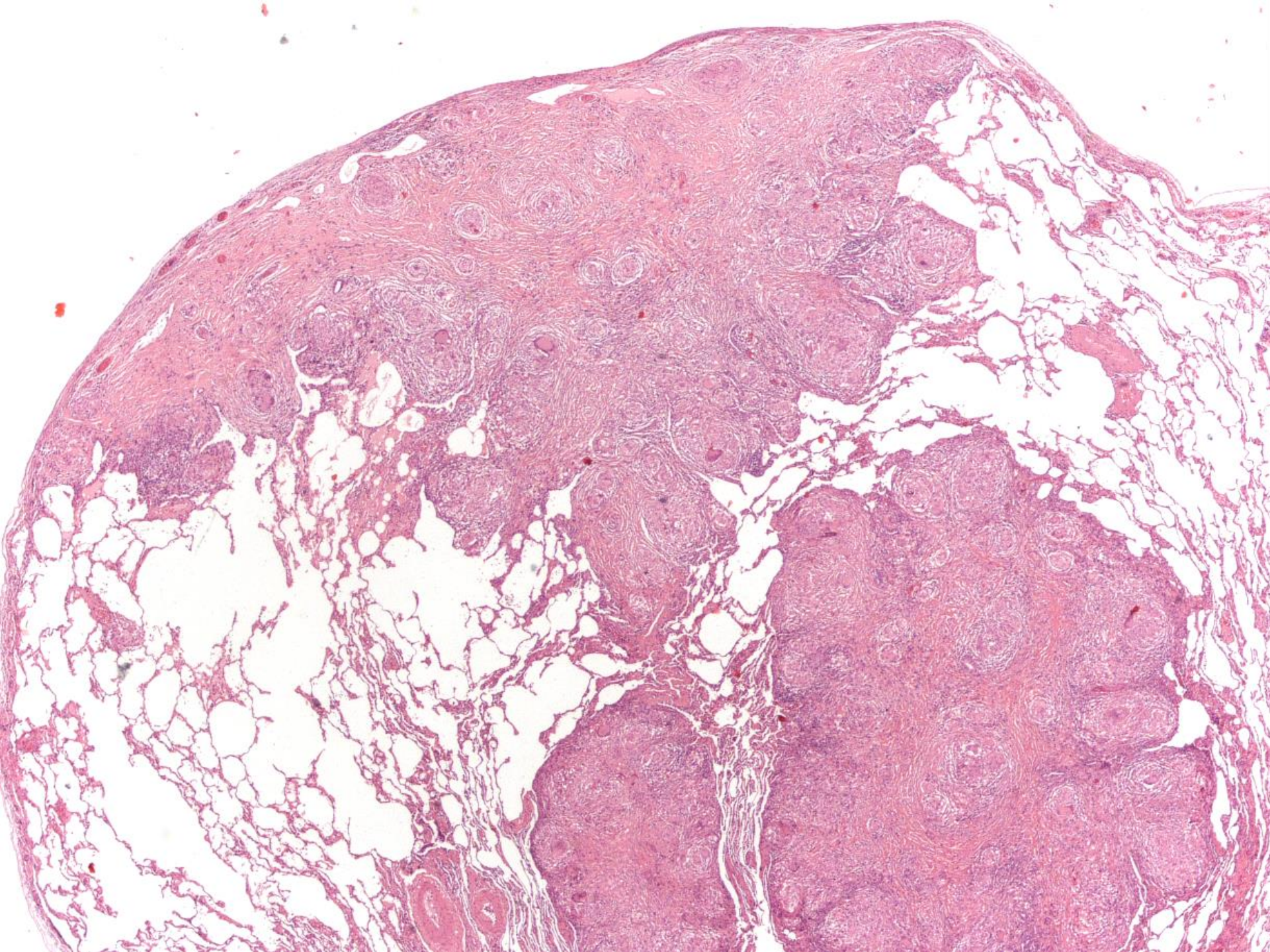


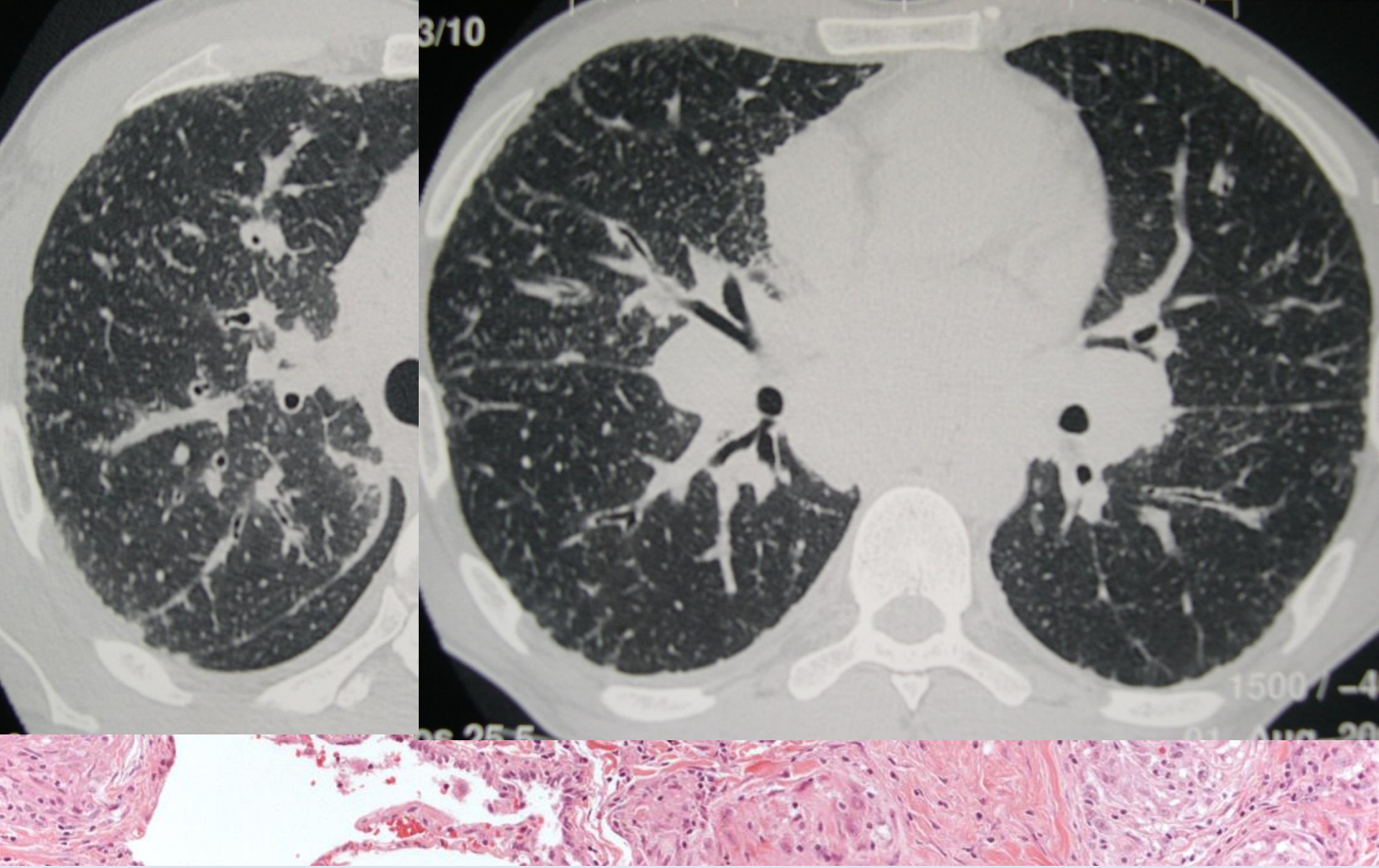
CD4/CD8 > 3.5

Sensitivity	53%
Specificity	94%

VATS 98%



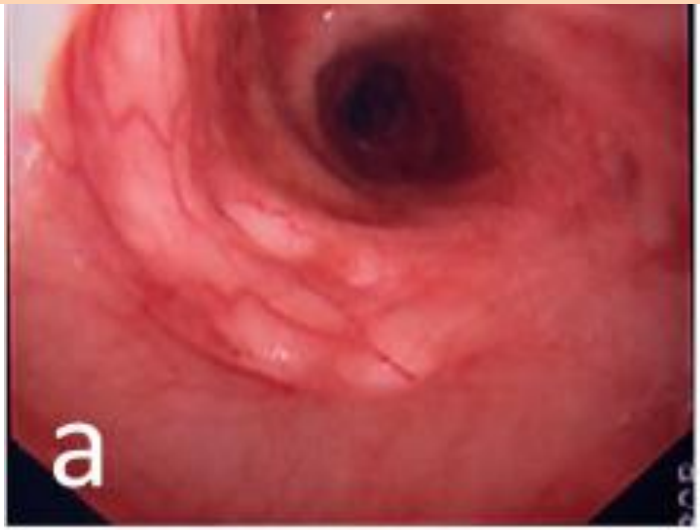


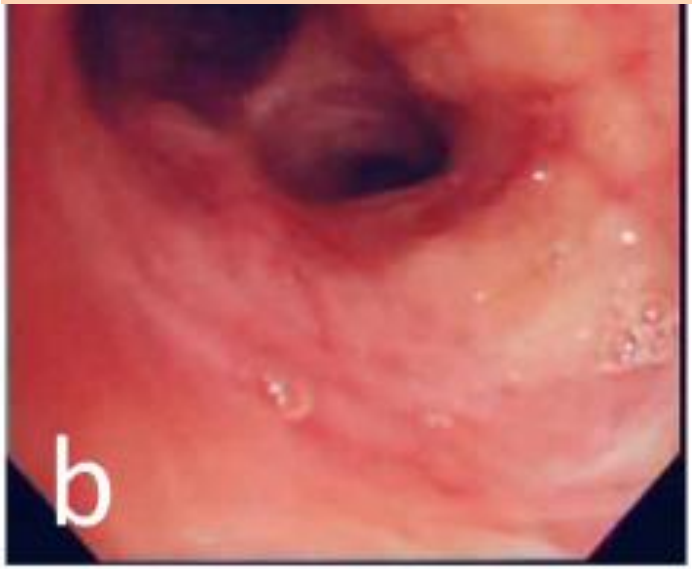


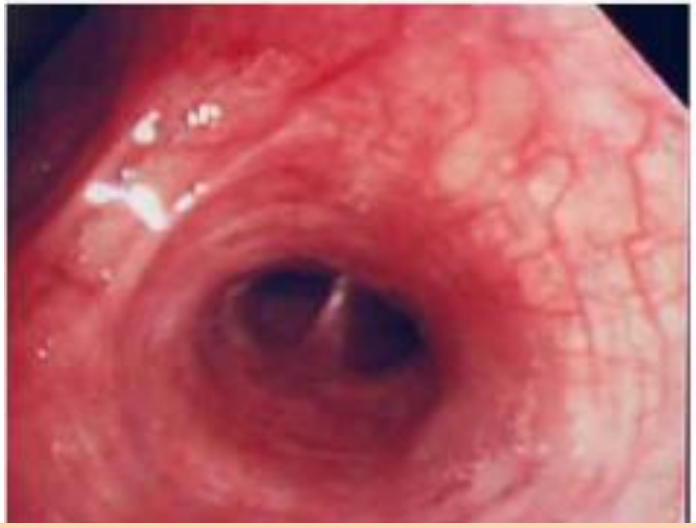
Sarcoidosi

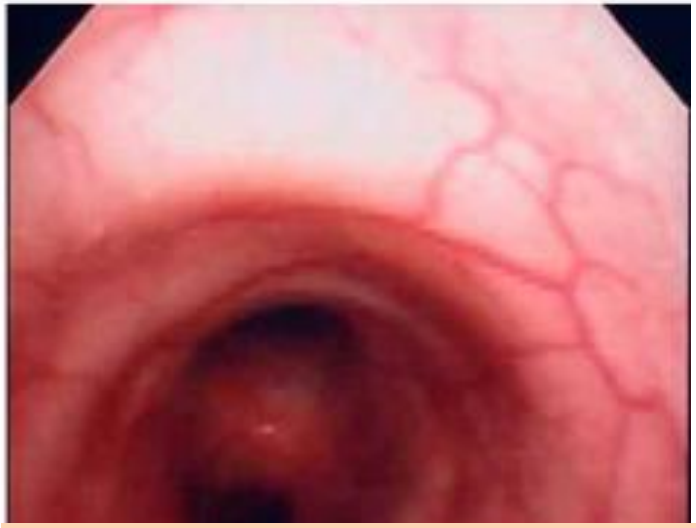
Flattened and pale-colored plaques arising from the bronchial mucosa, forming a “cobblestone appearance”

Bronchial lumen is crowded by pale-colored multiple nodules



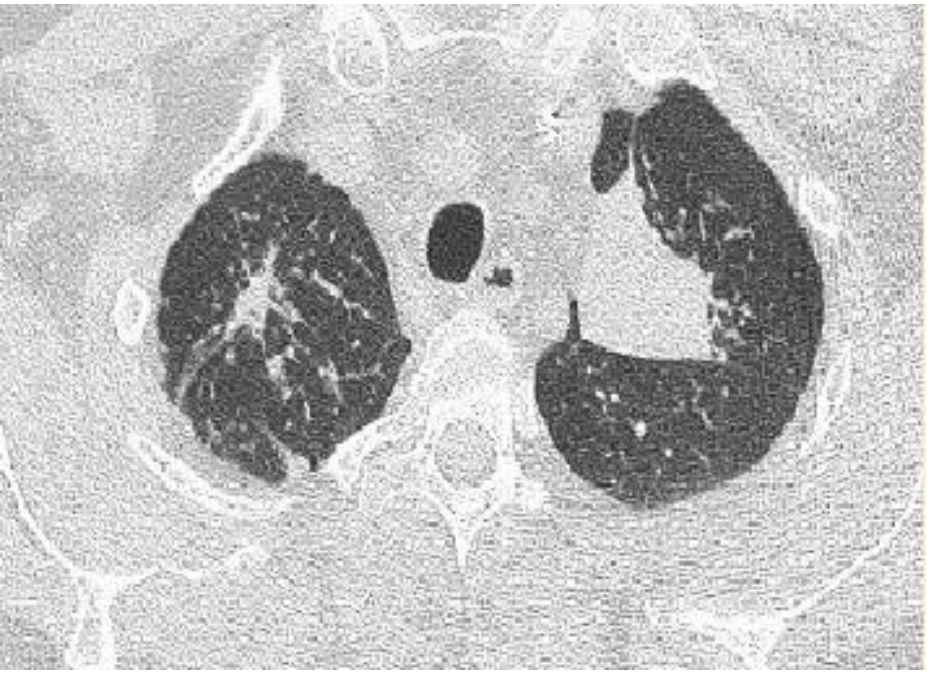


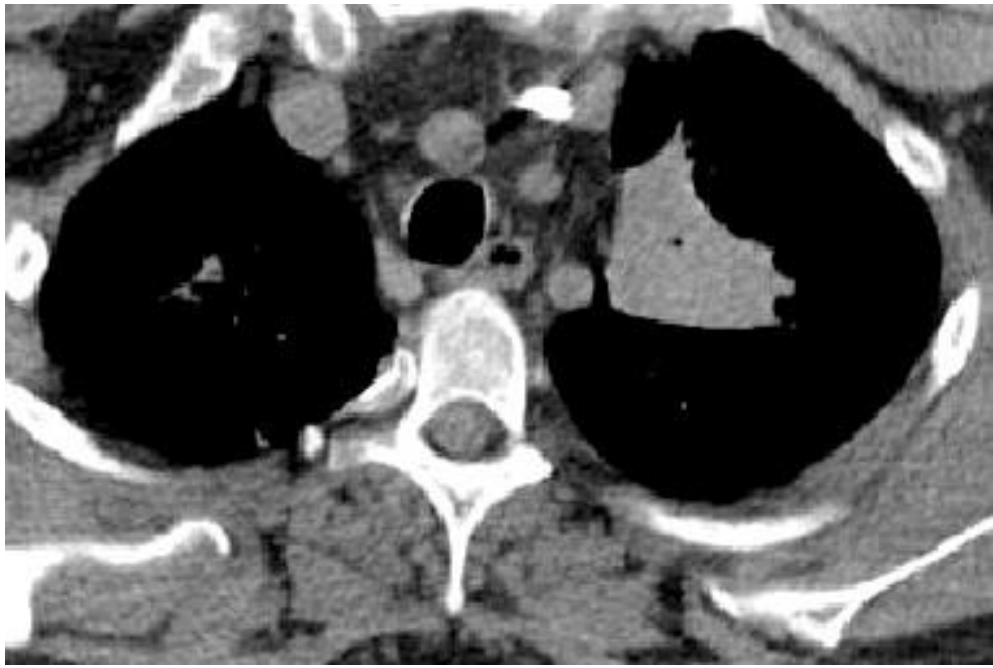


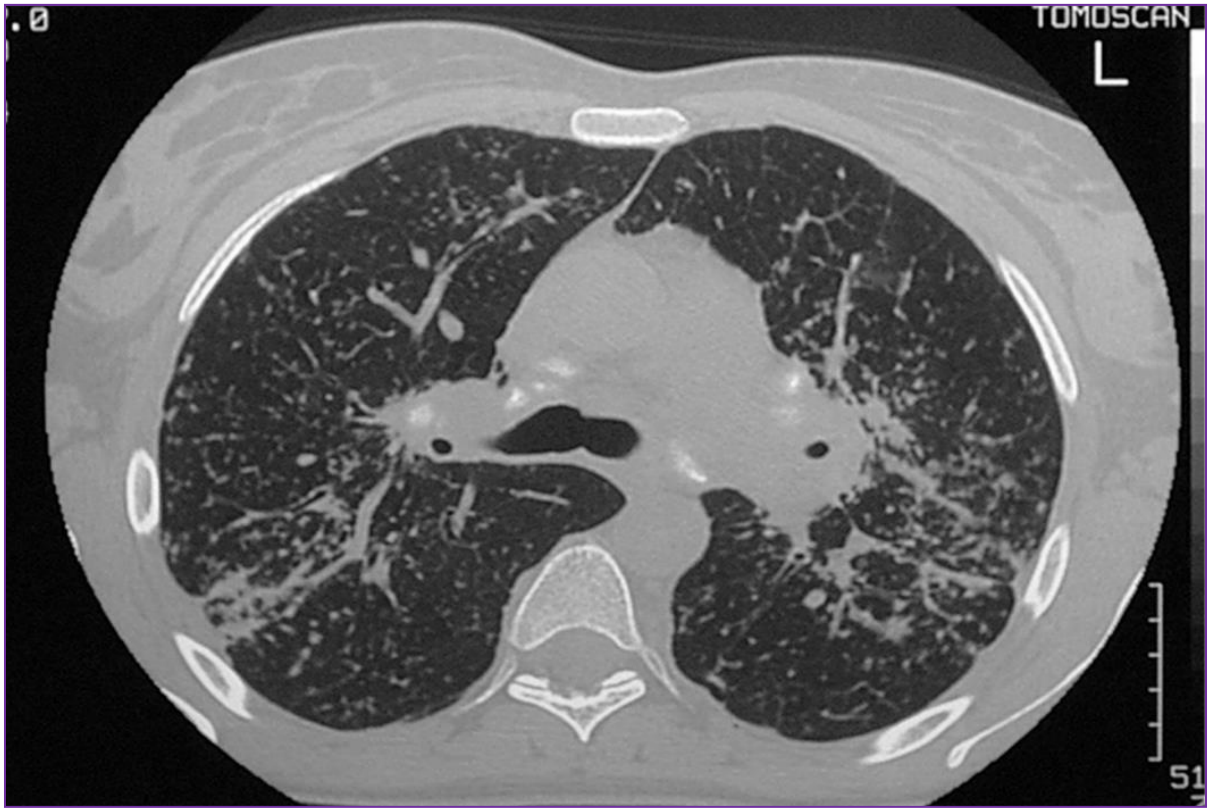


Mucosal hypervascularity with vessels running perpendicular to cartilaginous rings

Network formation of mucosal vessels in the left main bronchus, and mucosal edema of the left second carina



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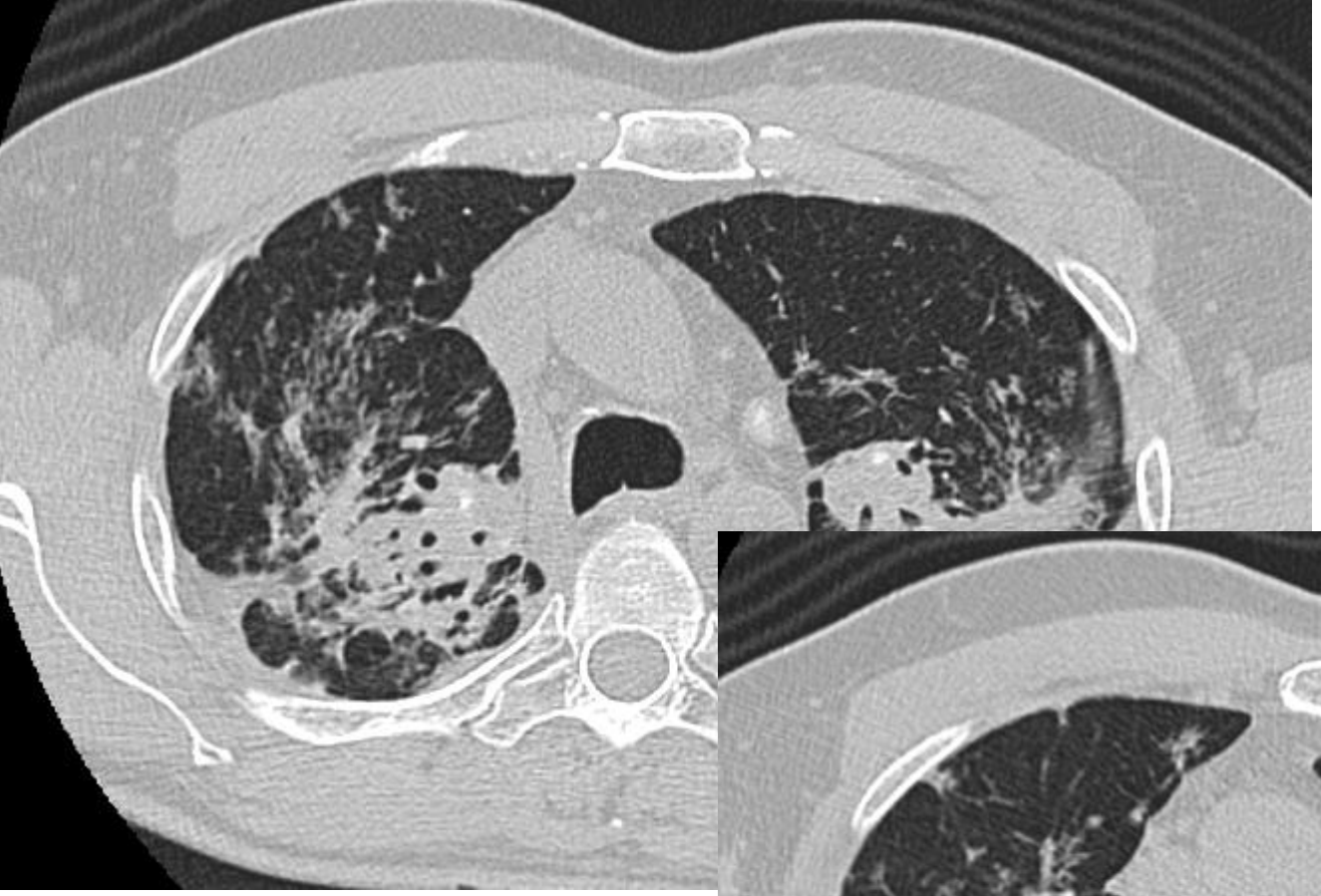
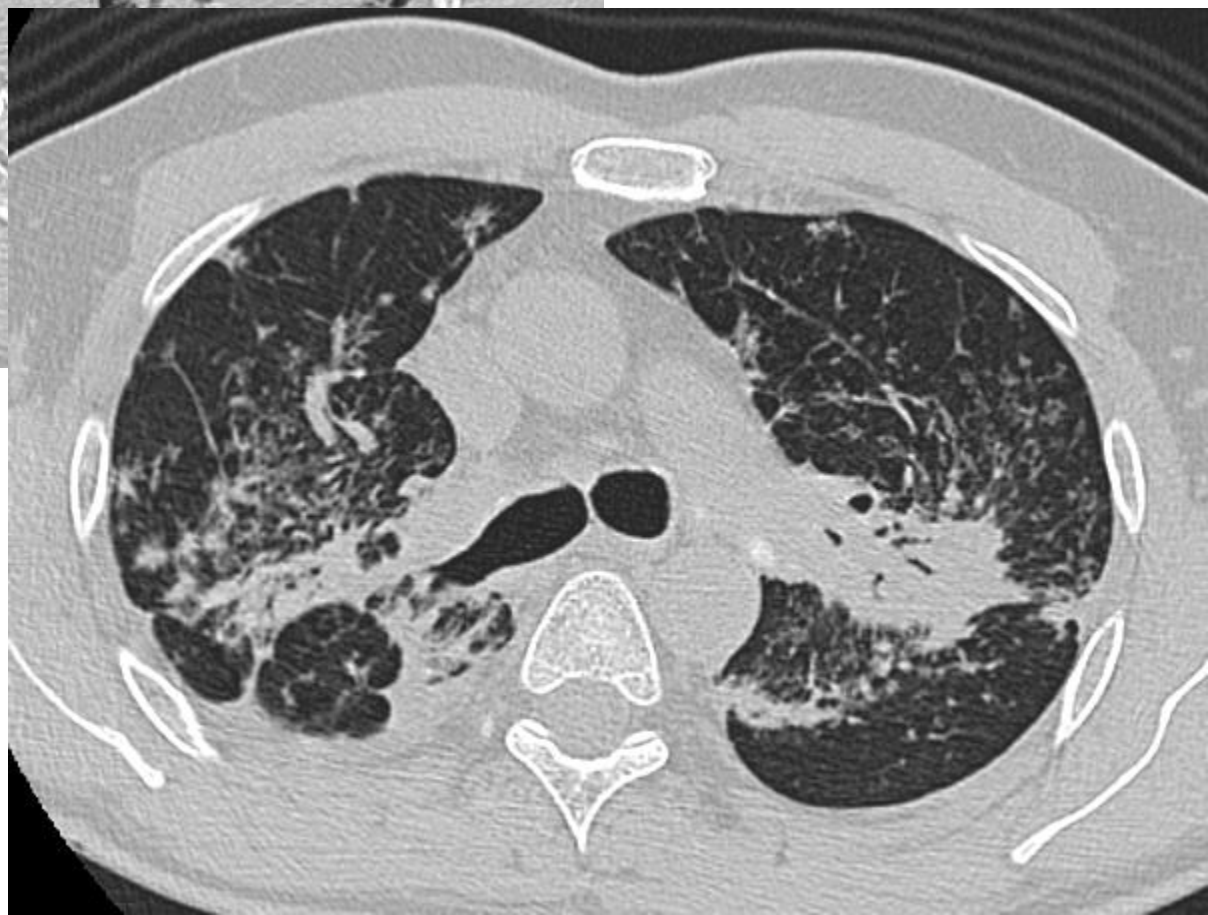
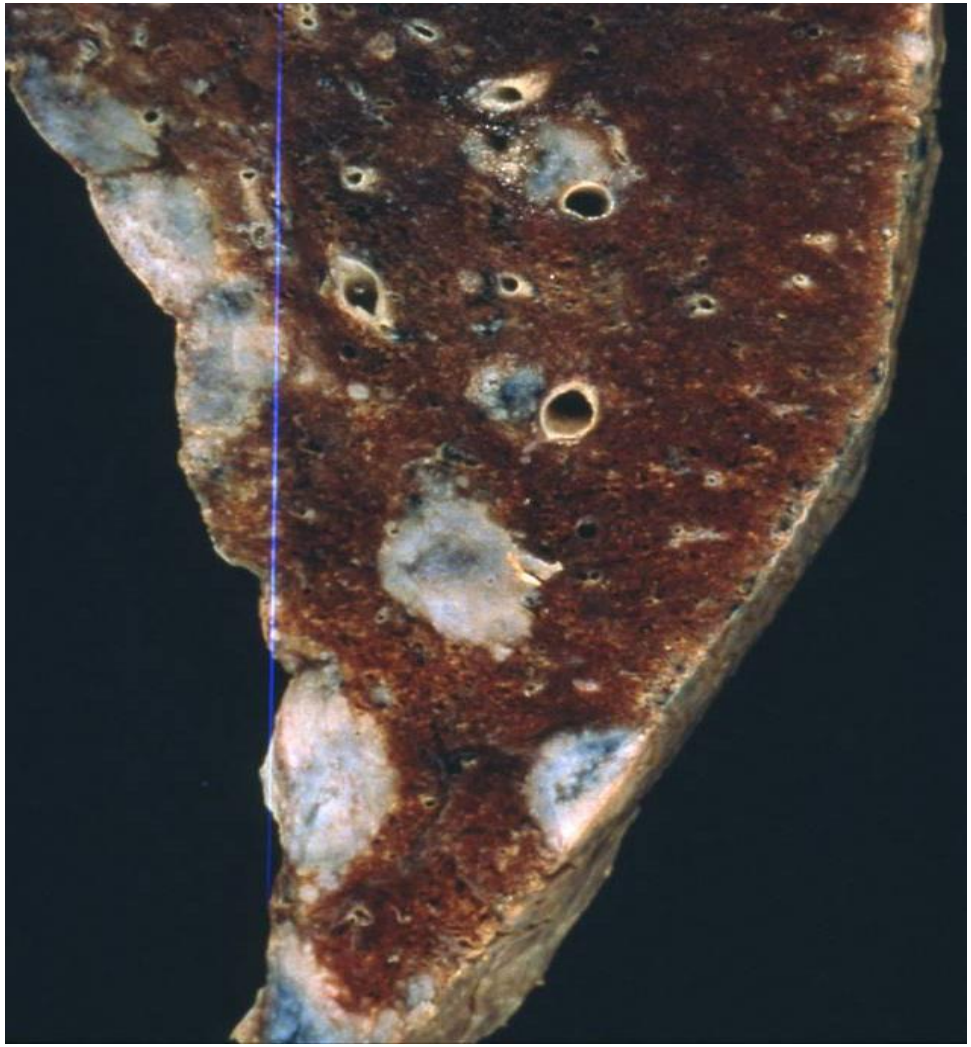
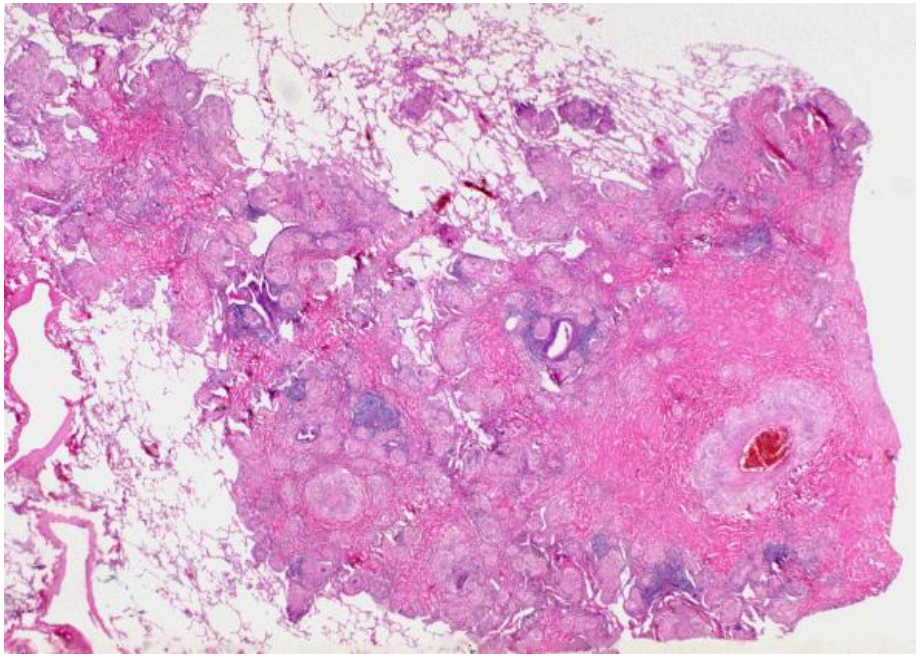
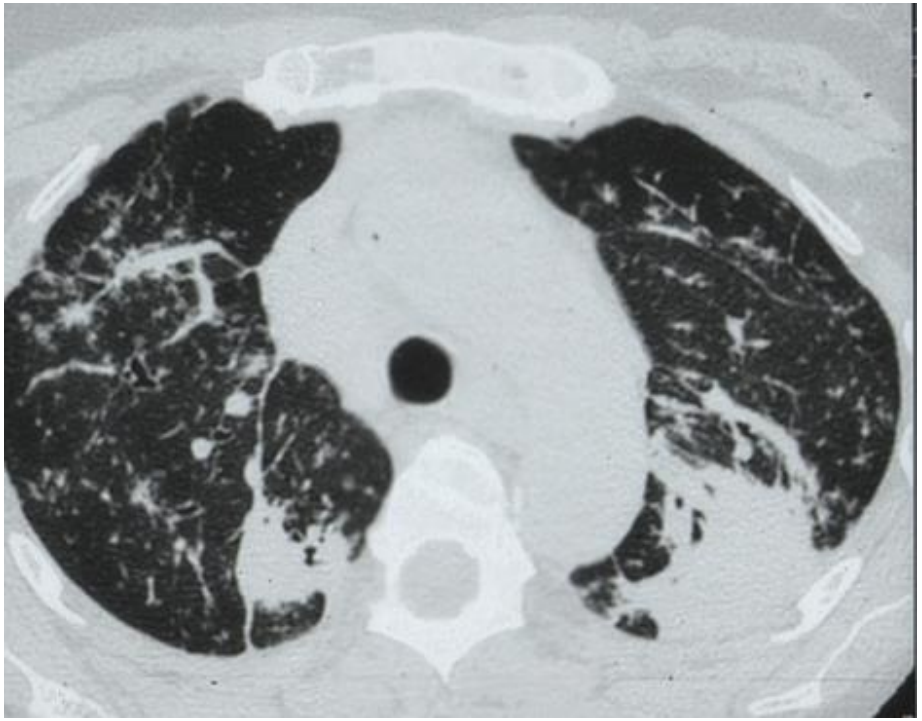




Nodular sarcoidosis







Question 3: Should patients with sarcoidosis who do not have ocular symptoms undergo screening for ocular sarcoidosis by routine eye examination?

- Sarcoidosis can involve almost **every portion of the eye**
- We suggest a baseline eye examination to screen for ocular sarcoidosis (conditional recommendation, very low-quality evidence).

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Table 5. Best Practice Recommendations for Detection of Delayed Onset of Extrapulmonary Sarcoidosis Manifestations after Negative Baseline Screening

Test Parameter	Routine Testing for New Sarcoidosis Involvement	New Conditions Triggering a Specific Testing for Extrapulmonary Sarcoidosis Involvement
Calcium	Annually	Kidney stones Acute or acute on chronic renal failure
Creatinine	Annually	—
Alkaline phosphatase	Annually	—
Eye exam	None	Change in vision • Floaters • Blurry • Visual field loss Eye pain, photophobia, or redness (sustained)
Cardiac testing (*see* Questions 9)	None	Chest pains Palpitations Near syncope/syncope Sustained bradycardia or tachycardia Dyspnea out of proportion to lung disease New ECG findings
Pulmonary hypertension testing (*see* Question 10)	None	Clinical signs of pulmonary hypertension (*see* main text)

Approximately 23% of patients with sarcoidosis will develop a new disease manifestation within 3 years of baseline evaluation. Annual testing is recommended for calcium, creatinine, and alkaline phosphatase, because these manifestations are often asymptomatic. In contrast, routine testing is not recommended for ocular or heart sarcoidosis, unless the patient presents with related symptoms, as above.

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Question 8: Should patients with sarcoidosis who do not have cardiac symptoms or signs undergo routine screening for cardiac sarcoidosis Using ECG, TTE, or 24-Hour ambulatory ECG monitoring?

- We suggest performing baseline ECG to screen for possible cardiac involvement (conditional recommendation, very low-quality evidence).

- We suggest NOT performing routine baseline TTE or 24-hour continuous ambulatory ECG (Holter monitor) to screen for possible cardiac involvement (conditional recommendation, very low-quality evidence).

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Question 9: Should patients who are suspected of having cardiac sarcoidosis undergo cardiac MRI, TTE, or PET as an initial imaging test?

- Imaging techniques are commonly used for cardiac sarcoidosis detection

- We suggest cardiac MRI, rather than cPET or TTE, to obtain both diagnostic and prognostic information (conditional recommendation, very low quality evidence).

Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Cardiac sarcoidosis

Cardiac sarcoidosis can be a benign, incidentally discovered condition or a life-threatening disorder causing sudden death

- 5% symtomatic involvement
- Up to 70% of sub-clinical involvement in autopsy studies
- 3.7-55% depending on the imaging methodology used

These observations suggest that the diagnosis of cardiac sarcoidosis **is difficult to establish**, especially in patients without evidence of sarcoid in other organs and thus cardiac sarcoidosis **is often underdiagnosed** in every day clinical practice

Cardiac sarcoidosis - symtoms

The symptoms and signs of cardiac sarcoidosis depend upon the location and extent of granulomatous inflammation

- conduction abnormalities (atrioventricular block or bundle-branch block), tachyarrhythmias
- cardiomyopathy, congestive cardiac failure
- sudden cardiac death

Cardiac involvement may precede, follow, or occur concurrently with involvement of the lungs or other organs

Histological sequence:

1) Edema
2) Granulomatous infiltrate
3) Scar

Clinical manifestations:

1) Conduction abnormalities
2) Congestive cardiac failure
3) Sudden cardiac death

The granulatous inflammation is mainly located at the level of the left ventrucular wall or at septum level:

→ Contractile dysfunction

→ Frequent involvement of conductive tissue

Pulmonary hypertension in sarcoidosis

Pulmonary hypertension in sarcoidosis

- Sarcoidosis associated PH occurs in 5–20% of patients seen in sarcoidosis clinics
- PH is an independent risk factor for increased mortality in sarcoidosis

Risk factors for presence of PH are:

* Dyspnea, exertional chest pain and/or syncope,
* reduced 6-minute walk distance, desaturation with exercise, reduced DLCO,
* increased pulmonary artery diameter relative to ascending aorta diameter (e.g., by CT scan),
* elevated brain natriuretic factor,
* fibrotic lung disease,

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Pulmonary hypertension in sarcoidosis

- For patients with sarcoidosis in whom PH is suspected, we suggest initial testing with TTE (conditional recommendation, very low-quality evidence).

- We suggest right heart catheterization to definitively confirm or exclude PH

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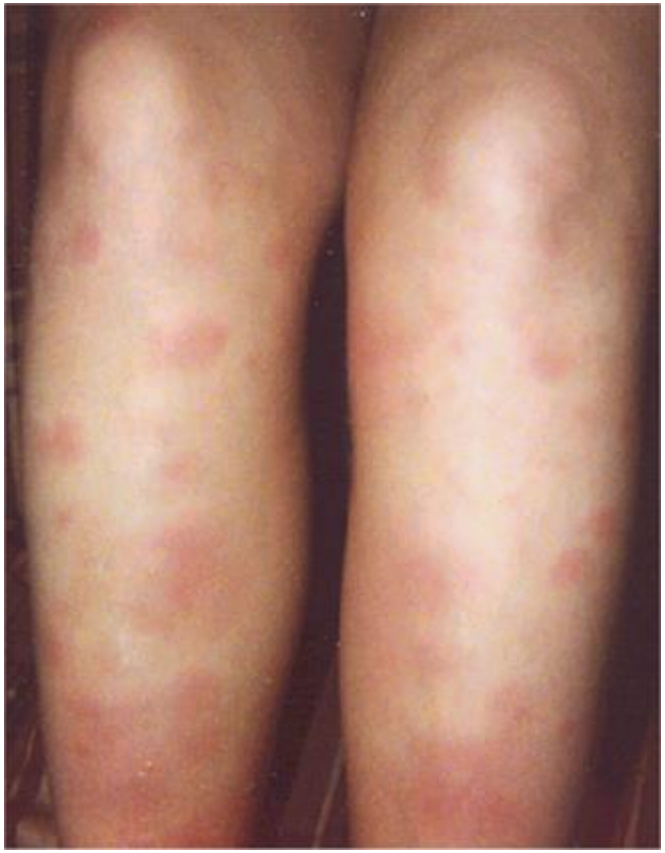
Clinical factors of prognostic value



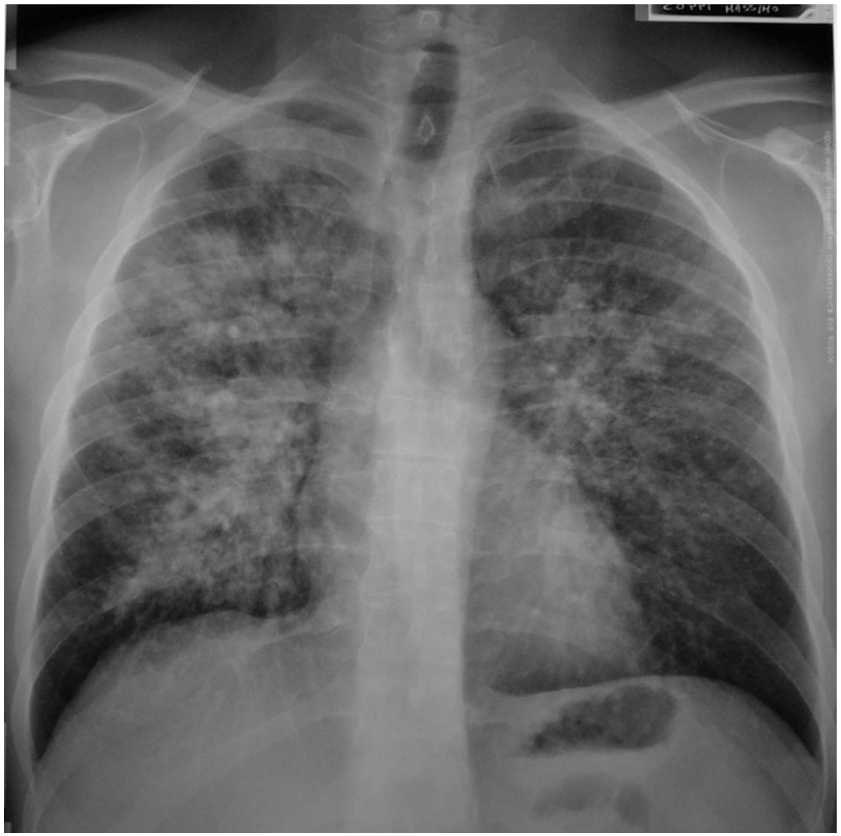
Good prognosis:

- Erythema nodosum and acute inflammatory manifestations: *e.g.* fever, polyarthritis
- race and certain HLA type (HLA-DR17+)
- Löfgren's syndrome

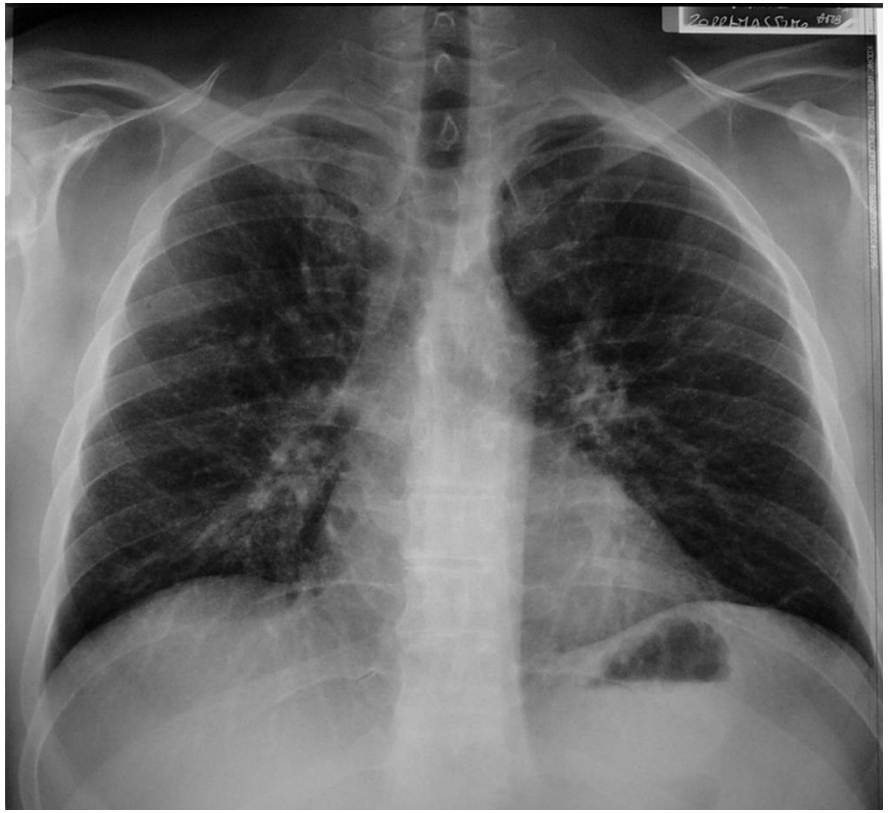
Clinical factors of prognostic value

Adverse prognostic factors:

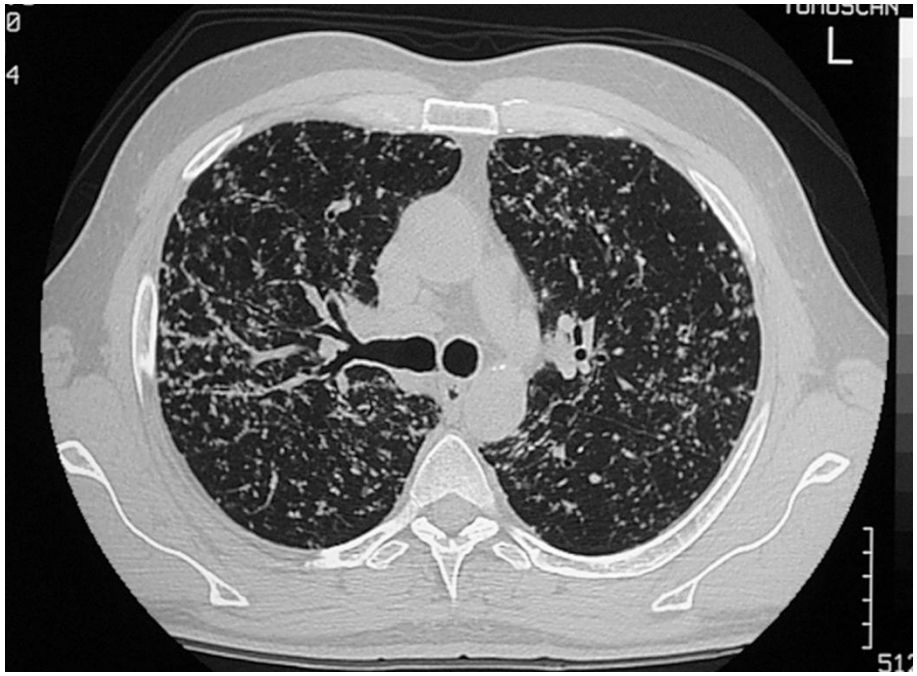
- black race, HLA-DR17-
- Lupus pernio
- chronic uveitis
- age at onset > 40 yrs
- hypercalcemia, nephrocalcinosis
- cystic bone lesions
- myocardial involvement
- **chronic respiratory insufficiency**
- **pulmonary hypertension**



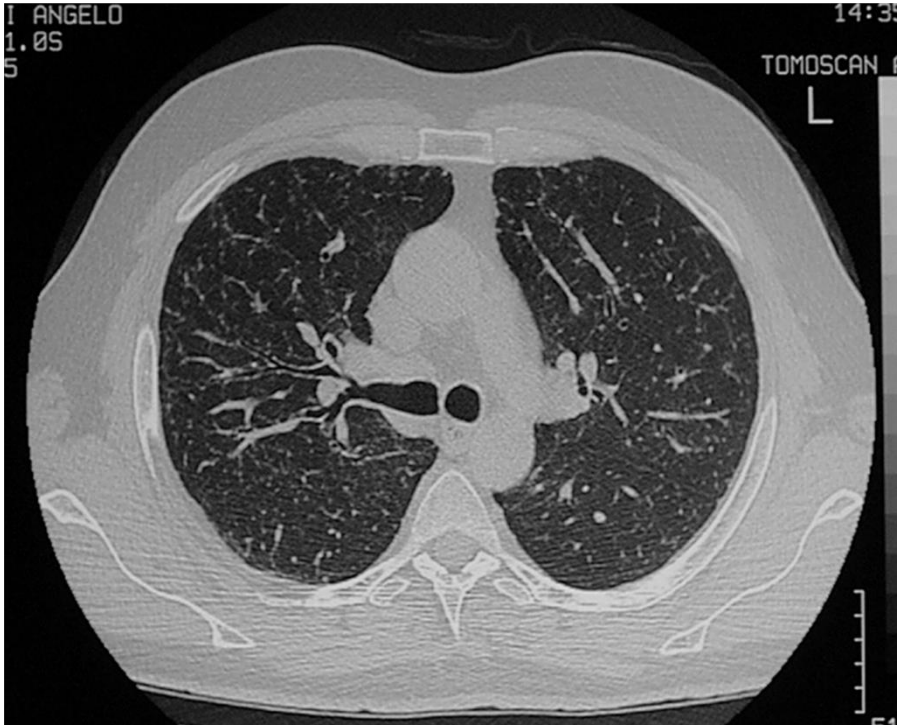
Spontaneous remission



Large variability in presentation and clinical course



Treatment Remission



Large variability in presentation and clinical course

EUROPEAN RESPIRATORY JOURNAL
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ERS clinical practice guidelines on treatment of sarcoidosis

Robert P. Baughman[1], Dominique Valeyre[2], Peter Korsten[3], Alexander G. Mathioudakis[4], Wim A. Wuyts[5], Athol Wells[6], Paola Rottoli[7], Hiliaro Nunes[8], Elyse E. Lower[1], Marc A. Judson[9], Dominique Israel-Biet[10], Jan C. Grutters[11,12], Marjolein Drent[11,13,14], Daniel A. Culver[15], Francesco Bonella[16], Katerina Antoniou[17], Filippo Martone[18], Bernd Quadder[19], Ginger Spitzer[20], Blin Nagavci[21], Thomy Tonia[22], David Rigau[23] and Daniel R. Ouellette[24]

Baughman RP et al. Eur Respir J 2021;https://doi.org/10.1183/13993003.04079-2020

Treatment of sarcoidosis

The major reasons to treat sarcoidosis are **to lower the morbidity and mortality risk or to improve quality of life (QoL).**

Pulmonary and cardiac disease are the most common reasons for death from sarcoidosis

While glucocorticoids (GC) remain the first choice for initial treatment of symptomatic disease, prolonged use is associated with significant toxicity.

Baughman RP et al. Eur Respir J 2021;https://doi.org/10.1183/13993003.04079-2020

Treatment of sarcoidosis

Recurrence of disease is common **if treatment is withdrawn too soon**, and at least a quarter of patients require treatment for more than two years

Baughman RP et al. Eur Respir J 2021;https://doi.org/10.1183/13993003.04079-2020

Relapse of sarcoidosis

Several studies have noted that relapse of symptomatic disease occurs in a significant number of patients upon withdrawal of therapy after one to two years.

The reported rate of relapse of disease upon GC withdrawal after two years of initial therapy **ranges from 20 to 80%**

Baughman RP et al. Eur Respir J 2021;https://doi.org/10.1183/13993003.04079-2020

Limitations

There is a **pressing need for higher-quality evidence** to guide clinical practice relating to the diagnosis and detection of sarcoidosis, and **to better define the natural history of disease progression** in each organ system.

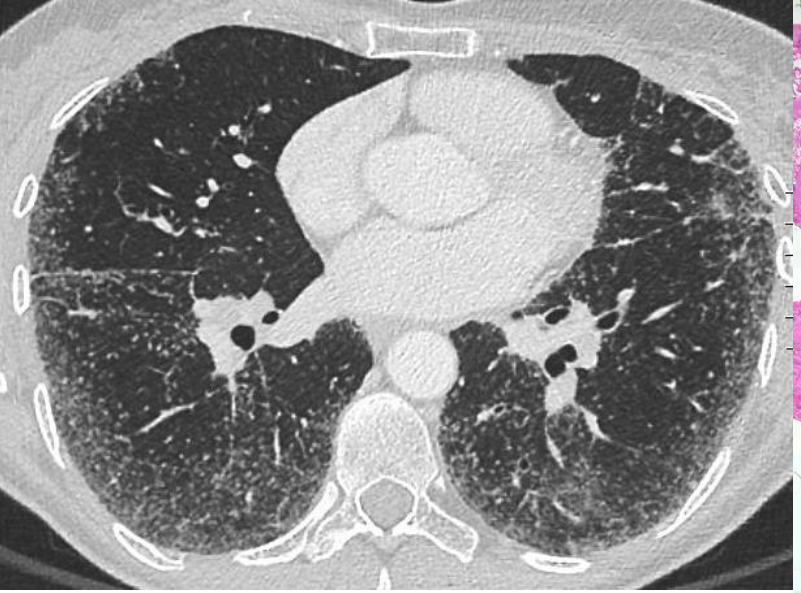
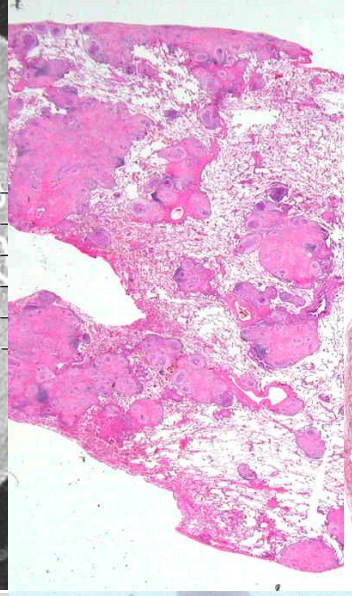
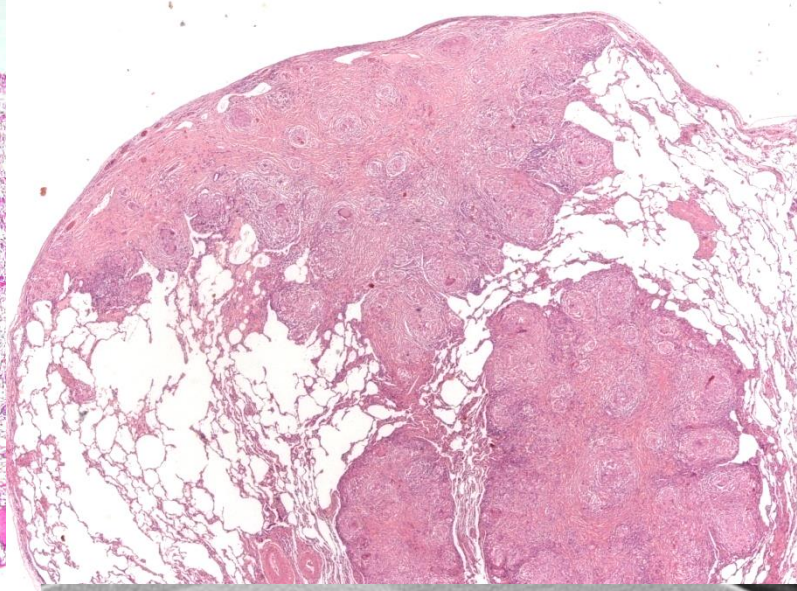
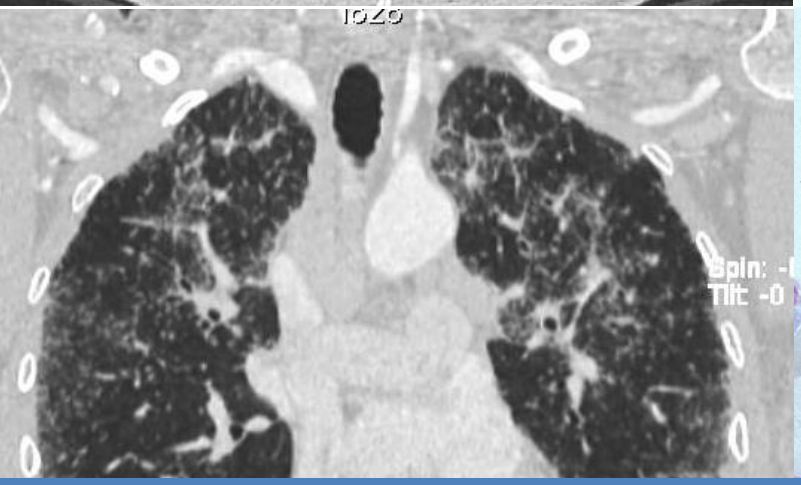
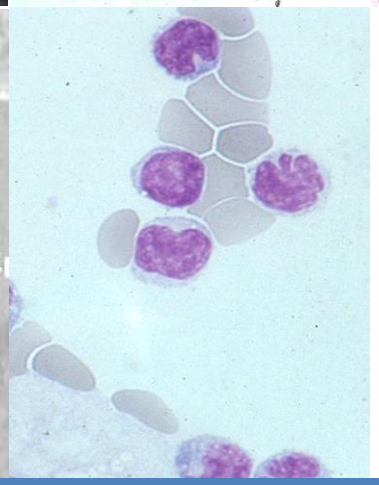
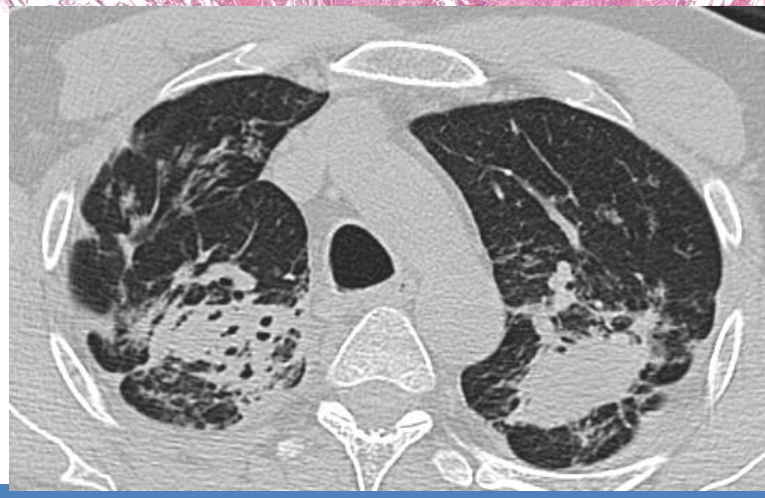
Crouser ED et al. Am J Respir Crit Care Med 2020; 201: e26-e51

Limitations

All authors **felt there was much to do**:

1) the indications for treatment remain unclear and mostly based on a case by case basis;
2) measurements of response to treatments are still too heterogeneous;
3) clinical trials may provide more information;
4) single endpoints such as FVC or chest imaging may not be reliable and a composite score evaluating physiology, radiology, QoL, and steroid-sparing may be more effective

Baughman RP et al. Eur Respir J 2021;https://doi.org/10.1183/13993003.04079-2020

La Sarcoidosi: luci ed ombre

Grazie dell'attenzione