Pulmonary granulomas: differential diagnosis, histologic features and algorithmic approach

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Abstract

Pulmonary granulomas are a common finding in routine diagnostic pathology. However, these lesions are often problematic because of the broad differential diagnosis, the time required for identifying organisms and the need for familiarity with subtle variations in morphology and distribution of granulomas. This review aims to discuss the differential diagnosis, to compare and contrast the histologic features of granulomatous lung diseases, and to provide a basic algorithmic approach to the histologic findings. Infectious causes of granulomas are most commonly diagnosed by identifying mycobacteria or fungi on histologic sections. While some non-infectious diseases can be diagnosed on the basis of specific histologic features, others require additional clinical, radiologic and/or microbiologic information for definitive diagnosis. Finally, we discuss our approach to granulomas of unknown aetiology.

Keywords fungi; granuloma; granulomatous; granulomatous with polyangiitis (Wegener's granulomatosis); infections; lung; mycobacteria; sarcoidosis

Granulomas are a common finding in routine diagnostic pathology in lung biopsies (bronchial, core or surgical) performed to evaluate nodules or interstitial lung disease. The differential diagnosis includes a daunting array of infectious and non-infectious conditions (Table 1). The purpose of this review is to provide guidance on the diagnostic approach to pulmonary granulomas supplemented by tables and an algorithm (Figure 1) which highlight key diagnostic findings. The presence or absence of necrosis is the starting point of the algorithm, with the understanding that necrotizing and non-necrotizing granulomatous inflammation coexist in some cases. We hope that this approach will complement existing reviews of the topic.[1–4]

Necrotizing granulomatous inflammation (Table 2)

Infections

Infections are the most common cause of necrotizing granulomas, fungi and mycobacteria being by far the most frequent etiologies.[3] However, it is important to exclude the possibility of an infectious aetiology even when non-necrotizing granulomas are encountered. Infectious granulomas can be single or multiple and are often associated with additional findings such as organizing pneumonia and chronic inflammation. The granulomas may destroy underlying lung architecture, or be centred on bronchioles, blood vessels, interstitium or airspaces. Hilar lymph nodes often contain granulomas. The necrosis of infectious granulomas is usually regular in contour, pink and paucicellular. However, exceptions abound; the appearance may vary from coagulative (infarct-like) to suppurative to eosinophil-rich, each variation potentially providing a clue to the causative organism. Vascular inflammation may be prominent and is usually comprised of lymphocytes. The presence of necrosis in the vessel wall, a neutrophilic infiltrate and/or nuclear debris indicate a true necrotizing vasculitis, and should suggest an alternative diagnosis such as granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis).

The search for microorganisms should begin on haematoxylin and eosin (H&E)-stained slides since several fungi (*Cryptococcus*, *Blastomyces*, *Coccidioides* and *Aspergillus*) are identifiable on this stain; H&E is superior to other stains for evaluating morphologic details of fungal organisms. Histochemical "special" stains such as Grocott Methenamine Silver (GMS) for fungi and Ziehl–Neelsen (ZN) for mycobacteria should be obtained in all cases in which organisms are not visible on H&E. Other stains such as periodic acid-Schiff (PAS) and mucicarmine may be used, although GMS is superior to these for fungal identification in most situations. An alternative to ZN is the auramine–rhodamine (AR) fluorescent stain. Although AR has been claimed to be more sensitive than acid-fast stains, this has not been our experience. In a study where we performed ZN, Fite and AR stains in 20 culture-proven mycobacterial infections, organisms were identified histologically in only four, no stain being superior to the others (unpublished data).

Pathologists should be aware of the common reasons for missing organisms on special stains. Since organisms are often present only within necrotic areas, it is important to ensure that necrotic tissue has not fallen off the ZN/GMS-stained slide in processing. Paucity of organisms is another common reason for false-negatives, especially in infections caused by *Histoplasma* and mycobacteria. This problem is occasionally compounded by weak staining. It is not unusual to find only a few organisms in the necrotic centre of a granuloma. Thus considerable length of time may be required to identify such organisms, particularly mycobacteria. Finally, if several blocks with necrotizing granulomas are available, staining more than one block may increase the yield.[5]

Overall, mycobacteria are the most common cause of pulmonary granulomas in lung biopsies worldwide, although with considerable geographic variation.[6] They include *Mycobacterium tuberculosis* and non-tubercular mycobacteria such as the *Mycobacterium avium* complex (MAC). The granulomas of tuberculosis are almost invariably necrotizing but are often admixed with non-necrotizing granulomas. The term "caseating", which is entrenched in the clinical literature, refers to the cheese-like macroscopic appearance of the necrosis and is not specific for tuberculosis. The appearance of tubercular granulomas is identical to those caused by non-tubercular mycobacteria,

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Differential diagnosis of granulomatous lung disease

Necrotizing	Non-necrotizing
Infections	Infections
• Mycobacteria[a]	• Mycobacteria
• Fungi[a] — *Histoplasma*, *Cryptococcus*, *Blastomyces*, *Coccidioides*, *Aspergillus*, *Pneumocystis*	• Fungi, especially *Cryptococcus*
• Parasites — *Dirofilaria*, *Paragonimus*	• Parasites
• Virus — *Varicella zoster*	Immunologic diseases
• Bacteria — *Brucella*, *Burkholderia*	• Chronic hypersensitivity pneumonitis[a]
Vasculitides	• Hot tub lung
• Granulomatosis with polyangiitis (Wegener's granulomatosis)	• Lymphoid interstitial pneumonia
• Allergic angiitis and granulomatosis (Churg—Strauss Syndrome)	Other
Other	Sarcoidosis[a]
Necrotizing sarcoid granulomatosis	Berylliosis
Rheumatoid nodule	Intravenous drug abuse (talc granulomatosis)
Bronchocentric granulomatosis	Particulate matter aspiration pneumonia
Unknown aetiology[a]	Crohn's disease
	Chronic granulomatous disease
	Common variable immunodeficiency
	Unknown aetiology[a]

[a] Common in routine diagnostic pathology.

Table 1

Histoplasma or *Coccidioides*. Diagnosis therefore requires identification of the causative organism, as described above. Once acid-fast bacteria are identified, there are no reliable histologic features that differentiate *M. tuberculosis* from non-tubercular mycobacteria. This distinction — which is understandably important for therapy — requires microbiologic cultures of unfixed tissue or application of the polymerase chain reaction (PCR) to formalin-fixed paraffin-embedded material. Although the latter may seem like an obvious solution to this problem, in practice PCR for mycobacteria is not available for clinical use on histologic material in most institutions.

Fungi are a major cause of necrotizing granulomas, although the incidence of fungal infection and the type of fungus identified varies considerably by geographic location.[6] While *Histoplasma* and *Coccidioides* are common in the United States, *Cryptococcus* and *Aspergillus* are found worldwide.

Histoplasmosis is endemic in the United States in a large swath of the country bordering the Ohio and Mississippi river valleys. The most common form of pulmonary histoplasmosis seen by pathologists is the so-called "histoplasmoma", which is a well-circumscribed necrotizing granuloma containing abundant pink necrosis that may be "infarct-like". Over time, hyalinization and calcification may supervene. In histoplasmomas, *Histoplasma* organisms are present exclusively within the central necrotic zone but cannot be seen on H&E; their detection requires GMS staining, where they appear as tiny (1—5 μm), round, oval or tapered yeasts that may show narrow-based budding (Figure 2a). Not uncommonly, the organisms are few in number, pale staining and difficult to identify.

Cryptococcus is ubiquitous. It usually causes non-necrotizing granulomatous inflammation rich in multinucleated giant cells, but necrotizing granulomas can also occur. Within granulomas and giant cells, cryptococci are visible on H&E as pale, grey-blue, round yeasts that are usually small but have a wide size range (2—15 μm). On H&E, the yeasts are often surrounded by a clear space/halo (retraction artefact), which imparts a "bubbly" appearance to the granulomas. Mucicarmine may stain the capsule red, a feature that distinguishes *Cryptococcus* from other fungi (Figure 2b). In practice, however, cryptococci are sometimes mucicarmine-negative, presumably because they are capsule-deficient.

Blastomycosis is an uncommon infection that occurs mainly in Mississippi river basin and the Great Lakes region of the Ohio river basin in the United States. A characteristic feature is the presence of suppurative (abscess-like) granulomas containing large numbers of viable and necrotic neutrophils. Within the necrosis, the surrounding granulomatous rim and multinucleated giant cells, large (8—15 μm), uniform, round yeasts with a thick refractile capsule, central nuclear material and occasional broad-based budding are readily visible on H&E (Figure 2c). GMS highlights the thick capsule.

Coccidioidomycosis is endemic in the Southwestern United States. It causes necrotizing granulomas that are often (but not always) rich in eosinophils. The organisms are large spherules (30—60 μm) filled with tiny round endospores (2—5 μm), both of which are visible on H&E (Figure 2d). The spherules are often empty, having ruptured and discharged their endospores. *Coccidioides* can be difficult to distinguish from *Blastomyces* because of overlap in size and morphology. The most helpful differentiating feature is broad-based budding, which is absent in *Coccidioides*.

Pneumocystis pneumonia usually manifests as an intra-alveolar frothy exudate; granulomatous inflammation is rare. When granulomas occur, they may be necrotizing or non-necrotizing, and are often accompanied at least focally by the pathognomonic frothy material. On GMS, *Pneumocystis* organisms are seen as cup-shaped or helmet-shaped cysts, occasionally containing intracystic bodies (sporozoites). The cysts (4—6 μm) are similar in size to *Histoplasma*; features favouring the latter include budding, and the absence of cup-shaped forms, crescent-shaped forms and intracystic dots.[7]

Pulmonary aspergillosis can be invasive, semi-invasive, saprophytic or allergic. Necrotizing granulomatous inflammation occurs in semi-invasive aspergillosis, which occurs in both immunocompromised and immunocompetent patients. Some present with a chronic, tuberculosis-like condition termed chronic necrotizing aspergillosis.[8] The appearance of *Aspergillus*-containing granulomas is not distinctive. Granulomatous inflammation may also be a feature of allergic bronchopulmonary aspergillosis (see bronchocentric granulomatosis below), a form of *Aspergillus* seen in atopic hosts.[9] Clues to the diagnosis allergic bronchopulmonary aspergillosis are a history of asthma,

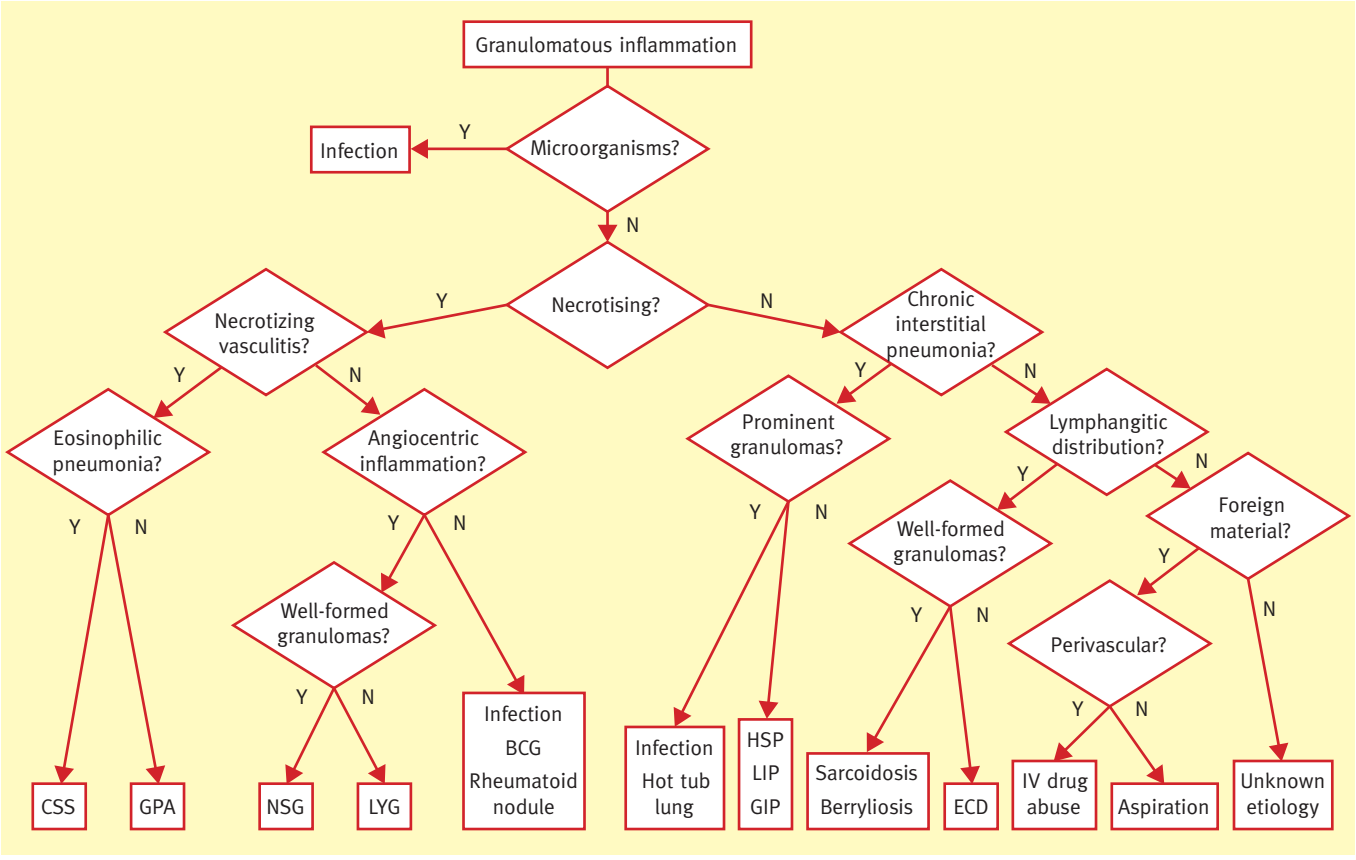

Figure 1 Algorithm illustrating histologic approach to the diagnosis of granulomatous lung diseases. CSS: Churg Strauss Syndrome; GPA: Granulomatosis with Polyangiitis; NSG: Necrotizing Sarcoid Granulomatosis; LYG: Lymphomatoid Granulomatosis; BCG: Bronchocentric Granulomatosis; HSP: Hypersensitivity Pneumonia; LIP: Lymphocytic Interstitial Pneumonia; GIP: Giant cell Interstitial Pneumonia; ECD: Erdheim-Chester Disease.

striking tissue eosinophilia and "allergic mucin" within airways. Organisms may be sparse and fragmented but septate hyphae with narrow-angle branching remain recognizable on H&E and GMS.

Vasculitis

The most common vasculitis associated with granulomatous inflammation is granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), a condition associated with anti-neutrophil cytoplasmic antibodies (ANCA). Less common ANCA-associated vasculitides include allergic angiitis and granulomatosis (Churg–Strauss syndrome, CSS) and microscopic polyangiitis. Although GPA is classically described as involving the head and neck, lungs and kidneys, this characteristic triad is seldom present in cases that come to biopsy. The most frequent scenario leading to a lung biopsy is the presence of solitary or multiple lung nodules or cavitary infiltrates in patients without evidence of multi-system involvement (localized/limited GPA).[10] A positive proteinase-3 (c-ANCA) or myeloperoxidase (p-ANCA) can be helpful since these autoantibodies are fairly specific for GPA and CSS, respectively. However, ANCA is negative in as many as 40% of cases of localized GPA; hence, a negative ANCA does not exclude the diagnosis, and pathologists must be prepared to recognize the characteristic histologic features regardless of the serologic findings. GPA is characterized by a combination of necrotizing granulomas and necrotizing vasculitis. The necrosis is classically basophilic, "dirty" (rich in nuclear debris derived from necrotic neutrophils), "geographic" (irregular in contour, like a country on a map) and surrounded by palisading histiocytes. However, "dirty" necrosis can also occur in infectious granulomas (Figure 3). Multinucleated giant cells containing dark-staining nuclei may be prominent at low magnification. Small suppurative microabscess-like granulomas are often scattered within in a background of fibrosis and intense acute and chronic inflammation. The most vital finding to differentiate GPA from other necrotizing granulomatous disorders is necrotizing vasculitis (Figure 4). Care should be taken to avoid misinterpreting necrotic vessels within areas of parenchymal necrosis as necrotizing vasculitis. True necrotizing vasculitis is characterized by focal fibrinoid necrosis of the vessel wall and/or destruction of the wall by a neutrophilic inflammatory infiltrate accompanied by karyorrhectic debris. The infiltrate often preferentially affects one side of the involved vessel ("eccentric vasculitis").

In contrast to GPA, CSS is characterized by eosinophilic pneumonia in addition to necrotizing granulomatous inflammation and necrotizing vasculitis. However, this combination is seen only in approximately 10–15% of lung biopsies.[11] Eosinophilic pneumonia (numerous eosinophils within airspaces admixed with macrophages) is the most common (and often the only) finding in CSS. When present, granulomas are typically necrotizing and are characterized by palisading histiocytes surrounding necrotic eosinophils (Figure 5). Eosinophils are also prominent in the affected vessels.

Histologic features of necrotizing granulomatous lung disease

	Infection	GPA	CSS	NSG	Rheumatoid nodule	BCG	Unknown aetiology
Granulomas							
a. NNG also present	+++	−	+	++	−	−	++
b. Giant cells	+	++	+	++	−/+	+	+
c. Lymphangitic	−	−	−	++	−	−	−
d. Bronchiolocentric	+/−	+/−	−	++	−	+++	+
e. Subpleural	+/−	+	−	+++	+++	−	−
f. Granulomas in vessels	−	++	++	++	−	−	−
g. "Dirty" necrosis	+	+++	−	+	++	+	+
h. Pink necrosis	++	−	++	++	+	+	++
i. Infarct-like necrosis	+	−	−	++	−	−	+
j. Contour of necrosis	Variable	Irregular	Regular	Irregular	Variable	Regular	Variable
k. Eosinophils	+	+	+++	−	−	+++	+
Hilar lymph node granulomas	+++	−	−	+++	−	−	+
Necrotizing vasculitis	No	Yes	Yes	No	No	No	No
Additional findings							
a. Organizing pneumonia	+++	++	+	−	−	+	++
b. Eosinophilic pneumonia	−	+	+++	−	−	++	−
c. MIB	−	−	−	−	−	+	−
Identifiable organisms	++	−	−	−	−	++	−
Positive cultures/fungal serologies	+++	−	−	−	−	+	−
Positive ANCA	+	++	+	−	−	−	−
Specific ANCA by ELISA (MPO or PR3)	None	PR3>MPO	Usually MPO	−	−	−	−

ANCA: anti-nuclear cytoplasmic antibody; BCG: bronchocentric granulomatosis; CSS: Churg–Strauss syndrome; GPA: granulomatosis with polyangiitis; MIB: mucoid impaction of bronchi; MPO: myeloperoxidase; NNG: non-necrotizing granulomas; NSG: necrotizing sarcoid granulomatosis; PR3: proteinase-3.

Table 2

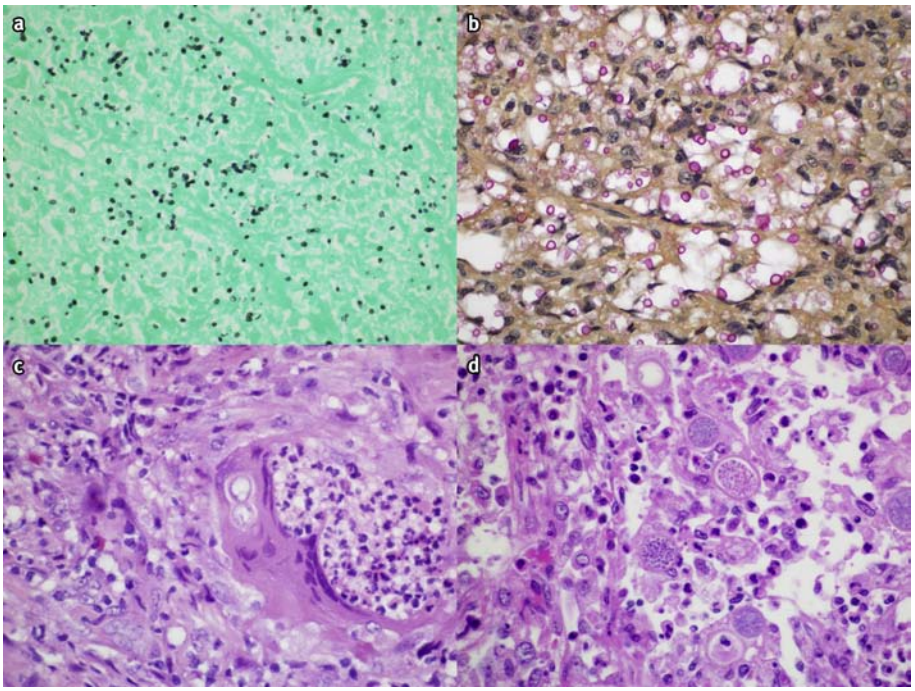

Figure 2 Morphologic features of common fungal causes of granulomatous inflammation in the lung (all photomicrographs at 600×). (**a**) *Histoplasma*. GMS stain showing small, uniform yeasts with occasional narrow-based budding. (**b**) *Cryptococcus*. Mucicarmine stains the capsule pink. Note the clear space/halo (retraction artefact) surrounding each organism. (**c**) *Blastomyces*. A large yeast showing characteristic broad-based budding is readily visible on H&E within a multinucleated giant cell. Note thick capsule and central nuclear material. (**d**) *Coccidioides*. Numerous spherules containing endospores are visible on H&E.

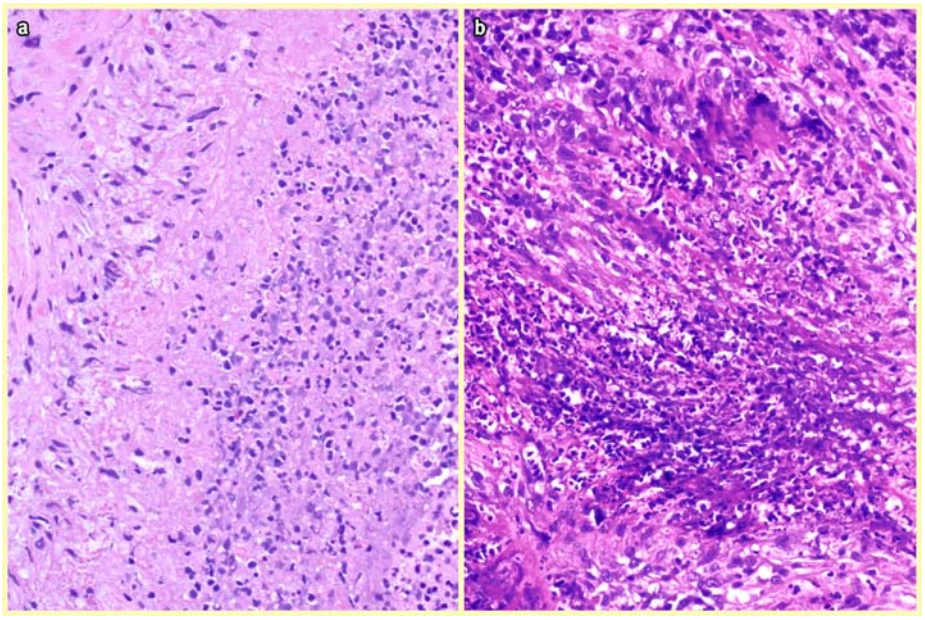

Figure 3 "Dirty" necrosis in mycobacterial granuloma (**a**) and granulomatosis with polyangiitis (Wegener's granulomatosis) (**b**).

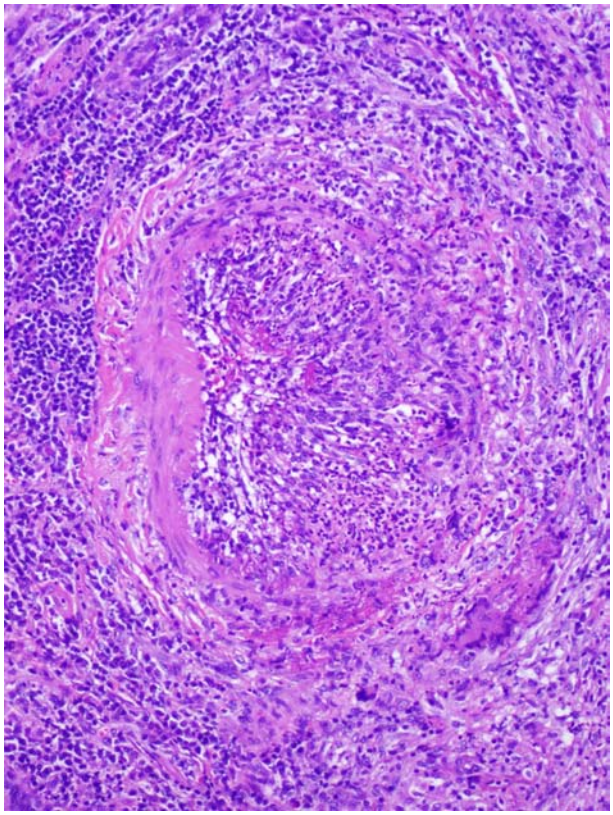

Figure 4 Necrotizing vasculitis in granulomatosis with polyangiitis (Wegener's granulomatosis). The right side of this blood vessel is infiltrated, expanded and destroyed by an inflammatory infiltrate composed predominantly of neutrophils. Note the relatively intact media at left. The combination of this type of vasculitis with necrotizing granulomatous inflammation supports the diagnosis of GPA, even if ANCA is negative.

Necrotizing sarcoid granulomatosis (NSG)

NSG is a rare variant of sarcoidosis characterized by extensive parenchymal necrosis in a background of non-necrotizing granulomas typical of sarcoidosis (see sarcoidosis below). The amount of necrosis exceeds the minimal, focal necrosis that may be seen in classic sarcoidosis, and vascular involvement (by granulomas) is more prominent.

Rheumatoid nodule

Rheumatoid nodules involving the lung are uncommon. They usually occur in patients with well-established rheumatoid arthritis and multiple lung nodules. Histologically, they are indistinguishable from necrotizing granulomas due to other causes. The necrosis may have irregular contours and a basophilic hue, along with vascular inflammation, mimicking GPA

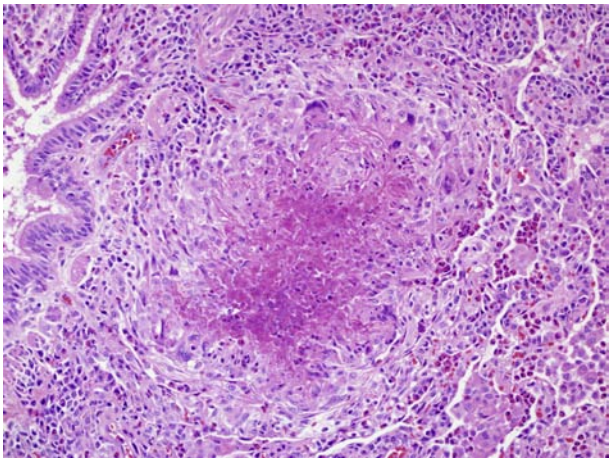

Figure 5 Churg—Strauss syndrome. The centre of this necrotizing granuloma is composed mainly of necrotic eosinophils. Note eosinophilic pneumonia to the right of the granuloma, characterized by the presence of numerous eosinophils and histiocytes within airspaces.

Histologic features of non-necrotizing granulomatous lung disease

	Sarcoidosis	Chronic HSP	Hot tub lung	LIP	Berylliosis	Aspiration	Infection
Cellular CIP	–	++	++	++	+/–	–	–
Chronic bronchiolitis	–	++	++	+	+/–	+	+
Granulomas							
a. Usual morphology	Well formed	Poorly formed	Well formed	Poorly formed	Variable	Well formed	Well formed
b. Giant cells	+	+	+/–	+	+/–	++	+
c. Lymphangitic	++	–	–	–	+/–	–	–
d. Bronchiolocentric	+	++	++	+/–	+/–	++	+/–
e. Inclusions	++	+	+/–	+/–	+/–	+/–	+/–
f. Foreign material	–	–	–	–	–	++	–
Organizing pneumonia	–	+	++	–	–	++	++/–
Positive cultures	–	–	+/–	–	–	–	+/–

CIP: chronic interstitial pneumonia (prominent lymphocytic infiltrate expanding alveolar septa); HSP: Hypersensitivity pneumonitis; LIP: Lymphoid interstitial pneumonia.

Table 3

(Wegener's granulomatosis). However, a true necrotizing vasculitis is absent.

Bronchocentric granulomatosis

Bronchocentric granulomatosis is defined as granulomatous inflammation centred exclusively on bronchi and bronchioles. It is most commonly a histologic manifestation of allergic bronchopulmonary aspergillosis (ABPA).[10] In early lesions, bronchioles are partially replaced by granulomatous inflammation and their lumens filled with necrotic debris. As the lesions progress, the entire bronchiolar wall is destroyed by granulomatous inflammation and replaced by a necrotizing granuloma containing numerous viable and necrotic eosinophils. Within the necrosis, fragments of degenerating fungal hyphae may be identified on GMS. The other major histologic manifestations of ABPA are eosinophilic pneumonia and mucoid impaction of bronchi with allergic mucin.

Necrotizing granulomatous inflammation of undetermined aetiology

Worldwide, pulmonary granulomas are histologically unexplained in 8–41% of cases.[6] Even in surgically resected necrotizing granulomas, which provide the best setting for identifying an organism or histologic features of non-infectious diseases, a definite aetiology cannot be established in 25% of cases.[5] In such cases, waiting for results of microbiologic cultures may be productive, as mycobacteria may grow in cultures even when they are undetectable in histologic sections. In histoplasmosis-endemic areas, reviewing the original GMS-stained slides can detect missed fungal yeasts, and staining additional blocks may reveal fungi in a few cases. Occasional cases can be shown to be GPA by a combination of review of the original histology for necrotizing vasculitis, ANCA testing, and clinical follow-up for subsequent development of overt vasculitis. A history of rheumatoid arthritis and multiple lung nodules helps to establish a diagnosis of rheumatoid nodule. Sarcoidosis may occasionally be diagnosed by review of the original histology if well formed, predominantly non-necrotizing granulomas are found in a lymphangitic distribution surrounded by concentric layers of hyalinized fibrosis in a compatible clinical setting. A small number of resected pulmonary necrotizing granulomas remain unexplained after rigorous re-examination of the original histology and incorporation of clinical and laboratory information as described above. Patients with such lesions appear to do well on long-term follow-up, even without medical therapy.

Non-necrotizing granulomatous inflammation (Table 3)

Sarcoidosis

Sarcoidosis is the prototype of non-necrotizing granulomatous lung disease and is the most common diagnosis when non-necrotizing granulomas are encountered in the lung.[6] It is characterized by well-formed interstitial granulomas composed of tightly clustered epithelioid histiocytes and multinucleated giant cells with few lymphocytes. Concentric layers of hyalinized fibrosis often surround and/or replace the granulomas. Vascular involvement ("granulomatous vasculitis") is common. A characteristic feature is the "lymphangitic" distribution of the granulomas, which refers to their arrangement along lymphatic pathways in the lung (bronchovascular bundles, interlobular septa and pleura) (Figure 6).[12] The granulomas do not involve airspaces, and lung parenchyma away from the granulomas appears normal. Organizing pneumonia is absent. The granulomas may be scattered individually but they often become confluent. Small foci of pink necrosis are not uncommon.[13] Non-specific cytoplasmic inclusions within giant cells should not be confused with exogenous material.[14] These include Schaumann bodies (lamellated calcified structures resembling psammoma bodies), asteroid bodies (pink spider-like inclusions) and birefringent crystals (calcium oxalate and carbonate). Transbronchial biopsy, the most frequent procedure performed to establish the diagnosis, yields granulomas in a majority of patients. Needless to say, a lymphangitic distribution cannot be appreciated on a transbronchial biopsy and histologic findings overlap considerably with other causes of non-necrotizing granulomas. Although Schaumann bodies are thought to be

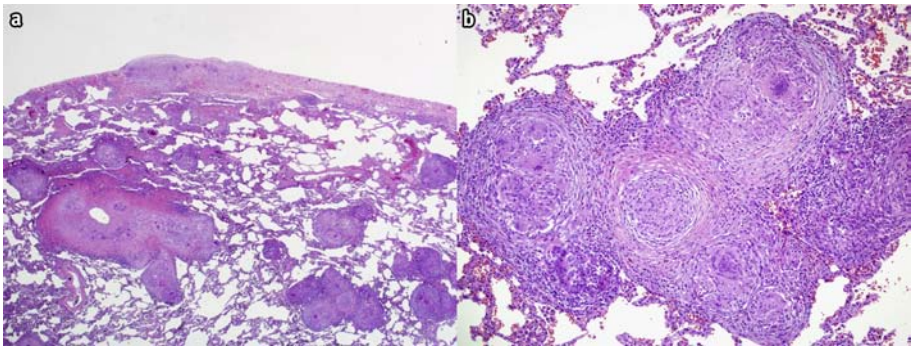

Figure 6 Sarcoidosis. (**a**) At low magnification, non-necrotizing granulomas are arranged in a "lymphangitic" distribution along the pleura, interlobular septa and bronchovascular bundles. Lung parenchyma away from the granulomas is normal. (**b**) The granulomas are prominent, well formed and exclusively interstitial. Note concentric fibrosis around the granuloma at centre.

more frequent in sarcoidosis than infectious granulomas,[13] they are not specific. Careful exclusion of infection by histology and cultures and an appropriate clinical and radiologic setting remain the most important features for establishing the diagnosis.

Immunologic diseases

Chronic hypersensitivity pneumonitis (HSP), also known as extrinsic allergic alveolitis, is caused by a type 4 hypersensitivity reaction to inhaled organic antigens such as thermophilic bacteria (farmer's lung) and bird feathers (bird fancier's disease). In contrast to sarcoidosis (Table 3), the main finding in HSP is a "cellular chronic interstitial pneumonia" (lymphocytic interstitial inflammatory infiltrate) with subtle accentuation around bronchioles ("chronic bronchiolitis"). Granulomas are small and inconspicuous. They consist either of poorly formed clusters of histiocytes or a few multinucleated giant cells scattered in the interstitial inflammatory infiltrate (Figure 7). The giant cells often contain intracytoplasmic inclusions similar to those seen in sarcoidosis. Airspace accumulation of foamy macrophages is frequent, and small foci of organizing pneumonia may also be present. A source of antigen exposure is found in some but not all patients, even when histologic findings are classic.[15]

"**Hot tub lung**" is currently thought to represent a hypersensitivity reaction to MAC organisms derived from aerosolized contaminated hot tub water. It is histologically similar to HSP except that the granulomas are larger (Figure 8), more conspicuous, and located *within* airspaces in addition to the interstitium.[16] Necrosis can occasionally be present but mycobacteria are rarely identified histologically. Cultures may or may not be positive. The diagnosis rests on the combination of the characteristic histologic findings and a history of hot tub exposure.

Lymphoid interstitial pneumonia (LIP) is an uncommon entity that can be histologically indistinguishable from chronic HSP. The interstitium is diffusely expanded by a lymphoplasmacytic inflammatory infiltrate. The peribronchiolar accentuation characteristically seen in HSP is absent. Poorly formed granulomas/isolated giant cells may be seen in bronchiolar walls. LIP is rarely diagnosed outside the clinical context of immunosupression (HIV) or connective tissue disease (especially Sjogren's syndrome).[17]

Pneumoconioses

Berylliosis (chronic beryllium disease) results from exposure to beryllium in mining, manufacturing of fluorescent light bulbs and the aerospace industry. The histological findings are often said to be identical to sarcoidosis, although a large series also described chronic interstitial inflammation with poorly formed granulomas.[18] The diagnosis is based on an exposure history and/or a beryllium lymphocyte proliferation test.

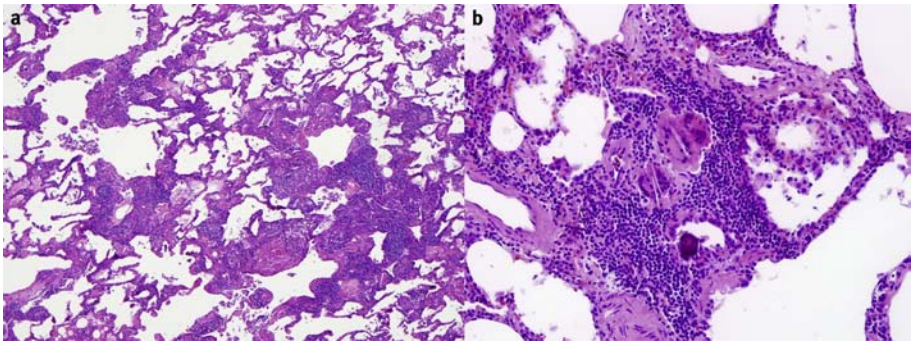

Figure 7 Chronic hypersensitivity pneumonitis. (**a**) At low magnification, the interstitium is thickened by chronic inflammation, which is accentuated around small bronchioles ("chronic bronchiolitis"). (**b**) High magnification, showing chronic inflammation within the wall of a small bronchiole and adjacent interstitium. A few multinucleated giant cells containing inclusions are present within the infiltrate. Note foamy macrophages in airspace to right of giant cells.

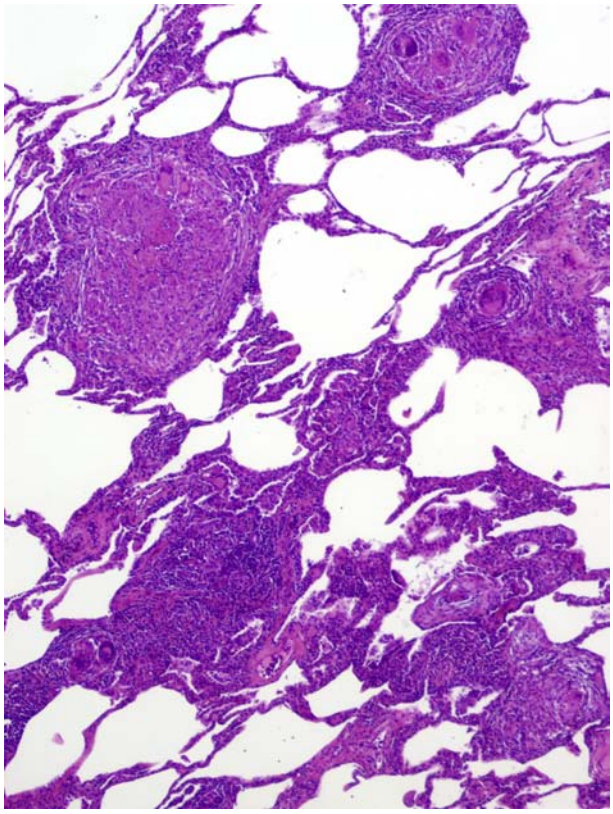

Figure 8 Hot tub lung, characterized by well formed granulomas (top), interstitial chronic inflammation (bottom left) and organizing pneumonia (bottom right). Note granuloma within airspace in centre of field. The large size of the granulomas argues against chronic hypersensitivity pneumonitis (see Figure 7) and the prominent interstitial chronic inflammation and organizing pneumonia argue against sarcoidosis (see Figure 6).

Intravenous drug abuse ("talc granulomatosis")

Intravenous injection of crushed oral pills can result in trapping of "filler" materials such as talc, microcrystalline cellulose and crospovidone in alveolar septal capillaries followed by extrusion of the material into the perivascular connective tissue followed by a granulomatous reaction confined to the interstitium (Figure 9a).[19] Since talc and microcrystalline cellulose are strongly birefringent, examination under polarized light facilitates the diagnosis. The granulomas can be fairly obvious, or tiny and subtle. They may be accompanied by vascular changes of pulmonary hypertension.

Aspiration pneumonia caused by aspiration of particulate material

Aspiration of particulate material derived from gastric contents (vegetable/food fragments or filler material from pills) results in bronchiolocentric granulomatous inflammation associated with acute or organizing pneumonia.[20,21] The granulomas are often of the foreign-body type with prominent multinucleated giant cells, but may be suppurative. The key to the diagnosis is recognition of foreign material within giant cells or granulomas. Vegetable particles may be intact and easy to recognize, but degenerated fragments are easily missed (Figure 9b).[20]

Infections

As mentioned above, infectious etiologies need to be ruled out in non-necrotizing granulomatous inflammation. Organisms can occasionally be demonstrated within non-necrotizing granulomas, especially mycobacteria and *Cryptococcus*.

Inflammatory bowel disease

Granulomas can occur in the lungs in inflammatory bowel disease, and if an infectious aetiology cannot be documented they

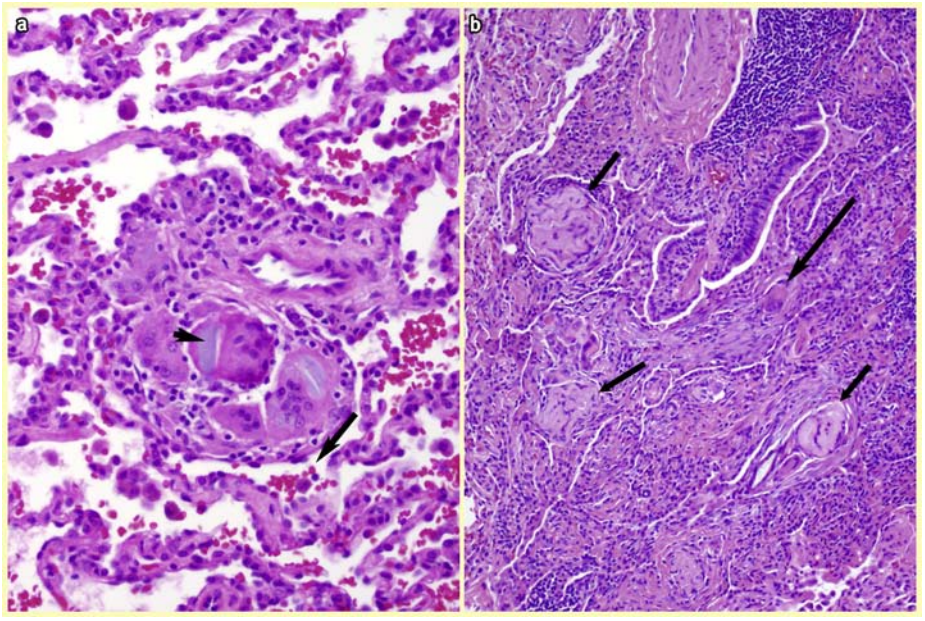

Figure 9 Granulomas containing foreign particles. (**a**) Intravenous drug abuse (talc granulomatosis). Numerous granulomas centred around perivascular foreign material expand the alveolar septa (interstitium). Arrowheads indicate foreign material and arrow indicates alveolar septal capillary. The material is derived from intravenously injected oral pills. (**b**) Aspiration pneumonia caused by aspiration of particulate material. Arrow points to a degenerated vegetable fragment surrounded by multinucleated giant cells. This type of foreign particle is often overlooked.

are assumed to be related to the underlying condition. Reported findings in Crohn's disease include chronic bronchiolitis with non-necrotizing granulomas, and non-specific interstitial pneumonia or organizing pneumonia with rare granulomas and/or giant cells.[22] The differential diagnosis includes infection (especially MAC-related airway disease), HSP and aspiration pneumonia.

Immunodeficiency syndromes

Chronic granulomatous disease (GCD) is a rare immunodeficiency syndrome caused by mutations in genes of the NADPH oxidase complex. Although most patients are diagnosed in infancy, milder disease may present in adulthood. Most pulmonary granulomas in this condition are necrotizing and/or suppurative and are related to fungal infection.[23] Non-necrotizing granulomas have also been reported. Although CGD is not a pathologic diagnosis, the identification of granulomatous inflammation in the absence of an identifiable infectious aetiology may prompt appropriate testing.

Common variable immunodeficiency (CVID) is an immunodeficiency syndrome characterized by hypogammaglobulinemia. As with CGD, infectious complications commonly involve the lung. However, peculiar patterns of non-infectious granulomatous lung disease have been reported and termed granulomatous-lymphocytic interstitial lung disease (GLILD). One report described various forms of lymphoid hyperplasia accompanied by loose clusters of epithelioid histiocytes and multinucleated giant cells.[24]

Potential mimic of granulomatous lung disease

Lymphomatoid granulomatosis

Lymphomatoid granulomatosis is a rare EBV-driven lymphoproliferative disorder characterized by nodular lymphohistiocytic infiltrates accompanied by necrosis and vascular infiltration. The combination of histiocytes and necrosis can closely mimic necrotizing granulomatous inflammation. However, the absence of well formed granulomas or multinucleated giant cells, and the presence of EBV-positive atypical lymphocytes differentiate lymphomatoid granulomatosis from true granulomatous processes. Special stains for organisms, particularly *Histoplasma*, must be examined carefully before diagnosing lymphomatoid granulomatosis since acute pulmonary histoplasmosis can mimic many of the histologic findings.[25] ◆

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Practice points

- Infectious etiologies are the most common cause of necrotizing granulomas.
- The search for microorganisms requires time, patience and good quality tissue sections containing the necrotic areas.
- The main differential diagnosis of infectious necrotizing granulomas is granulomatosis with polyangiitis (Wegener's granulomatosis). The key distinguishing feature is the presence of a true necrotizing vasculitis.
- A subset of necrotizing granulomas will not have an identifiable aetiology histologically or clinically.
- Sarcoidosis is the most common cause of non-necrotizing granulomas. Histologically, the granulomas show a lymphangitic distribution and are not associated with organizing pneumonia or inflammation.
- Other diseases with non-necrotizing granulomas are distinguished based on the presence of specific histologic features (cellular chronic interstitial pneumonia in chronic hypersensitivity pneumonia) and/or clinical features (history of hot tub use in hot tub lung).