Granulomatous Lung Disease
An Approach to the Differential Diagnosis
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Context.—Granulomas are among the most commonly encountered abnormalities in pulmonary pathology and often pose a diagnostic challenge. Although most pathologists are aware of the need to exclude an infection in this setting, there is less familiarity with the specific histologic features that aid in the differential diagnosis.

Objective.—To review the differential diagnosis, suggest a practical diagnostic approach, and emphasize major diagnostically useful histologic features. This review is aimed at surgical pathologists who encounter granulomas in lung specimens.

Data Sources.—Pertinent recent and classic peer-reviewed literature retrieved from PubMed (US National Library of Medicine) and primary material from the institutions of both authors.

Conclusions.—Most granulomas in the lung are caused by mycobacterial or fungal infection. The diagnosis requires familiarity with the tissue reaction as well as with the morphologic features of the organisms, including appropriate interpretation of special stains. The major noninfectious causes of granulomatous lung disease are sarcoidosis, Wegener granulomatosis, hypersensitivity pneumonitis, hot tub lung, aspiration pneumonia, and talc granulomatosis.

DEFINITION AND TERMINOLOGY
A granuloma is a compact aggregate of histiocytes (macrophages). The histiocytes in granulomas are often described as “epithelioid.” Epithelioid histiocytes have indistinct cell borders and elongated, sole-shaped nuclei, as opposed to the well-defined cell borders and round, oval, or kidney bean–shaped nuclei of ordinary histiocytes. Aggregation of histiocytes is the minimum requirement of a granuloma, regardless of whether the lesion also contains necrosis, lymphocytes, plasma cells, or multinucleated giant cells.

APPROACH TO THE DIFFERENTIAL DIAGNOSIS OF GRANULOMATOUS LUNG DISEASE
The differential diagnosis of granulomatous lung disease is listed in Table 1. The following is our recommended step-by-step approach to pulmonary granulomas.

Step 1: Attempt to identify an organism.
Step 2: Look for histologic features of noninfectious granulomatous diseases (Table 2).
Step 3: If steps 1 and 2 do not yield a specific diagnosis, ensure that an adequate number of blocks have been stained with special stains and reexamine the special stains. If no organisms are found despite a thorough reexamination, issue a descriptive diagnosis including the type of granulomas (necrotizing, nonnecrotizing, or both) and the absence of identifiable organisms. Suggest a differential diagnosis in a comment.

Step 1: Identifying Organisms
Since infection is the most common cause of pulmonary granulomas, it is always important to carefully exclude an.
Histoplasma in the United States, the prevalence of these fungi varies by geographic region. In the central and eastern states, Histoplasma is primarily seen in the Southwest, Cryptococcus is ubiquitous, and Blastomyces is endemic in the United States.

### Table 1. Differential Diagnosis of Granulomatous Lung Disease

<table>
<thead>
<tr>
<th>Infections</th>
<th>Fungi</th>
<th>Parasites</th>
<th>Noninfectious Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacteria</td>
<td>Histoplasma</td>
<td>Dirofilaria</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Mycobacterium tuberculosism</td>
<td>Cryptococcus</td>
<td></td>
<td>Chronic beryllium disease</td>
</tr>
<tr>
<td>Nontuberculous mycobacteria</td>
<td>Coccidioides</td>
<td></td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Fungi</td>
<td>Blastomyces</td>
<td></td>
<td>Hot tub lung</td>
</tr>
<tr>
<td></td>
<td>Pneumocystis</td>
<td></td>
<td>Lymphoid interstitial pneumonia</td>
</tr>
<tr>
<td></td>
<td>Aspergillus</td>
<td></td>
<td>Wegener granulomatosis</td>
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</tbody>
</table>

### Table 2. Key Diagnostic Features of Major Noninfectious Granulomatous Lung Diseases

<table>
<thead>
<tr>
<th>Key Features</th>
<th>Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Prominent, well-formed, discrete, nonnecrotizing granulomas in pleura, interlobular septa, and walls of bronchioles*</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Normal lung away from granulomas</td>
<td></td>
</tr>
<tr>
<td>Prominent interstitial chronic inflammation</td>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Scattered, small, poorly formed granulomas or multinucleated giant cells in interstitium</td>
<td>Hot tub lung</td>
</tr>
<tr>
<td>Granulomas within bronchiolar lumens</td>
<td></td>
</tr>
<tr>
<td>History of hot tub use*</td>
<td></td>
</tr>
<tr>
<td>Suppurative granulomas with “dirty” necrosis</td>
<td>Wegener granulomatosis</td>
</tr>
<tr>
<td>Necrotizing vasculitis</td>
<td></td>
</tr>
<tr>
<td>Necrotizing granulomas</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>Necrotizing vasculitis</td>
<td></td>
</tr>
<tr>
<td>Prominent eosinophils</td>
<td></td>
</tr>
<tr>
<td>Vegetable material surrounded by foreign body–type granulomas or multinucleated giant cells</td>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Interstitial foreign body–type granulomas containing talc, microcrystalline cellulose, or crospovidone</td>
<td>Talc granulomatosis</td>
</tr>
<tr>
<td>Active, seropositive rheumatoid arthritis*</td>
<td>Rheumatoid nodule</td>
</tr>
<tr>
<td>Multiple, bilateral lung nodules</td>
<td></td>
</tr>
<tr>
<td>Subpleural necrotizing granuloma</td>
<td></td>
</tr>
</tbody>
</table>

*Features not consistent with sarcoidosis include extensive necrosis or suppuration, interstitial inflammation away from the granulomas, organizing pneumonia, granulomas within alveolar or bronchiolar airspaces, numerous eosinophils, and vegetable material.

a Clinical information essential for diagnosis.

Infrequent. Aspergillus rarely causes granulomatous lung disease. Other fungi (Chrysosporium and Sporothrix) and bacteria (Brucella and Burkholderia) may also rarely cause granulomatous lung disease.

### Using the Tissue Reaction as a Clue.

Organisms must be sought in both necrotizing and nonnecrotizing granulomas since they may be found in either type. However, the search must be especially thorough in necrotizing granulomas since these are more likely to yield an organism. Other features of the tissue reaction often provide a clue to the type of organism present. For example, the presence of neutrophils in granulomas should prompt a search for Blastomyces, while the association of eosinophils with granulomas often indicates the presence of Coccidioides. "Infarctlike" necrosis may be seen in granulomas caused by Histoplasma or M tuberculosis, while a bubbly appearance of the cytoplasm of histiocytes and multinucleated giant cells is a clue to the presence of Cryptococcus. Despite these helpful associations, there is enough histologic overlap in tissue reactions that no one feature is absolutely specific for a particular organism.

### Examining Special Stains for Organisms.

The search for organisms must always begin with hematoxylin-eosin (H&E)–stained sections. Many pathologists, incorrectly assuming that organisms will not be visible on H&E, skip this vital step and go directly to the special stains. Although this is true for mycobacteria, most fungi are readily identified on careful examination of an H&E stain. Examination of H&E–stained sections also enables the pathologist to discern subtle differences in morphology between organisms and place the organism in the context of the associated tissue reaction. The notable exception to this general rule is Histoplasma, which is virtually impossible to detect within necrotizing granulomas on H&E–stained sections.

The histochemical stains used most often for identification of organisms are GMS for fungi and ZN (often colloquially called “AFB” for acid-fast bacteria) for mycobacteria. Although some laboratories additionally perform a periodic acid–Schiff stain for fungi, the GMS...
Granulomas pose a particularly difficult problem because Histoplasma controls in every case. Results; thus, it is important to check standard tissue artifacts. It is also important to note that, on occasion, GMS stains in certain cases and should not be dismissed as an artifact. Mycobacterial organisms may occasionally be seen with shapes and budding forms associated with fungal yeasts. Dust particles are smaller in size and lack the characteristic particles pose a particular challenge because they may and dust particles in the background lung. Dust and pollen microorganisms, as it often stains mucin, elastic tissue, to remember that GMS is not a specific stain for ZN-stained sections, hunting with a objective. If results with the GMS stain are negative, the may be missed without a careful search with a 40 objective. Scanning at a relatively low magnification (×10 ocular, ×20 objective) suffices to pick out most organisms, although Histoplasma may be missed without a careful search with a 40 objective. If results with the GMS stain are negative, the pathologist should then spend more time examining the ZN-stained sections, hunting with a 40 objective for mycobacteria, which are often few and difficult to find. The morphologic features of the common fungal causes of lung granulomas are compared in Table 3. It is important to remember that GMS is not a specific stain for microorganisms, as it often stains mucin, elastic tissue, and dust particles in the background lung. Dust and pollen particles pose a particular challenge because they may mimic the appearance of fungal yeasts. However, these particles are smaller in size and lack the characteristic shapes and budding forms associated with fungal yeasts. Mycobacterial organisms may occasionally be seen with GMS stains in certain cases and should not be dismissed as an artifact. It is also important to note that, on occasion, a poorly performed GMS stain may yield falsely negative results; thus, it is important to check standard tissue controls in every case. Histoplasma yeasts in necrotizing granulomas pose a particularly difficult problem because they may stain very weakly with GMS and be overlooked. Fungi of any type may also be missed if they are few. Regarding the ZN stain, the most important point to remember is that, in most cases, mycobacteria are few and difficult to find, partly because of the use of xylene in routine processing. Therefore, cursory scanning at low magnification will miss most mycobacteria. We recommend spending at least a few minutes at high magnification (×10 ocular lens, ×40 objective) for mycobacteria in the necrotic area of each necrotizing granuloma, constantly adjusting the fine focus to ensure detection of organisms that appear only on certain planes. Other authors go further and use a high-power oil immersion objective. Organisms are by far more common in the center of the necrosis but may occasionally be found in the periphery of the necrosis or even within the cellular granulomatous rim. It is not uncommon to examine several large necrotizing granulomas and find only a few mycobacteria. When mycobacteria are identified, the next step, for the purpose of choosing appropriate antibiotic therapy, is to differentiate between tuberculous and nontuberculous mycobacteria. Unfortunately, the morphologic appearance of mycobacteria on histologic sections is not reliable for speciation. The published literature on speciation of mycobacteria by using microscopic morphologic features of the organisms is based mostly on smears made from microbiologic cultures rather than formalin-fixed, paraffin-embedded histologic material. Histologic studies that claim distinctive morphologic features for particular mycobacterial species have included only nontuberculous mycobacteria, and no data exist to show the accuracy of mycobacterial subtyping by pathologists blinded to culture results. Even in smears made from microbiologic culture material, morphologic features such as cording, beading, or size, although associated with certain species, do not allow accurate or definitive speciation of mycobacteria. Currently, the only definitive methods of mycobacterial speciation are microbiologic culture and molecular methods such as the polymerase chain reaction (PCR) (see below). In most cases, speciation is not a problem because culture test results are also positive. In fact, mycobacteria often grow in cultures even when special staining of histologic material shows negative results. When results with histologic special stains are positive but those of cultures are negative, or when biopsied tissue was not submitted for culture, PCR is the only means of determining the species of the organism. Finally, if PCR yields a negative result or is unavailable, the clinician may elect to initiate empiric therapy.

**Role of PCR and Other Molecular Methods for Detection and Speciation of Mycobacteria.**—Pathologists and clinicians are sometimes faced with the difficult situation whereby mycobacteria are identified by histologic methods but speciation is not possible because no specimen was submitted for culture or culture results are negative. In an attempt to find a solution to this problem, the role of PCR and other molecular methods in the detection and speciation of mycobacteria in formalin-fixed, paraffin-embedded tissue has come under intense

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**Table 3. Morphologic Features of the Common Fungi Causing Granulomatous Lung Disease**

<table>
<thead>
<tr>
<th></th>
<th>Histoplasma</th>
<th>Cryptococcus</th>
<th>Coccidioides</th>
<th>Blastomyces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visualized on hematoxylin-eosin</td>
<td>No (in necrotizing granulomas)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes (in disseminated histoplasmosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spherules and endospores</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Usual size*</td>
<td>Small</td>
<td>Small</td>
<td>3 μm</td>
<td>Large</td>
</tr>
<tr>
<td></td>
<td>4–7 μm</td>
<td>30–60 μm (spherules)</td>
<td>2–5 μm (endospores)</td>
<td>8–15 μm</td>
</tr>
<tr>
<td>Shape</td>
<td>Mostly oval, often tapered at one or both ends</td>
<td>Round</td>
<td>Round or fragmented (spherules)</td>
<td>Round</td>
</tr>
<tr>
<td>Size variation</td>
<td>Minimal</td>
<td>Marked</td>
<td>Considerable</td>
<td>Marked</td>
</tr>
<tr>
<td>Budding</td>
<td>Narrow based</td>
<td>Occasional</td>
<td>Broad based</td>
<td>Occasional</td>
</tr>
<tr>
<td>Nuclei</td>
<td>Single (when intracellular)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Staining with mucicarmine</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

* Sizes listed are the usual sizes encountered. Greater size variation has been reported with most of the fungi listed but is unusual.
in general, these studies show that PCR is as sensitive as microbiologic cultures for the detection of mycobacteria in formalin-fixed tissues and is more sensitive than ZN staining. It is also possible to determine the species of organisms by this method. Currently, however, PCR for detection and speciation of mycobacteria in formalin-fixed, paraffin-embedded sections is not in routine diagnostic use in most laboratories and remains restricted to a few reference centers.

**How to Report the Presence of Organisms.**—The subtyping of infectious mycobacterial or fungal disease (acute histoplasmosis versus histoplasmosa, progressive primary tuberculosis versus secondary tuberculosis, etc.) often requires clinical and radiographic information that is usually unavailable to the pathologist. Therefore, for the purposes of the pathology report, describing the tissue reaction and stating the organism present is sufficient in most instances. A pathologic diagnosis for a case in which Histoplasma yeasts are identified within a necrotizing granuloma would be described as “necrotizing granuloma (Histoplasma identified).” If more clinical information is available, a more specific diagnosis may be rendered. For example, if Histoplasma yeasts are identified in a necrotizing granuloma and the pathologist is provided with the information that the lesion is an incidentally detected solitary lung nodule, a diagnosis of histoplasmosa can be rendered.

**Step 2: Identifying Histologic Features of Noninfectious Granulomatous Lung Diseases**

The key diagnostic features of the common noninfectious granulomatous lung diseases are listed in Table 2. These are the major features that are required for a pathologic diagnosis. In the absence of these features, a definitive pathologic diagnosis is usually not possible and a descriptive diagnosis must suffice. Note that some diagnoses require clinical input, while others can be rendered (or suggested) solely on the basis of their histologic features. We recommend using Table 2 to quickly narrow the differential diagnosis. Details of the pathologic findings and the differential diagnosis can then be obtained from the text (see below).

**Step 3: Review of Special Stains and Descriptive Diagnoses**

**What to Do When Organisms Are Not Found in a Granuloma.**—Often, organisms are not found within granulomas despite a meticulous search. Even in necrotizing granulomas, this is a fairly frequent scenario. In such cases, the most productive next step for the pathologist is to reevaluate the special stains: reexamination of the GMS-stained sections, in particular, results in the detection of several cases of initially overlooked Histoplasma infection (S.M., unpublished data, March 2009). If the necrotic portion of the granuloma is not represented on the slide with the special stains, it may be productive to recut the block and repeat the stain. In a study by Goodwin and Snell, 10 of 17 histoplasmas were diagnosed only after an effort was made to include the necrotic center in a recut. If some blocks with necrosis are not initially stained with special stains, staining these may also be productive. Ulbright and Katzenstein suggested that examining 2 blocks with necrosis is adequate in most cases, with the caveat that examination of more sections is probably indicated when the histologic appearance is especially suggestive of infection or when a specific noninfectious diagnosis is being considered.

Despite these steps, a substantial proportion of necrotizing granulomas remain unexplained. Ulbright and Katzenstein suggested that such cases might represent infectious granulomas in which the organism has been killed or removed by the inflammatory reaction. In such cases, we recommend issuing a descriptive diagnosis including the presence/absence of necrosis and the absence of identifiable organisms. In the case of necrotizing granulomas, a comment such as “the etiology is most likely infectious despite negative special stains” may be appropriate. In some cases in which organisms cannot be found by histologic examination, results of cultures may be productive. From surgically excised granulomas, mycobacteria (mainly nontuberculous) often grow in culture despite negative ZN and auramine-rhodamine staining results on histologic material. Finally, clinicians may classify a small number of unexplained necrotizing granulomas as histoplasmosis or anti-neutrophil cytoplasmic antibody (ANCA)–related vasculitides on the basis of serologic studies.

**MYCOBACTERIA**

**Tuberculosis**

Worldwide, Mycobacterium tuberculosis outnumbers nontuberculous mycobacteria and fungi such as Histoplasma as the leading cause of granulomatous lung disease. Considering the prevalence of the disease, there are surprisingly few papers in the current literature on the histologic features of culture-proven pulmonary tuberculosis. The few histologic studies available are mainly from the years when the mere presence of necrotizing granulomas was considered diagnostic of tuberculosis. In fact, before 1953, all rounded granulomas of the lung were assumed to be tuberculomas. The granulomas of tuberculosis are typically necrotizing (Figure 1, A) but may be nonnecrotizing or a mix of both types. As discussed in step 3 above, acid-fast organisms (Figure 1, B) may be few and difficult to find. The granulomas of tuberculosis may be randomly located or bronchiolocentric, although it is important to remember that granulomas may involve bronchi and bronchioles in virtually any infection, as well as sarcoidosis and hypersensitivity pneumonitis. The granulomas of tuberculosis may also involve blood vessels, although less frequently than in sarcoidosis. The features may remotely resemble a true primary vasculitic disorder, such as Wegener granulomatosis. The histologic appearance of tuberculous granulomas may be indistinguishable from those of nontuberculous mycobacterial infection. This was most elegantly demonstrated in a 1963 study by Corpe and Stergus in which 27 pathologists with expertise in mycobacterial disease were blinded to culture results and asked whether histologic changes on 25 slides were due to M tuberculosis or Runyon group III nontuberculous mycobacteria. In most cases, the pathologists could not differentiate between the 2 infections, and when they felt they could, they were often mistaken. Fungi such as Histoplasma and Coccidioides may also produce a tissue response identical to tuberculosis. Because the histologic features of tuberculosis are not organism-specific, the diagnosis rests on detection (and subsequent speciation) of mycobacteria. Issues relating to identification and speciation of mycobacteria are discussed in detail in “Examining Special Stains for Organisms” (see 2nd page of this article).
Nontuberculous Mycobacteria

In the United States, NTM are increasingly being recognized as an important cause of lung disease. In the past, lung infection by NTM was thought to occur mainly in the setting of immunodeficiency or preexisting lung disease, such as chronic obstructive pulmonary disease or cystic fibrosis. It is now well known that NTM-related

Figure 1. Infectious necrotizing granulomas. A, Tuberculosis. Necrotizing granuloma. B, Same case as A. Single acid-fast bacterium (arrow). C, Nontuberculous mycobacterial infection. Mycobacterium intracellulare was isolated in cultures. Necrotizing granuloma with abundant necrosis, indistinguishable from tuberculosis. Epithelioid histiocytes are at bottom right. D, Same case as C. Mycobacteria (arrows) are identical in morphology to the single organism seen in B. E, Histoplasmosis. Necrotizing granuloma larger than, but otherwise identical to, the granulomas in A and C. F, Same case as E. Histoplasma yeasts (hematoxylin-eosin, original magnifications ×100 [A, C, and E]; Ziehl-Neelsen, original magnifications ×1600 [B and D]; Grocott methenamine silver, original magnification ×400 [F]).

Nontuberculous Mycobacteria

In the United States, NTM are increasingly being recognized as an important cause of lung disease. In the
lung disease also occurs in immunocompetent individuals without preexisting lung disease.\textsuperscript{39}

In immunocompromised patients, such as those with the acquired immunodeficiency syndrome (AIDS), NTM infection is characterized by collections of mycobacteri-laden foamy histiocytes, poorly formed granulomas, or the lack of any significant inflammatory response.\textsuperscript{40,41} Mycobacteria in this form of NTM disease are numerous and easy to find, and culture results are usually positive.

In immunocompetent patients, NTM infection has been associated with a wide variety of histologic findings, including granulomatous inflammation indistinguishable from tuberculosis (Figure 1, C and D, and “Tuberculosis” above).\textsuperscript{24,34,25,26} Like tuberculosis, both necrotizing and nonnecrotizing granulomas may be found\textsuperscript{25,26} and the granulomas may be peribronchiolar. Cases with nongranu-lomatous inflammation have also been described, but since NTM are frequent colonizers of the respiratory tract, it is debatable whether NTM infection in such cases is etiologic or merely coincidental.\textsuperscript{25,26} Nontuberculous mycobacteria infection may also be associated with airway disease, manifested histologically as bronchiectasis or chronic bronchiolitis.\textsuperscript{41,42} Nontuberculous mycobacteria have been isolated from cases of the middle lobe syndrome, suggesting a predilection for this location.\textsuperscript{43}

Definitive diagnosis of NTM disease rests on identification and speciation of mycobacteria (see “Examining Special Stains for Organisms” on the 2nd page of this article).

Finally, exposure to aerosolized NTM can cause a hypersensitivity pneumonitis-like illness known as “hot tub lung.” In keeping with current concepts of the pathogenesis of this condition, this entity will be discussed in the section on noninfectious granulomatous lung disease (below).

### FUNGI

The tissue reaction to the common pulmonary fungi discussed in this section varies greatly, depending on the size of the inoculum, the duration since exposure, and the immunologic status of the host. The sequence of events and the wide variety of inflammatory responses and outcomes are similar in many respects to mycobacterial infections. In most immunocompetent individuals, exposure to a small inoculum leads to asymptomatic self-limited infection. Heavier exposure may lead to an acute flulike or pneumonia-like illness (acute pulmonary histoplasmosis, acute blastomycosis, or acute coccidioidomy-cosis/valley fever).\textsuperscript{44,50} Such cases may be diagnosed clinically as influenza or community-acquired pneumo-nia. When the correct diagnosis is made, it is usually based on serologic rather than histologic findings.\textsuperscript{49,51} Since a biopsy is rarely performed in acute disease, the pathologic findings remain poorly described. Both asymptomatic infection and acute symptomatic disease clear completely in most cases.

In some individuals, healing is not accompanied by complete clearance of organisms. Instead, organisms persist in a walled-off nodule characterized by a well-formed, necrotizing granuloma similar to a tuberculosis (eg, histoplasmosma, cryptococcom, coccidioidom).\textsuperscript{12,14,43,46,49,52,55}

This is the most common form of granulomatous fungal disease encountered by surgical pathologists. These lesions are biopsied or resected because they form nodules, which are difficult to separate from malignant tumors on clinical and radiographic grounds.

In some patients, usually those with an underlying predisposing illness, infection progresses instead of being cleared or contained. This results in chronic symptomatic fungal lung disease (eg, chronic pulmonary histoplasmo-sis, chronic blastomycosis, persistent coccidioidal pneu-monia).\textsuperscript{45,54} The pathologic manifestaton of this form of fungal lung disease is complex and includes necrotizing granulomas in combination with evidence of the underlying predisposing illness (such as emphysema) or superimposed complications (such as cavities).

The final piece in the spectrum of fungal lung disease does not typically involve granulomatous inflammation but is mentioned here to give the reader a sense of the gamut of tissue responses to fungal organisms. This type of disease occurs in immunocompromised individuals, who often develop disseminated infection characterized by unchecked proliferation of organisms accompanied by little or no inflammatory response (eg, disseminated histoplasmosis, disseminated blastomycosis, disseminated cryptococcosis, disseminated coccidioidomycosis).\textsuperscript{55,56} Granulomas are absent, and if present, are poorly formed. This form of disease is often widespread, with a predilection for the lymphohematopoietic system, but it may also involve the lungs.

### Histoplasma

Lung involvement in \textit{Histoplasma} infection takes many forms, but the tissue reaction can be broadly divided into 3 main types. The first is an intra-alveolar lymphohistiocytic infiltrate with small granulomas and variable necrosis, seen in acute pulmonary histoplasmosis. The second is well-formed necrotizing granulomatous inflammation, exemplified by histoplasmosmas but also seen in chronic pulmonary histoplasmosis.\textsuperscript{12,14,43,54} The third type of tissue reaction consists of sheets of histiocytes within the interstitium, packed with numerous organisms, as seen in disseminated histoplasmosis.\textsuperscript{55} By far the most common form of \textit{Histoplasma}-related lung disease encountered by surgical pathologists is a histoplasmosma (Figures 1, E and F, and 2, A and B). The classic lesion is a large nodule with abundant central necrosis surrounded by a thin rim of epithelioid histiocytes and a fibrotic capsule of variable thickness (Figure 1, E). Small calcific particles may be present within the necrosis or the calcification may be more irregular. Overall, the histologic appearance is identical to a tuberculoma or coccidioidoma.\textsuperscript{13} Blood vessels in and around the granuloma may show a prominent nonnecrotizing vasculitis, as noted previously for mycobacterial disease.\textsuperscript{10,34} It is important to note that the “vasculitis” in histoplasmosis and other granuloma-tous infections is a secondary phenomenon related to the granulomatous inflammation, in contrast to a true primary vasculitis such as Wegener granulomatosis. In describing cases with such vascular changes, it is advisable for pathologists to avoid the term \textit{vasculitis} in their reports because clinicians may misconstrue this as a true primary vasculitis. The vascular changes in \textit{Histoplasma} infection often result in parenchymal necrosis with an infarctlike quality; that is, ghosts of alveoli can be discerned within the necrotic areas.\textsuperscript{14,34,54,57} As with other infections, smaller satellite, nonnecrotizing granulomas and areas of organizing pneumonia may be scattered in the lung parenchyma around the main necrotizing granuloma. With time, the necrotic center is progressively replaced by fibrosis and calcification.
Figure 2. Fungal granulomas. A, Necrotic center of a histoplasmosis. Organisms are not visible on a hematoxylin-eosin stain, even at high magnification. B, Same case as A. Uniform, mostly oval Histoplasma yeasts are clearly visible on a silver stain. Note that some organisms are tapered at one or both ends. C, Nonnecrotizing granulomas containing Cryptococcus. Round yeasts with blue-gray cell walls are visible within histiocytes. Note the characteristic “halo” around the organisms. D, Same case as C. Note the mostly round shape and marked variation in size. E, Granulomatous Pneumocystis pneumonia. Histiocytes palisade loosely around an intra-alveolar eosinophilic exudate. F, Same case as E. Small, round, yeastlike Pneumocystis cysts within an alveolar space. Crescentlike forms are characteristically seen (hematoxylin-eosin, original magnifications ×400 [A, C, and E]; Grocott methenamine silver, original magnifications ×1600 [B, D, and F]).
One key point to remember is that the visibility of *Histoplasma* on H&E-stained sections depends on the histologic context. While *Histoplasma* is readily identifiable within macrophages in disseminated histoplasmosis, it is not visible on H&E-stained sections within necrotizing granulomas (histoplasmonas).10–13 Although organisms are present within the necrotic areas, they cannot be resolved from the background necrotic debris on H&E-stained sections (Figure 2, A). Structures that at first glance appear to be *Histoplasma* yeasts are invariably small microcalcifications, which are common in old necrotizing granulomas of any etiology.10,11 They can be distinguished from fungal yeasts because they are usually GMS-negative, basophilic, and pleomorphic. Demonstration of *Histoplasma* in necrotizing granulomas is best accomplished by performing GMS staining. The presence of yeast forms that are not appreciated on H&E, but visible on GMS, is virtually pathognomonic of *Histoplasma*. With a GMS stain, *Histoplasma* yeasts are small, uniform, and oval (Figures 1, F, and 2, B). A characteristic feature is that some taper to a point at one end or sometimes both ends. They are scattered within the necrotic center of the granuloma and may be present in clusters or singly. Narrow-based budding, although often cited as a characteristic finding, is not always identifiable, especially when organisms are few. *Histoplasma* yeasts tend to be a mixture of lightly stained, hollow-appearing forms with thin, delicate outlines and more darkly stained solid forms, with the staining characteristics varying with the strength of the stain in an individual case.10,11 Rare hyphal forms have also been described.11,18 *Histoplasma* seldom grows in culture from histoplasmonas probably because the organisms are nonviable in most of these lesions.10,13,56 Therefore, histopathologic examination is often the only means of confirming the diagnosis.14

*Histoplasma* may be confused with *Cryptococcus*, which can be associated with an identical granulomatous response. Small, capsule-deficient forms of *Cryptococcus* pose a particular challenge. A helpful morphologic feature in the differential diagnosis is that *Histoplasma* cannot be seen (in necrotizing granulomas) on H&E-stained sections, whereas *Cryptococcus* yeasts can (Figure 2, A and C). Both organisms are highlighted by the GMS stain, whereby the organisms are highlighted by the GMS stain, whereby the main differentiating features are the uniform size, oval shape, and occasional tapered forms of *Histoplasma* as opposed to the nonuniform size, round shape, and lack of tapering of *Cryptococcus* (Figure 2, B and D). *Histoplasma* may also be confused with *Pneumocystis*, Fortunately, this is not a common problem because, in most cases, *Pneumocystis* pneumonia is characterized by an intra-alveolar frothy exudate, while *Histoplasma* infection is characterized by a necrotizing granuloma. However, in 5% to 17% of cases, *Pneumocystis* may elicit a granulomatous response16–62 (Figure 2, E). Such cases, termed granulomatous *Pneumocystis* pneumonia, can mimic acute pulmonary histoplasmosis, since both conditions feature granulomas. While the frothy intra-alveolar exudate of *Pneumocystis* differs from the fibrinous intra-alveolar exudate of acute pulmonary histoplasmosis, it is not always present. Morphologic appearance of the organisms with GMS is the key differentiating feature. Although *Histoplasma* and *Pneumocystis* are similar in size, *Pneumocystis* cysts are round rather than oval, are often crescent-shaped or sickle-shaped (Figure 2, F), and do not bud or taper. In difficult cases, results of microbiologic cultures or immunohistochemical stains may be helpful.

**Cryptococcus**

Cryptococcosis of the lung includes a wide spectrum of tissue reactions13–45 that depend on the immunologic status of the host. Immunocompetent patients tend to develop granulomas, whereas the reaction is more variable in immunocompromised patients. The typical granulomatous reaction to *Cryptococcus* is confluent nonnecrotizing granulomatous inflammation with numerous multinucleated giant cells and scattered chronic inflammation (Figures 2, C, and 3, A). Multinucleated giant cells may predominate over granulomas. At low magnification, the presence of engulfed *Cryptococcus* yeasts imparts a bubbly appearance to the cytoplasm of histiocytes and multinucleated giant cells. At high magnification, *Cryptococcus* yeasts can be identified by careful examination within multinucleated giant cells and granulomas (Figures 2, C, and 3, A). *Cryptococcus* can also be identified within necrotizing granulomas (cryptococcomas) similar to those seen with mycobacterial or other fungal infections. In this setting, too, organisms are identifiable, both within the necrotic areas and the surrounding granulomatous rim.10

Finally, in immunocompromised patients, innumerable *Cryptococcus* yeasts grow in sheets within alveolar spaces, alveolar septa (interstitium), and alveolar septal capillaries and bronchioles, with little or no inflammatory reaction.65–67 Not surprisingly, patients with AIDS occasionally have concurrent *Pneumocystis* infection.68 On H&E-stained sections, *Cryptococcus* yeasts are round with well-defined but pale-staining blue-gray walls (Figures 2, C, and 3, A). Because of the pale-staining walls, the organisms may easily be overlooked at low magnification.7 Characteristically, the organism retracts from the cytoplasm of the cell that engulfs it, resulting in the formation of a halo around the organism. Grocott methenamine silver stains the organisms well and, as with other fungi, often highlights far more organisms than initially appreciated (Figures 2, D, and 3, B). The capsule of *Cryptococcus* stains deep red with mucicarmine and this feature may be used to support the diagnosis.74 However, it is important to remember that absence of mucicarmine staining does not exclude *Cryptococcus* because the organism may lack a capsule (“capsule-deficient Cryptococcus”).66,68–70 In such cases, the Fontana-Masson stain is useful because it stains the cell wall of *Cryptococcus*, including that of capsule-deficient forms.15,70

The differential diagnosis includes *Histoplasma* and *Blastomyces*.70 For details of the features useful in the differential diagnosis, see Table 3 and the sections on *Histoplasma* and *Blastomyces*.

**Coccidioides**

The most common form of *Coccidioides* infection encountered by the surgical pathologist is the necrotizing granuloma (coccidioidoma).46,52 Eosinophils may be numerous,73 scant, or absent and neutrophils may be prominent. As with other infections, the granulomas may be peribronchiolar or may communicate with or destroy bronchioles. An accompanying nonnecrotizing vasculitis, as noted previously with other infections, may be present.10 Smaller satellite, nonnecrotizing granulomas are often seen in surgically resected specimens. The
Figure 3. Fungal granulomas. A, Cryptococcus. Numerous round yeasts within histiocytes, some surrounded by haloes. B, Same case as A. Note pleomorphism and compare size with D and F. C, Coccidioides in a patient with disseminated coccidioidomycosis. Both endospore-filled and empty spherules are present. Note similarity of endospores to Cryptococcus (A) and of endospore-filled spherules to Blastomyces (E). D, Same case as C. E, Blastomyces. Single, large, thick-walled, nucleated yeast (arrow) within multinucleated giant cell. Note characteristic neutrophilic response. F, Same case as E. Large yeast with single broad-based bud (hematoxylin-eosin, original magnifications ×400 [A, C, and E]; Grocott methenamine silver, original magnifications ×400 [B, D, and F]).
overall picture is indistinguishable from granulomas caused by mycobacteria or other fungi. Demonstration of organisms is therefore essential for diagnosis. 

Coccidioides organisms are most often found within the necrotic centers of necrotizing granulomas, although they show less of a propensity for the center than Histoplasma and may also be found within nonnecrotizing granulomas. The organisms consist of large, thick-walled, spherical structures ("spherules") filled with smaller yeastlike structures ("endospores") (Figure 3, C and D). Not uncommonly, spherules are found in a ruptured, fragmented, emptying or empty state. Endospores of various sizes may lie scattered in the necrotic debris, mimicking other fungal yeasts. Neither spherules nor endospores show budding. Although some authors have reported difficulty in detecting organisms on H&E-stained sections, they are usually easily found. As with other fungi, the GMS stain reveals more organisms than initially appreciated on H&E-stained sections. Grocott methenamine silver highlights the spherules as well as the endospores. A mycelial form of the fungus, consisting of septate hyphae with arthrospores, may also be encountered if there is communication with ambient temperature. As with Histoplasma, the organism may not grow in cultures (especially from coccidioidomycosis), in such cases, histologic examination may be the only means of establishing the diagnosis.

If spherules and endospores are both present (Figure 3, C and D), the diagnosis is straightforward. However, in many cases it may be difficult to find these characteristic fungal structures. In the absence of one or the other form, differentiation from Blastomyces can be difficult (see Table 3 and "Blastomyces" below). Size of the organism is a helpful feature because Coccidioides spherules are usually larger than Blastomyces yeasts. Broad-based budding is a feature of Blastomyces but not of Coccidioides. In difficult cases, correlation with the results of microbiologic cultures is prudent.

Blastomyces

Infection with Blastomyces is uncommon. It must be suspected when granulomas or multinucleated giant cells are accompanied by acute inflammation (Figure 3, E and F). Classic cases show granulomas with frankly suppurative centers, in contrast to the pink or slightly "dirty" necrosis seen in granulomas due to other organisms. As with other infections, the granulomas may be bronchiocentric. The large, thick-walled yeast forms of Blastomyces can be identified on H&E-stained sections, although they may be few and difficult to find. Broad-based budding is fairly characteristic but not always present. On H&E-stained sections, nuclear material (multiple nuclei) can often be identified within the yeasts; this can mimic the endospore-filled spherules of Coccidioides (compare Figure 3, C, and 3, E).

Blastomyces yeasts are larger than the yeasts of Histoplasma and Cryptococcus and the endospores of Coccidioides but smaller than Coccidioides spherules (Table 3); however, enough overlap and size variation exists to cause potential confusion between these organisms (Figure 3, A through F). Mucicarmine staining, while characteristic of Cryptococcus, can also be seen with Blastomyces, although it tends to be weaker in the latter and has been attributed by some authors to overstaining. Multinucleation and broad-based budding are features of Blastomyces that are absent in Cryptococcus. Blastomyces differs from Histoplasma in that it is visible on H&E-stained sections, has a thick wall, broad-based budding, multiple nuclei, and a suppurative tissue reaction. Differentiation of Blastomyces from Coccidioides can be difficult. For features helpful in separating the two, see Figure 3, C through F; Table 3; and "Coccidioides" above.

Pneumocystis

Most pathologists are familiar with the usual picture of Pneumocystis pneumonia, which is a frothy, eosinophilic, intra-alveolar exudate accompanied by mild interstitial chronic inflammation. In 5% to 17% of cases, a granulomatous reaction is encountered (Figure 2, E). In most, it consists of poorly formed intra-alveolar granulomas characterized by epithelioid histiocytes palisading loosely around an eosinophilic exudate. Some cases may show intra-alveolar nonnecrotizing granulomas without an exudate, scattered multinucleated giant cells, organizing granulomatus pneumonia, or well-formed granulomas with or without central necrosis.

In immunocompromised patients, the above histologic appearance is highly suggestive of granulomatous Pneumocystis pneumonia and calls for especially close scrutiny of the GMS-stained section. A frothy intra-alveolar exudate should also raise the possibility of Pneumocystis, although it is not always present. Organisms can be scarce and difficult to find. They consist of small, round, sickle-shaped or crescent-shaped cysts (Figure 2, F). Differentiation from acute pulmonary histoplasmosis is discussed in the section on Histoplasma.

Aspergillus

Aspergillus may cause invasive, saprophytic, or allergic lung disease, depending primarily on the immune status of the host. The 2 most common forms of lung involvement by Aspergillus (aspergilloma and invasive aspergillosis) do not feature granulomas. However, granulomas are a prominent feature of 2 less common forms of pulmonary aspergillosis (chronic necrotizing pulmonary aspergillosis and allergic bronchopulmonary aspergillosis).

In the rare condition known as chronic necrotizing pulmonary aspergillosis, Aspergillus infection results in semi-invasive, chronic, indolent, cavitary disease in patients who have preexisting chronic lung disease or are mildly immunocompromised. The histologic picture is characterized by necrotizing granulomas containing Aspergillus hyphae. The presence of granulomas is indicative of limited tissue invasion. The granulomas may cause extensive parenchymal consolidation, may lead to bronchietatic cavities, or may be exclusively bronchocentric. The bronchocentric cases may be accompanied by nonnecrotizing granulomas in a lymphangitic distribution. A nonnecrotizing vasculitis can occur. Eosinophils are not prominent.

Chronic necrotizing pulmonary aspergillosis should be differentiated from other forms of Aspergillus-related lung disease. In mycetomas (aspergillomas), the fungal organisms do not invade the surrounding parenchyma or evoke a granulomatous response. Allergic bronchopulmonary fungal disease (see below) occurs in persons with asthma and is easily differentiated from chronic necrotizing pulmonary aspergillosis by the prominence of tissue eosinophils (see below). Invasive aspergillosis differs

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from chronic necrotizing pulmonary aspergillosis because it features vascular invasion by fungal hyphae and extensive parenchymal necrosis without granuloma formation.

Allergic bronchopulmonary aspergillosis is a noninvasive form of Aspergillus lung disease characterized by a hypersensitivity response to Aspergillus antigens, occurring mostly in asthmatic patients. Less commonly, other fungi such as Curvularia and Candida may cause similar morphologic changes. Hypersensitivity to the fungus results in a distinctive tissue reaction characterized by the triad of mucoid impaction of bronchi, bronchocentric granulomatosis, and eosinophilic pneumonia (Figure 4, A through D). Mucoid impaction of bronchi is characterized by obstruction of proximal bronchi by large, laminated, gelatinous mucus plugs filled with viable and necrotic eosinophils, neutrophils, fibrin, and necrotic debris (Figure 4, A). Charcot-Leyden crystals are often present, reflecting the eosinophil-rich infiltrate (Figure 4, B). Aspergillus hyphae may be found within the mucus (Figure 4, B [inset]). Bronchocentric granulomatosis is characterized by necrotizing granulomas centered exclusively on bronchi and bronchioles distal to the bronchi affected by mucoid impaction (Figure 4, C). The necrotic centers of the granulomas are rich in eosinophils and necrotic debris (Figure 4, D). Eosinophilic pneumonia is usually a focal finding in allergic bronchopulmonary aspergillosis. The main histologic feature is filling of the alveolar spaces with eosinophils. Histocytes often accompany the eosinophil-rich infiltrate. The interstitium is usually thickened by a combination of eosinophils, lymphocytes, and plasma cells. A mild nonnecrotizing vasculitis may be present. The pathologic diagnosis of allergic bronchopulmonary aspergillosis is confirmed by the identification of Aspergillus hyphae scattered within the lumens of bronchi or bronchioles (Figure 4, B [inset]).

Other infective causes of eosinophilic pneumonia include parasitic infections such as Dirofilaria immitis, a respiratory tract parasite. Dirofilaria (the dog heartworm) infects dogs but may rarely infect humans via a mosquito vector. The organism is a filarial nematode that typically infects dogs but may rarely infect humans via a mosquito vector. It is not a common cause of pulmonary disease in humans. However, in the United States, sarcoidosis is the most common noninfectious cause of lung granulomas encountered by surgical pathologists. However, it is important to emphasize at the outset that nonnecrotizing granulomas occur in the lung in several conditions other than sarcoidosis and that none of the histologic features listed below are absolutely pathognomonic for sarcoidosis. In histologically, sarcoidosis is characterized by discrete, well-formed, interstitial nonnecrotizing granulomas (Figure 5, A and B). Although nonnecrotizing granulomas predominate, small foci of pink necrosis are occasionally encountered. An underappreciated feature of sarcoidosis is the lymphangitic (“following the lymphatics”) distribution of the granulomas (Figure 5, A). In the lung, lymphatics run in the pleura, interlobular septa, and bronchovascular bundles (bronchi/bronchioles and arteries); it is in these locations that the granulomas of sarcoidosis are found. This distribution also explains why transbronchial biopsies are so effective in detecting sarcoid granulomas. Needless to say, a lymphangitic distribution can only be appreciated in a surgical biopsy (or larger specimen), not in a transbronchial biopsy. A frequent finding in sarcoidosis is the presence of intracytoplasmic inclusions (Figure 6, A and B), which are thought to represent (endogenous) products of macrophage metabolism. These include pink spiderlike structures (asteroid bodies) (Figure 6, A), basophilic concentric calcifications (Schaumann bodies), and calcium oxalate crystals. Calcium oxalate crystals and Schaumann bodies are birefringent (Figure 6, B) and must not be mistaken for foreign (exogenous) material. Although these inclusions are more frequent and numerous in sarcoidosis, they are also found in other granulomatous diseases such as hypersensitivity pneumonitis (Figure 6, C and D), chronic beryllium disease, tuberculosis, histoplasmosis, nontuberculous mycobacterial infection, and talc granuloma.
tosis (Figure 6, E and F). In an individual case, therefore, they cannot be used as a specific indicator of sarcoidosis.

Other frequent findings in sarcoidosis are concentric, lamellated fibrosis around granulomas (Figure 5, B), hyalinization of and within granulomas, granulomatous vasculitis,36,98 absence of granulomas within air spaces, absence of organizing pneumonia, and absence of interstitial inflammation away from the granulomas.2,3,94

The differential diagnosis includes infection, hypersensitivity pneumonitis, hot tub lung, and chronic beryllium disease (Figure 5, A through F). As discussed previously, infectious granulomas may be nonnecrotizing, well formed (sarcoïdlike), and peribronchiolar. A careful search for organisms is therefore mandatory before suggesting a diagnosis of sarcoidosis. Organisms especially likely to cause a similar histologic picture include mycobacteria and Cryptococcus. Although the presence of necrosis does not exclude sarcoidosis, it should prompt a more vigorous search for organisms.91 Other features common in infection but absent in sarcoidosis are organizing pneumonia and extensive necrosis or suppuration. Hypersensitivity pneumonitis enters the differential diagnosis because of the presence of nonnecrotizing granulomas and frequent intracytoplasmic inclusions (Figure 6, C and D). It is usually easily differentiated from sarcoidosis because the picture is dominated by interstitial chronic inflammation rather than granulomas (Figure 5, C). Interstitial inflammation also involves alveolar septa away from the granulomas in hypersensitivity pneumonitis, while it is limited to the granulomatous foci in sarcoidosis. A lymphangitic distribution, well-formed granulomas, and granulomatous vasculitis occur in sarcoidosis but not in hypersensitivity pneumonitis. Hot tub lung can be a more challenging problem because granulomas are more prominent than in hypersensitivity pneumonitis and thus closer in appearance to sarcoidosis (Figure 5, E and F). The main discriminant histologic feature is that granulomas of hot tub lung occur predominantly within air spaces (mainly the lumens of small bronchioles), while those of sarcoidosis are intersti-

Figure 4. Allergic bronchopulmonary aspergillosis. A, Mucoid impaction of bronchi. A dilated bronchus is filled with lamellated, eosinophilic debris. B, Same case as A. The intrabronchial debris is composed of necrotic eosinophils and mucus. Note characteristic Charcot-Leyden crystals (arrow). Branching hyphae are present within the debris (inset). C, Same case as A, showing bronchocentric granulomatosis. Necrotizing granulomatous inflammation (arrows) destroying a bronchiole (arrowhead). Note the necrotic debris filling the bronchiolar lumen. D, Same case as A, showing a bronchocentric necrotizing granuloma at high magnification. Palsading histiocytes at bottom left, necrosis rich in eosinophils at top right (hematoxylin-eosin, original magnifications ×20 [A], ×400 [B], ×40 [C], ×200 [D]; Grocott methenamine silver, original magnification ×400 [B, inset]).
Figure 5. Noninfectious nonnecrotizing granulomas. A, Sarcoidosis. Granulomas are distributed along the pleura (top), interlobular septum (arrows) and bronchovascular bundles (arrowhead) ("lymphangitic distribution"). The inflammation is localized to the granulomas and does not extend into the adjacent lung parenchyma. B, Sarcoidosis. Well-formed, nonnecrotizing granuloma surrounded by characteristic concentric fibrosis. C, Hypersensitivity pneumonitis. The main abnormality is mild thickening of the alveolar septa (interstitium). Granulomas are not visible at this magnification. D, Hypersensitivity pneumonitis. Interstitial chronic inflammation with a loose cluster of histiocytes (poorly formed granuloma). E, Hot tub lung. The granulomas show a predilection for bronchioles (arrows). F, Hot tub lung. A well-formed, nonnecrotizing granuloma is seen within an air space (hematoxylin-eosin, original magnifications ×20 [A, C, and E] and ×200 [B, D, and F]).
Figure 6. Endogenous and exogenous material within granulomas. A, Asteroid body (endogenous) in sarcoidosis. B, Crystalline inclusion (endogenous) in sarcoidosis (the inclusion is birefringent [inset]). C, Needle-shaped, crystalline inclusion (endogenous) in hypersensitivity pneumonitis. D, Cholesterol cleft (endogenous) in hypersensitivity pneumonitis. E, Two asteroid bodies (endogenous) in talc granulomatosis. Exogenous material is also present (arrow). F, Microcrystalline cellulose (exogenous) in “talc” granulomatosis (birefringence [inset]). G, Vegetable particles (exogenous) in aspiration pneumonia. Legumes of various kinds (“lentils”) share this morphology. H, Degenerated vegetable material
Lymphangitic granulomas and granulomatous vasculitis favor sarcoidosis, while identification of mycobacteria and a history of hot tub use support a diagnosis of hot tub lung.

The main role of the pathologist in the diagnosis of sarcoidosis is to exclude other etiologies. First, the specimen should be carefully examined for organisms. Second, an attempt should be made to identify features that are not consistent with sarcoidosis. Such features (used to argue for an alternative diagnosis) include granulomas within alveolar or bronchiolar air spaces, organizing pneumonia, interstitial inflammation in alveolar septa away from the granulomas, extensive necrosis or suppuration, numerous eosinophils, or vegetable material. If these features are present, sarcoidosis is unlikely, and this should be communicated clearly to the clinician.

In a surgical biopsy (or larger specimen) with well-formed nonnecrotizing granulomas distributed along lymphatic pathways, in the absence of features that would argue against sarcoidosis, it is reasonable for a pathologist to state that the features are “consistent with sarcoidosis.” In most transbronchial biopsy specimens, however, many of the above features cannot be evaluated, and therefore more caution must be exercised. It is acceptable with these specimens to simply diagnose “nonnecrotizing granulomas” and indicate in a comment that no organisms are identified. One could also outline the differential diagnosis or comment that the features are consistent with sarcoidosis in the appropriate clinical context, while realizing that the final diagnosis of sarcoidosis lies with the clinician, who has access to the results of cultures and knowledge of the clinical and radiologic settings. Even armed with this information, the diagnosis of sarcoidosis can be difficult because of the absence of a uniformly accepted clinical or morphologic gold standard.

**Chronic Beryllium Disease**

Chronic beryllium disease is characterized by granulomatous inflammation in the lung to inhaled beryllium. The histologic picture is characterized by nonnecrotizing granulomas. The appearance is thought to mimic sarcoidosis in almost every respect, including lymphangitic granulomas. The appearance is thought to mimic sarcoidosis or comment that the features are consistent with sarcoidosis. The histologic triad is sufficiently characteristic that the pathologist can suggest the diagnosis solely on the basis of microscopic examination. Interstitial chronic inflammation is the most consistent finding and usually dominates the histologic picture (Figure 5, C). It is often accentuated around bronchioles and may be associated with acute or chronic bronchiolitis. Small, poorly formed granulomas or multinucleated giant cells are randomly scattered within the interstitial inflammation and/or bronchiolar walls. The granulomas can be small and difficult to identify and often consist of only a few loosely aggregated histiocytes (Figure 5, D). In some cases, there are only rare multinucleated giant cells in the interstitium without frank granulomas (Figure 6, C and D). Cytoplasmic inclusions (such as asteroid bodies, Schaumann bodies, or cholesterol clefts) are often prominent within granulomas or multinucleated giant cells (Figure 6, C and D). They represent products of macrophage metabolism (endogenous) and must not be confused with foreign material (exogenous) (Figure 6, G and H). The occasional birefringence of the endogenous inclusions seen in hypersensitivity pneumonitis can also lead to misinterpretation as foreign material. Foamy macrophages often accumulate within alveolar spaces in hypersensitivity pneumonitis and are a manifestation of bronchiolar obstruction.

The presence of nonnecrotizing granulomas can raise the possibility of sarcoidosis. In contrast to hypersensitivity pneumonitis, sarcoid granulomas are well formed and...
have a lymphangitic distribution. Moreover, the lung away from the granulomas in sarcoidosis is normal, while in hypersensitivity pneumonitis there is significant interstitial inflammation even in areas where no granulomas are present (Figure 5, A through D). Granulomatous vasculitis may be present in sarcoidosis but not in hypersensitivity pneumonitis. Finally, small foci of organizing pneumonia are common in hypersensitivity pneumonitis but not in sarcoidosis.

Differentiation from hot tub lung (a hypersensitivity pneumonitis-like disease; see below) is more difficult and may be impossible on histologic grounds. Many of the morphologic features of hypersensitivity pneumonitis and hot tub lung overlap, including mixed interstitial and air space involvement, interstitial chronic inflammation, and organizing pneumonia. In classic cases, however, hot tub lung is characterized by fairly large, well-formed granulomas located predominantly within bronchiolar lumens, as opposed to the small, poorly formed interstitial granulomas of hypersensitivity pneumonitis (Figure 5, C through F). In difficult cases, a final determination of the diagnosis may require a clinical history of hot tub use and identification of mycobacterial organisms (hot tub lung) or a history of other antigenic exposure such as birds or a moldy home (for hypersensitivity pneumonitis). Both conditions may resolve with cessation of exposure to the causative agent.

Lymphoid interstitial pneumonia can be difficult to differentiate from hypersensitivity pneumonitis because it features an interstitial lymphoid infiltrate with loosely formed granulomas. The findings that differentiate lymphoid interstitial pneumonia from hypersensitivity pneumonitis include lack of peribronchiolar accentuation and organizing pneumonia and the frequent presence of an underlying condition such as Sjögren syndrome or human immunodeficiency virus (HIV) infection. Finally, hypersensitivity pneumonitis also needs to be differentiated from other, nongranulomatous causes of chronic interstitial inflammation such as nonspecific interstitial pneumonia or usual interstitial pneumonia.

**Hot Tub Lung**

Hot tub lung is a recently described entity characterized by a hypersensitivity pneumonitis-like response to nontuberculous mycobacteria (specifically, *Mycobacterium avium* complex, abbreviated as MAC) inhaled in aerosol form from hot tubs. Hot tubs provide an ideal temperature for the growth of the organisms and a means for their aerosolization. However, since other sources like shower heads and therapy pools potentially provide similar conditions, the more inclusive term MAC hypersensitivity–like disease has been used. *M avium* complex organisms are cultured from the sputum, lung tissue, and/or hot tubs in most, but not all, cases. Optimal treatment (cessation of hot tub use and/or corticosteroid or anti-mycobacterial therapy) is unclear, but there is expert consensus that patients should completely avoid reexposure to indoor hot tubs. The condition resolves in most patients regardless of the treatment modality.

The most characteristic pathologic finding of hot tub lung is the presence of granulomas within air spaces (usually the lumens of small bronchioles) (Figure 5, E and F). All other findings are variable: the granulomas may also be located randomly within alveolar spaces or bronchiolar walls, are usually nonnecrotizing but necrotizing granulomas are occasionally present, and are better defined than those seen in hypersensitivity pneumonitis but not as well formed as those of sarcoidosis. Organizing pneumonia is often present. Mycobacteria may or may not be identifiable with acid-fast stains. Interstitial inflammation may be present but is variable in extent. Definitive diagnosis requires a history of hot tub use or, more rarely, exposure to aerosolized water contaminated with mycobacterial organisms. In summary, hot tub lung can be suspected, but not definitively diagnosed, solely on the basis of histologic findings.

The main differential diagnostic considerations (Figure 5, A through F) are hypersensitivity pneumonitis (due to causes other than MAC), MAC infection (in patients without hot tubs), and sarcoidosis. The differential diagnosis with hypersensitivity pneumonitis due to other causes is discussed in the section on the latter entity. *M avium* complex infection in patients without hot tubs may cause an organizing granulomatous pneumonia. Acid-fast organisms may be present (or absent) in both entities. In the absence of a history of hot tub use, therefore, it is impossible to differentiate hot tub lung and MAC infection. Sarcoidosis is easier to distinguish from hot tub lung: it is characterized by better-defined, exclusively interstitial granulomas, a lymphangitic distribution, and granulomatous vasculitis, none of which are features of hot tub lung. Features that favor hot tub lung over sarcoidosis include identification of mycobacteria, air space granulomas, interstitial inflammation away from the granulomas, and organizing pneumonia.

**Lymphoid Interstitial Pneumonia**

Lymphoid interstitial pneumonia (LIP) is an uncommon form of interstitial lung disease, usually diagnosed in the setting of human immunodeficiency virus/AIDS, Sjögren syndrome, or other diseases involving immune dysregulation. LIP is not usually considered a granulomatous disease, but it is mentioned here because small granulomas are commonly part of the histologic picture. Histologically, LIP is characterized by dense and diffuse alveolar septal (interstitial) lymphoplasmacytic chronic inflammation and scattered histiocytes. Germinatal centers may be prominent. Small, loosely formed, nonnecrotizing granulomas are often present. Immunohistochemical stains show that the inflammatory infiltrate contains more T lymphocytes than B lymphocytes. Gene rearrangement studies demonstrate that the B lymphocytes are polyclonal.

The differential diagnosis includes hypersensitivity pneumonitis and low-grade B-cell lymphomas of extranodal marginal zone/mucosa-associated lymphoid tissue type, both of which may be associated with poorly formed granulomas. The main histologic features differentiating LIP from hypersensitivity pneumonitis are the greater density of the alveolar septal infiltrate and the presence of germinatal centers in LIP versus peribronchiolar accentuation of interstitial inflammation and foci of organizing pneumonia in hypersensitivity pneumonitis. Lymphoid interstitial pneumonia must also be differentiated from low-grade B-cell lymphomas. The predominance of T cells over B cells, polyclonality of the B cells, and the absence of a lymphangitic distribution are features that favor LIP.
Wegener Granulomatosis

Ideally, Wegener granulomatosis is diagnosed in patients with upper respiratory tract symptoms, multifocal lung involvement, kidney disease, anti-neutrophil cytoplasmic antibodies (ANCA), and necrotizing granulomas with necrotizing vasculitis. However, this is not always the case in practice. Renal involvement may be absent at presentation, the clinical features may overlap with infectious diseases, disease may be limited to the lungs, and the lung lesions may be solitary. The role of pathologic examination is crucial from the surgical pathologist’s perspective, relevant clinical history and results of biopsy are often unavailable at the time of biopsy. The role of pathologic examination is crucial in such cases and often helps the clinician to initiate therapy in a timely fashion. When classic histologic features are present, Wegener granulomatosis can be diagnosed even in an unusual clinical setting.

On the other hand, if histologic findings are not classic, clinical input and ANCA results assume greater importance; cases without necrotizing vasculitis, in particular, should not be diagnosed as Wegener granulomatosis on the basis of pathologic findings alone. In the appropriate setting, the diagnosis can occasionally be made with transbronchial biopsies.

The classic histologic picture of Wegener granulomatosis consists of necrotizing granulomatous inflammation accompanied by necrotizing vasculitis (Figure 7, A, C, and E). The granulomas are suppurative (neutrophil-rich) and resemble abscesses at low magnification (Figure 7, A). The necrotic (suppurative) areas are usually irregular in contour, with a deeply basophilic, “dirty” appearance owing to the presence of neutrophils and nuclear debris (Figure 7, C). Palisading histiocytes, acute and chronic inflammation, and granulation tissue surround the suppurative necrosis. Multinucleated giant cells, when present, are distinctive but not pathognomonic for Wegener granulomatosis. They stand out at low magnification because of the presence of multiple, closely packed, hyperchromatic nuclei. In contrast, compact, “sarcoidlike,” nonnecrotizing granulomas are exceptional in Wegener granulomatosis. Eosinophils may be absent or present in small numbers; only rarely are they numerous.

Necrotizing vasculitis is the single most important feature in the histologic diagnosis of Wegener granulomatosis. They stand out at low magnification because of the presence of multiple, closely packed, hyperchromatic nuclei. In contrast, compact, “sarcoidlike,” nonnecrotizing granulomas are exceptional in Wegener granulomatosis. Eosinophils may be absent or present in small numbers; only rarely are they numerous.

Necrotizing vasculitis is the single most important feature in the histologic diagnosis of Wegener granulomatosis but has been poorly defined in the literature. Several points must be stressed regarding its identification.

1. Necrotizing vasculitis can sometimes be very difficult to identify because the affected vessels may be completely necrotic. Since neutrophils in Wegener granulomatosis are commonly necrotic and karyorrhectic, the presence of necrotic neutrophils in the vessel wall is an acceptable surrogate for necrosis of the wall itself. Thus, the vessel-destructive vascular infiltrate that defines necrotizing vasculitis may consist of necrotic neutrophils, a mixture of necrotic neutrophils and histiocytes (Figure 7, E), suppurative necrosis, or fibrinoid necrosis.

2. Although a vasculitis comprising lymphocytes or a mixture of lymphocytes and histiocytes is very common in Wegener granulomatosis, this finding by itself does not constitute necrotizing vasculitis. This type of nonnecrotizing vasculitis is common in infectious granulomas (Figure 7, F). Granulomatous vasculitis without necrosis is also common in sarcoidosis.

3. Necrotizing vasculitis is usually found within the inflamed, but nonnecrotic area in the lesion, and this is where it should be sought. Vasculitis, necrotizing or otherwise, is uncommon in the normal lung surrounding the inflamed area. Within the inflamed area, it is important to identify necrotizing vasculitis in viable parenchyma. Such viable areas are located adjacent to, but not within, the necrosis. Completely necrotic vessels within areas of parenchymal necrosis do not constitute acceptable evidence of necrotizing vasculitis, since it is impossible to determine if they are merely included in the necrosis as “innocent bystanders.”

4. Necrotizing vasculitis is most readily identified when it is “eccentric,” affecting the vessel focally and leaving the rest of the wall uninvolved. Since the affected vessel is not completely necrotic, recognition of necrotizing vasculitis is facilitated. This type of involvement is common in Wegener granulomatosis.

5. Vasculitis in Wegener granulomatosis affects both arteries and veins; occasionally, capillaries may be involved in a process known as necrotizing capillaritis (see below). Necrotizing capillaritis results in intra-alveolar hemorrhage, which may be massive and potentially fatal.

Other histologic features that may be present in Wegener granulomatosis include small microabscesses, small suppurative granulomas, necrosis of collagen, and organizing pneumonia at the periphery of the main lesion. Several uncommon histologic variants of Wegener granulomatosis have been described. These are characterized by unusual prominence of 1 histologic feature, often at the expense of the other classic features described above. These include the bronchocentric variant, bronchiolitis obliterans-organizing pneumonia–like variant, eosinophilic variant, and the alveolar hemorrhage and capillaritis variant.

The main differential diagnosis is with infections, which can show necrotizing granulomas, “dirty” necrosis, and vasculitis-like changes (Figure 7, B, D, and F). Solitary lesions, in particular, are far more likely to be infections. A careful search for organisms is therefore mandatory before a diagnosis of Wegener granulomatosis is made. The absence of organisms and presence of a necrotizing vasculitis are the key features required for a pathologic diagnosis of Wegener granulomatosis. Histologic clues that favor infectious granulomas include admixed compact, sarcoidlike, nonnecrotizing granulomas and lymph node involvement, both of which are absent in Wegener granulomatosis. The clinical picture may help if there is a history of renal or upper respiratory tract involvement or ANCA positivity (especially cytoplasmic [c]-ANCA). However, overreliance
Figure 7. Wegener granulomatosis (left) compared with an infectious granuloma (right). A, Wegener granulomatosis. Basophilic, “dirty” necrosis with irregular contours. B, Mycobacterial granuloma. Necrotizing granuloma with “dirty” necrosis but more regular contours than A. C, Same case as A. Suppurative necrosis with a rim of palisading histiocytes. D, Same case as B. Neutrophils are present within the necrotic area (arrow) but are fewer than in C. E, True vasculitis in Wegener granulomatosis, same case as A. The top portion of the vessel wall is destroyed by an inflammatory infiltrate (arrows). The infiltrating cells are predominantly neutrophils (inset). F, Same case as B. Mild nonnecrotizing vasculitis (arrows) in a case of mycobacterial infection. Vessel wall is thickened by edema and a few inflammatory cells (arrows). The inflammatory cells are predominantly lymphocytes (inset) (hematoxylin-eosin, original magnifications ×40 [A and B], ×200 [C and D], ×100 [E and F], ×400 [insets E and F]).
ance on the results of these studies can be dangerous, as an expanding number of infections and other diseases may lead to false-positive results for ANCA tests. As noted above, isolated lung involvement does occur in Wegener granulomatosis, and such cases are more often ANCA-negative than those with severe, active, multisystem disease. In the setting of isolated lung involvement, a case could be made for erring on the side of conservatism rather than overdiagnosing Wegener granulomatosis. A descriptive diagnosis of “necrotizing granulomatous inflammation” is appropriate in such cases. Differentiation of Wegener granulomatosis from Churg-Strauss syndrome is discussed in the following section.

Churg-Strauss Syndrome

Churg-Strauss syndrome is a rare condition usually diagnosed on the basis of clinical criteria. Histologic support for the diagnosis may come from biopsies of the lung but other sites are more commonly biopsied. The classic histologic picture in the lung consists of necrotizing granulomas, necrotizing vasculitis, and eosinophilic pneumonia, but this characteristic triad is only infrequently present. The diagnosis is therefore rarely made on the basis of pathologic findings alone. The granulomas of Churg-Strauss syndrome are well formed, with central necrosis rich in eosinophils. They involve blood vessels as well as bronchioles. The accompanying necrotizing vasculitis is rich in multinucleated giant cells and eosinophils. The surrounding alveolar spaces are filled with eosinophils (eosinophilic pneumonia) and may show evidence of organization. Since the classic triad of findings is rarely encountered on lung biopsy, the pathologist’s role in most cases is to recognize and document the presence of tissue eosinophilia and/or necrotizing vasculitis and communicate the significance of these findings effectively to the clinician. A pathologic diagnosis of eosinophilic pneumonia alone (without necrotizing vasculitis) may be sufficient for a clinical diagnosis of Churg-Strauss syndrome in the appropriate setting. Definitive diagnosis requires clinical input and ANCA testing; clinical diagnostic criteria vary widely. The main entities to consider in the histologic differential diagnosis are infection, eosinophilic pneumonia, and Wegener granulomatosis. The combination of prominent eosinophils and vasculitis-like change may be encountered in infection due to parasites such as Dirofilaria and fungi such as Aspergillus or Coccidioides. Allergic bronchopulmonary fungal disease (see above) can mimic Churg-Strauss syndrome because both occur in asthmatic patients and feature eosinophilic pneumonia along with granulomatous inflammation rich in eosinophils. Mucoid impaction of bronchi is a clue to allergic bronchopulmonary fungal disease; GMS-stained sections should be scrutinized carefully for Aspergillus hyphae when this finding is identified. Necrotizing vasculitis is not a feature of allergic bronchopulmonary fungal disease. Eosinophilic pneumonia is far more common in settings other than Churg-Strauss syndrome or as an idiopathic condition. The clinical features of eosinophilic pneumonia in these settings may be difficult, and sometimes impossible, to separate from Churg-Strauss syndrome. In eosinophilic pneumonia, eosinophils fill the air spaces and perivascular inflammation may be prominent. The histologic features that favor Churg-Strauss syndrome over eosinophilic pneumonia (occurring in other settings) include necrotizing granulomas, necrotizing vasculitis, and tissue necrosis without eosinophils. In the absence of these features (especially necrotizing vasculitis), it may be impossible to differentiate Churg-Strauss syndrome from eosinophilic pneumonia on histologic grounds. Clinical features (perinuclear [p]-ANCA positivity and extrapulmonary involvement in Churg-Strauss syndrome) can be helpful in difficult cases. Wegener granulomatosis is usually not difficult to differentiate from Churg-Strauss syndrome. Although the 2 conditions share a combination of necrotizing granulomas and necrotizing vasculitis, neutrophils predominate in the former, while eosinophils are the hallmark of the latter. Although eosinophils may be present in Wegener granulomatosis, only rarely are they present in sufficient numbers to create diagnostic problems. In such cases, the clinical setting is helpful. Unlike Churg-Strauss syndrome, Wegener granulomatosis is frequently associated with destructive upper respiratory tract lesions and c-ANCA positivity but not with asthma or peripheral blood eosinophilia.

Aspiration Pneumonia (Due to Aspiration of Particulate Material)

A variety of substances, including oropharyngeal bacteria, foreign bodies, milk, barium, exogenous lipids, and gastric contents can be aspirated into the lungs, leading to a wide variety of tissue reactions and clinical consequences. Aspiration of oropharyngeal flora leads to the classic acute necrotizing bronchopneumonia known to clinicians as “aspiration pneumonia.” Aspiration of gastric acid leads to the acute respiratory distress syndrome, classically occurring in anesthetized patients and characterized histologically by diffuse alveolar damage.

In contrast to these well-characterized conditions, aspiration of particulate gastric contents (food and/or pill fragments) is underrecognized. This entity is particularly relevant to pathologists because it is usually unsuspected clinically and because histologic identification of aspirated material within the lungs is the only means of confirming a definitive pathologic diagnosis of aspiration. The tissue response to the particulate material is quite characteristic. The earliest event is acute bronchopneumonia associated with a foreign body giant cell reaction, followed later by organizing pneumonia. In surgical biopsies, organizing pneumonia is often the predominant finding (Figure 8, A). In the most classic cases, it is associated with acute inflammation and/or foreign body granulomas or multinucleated giant cells containing aspirated foreign material (Figure 8, B). The presence of particulate foreign material is the key diagnostic finding. It usually consists of vegetable fragments in various stages of degeneration (Figures 6, G and H, and 8, B). Other forms of aspirated particulate foreign material are less common and include excipients derived from oral pills (talc, microcrystalline cellulose, crospovidone) or sodium polystyrene sulfonate.

The differential diagnosis includes infection, Wegener granulomatosis, and talc granulomatosis. Both infection and Wegener granulomatosis may show a combination of bronchocentric granulomas, acute inflammation, and...
organizing pneumonia, mimicking the appearance of aspiration. The key diagnostic findings that separate these conditions are necrotizing vasculitis (Wegener granulomatosis), organisms (infection), and vegetable or other aspirated particulate material (aspiration). Aspiration pneumonia due to aspiration of pill fragments containing talc may raise the possibility of talc granulomatosis. The location of the granulomas is important. The granulomas of aspiration pneumonia occur in peribronchiolar parenchyma, while those of talc granulomatosis occur within alveolar septa. Vegetable fragments, organizing pneumonia, and acute inflammation are seen in aspiration but are absent in talc granulomatosis.

Talc Granulomatosis

The entity of talc granulomatosis was recently in the spotlight due to a controversial case reported in The New Yorker in September 2008. Talc (hydrated magnesium silicate), like microcrystalline cellulose and crospovidone, is an excipient. Excipients are inactive substances used as carriers for the active ingredients of medications. In oral pills/tablets, they provide bulk (“fillers”), hold the ingredients together (“binders”), and cause the pills to dissolve when wet (“disintegrants”). Talc granulomatosis results from intravenous injection of aqueous suspensions of crushed oral medications such as methadone, methylphenidate, tripelemamine, and pentazocine. The injected material travels via veins and the right side of the heart to the lungs. There, it is trapped within pulmonary arterioles and capillaries, eliciting a foreign body–type granulomatous response around these vessels (Figure 8, C and D). The perivascular location of the granulomas is not always readily apparent but can be inferred from the alveolar septal distribution. Obstruction of blood flow by the foreign material and the associated granulomatous response may lead to pulmonary hypertensive changes. Intravascular thrombi and vascular dilatation may accompany these changes. Talc (and/or microcrystalline cellulose or crospovidone) is identified histologically within the granulomas. Since talc is the most

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Figure 8. Granulomas containing exogenous material. A. Aspiration pneumonia. At low magnification, the abnormalities are located in peribronchiolar parenchyma (long arrow). Fibroblast plugs fill air spaces (organizing pneumonia) (short arrows). A fragment of foreign material is barely visible at the top of the picture (arrowhead). B. Same case as A. Foreign (vegetable) material is surrounded by multinucleated giant cells and acute inflammation. C. Talc granulomatosis found at autopsy in a drug addict. The abnormalities are distributed around blood vessels in the interstitium. D. Same case as C. Filler material (probably microcrystalline cellulose) surrounded by multinucleated giant cells. An alveolar septal capillary is at the top of the picture. The material is strongly birefringent (inset) (hematoxylin-eosin, original magnifications ×20 [A and C], ×400 [B, D, and inset]).

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common material found and comprises the bulk of the material in most cases, the umbrella term talc granulomatosis, though not entirely accurate, is widely used. Other filler materials, such as microcrystalline cellulose and crospovidone, may also be present. On occasion, the foreign material is scant and the granulomatous response subtle; in such cases, the diagnosis is easily overlooked. A polarizing lens is useful in this situation, since talc and microcrystalline cellulose (but not crospovidone) are strongly birefringent (Figure 8, D [inset]) and stand out at low magnification. Often, far more foreign material becomes evident upon polarization than was evident on H&E.

The presence of interstitial granulomas with birefringent material can raise the possibility of sarcoidosis. The granulomas of sarcoidosis are large, round, and discrete and their distribution is lymphangitic (see “Sarcoidosis”) rather than purely alveolar septal. The amount of birefringent material is greater in talc granulomatosis than in sarcoidosis. However, occasional cases of sarcoidosis can show abundant birefringent material, and these may be particularly difficult to distinguish from talc granulomatosis. The foreign material in talc granulomatosis is large, sheet/platelike (talc), fiber/rod-like (microcrystalline cellulose), or deep blue and corallike (crospovidone). In contrast, the inclusions of sarcoidosis are small and crystalline. In difficult cases, acid digestion can be a useful histochemical technique because it removes calcium but not talc. Inhalation (as opposed to intravenous injection) of talc leads to a condition known as inhalation talcosis or talc pneumoconiosis. The pathologic findings of talc pneumoconiosis are poorly described but include interstitial fibrosis and scarring. The condition may be difficult to distinguish from talc granulomatosis. As the case reported in the New Yorker illustrates, a history of drug abuse may not be available and a history of occupational exposure may not always settle the issue. Measurement of particle size may be helpful because inhaled talc particles tend to be smaller than injected talc. Aspiration of pill fragments can also be confused with talc granulomatosis. Fortunately, the latter occurrence is quite uncommon; it can be differentiated from talc granulomatosis by the peribronchiolar localization of the granulomas and the frequent association with organizing pneumonia and acute inflammation (both absent in talc granulomatosis).

Rheumatoid Nodule

The possibility of a rheumatoid nodule should be considered when a necrotizing granuloma is encountered in the lung of a patient with rheumatoid arthritis. The clinical context is helpful, since most rheumatoid nodules are multiple and subpleural and occur in seropositive patients with active joint disease. In the absence of this information, the diagnosis must be made with caution. The histologic appearance is that of a necrotizing granuloma with abundant central necrosis and a rim of palisading epithelioid histiocytes. There is often basophilic karyorrhectic debris at the interface between the necrosis and the granulomatous rim. There may be associated vasculitis but necrotizing vasculitis is not found. The changes described above are histologically indistinguishable from infectious necrotizing granulomas, which, of course, may occur in patients with rheumatoid arthritis; infectious granulomas can also be multiple, bilateral, and subpleural. Therefore, the diagnosis of a rheumatoid nodule is essentially one of exclusion. Test results with special stains for organisms and microbiologic cultures must be negative before a necrotizing granuloma in the lung is presumed to be a rheumatoid nodule.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis refers to the presence of necrotizing granulomas centered exclusively on bronchi and bronchioles. This definition excludes most ordinary granulomatous diseases, which are not limited to bronchi and bronchioles but also involve other components of the lung parenchyma. Some cases that fit this definition are encountered in asthmatic patients as part of the spectrum of allergic bronchopulmonary fungal disease (see Figure 4 and “Aspergillus” above). In such cases, eosinophils are numerous in the necrotic areas. The remaining cases occur in patients without a history of asthma and probably represent undiagnosed infections. Tissue eosinophilia is less marked or absent in this group. Rarely, a bronchocentric granulomatosis-type pattern may be found in Wegener granulomatosis.

To summarize, bronchocentric granulomatosis is best thought of as an unusual and distinctive tissue reaction seen predominantly in allergic bronchopulmonary fungal disease and various other infections, rather than as the discrete entity that Liebow had originally envisioned. When bronchocentric granulomas are associated with prominent eosinophils, a GMS-stained section should be examined carefully and the possibility of allergic bronchopulmonary fungal disease should be communicated to the clinician. In cases without eosinophils and no history of asthma, the likely infectious nature of the process should be communicated, even if organisms are not detected.

CONCLUSION

In this review, we have outlined a practical, step-by-step approach for surgical pathologists faced with granulomatous lung disease. Several practical tips regarding examination and interpretation of special stains are included to help pathologists detect and identify organisms. The common fungi are illustrated side by side at identical magnification to facilitate recognition of the major differentiating features. Next, we have listed the key features of the noninfectious granulomatous lung diseases in a concise table so that pathologists can rapidly narrow their differential diagnosis and subsequently obtain details of the differential diagnosis from the text. Finally, we address the common situation for which a specific diagnosis cannot be made and suggest practical tips to handle this problem.

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