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Pathology of Sarcoidosis

Giulio Rossi · Alberto Cavazza · Thomas V. Colby

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Abstract Pathologists are frequently involved in the diagnosis of sarcoidosis on conventional biopsies or examining bronchoalveolar lavage fluid and assisting bronchoscopists when performing bronchial or transbronchial biopsies or transbronchial needle aspiration (TBNA)/endobronchial ultrasound (EBUS)-guided biopsies of enlarged lymph nodes. Histology generally does not pose difficult tasks in the correct clinical and imaging scenario, but atypical forms of sarcoidosis exist, and in these cases, the diagnosis may become difficult. 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. 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 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 granulomatous infections, hypersensitivity pneumonitis, pneumoconiosis, autoimmune diseases (e.g., inflammatory bowel disease, primary biliary cirrhosis, several collagen vascular diseases (particularly Sjögren), drug reactions, chronic aspiration, and even diffuse fibrosing diseases. In this review, conventional and unusual histologic findings of pulmonary sarcoidosis are presented, highlighting the role of the pathologist and discussing the main differential diagnoses.

Keywords Sarcoidosis · Lung · Granuloma · Lymphatics · Infection · Necrosis · Biopsy

Introduction

With the exception of classic Lofgren's syndrome, in which a clinico-radiologic diagnosis is often acceptable, the diagnosis of sarcoidosis generally requires a histologic biopsy or a cytologic specimen showing granulomas in the correct clinico-radiologic context [1, 2]. As a consequence, pathologists are frequently involved in the workup of these patients, and sarcoidosis represents one of the granulomatous diseases they encounter most commonly. In many cases, the pathologist's role in this setting is not particularly difficult, providing that a strict collaboration with clinicians and radiologists is ensured. However, examples of sarcoidosis with atypical histology present diagnostic difficulties. Moreover, the widespread diffusion of transbronchial needle aspiration (TBNA) requires pathologists to recognize granulomas in limited cytologic material [3]. Herein, we provide a practical review on the role of pathologists in the diagnosis of sarcoidosis, focusing particularly on these problematic areas.

G. Rossi (✉)
Department of Diagnostic Laboratories, Operative Unit of Pathologic Anatomy, Azienda Policlinico, University of Modena and Reggio Emilia, Via del Pozzo, 71-41124 Modena, Italy
e-mail: giurossi68@gmail.com

A. Cavazza
Department of Oncology and Advanced Technology, Operative Unit of Pathologic Anatomy, Azienda Arcispedale S. Maria Nuova/I.R.C.C.S, Reggio Emilia, Italy

T. V. Colby
Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, AZ, USA

Classical and Atypical Histologic Features

The histology of sarcoidosis is well described in textbooks [4–9] and review articles [10–14]. Classical sarcoidosis (Fig. 1) consists in well-formed, tightly packed, non-necrotizing granulomas surrounded by lamellar hyaline collagen. Occasionally, granulomas are rimmed by a more edematous, myofibroblastic-rich tissue. In the lung, sarcoid granulomas typically coalesce along the lymphatic routes in the pleura, interlobular septa, and bronchovascular bundles. One of these anatomic compartments may be more involved than the others, generally the bronchovascular bundles but sometimes the pleura. This typical distribution of granulomas, together with their qualitative features (non-necrotizing, compact and associated with hyaline fibrosis), is the main histologic clue of pulmonary sarcoidosis. The disease tends to have an upper lung zone distribution, and this is a helpful feature in differential diagnosis with other granulomatous processes.

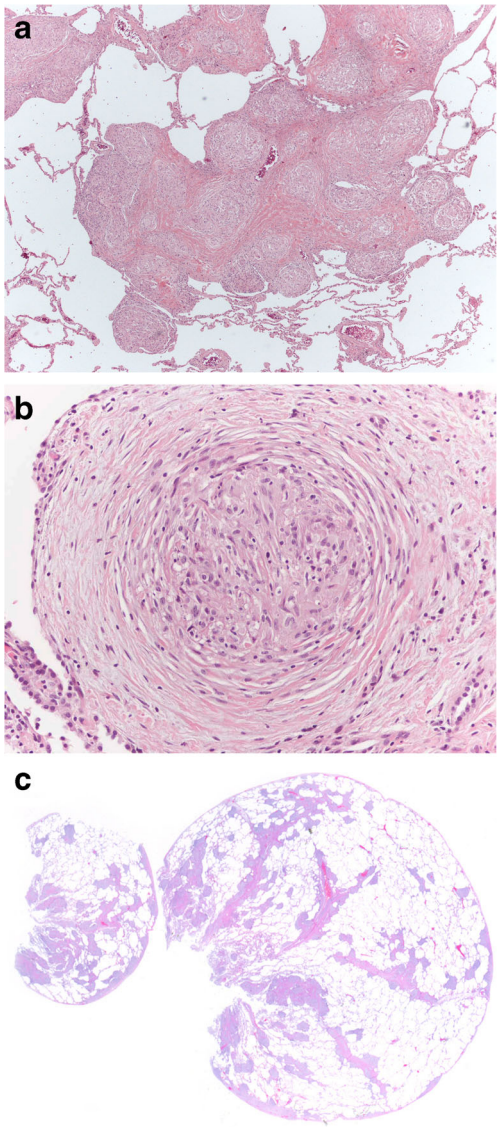

Fig. 1 **a** Classical histology of pulmonary sarcoidosis consists in compact, non-necrotizing granulomas rimmed by hyaline collagen and coalescing along the lymphatic routes, sparing the alveolar parenchyma (hematoxylin-eosin stain, X100). **b** Occasionally, sarcoid granulomas are rimmed by a more active, myofibroblastic-rich fibrosis (haematoxylin-eosin, X200). **c** The disease has a peculiar lymphagitic distribution in the upper lobe zone (hematoxylin-eosin, X15)

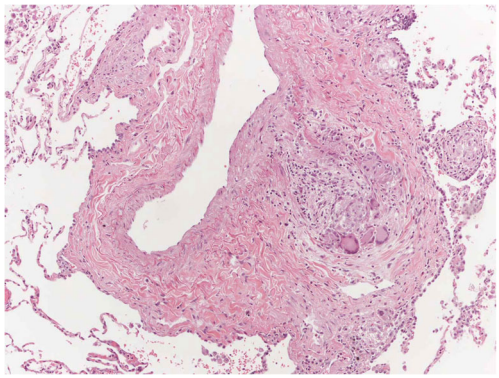

Fig. 2 Vascular involvement by granulomas, a frequent finding in sarcoidosis (hematoxylin-eosin, X100)

The fact that sarcoid granulomas tend to localize in the interstitium along lymphatic routes, where bronchovascular structures are found, with relative sparing of alveolar parenchyma, has some important consequences: First, it closely

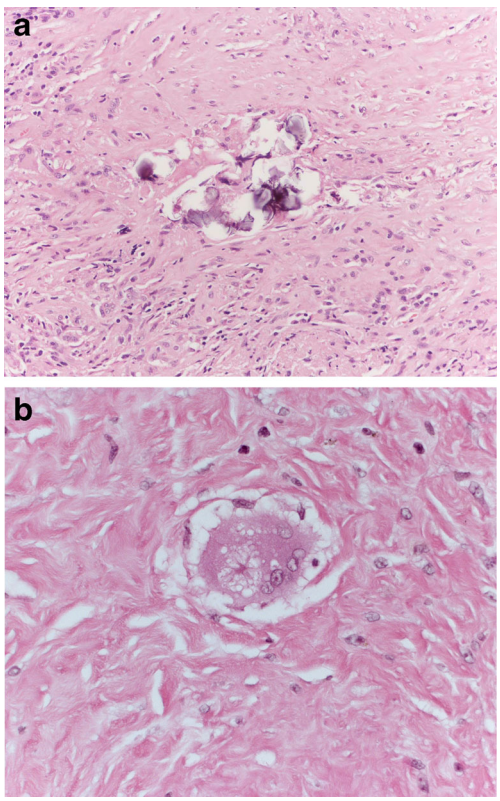

Fig. 3 Schaumann bodies (**a**) (hematoxylin-eosin, X400) and asteroid bodies (**b**) (hematoxylin-eosin, X400) are non-specific inclusions, that can be found in any granulomatous disease. They should not be misinterpreted as exogenous material

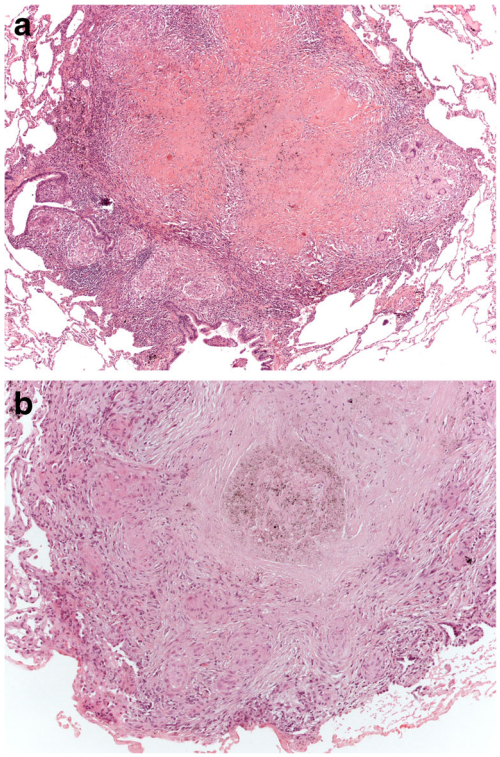

Fig. 4 **a** An example of nodular sarcoid. The central hyaline fibrosis should not be misinterpreted as necrosis (hematoxylin-eosin, X100). **b** Occasionally, fibrosis in nodular sarcoid incorporates a large amount of coniotic pigment, simulating a silicotic nodule. The presence of a rim of granulomas (absent in silicotic nodules unless infected) is the clue to recognize sarcoidosis in these cases (hematoxylin-eosin, X200)

correlates with the "perilymphatic" distribution seen on high-resolution computer tomography (HR-CT) of the chest [15]; second, it is the reason of the high diagnostic yield of bronchoscopic biopsies; third, it explains why some patients have few/no symptoms and normal function tests in spite of a significant pathology radiologically; fourth, it explains why in some patients the clinical picture is dominated by airway involvement (wheezing, functional obstruction) [16]; fifth, it is the reason for the frequent occurrence of vascular involvement in sarcoidosis, reported in 53 % of transbronchial biopsies [17], in 69 % of surgical lung biopsies [18], and in 100 % of autopsies [19]. Vascular involvement generally consists of granulomas variably involving the adventitia, media, or intima of pulmonary arteries and/or veins (Fig. 2). Occasionally, a more pronounced vasculitic inflammation may be present, but necrosis of the vessel wall is distinctly unusual. Vascular involvement likely accounts for the rare occurrence of pulmonary hypertension in sarcoidosis, sometimes with features of veno-occlusive disease [20].

Intracytoplasmic inclusions (Schaumann bodies, birefringent calcium oxalate crystals, cholesterol crystals, and asteroid bodies) are frequent in giant cells of sarcoid granulomas (Fig. 3). Although Schaumann bodies are relatively more common in sarcoidosis than in other granulomatous diseases

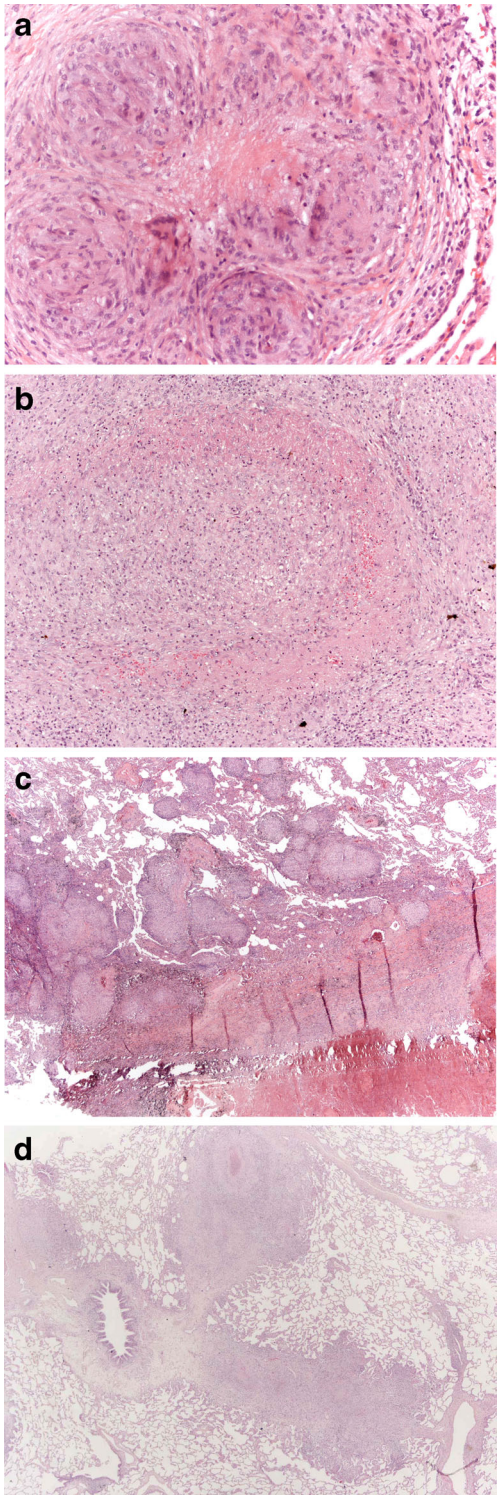

Fig. 5 Necrosis in sarcoidosis. **a** A granulomas with a small foci of fibrinoid necrosis, a not uncommon phenomenon in sarcoidosis (hematoxylin-eosin, X400). **b** A more extensive area of fibrinoid necrosis (hematoxylin-eosin, X100). **c** Hemorrhagic, infarct-like necrosis probably secondary to vascular obstruction by granulomas (hematoxylin-eosin, X20). **d** A granulomatous inflammation expanding the interlobular septa in a 12-year-old boy presenting with mild fever and bilateral pulmonary infiltrates. The disease had a prompt response to steroids, and the multidisciplinary (clinic-radiologic-pathologic) interpretation was necrotizing sarcoid granulomatosis (hematoxylin-eosin, X20)

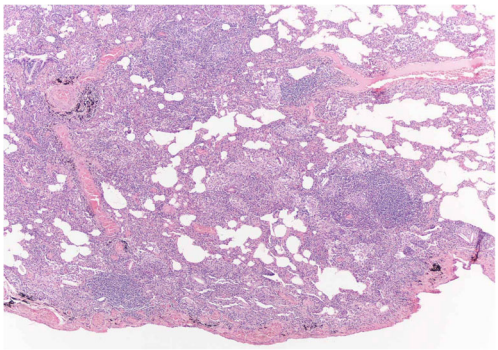

Fig. 6 A significant cellular infiltrate, an unusual finding in sarcoidosis somehow calling to mind hypersensitivity pneumonitis, Sjogren's syndrome, drug reactions. Other areas of the biopsy showed a classical sarcoidosis (hematoxylin-eosin, X20)

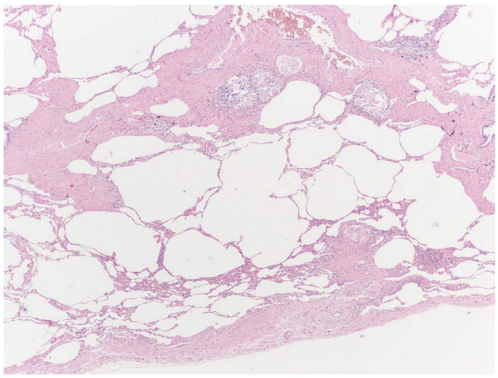

Fig. 7 Mild dense fibrosis with scattered small granulomas in a patient with chronic sarcoidosis (hematoxylin-eosin, X40)

[21], none of these inclusions is specific and they can occur in granulomas of any cause. They are endogenous by-products of macrophage metabolism, and they should not lead the pathologist to the erroneous diagnosis of foreign material and foreign-body granulomas.

Sarcoid granulomas may fuse into large fibrogranulomatous masses, so-called nodular sarcoid, which can simulate a neoplastic process radiologically (Fig. 4). In nodular sarcoid, the lymphatic distribution of granulomas may not be readily apparent: A clue is to look at the periphery of the mass, where sometimes the lymphatic localization is still recognizable. Nodules may become extensively fibrotic, and it is important to do not misinterpret this hyaline, acellular fibrosis as necrosis. Occasionally, the fibrosis assumes a lamellar configuration and incorporates dust, simulating a silicotic nodule.

Although classically described as non-necrotizing, some necrosis is in fact quite common in sarcoid granulomas, being present in about 20 % of transbronchial biopsies [11] and more frequently in surgical biopsies. It generally consists of small foci of fibrinoid ("rheumatoid-like") necrosis punctuating occasional granulomas, but larger areas of fibrinoid, infarct, or suppurative ("Wegener-like") necrosis may be rarely seen (Fig. 5). The controversial entity necrotizing sarcoid granulomatosis [22, 23] is probably just an unusual variant of sarcoidosis in which necrosis is particularly prominent. In general, the presence of necrosis in granulomas should always raise the possibility of infection, and a diagnosis of necrotizing sarcoid granulomatosis should not even be considered until an infection has been rigorously excluded.

In sarcoidosis, inflammation is generally inconspicuous and limited to a thin rim of lymphocytes around granulomas: A significant cellular infiltrate with organizing pneumonia is unusual and should suggest an alternative diagnosis. However, rare examples of sarcoidosis are characterized by a significant inflammation (Fig. 6), particularly in early phases or as an expression of obstructive pneumonia when granulomas occlude the bronchial tree.

Table 1 Histologic differential diagnosis of some granulomatous diseases in the lung (modified from ref. 14)

	Qualitative features of granulomas	Anatomic localization	Significant inflammation/ organizing pneumonia
Sarcoidosis	Non-necrotizing or with minimal fibrinoid necrosis; compact; coalescent; embedded within hyaline fibrosis; frequent vascular involvement	Along lymphatics	Very unusual
Granulomatous infection	Necrotizing (but necrosis can be absent); well-formed but not very compact; tend to be solitary; not much peri-granuloma fibrosis	Random or broncho-bronchiolocentric	Frequent
Chronic aspiration	Giant cells and granulomas often with polys and foreign particles	Bronchiolocentric	Frequent
Hypersensitivity pneumonitis	Loose/inconspicuous (frequently just giant cells isolated or in small groups); no necrosis	Bronchiolocentric	Typically present (with centrolobular accentuation)

With time, hyaline collagen penetrates the granulomas, which may become so fragmented to be barely recognizable. Occasionally, scattered giant cells (or even just isolated Schaumann bodies) entrapped within dense fibrosis may remain as the only marker of an old sarcoidosis. In some of these cases, the lymphatic distribution of the fibrosis is still recognizable, and when this occurs, it is a helpful diagnostic clue (Fig. 7). Sarcoidosis generally heals leaving normal or slightly scarred lung but occasionally progresses to significant fibrosis with traction bronchiectasies and honeycombing [24]. Aspergilloma may colonize these chronic cystic cavities.

Being frequently asymptomatic, sarcoidosis may occasionally represent just a background incidental finding in a biopsy performed for another disease.

Differential Diagnosis

The diagnosis of sarcoidosis cannot be rendered solely by the pathologist (except perhaps at autopsy), since there are several other granulomatous disorders that mimic sarcoidosis, particularly infections (Table 1 and Fig. 8) [11, 25], and in individual cases, the clinical, laboratory, and radiologic findings are critical in determining a final diagnosis.

Mycobacteria and some fungi are an important cause of granulomatous inflammation, most commonly necrotizing. However, when non-necrotizing infectious granulomas occur, a random rather than lymphangitic distribution of granulomas in the lung parenchyma as well as the presence of polymorphonucleates in and around granulomas are further histologic findings favoring an infection. Non-tuberculous mycobacteria lung involvement (e.g., *Mycobacterium avium-intracellulare*) may mimic sarcoidosis, forming bronchiolocentric non-necrotizing granulomas, as seen in hot tub lung [26].

Several fungal infections (e.g., Aspergillosis, Coccidioidomycosis, Blastomycosis, Histoplasmosis, and others) may produce granulomas in the lungs, but suppurative necrosis is often present and organisms apparent on methenamine silver staining [27, 28].

Although rare, *Pneumocystis jiroveci* infection may be responsible of granulomas (sometimes non-necrotizing), in patients with AIDS or bone marrow transplant recipients [29].

Hypersensitivity pneumonia may enter in differential diagnosis with sarcoidosis, but it is characterized by the presence of bronchiolocentric and/or interstitial, ill-defined, tiny, discohesive non-necrotizing granulomas and/or scatterd multinucleated giant cells. Moreover, the cellular infiltrate is generally much more prominent than the granulomas in hypersensitivity pneumonitis [11, 30].

Bronchiolocentric and vascular-centered non-necrotizing granulomas may be observed in chronic aspiration pneumonia and intravenous drug/talc injection, respectively. A careful search for exogenous matter and birefringent material (e.g.,

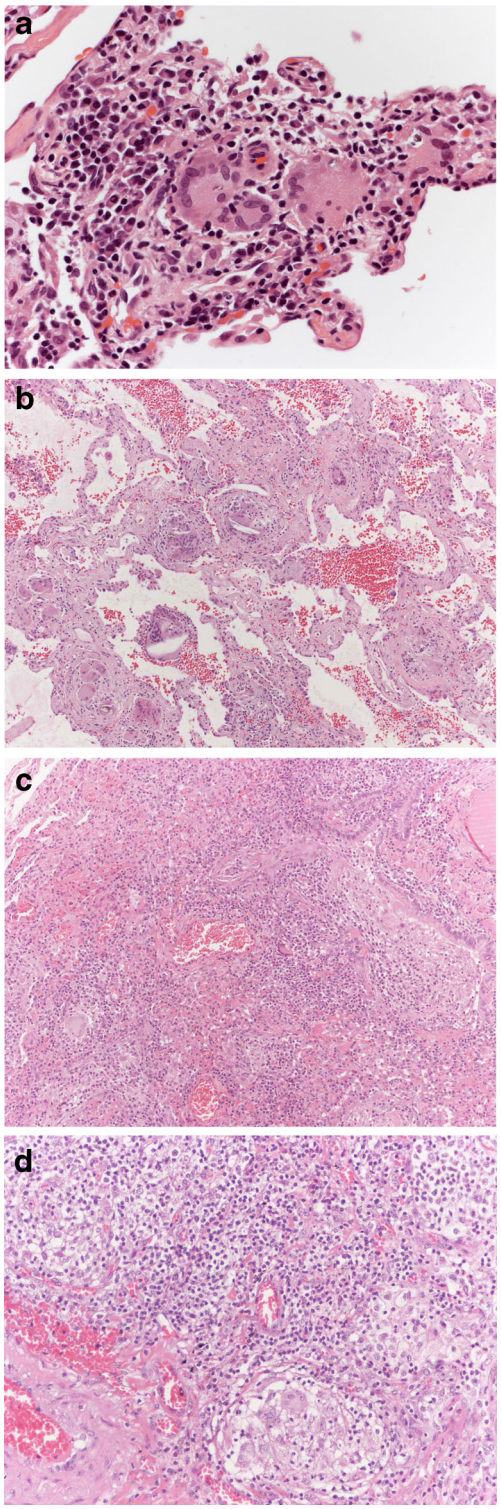

Fig. 8 Some granulomatous diseases potentially mimicking sarcoidosis: hypersensitivity pneumonitis (**a**) (hematoxylin-eosin, X400), berilliosis (**b**) (hematoxylin-eosin, X100), primary biliary cirrhosis (**c**) (hematoxylin-eosin, X200), and common variable immunodeficiency (**d**) (hematoxylin-eosin, X200)

talc, microcrystalline cellulose) in the cytoplasm of foreign body giant cells can confirm the diagnosis (for both aspiration and IV talcosis [31, 32]. Pulmonary involvement from systemic extrapulmonary granulomatous disorders, such as Crohn's disease or primaty biliary cirrhosis, may pose some diagnostic problems, but knowledge of clinical history and the finding of chronic bronchiolitis with non-necrotizing granulomas without the classic lymphangitic pattern are key features in differential diagnosis [33, 34].

An occupational history of chronic exposure to beryllium may be the only finding in discriminating berylliosis from sarcoidosis [35].

Invasive Diagnostic Procedures

The demonstration of granulomas in the correct clinico-radiologic context is generally required for the diagnosis of sarcoidosis [1, 2]. The biopsy should be directed to the most accessible affected site: For example, if the skin is involved, a cutaneous biopsy may lead to a rapid diagnosis. Frequently, however, the lung or the mediastinal lymph nodes are the target organs, because they are almost universally involved. The localization of the granulomas along the lymphatics in the lung enables a high diagnostic yield of the bronchoscopic procedures. The different bronchoscopic procedures can be combined together, further increasing their diagnostic yield [36]. Surgical lung and mediastinal lymph node biopsies should be reserved for atypical cases and for those patients in whom the diagnosis remains uncertain after bronchoscopy.

Bronchoalveolar Lavage (BAL)

Since a CD4+T-helper 1 (Th1) lymphocytic alveolitis represents the early immunologic feature of sarcoidosis, a careful examination of bronchoalveolar lavage (BAL) fluid in patients with suspected sarcoidosis may be very helpful. Although the results of BAL cell count should always be interpreted together with clinical, imaging, and laboratory data, macrophages and lymphocytes are the main cells observed in BAL, with few neutrophils, about 1 % of eosinophils and lack of plasma cells and foamy macrophages [37]. This is particularly true in early phase of sarcoidosis, while an increase of neutrophils and mast cells is often found in advanced or chronic phase of the disease. Although the

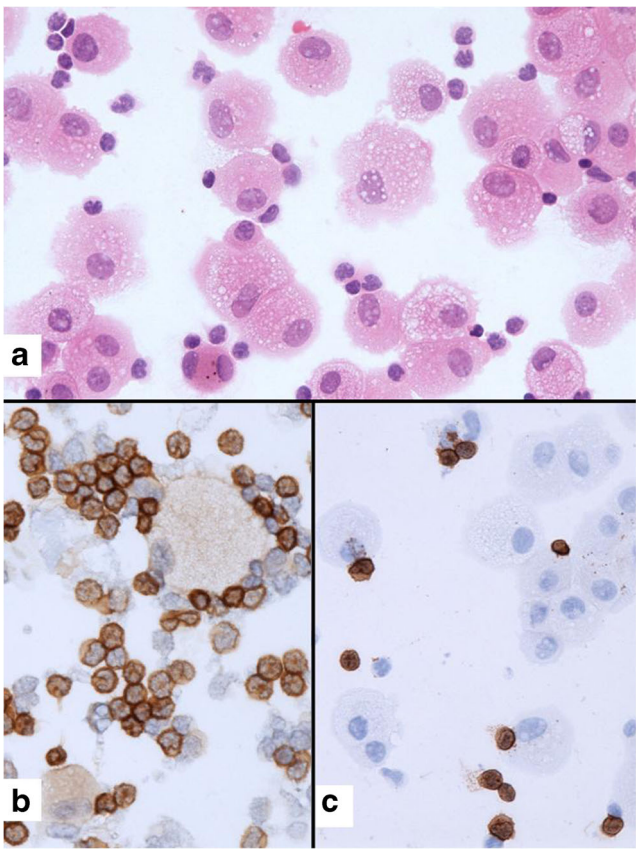

Fig. 9 Alveolar lymphocytosis in BAL fluid (**a**) (hematoxylin-eosin stain, X400) with predominance of CD4+ (**b**), (immunohistochemistry, X400) over CD8+ (**c**), (immunohistochemistry, X400) lymphocytes

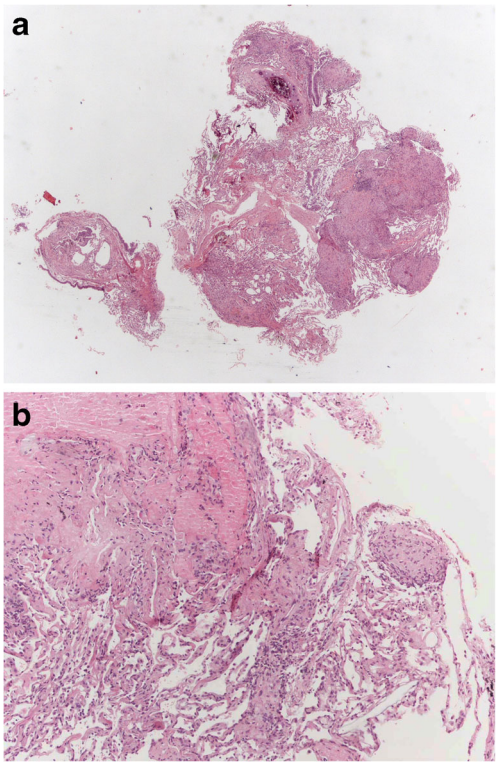

Fig. 10 **a** Transbronchial biopsy showing numerous compact, coalescing non-necrotizing granulomas, a combination of findings almost diagnostic of sarcoidosis (hematoxylin-eosin, X40). **b** Transbronchial biopsy in a different patient with sarcoidosis, showing just a small granuloma. Contrary to the previous biopsy, here the differential diagnosis among the various granulomatous diseases should be based entirely on clinical findings (hematoxylin-eosin, X100)

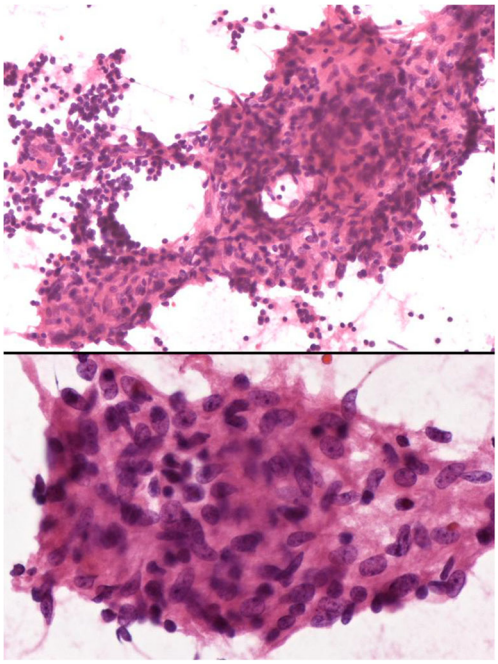

Fig. 11 Cytological smears from TBNA of mediastinal lymph nodes showing a granulomatous process surrounded by numerous lymphocytes and lacking necrosis (top, hematoxylin-eosin stain, X200). At higher magnification, the granuloma shows relatively well-defined margins with several tightly packed epithelioid histiocytes (bottom, hematoxylin-eosin stain, X400)

percentage of lymphocytes (ranging from 20 to 80 % with a mean value of 40 %) and an elevated CD4/CD8 ratio (≥3.5) may represent important findings (Fig. 9), about 10–15 % of patients with sarcoidosis may show normal or even decrease CD4/CD8 ratio in BAL. Increased CD4/CD8 ratio (over 3.5) on BAL has a sensitivity of 60 % and a specificity of 90–95 %, similar to that reported for transbronchial biopsy [38, 39].

More than 90 % of patients with sarcoidosis at diagnosis may show a lymphocytic alveolitis with a slightly increased total cell count. Nevertheless, several diseases in differential diagnosis with sarcoidosis may show lymphocytosis on BAL, such as hypersensitivity pneumonia (HP), connective tissue diseases (CTD), drug toxicity, or even extrapulmonary conditions involving the lung (e.g., Crohn disease or primary biliary cirrhosis) [38, 40].

The presence of plasma cells in BAL does exclude sarcoidosis, but it favors HP, CVD, or drug reaction. The finding of lymphocytosis with hemosiderin-laden macrophages is more consistent with vasculitis, CTD, idiopathic hemosiderosis, or drug toxicity [37, 38]. Immunocytochemistry using lymphoid markers (e.g., CD3, CD20, CD30) works quite well on BAL and may be useful to rule out lymphoproliferative disorders.

In summary, BAL fluid examination is a useful tool in the diagnostic workup of sarcoidosis. In addition, BAL examination together with the use of special stains (e.g., methenamine silver stain, Ziehl-Neelsen, periodic-acid Shiff) is particularly important in excluding a possible opportunistic infection in patients with sarcoidosis who show clinical deterioration while undergoing long-term immunosuppression.

Bronchial and Transbronchial Biopsies

Good-quality bronchial and transbronchial biopsies have a diagnostic yield (i.e., granulomas are present) of about 50 % (higher if a macroscopic lesion is seen) and 90 %, respectively, in patients with sarcoidosis [41–43]. Bronchial and transbronchial cryobiopsies, which obtain larger pieces of lung tissue, may further increase these percentages [44]. Since sarcoidosis may involve l the entire respiratory tree, it is not surprising to observe tiny granulomas at histology even in biopsies from "normal" or nearly normal appearing mucosa (e.g., localized erythema or slight thickening). So, it is useful to perform multiple endobronchial biopsies in all cases of suspected sarcoidosis, particularly when transbronchial biopsy is contraindicated [45].

When examining transbronchial biopsies, if the first section is negative, the pathologist should obtain additional levels to increase the probability to detect granulomas [46]. Sometimes, a transbronchial biopsy shows features which are almost diagnostic of sarcoidosis per se, namely numerous compact, non-necrotizing granulomas embedded within hyaline collagen. More often, however, bronchial or transbronchial biopsies show just a few tiny granulomas or even a single giant cell or a Schaumann body: In these cases, the pathologist can say

Table 2 Potentially misleading histologic features of sarcoidosis (modified from ref. 14)

Histologic feature	Frequency	May lead to an erroneous diagnosis of
Cytoplasmic inclusions	Frequent	Granulomatous reaction to exogenous material (inhalation, aspiration, intravenous injection)
Necrosis	Quite frequent as tiny foci, rare as large areas	Infection, granulomatosis with polyangiits (GPA, so-called Wegener's granulomatosis), aspiration
Fibrosis	Quite frequent	Other fibrosing interstitial lung diseases, pneumoconioses (if associated with coniotic pigment), infection (if misinterpreted as necrosis in nodular sarcoid)
Significant inflammation/ organizing pneumonia	Rare	Infection, hypersensitivity pneumonitis, aspiration, collagen vascular diseases, inflammatory bowel diseases, drug reactions

just there is a granulomatous lesion, but the differential diagnosis among the different granulomatous diseases should be based on clinical data (Fig. 10).

Transbronchial Needle Aspiration (TBNA)

Sarcoidal granulomas may be reliably seen in smeared aspirates from transbronchial needle aspiration (TBNA) of hilar and mediastinal lymph nodes (Fig. 11). This technique is a useful diagnostic procedure in sarcoidosis, and non-necrotizing epithelioid granulomas may be observed in about 80 % of stage I and stage II disease. Sampling of at least two different lymph nodes and rapid-on-site evaluation (ROSE) of transbronchial aspirates significantly increase the diagnostic yield and reduce the complication rate of bronchoscopy, respectively [47, 48].

Cell block preparation from TBNA is an excellent method to better appreciate the architectural morphology of granulomas sampled from hilar or mediastinal lymph nodes, also consistently permitting immunostains when required (i.e., to exclude lymphoproliferative diseases).

The presence of a necrotic background around granulomas favors an infectious agent, mainly tuberculosis [3].

Final Remarks

- Sarcoidosis is probably the most common cause of non-necrotizing granulomas in the lungs.
- On histology, tightly packed, non-necrotizing granulomas surrounded by lamellar hyaline fibrosis and displaying a lymphangitic distribution are quite characteristic of sarcoidosis.
- BAL fluid examination may be a diagnostic tool in the adequate clinico-radiologic scenario, either in supporting a diagnosis of sarcoidosis and in ruling out opportunistic infections in deteriorated patients with sarcoidosis treated with steroids.
- Sarcoidal granulomas may be reliably identified on cytology obtained from TBNA of mediastinal lymph nodes (with or without EBUS).
- Atypical forms of sarcoidosis may occur and knowledge of unusual histologic features (Table 2) is mandatory to prevent misdiagnoses.

Compliance with Ethical Standards The manuscript has not been submitted to more than one journal for simultaneous consideration.

The manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work (please provide transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism")).

A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g., "salami publishing").

No data have been fabricated or manipulated (including images) to support your conclusions.

No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized, and/or paraphrased); quotation marks are used for verbatim copying of material, and permissions are secured for material that is copyrighted.

Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities—tacitly or explicitly—at the institute/organization where the work has been carried out, before the work is submitted.

Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

This is a review article that does not involve human participants and does not require informed consent.

The study does not involve animals.

Conflict of Interest The authors declare that they have no conflict of interest.

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