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# The Histology of Pulmonary Sarcoidosis: A Review With Particular Emphasis on Unusual and Underrecognized Features

Alberto Cavazza, MD, Sergio Harari, MD, Antonella Caminati, MD, Mattia Barbareschi, MD, Cristiano Carbonelli, MD, Lucia Spaggiari, MD, Massimiliano Paci, MD, and Giulio Rossi, MD

The pathologist is frequently involved in the diagnostic approach to the patient with suspected sarcoidosis. Although the histologic diagnosis is generally not difficult, atypical and underrecognized features may occasionally occur and may result in diagnostic problems. The authors review the histology of pulmonary sarcoidosis, focusing particularly on these unusual problematic findings.

**Keywords:** sarcoidosis; lung; review; histology; granuloma; necrosis

Sarcoidosis is a multisystem disease of unknown cause, frequent enough to be encountered with some regularity by the general pathologist. The diagnosis requires the histologic finding of granulomas in the correct clinicoradiological context, a task easily performed by the pathologist in the majority of cases. The classic histology of sarcoidosis as well as some unusual morphologic variations are well described in several textbooks[1-7] and review articles.[8-11] However, we encountered several examples of sarcoidosis in which unusual, poorly recognized histologic findings resulted in diagnostic difficulties. Our goal is to provide the pathologist with a practical review on pulmonary sarcoidosis, focusing particularly on these problematic histologic aspects.

Operative Units of Pathology (A Cavazza), Pulmunology (CC), Radiology (LS), and Thoracic Surgery (MP), Ospedale S. Maria Nuova, Reggio Emilia; Operative Unit of Pulmunology, Ospedale S. Giuseppe Fatebenefratelli, Milan (SH, A Caminati); Operative Unit of Pathology, Ospedale S. Chiara, Trento (MB); Section of Pathologic Anatomy, Azienda Ospedaliero-Universitaria Policlinico, Modena (GR), Italy.

Address correspondence to: Alberto Cavazza, MD, Operative Unit of Pathology, Ospedale S. Maria Nuova, Viale Risorgimento 80, 42100 Reggio Emilia, Italy; e-mail: cavazza.alberto@asmn.re.it.

## Clinical and Radiologic Features[12-16]

### General Features

Sarcoidosis affects both sexes at any age, with a slight female predominance and a peak incidence at 20 to 40 years. About 30% to 60% of patients are asymptomatic, and the disease is discovered by an incidental chest radiograph. Nonspecific constitutional symptoms such as fatigue, malaise, fever, arthralgias, night sweats, and weight loss occur in about 30% of the patients.

### Pulmonary Involvement

Pulmonary involvement is almost universal, and nonspecific pulmonary symptoms are frequent, particularly cough, dyspnea, and chest discomfort. Because sarcoidosis can involve the airways, a significant wheezing may occur.

On examination, crackles and clubbing are frequently lacking, and their absence is a distinguishing feature from other interstitial lung diseases, particularly idiopathic pulmonary fibrosis (IPF). Pulmonary function tests may range from normal to severe defect, generally restrictive but sometimes obstructive. Characteristically, some patients may

**Table 1.** Some Clinical Scenarios That Support the Diagnosis of Sarcoidosis

| | |
|---|---|
| Diagnostic | Erythema nodosum, bilateral symmetric hilar lymphadenopathy, arthritis, fever (Löfgren's syndrome) |
| Very characteristic | Asymptomatic, symmetric hilar lymphadenopathy in a young adult |
| | Bilateral nodules in a lymphatic distribution on pulmonary HRCT (particularly if associated with hilar lymphadenopathy) |
| | Panda and lambda signs on gallium scan |
| | Parotid gland enlargement, uveitis, fever, cranial nerve palsies (Heerfordt syndrome) |
| | Bone cysts in the phalanges |
| Situations in which the possibility of sarcoidosis should be considered | Bilateral pulmonary nodules in an asymptomatic young adult (frequently PET-positive and clinically suspicious for tumor) |
| | Interstitial lung disease with any of the following: upper lobe prevalence; discrepancy between a paucity of symptoms/function abnormalities and a significant radiologic impairment; absence of crackles and clubbing; presence of wheezing (some patients are misdiagnosed as asthmatic); history of interferon-α therapy[28] |
| | Constitutional symptoms of unknown cause over a period of several months |
| | Skin lesions (erythema nodosum, lupus pernio, keloids, macules, and plaques), ocular lesions, hepatosplenomegaly |
| | Hypercalcemia, elevated ACE, and liver function tests |

NOTES: HRCT = high-resolution computed tomography; PET = positron emission tomography; ACE = angiotensin-converting enzyme.

have normal functions in spite of an impressive radiologic disease.

## Extrapulmonary Involvement

Extrapulmonary manifestations in sarcoidosis are common and may provide important diagnostic clues.[17] Apart from the lungs and lymph nodes, sarcoidosis frequently involves skin, eyes, liver, central nervous system, and heart, but basically any organ can be affected.

## Imaging Features

Chest radiographs are abnormal in more than 90% of the patients. Bilateral, symmetric hilar lymphadenopathy is the most frequent and characteristic finding; pulmonary nodular or reticulonodular infiltrates, typically symmetrical, bilateral, and prevailing in the upper lobes, are seen in 25% to 60% of the cases. Pulmonary fibrosis develops in about 10% of the patients and may lead to architectural distortion with upward retraction of the hila, upper lobe volume loss, traction bronchiectasies, and honeycomb cysts. The chest radiograph in sarcoidosis is divided into 5 stages: stage 0, normal; stage I, bilateral hilar lymphadenopathy without pulmonary infiltrates; stage II, bilateral hilar lymphadenopathy with pulmonary infiltrates; stage III, pulmonary infiltrates alone; and stage IV, pulmonary fibrosis.

High-resolution computer tomography of the chest,[18] although not necessary in all patients, is more sensitive (revealing pulmonary infiltrates in almost all cases, even in stage I) and more specific than chest radiograph. It typically shows bilateral nodules with a lymphatic distribution (along bronchovascular bundles, pleura, and interlobular fissures). Atypical radiographic appearances include large pulmonary nodules,[19] cavitations,[20] ground-glass opacities,[21] bronchial-bronchiolar stenosis with secondary atelectasis and/or air trapping,[18,22] pleural effusion, bullous emphysema with pneumothorax,[23] and lymph node calcifications.

Gallium scan may be useful in confirming a diagnosis of sarcoidosis showing characteristic uptakes in mediastinum (lambda sign) and in lacrimal glands (panda sign). Positron emission tomography is more sensitive than gallium and may be helpful in identifying sites for biopsy. Magnetic resonance is useful for early detection of cardiac and neurologic involvement.

## Laboratory Features

Among several nonspecific laboratory alterations, hypercalcemia, hypercalciuria (which may lead to nephrocalcinosis and urolithiasis), elevated liver function tests, and elevated levels of serum angiotensin-converting enzyme are the most characteristic. angiotensin-converting enzyme has a low sensitivity, and its clinical utility is controversial.

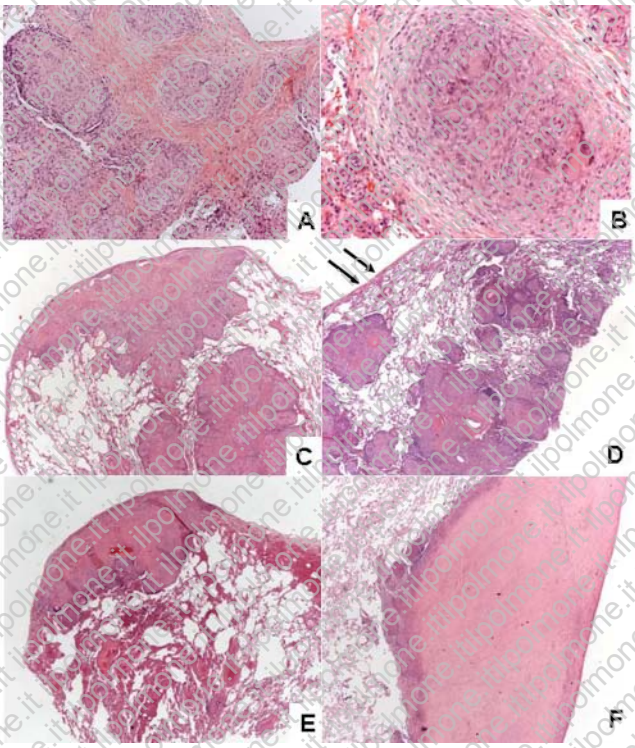


**Figure 1.** Classic histology of pulmonary sarcoidosis. A, Well-formed, compact granulomas embedded within hyaline lamellar collagen (hematoxylin–eosin [H&E], 100×). B, Occasionally, granulomas are surrounded by a rim of more edematous and cellular tissue (H&E, 200×). C, Sarcoid granulomas typically coalesce forming nodules along the lymphatics (H&E, 40×). D, Sarcoid granulomas prevailing in the centrolobule, along the bronchovascular bundles, and sparing the pleura (arrows). This localization makes the lesion particularly suitable to be reached by the bronchoscope (H&E, 20×). E, A more infrequent situation, wherein granulomas are prevalent in the pleura (H&E, 20×). F, Another example of pleural sarcoidosis with a few residual granulomas and a large amount of fibrosis, simulating a pleural plaque (H&E, 40×). In parts C, D, E, and F, note the relative sparing of the alveoli.

## Natural History and Prognosis

The clinical course of sarcoidosis is highly variable and poorly predictable in the individual case. Depending on the presentation, 2 distinct forms of sarcoidosis are recognized: the acute form, which may present as the classic Löfgren's syndrome characterized by fever, bilateral hilar lymphadenopathy, arthritis in ankle joints, and erythema nodosum; and the chronic form, characterized by lupus pernio, chronic uveitis, hypercalcemia with nephrocalcinosis, pulmonary fibrosis, cystic bone lesions, and sinonasal,[24] myocardial, and neurological involvement. The acute form prevails in white people and frequently shows a favorable outcome with spontaneous remission (the evaluation of human leukocyte antigens may provide further prognostic stratification in this subgroup[25]), whereas the chronic form prevails in Afro-Americans and has a more insidious onset and a more progressive course. In general, about two thirds of patients with sarcoidosis have a remission, even with no treatment, but unfortunately about a third have progressive disease leading to significant organ impairment. Pulmonary hypertension is a life-threatening complication of sarcoidosis, reported in 1% to 28% of cases.[26,27] Less than 5% of patients die of disease, more frequently of lung fibrosis, cardiac failure, and neurologic involvement.

Table 1 summarizes some clinical scenarios that support the diagnosis of sarcoidosis.

## Histologic Features

The histologic hallmark of sarcoidosis is the *granuloma*. The classic sarcoid granulomas (Figure 1) are well formed, generally nonnecrotizing, and typically surrounded by a rim of lamellar hyaline collagen, which contributes to their compact character. Occasionally, probably in the early phases, granulomas are rimmed by a more edematous myofibroblastic tissue. Apart from these qualitative features, equally important for the diagnosis of sarcoidosis is the anatomic distribution of granulomas: in the lung, they typically coalesce along the lymphatic routes in the pleura, interlobular septa, and bronchovascular bundles. Occasionally, granulomas are more prevalent in one of these anatomic compartments, generally the bronchovascular bundles but sometimes the pleura. Compact, nonnecrotizing granulomas embedded together within hyaline collagen in a lymphatic distribution is the classic histologic appearance of pulmonary sarcoidosis.

This characteristic localization within the lymphatic interstitium with relative sparing of the alveolar parenchyma has several important consequences:

1. It closely correlates with the lymphatic distribution seen at high-resolution computer tomography of the chest.
2. It explains why in some patients the clinical picture is dominated by airway involvement (wheezing, functional obstructive defect).[22]

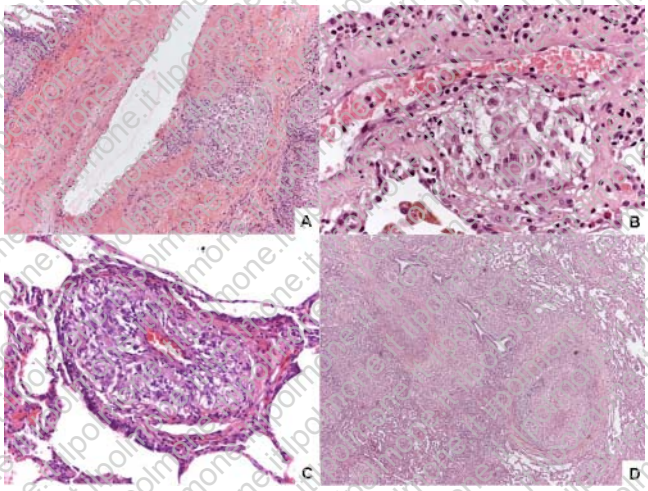


**Figure 2.** Examples of vascular involvement in sarcoidosis. Discrete well-formed granulomas in the wall of a pulmonary artery (A; hematoxylin–eosin [H&E], 200×) and vein (B; H&E, 400×). A circumferential involvement of a vessel (C; H&E, 200×) and a more marked granulomatous inflammation of the pulmonary arteries (D; case courtesy of Prof T. V. Colby, Scottsdale, Arizona). Such a kind of severe vasculitic involvement is unusual in sarcoidosis (H&E, 100×).

3. It explains why some patients have few/no symptoms and normal function tests in spite of a significantly impaired chest roentgenogram.
4. It is the reason for the high diagnostic yield of bronchial and transbronchial biopsies.
5. It is the reason for the frequent occurrence of vascular involvement in sarcoidosis, reported in 53% of transbronchial biopsies,[29] in 69% of open lung biopsies,[30] and in 100% of autopsies.[31] Vascular involvement (Figure 2) generally consists of granulomas or giant cells in the adventitia, media, or intima of pulmonary arteries or veins. Occasionally, a more prominent inflammation may be present, but necrosis of the vessel wall is distinctly unusual. Sarcoid vascular involvement may rarely cause pulmonary hypertension, sometimes with features of veno-occlusive disease.[27]

Confluent sarcoid granulomas may form large fibrogranulomatous masses (the so-called nodular sarcoid), which radiologically can mimic a carcinoma (Figure 3). In these cases, the lymphatic distribution may not be so obvious: a diagnostic clue is to look at the periphery of the mass, where sometimes the localization of the granulomas along the lymphatics is still recognizable. In old nodules, fibrosis may become prominent: it is important not to misinterpret this hyaline, acellular fibrosis as necrosis. Occasionally, fibrosis assumes an "onion-skin" configuration and incorporates a large amount of birefringent coniotic pigment, simulating a silicotic nodule.


**Figure 3.** Nodular sarcoid.
A, Sarcoid granulomas may fuse together to form large fibrogranulomatous nodules. Note the marked fibrosis in the center of the nodule (which should not misinterpreted as necrosis) and the bronchovascular localization still recognizable at the periphery: the latter represents a helpful diagnostic clue (hematoxylin–eosin, 20×). B, Occasionally, nodular sarcoid incorporates a large amount of coniotic pigment, superficially resembling a silicotic nodule. The differential diagnosis is based on the presence of granulomas, frequently limited at the periphery like in this case: granulomas are absent in silicotic nodules until sovrainfected (hematoxylin–eosin, 40×).

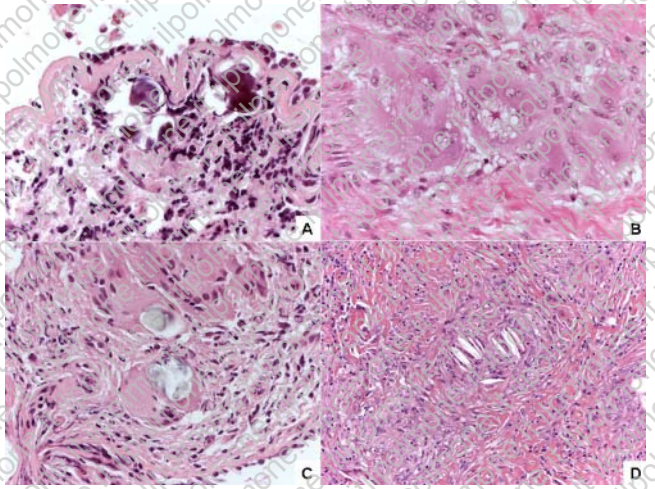


**Figure 4.** Some examples of inclusions in sarcoid granulomas. A, Schaumann or conchoidal bodies, reported in 30% to 50% of the cases and generally present within multinucleated giant cells, are concentric, laminated basophilic calcifications, 20 to 200 μm in diameter (hematoxylin–eosin [H&E], 400×). B, Asteroid bodies are star-shaped inclusions found in giant cells of sarcoidosis in about 5% of the cases (H&E, 400×). C, Birefringent calcium oxalate crystals, sometimes associated with Schaumann bodies, are frequent (H&E, 400×). D, Rarer are cholesterol clefts (H&E, 200×). None of these inclusions is specific for sarcoidosis, and they should not be misinterpreted as foreign material.

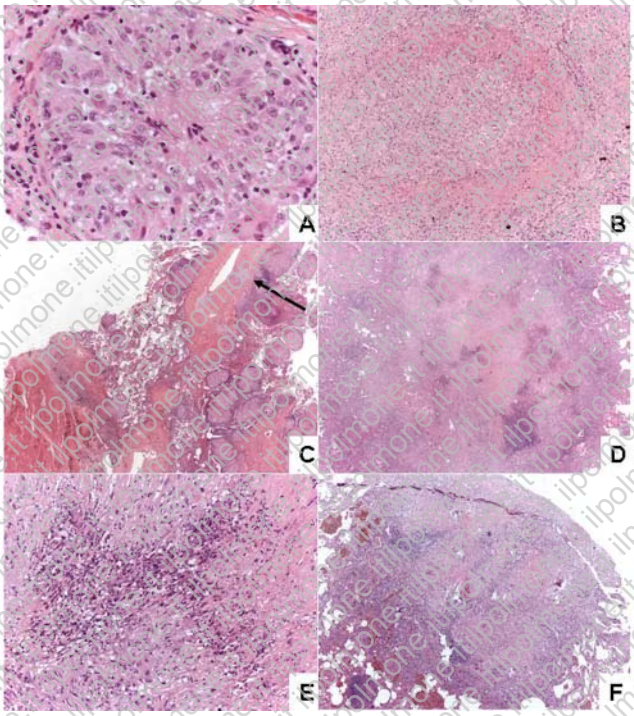


**Figure 5.** Necrosis in sarcoidosis.
A, It typically consists of tiny foci of central fibrinoid necrosis. This kind of necrosis is frequent, particularly in surgical material (hematoxylin–eosin [H&E], 200×). B, Occasionally, fibrinoid necrosis is more extensive. This quantity of necrosis is still consistent with a diagnosis of sarcoidosis but should raise concern about the possibility of infection (H&E, 100×). C, An example of infarct necrosis (on the left) secondary to vascular involvement by granulomas (arrow; a high magnification of this field is shown in Figure 2A). Note that apart from necrosis all the other features are classic for sarcoidosis (H&E, 20×). D, Surgical resection of one of multiple pulmonary nodules, clinically suspicious for neoplasm, in an asymptomatic 42-year-old man. The nodule consisted of inflammatory tissue with large areas of geographic, suppurative necrosis reminiscent of Wegener (H&E, 40×). E, Higher magnification of "D" (H&E, 200×). F, At the periphery of the nodule and in the surrounding parenchyma, however, there were granulomas too well-formed for Wegener and most consistent with sarcoidosis (H&E, 40×). No microorganisms were found, antineutrophilic cytoplasmic antibodies were negative, and the patient had a good response to steroids. The final clinical–radiologic–pathologic diagnosis was necrotizing sarcoid granulomatosis, but in such cases the alternative possibilities of infection or Wegener superimposed on sarcoidosis should be carefully excluded clinically. In this patient, a subtle clinical clue favoring sarcoidosis over infection or Wegener was the absence of symptoms.

Intracytoplasmic inclusions in giant cells are frequently present in sarcoid granulomas[7] (Figure 4), including calcium oxalate crystals and asteroid and Schaumann bodies: the latter are more frequent in sarcoidosis than in other granulomatous diseases,[32]

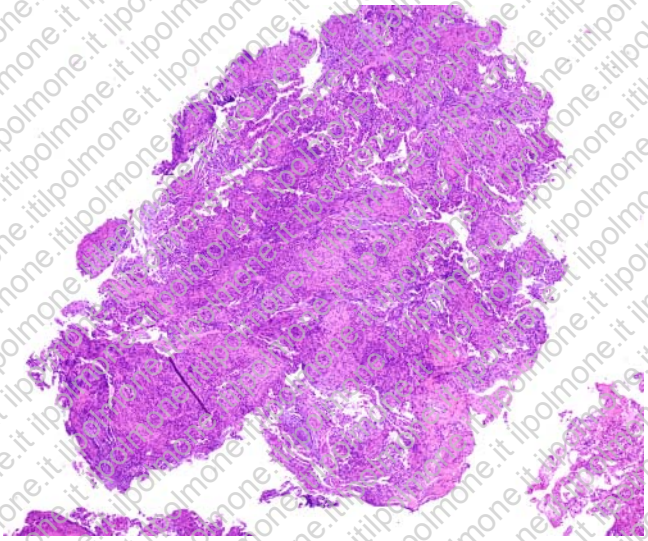

**Figure 6.** Transbronchial biopsy in a 27-year-old woman presenting with thoracic discomfort and multiple nodules in the lung. The biopsy showed a chronic interstitial inflammation with foci of organizing pneumonia and several nonnecrotizing granulomas. Granulomas were not particularly compact, and their localization was apparently random. The disease resolved spontaneously and presented again after some months with the classic radiologic features of sarcoidosis; thus, sarcoidosis was the final clinical–radiologic–pathologic interpretation. In such cases, the differential diagnosis with other diseases (particularly infection but also hypersensitivity pneumonitis, collagen vascular disease, pulmonary localization of inflammatory bowel disease, drug reaction, and aspiration) is basically impossible just on histologic ground and requires a strict clinical correlation (hematoxylin–eosin, 40×). Case courtesy of Dr N. Cingolani and Dr A. Tubaldi, Macerata, Italy.

but none of these inclusions is specific. They are probably by-products of macrophage metabolism (in other words, they are endogenous, not exogenous material); their only importance resides in the fact they may mislead the pathologist to the erroneous diagnosis of foreign-body granulomas.

Sarcoid granulomas, although classically nonnecrotizing, show *necrosis* in about 20% of transbronchial biopsies[9] (and more frequently in surgical biopsies; Figure 5). It generally consists of tiny foci of central fibrinoid ("rheumatoid-like") necrosis, but rarely larger areas of fibrinoid, infarct, or suppurative ("Wegener-like") necrosis may be seen. The controversial entity necrotizing sarcoid granulomatosis[33,34] is probably just a variant of sarcoidosis, in which necrosis is particularly prominent. In general, the presence of necrosis within granulomas should always raise the possibility of infection (see differential diagnosis).

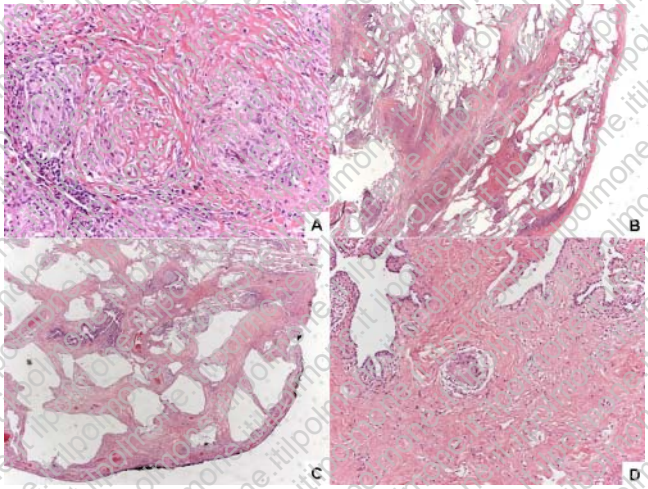


**Figure 7.** Chronic sarcoidosis.
A, Fragmentation of the granulomas by lamellar hyaline collagen (hematoxylin–eosin [H&E], 200×). B, Dense fibrosis along the lymphatic routes associated with well-formed granulomas. In this example of chronic sarcoidosis, the pulmonary architecture is still quite preserved (H&E, 40×). C, A more severe example of chronic sarcoidosis, in which the architecture is more disturbed (H&E, 40×). D, A giant cell embedded in dense fibrosis as the only clue of an old, scarred sarcoidosis (H&E, 200×).

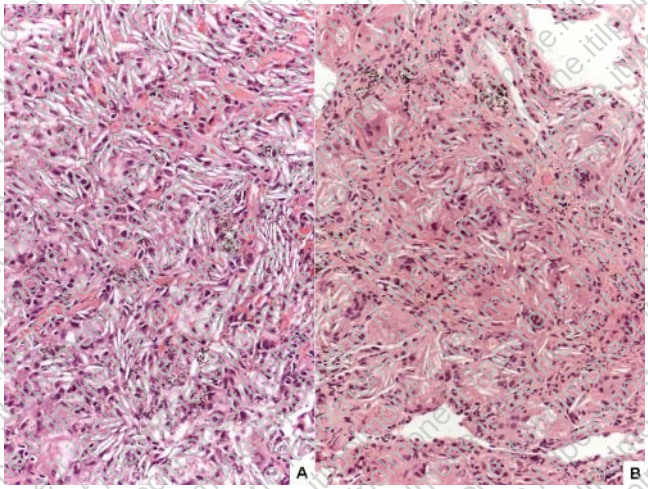


**Figure 8.** A, B, Two different fields of a transbronchial biopsy in a 73-year-old woman with no professional exposure and with the classic radiologic features of chronic sarcoidosis. A large amount of cholesterol clefts and coniotic pigment are embedded in dense fibrosis with sparse giant cells. A case like this can be misinterpreted as a pneumoconiosis, particularly silicatosis (compare with Figure 12F; hematoxylin–eosin, 200×).

In sarcoidosis, inflammation is generally mild and limited to a thin rim of lymphocytes around granulomas ("naked granulomas"); a significant cellular interstitial infiltrate with organizing pneumonia is distinctly unusual, and its presence should suggest an alternative diagnosis (particularly infection, hypersensitivity pneumonitis, collagen vascular disease, pulmonary localization of inflammatory bowel disease, aspiration, drug reaction). However, particularly in early phases, sarcoid granulomas may be rarely associated with significant inflammation (Figure 6).

With time, hyaline collagen penetrates and destroys the granulomas (Figure 7), which may become so fragmented that they are barely recognizable. Occasionally, giant cells (or even just Schaumann bodies) entrapped in dense fibrosis may remain as the only marker of an old sarcoidosis; in these cases, the localization of the fibrosis along the lymphatics is a helpful diagnostic clue. We have seen rare examples of chronic sarcoidosis in which dense fibrosis and scattered giant cells were engulfed with large amounts of cholesterol clefts and coniotic pigment, simulating pneumoconiosis (Figure 8). Sarcoidosis generally he als and leaves normal or slightly scarred lung; rarely, it progresses to significant fibrosis with traction bronchiectasies and honeycombing. Aspergilloma may complicate these chronic cystic cavities.

Because it is frequently asymptomatic, the pathologist may occasionally encounter sarcoidosis in association with other diseases. In many of these cases, sarcoidosis represents just a background incidental finding. Some examples are presented in Figures 9, 10, and 11.

## Differential Diagnosis

When faced with granulomas in the lung, the evaluation of their qualitative features, anatomic distribution, and accompanying findings usually allows the pathologist to narrow considerably the differential diagnosis.[9] These characteristics are better evaluated on surgical biopsy, but sometimes can be appreciated (more or less depending on the case) also on transbronchial biopsy (see "Invasive Diagnostic Procedures"). The final diagnosis always requires the careful integration of the histology with the clinical, laboratory, and radiologic findings. How robust is the histologic component of the diagnosis varies from case to case, and the pathologist should

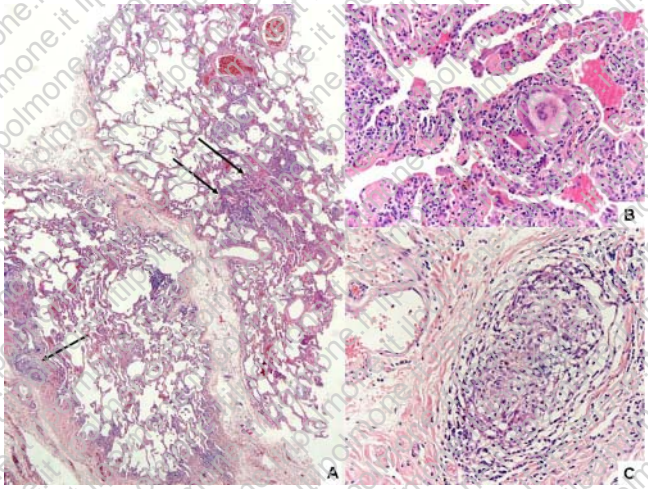


**Figure 9.** Surgical biopsy in a 55-year-old woman. At low magnification (A; hematoxylin–eosin [H&E], 20×), there was a cellular infiltrate with centrolobular accentuation (double arrows) and scattered interstitial giant cells characteristic of hypersensitivity pneumonitis (B; H&E, 200×). In the pleura, rare well-formed granulomas more typical of sarcoidosis were also present (single arrow; a pleural granuloma is shown in "C"; H&E, 200×). The final clinical–radiologic–pathologic diagnosis was hypersensitivity pneumonitis in a patient with underlying sarcoidosis. Case courtesy of Prof A. D'Errico, Bologna, Italy.

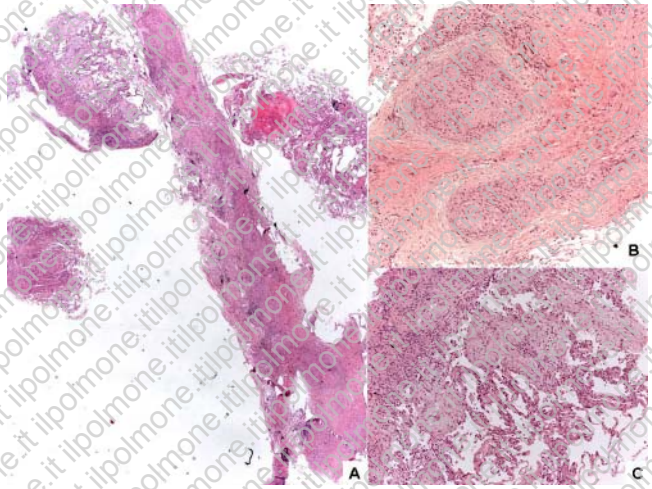


**Figure 10.** Transbronchial biopsy in a 36-year-old man (A; hematoxylin–eosin [H&E], 20×). This generous biopsy showed 2 different lesions: on the center, a strip of dense fibrosis with compact granulomas typical of sarcoidosis (B; H&E, 100×); on the left upper corner, a focus of organizing pneumonia (C; H&E, 100×). The final clinical–radiologic–pathologic diagnosis was cryptogenic organizing pneumonia (idiopathic BOOP) in a patient with underlying sarcoidosis. This case has been previously reported.[35]

always clearly discuss this point with the clinician; in general, the weaker the histology is, the stronger should be the clinical–radiologic findings, and vice versa.

The differential diagnosis of sarcoidosis includes the following entities (some of which are shown in Figure 12).

## Granulomatous Infections

Usually, the most difficult differential diagnosis is with granulomatous infections. The typical infective granuloma[9,10] is quite well-formed but less compact, with less lamellar fibrosis and less tendency to coalesce than the classic sarcoid granuloma. Infectious granulomas are frequently necrotic, although occasionally the amount of necrosis is minimal or it can be absent altogether, particularly in some atypical mycobacterial infections; moreover, necrosis can be seen also in sarcoid granulomas, as described above. In general, the more necrotic the granuloma, higher the probability of infection (and consequently more meticulous should be the search for microorganisms). Also, the quality of necrosis tends to be different: in infection necrosis it is often eosinophilic and granular ("caseous") or suppurative, whereas in sarcoidosis it is often fibrinoid (there are however exceptions, see Figure 5). The anatomic distribution of granulomas is another useful criterion: in infection, granulomas are generally randomly localized in the lung parenchyma or around the bronchioles, and lack the lymphatic distribution typical of sarcoidosis. In a case in which granulomas are localized particularly around the bronchioles, the finding of some well-formed granulomas also in the *visceral* pleura is useful in favoring sarcoidosis over infection, because it indicates a lymphatic rather than simply a peribronchiolar distribution. On the contrary, granulomas on the *parietal* pleura in a pleural biopsy are more frequent in infection. Well-formed granulomas in the vessel walls are another subtle clue to look for, because they are quite unusual in infection, and they slightly favor sarcoidosis. Finally, a significant cellular interstitial infiltrate with organizing pneumonia may or may not be present in infection, but is typically absent in sarcoidosis (with a few exceptions, see Figure 6): scattered granulomas embedded in foci of organizing pneumonia and associated with significant inflammation favor

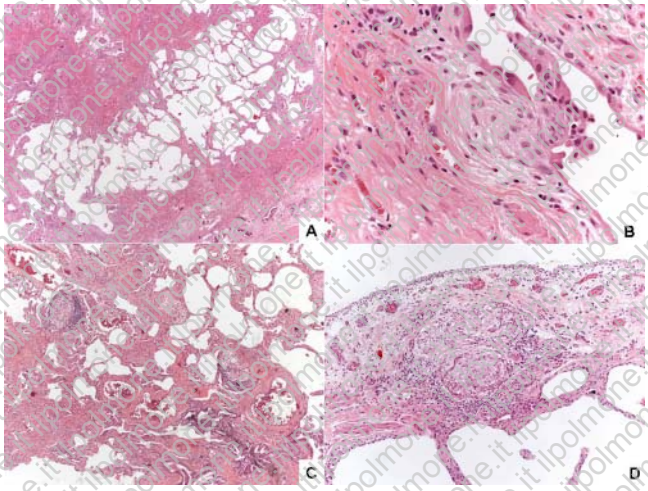


**Figure 11.** Surgical biopsy in a 65-year-old man with an idiopathic fibrosing interstitial pneumonia prevailing in the lower lobes.
The low magnification (A; hematoxylin–eosin [H&E], 20×) showed a "patchwork" fibrosis typical of usual interstitial pneumonia (UIP). Numerous fibroblastic foci (B; H&E, 400×) were also present. Focally, there were well-formed granulomas distributed in the centrolobule (C; H&E, 40×) and in the pleura (D; H&E, 100×). The "patchwork" fibrosis, the fibroblastic foci, and the lower-lobe predominance at computed tomography scan favored UIP over chronic sarcoidosis, and the presence of granulomas also in the pleura favored sarcoidosis over mycobacterial infection or aspiration complicating UIP; moreover, the well-formed character of granulomas excluded a chronic hypersensitivity pneumonitis.[36,37] The final clinical–radiologic–pathologic diagnosis was idiopathic UIP (IPF) in a patient with underlying incidental sarcoidosis.

infection. In general, it is wise to exclude an infection in any case in which sarcoidosis is a consideration, and special stains (and possibly cultures) should always be performed and carefully evaluated.

## Hypersensitivity Pneumonitis

The histology of subacute hypersensitivity pneumonitis[38,39] (also known as extrinsic allergic alveolitis) is characterized by a triad of lymphoplasmacitic interstitial inflammation, accentuation of the inflammation around the bronchioles (bronchiolitis), and small, loose interstitial granulomas, sometimes consisting just of scattered giant cells. Foci of organizing pneumonia and accumulation of foamy histiocytes in the peribronchiolar alveoli are also frequent. Hypersensitivity pneumonitis differs form sarcoidosis with respect to the character of the granulomas

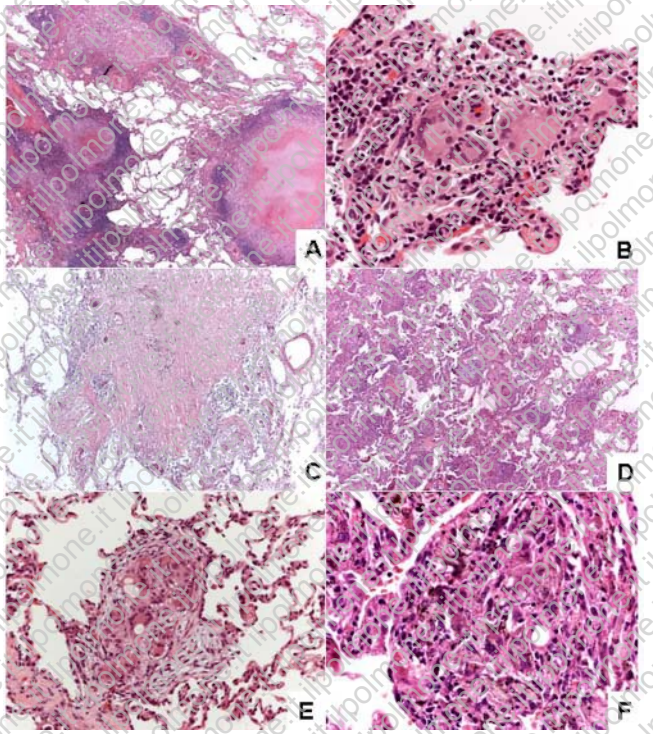


**Figure 12.** Some examples of granulomatous diseases other than sarcoidosis.
A, Large, bronchiolocentric necrotizing granulomas in a case of atypical mycobacterial infection. Note the associated cellular inflammation (hematoxylin–eosin [H&E], 40×). B, An inconspicuous interstitial collection of giant cells in hypersensitivity pneumonitis (H&E, 200×). C, An old fibrosing granulomatous lesion, morphologically indistinguishable from sarcoidosis, in a patient with chronic berylliosis (H&E, 40×). D, A different case, more cellular, of chronic berylliosis (H&E, 40×). E, A quite well-formed granuloma in a patient with Crohn's disease (H&E, 200×). F, An example of granulomatous silicatosis; in contrast to Figure 8, here the giant cells contain birefringent silicates, not cholesterol (H&E, 400×). Cases C and D are courtesy of Prof T. V. Colby, Scottsdale, Arizona.

(much less compact), their localization (peribronchiolar and not along pleura and interlobular septa), and the cellular inflammation (much more abundant). Occasionally, particularly when the antigen is *Mycobacterium avium* (the so called "hot tub lung"[40-42]), and also in rare cases of farmer's lung,[43] granulomas of hypersensitivity pneumonitis are larger, but still less compact than sarcoid.

## Pneumoconiosis[44]

Berylliosis is caused by inhalation of beryllium, a metal with many uses in advanced technology.

**Table 2.** Histologic Differential Diagnosis of Some Granulomatous Lung Diseases

| | Characteristics of Granulomas | Anatomic Distribution | Associated Interstitial Inflammation/Organizing Pneumonia |
|---|---|---|---|
| Sarcoidosis | Compact, coalescing, embedded within hyaline collagen; nonnecrotizing or with minimal fibrinoid necrosis; frequent vascular involvement | Along lymphatics | Very unusual |
| Granulomatous infection | Well-formed but not very compact, tend to be solitary; not much perigranuloma fibrosis; necrotizing (but necrosis can be minimal or absent) | Random or bronchiolocentric | Frequent |
| Hypersensitivity pneumonitis | Loose/inconspicuous (frequently just scattered interstitial giant cells); no necrosis | Bronchiolocentric | Always present (with a typical centrolobular accentuation) |

Exposure to beryllium may occur in several settings, including mining, ceramics, rocket and aerospace manufacturing, computer industry, and dental laboratories that use beryllium alloys. Acute (mainly of historical interest) and chronic forms of berylliosis have been reported. The histology of chronic berylliosis may vary from a cellular interstitial inflammation with granulomas to a granulomatous disease morphologically indistinguishable from sarcoidosis. The diagnosis is based on anamnesis, on in vitro lymphocyte proliferation (indicative of sensitivity to beryllium), and on chemical identification of beryllium in lung tissue.

Fibrous tissue in chronic sarcoidosis can assume a large amount of coniotic pigment, leading to some similarities with silicotic nodules (see Figure 3B) or granulomatous silicatosis (see Figure 8); however, granulomas are absent in silicotic nodules (unless they are infected), and the clefts that may be seen in sarcoidosis contain cholesterol (and so are empty in routinely processed material), not silicates. Endogenous, birefringent calcium oxalate is frequent in sarcoidosis (and in other granulomatous lesions) and should be not confused with exogenous material.

### Miscellaneous Lung Diseases

Collagen vascular disease (particularly Sjögren),[45] inflammatory bowel disease,[46,47] primary biliary cirrhosis,[48] and some drugs (eg, methotrexate[49]) may cause a granulomatous lung disease that can simulate sarcoidosis. However, granulomas are generally less compact, not lymphatic in distribution, and associated with more inflammation, bronchiolitis, and organizing pneumonia.

Wegener's granulomatosis and aspiration pneumonia are easily differentiated from sarcoidosis; they are discussed in detail elsewere.[50,51] Although very rarely can sarcoidosis have a suppurative "Wegener-like" necrosis, the well-formed character of the granulomas excludes Wegener (see Figure 5).

In the chronic phase, sarcoidosis can simulate other fibrosing diseases, particularly UIP/IPF.[52] The diagnosis of sarcoidosis in these cases is based on the presence of granulomas (which can be few), on the uniformly dense fibrosis with absent/inconspicuous fibroblastic foci, and on the characteristic radiographic findings. It is worth noting, however, that isolated granulomas can occasionally be seen in IPF and are generally due to superimposed atypical mycobacterial infection, aspiration, or underlying incidental sarcoidosis (see Figure 11).

Finally, "sarcoid-like" granulomas can be found in malignancy, adjacent to the tumor or in the draining lymph nodes.[7] Probably some of the reported cases represent genuine examples of sarcoidosis, incidentally detected during staging or follow-up. The relationship between sarcoidosis and malignancy remains controversial.[53]

Table 2 contrasts the histology of some frequent granulomatous lung diseases, and Table 3 summarizes some potentially misleading histologic features of sarcoidosis.

## Invasive Diagnostic Procedures

In the vast majority of cases (probably with the exception of Löfgren's syndrome, which is per se diagnostic), the diagnosis of sarcoidosis requires the histologic demonstration of granulomas in the correct

**Table 3.** Potentially Misleading Histologic Features of Sarcoidosis

| Histologic Feature | Frequency | May Lead to an Erroneous Diagnosis of |
|---|---|---|
| Cytoplasmic inclusions | Frequent | Granulomatous reaction to exogenous material |
| Necrosis | Quite frequent as tiny foci, rare as large areas | Infection, Wegener |
| Fibrosis | Quite frequent | Other fibrosing interstitial lung diseases, pneumoconiosis (if associated with coniotic pigment or cholesterol clefts), infection (if misinterpreted as necrosis in nodular sarcoid) |
| Inflammation/ organizing pneumonia | Rare | Infection, hypersensitivity pneumonitis, aspiration, collagen vascular diseases, inflammatory bowel diseases, drug reactions |

clinical and radiologic context.[12-16] The most accessible involved site should be selected for the biopsy; for example, if the skin is affected, a cutaneous biopsy may lead to a rapid diagnosis. Frequently, however, the lung is the target organ because it is almost universally involved. The distribution of the granulomas along the bronchovascular bundles allows a high diagnostic yield of the bronchoscopic procedures.

Bronchoalveolar lavage (BAL) is safe and provides useful information. The characteristic BAL finding is a lymphocytosis with a CD4/CD8 ratio greater than 3.5, which has a relatively low sensitivity (is present in about 50% of the patients) but has a high specificity for sarcoidosis.[15]

Bronchial and transbronchial biopsies[54,55] have a diagnostic yield of 40% to 60% and about 90%, respectively. The diagnostic yield of bronchial biopsies is higher if a macroscopic lesion is seen. To achieve the above high diagnostic yield, transbronchial biopsies should consist of at least 4 good pieces of lung parenchyma. When examining histological sections from these biopsies, it might be important to obtain serial sections, as these sections increase the probability of detecting granulomas.[56] Sometimes, a generous transbronchial biopsy may show numerous compact, coalescent, nonnecrotizing granulomas embedded within hyaline collagen, that is, features almost diagnostic of sarcoidosis. Frequently, however, not only bronchial

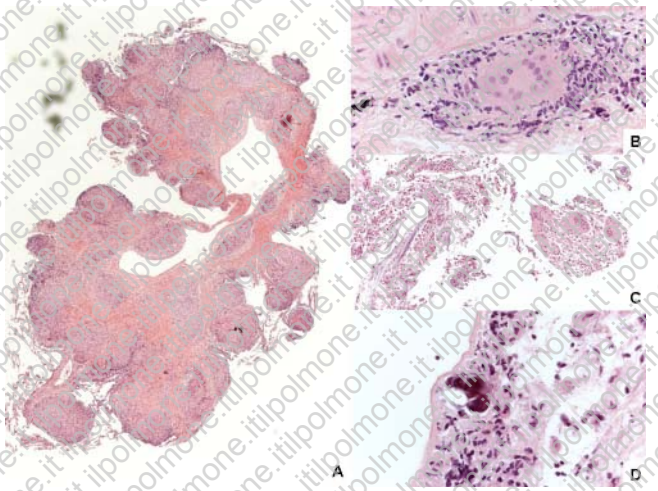


**Figure 13.** Examples of positive bronchial and transbronchial biopsies in different patients with sarcoidosis.
A, A generous transbronchial biopsy with the classic coalescing, compact, nonnecrotizing granulomas embedded within hyaline collagen (hematoxylin–eosin [H&E], 40×). Bronchial biopsies showing a single interstitial giant cell (B; H&E, 400×), a cluster of detached giant cells (C; H&E, 100×), and a Schaumann body (D; H&E, 400×). Biopsy A is almost diagnostic per se, whereas in biopsies B, C, and D the pathologist can just note the presence of tiny granulomas, and the final diagnosis requires a strong clinical support.

but also transbronchial biopsies show just a tiny granuloma, or even a single giant cell or a Schaumann body, which may be enough for the diagnosis but require a more robust clinical support. Some examples of bronchial and transbronchial biopsies in sarcoidosis are shown in Figure 13.

Transbronchial needle aspiration is a safe and useful procedure to sample mediastinal lymph nodes, with a high diagnostic yield in experienced hands.[57] The various bronchoscopic procedures can be combined together, further increasing their diagnostic rate.[58] Surgical lung and mediastinal biopsies should be reserved for those patients in whom the diagnosis remains uncertain after bronchoscopy.

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