Common Diagnostic Challenges in the Pathology of Nonneoplastic Lung Diseases

A Case-Based Review

Amir Lagstein, MD; Jeffrey L. Myers, MD

We use a case-based format to review 4 relatively common, diagnostic challenges in surgical pathology of nonneoplastic lung diseases. All cases are linked to virtual slides so that the reader can participate in a manner that simulates the breakout session held at the 2008 New Frontiers in Pathology course at the University of Michigan, from which, this material was excerpted. Brief clinical histories and a summary of radiologic findings are followed by a description of the pertinent histologic findings and a concise topic review, intended to focus on practical diagnostic considerations. Our goal is that readers gain a greater understanding of those features most helpful in recognizing usual interstitial pneumonia, Langerhans cell histiocytosis, aspiration pneumonia, and Wegener granulomatosis.

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The case studies that follow are taken from a breakout session held at the 2008 New Frontiers in Pathology meeting at the University of Michigan in Ann Arbor. The intent was to review, in a classic clinicopathologic conference format, real patients who illustrate common diagnostic challenges that surgical pathologists are likely to confront when interpreting lung biopsies. We have selected 4 patients and included clinical histories, a description of relevant radiologic and histologic findings, and a brief overview of the topic. Table 1 provides a key for linking patients presented in this manuscript to virtual slides used for the actual breakout session.

First, however, we offer a prefatory note of caution regarding the relative roles of clinical history, radiologic findings, and histopathology. Many patients with nonneoplastic lung disease proceed to surgical biopsy because neither the clinical nor the radiologic findings offer a specific diagnosis with a high degree of certainty. That is, patients are more likely to undergo surgical lung biopsy because their illness lacks certain expected clinical and/or radiologic features. This at a time when imaging techniques provide increasingly accurate diagnoses in a subset of patients, fueling the sometimes unrealistic expectation that radiologic findings are always highly sensitive and specific, independent of the clinical context. Thus, the surgical pathologist is frequently in the position of issuing an unanticipated diagnosis or a diagnosis in conflict with expectations based on clinical or radiologic findings.

Our preference is to first review biopsies with no knowledge of the clinical and radiologic findings to allow an objective and unbiased view of the findings. Should you choose to do the same, use Table 1 to first review the virtual slide before reading the histories and diagnoses provided. In our own daily workflow, the clinical history is consulted only after reviewing the slides as a means to corroborate or expand on histologic interpretation, rather than as a means of constructing it. To do otherwise runs the risk of either misinterpreting the relevance of a particular set of findings or being mislead by the history in the face of diagnostic histopathology. In either circumstance, the opportunity to add unique value to the patient-care process, the very reason for pathologic consultation, has been lost. Consulting relevant information after reviewing the slides is helpful in avoiding diagnoses that are clearly incompatible with clinical and/or radiologic features.

CASE 1

Clinical History

A 66-year-old man had been followed as an outpatient for a 3- to 4-year history of slowly progressive shortness of breath. Pulmonary function studies showed severe restriction characterized by a forced vital capacity of 2.15 L (48% of the predicted value) and a diffusion capacity for carbon monoxide of 12.03 mL/min/mm Hg (44% of the predicted value). A computed tomography scan performed 4 months before biopsy showed a combination of bilateral ground-glass opacities, reticular lines, and bronchiectasis, without definite honeycomb change (Figure 1). The findings were more suggestive of nonspecific interstitial pneumonia. He underwent surgical lung biopsy.

Lung Biopsy Findings

As illustrated in the virtual slide, the main change at low magnification is a chronic interstitial pneumonia in...
which fibrosis predominates (Figure 2). The fibrosis has a distinctly “patchwork” distribution and includes areas of cystic honeycomb change. In addition, there are scattered subepithelial fibroblast foci (Figure 3).

Diagnosis.—Usual interstitial pneumonia (UIP).

Discussion

Clinical Features.—Usual interstitial pneumonia is the most common of the idiopathic interstitial pneumonias, which include respiratory bronchiolitis interstitial pneumonia/desquamative interstitial pneumonia, acute interstitial pneumonia (also known as Hamman-Rich disease) and nonspecific interstitial pneumonia.1-3 Usual interstitial pneumonia is the histologic counterpart of the clinical syndrome referred to as idiopathic pulmonary fibrosis and is typically diagnosed in patients of late middle age or older (50–70 years old), although younger patients can be affected.4

Understanding of variations in clinical presentation and the natural history of UIP has altered dramatically during the past decade. Formerly, almost all patients were characterized as presenting with progressive shortness of breath developing for months to years. Increasing use of chest imaging, performed for other reasons, now identifies patients with UIP who are asymptomatic. The traditional view that patients experienced a relentlessly progressive and steady decline has been supplanted by more recent experience with untreated patients suggesting that plateaus of relative stability are more typically punctuated by sudden and unexplained precipitous declines in lung function, termed acute exacerbation of idiopathic pulmonary fibrosis.5,6 Occasionally, patients without a previously suspected diagnosis of UIP present in this rapidly progressive phase of their illness, thus simulating acute interstitial pneumonia.7

High-resolution computed tomography (HRCT) scans of the chests of patients with UIP usually show bilateral interstitial or reticular lines and traction bronchiectasis, most prominently in the periphery and lung bases.8,9 Classic examples also show honeycomb change in the same distribution; however, only between 30% and 50% of patients have “classic” HRCT findings of the sort that allow confident diagnosis on the basis of imaging studies alone.10,11 In patients who lack radiologic features diagnostic of UIP, the radiologic interpretation is more likely to favor nonspecific interstitial pneumonia, thus setting the stage for diagnostic discordance, as was true in this patient. This is precisely the situation in which biopsy is likely, and in which the pathologist’s interpretation is pivotal in establishing the diagnosis of UIP.12

Pathologic Features.—Usual interstitial pneumonia is a disease of pathologic fibrosis. Some degree of interstitial inflammation is usually present, especially in areas of honeycomb change, but the very patchy inflammation is overshadowed by fibrosis as the dominant finding. The most notable feature at low magnification is the variegated nature of the fibrosis (Figure 4).3,12-14 Areas of abnormality are qualitatively heterogeneous and characterized by a distinctive patchwork distribution, in which some areas are more severely affected than others. This is the spatial heterogeneity typical of UIP, in which minimally affected areas are juxtaposed with dense and often confluent fibrosis. Characteristically, the most severely affected areas are subpleural and along interlobular septa, whereas in a subset of biopsies, the fibrotic zones have a more haphazard distribution. Temporal heterogeneity in UIP refers to qualitative variability within fibrotic zones. Much of the fibrosis in UIP consists of dense collagen deposits that contrast with scattered, small, interstitial, subepithelial foci of pale-blue, immature collagen with admixed myofibroblasts, so-called fibroblast foci (see Figure 3).

Fibrosis in UIP is often sufficiently advanced by the time of biopsy to result in architectural distortion in the form of collagenous scarring and honeycomb change. Honeycomb change refers to cystically dilated airspaces within zones of scar (Figure 5). A mucopurulent exudate is often present within the dilated airspaces, accumulating as a consequence of the stasis of secretions in these areas.

Histopathologic features that allow a confident diagnosis of UIP are summarized in Table 2 and include (1) fibrosis with a characteristic patchwork distribution; (2) inflammation that is only mild and focal and is outside the areas of honeycomb change; (3) fibrosis that is new and active and is in the form of fibroblast foci juxtaposed with established scar; and (4) architectural distortion in the form of either confluent scarring or honeycomb change.

Most surgical lung biopsies of UIP will show all of these features allowing for a confident diagnosis. Occasionally, however, one or more elements are lacking. A diagnosis of UIP can still frequently be made if the other morphologic findings are supportive. In diagnostically challenging cases, reference to the clinical and radiologic findings may also be useful, recognizing that HRCT findings are unlikely to be diagnostic in patients selected for biopsy and may instead suggest nonspecific interstitial pneumonia as an alternative. A subset of patients remain for whom the differential diagnosis cannot be resolved on the basis of all available data; the terms unclassifiable interstitial pneumonia and unclassifiable fibrosis have been proposed for this subset of patients.1,13

Table 1. Summary of Case Presentations with Links to Virtual Slides

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<th>Breakout Session Case, No.</th>
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CASE 2

Clinical History

A 72-year-old woman underwent thoracoscopic lung biopsy for evaluation of multiple nodules.
Figure 1. High-resolution computed tomography scan from case 1. There is a combination of reticular lines, ground-glass opacities, and traction bronchiectasis that are not pathognomonic for a single condition but, in this case, were thought to be most consistent with nonspecific interstitial pneumonia.

Figure 2. Low-magnification photomicrograph of usual interstitial pneumonia (case 1). There is patchy fibrosis in which areas of severely abnormal lung are juxtaposed in a somewhat random, patchwork fashion with areas of less-involved parenchyma (hematoxylin-eosin, original magnification $\times 20$).

Figure 3. High-magnification view of a fibroblast focus (case 1). Notice its subepithelial location and the presence of spindled fibroblasts and myofibroblasts arrayed in parallel to the surface epithelium within a pale stroma of immature collagen (hematoxylin-eosin, original magnification $\times 400$).
Table 2. Criteria for Diagnosing Usual Interstitial Pneumonia in Surgical Lung Biopsies

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<th>Lung Biopsy Findings</th>
<th>Pathologic Features</th>
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<td>Diagnosis.—Langerhans cell histiocytosis.</td>
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<td>Patchwork distribution of abnormal findings (Figures 2 and 4)</td>
<td>Clinical Features.—Pulmonary Langerhans cell histiocytosis (LCH) is a disorder of proliferating Langerhans cells. It should be distinguished from histiocytosis X, a systemic condition characterized by a neoplastic, clonal proliferation of Langerhans cells, with variable manifestations, including Letterer-Siwe and Hans-Schüller-Christian diseases. These latter conditions may secondarily involve the lung and carry a different prognosis than primary pulmonary LCH.</td>
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<td>Fibroblast foci (Figure 3)</td>
<td>It is important to remember that late-stage, cystic LCH is often sufficiently characteristic from the radiologic perspective that the combination of pathology and imaging may be extremely helpful in establishing the diagnosis with greater certainty.</td>
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<tr>
<td>Destructive scarring and/or honeycomb changes (Figure 5)</td>
<td>Cystic change in LCH can result from dilatation of the lumens of affected bronchioles (ie, bronchiolectasis) but is more commonly the consequence of scarring and secondary enlargement of peribronchiolar air spaces, a lesion referred to as respiratory bronchiolitis, which may mimic desquamative interstitial pneumonia both radiologically and histologically (so called, desquamative interstitial pneumonia-like changes).</td>
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Discussion

Clinical Features.—Pulmonary Langerhans cell histiocytosis (LCH) is a disorder of proliferating Langerhans cells. It should be distinguished from histiocytosis X, a systemic condition characterized by a neoplastic, clonal proliferation of Langerhans cells, with variable manifestations, including Letterer-Siwe and Hans-Schüller-Christian diseases. These latter conditions may secondarily involve the lung and carry a different prognosis than primary pulmonary LCH.

Langerhans cell histiocytosis is an interstitial lung disease of current or former smokers,15–18 The constituents of inhaled smoke result in disordered immune regulation, resulting in recruitment and proliferation of Langerhans cells.18,19 Although the short-term prognosis is favorable, long-term complications include pulmonary hypertension, development of malignancy, and progressive fibrosis.20–22 Pulmonary LCH has characteristic radiologic findings on HRCT, including a unique combination of thin-walled cysts, nodules, and reticulations with a predilection for upper lung zones.23,24 Given the diagnostic accuracy of HRCT, biopsy is often reserved for those patients for whom the radiologic findings are either not diagnostic or suggestive of another condition.

Pathologic Features.—As illustrated in this example, pulmonary LCH shows patchy, interstitial nodules with a distinctly airway-centered distribution when examined at low magnification (Figure 6).25 Early lesions of LCH are characterized as cellular and stellate-shaped, which is caused by expansion of contiguous peribronchiolar alveolar septa by the cellular infiltrate (Figure 8). At higher magnification, the cellular infiltrate is polymorphic, comprising variable numbers of histiocyte-like cells, with reniform, convoluted, or grooved nuclei and abundant cytoplasm (Figure 9). These are, of course, the diagnostic Langerhans cells. Langerhans cells in pulmonary LCH are accompanied by other inflammatory cells, including variable numbers of eosinophils, although the latter are not necessary for the diagnosis. In histologically and cytologically classic cases, the diagnosis can be made without special stains. Immunohistochemical stains for S100 protein and/or CD1a may be helpful in highlighting the cells of interest in diagnostically challenging cases. More recently, langerin has emerged as an immunohistochemical marker that is more specific for Langerhans cells.26,27

Pigmented (smokers') alveolar macrophages are a frequent finding in pulmonary LCH. Pigmented macrophages typically accumulate in bronchioles and peribronchiolar airspaces, a lesion referred to as respiratory bronchiolitis, which may mimic desquamative interstitial pneumonia both radiologically and histologically (so called, desquamative interstitial pneumonia-like changes).26

Collagenization of the airway-centered nodules progresses from the inside out, resulting in paucicellular fibrotic nodules with absent or scant Langerhans cells limited to the periphery of the lesions. In biopsies showing predominantly acellular, fibrotic lesions, careful review of all of the available tissue is sometimes helpful in demonstrating diagnostic cellular lesions elsewhere. Immunohistochemical stains may be attempted but are frequently found to be negative, attesting to the absence of Langerhans cells in late-stage disease. The stellate configuration of airway-centered fibrotic nodules is the most helpful clue in the absence of pathognomonic cellular lesions (Figure 10) and is an important feature separating fibrotic LCH from UIP (see Table 3).

CASE 3

Clinical History

A 72-year-old woman, following radiation and total laryngectomy for squamous cell carcinoma, was discov-
Figure 7. High-magnification view of the interstitial infiltrate in Langerhans cell histiocytosis (case 2). The predominant cells in this field are histiocyte-like cells, with convoluted nuclei and eosinophilic cytoplasm (hematoxylin-eosin, original magnification ×600).

Figure 8. Low-magnification view of a bronchiolocentric interstitial nodule in pulmonary Langerhans cell histiocytosis. At this early stage, the lesion is more cellular than fibrotic, and its stellate configuration is clearly evident (hematoxylin-eosin, original magnification ×40).

Figure 9. High-magnification photomicrograph of the cellular infiltrate in early stage Langerhans cell histiocytosis. Diagnostic Langerhans cells—histiocyte-like cells with convoluted or grooved nuclei and abundant cytoplasm—are in abundance, admixed with scattered eosinophils and lymphocytes (hematoxylin-eosin, original magnification ×600).

Figure 10. Low-magnification view of later stage interstitial nodule in Langerhans cell histiocytosis. Fibrosis predominates, although the characteristic stellate shape is maintained. Notice the architectural distortion is very different from the honeycomb change characteristic of usual interstitial pneumonia, consisting instead of paracicatrical air space enlargement (also termed scar or traction emphysema) resulting in dilatation of peribronchiolar airspaces (hematoxylin-eosin, original magnification ×20).
ered to have a 1.4-cm, right upper lobe apical mass. Core biopsy showed adenocarcinoma. In addition, computed tomography scan showed 2 nodules in the right lower lobe, the largest measuring 0.6 cm in greatest dimension. The biopsy is from a lower lobe nodule.

**Lung Biopsy Findings**

The main change in the surgical lung biopsy from the lower lobe nodule is necrotizing granulomatous inflammation with a distinctly bronchiolocentric distribution (Figure 11). The granulomas are unusual, in that many of the multinucleated giant cells contain degenerated plant material (Figure 12).

**Diagnosis.**—Aspiration pneumonia.

**Discussion**

**Clinical Features.**—Acute aspiration pneumonia results from aspiration of gastric contents. The manifestations are variable, depending on the amount and type of material aspirated. Patients who suffer an episode of massive aspiration develop diffuse alveolar damage and are very unlikely to be biopsied. The most common finding at autopsy in debilitated patients, for whom a history of aspiration may not be known, is acute bronchopneumonia with a granulomatous response to foreign material.

Chronic, recurrent episodes of clinically unsuspected aspiration pose a more difficult diagnostic challenge. Affected patients are often relatively healthy, with the exception of certain risk factors, such as severe gastroesophageal reflux disease, neurologic impairment, previous surgery affecting the upper aerodigestive track, or use of legitimate or illicit pharmacologic agents that may suppress the central nervous system. A history of recurrent pneumonia, associated with dyspnea and cough, is common. In these patients, the diagnosis of aspiration is rarely suspected before lung biopsy. Radiographically, about one-half of patients show bilateral involvement, which usually takes the form of infiltrates on conventional posterior-anterior roentgenograms and centrilobular nodules on computed tomography scans. When unilateral, nodules predominate and may be solitary, thus mimicking the appearance of a neoplasm.

**Pathologic Features.**—Surgical lung biopsies from patients with chronic recurrent aspiration of gastric contents commonly show patchy bronchiolitis obliterans-organizing pneumonia, also termed organizing pneumonia, with a distinctly bronchiolocentric distribution (Figure 13). The specific finding that distinguishes aspiration from other causes of bronchiolitis obliterans-organizing pneumonia is well illustrated in this case and comprises airway-centered granulomas with central suppuration or foreign-body giant cells with exogenous material. These can be very focal and sometimes require a diligent search. Less commonly, organizing pneumonia is minimal or absent, and instead, the findings are those of acute bronchiolitis with or without bronchopneumonia characterized by airway-centered acute inflammation and necrosis.

The key to recognizing aspiration as the etiology is to identify the accompanying foreign-body giant cells or suppurative granulomas with characteristic exogenous material.

Aspirated materials comprise either vegetable matter, skeletal muscle, or crystalline inorganic “fillers” found in oral medications (Figure 14). Depending on the age of the process, organic material ranges from recognizable plant cellular structures and skeletal muscle to amorphous, degenerated, pale eosinophilic material situated within peribronchial interstitium. Inorganic fillers from medications usually take the form of either microcrystalline cellulose, which is strongly birefringent, or crospovidone. One must take care not to mistake various endogenous substances, such as blue bodies, asteroid bodies, and various birefringent calcium salts, for aspirated material (Figure 15).

Occasionally, biopsies demonstrate only airway-centered, suppurative granulomas without exogenous material, a combination of findings that raises the possibility of aspiration but is not conclusive. In such cases, special stains should be used to exclude granulomatous infection. Organisms that may cause suppurative granulomatous inflammation, potentially resembling that seen in aspiration, include *Nocardia, Actinomyces*, and *Blastomyces*. Rare forms of pulmonary infection that may mimic foreign-body granulomatous inflammation include ruptured echinococcal cysts and other parasitic infestations, most notably, schistosomiasis, paragonimiasis, and strongyloidiasis.

**CASE 4**

**Clinical History**

A previously healthy, 66-year-old man presented with complaint of cough for several months, occasionally productive of sputum. Computed tomography scan results showed a left upper lobe mass that was positive...

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**Table 3.** Distinguishing Fibrotic Langerhans cell histiocytosis (LCH) From Usual Interstitial Pneumonia (UIP) in Surgical Lung Biopsies

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<th>Findings</th>
<th>UIP</th>
<th>LCH</th>
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<td>Low-magnification distribution</td>
<td>Patchwork, peripheral/subpleural, paraseptal</td>
<td>Bronchiolocentric (Figures 6 and 10)</td>
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<tr>
<td>Configuration of fibrotic scarring</td>
<td>Irregular (Figures 2 and 4)</td>
<td>Stellate (Figure 10)</td>
</tr>
<tr>
<td>Honeycombed change</td>
<td>Present (Figure 5)</td>
<td>Absent</td>
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<tr>
<td>Paracicatricial airspace enlargement (scar</td>
<td>Absent (Figures 2 and 4)</td>
<td>Present (Figure 10)</td>
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<td>emphysema)</td>
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**Figure 11.** Low-magnification view of bronchiolocentric necrotizing granulomatous inflammation in aspiration pneumonia (case 3). Even at this low power, the granulomas appear to be centered on amorphous eosinophilic material (hematoxylin-eosin, original magnification ×20).

**Figure 12.** High-magnification view of palisaded granuloma surrounding degenerated plant material (case 3) (hematoxylin-eosin, original magnification ×400).
on positron emission tomography scan. He underwent surgical excision.

**Lung Biopsy Findings**

At low magnification, the main change in the digitized section available for your review is a distinctive pattern of necrotizing granulomatous inflammation (Figure 16). Irregularly shaped zones of necrosis have a granular, basophilic appearance and are bounded by a mixed inflammatory infiltrate, in which there are variable numbers of multinucleated giant cells (Figure 17). The polymorphic inflammatory infiltrate in nonnecrotic areas includes distinctive granulomatous microabscesses, in which small, punctate foci of necrotizing polymorphonuclear neutrophils are surrounded by palisaded and multinucleated histiocytes (Figure 18). Finally, there are multiple small vessels, including capillaries (capillaritis), that show necrotizing vasculitis (Figure 19).

**Diagnosis.**—Wegener granulomatosis.

**Discussion**

**Clinical Features.**—Wegener granulomatosis is a form of systemic small-vessel vasculitis that most frequently

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**Figure 13.** Low-magnification view of bronchiolitis obliterans-organizing pneumonia, comprising whorls of proliferating fibroblasts within distal airways and adjacent airspaces, with associated chronic inflammation. A suppurative granuloma characteristic of those found in aspiration pneumonia is seen on higher power (inset) with degenerated plant material at the center associated with neutrophils (hematoxylin-eosin, original magnifications ×40 and ×400 [inset]).

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**Figure 14.** High-magnification photomicrographs demonstrating exogenous materials in aspiration pneumonia. A, Plant material. B, Amorphous, eosinophilic material consistent with degenerated organic matter. C, Chunky, crystalline material that is strongly birefringent under polarized light, consistent with microcrystalline cellulose. D, Small, round, hematoxyphilic globules, indicative of crospovidone (hematoxylin-eosin, original magnifications ×400 [A, B, and D] and ×600 [C]).
involves the upper respiratory tract and lungs, with the classic triad occurring when the kidneys are also affected. Numerous other sites can be involved, including the skin, joints, eyes, and nervous system. Upper and lower respiratory tract involvement is common early in the disease course. When the lungs are the sole site of disease, it is referred to as limited or localized Wegener. More recently, the term limited has been used to distinguish patients without severe or life-threatening disease, based on (1) the absence of red blood cell casts in the urine; (2) a serum creatinine of less than 1.4 mg/dL or less, and no rise in creatinine greater than 25% from baseline in patients with hematuria (without red cell casts); (3) “circumscribed” pulmonary involvement characterized by a room-air $PO_2$ greater than 70 mm Hg or room-air $SO_2$ greater than 92% using pulse oximetry; and (4) no disease in a critical organ that, without immediate institution of maximal therapy, threatens organ function or the patient’s life. Presenting complaints include nonspecific, generalized symptoms, such as fever, weakness, and weight loss, as well as more specific symptoms depending on sites of involvement. Chronic pansinusitis, rhinorrhea, and epistaxis characterize upper respiratory involvement, whereas cough, dyspnea, and hemoptysis may be seen with lung involvement. Glomerulonephritis leading to chronic renal impairment is a common manifestation of the generalized form. Studies using aggressive immunosuppressive therapies demonstrate mortality rates of between 10% and 30%. Recent experience suggests that rituximab may have value in patients who fail conventional immunosuppressive treatment.

Antineutrophil cytoplasmic autoantibodies (ANCA) directed against serine proteinase-3 (PR3-ANCA) are highly specific for Wegener granulomatosis, although they occasionally occur in other conditions and do not, by themselves, establish a diagnosis of Wegener granulomatosis. PR3-ANCA corresponds to a cytoplasmic (cANCA), as opposed to perinuclear (pANCA), pattern of fluorescence when an indirect immunofluorescence technique applied to ethanol-fixed neutrophils is used. Enzyme-linked immunosorbent assay tests are more specific, although a testing strategy that employs both assays provides greater diagnostic accuracy and precision. At least 90% of patients with generalized Wegener granulomatosis that includes renal involvement will have a positive cANCA result as opposed to about 60% of those with disease localized to the lung. pANCA occurs in a very few patients with Wegener granuloma-
Figure 16. Low-magnification photomicrograph (case 4) showing necrotizing granulomatous inflammation in Wegner granulomatosis. The necrotic zones are irregularly shaped and have a deeply basophilic, “dirty” appearance because of karyorrhexis of polymorphonuclear neutrophils (hematoxylin-eosin, original magnification ×40).

Figure 17. High-magnification view of the mixed inflammatory infiltrate in Wegener granulomatosis (case 4), including prominent acute inflammation, histiocytes, and scattered multinucleated giant cells (hematoxylin-eosin, original magnification ×200).

Figure 18. High-magnification view of a granulomatous microabscess (case 4). A periphery of palisaded histiocytes and giant cells surround an area of centrally situated neutrophils with karyorrhexis (hematoxylin-eosin, original magnification ×400).

Figure 19. High-magnification view of necrotizing vasculitis in Wegener granulomatosis (case 4). The wall of this artery has been destroyed and infiltrated by neutrophils, histiocytes, and giant cells with associated fibrinoid necrosis (hematoxylin-eosin, original magnification ×400).
tosis and is usually directed against myeloperoxidase. Given the increasing reliance on ANCA testing as a diagnostic tool, the diagnosis of Wegener granulomatosis on a surgical lung biopsy is often a surprise for patients with either negative ANCA studies or atypical radiologic findings. In addition to being a powerful diagnostic tool, recent evidence suggests that ANCA may play a role in the pathogenesis of Wegener granulomatosis and other forms of small vessel vasculitis.48 Imaging studies of the chest in patients with Wegener granulomatosis and lung involvement classically show multiple, cavity nodules.49 Solitary nodules or infiltrates, as demonstrated in this patient, are uncommon but have been described.50

Pathologic Features.—The classic findings in lung biopsies from patients with Wegener granulomatosis are well illustrated in this case and are summarized in Table 4. Perhaps the most striking change on lung biopsy is geographic parenchymal necrosis, which is characteristically deeply basophilic due to abundant karyorrhectic debris (Figure 16).51 The term geographic refers to the highly irregular shape the necrosis takes and is a helpful clue to the diagnosis. The periphery of these necrotic zones comprises a variable combination of epithelioid histiocytes, other mononuclear inflammatory cells, neutrophils, eosinophils, and multinucleated giant cells. In some patients, eosinophils may be an especially conspicuous component of the inflammatory infiltrate, a variation on an otherwise classic theme, for which, the term eosinophilic variant has been proposed.52 Another helpful feature that is well demonstrated in this case is the presence of small, suppurative, palisaded granulomas outside of the large, necrotic zones (Figure 18). The airways are often a target of granulomatous inflammation in Wegener granulomatosis, and in some patients, bronchocentric granulomatous inflammation may be a dominant feature.53 The bronchiolitis obliterans-organizing pneumonia–like variant of Wegener granulomatosis refers to patients in whom secondary organizing pneumonia is a predominant finding that may obscure the concomitant granulomatous inflammation and vasculitis that is essential to diagnosis.54

Necrotizing vasculitis is the sine qua non of Wegener granulomatosis, although it may be neither a prominent feature nor present in a subset of lung biopsies.55 Most commonly, the vasculitis of Wegener granulomatosis takes the form of punctate transmural zones of necrosis, comprising a combination of fibrin and karyorrhectic debris (fibrinoid necrosis), eccentrically located within the walls of small muscular arteries and veins (Figure 20). The vascular infiltrate may include granulomas or isolated giant cells, but a granulomatous component is not required for the diagnosis. The vascular infiltrate may also be rich in lymphocytes and mononuclear histiocytes. Occasionally, the vasculitis in Wegener granulomatosis affects predominantly alveolar capillaries, resulting in a combination of necrotizing capillaritis and alveolar hemorrhage,56 which is manifested by acute inflammation distributed along alveolar septal capillaries, with focal necrosis and karyorrhectic debris (Figure 21). The alveolar septa often appear thickened or disrupted because of the infiltrate. Capillaritis can be subtle and is easily missed, even by experienced pathologists. Moreover, the otherwise usual findings of Wegener granulomatosis described above are frequently lacking. The presence of diffuse alveolar hemorrhage, characterized by a combination of fresh blood, fibrin, organizing fibroblasts and myofibroblasts, nonspecific alveolar septal thickening, and hemosiderin-laden macrophages within alveolar airspaces, should trigger a diligent search for capillaritis. Diffuse alveolar hemorrhage with capillaritis is not unique to Wegener granulomatosis, however, and can be seen in a variety of other conditions, including microscopic polyangiitis and systemic lupus erythematosus.57 Specific diagnosis ultimately requires correlation with other data, including the results of ANCA testing.

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<td>Necrotizing granulomatous inflammation</td>
<td>• Geographic configuration at low magnification (Figure 16)</td>
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<td></td>
<td>• Karyorrhectic debris resulting in basophilic, “dirty” appearance (Figures 16 and 17)</td>
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<td></td>
<td>• Mixed inflammatory infiltrates, comprising neutrophils, eosinophils, lymphocytes, and both mononuclear (epithelioid, palisaded) and multinucleated histiocytes (hyperchromatic nuclei) (Figure 17)</td>
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<td></td>
<td>• Granulomatous microabscesses (Figure 18)</td>
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<td>• Nonnecrotizing, sarcoidealike granulomas are absent</td>
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<tr>
<td>Necrotizing vasculitis</td>
<td>• Focal, eccentric, transmural (Figure 20)</td>
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<td>• Mixed inflammatory infiltrate with or without multinucleated giant cells (Figures 19 and 20)</td>
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<tr>
<td></td>
<td>• Fibrinoid necrosis (Figure 19)</td>
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<td>• Capillaritis (Figure 21)</td>
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<tr>
<td>Secondary features</td>
<td>• Small and large airway involvement (bronchocentric variant)</td>
</tr>
<tr>
<td></td>
<td>• Prominent eosinophilia (eosinophilic variant)</td>
</tr>
<tr>
<td></td>
<td>• Organizing pneumonia (BOOP-like variant)</td>
</tr>
<tr>
<td></td>
<td>• Diffuse alveolar hemorrhage</td>
</tr>
</tbody>
</table>

Abbreviation: BOOP, bronchiolitis obliterans-organizing pneumonia.

Figure 20. High-magnification photomicrograph of punctate involvement of the blood vessel wall in Wegener granulomatosis. The vascular infiltrate is transmural, is located eccentrically within the vessel wall, and includes neutrophils, histiocytes, and lymphocytes (hematoxylin-eosin, original magnification ×400).

Figure 21. High-magnification view of necrotizing capillaritis in Wegener granulomatosis. Alveolar septa are thickened and disrupted secondary to an acute inflammatory infiltrate. The airspaces are filled with erythrocytes and fibrin (hematoxylin-eosin, original magnification ×400).
References


