Sarcoidosis Pulmonar: 4 caras de la misma enfermedad

Unidad Académica Clínica Médica B - Prof. Dra. Laura Llambí

CEDA COSEM IAMPP

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Hoja de ruta

Presentación de casos clínicos.

Revisión de lectura:

- Definición
- Epidemiología
- Etiopatogenia
- Manifestaciones clínicas
- Sarcoidosis pulmonar
- Diagnóstico y diagnósticos diferenciales
- Tratamiento de la sarcoidosis pulmonar
- Mensajes finales

Caso clínico 1

FP: SF. 56 años.

AP:

- FRCV: DM tipo II, HTA esencial, obesidad central.
- Gammapatía monoclonal de significado incierto (GMSI).
- Enfermedad pulmonar intersticial difusa (EPID) diagnosticada en 2023 a punto de partida de disnea grado 3 mMRC. Sin demostración de enfermedad autoinmune subyacente hasta el momento

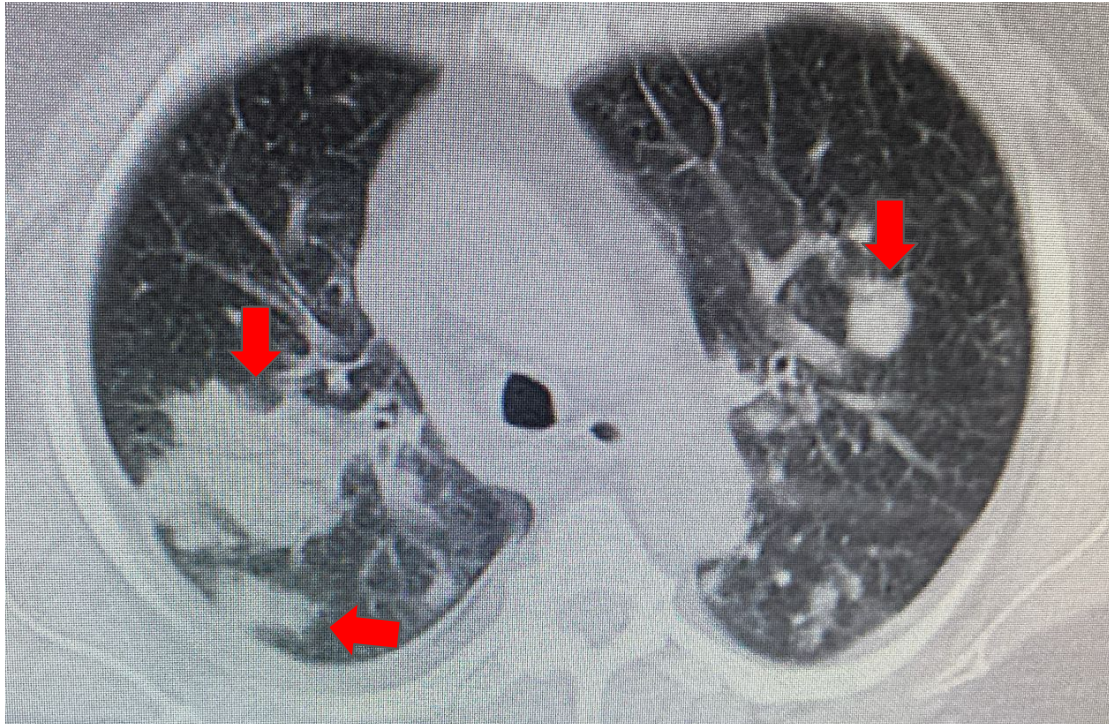
De forma ambulatoria se estudia en profundidad etiología de la disnea:

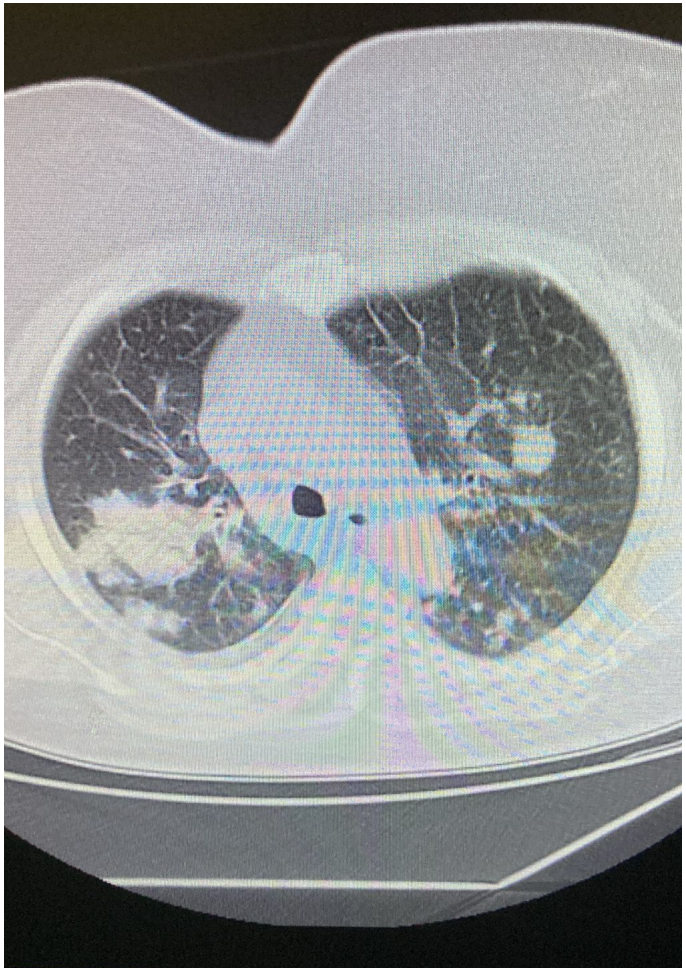
- ANA 1/160; anti-ENA U1-RNP positivo débil; resto de la valoración autoinmune negativa (FR, anticuerpos citrulinados, aldolasa, panel de miositis con CPK normal).
- Biopsiada en dos oportunidades por EPID sin diagnóstico concluyente (negativa para malignidad, inflamación bronquial crónica inespecífica con fibrosis leve, sin granulomas).
- FBC con LBA sin desarrollo bacteriológico y micológico.GeneXpert negativo.
- TM6M: DR 116,04% 290 mts con caída de SatO2 de 97 a 93%.
- Dada alta sospecha de enfermedad autoinmune y habiendo descartado enfermedades infecciosas se realiza bolos iv de Metilprednisolona 500 mg por 3 días y luego dosis de mantenimiento de Prednisona 20 mg/día con mejoría parcial.

A pesar de tratamiento con corticoides, persiste con disnea progresiva por lo cual se decide ingreso sanatorial.

Tomografía de tórax al ingreso...

Múltiples lesiones nodulares y pseudonodulares nivel pulmonar bilateral y difusas, las de mayor tamaño en LSD y LID de 46 y 34 mm, el resto de las lesiones son bilaterales y de distribución aleatoria.





Planteos clínicos

- ¿Cáncer bronco-pulmonar?
- ¿Enfermedad autoinmune?
  - Sarcoidosis
  - Vasculitis

PET-CT

Se solicita PET-CT en vistas a guiar nueva biopsia que informa masa en LSD hipermetabólica y nódulos pulmonares hipermetabólicos bilaterales que no permiten descartar malignidad.

La anatomía patológica concluye la presencia de neumonitis granulomatosa cuyas características son consistentes con una sarcoidosis.

Persiste con lesiones pulmonares pese a tratamiento múltiple: cortico-refractariedad, 2 fármacos ahorradores de corticoides, sin cambios pulmonares, actualmente en recurso de amparo para anti TNF-alfa.

Caso clínico 2

FP: SM. 30 años.

AP:

- Nefrolitiasis a repetición con estudio litogenico normal.
- Roncador con polisomnografía sin apenas.

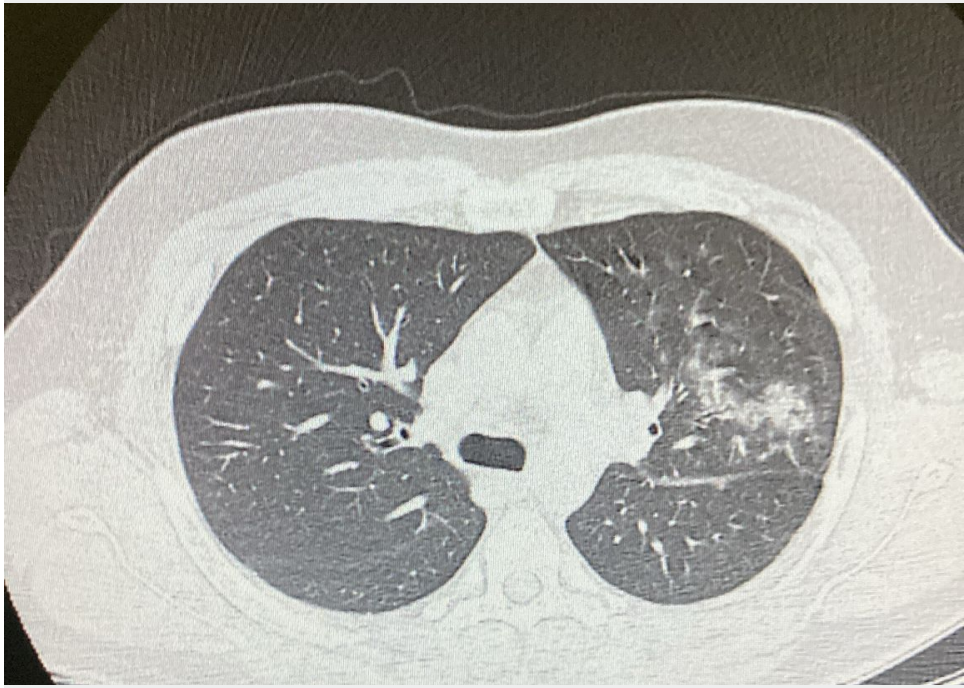
AEA: presentó en 2 oportunidades episodios dados por dolor lumbar y fiebre que se interpretaron como pielonefritis sin confirmación microbiológica (asépticas).

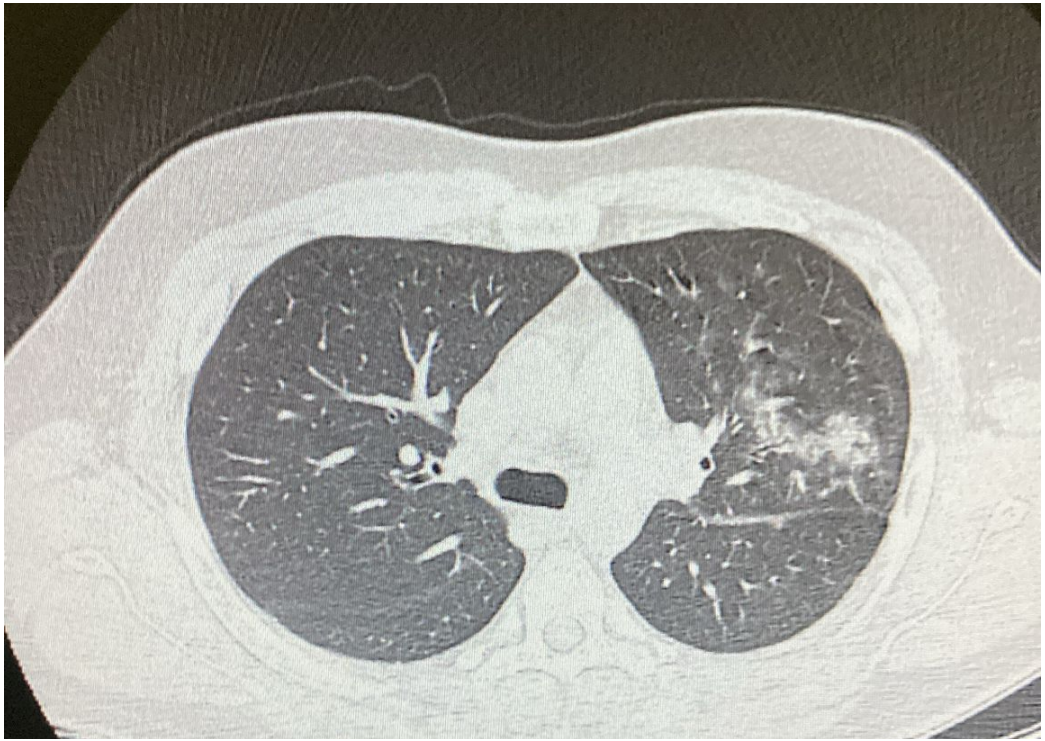
EA: consulta nuevamente por episodio de dolor lumbar y fiebre de hasta 38°C.

- Sin elementos de SUB. Sin hematuria u orinas espumosas.
- Tos seca de meses de evolución con sudoración nocturna, sin otros elementos de sd. toxi-bacilar, sin repercusión general, sin elementos de sd. mediastinal. Sin nexo epidemiológico establecido.

Planteo clínico

¿Tuberculosis pulmonar?





Causes of the Tree-in-Bud Pattern

- Peripheral airway disease
  - Infection
    - Bacterial
      - *Mycobacterium tuberculosis*
      - *M avium-intracellulare* complex
      - *Staphylococcus aureus*
      - *Haemophilus influenzae*
    - Fungal
      - *Aspergillus*
    - Viral
      - Cytomegalovirus
      - Respiratory syncytial virus
  - Congenital disorders
    - Cystic fibrosis
    - Kartagener syndrome
  - Idiopathic disorders
    - Obliterative bronchiolitis
    - Diffuse panbronchiolitis
  - Aspiration
  - Inhalation
    - Toxic fumes and gases
  - Immunologic disorders
    - Allergic bronchopulmonary aspergillosis
  - Connective tissue disorders
    - Rheumatoid arthritis
    - Sjögren syndrome
- Peripheral pulmonary vascular disease
  - Neoplasms
    - Gastric cancer
    - Breast cancer
    - Ewing sarcoma
    - Renal cancer

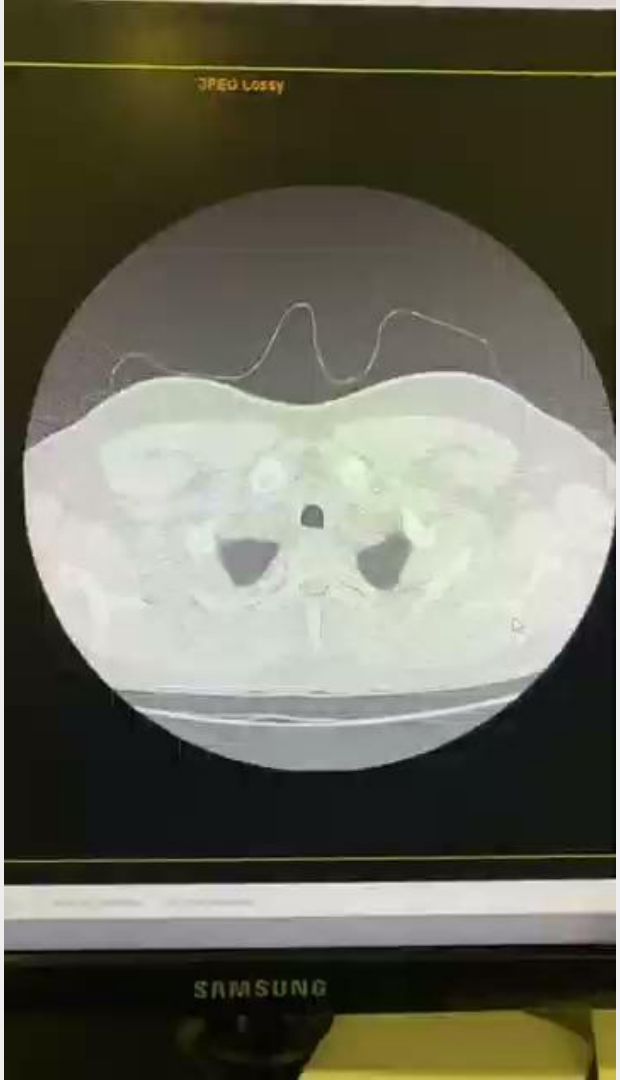
Estudios etiológicos

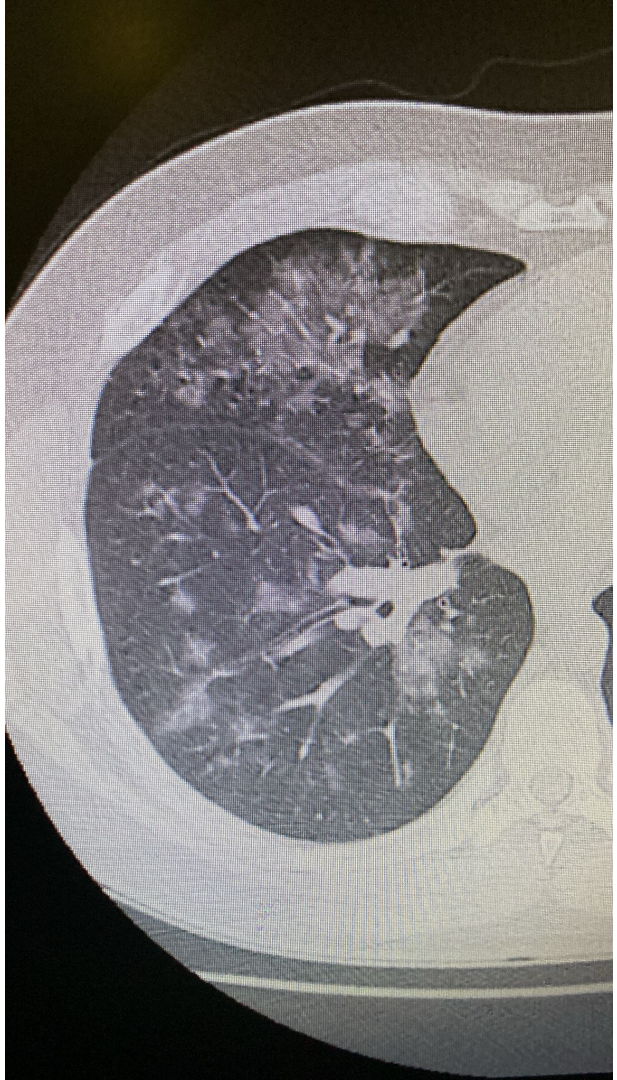
- VIH negativo
- Ag neumocócico negativo
- VES 100
- Examen de orina normal, UC negativo

FBC con LBA:

- Directo y cultivo bacteriológico negativo
- Baciloscopia y GeneXpert negativos
- Galactomanano negativo
- Panel viral respiratorio negativo

Tomografía de control al mes con resolución del patrón de árbol en brote





Opacidades nodulares en vidrio deslustrado centroacinares peribroncovasculares con tendencia a la consolidación en pulmón izquierdo, impresiona patrón migratorio que podría verse en vasculitis.

Negativos:

- Anti-MBG
- Anti-DNA
- ANA
- ANCA
- Anti Jo/Ro/La

Biopsia transparietal compatible con sarcoidosis pulmonar

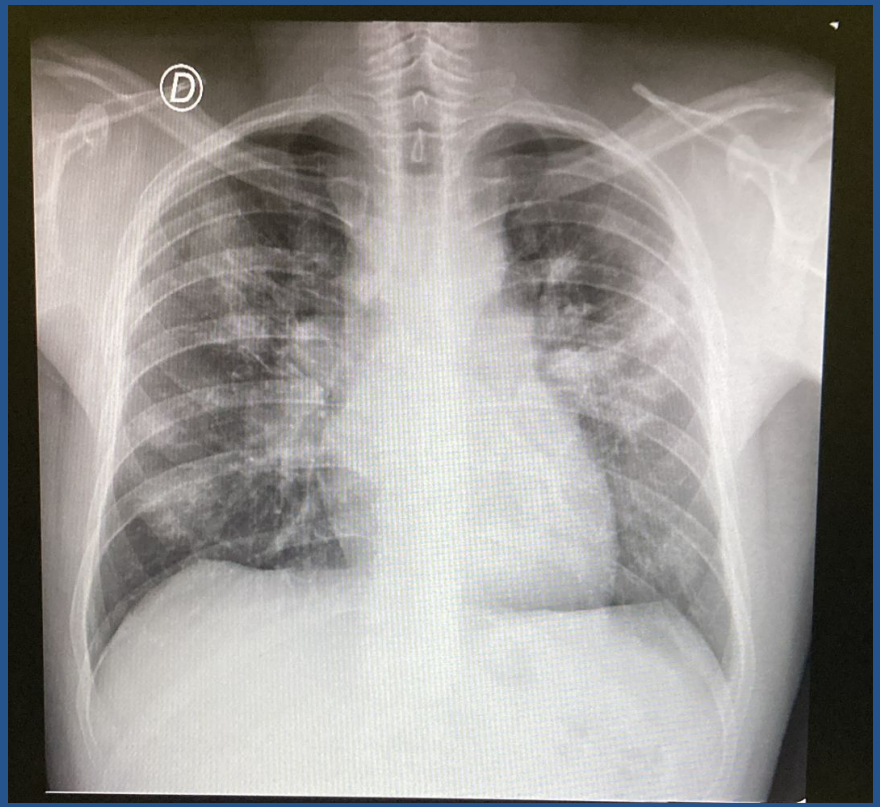
Caso clínico 3

FP: SM. 32 años.

AP:
- Dislipemia
- Tabaquismo ocasional de 2-3 cigarrillos. No BC.

EA: consulta en emergencia por dolor en hipocondrio derecho tipo puntada sin irradiaciones, de intensidad moderada. En ausencia de otros síntomas orientadores.

Examen físico abdominal normal.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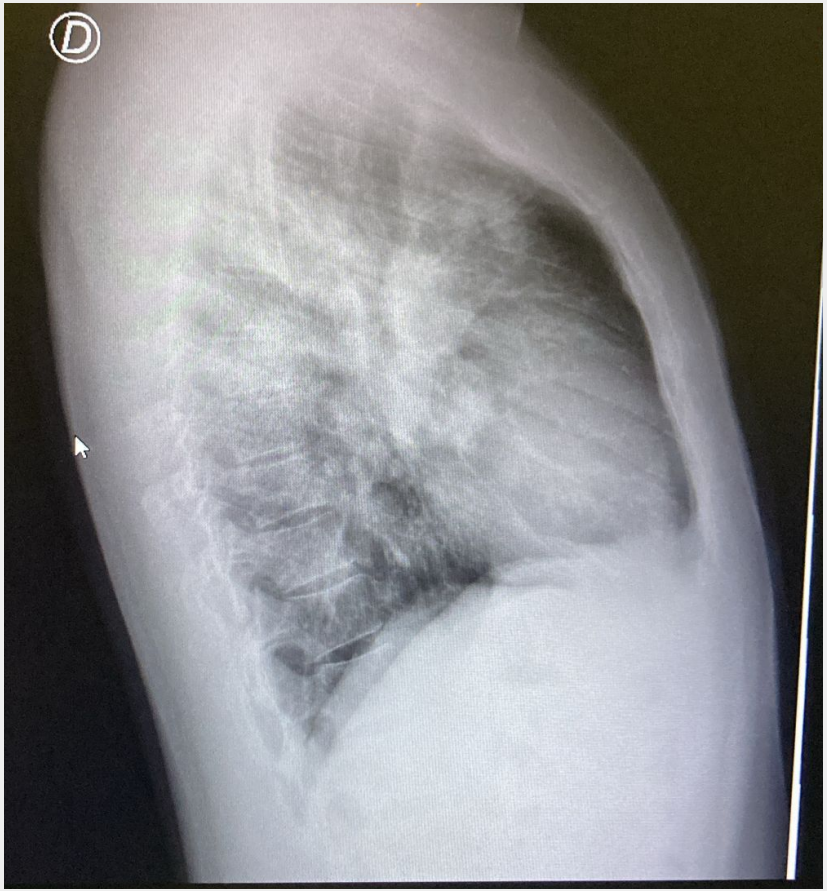
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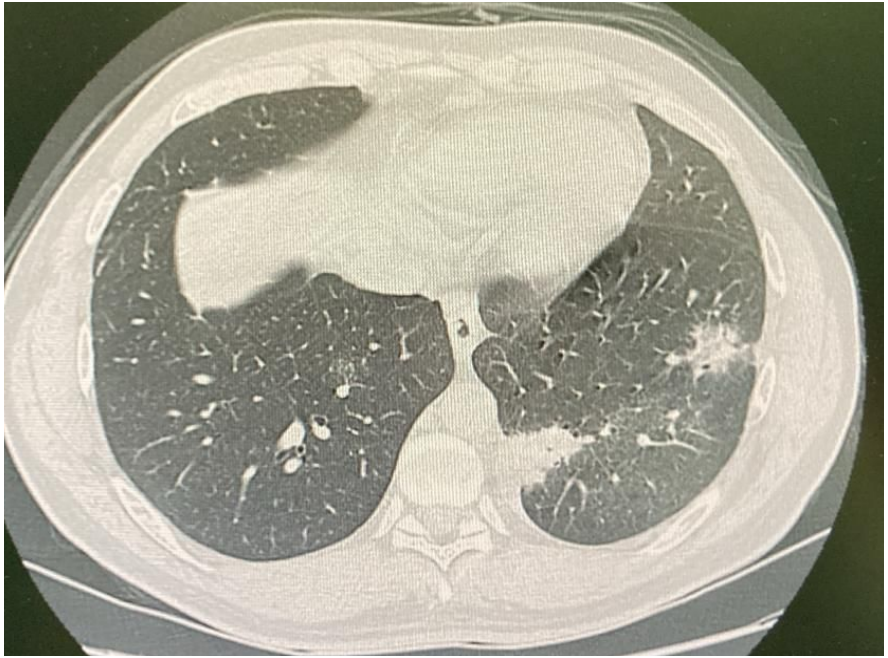
Tomografía de tórax

Se identifican múltiples adenomegalias y conglomerados adenopáticos a nivel mediastinal y ambos hilios pulmonares de hasta 27 mm. Múltiples nódulos pulmonares bilaterales y de distribución difusa de hasta 28 mm, algunos de ellos con broncograma aéreo, asocian áreas en vidrio deslustrado periférica (signo del halo).



Estudios etiológicos

Infeccioso:

- VIH negativo
- FBC con LBA: directo y cultivo bacteriológico sin desarrollo. Galactomanano negativo. GeneXpert negativo.
- Virus respiratorios negativos: Influenza A/B, VRS y COVID-19

Oncológico:

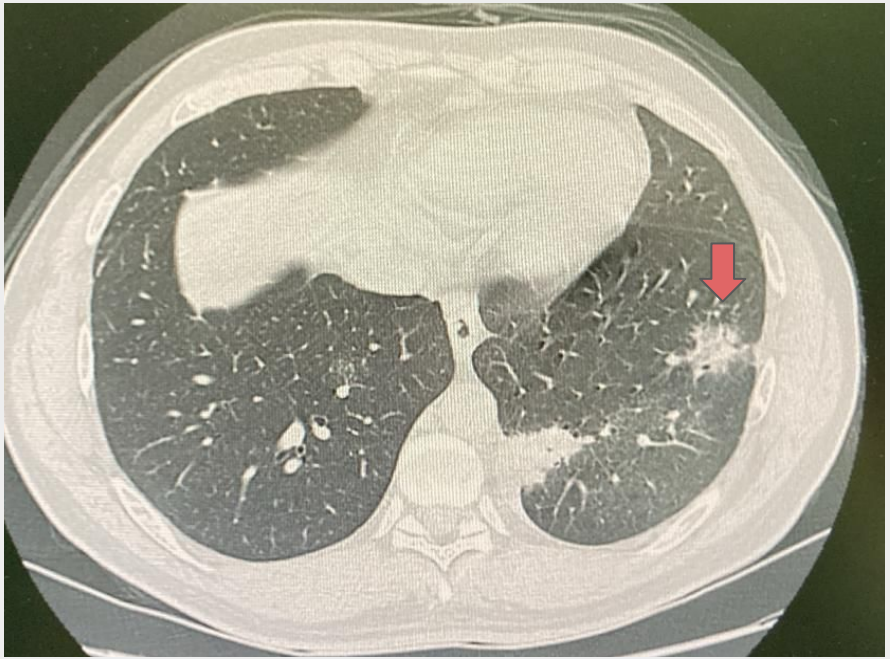
- TC abdomen y pelvis sin adenopatías o tumoraciones.
- Ecografía testicular sin lesiones.
- LDH y B2-microglobulina en rango.

Inflamatorio:

- VES 8 PCR de 0,07

Biopsia transbronquial de lesiones pulmonares

Anatomía patológica:
proceso crónico granulomatoso no necrotizante compatible con sarcoidosis a forma pulmonar y ganglionar.



Caso clínico 4

FP: SM. 35 años.

AP:

- VIH positivo con inmunidad conservada y carga viral indetectable de larga data bajo TARV. Nunca enfermedades marcadoras.
- No otras patologías médicas
- No alergias medicamentosas

EA: se presenta en policlínica con tos seca de 1 mes de evolución, agrega lesiones de piel a predominio de ala nasal.

- Nunca fiebre o equivalentes, no síntomas respiratorios altos, no movilización de secreciones, no episodios rojos, no dolor pleurítico.
- Sin elementos de sd. mediastinal, no sudoración nocturna o síntomas B.
- No repercusión general o sd toxi-bacilar
- No otras lesiones en piel o faneras, sin alteraciones a nivel del cuero cabelludo. No artritis o artralgias de manos

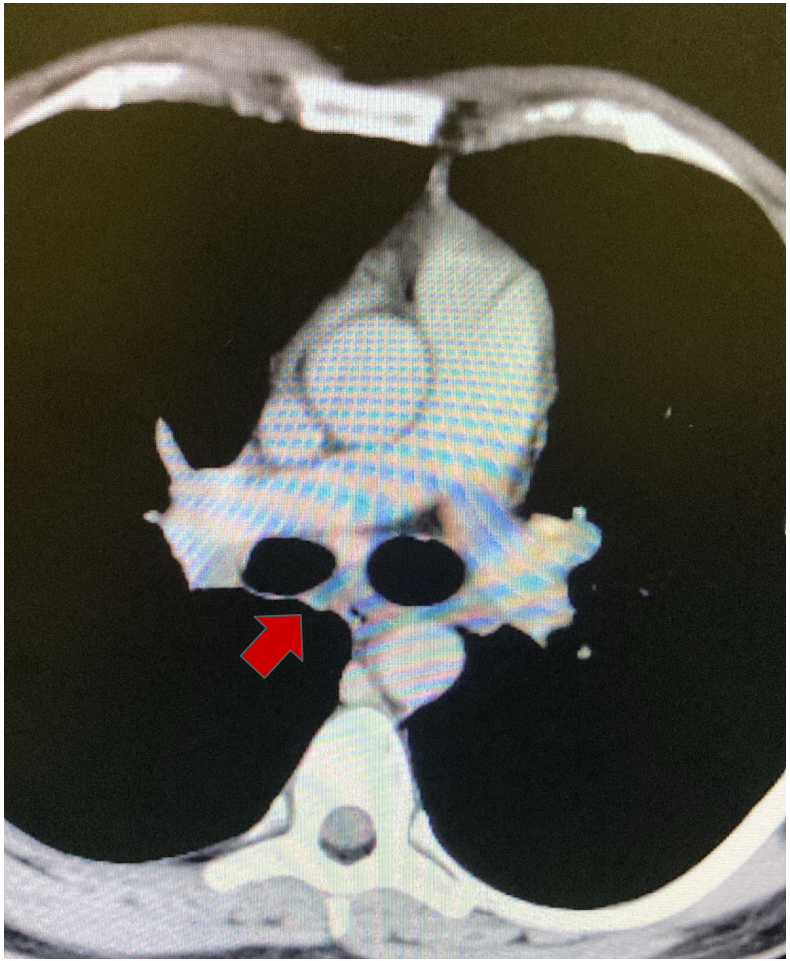
Tomografía de tórax

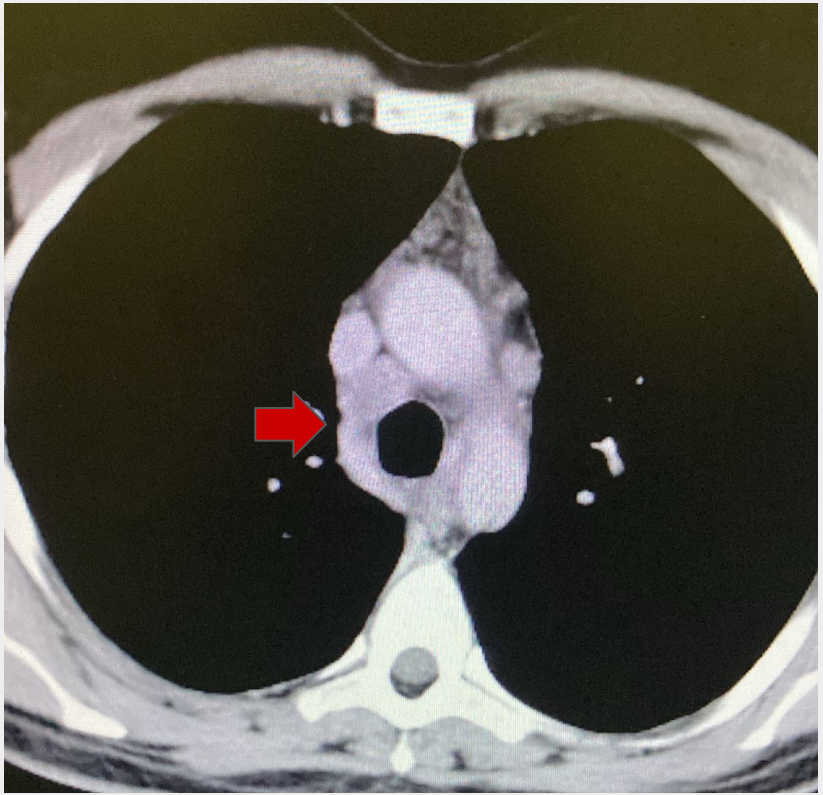
Conglomerado ganglionar mediastinal en distintas regiones, la mayor a nivel interno carinal de 34 mm.

Micronódulos en lóbulos pulmonares superiores.

Ganglios linfáticos axilares de hasta 19 mm e interpectorales de hasta 12 mm.

Adenomegalias lumbo aórticos, mesentéricas y pelvianas entre 13 y 16 mm.





Ganglios laterotraqueales

Estudios etiológicos

Planteos:

- Sd. poliadenomegálico transcurriendo en paciente VIH positivo pero con inmunidad conservada.
- Asocia compromiso cutáneo y respiratorio.

Infeccioso:

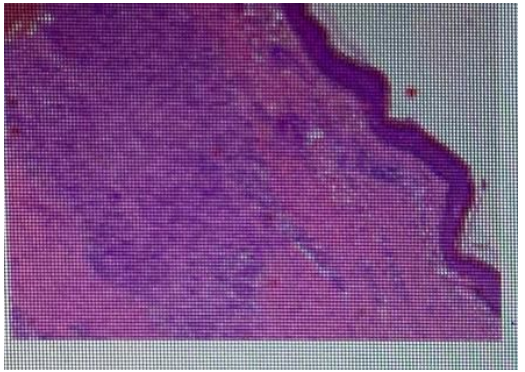
- FBC con LBA: cultivos bacteriológicos y micológicos negativos, GeneXpert negativo, Galactomanano negativo, PCP negativo.

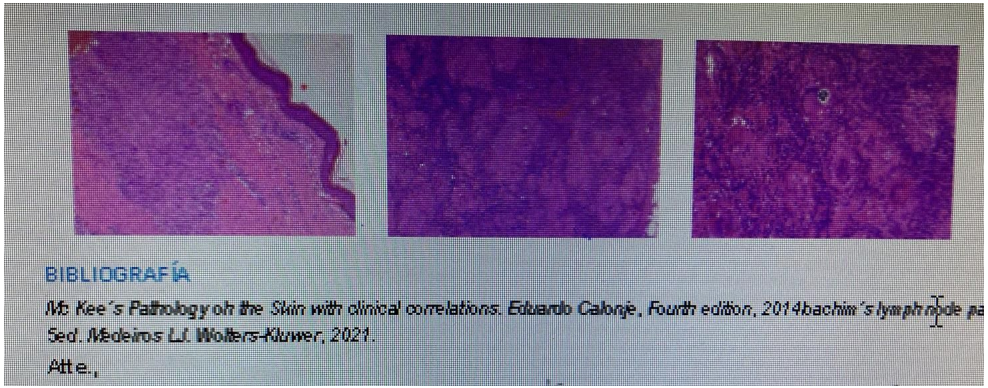
Oncológico:

- Biopsia de conglomerado con IF/citogenético descartan linfoma.
- Descarta sarcoma Kaposi

Biopsia ganglionar

Dermatitis granulomatosa posiblemente compatible con proceso de sarcoidosis





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Sed. Medeiros LJ. Wolters-Kluwer, 2021.

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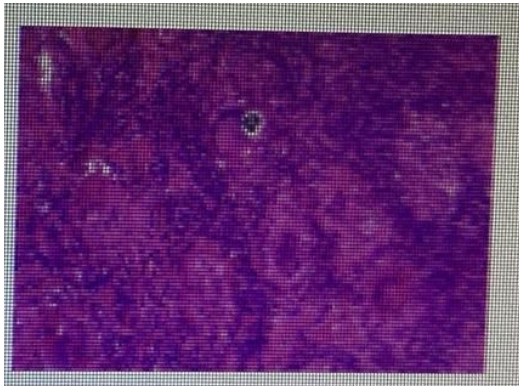


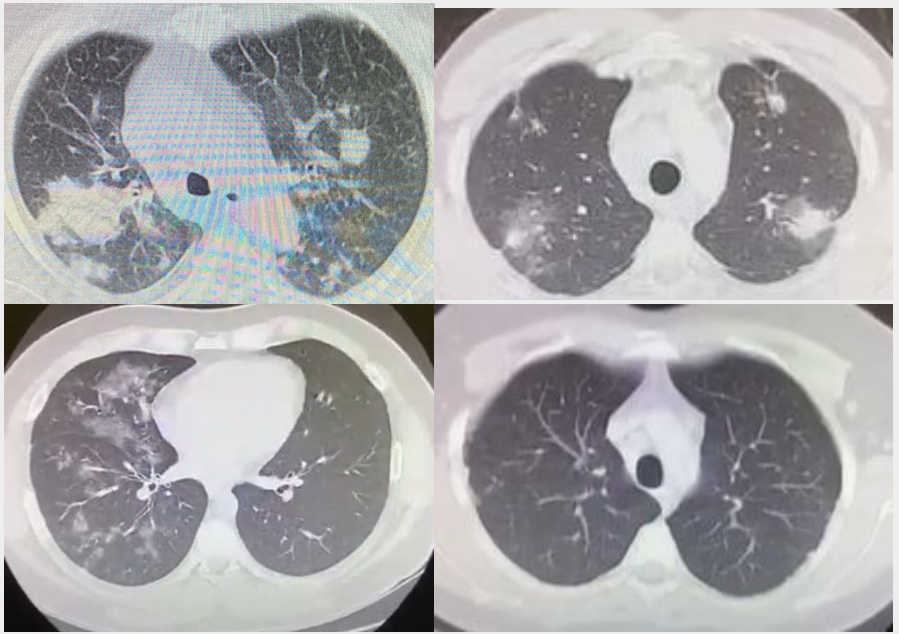
En suma: 4 formas pulmonares de una misma enfermedad

1. **Sarcoidosis a forma de masa pulmonar.**

2. **Sarcoidosis a punto de partida de árbol en brote.**

3. **Sarcoidosis a punto de partida de nódulos pulmonares.**

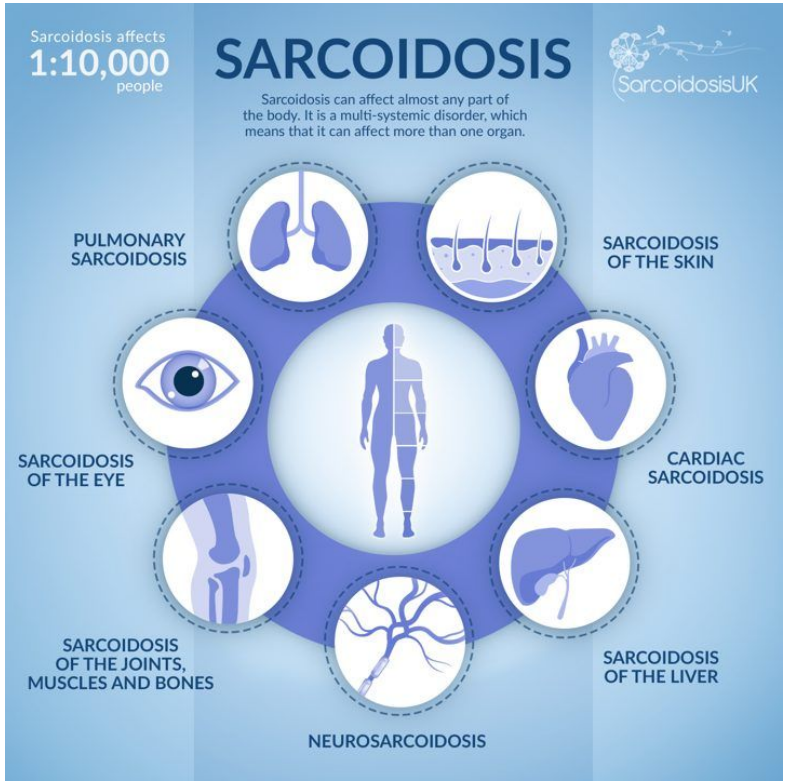
4. **Sarcoidosis como conglomerado mediastinal con micronódulos pulmonares**



Revisión de lectura

Definición

- Enfermedad inflamatoria granulomatosa multisistémica (predilección pulmonar).
- Caracterizada por la formación de granulomas no necrotizantes.
- Curso clínico y pronóstico muy variable (desde resolución espontánea hasta fibrosis irreversible).



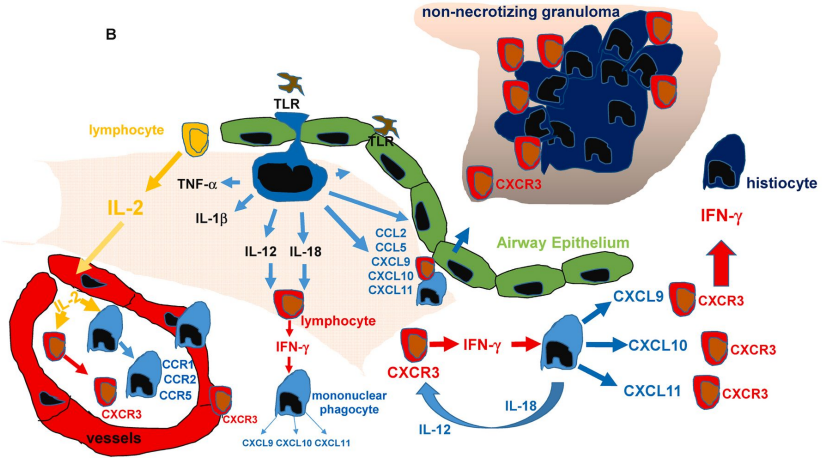
SarcoidosisUK. Sarcoidosis [imagen en Internet]. [sin fecha; citado el 11 de junio de 2025]. Disponible en: https://www.sarcoidosisuk.org/

Epidemiología

- Variación de riesgo según edad, sexo, raza y origen étnico.
- Incidencia 1 - 71 casos/100.000 habitantes/año, prevalencia 5 - 50 casos/100.000 habitantes.
- Distribución universal.
- Patrón bimodal: pico inicial 30 años, segundo pico posterior 50 años.

Etiopatogenia

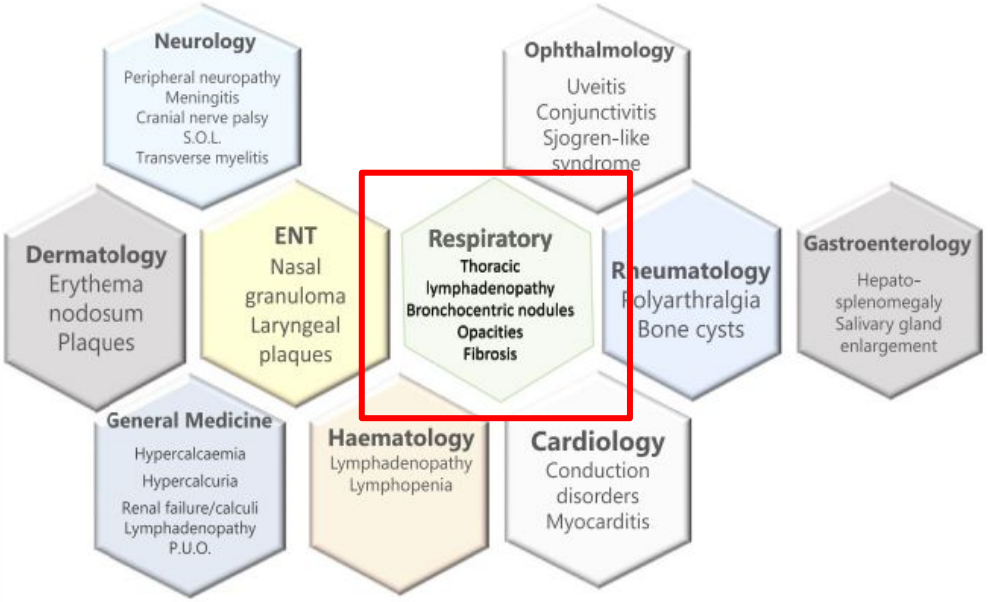
- Causa desconocida, multifactorial.
- Predisposición genética + exposición a antígenos ambientales/infecciosos.
- Activación de la inmunidad celular (LT CD4+).
- Liberación de citoquinas (IFN-y, IL-2, TNF-a).
- Reclutamiento de macrofagos y formacion de granulomas no caseificantes.
- Fallo en la resolución del granuloma → inflamación crónica y fibrosis



Belperio JA, Fishbein MC, Abtin F, Channick J, Balasubramanian SA, Lynch JP III. Pulmonary sarcoidosis: A comprehensive review: Past to present. J Autoimmun. 2024;149:103107.

Clínica

- Asintomática.
- Síntomas inespecíficos sistémicos.
- Síntomas específicos del órgano afectado.



Coker RK, Cullen KM. Sarcoidosis: Key disease aspects and update on management. Clin Med (Lond). 2025;25:100326. doi:10.1016/j.clinme.2025.100326.

- Síndromes específicos:
  - **Sd. de Lofgren**: eritema nodoso, adenopatías hiliares bilaterales, poliartritis, fiebre aguda.
  - **Sd. de Heerfordt**: fiebre, uveítis anterior, parotiditis, parálisis VII par.
  - **Lupus pernio**: placas violáceas, infiltradas, induradas, afectan nariz, mejillas, labios y orejas.

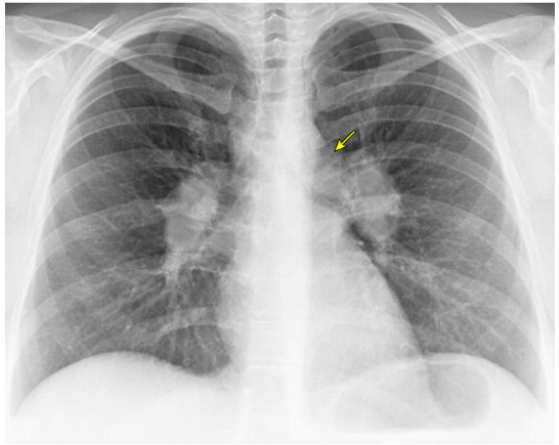
Sarcoidosis pulmonar

Table 1 Staging of sarcoidosis on a chest radiograph

Scadding stage	Findings	% at presentation	% with clinical and radiographic resolution untreated[150]
0	Normal	5 to 15	n/a
I	Enlarged nodes only	45 to 65	50 to 90
II	Enlarged nodes and parenchymal changes	30 to 40	30 to 70
III	Parenchymal changes without enlarged nodes or fibrosis	10 to 15	10 to 20
IV	Fibrosis	5	0

Thillai M, Atkins CP, Crawshaw A, Hart SP, Ho L-P, Kouranos V, Patterson K, Screaton NJ, Whight J, Wells AU. BTS Clinical Statement on pulmonary sarcoidosis. Thorax. 2021;76(1):4-20. doi: 10.1136/thoraxjnl-2019-214348.

Sarcoidosis, stage 1



Chest radiograph in a 35-year-old man shows symmetric bilateral hilar lymphadenopathy. Also noted is lymphadenopathy in the aortopulmonary window (arrow).

Courtesy of Nestor Muller, MD, PhD.

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

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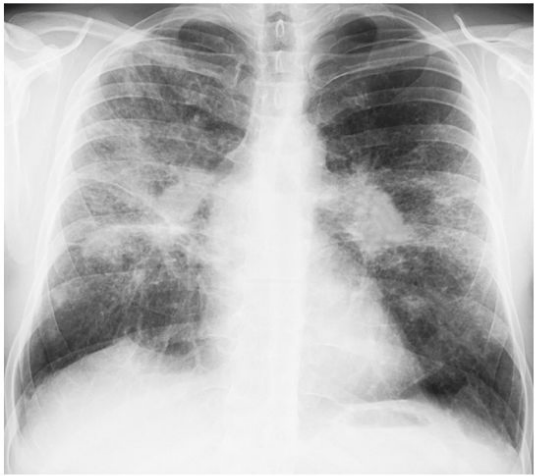
Sarcoidosis, stage 2



Chest radiograph in a 47-year-old man shows bilateral hilar lymphadenopathy and extensive reticulonodular opacities involving mainly the middle and upper lung zones.

Courtesy of Nestor Muller, MD, PhD.

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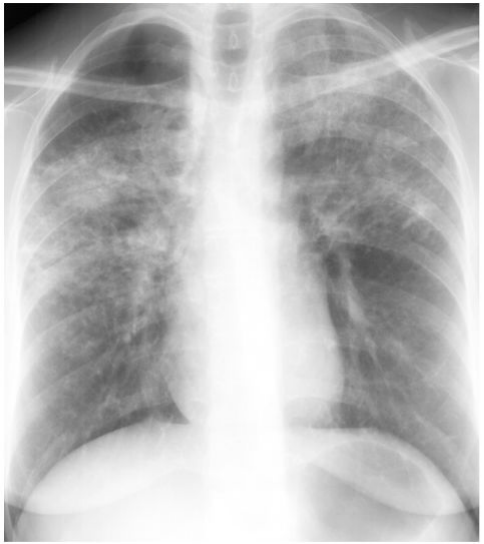
Sarcoidosis, stage 3 with consolidation



Chest radiograph in a 35-year-old woman demonstrates bilateral upper lobe predominant reticulonodular opacities and patchy bilateral areas of consolidation. The hila are normal.

Courtesy of Nestor Muller, MD, PhD.

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

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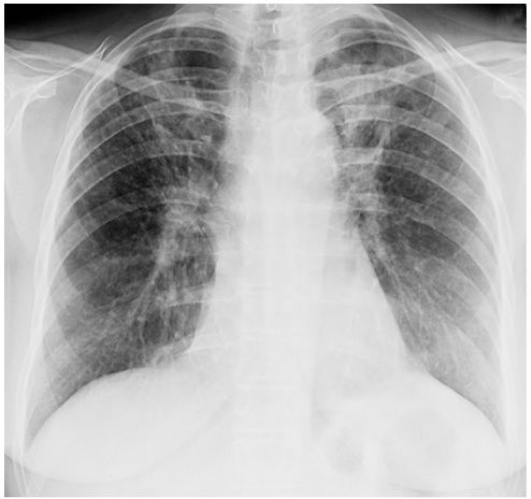
Sarcoidosis, Stage 4

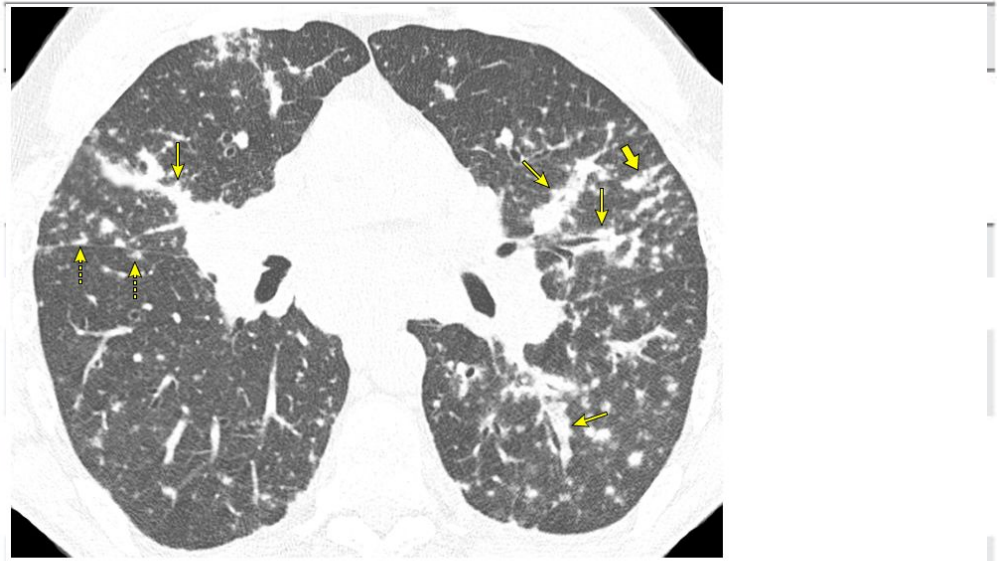


Chest radiograph in a 62-year-old woman demonstrates bilateral upper lobe fibrosis with associated volume loss and elevation of the hila. Conglomeration of fibrosis is evident in the left upper lobe.

Courtesy of Nestor L Muller, MD, PhD

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

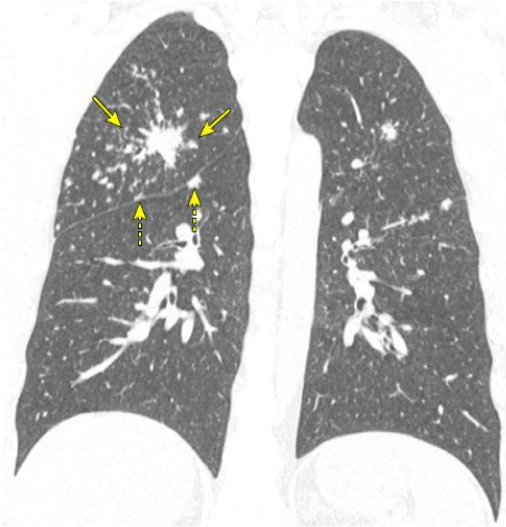
Sarcoidosis pulmonar



Axial image from high resolution CT in a 29-year-old man demonstrates nodular thickening of the peribronchial and perivascular interstitium (arrows), nodules along the pleura including interlobar fissures (dashed arrows), and nodules along the interlobular septa (thick arrow).

Courtesy of Nestor Muller, MD, PhD.

Sarcoidosis: Galaxy sign



Coronal high-resolution computed tomography (CT) demonstrates a large right upper lobe nodule surrounded by multiple small nodules (arrows), resembling a galaxy. Also noted are nodules along the right major fissure (dashed arrows) and mild involvement of the left lung.

Courtesy of Nestor L Muller, MD, PhD.

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

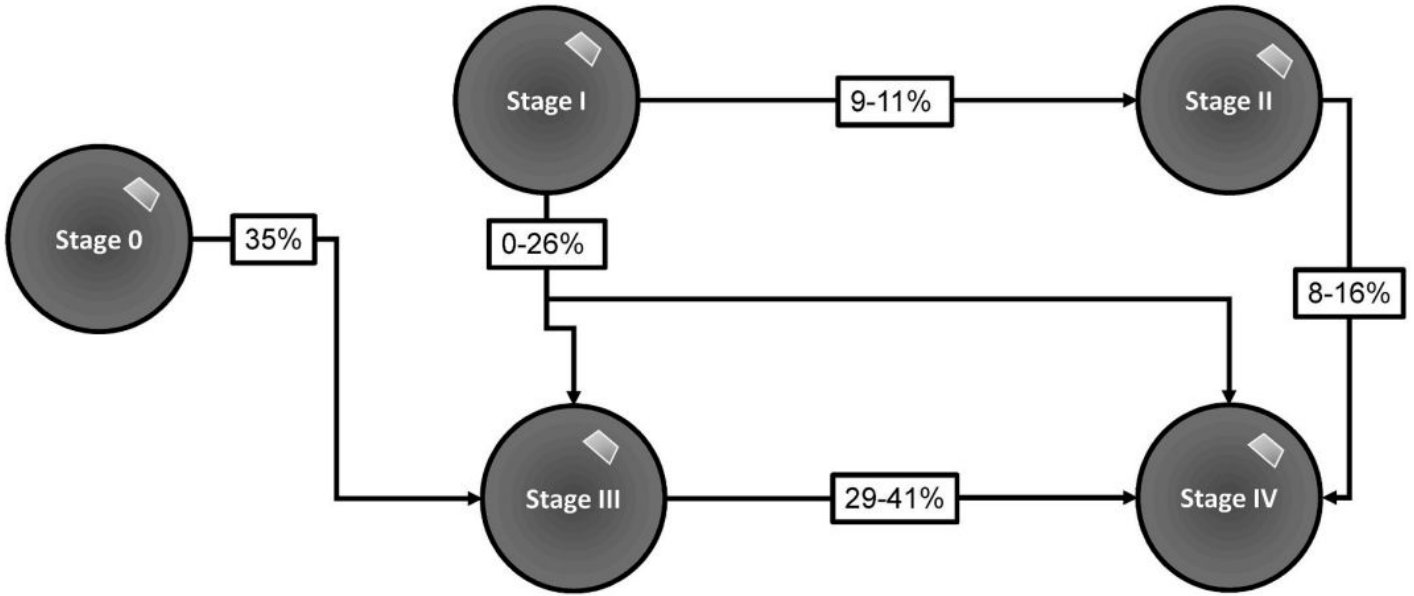


Fig. 5. Pulmonary Sarcoidosis can progress. Based on 5 sarcoidosis studies involving 308 patients from Sweden, 116 from Denmark, 136 from the UK, 215 from the US, and another 86 from the US followed for 1–15 years demonstrate pulmonary sarcoidosis can progress in 9–41% of cases depending on geographic location, sex, number and types of other organs involved, socioeconomic status and type of treatment [26,96,115,111,124].

Belperio JA, Fishbein MC, Abtin F, Channick J, Balasubramanian SA, Lynch JP III. Pulmonary sarcoidosis: A comprehensive review: Past to present. J Autoimmun. 2024;149:103107.

Diagnóstico

- Clínico
- Imagenológico
- Histopatológico
- **Exclusión de otras causas**

Estudios complementarios:

- Evaluación extrapulmonar:
  - Analítica ↓ especificidad
  - Valoración OFT (todos)
  - ECG (tamizaje cardíaco)
- Extensión lesional:
  - Pruebas funcionales
- Lavado broncoalveolar:
  - Diagnósticos alternativos
  - Linfocitosis > 15% + CD4:CD8 > 3,5 → **E 96%**
  - No patognomónico

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, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

Diagnosis and Detection of Sarcoidosis

An Official American Thoracic Society Clinical Practice Guideline

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

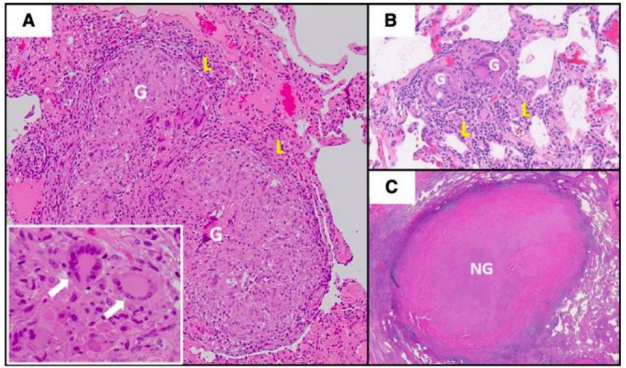


Figure 1. Comparison of pulmonary sarcoidosis granuloma histology to other granulomatous lung diseases. (*A*) Typical sarcoidosis histology with well-formed granulomas comprised of macrophage aggregates (G) and featuring multinucleated giant cells (white arrows, inset), with minimal surrounding lymphocytic inflammation (L). (*B*) Hypersensitivity pneumonitis featuring smaller granulomas (G) with more extensive surrounding lymphocytic alveolitis (L). (*C*) A large acellular necrotizing granuloma (NG) caused by pulmonary *Histoplasma capsulatum* infection.

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;201(8):e26–e51. doi: 10.1164/rccm.202002-0251ST.

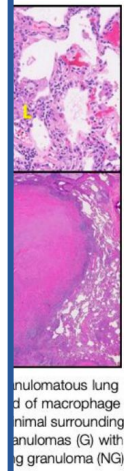
Diagnosis and Detection of Sarcoidosis
An Official American Thoracic Society Clinical Practice Guideline

Confirmación histopatológica frente afectación pulmonar:

- EBUS-TBNA: adenopatías mediastínicas, rendimiento diagnóstico 80 - 90%.
- BTB y/o BEB: afectación pulmonar, sin adenopatías.
- Mediastinoscopia: invasivo, reservada para casos seleccionados.

Table 2.

Favors	
Granulon Numer Absent gran dete	
Granulon Compa and Nonne	
Fibrosi cent	
Lesion lo Perilym cont In necr angi	
Accompa Sparse	
Microorganism stains and cultures Negative	Positive
Multidisciplinary clinical features Intra- and extrathoracic involvement	Extrathoracic involvement only



nulomatous lung
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nimal surrounding
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g granuloma (NG)

orgenthau AS, Patterson KC, et al. Diagnosis and Detection of Sarcoidosis. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;201(8):e26–e51. doi: 10.1164/rccm.202002-0251ST.

¿Siempre se biopsia?

ORIGINAL ARTICLE: CLINICAL RESEARCH

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2014; 31; 19-27

THE WASOG SARCOIDOSIS ORGAN ASSESSMENT INSTRUMENT: AN UPDATE OF A PREVIOUS CLINICAL TOOL

Judson MA, Costabel U, Drent M, Wells A, Maier L, Koth L, et al. The WASOG Sarcoidosis Organ Assessment Instrument: An update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31:19–27.

Clasifica manifestaciones por órgano según su probabilidad diagnóstica de sarcoidosis:

- Altamente probable: 3 puntos
- Al menos probable: 2 puntos.
- Compatible pero no específica: 0 puntos

¿Siempre se biopsia?

[Original Research **Diffuse Lung Disease**]

CHEST

Sarcoidosis Diagnostic Score

A Systematic Evaluation to Enhance the Diagnosis of Sarcoidosis

Alexandra N. Bickett; Elyse E. Lower, MD; and Robert P. Baughman, MD

CONCLUSIONS: For sarcoidosis, the presence of specific clinical features, especially multiorgan involvement, can enhance the diagnostic certainty. The SDS scoring system quantitated the clinical features consistent with sarcoidosis.

CHEST 2018; 154(5):1052-1060

Bickett AN, Lower EE, Baughman RP. Sarcoidosis Diagnostic Score: A Systematic Evaluation to Enhance the Diagnosis of Sarcoidosis. Chest. 2018 Nov;154(5):1052-1060. doi: 10.1016/j.chest.2018.05.003.

Objetivo: desarrollar y validar score clínico para estimar la probabilidad de sarcoidosis (con o sin biopsia).

- **SDS Clinical**: permite sospechar o confirmar sarcoidosis sin biopsia (> 13 puntos).
- **SDS Biopsy**: agrega 5 puntos si hay biopsias compatibles con granulomas no necrotizantes (o Sd. Lofgren).

¿Siempre se biopsia?

ORIGINAL RESEARCH

Validation of the Sarcoidosis Diagnostic Score in a Multicontinental Study

Florence Jeny[1,2], Violetta Vucinic[3,4], Ying Zhou[5], Dominique Valeyre[1,6], Parathasarathi Bhattacharyya[7], Alexandra N. Bickett[8], Marc A. Judson[9], Ogugua Ndili Obi[10], Jacques E. Denis[10], Deepak Talwar[11], Irina Strambu[12], Elyse E. Lower[8], and Robert P. Baughman[8]

Conclusions: This multicontinental study confirms that both SDS Clinical and SDS Biopsy have good to excellent performance in discriminating sarcoidosis from alternative diagnoses.

Jeny F, Vucinic V, Zhou Y, Valeyre D, Bhattacharyya P, Bickett AN, et al. Validation of the Sarcoidosis Diagnostic Score in a Multicontinental Study. Ann Am Thorac Soc. 2023;20(3):371–80.

¿Siempre se biopsia?

NO se biopsi

- Presentaciones “patognomónicas:
  - **Sd. Lofgren**.
  - **Sd. Heereford**.
  - **Lupus pernio**.
- Estadío I Scadding asintomático y con bajo riesgo de etiología alternativa.
- Alta certeza diagnóstica basada en SDS clínico (> 9 puntos).
- Accesibilidad del tejido afectado.
- Riesgo vs beneficio.

BTS Clinical Statement on pulmonary sarcoidosis

Muhunthan Thillai,[1] Christopher P Atkins,[2] Anjali Crawshaw,[3] Simon P Hart ,[4] Ling-Pei Ho,[5,6] Vasileios Kouranos,[7] Karen Patterson,[8] Nicholas J Screaton,[9] Joanna Whight,[10] Athol U Wells[7]

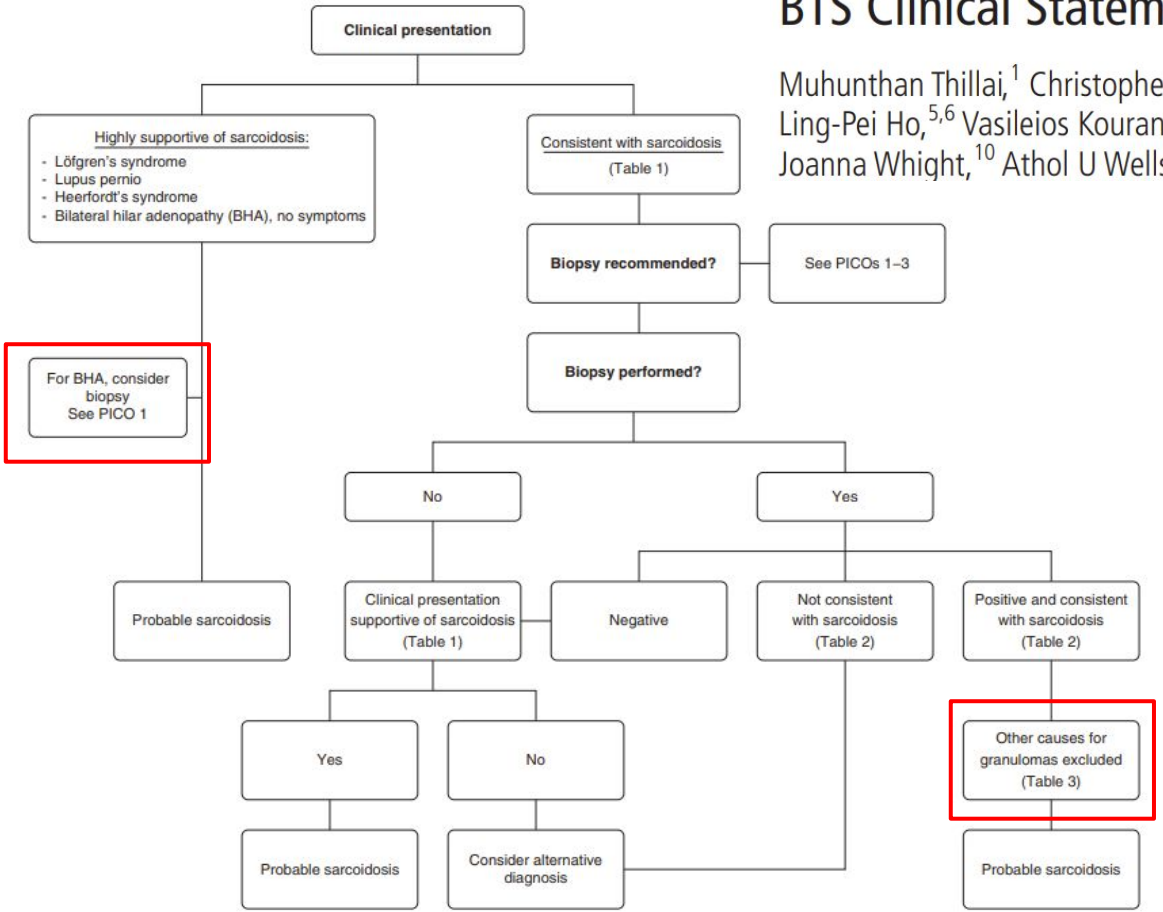

Figure 3. Schematic of recommended diagnostic algorithm. The figure outlines a general approach to the diagnosis of sarcoidosis and refers to tables presented with this article. PICO = problem, intervention, comparison, outcome question format.

Diagnóstico diferencial

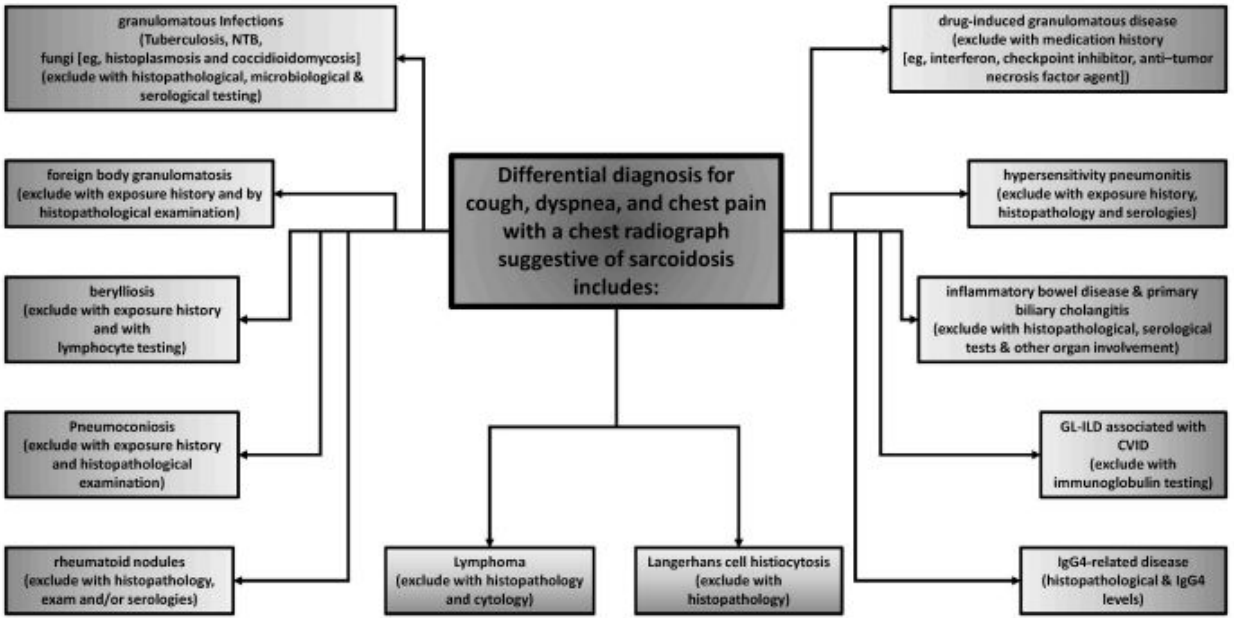

Fig. 4. Alternative causes of granulomas must be excluded before diagnosing and treating sarcoidosis. Pulmonary Sarcoidosis is a diagnosis of exclusion and here are many, but not an exhaustive list of the causes of pulmonary granulomas.

Belperio JA, Fishbein MC, Abtin F, Channick J, Balasubramanian SA, Lynch JP III. Pulmonary sarcoidosis: A comprehensive review: Past to present. J Autoimmun. 2024;149:103107.

Table 3. Key Infectious and Noninfectious Differential Diagnoses for Granulomatous Lesions within Commonly Biopsied Sites

	Granulomatous Lesion within These Sites:					
	Lung	Lymph Node	Skin	Liver	Bone Marrow	Testing and Clinical Pearls
Infectious etiologies						
Bacteria						
Tuberculosis*	X	X	X	X	X	Culture is diagnostic gold standard; IFN-γ release assay used for screening, and preferable to tuberculin skin testing due to anergy
Nontuberculous mycobacteria (MAC and *M. kansasii*)*	X	X	X	X	X	Culture is the gold standard
Aspiration pneumonia*	X					Culture
Brucella		X	X	X	X	Serum agglutination and ELISA; livestock exposure history
Tropheryma whippelii		X		X		Periodic acid–Schiff stain; immunohistochemistry testing; diarrhea, weight loss, and joint pains
Mycobacterium leprae			X			Culture is the gold standard, but can be difficult; histology; PCR
Francisella tularensis		X	X			Serologic assay, then repeat in 2 wk; rabbit exposure
Bartonella henselae		X	X			Titers >1:256; cat exposure
Coxiella burnetii				X	X	Serology; PCR; livestock exposure
Fungi						
*Aspergillus**	X		X		X	Culture; *Aspergillus* IgG; histology
*Histoplasma**	X	X	X		X	Culture; urine histoplasma antigen
*Blastomyces**	X		X			Culture; histology; blasto Ag is nonspecific
*Coccidioides**	X				X	Serologic tests using EIA for IgM and IgG; then confirmatory immunodiffusion
Cryptococcus	X		X	X	X	Cryptococcal serum antigen
Pneumocystis	X					Histology; screen with β-D-glucan assay
Viruses						
Herpes zoster	X		X			Granulomas may occasionally be found
Parasitic						
Toxoplasma gondii		X	X	X		Toxoplasma serologic assay IgM and IgG
Schistosomiasis	X		X	X		Serology and microscopic visualization of eggs in stool or urine
Leishmaniasis			X	X		Histology and PCR for *Leishmania*
Echinococcosis			X	X		EIA; ultrasound imaging
Enterobius			X	X		Pinworm paddle test, then microscopy
Dirofilaria	X					Histology; eosinophilia
Noninfectious etiologies						
Malignancy						
Lymphoma*	X	X	X	X	X	Clonal cell population; rarely can have elevated serum ACE
Sarcoid-like reaction to tumor*	X	X	X	X	X	PET useful for selecting biopsy site but not diagnostic; biopsy must be performed to diagnose
Lymphomatoid granulomatosis			X			Atypical clonal EBV-positive B cells; multiple pulmonary nodules with lymphocytic transmural angiitis and granulomas noted sometimes in skin
Germ cell tumor		X				Serum α fetoprotein, human chorionic gonadotropin, lactate dehydrogenase
Autoimmune or immune dysfunction						
ANCA-associated vasculitides (GPA, MPA, and EGPA)	X		X			MPO or PR3 ANCA+, renal disease, necrotizing vasculitis; eosinophilic infiltration if EGPA
GLILD associated with CVID	X	X				Nonnecrotizing granulomas, LIP, and follicular bronchiolitis on lung biopsy; hypogammaglobulinemia and recurrent infections
Rheumatoid nodules			X			Multiple subpleural nodules in patient with anti-CCP antibodies, arthralgias; necrotizing granulomas

(Continued)

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

Table 3. (*Continued*)

	Granulomatous Lesion within These Sites:					
	Lung	Lymph Node	Skin	Liver	Bone Marrow	Testing and Clinical Pearls
Langerhans cell histiocytosis	X	X	X	X	X	Young smoker; multiple bizarre-shaped upper lung zone cysts and/or nodules; Langerhans cell stain CD1a and S100 positive; eosinophilic granulomas most common
IgG4-related disease	X	X	X	X	X	Elevated serum IgG4; elevated tissue IgG4+ plasma cell count and IgG4:IgG ratio; granulomas rare; differential diagnosis with multicentric Castleman disease
Inflammatory bowel disease	X		X	X		GI symptoms; granulomatous bronchiolitis
Primary biliary cholangitis				X		Cholestasis; antimitochondrial antibodies; portal based, poorly formed granulomas with bile duct destruction
Primary sclerosing cholangitis				X		Cholestasis; P-ANCA+; ulcerative colitis associated; biliary strictures present, granulomas rare and not associated with bile duct destruction
Autoimmune hepatitis						Abnormal liver function tests and autoantibodies (e.g., anti–smooth muscle); syncytial multinucleated giant cells are rare in adults but may be observed in children or adolescents
Exposures						
Hypersensitivity pneumonitis*	X	X				Organic exposure, small poorly formed interstitial granulomas in interstitium, prominent lymphocytic infiltrates, chronic inflammatory infiltrates accentuated around bronchioles
Hot tub lung syndrome (MAC exposure with hypersensitivity features)	X	X				Aerosolized water exposure, MAC cultured from sputum, lung or hot tub, large well-formed granulomas in bronchiole lumens
Pneumoconiosis (such as beryllium, titanium, aluminum, zirconium, cobalt, and others)	X	X	X			Inorganic exposure history
Drug-induced granulomatous disease (including but not limited to IFN, checkpoint inhibitor, anti-TNF, and/or biologic therapies)*	X	X	X	X	X	Usually nonnecrotizing granulomas. Drug exposure history essential. *See* www.pneumotox.com for full list
Foreign body granulomatosis (such as talc aspirated or injected, tattoo ink)*	X	X	X			Serum ACE elevated in many patients; particles found on biopsy; perivascular granulomas
Steatosis (lipogranulomas)				X		Central lipid vacuole; ingestion of mineral oil or hepatic steatosis
Idiopathic						
Sarcoidosis	X	X	X	X	X	Multisystemic; well formed, usually nonnecrotic granulomas
Necrotizing sarcoid granulomatosis	X	X				Granulomatous pneumonitis with necrosis and vasculitis; multiple necrotic lung nodules
Histiocytic necrotizing lymphadenitis (Kikuchi's disease)		X				Cervical lymphadenopathy and low-grade fever. Granulomas are not found, although necrotic areas with histiocytes are present
GLUS		X	X	X	X	Lacks progressive lung parenchymal disease, elevated serum calcium, 1,25-dihydroxyvitamin D, and ACE
Bronchocentric granulomatosis	X					Associated with asthma and *Aspergillus* infection in 50%. Necrotizing granulomas exclusively in bronchi and bronchioles

Table 4. Key Differential Diagnoses for Sarcoidosis within Individual Organ Systems

Organ System	Noninfectious Differential Diagnoses	Infectious Differential Diagnoses
Central nervous system	IgG4-related disease Chronic variable immunodeficiency Rosai-Dorfman disease Histiocytoses • Histiocytosis X • Erdheim-Chester Lymphomatoid granulomatosis Granulomatosis with polyangiitis Rheumatoid nodules Amyloidosis Cholesterol granuloma Foreign body Drugs/toxins/heavy metals Sarcoid-like reaction to tumor CNS malignancies ranging from glioblastoma to lymphoma	Bacteria • Tuberculosis • *Brucella* Fungi • *Aspergillus* • Coccidioidomycosis • Cryptococcosis Parasites • Amoeba • Toxoplasmosis • Schistosomiasis • *Taenia solium* • *Echinococcus* • Paragonimiasis Viruses • *Varicella zoster* • Herpes simplex
Eyes	Inflammatory bowel disease ANCA vasculitides Vogt-Koyanagi-Harada disease Blau syndrome	Parinaud oculoglandular syndrome • *Bartonella* • *Francisella* Bacteria • Tuberculosis • Syphilis Viruses • Cytomegalovirus • *Varicella zoster* Toxoplasmosis
Sinonasal	Granulomatosis polyangiitis Eosinophilic granulomatosis with polyangiitis Cholesterol granuloma NK/T-cell lymphoma Foreign body Drugs/toxins • Cocaine • Narcotics	Bacteria • Tuberculosis • Atypical Mycobacteria • *Klebsiella* Rhinoscleromatis • Syphilis Fungi • *Aspergillus flavus* • Histoplasmosis Parasites • Leishmaniasis • Rhinosporidiosis
Parotid/salivary/lacrimal glands	Granulomatosis polyangiitis Ductal obstruction (calculus, tumor) Crohn's disease	Bacteria • Tuberculosis • Atypical mycobacteria
Heart	Giant cell myocarditis Acute rheumatic heart disease Granulomatosis with polyangiitis Erdheim-Chester Arrhythmogenic right ventricular dysplasia Foreign body Drugs/toxins Granulomatous lesions of unknown significance	Bacteria • Tuberculosis • Syphilis • *Tropheryma whippelii* Fungi • *Aspergillus*
Spleen	Chronic variable immunodeficiency Sarcoid-like reaction to tumor	Bacteria • Tuberculosis Fungi • Histoplasmosis Parasites • Leishmaniasis

(Continued)

Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis: an official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med. 2020 Apr 15;201(8):e26–51. doi:10.1164/rccm.202002-0251ST.

Table 4. *(Continued)*

Organ System	Noninfectious Differential Diagnoses	Infectious Differential Diagnoses
Kidney	Granulomatosis polyangiitis Chronic lymphocytic leukemia Drugs • Allopurinol • Antivirals • Anticonvulsants • β-Lactams • Diuretics • Erythromycin • Fluoroquinolones • NSAIDs • Proton pump inhibitors • Rifampin • Sulfonamides • Vancomycin	Bacteria • Tuberculosis Fungi • Histoplasmosis • Coccidioidomycosis Viral • Adenovirus
Muscle	Non-Hodgkin lymphoma Crohn's disease Thymoma-myasthenia gravis Foreign body Primary biliary cirrhosis (primary biliary cholangitis) Cryofibrinogenemia	Bacteria • Tuberculosis • Syphilis • *Brucella* Fungi • *Pneumocystis jirovecii* • Cryptococcosis Virus • Human T-lymphotrophic virus 1

Definition of abbreviations: ANCA = antineutrophil cytoplasmic antibody; CNS = central nervous system; NK = natural killer; NSAIDs = nonsteroidal antiinflammatory drugs.

Tratamiento

Controlar la enfermedad sin sobretratar:

- Prevenir daño orgánico irreversible.
- Preservar función orgánica y QoL.
- Minimizar EA del tratamiento.

¿Cuándo tratar?

- Riesgo vital o daño orgánico:
  - ↓CVF, ↓DLCO, fibrosis, HTP
- Síntomas que afectan QoL.
- Enfermedad progresiva → evaluación estructural y funcional integral

Consideraciones:

- Interdisciplinario.
- Balance lesional.
- Decisión individualizada y compartida con el paciente (balance riesgo vs beneficio)

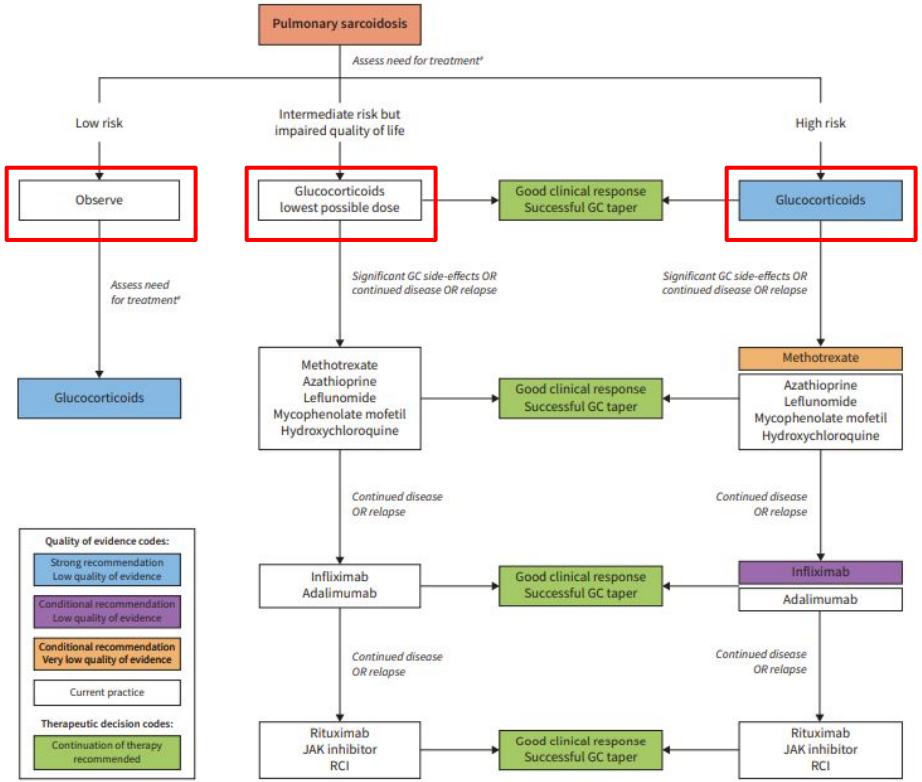

FIGURE 1 Approach for pulmonary sarcoidosis. Use of rituximab, JAK inhibitor and repository corticotropin injection (RCI) should be on a case-by-case basis. This figure is a combination of the recommendations made in this guideline and a description of Task Force members' current practice in situations where there was not enough evidence to warrant a recommendation or for questions for which a systematic review of the literature was not undertaken. Note that the information depicted as current practice (in white boxes) is not intended as a recommendation for clinical practice. #: assess need for treatment based on low risk, intermediate risk but impaired quality of life or high risk as discussed in text. GC: glucocorticoid.

Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. 2021;58:2004079.

ERS clinical practice guidelines on treatment of sarcoidosis

EUROPEAN RESPIRATORY JOURNAL
ERS OFFICIAL DOCUMENTS
R.P. BAUGHMAN ET AL.

TABLE 1 Task Force recommendations

PICO question	Recommendations
1) In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used *versus* no immunosuppressive treatment?	• For untreated patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid treatment to improve and/or preserve FVC and QoL. *(Strong recommendation, low quality of evidence.)*
2) In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?	• For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side-effects from glucocorticoids, we suggest the addition of methotrexate to improve and/or preserve FVC and QoL. *(Conditional recommendation, very low quality of evidence.)* • For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease, we suggest the addition of infliximab to improve and/or preserve FVC and QoL. *(Conditional recommendation, low quality of evidence.)*

Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. 2021;58:2004079.

Comment > Eur Respir J. 2022 Feb 10;59(2):2103114.
doi: 10.1183/13993003.03114-2021. Print 2022 Feb.

Comparison of the treatment guidelines for sarcoidosis: common sense in the search for evidence

Kahlmann V, Moor CC, Miedema JR, Wijsenbeek MS. Comparison of the treatment guidelines for sarcoidosis: common sense in the search for evidence. Eur Respir J. 2022;59(2):2103114. doi:10.1183/13993003.03114-2021.

TABLE 1 Comparison of the treatment guidelines for pulmonary sarcoidosis[#]

	ERS guidelines 2021	BTS statement 2020
Methodology	Task force formulated PICO questions and used the GRADE methodology to rate the level of evidence	Clinical statement group (pulmonologists, nurses, radiologist and patients) provided clinical practice points; the content was developed in accordance with the BTS Standards of Care Committee
When to start treatment	Patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis (strong recommendation, low quality of evidence)	Potential danger of a fatal outcome or permanent disability Unacceptable loss of QoL
First-line treatment		
Prednisone	1) High risk: Initial treatment 20 mg per day Maintenance dose 5–10 mg per day to every other day Inhaled steroids not advised 2) Intermediate risk, but impaired QoL: 5 to 10 mg per day	1) Pulmonary sarcoidosis: Initial treatment 20–40 mg per day for 4 to 6 weeks Slow tapering to maintenance dose of 5–10 mg per day Inhaled steroids not advised 2) Loss of QoL: the choice and dose of agent should be negotiated with the patient
Second-line treatment		
General statement	Addition of MTX is advised for symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side-effects from glucocorticoids (conditional recommendation, very low quality of evidence) AZA, mycophenolate and leflunomide are also effective in pulmonary sarcoidosis; chloroquine was mildly beneficial (not assessed per GRADE methodology)	Review diagnosis and treatment compliance before introducing second-line agents Indications for second-line therapy: 1) uncontrolled disease or unacceptable symptoms, 2) intolerable side-effects, 3) inability to taper prednisone below 10–15 mg per day, 4) presents comorbidities likely related to corticosteroids, and 5) strong patient aversion against steroids (can occasionally be used as first-line treatment)
MTX	10–15 mg once a week	Most frequently used Initiate at 5–10 mg per week and increase every two weeks to a target of 15–20mg
AZA	50–250 mg per day	Initiate at 50 mg per week, increase by 25 mg every 2–3 weeks until the maintenance dose is reached (typically 2 mg per kg)
Mycophenolate mofetil	500–1500 mg twice a day	In general: do not consider before MTX and AZA Usual dose between 1000–1500 mg twice a day
Leflunomide	10–20 mg per day	No advice on treatment dose
Cyclophosphamide	Not mentioned	Rarely used as second-line treatment due to its toxicity profile
Hydroxychloroquine/ chloroquine	200–400 mg per day	Mainly advocated for use in fatigue, joint and skin sarcoidosis; might help reduce prednisone dose in pulmonary sarcoidosis Usual dose 200 mg once or twice per day
Third-line treatment		
General statement	Infliximab is advised for symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease (conditional recommendation, very low quality of evidence) Adalimumab was also found to be effective (not assessed per GRADE methodology)	Biological agents are considered third-line therapeutic agents, to be initiated in pulmonary disease only after failure of second line treatment Screen for latent tuberculosis infection
Infliximab	Initiate at a dose of 3–5 mg per kg, second dose 2 weeks later, than once every 4–6 weeks	Improves disease control in combination with MTX and AZA Should initially be given every 2 weeks and then every 4–8 weeks as part of maintenance therapy No advice on treatment dose
Adalimumab	40 mg every 1–2 weeks	Not mentioned
Continued disease after third-line treatment		
General statement	To consider on a case by case basis (not assessed per GRADE methodology)	Not mentioned
Rituximab	Small case series supports the use of rituximab 500–1000 mg every 1–6 months	Not mentioned
Repository corticotropin injection	Retrospective studies showed a steroid sparing effect 40–80 units twice a week	Not mentioned
JAK inhibitor	Response reported in small retrospective case series No advice on treatment dose	Not mentioned
Antifibrotic therapy		
General statement	Future research: also the role of anti-fibrotic agents such as nintenanib and pirfinedone need to be further studied	At time of publication pirfenidone and nintedanib were only registered for idiopathic pulmonary fibrosis

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Comparison of the treatment guidelines for sarcoidosis: common sense in the search for evidence

Kahlmann V, Moor CC, Miedema JR, Wijsenbeek MS. Comparison of the treatment guidelines for sarcoidosis: common sense in the search for evidence. Eur Respir J. 2022;59(2):2103114. doi:10.1183/13993003.03114-2021.

TABLE 1 Comparison of the treatment guidelines for pulmonary sarcoidosis[#]

	ERS guidelines 2021	BTS statement 2020
Methodology	Task force formulated PIC methodology to rate th	
When to start treatment	Patients with major involv sarcoidosis believed to mortality or permanent (strong recommendatio	
First-line treatment		
Prednisone	1) High risk: Initial treatment 20 m Maintenance dose 5– Inhaled steroids not 2) Intermediate risk, but i	
Second-line treatment		
General statement	Addition of MTX is advised sarcoidosis believed to mortality or permanent have been treated with continued disease or ur glucocorticoids (conditional recommendation, very low quality of evidence) AZA, mycophenolate and leflunomide are also effective in pulmonary sarcoidosis; chloroquine was mildly beneficial (not assessed per GRADE methodology)	10–15 mg per day, 4) presents comorbidities likely related to corticosteroids, and 5) strong patient aversion against steroids (can occasionally be used as first-line treatment)
MTX	10–15 mg once a week	Most frequently used Initiate at 5–10 mg per week and increase every two weeks to a target of 15–20mg
AZA	50–250 mg per day	Initiate at 50 mg per week, increase by 25 mg every 2–3 weeks until the maintenance dose is reached (typically 2 mg per kg)
Mycophenolate mofetil	500–1500 mg twice a day	In general: do not consider before MTX and AZA Usual dose between 1000–1500 mg twice a day

TABLE 1 Continued

	ERS guidelines 2021	BTS statement 2020
		No advice on treatment dose
		Rarely used as second-line treatment due to its toxicity profile
		Mainly advocated for use in fatigue, joint and skin sarcoidosis; might help reduce prednisone dose in pulmonary sarcoidosis
		Usual dose 200 mg once or twice per day
		Biological agents are considered third-line therapeutic agents, to be initiated in pulmonary disease only after failure of second line treatment
		Screen for latent tuberculosis infection
		Improves disease control in combination with MTX and AZA
		Should initially be given every 2 weeks and then every 4–8 weeks as part of maintenance therapy
		No advice on treatment dose
		Not mentioned
	GRADE methodology)	Not mentioned
Rituximab	Small case series supports the use of rituximab 500–1000 mg every 1–6 months	Not mentioned
Repository corticotropin injection	Retrospective studies showed a steroid sparing effect 40–80 units twice a week	Not mentioned
JAK inhibitor	Response reported in small retrospective case series No advice on treatment dose	Not mentioned
Antifibrotic therapy		
General statement	Future research: also the role of anti-fibrotic agents such as nintenanib and pirfinedone need to be further studied	At time of publication pirfenidone and nintedanib were only registered for idiopathic pulmonary fibrosis

- Basadas en consenso y experiencia.
- Falta de evidencia sólida.
- Variabilidad en indicaciones y tratamiento.
- Decisión individualizada, centrado en el paciente
- **Llamado a generar más conocimiento científico.**

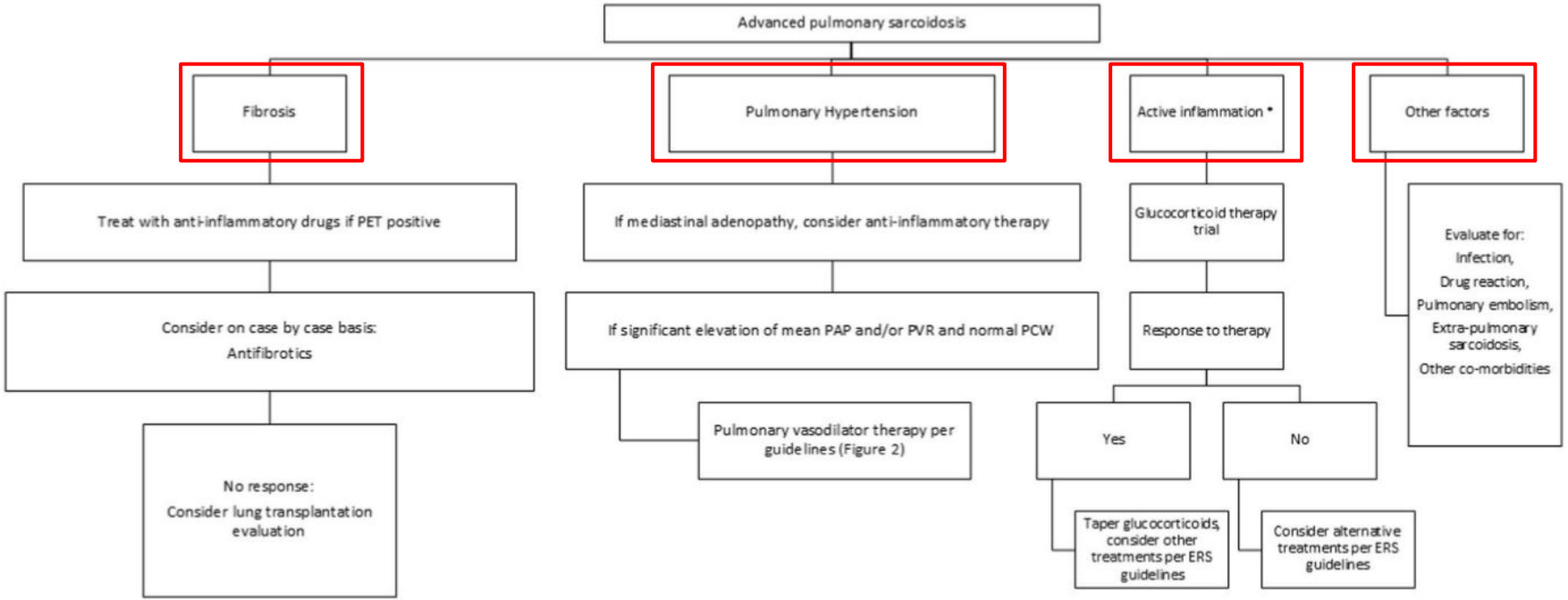

Fig. 5. A summary of the four major causes of advanced pulmonary sarcoidosis with recommendations for treatment. The European Respiratory Society guidelines provide treatment recommendations for chronic pulmonary inflammation and extra-pulmonary sarcoidosis [33].

Jeny F, Valeyre D, Lower EE, Baughman RP. Advanced pulmonary sarcoidosis. J Autoimmun. 2025;152:103397.

Mensajes finales

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- **La sarcoidosis es la gran simuladora**: debe considerarse en cuadros respiratorios atípicos o prolongados.

- **Su presentación es variable y multisistémica**: siempre explorar más allá del pulmón.

- **El diagnóstico es de exclusión**: se requiere compatibilidad clínica-radiológica, histológica y descarte de otras causas.

- **No nos apuremos**: no todos los pacientes requieren tratamiento.

- El seguimiento es siempre **a largo plazo** y requiere una **visión integral**.

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