Noninfectious Diffuse Granulomatous Lung Diseases

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This chapter illustrates the two main forms of noninfectious diffuse granulomatous lung disease likely to be encountered in lung biopsies: hypersensitivity pneumonia and sarcoidosis. Hypersensitivity pneumonia and sarcoidosis have in common an ability to cause respiratory symptoms in patients with diffuse radiologic abnormalities. Affected patients frequently undergo biopsies to rule out neoplasms and/or other forms of diffuse lung disease. Non-necrotizing granulomatous inflammation is an important diagnostic clue in both conditions, each distinguished by a very different combination of associated histologic findings. When encountered by surgical pathologists, the differential diagnosis for both often includes granulomatous infections, an especially important consideration in immunocompromised patients (*see* Chap. 4). Other conditions that may enter the differential diagnosis include aspiration pneumonia, which is illustrated in Chap. 5.

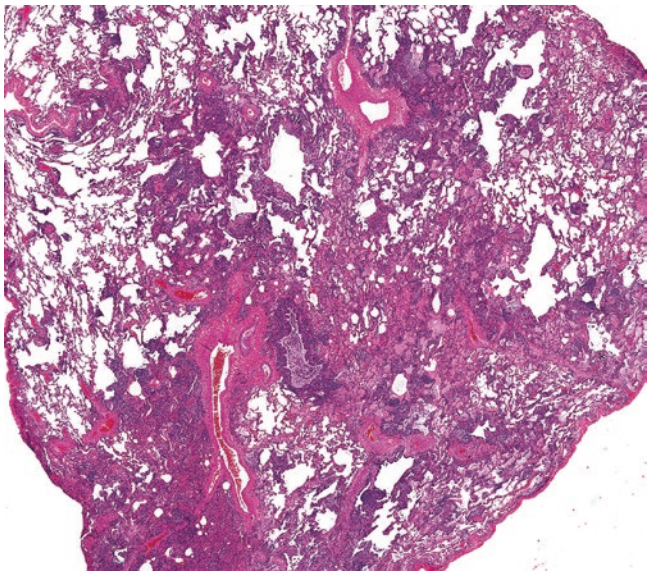

Fig. 7.1 Hypersensitivity pneumonia. A low-magnification whole-mount section showing a cellular interstitial pneumonia that is accentuated around the small airways. The more distal alveoli are less involved. The overall alveolar architecture is preserved with no significant fibrosis

Hypersensitivity Pneumonia

Hypersensitivity pneumonia (Figs. 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8 and 7.9) is an immunologic reaction of the lung to inhaled antigens, most frequently organic antigens from animal proteins, thermophilic bacteria, or molds. Animal proteins are mainly of avian origin; feather pillows and bedding are increasingly recognized as a potential antigenic source in patients with hypersensitivity pneumonia. An exposure source may not always be identifiable. The radiologic changes vary from ground-glass opacities with centrilobular nodules and mosaic attenuation in early disease to honeycomb changes resembling usual interstitial pneumonia (UIP) in patients with long-standing disease. Because the presenting symptoms and radiologic findings may be relatively nonspecific, especially in patients with no identifiable antigenic exposure, lung biopsy often plays a key role in diagnosis.

The combination of a bronchiolocentric chronic interstitial pneumonia and loosely formed epithelioid granulomas centered within peribronchiolar interstitium is the most important histologic clue to a diagnosis of hypersensitivity pneumonia. Although they are often included with the granulomatous lung diseases, granulomas may be absent altogether in lung biopsies from patients with well-established

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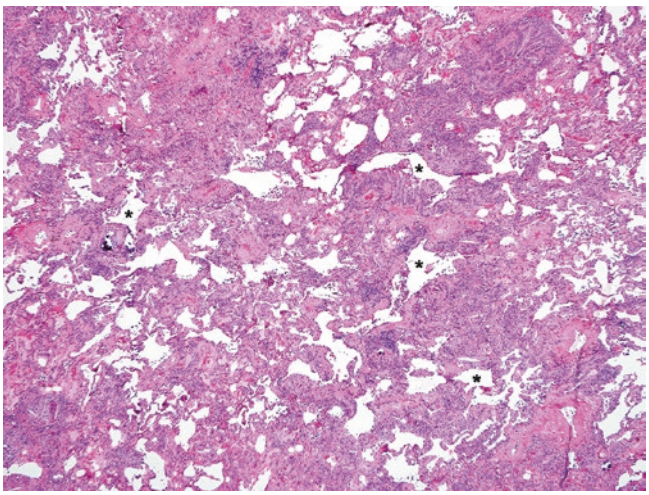

Fig. 7.2 Hypersensitivity pneumonia. Low-magnification photomicrograph showing a variably dense, lymphocyte-rich, cellular inflammatory infiltrate that expands the interstitium and is accentuated around distal bronchioles (asterisks)

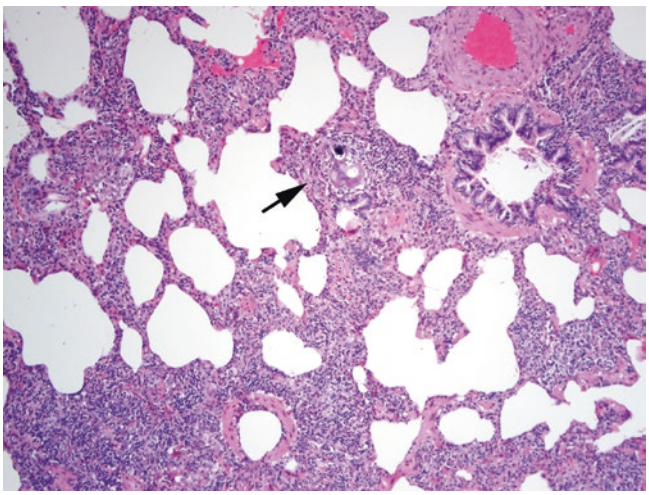

Fig. 7.3 Hypersensitivity pneumonia. Intermediate-magnification photomicrograph showing a small poorly formed granuloma composed of a loose cluster of multinucleated giant cells (arrow) situated within the peribronchiolar interstitium. Note the background cellular interstitial pneumonia with peribronchiolar accentuation. It is this combination of features that is most helpful in establishing a histologic diagnosis of hypersensitivity pneumonia

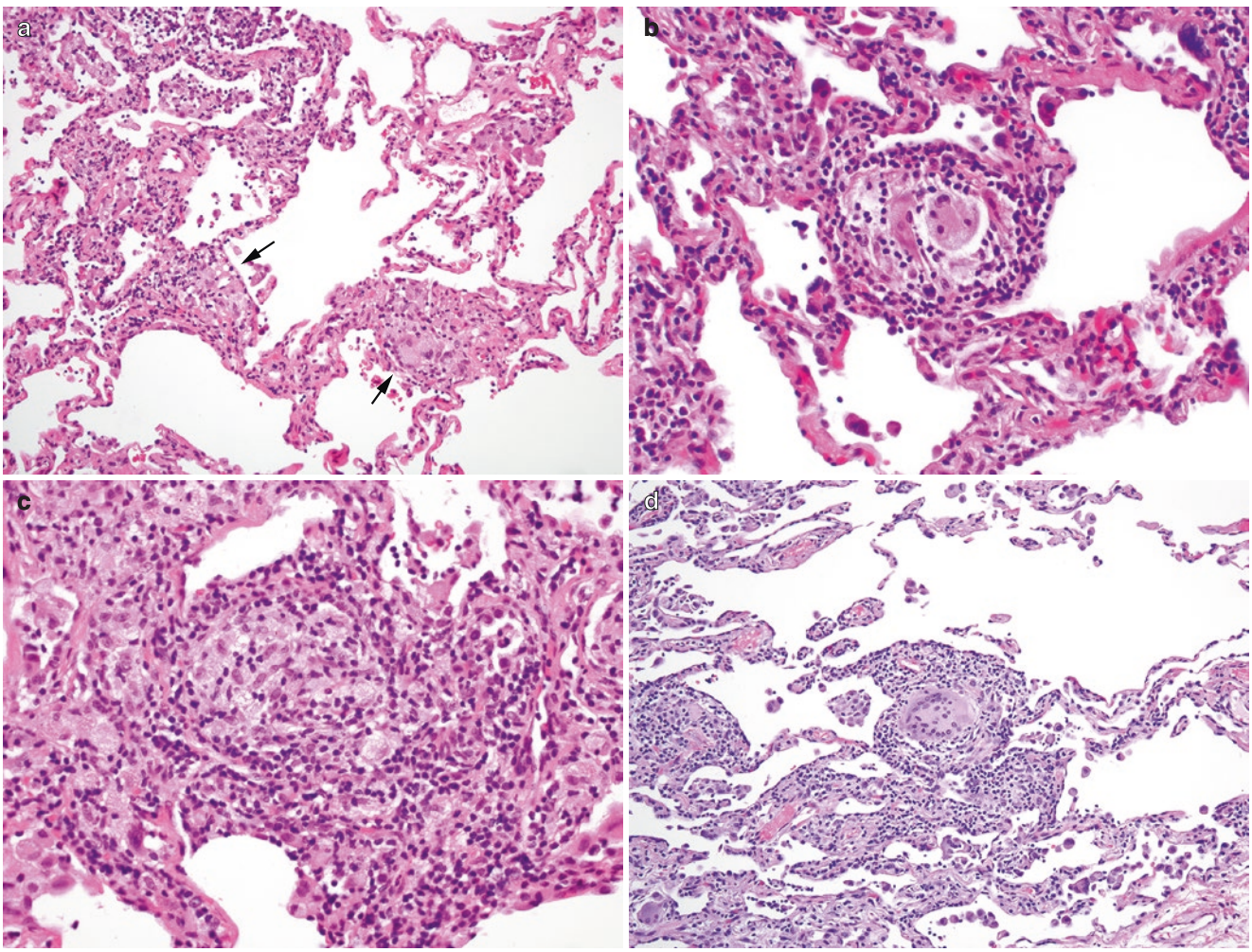

Fig. 7.4 Granulomatous inflammation in hypersensitivity pneumonia. (**a**) Photomicrograph showing a characteristic pattern of loosely formed granulomas (arrows) consisting of epithelioid histiocytes and giant cells centered on the peribronchiolar interstitium. (**b**) High-magnification view of a loosely formed granuloma consisting of a giant cell and a few histiocytes and surrounded by mononuclear inflammatory cells in which lymphocytes predominate. (**c**) Another example of a loosely formed granuloma consisting of epithelioid histiocytes within the peribronchiolar interstitium accompanied by a dense infiltrate of chronic inflammatory cells. (**d**) An isolated giant cell is seen within the interstitium in a background of chronic inflammatory cells

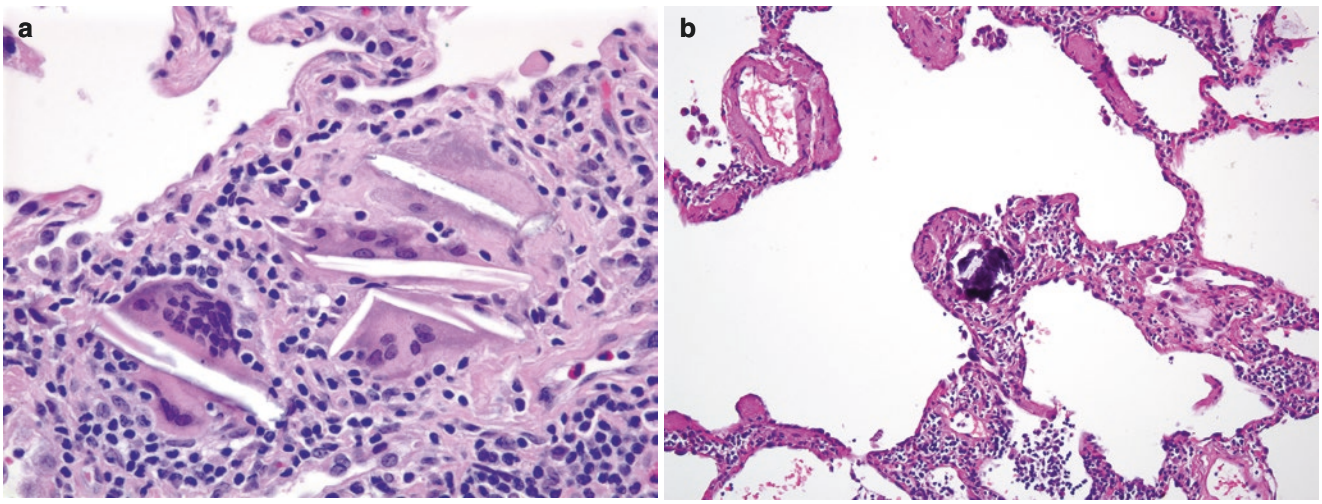

Fig. 7.5 Granulomatous inflammation in hypersensitivity pneumonia. The giant cells in hypersensitivity pneumonia often contain a variety of nonspecific endogenous cytoplasmic inclusions, including cholesterol-like clefts (**a**), calcified Schaumann bodies (**b**), and other nonspecific pale-staining birefringent crystalline salts (not illustrated). These inclusions are not linked to any specific antigenic exposures

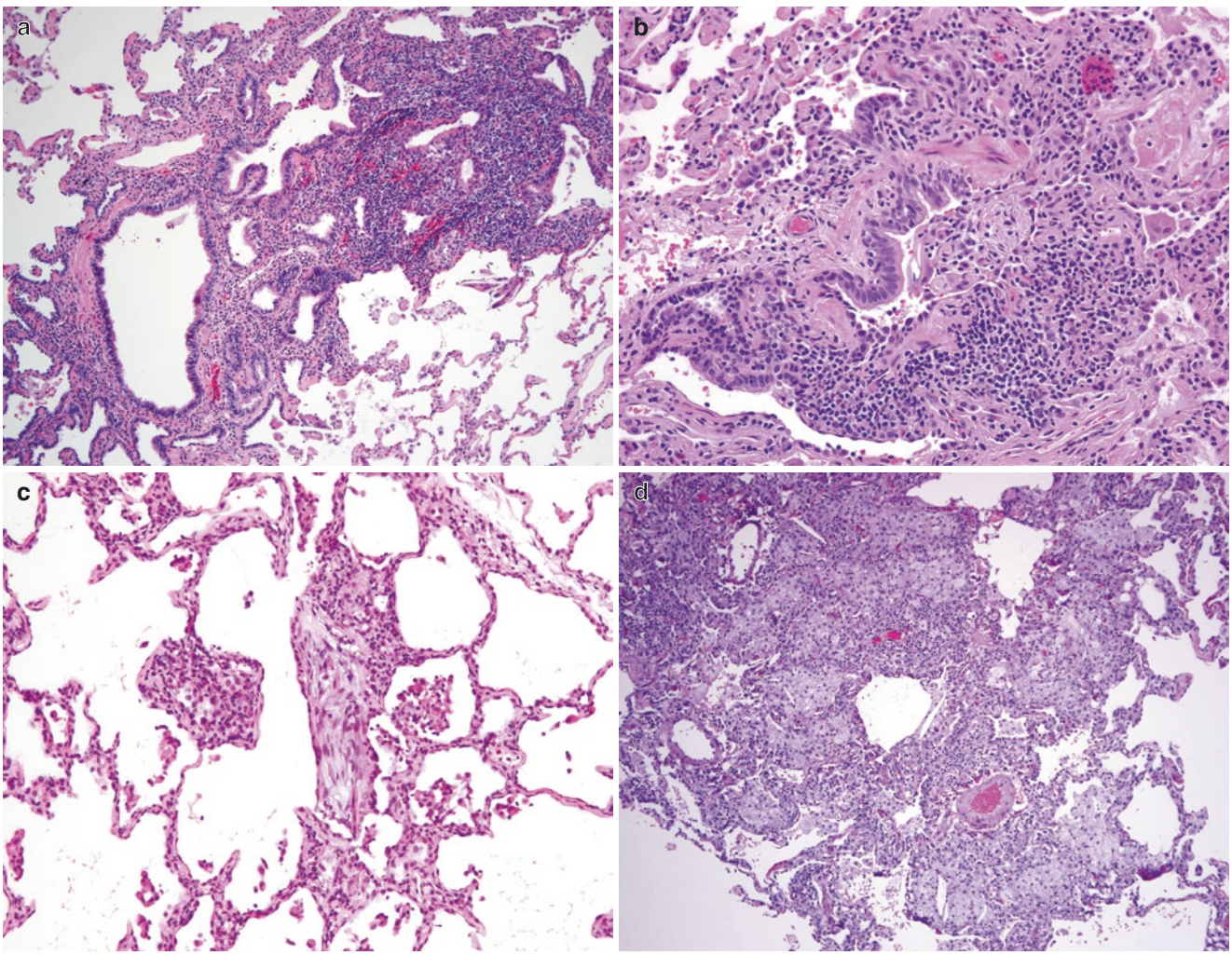

Fig. 7.6 Chronic bronchiolitis in hypersensitivity pneumonia. (**a**) High-magnification photomicrograph showing chronic bronchiolitis characterized by a chronic inflammatory infiltrate that expands the peribronchiolar interstitium. The hyperplastic columnar respiratory epithelium extends along peribronchiolar alveolar septa thickened by inflammation and fibrosis, a combination of findings referred to as peribronchiolar metaplasia (*see* Fig. 7.7). (**b**) Another high-magnification view showing chronic bronchiolitis with focal intraluminal fibroblast proliferation (bronchiolitis obliterans also referred to simply as organizing pneumonia). (**c**) Photomicrograph showing focal organizing pneumonia made up of a polypoid plug of organizing fibroblasts situated within the lumen of a respiratory bronchiole in a patient with hypersensitivity pneumonia. (**d**) Accumulation of foamy alveolar macrophages in peribronchiolar air spaces is a form of microscopic obstructive pneumonia and is another sign of small airway dysfunction that is common in lung biopsies from patients with hypersensitivity pneumonia

diagnoses of hypersensitivity pneumonia. The constant is a lymphocyte-rich interstitial infiltrate distributed in a distinctly bronchiolocentric fashion. Signs of small airway dysfunction such as organizing pneumonia and foamy alveolar histiocytes (microscopic obstructive pneumonia) are relatively nonspecific but are commonly seen.

Hot tub lung is a special variant in which a hypersensitivity pneumonia-like syndrome results from sensitization to hot tubs contaminated with atypical mycobacterial organisms, most commonly *Mycobacterium avium* complex (MAC). Unlike other forms of hypersensitivity pneumonia, the causative antigen/organism can be identified in and cultured from the tissue. The histology is also unique as illustrated in Chap. 4 (*see* Fig. 4.13) and consists of relatively well-formed and focally necrotizing granulomas situated within the lumens (rather than the interstitium) of distal bronchioles without the other features more typical of classic hypersensitivity pneumonia.

The presence of fibrosis in lung biopsies is associated with a greater likelihood of disease-related mortality in patients with hypersensitivity pneumonia. Fibrotic disease may include areas of honeycomb change that closely mimic UIP. Honeycomb change in patients with hypersensitivity pneumonia is accompanied by a distinctive pattern of airway-centered fibrosis referred to as peribronchiolar metaplasia, a finding that is not specific but is a clue to the possibility of hypersensitivity pneumonia. Establishing the diagnosis in patients with fibrotic disease hinges on identifying classic histologic features in less fibrotic lung tissue combined with supportive clinical and radiologic findings.

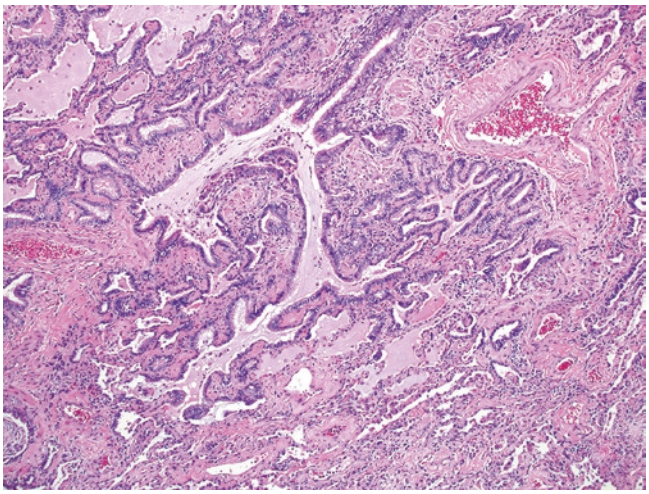

Fig. 7.7 Fibrotic hypersensitivity pneumonia. Photomicrograph showing prominent peribronchiolar metaplasia in a surgical lung biopsy from a patient with hypersensitivity pneumonia. Peribronchiolar metaplasia is not specific but is a very characteristic and universal finding in fibrotic hypersensitivity pneumonia. It is not sufficient to establish the diagnosis on its own but should spark a careful search for the other findings helpful in establishing a histologic diagnosis of hypersensitivity pneumonia

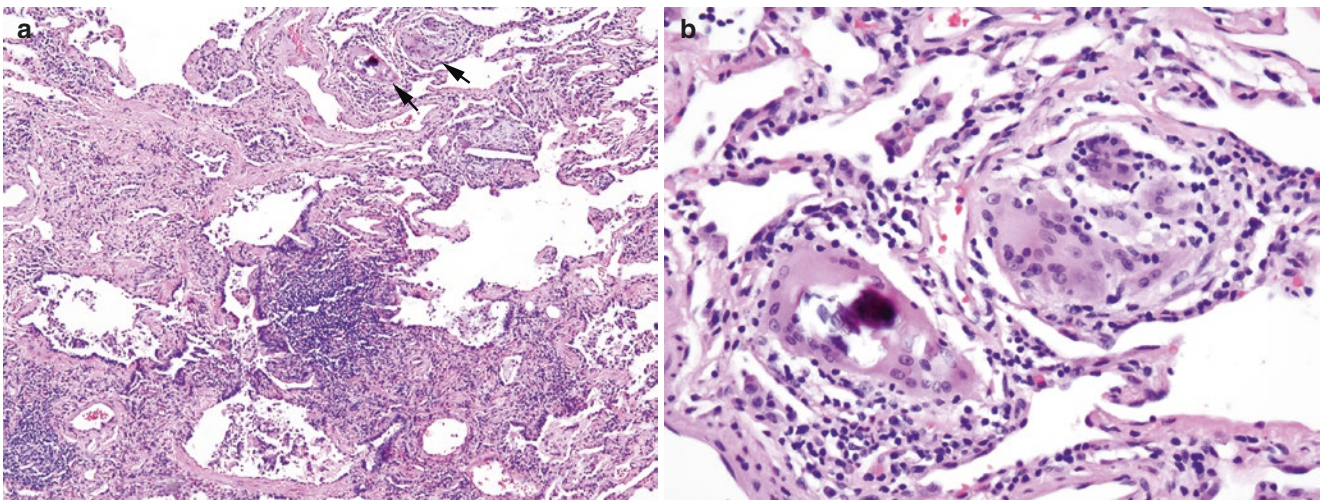

Fig. 7.8 Fibrotic hypersensitivity pneumonia. (**a**) Photomicrograph showing long-standing hypersensitivity pneumonia characterized by a considerable degree of fibrosis that includes architectural distortion in the form of scarring and early honeycomb change resembling usual interstitial pneumonia. However, the patchy peribronchiolar infiltrate of lymphocytes combined with the cluster of multinucleated giant cells (arrows) are clues to the diagnosis of hypersensitivity pneumonia. (**b**) High-magnification view of the small clusters of multinucleated giant cells, one of which contains calcified cytoplasmic inclusions

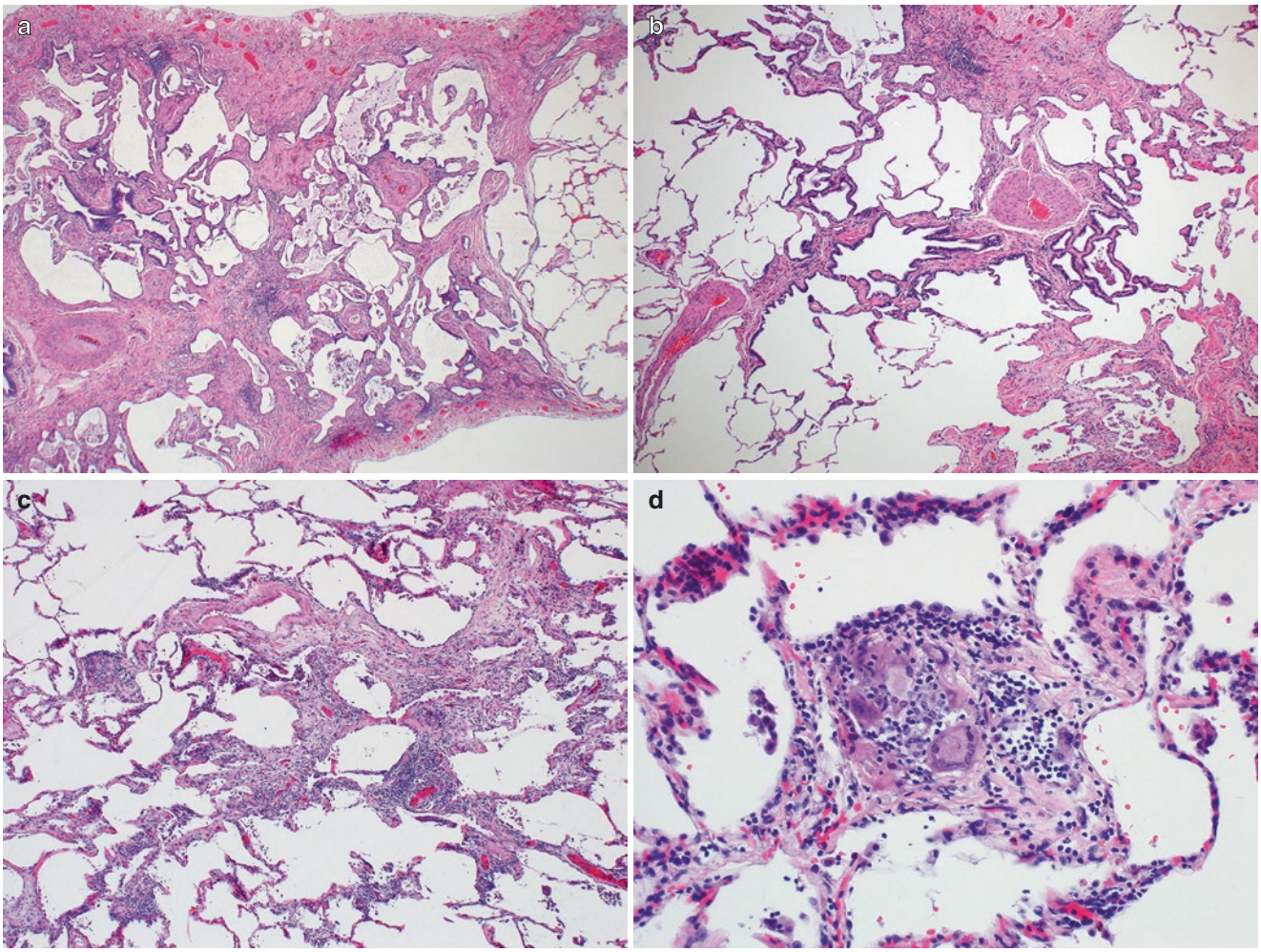

Fig. 7.9 Fibrotic hypersensitivity pneumonia. (**a**) Low-magnification photomicrograph of surgical lung biopsy showing patchwork fibrosis and microscopic honeycomb changes resembling UIP. (**b**) Photomicrograph from same biopsy showing prominent peribronchiolar metaplasia. (**c**) Low-magnification photomicrograph of a biopsy obtained from a different lobe from the same patient showing features typical of hypersensitivity pneumonia, including a bronchiolocentric lymphocytic infiltrate and a poorly formed granuloma in the peribronchiolar interstitium. (**d**) High-magnification photomicrograph showing a loose cluster of multinucleated giant cells in the peribronchiolar interstitium

Sarcoidosis

Sarcoidosis (Figs. 7.10, 7.11, 7.12, 7.13, 7.14, 7.15, 7.16, 7.17, 7.18, 7.19, 7.20 and 7.21) is a disease of unknown etiology characterized by granuloma formation involving multiple organ sites. The lung is the most commonly involved organ. Young and middle-aged adults are most often affected, although the age range is wide. The incidence rate is higher in women and in African-Americans. The diagnosis requires a combination of typical clinicoradiologic features, non-necrotizing epithelioid granulomas in a tissue biopsy, and exclusion of other possible etiologies, particularly granulomatous infection. Most cases of pulmonary sarcoidosis follow a benign course and tend to resolve spontaneously or with steroid treatment. However, 10–30% of patients develop progressive fibrosis resulting in respiratory failure and lung transplantation.

The classic histologic findings in sarcoidosis are well-formed, tightly clustered, non-necrotizing granulomas confined to the interstitial compartment and distributed in a characteristic lymphangitic pattern. The features illustrated here draw primarily on surgical lung biopsies, but most patients are diagnosed using smaller closed biopsies, including some combination of endobronchial ultrasound (EBUS)-guided transbronchial needle aspirations and transbronchial lung biopsies. The findings in these smaller biopsies may be subtle, but in experienced hands they have demonstrated high diagnostic sensitivity but lower specificity. Determining the significance of non-necrotizing granulomas in these smaller specimens hinges to a large degree on the clinical and radiologic context and the associated pretest probabilities.

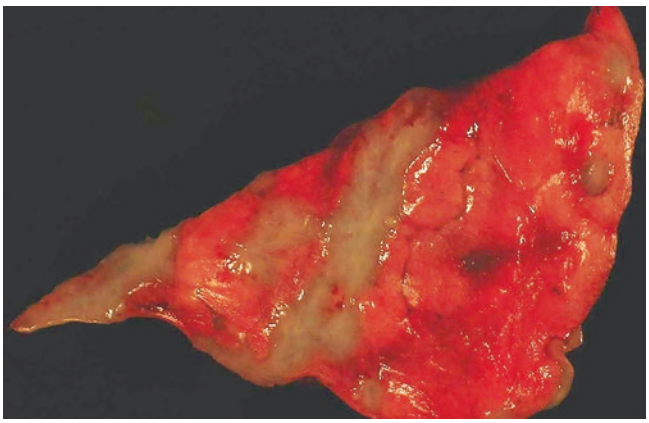

Fig. 7.10 Sarcoidosis. Gross photograph demonstrating the cut surface of a surgical lung biopsy involved by sarcoidosis. The abnormalities have an exquisitely lymphangitic distribution and include pale nodular and linear fibrous bands that expand interlobular septa, bronchovascular bundles, and visceral pleura

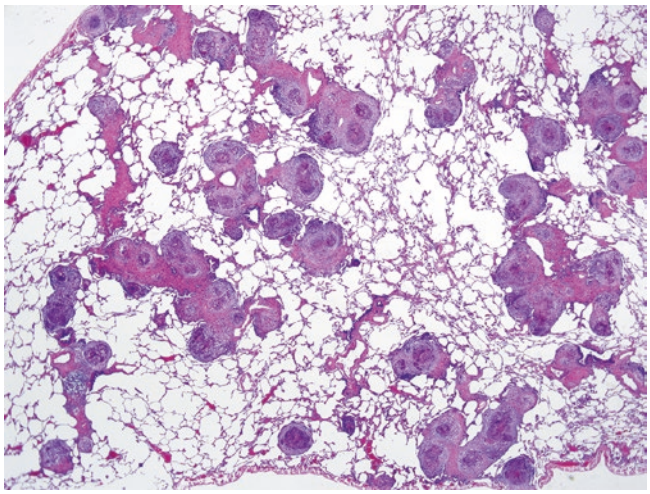

Fig. 7.11 Sarcoidosis. Low-magnification photomicrograph showing the lymphangitic distribution of non-necrotizing granulomas. The granulomas are confined to the interstitium and distributed within interlobular septa, bronchovascular bundles, and visceral pleura. As a consequence, vessel walls are frequently affected but without true necrotizing vasculitis

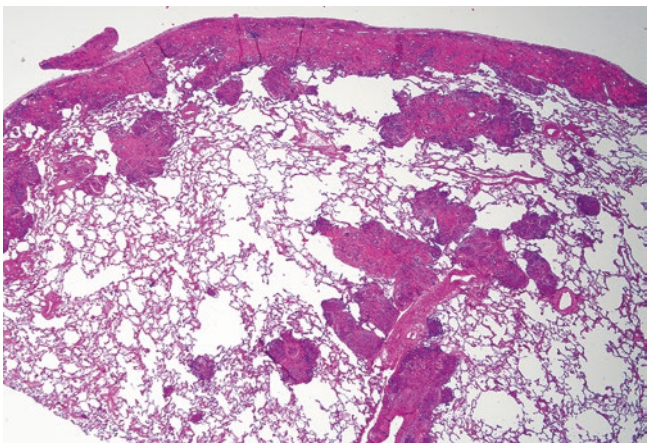

Fig. 7.12 Sarcoidosis. Low-magnification photomicrograph showing another example of sarcoidosis with classic lymphangitic distribution. Well-formed non-necrotizing granulomas are located along the visceral pleura, interlobular septa, and bronchovascular bundles

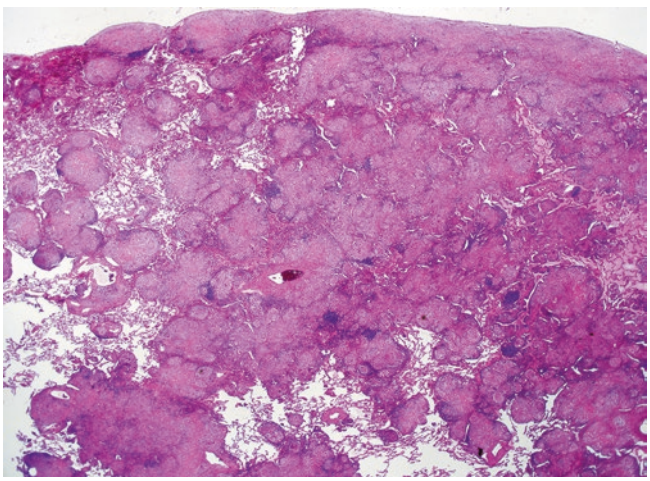

Fig. 7.13 Sarcoidosis. As illustrated in this low-magnification photomicrograph, sometimes the granulomas are confluent and form larger nodules that replace portions of lung parenchyma. The granulomas maintain their interstitial location and lymphangitic distribution

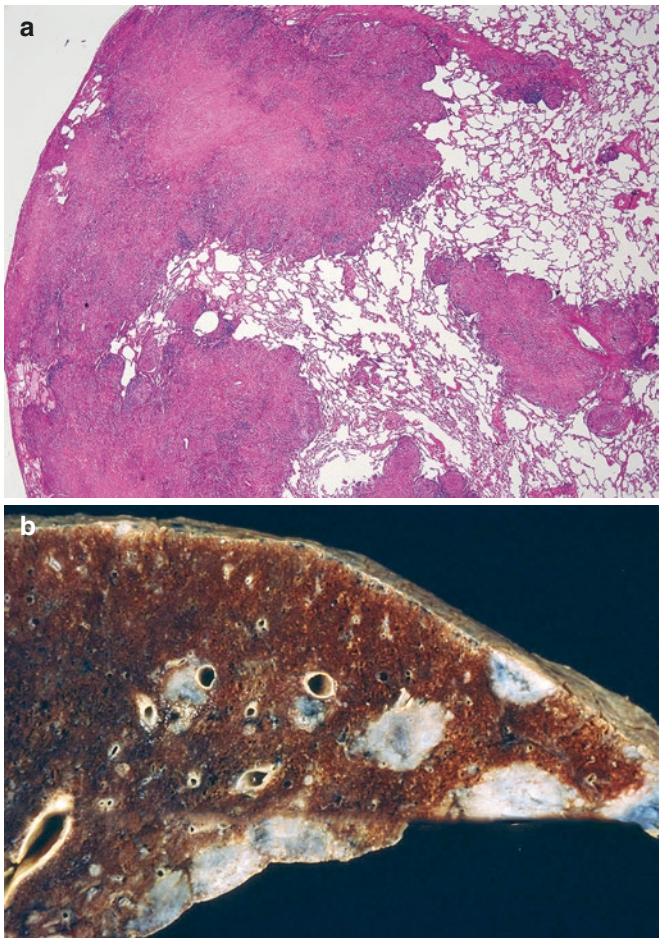

Fig. 7.14 Nodular sarcoidosis. (**a**) Low-magnification photomicrograph showing coalescence of well-formed granulomas in a collagenous stroma resulting in macroscopic nodules. (**b**) Cut surface of surgical lung specimen showing macroscopic nodules situated along visceral pleura and bronchovascular bundles in a patient with nodular sarcoidosis

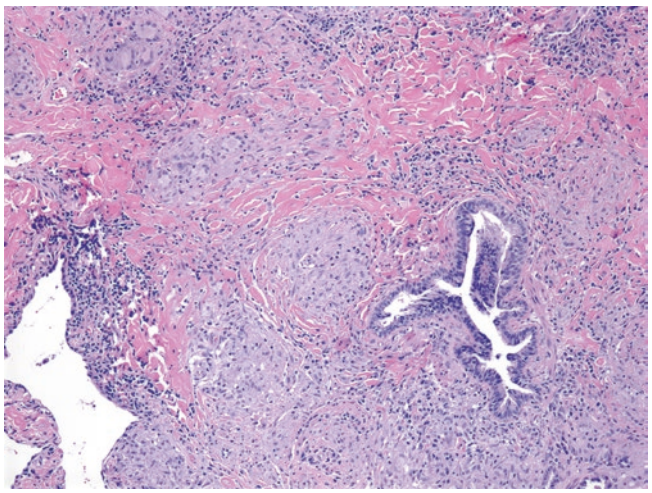

Fig. 7.15 Sarcoidosis. Photomicrograph showing multiple well-formed non-necrotizing granulomas next to a bronchiole, expanding the bronchovascular bundle. Dense collagen fibrosis characterized by concentric lamellar bands is characteristic of, but not specific for, sarcoidosis

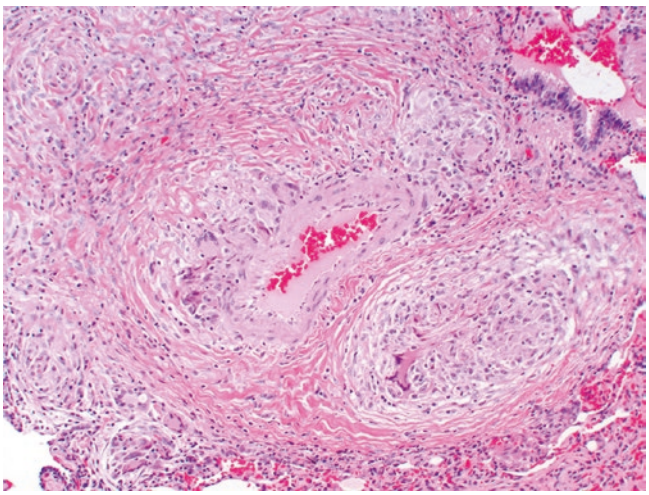

Fig. 7.16 Sarcoidosis. Photomicrograph showing non-necrotizing granulomas within a bronchovascular bundle (bronchiole in right upper corner), in this example involving the wall of a small muscular pulmonary artery. Non-necrotizing granulomatous vasculitis is a common finding in surgical lung biopsies from patients with sarcoidosis and is occasionally present in smaller transbronchial biopsies

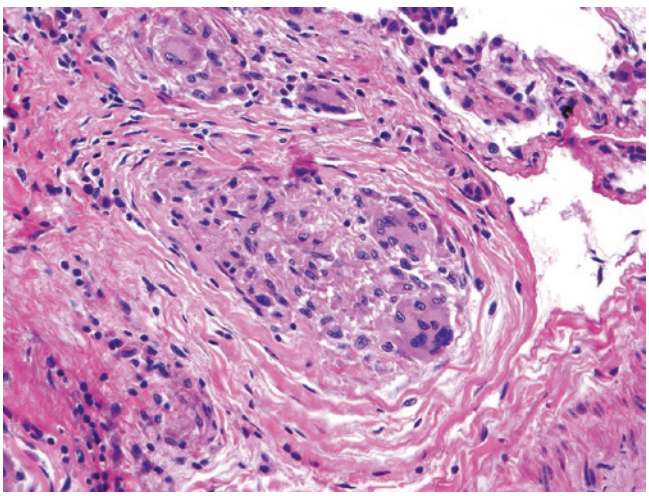

Fig. 7.17 Sarcoidosis. High-magnification photomicrograph showing a well-formed non-necrotizing granuloma consisting of tightly clustered multinucleated giant cells and epithelioid histiocytes, surrounded by a rim of fibroblasts and concentric bands of collagen fibrosis

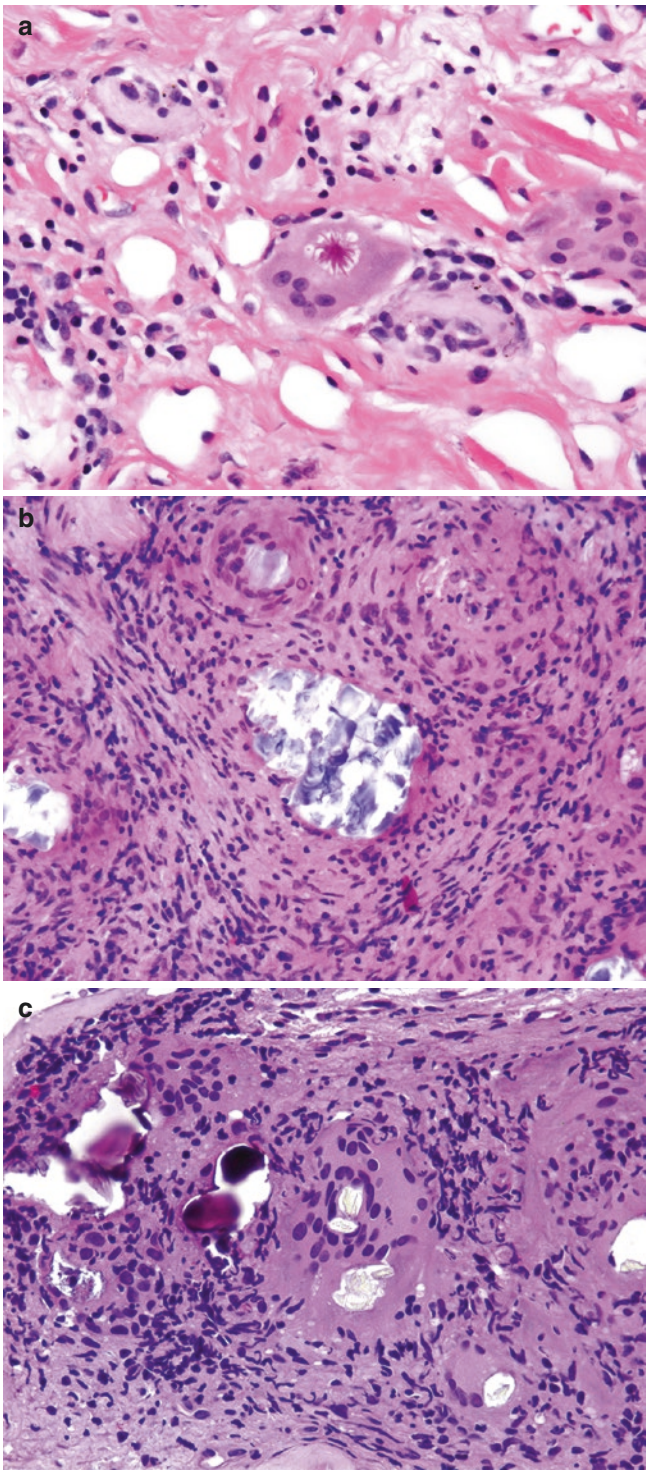

Fig. 7.18 Sarcoidosis. A number of cytoplasmic inclusions are commonly seen within the histiocytes and especially the giant cells of sarcoidosis, including asteroid bodies (**a**), Schaumann bodies (**b**), and calcium oxalate crystals (**c**), as illustrated in these high-magnification photomicrographs. The calcium oxalate crystals are relatively translucent in routinely stained sections but are brightly birefringent when viewed with polarized light. These inclusions are not specific for sarcoidosis and can be seen in any chronic granulomatous lesions, including infections and hypersensitivity pneumonia

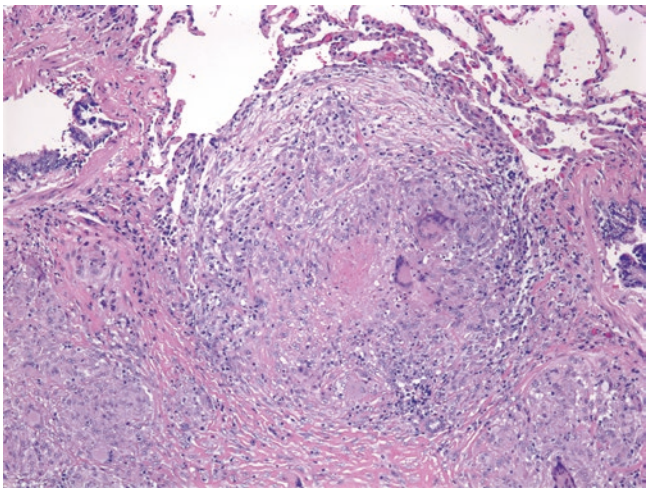

Fig. 7.19 Sarcoidosis. Photomicrograph showing a small focus of central necrosis in a granuloma in a patient with sarcoidosis. Although the predominant pattern of granulomatous inflammation in sarcoidosis is non-necrotizing, small foci of necrosis like this one in occasional granulomas are not uncommon in well-sampled cases

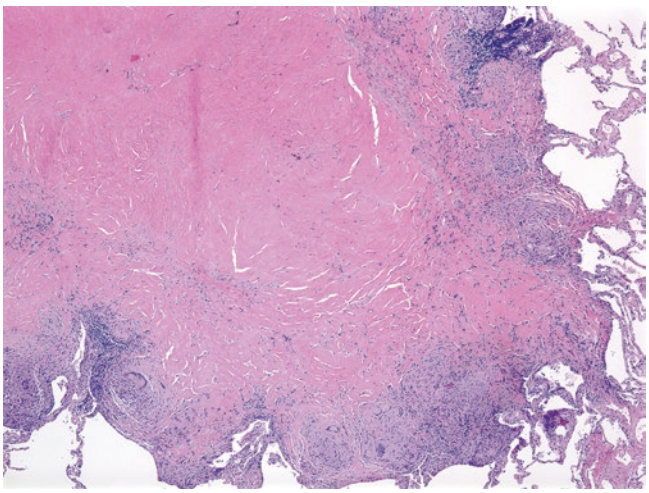

Fig. 7.20 Sarcoidosis. Low-magnification photomicrograph showing an example of late-stage disease characterized by a large area of dense hyalinized fibrosis. Tightly formed (sarcoidal) non-necrotizing granulomas are still appreciated at the edge of the fibrosis. This combination of features overlaps with the histology of hyalinizing infectious granulomas and is a finding that sometimes complicates diagnostic interpretation

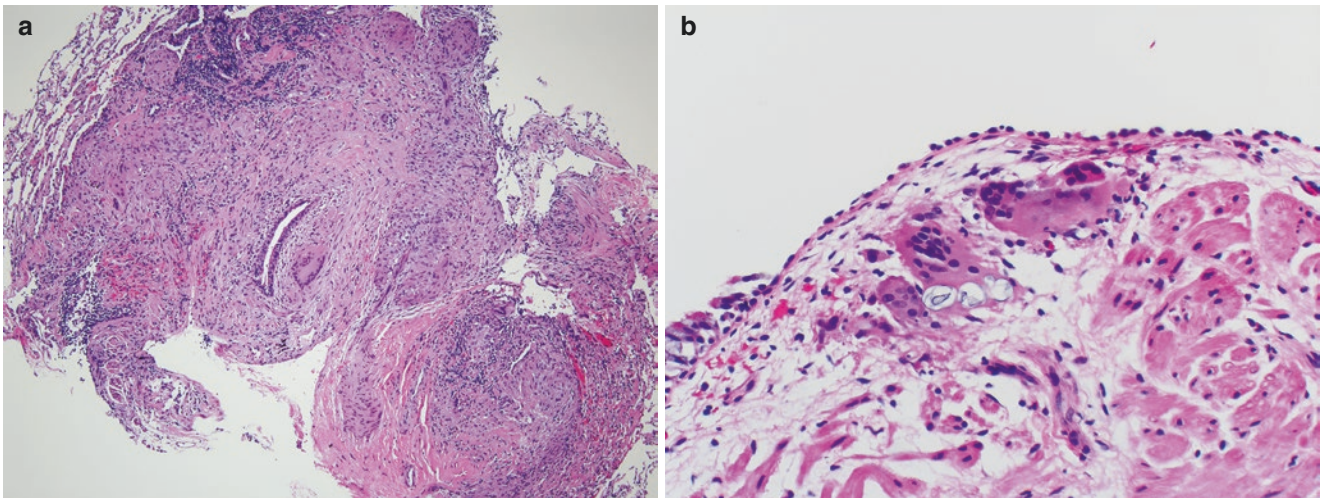

Fig. 7.21 Sarcoidosis in transbronchial and endobronchial biopsies. (**a**) Photomicrograph of transbronchial biopsy showing a classic combination of well-formed non-necrotizing granulomas with associated collagen fibrosis confined to the interstitium and involving a bronchovascular bundle. (**b**) High-magnification photomicrograph of endobronchial biopsy showing poorly formed granuloma containing a loose cluster of isolated multinucleated giant cells in a bronchial wall from a patient with sarcoidosis. In the appropriate clinical and radiologic setting, even poorly formed granulomas are supportive of sarcoidosis

Suggested Readings

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