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Pulmonary Angiitis and Granulomatosis: Wegener Granulomatosis

Charles M. Lombard

Although Klinger, a friend of Wegener, published the first description of what is presently recognized as Wegener granulomatosis (WG),[1] it was Wegener who clearly separated this disease from other vasculitides, specifically from periarteritis nodosa. Wegener saw his first case in 1934 and presented his findings at a meeting of the German Pathological Society in 1936.[2] He described the case of a 38-year-old truck driver who presented with maxillary pain and subsequently developed ulcers of the mouth and stomach, saddle-nose deformity, deafness, pneumonia, and renal failure. By the time of publication in 1939, Wegener had seen two additional cases.[3] At that time, Wegener felt sure that what he was describing was a new disease. In his article, he made the following observations.

> Similar lesions in these three cases argues for the systemic nature of this process which is characterized by generalized periarteritis nodosa and granuloma formation. I do not favor the idea to include this well-defined clinical entity into the larger group of hyperergic diseases. For future research, it will be advantageous to separate this well-defined entity which is a specific and peculiar disease characterized by its clinical course and unequivocal anatomical findings.

World War II interrupted Wegener's work; following the war, more reports of this disease appeared in the literature. It was the paper by Ringertz, in 1947, that attached the eponym "Wegener granulomatosis" to the disease.[4] In 1954, Godman and Churg summarized the literature and articulated the diagnostic triad of WG: necrotizing granulomata in the upper and lower respiratory tract, generalized necrotizing vasculitis, and glomerulonephritis.[5] Wegener, who died in 1990 at the age of 88, lived to see remarkable changes in the spectrum of disease that bears his name, as well as dramatic improvements in both the diagnosis and treatment of this previously lethal condition.

CLINICAL MANIFESTATIONS

Display 68-1 presents some of the usual and unusual manifestations of WG. A series of 158 patients at the National Institute of Allergy and Infectious Diseases has been compiled, with notation made of the frequency of involvement of various organ systems.[6] About three fourths of patients present with ear or upper respiratory disease. The most common problems are chronic sinusitis and serous otitis media.[7] Over the course of the disease, 90% of patients develop evidence of disease in the ear, nose, and throat system.

Pulmonary disease may appear as infiltrates or nodules mimicking metastatic disease. About 40% to 50% of patients present with pulmonary lesions, and over 80% will develop them over the course of the disease. However, in as many as one third of patients, radiographic pulmonary disease is inapparent.

Although fewer than 20% of patients present with renal disease, eventually three fourths of patients develop glomerulonephritis. The latter is usually a focal segmental necrotizing glomerulonephritis; however, a diffuse crescentic glomerulonephritis may also develop.[8] Occasionally, the pathologist can identify a necrotizing vasculitis in renal biopsy specimens from these patients. Cases with glomerulonephritis preceding the other manifestations do occur, and an erroneous diagnosis of primary idiopathic glomerulonephritis is usually made.[9] A rare case of WG presenting as a renal mass has been reported.[10]

The above three sites are the most commonly involved and have led to the ELK system (*i.e.*, ear and upper respiratory tract, lung, kidney) of classifying WG. The relative proportion of cases with these involved sites is shown in Display 68-2. The data are derived from cases of WG seen at the Mayo Clinic between 1965 and 1989.[11]

DISPLAY 68-1. MANIFESTATIONS OF WEGNER GRANULOMATOSIS

Upper Respiratory Tract
Chronic sinusitis
Epistaxis
Rhinitis
Nasal perforation
Nasal deformities
Subglottic stenosis

Ear
Otitis externa
Serous otitis
Deafness
Vertigo

Gastrointestinal
Necrotizing enteritis
Perianal ulcers
Pancreatitis
Pancreatic mass

Lung
Cough
Hemoptysis
Pleuritis
Infiltrates

Neurologic
CNS infarcts
CNS hemorrhage
Diabetes insipidus
Cranial nerve palsy
Meningitis
Peripheral neuropathy
Mononeuritis multiplex

Rheumatologic
Arthritis
Myalgias
Polymyalgia rheumatica

Kidney
Glomerulonephritis
Renal mass

Cutaneous
Papules
Vesicles
Ulcers
Petechiae
Ecchymoses
Pyoderma gangrenosum

Ocular
Conjunctivitis
Uveitis
Iritis
Retinitis
Vasculitis
Proptosis or pseudotumor

Oral
Parotid enlargement
Sicca syndrome
Oral ulcers
Gingivitis

Lymphoreticular
Hilar or mediastinal
Lymphadenopathy

Genitourinary
Cystitis
Prostatitis

Constitutional
Fever
Weight loss
Anorexia
Malaise

Heart
Arrhythmias
Pericarditis

CNS, central nervous system.

DISPLAY 68-2. ELK CLASSIFICATION OF WEGENER GRANULOMATOSIS (100%)

E	29%
L	6%
EL	22%
EK	13%
LK	9%
ELK	21%

E, ear and upper right respiratory tract; K, kidney; L, lung.
From DeRemee RA. ANCA-associated diseases: a pulmonologist's perspective. Am J Kidney Dis 1991;28:180.

extremities.[12] Rheumatologic manifestations include arthralgias, arthritis, and myalgias in as many as 70% of patients. Occasionally, the disease mimics polymyalgia rheumatica[13] or rheumatoid arthritis; false-positive tests for rheumatoid factor (RF) occur in 60% of patients.[6]

Gastrointestinal involvement is rare. Cases with necrotizing enteritis,[14] perianal ulcers,[15] cases mimicking Crohn disease, intestinal perforation,[16] pancreatitis,[17] and a pancreatic mass[18] masquerading as pancreatic carcinoma have all been reported. Salivary gland involvement,[19] including parotid and submandibular glands, has been described. Oral ulcers occur in as many as 10% of patients. An unusual but distinctive hyperplastic (i.e., strawberry) or granular gingivitis has been described.[20]

Genitourinary manifestations of this disease include prostatitis[21] and cystitis.[22] Rare cases of biopsy-proven WG have been documented in the urethra, cervix, and vagina.[6]

Cardiac involvement in WG is uncommon; about 5% of patients develop a pericarditis and rarely cardiac tamponade.[23] Hilar and mediastinal lymphadenopathy are rare manifestations, described in association with a limited form of WG associated with severe ulcerative disease of the respiratory and digestive tracts.[24] Finally, a variety of nonspecific constitutional signs and symptoms are present in about one half of patients, including fever, anorexia, malaise, and weight loss.

The manifestations of WG are protean, and the clinical presentations vary accordingly. Display 68-3 lists the clinical syndromes encompassed by WG. Classic WG, with involvement of the upper respiratory tract, lung disease, and glomerulonephritis, accounts for only 21% of cases.[11] These patients typically have fulminant disease and require therapy with prednisone and cyclophosphamide.

Limited WG applies to those patients that lack renal and upper respiratory tract involvement.[25] These cases have a better prognosis than the classic form of the disease. It appears that the

DISPLAY 68-3. CLINICAL SYNDROMES OF WEGENER GRANULOMATOSIS

Classic Wegener granulomatosis (i.e., ELK)
Limited Wegener granulomatosis (i.e., no renal disease)
Protracted superficial Wegener granulomatosis
Pulmonary hemorrhage syndrome
Glomerulonephritis

E, ear and upper respiratory tract; K, kidney; L, lung.

Ocular disease is encountered in one half of patients with WG. Conjunctivitis is the most common manifestation. Unusual complications include retinal arteritis with occlusion and optic nerve vasculitis.[7] Neurologic involvement at presentation is rare, although about 15% of patients develop a peripheral neuropathy over the course of the disease. Central nervous system involvement is less common, with fewer than 10% of patients developing stroke, hemorrhage, or a cranial nerve palsy.

Cutaneous disease is present at onset in about 10% of patients, but 40% to 50% of them eventually develop skin lesions. A variety of lesions have been described, including papules, ulcers, purpura, nodules, vesicles, pustules, petechiae, and ecchymoses. The most common lesion is a papulonecrotic eruption on the

absence of renal disease is the crucial factor in accounting for the better prognosis.[26] However, some patients with limited WG eventually progress to the classic form.

A protracted superficial variant of WG has been described by Fienberg.[27] These patients can have many years of chronic inflammatory and ulcerative disease involving predominantly nasal and sinus mucosa. However, involvement of the larynx, trachea, and large airways has been noted. Indeed, these patients may have chronic indolent disease for years before developing a fulminant episode.

Diffuse pulmonary hemorrhage is an unusual but well-documented presentation of WG.[28] These patients have fulminant disease, and some patients eventually develop more typical lesions of WG in the lung. Finally, rare patients present with glomerulonephritis without evidence of extrarenal disease,[9] only to develop classic WG later.

PATHOLOGY

The observation that WG was not simply a vasculitis was first made by Fienberg in 1955.[29] The use of the term pathergic to emphasize this point, however, has not been well accepted. Pathergy, defined as the totality of the morbid phenomena that can be produced by a state of altered reactivity, is a concept difficult to grasp and lacks specific meaning. However, it is important to recognize that there are parallel processes taking place in active WG: tissue necrosis and vasculitis. It is clear that the necrosis is not simply ischemic or infarctlike necrosis secondary to the vasculitis; tissue necrosis is a primary component of the disease process and may be found in the absence of vasculitis. There is a progression from tissue micronecrosis to larger zones of macronecrosis that eventually heal by fibrosis (Fig. 68-1).[30]

Micronecrosis refers to microscopic foci of fibrinoid necrosis of collagen. These foci are usually associated with neutrophilic inflammation admixed with histiocytes and a scattering of multinucleate giant cells. As these foci enlarge and coalesce, the zones of necrosis become geographic and surrounded by pallisading granulomatous inflammation. The necrotic tissue frequently appears granular and basophilic from degenerating neutrophils and nuclear dust.

The vasculitis in WG can be thought of as a capillaritis and as a granulomatous, lymphocyte- and histiocyte-dominated vasculitis. Capillaritis (Color Fig. 68-1; Fig. 68-2) is characterized by neutrophilic infiltration of alveolar septa, fibrin thrombi in alveolar
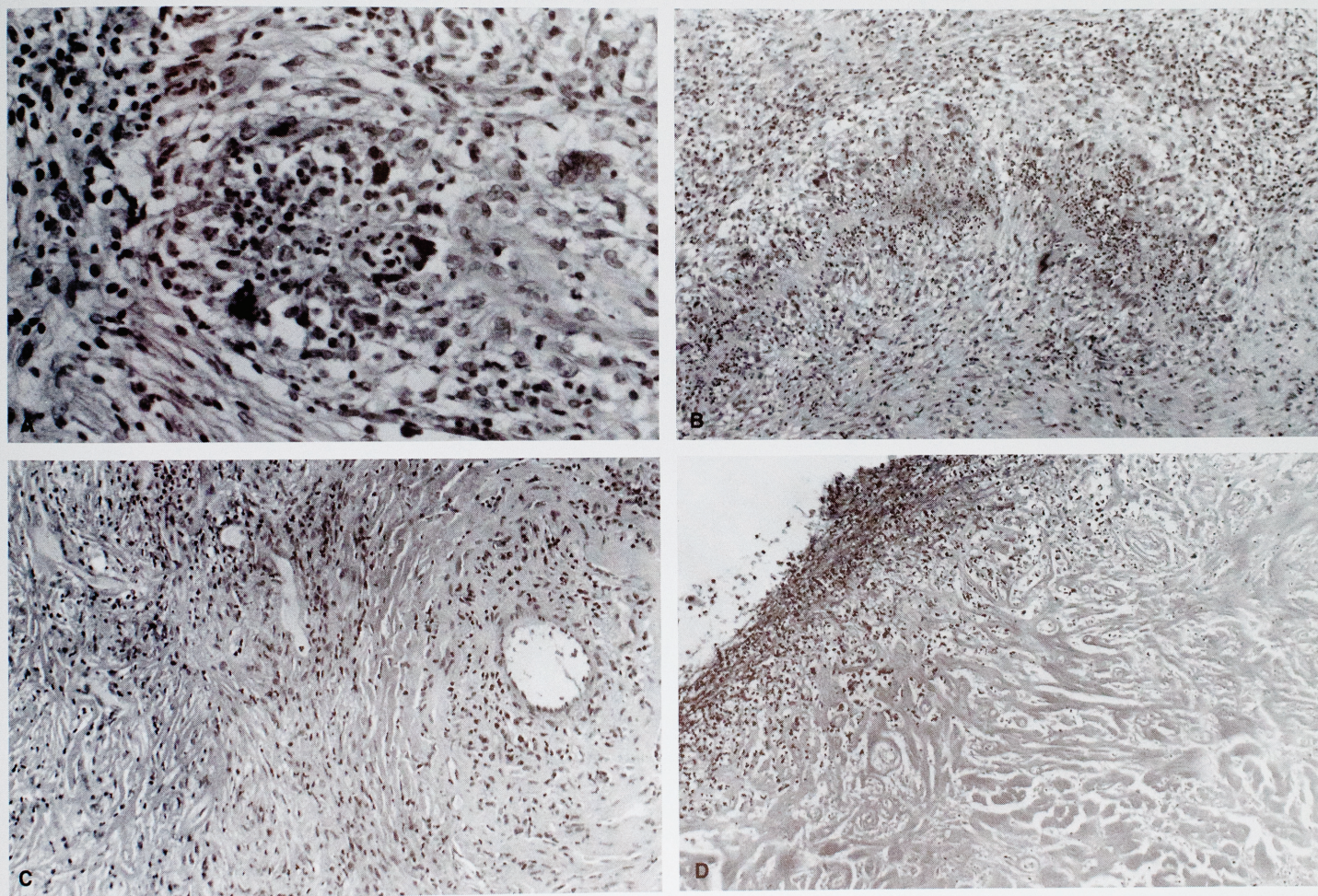
FIGURE 68-1. (**A**) An area of early micronecrosis of collagen is surrounded by neutrophils and histiocytes, including multinucleate giant cells. (**B**) Coalescing areas of necrosis are seen in Wegener granulomatosis with palisading of histiocytes. (**C**) An area of fibrosis is present in Wegener granulomatosis; note the area of fibrosis of the vessel wall as well as of the surrounding tissues. (**D**) A cavity is present in Wegener granulomatosis with extensive hyaline fibrosis of wall. This patient had limited Wegener granulomatosis with an indolent clinical course. (H & E stains; low magnifications.)

FIGURE 68-2. A chest x-ray film shows bilateral alveolar infiltrates in a patient with Wegener granulomatosis presenting as diffuse alveolar hemorrhage (see Color Fig. 68-1).

capillaries, interstitial hemosiderin and nuclear dust, and septal necrosis; the result is intraalveolar hemorrhage.[31] Less commonly, a microgranulomatous capillaritis may be encountered (Fig. 68-3). Capillaritis is a common, although frequently inconspicuous, finding in WG. However, it may be the sole manifestation of disease in the lung in rare cases.

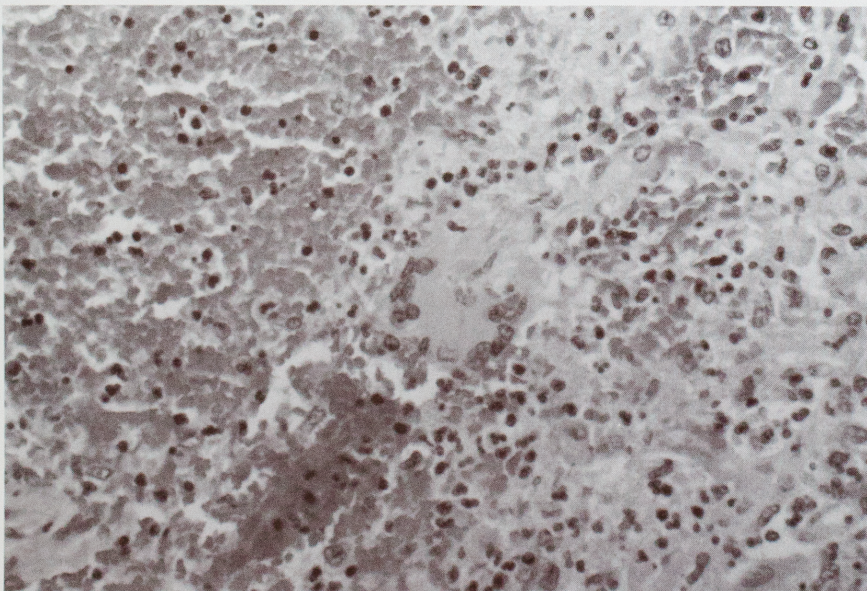Granulomatous vasculitis involves both arteries and veins. It is thought to be a reflection of micronecrosis of the collagenous tissues in these structures, and it evolves in a manner similar to that of collagenous necrosis elsewhere. The frequent eccentric location of vasodestructive lesions, which appear to start in the adventitia of vessels and spread in a centripetal way, supports this concept (Fig. 68-4A–C). Occasionally, the physician can identify a neutrophil-dominated vasculitis with fibrinoid necrosis (Fig. 68-4D). As the disease progresses, fibrosis ensues, with scarring of the vessel walls.

The third component of WG is granulomatous inflammation. Areas of diffuse granulomatous inflammation characterized by sheets of epithelioid histiocytes admixed with multinucleate giant cells, neutrophils, lymphocytes, and a scattering of other inflammatory cells, including eosinophils, are common (Fig. 68-5). Sarcoidlike granulomas are not a feature of WG.

These pathologic changes may be combined in a number of ways to produce a histologic pattern of disease in the lung (Display 68-4). A chronic mucositis is best described for cases involving the nose and paranasal sinuses.[27] However, there are cases suggesting the large airways as the major site of disease, resulting in a chronic suppurative bronchitis.[32] The histologic changes in these cases are those of mucosal ulceration with tissue necrosis as described above; vasculitis is inconspicuous or absent in these cases.

The classic nodular WG of the lung is characterized by three major histologic features: large zones of basophilic geographic necrosis, granulomatous vasculitis, and areas of granulomatous inflammation (Color Fig. 68-2; Fig. 68-6). Capillaritis can frequently be recognized in the alveoli surrounding these nodules. Exudative or consolidative WG has been associated with a more fulminant clinical course.[33] Radiographically and grossly, these represent pneumoniclike consolidation of the lung. Microscopically, there is an extensive granulomatous alveolitis with both interstitial and alveolar filling disease. Large numbers of neutrophils admixed with histiocytes and scattered multinucleate histiocytes are the dominant features (Fig. 68-7). Vasculitis is also diffuse and widespread; small vessels show extensive fibrinoid necrosis and proliferative changes.

An eosinophilic variant of WG has been described.[34] These cases appear similar to classic WG, except for the marked infiltration by eosinophils (Color Fig. 68-3; Fig. 68-8). The eosinophilic


FIGURE 68-3. Granulomatous capillarities with associated hemorrhage are present in a patient with Wegener granulomatosis. (H & E stain; low magnification.)
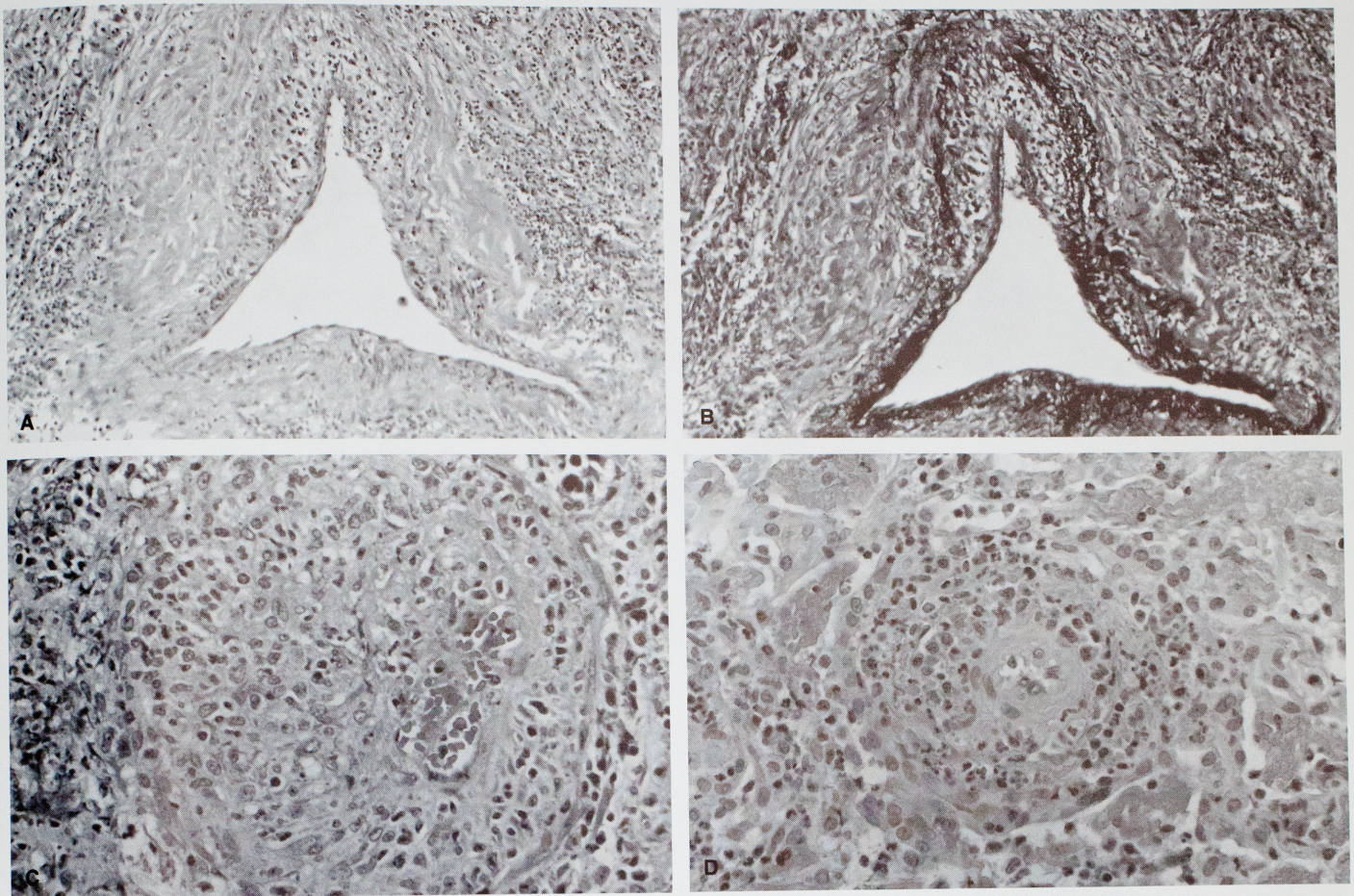
FIGURE 68-4. Vasculitis in Wegener granulomatosis. (**A**) Eccentric involvement of vessel by inflammatory infiltrate occurs (H & E stain; low magnification.). (**B**) Elastic tissue stain demonstrates destruction of elastica (low magnification.). (**C**) Granulomatous vasculitis occurs with numerous histiocytes and associated lymphocytes. (H & E stain; low magnification.) (**D**) Neutrophil-dominated vasculitis is present in a patient with Wegener granulomatosis. (H & E stain; low magnification.)
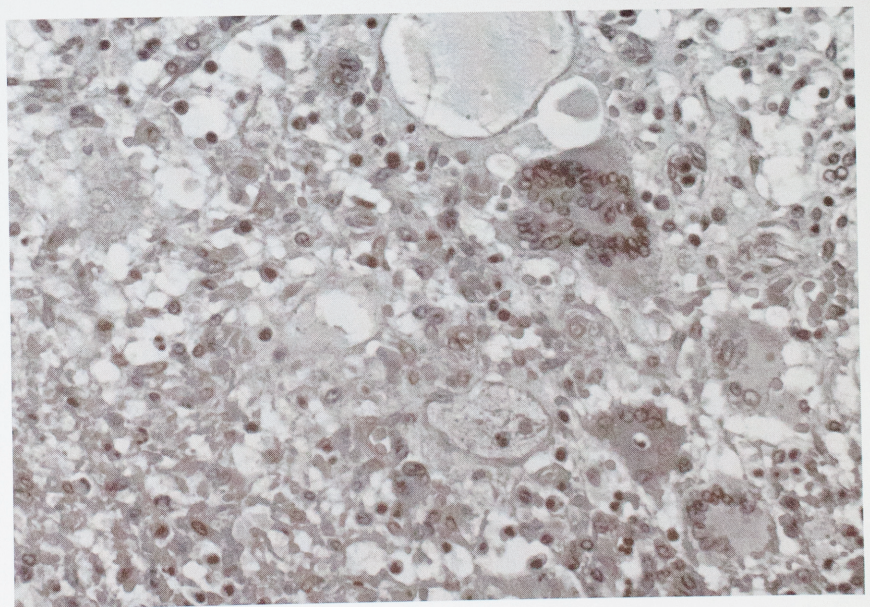
FIGURE 68-5. Granulomatous inflammation in Wegener granulomatosis is composed of histiocytes admixed with multinucleate giant cells and other assorted inflammatory cells. (H & E stain; low magnification.)
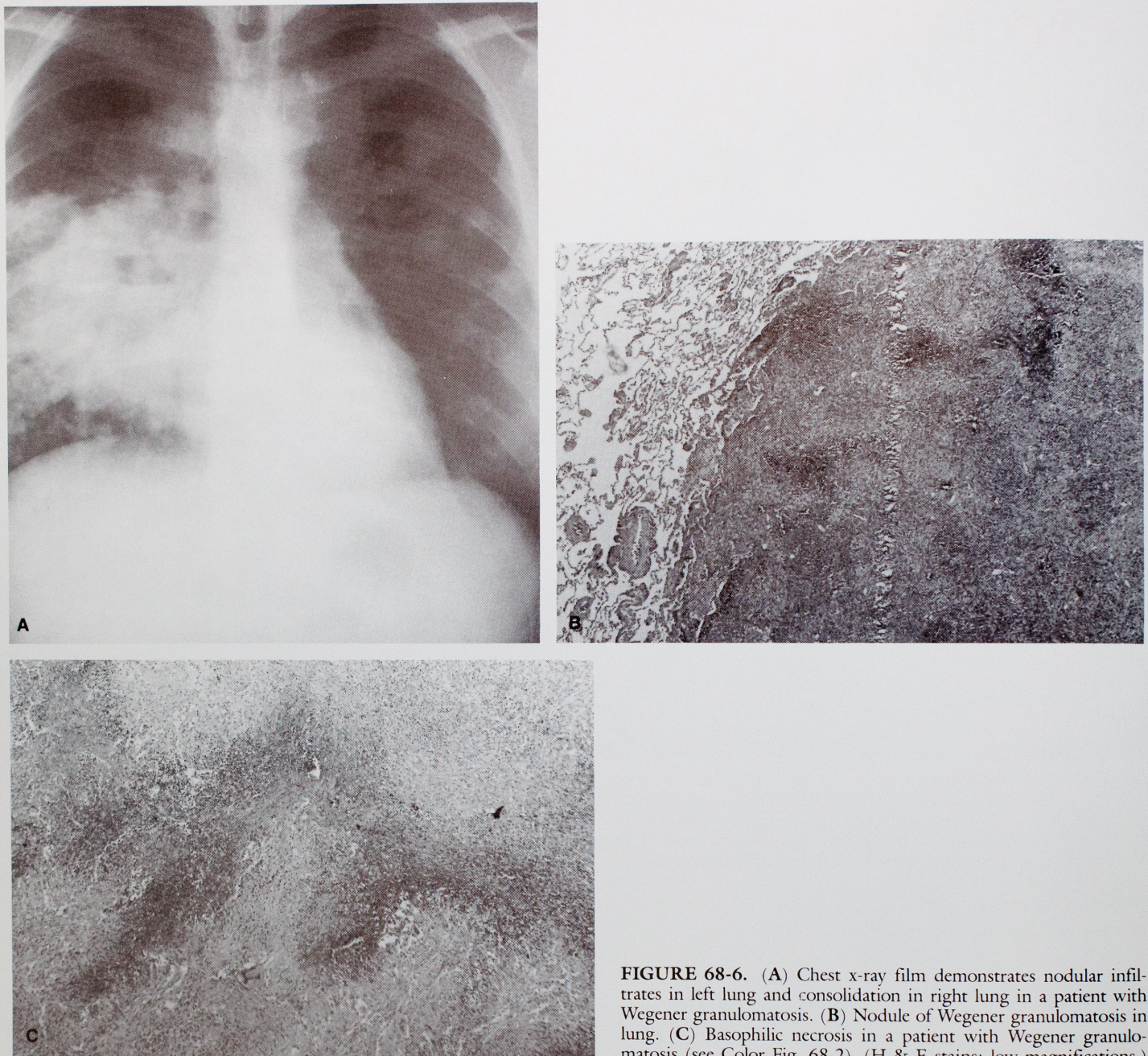
FIGURE 68-6. (**A**) Chest x-ray film demonstrates nodular infiltrates in left lung and consolidation in right lung in a patient with Wegener granulomatosis. (**B**) Nodule of Wegener granulomatosis in lung. (**C**) Basophilic necrosis in a patient with Wegener granulomatosis (see Color Fig. 68-2). (H & E stains; low magnifications.)

infiltrates may be sufficiently intense to invoke the differential diagnosis of Churg-Strauss allergic angiitis and granulomatosis. These cases require clinicopathologic correlation for diagnosis; the cases of eosinophil-rich WG are clinically indistinguishable from classic WG.

Bronchial lesions are a common, although usually inconspicuous, finding in cases of WG.[35] These changes include the following:

- nonspecific chronic inflammation
- necrotizing bronchiolitis
- bronchiolitis obliterans
- follicular bronchiolitis
- necrotizing granulomatous bronchocentric inflammation.

Although these changes are usually a minor feature, cases have been reported in which the necrotizing bronchocentric granulom-

atous inflammation is a main feature of the disease (Color Fig. 68-4; Fig. 68-9).[36] In these cases, the differential diagnosis of WG as compared with granulomatous infection and bronchocentric granulomatosis can be difficult. However, the other histologic features of bronchocentric WG are identical to those seen in the classic form, in particular, granulomatous vasculitis. As with the eosinophilic variant, bronchocentric WG behaves clinically like typical WG.

Diffuse alveolar hemorrhage as the presenting manifestation has been well documented. In one series, cases of WG and probable WG accounted for one third of all cases of diffuse alveolar hemorrhage.[28] Pulmonary hemorrhage may precede or follow the development of the nodular lesions of WG by months or years.[37, 38] These patients have a fulminant onset of disease but respond well to immunosuppressive therapy. Because these various patterns of disease are all manifestations of WG, it is not surprising that one

DISPLAY 68-4. HISTOLOGIC PATTERNS OF WEGENER GRANULOMATOSIS

Mucosal (*i.e.*, bronchitis)
Nodular (*i.e.*, classic)
Exudative (*i.e.*, consolidative)
Eosinophilic
Bronchocentric
Diffuse alveolar hemorrhage
Mixed

commonly encounters a mixture of them in any given biopsy specimen.

PATHOLOGY IN EXTRAPULMONARY SITES

Biopsy specimens of extrapulmonary sites are commonly obtained in patients suspected of having WG because they are more readily accessible than biopsy specimens of the lung (*i.e.*, nose, sinuses, oral pharynx, larynx, ear, eye, and salivary glands). The key features include mucosal ulceration, granulomatous inflammation, necrosis, and vasculitis.

Although mucosal ulcerations are found in most cases, this is a nonspecific feature. The other three findings are found in about 50% of cases,[39] although as few as 16% of cases[40] may have all three findings. When present, the finding of scattered multinucleate giant cells admixed in the inflammatory infiltrate is helpful. An example of WG with nasal involvement is shown in Fig. 68-10.

In general, the less clinical evidence there is of WG (*i.e.*, in the absence of glomerulonephritis, lung disease, or upper respiratory tract disease), the more strict the histologic criteria must be. In some of these cases, the serologic presence of a positive cytoplasmic-staining antineutrophil cytoplasmic antibody may provide additional evidence for the diagnosis of WG (see Antineutrophil Cytoplasmic Antibodies).

Biopsies of skin have demonstrated a number of findings, including leukocytoclastic vasculitis, ulcers with nonspecific chronic inflammation, ulcers with granulomatous inflammation, granulomatous vasculitis, and necrotic granulomas.[11, 12] Renal biopsies in WG show a segmental necrotizing glomerulonephritis frequently associated with glomerular thrombosis.[41] Although rare electron-dense deposits can be identified on electron microscopy, they are not believed to be of pathogenic significance.

## ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES

A major advance in the diagnosis and understanding of WG has been the discovery of antineutrophil cytoplasmic antibodies (ANCA) in these patients.[42] It is somewhat ironic that these antibodies were discovered in an effort to prove Fauci's theory that circulating immunocomplexes are present in this disease.[43] There are two patterns of ANCA: cytoplasmic-staining ANCA (C-ANCA) and perinuclear/nuclear-staining ANCA (P-ANCA). Both antibodies are predominantly of the IgG subclass. The C-ANCA antibodies are directed against proteinase 3 (*i.e.*, myeloblastic)[44]; the P-ANCA antibodies are directed predominantly against myeloperoxidase.

It is the C-ANCA pattern that has been demonstrated to have a high degree of specificity for WG.[45] In a study of 222 patients with biopsy-proven WG, 76% had a positive C-ANCA. Patients with other autoimmune diseases (*e.g.*, systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome), granulomatous diseases (*e.g.*, sarcoid, tuberculosis, Crohn disease), lymphoproliferative diseases, and other idiopathic pulmonary diseases lack this autoantibody. Rarely, false-positive C-ANCA has been noted in patients with non-Wegener glomerulonephritis. Although additional false-positive C-ANCA tests are to be expected with time and experience, it appears that this test will remain an important adjunctive tool in the diagnosis of WG in the future.

Some authors have suggested that following titers and basing treatment on a rising C-ANCA titer may help prevent relapses in WG.[46] This concept is not widely accepted, and more investigation is required to define the role of C-ANCA titers in the management of this disease.
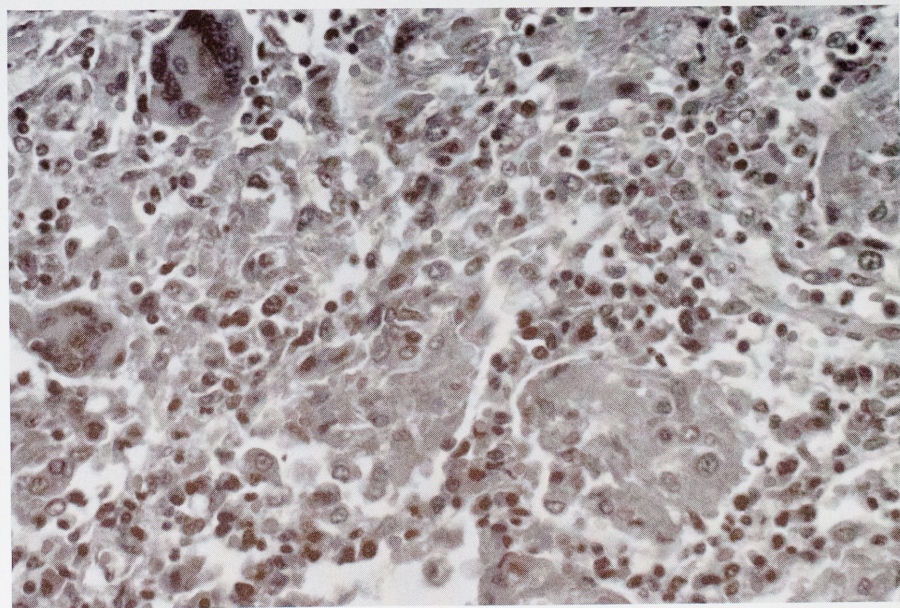
FIGURE 68-7. Exudative Wegener granulomatosis occurred in a 25-year-old man with sudden onset of respiratory failure and bilateral consolidations; there is extensive granulomatous alveolitis. (H & E stain; intermediate magnification.)
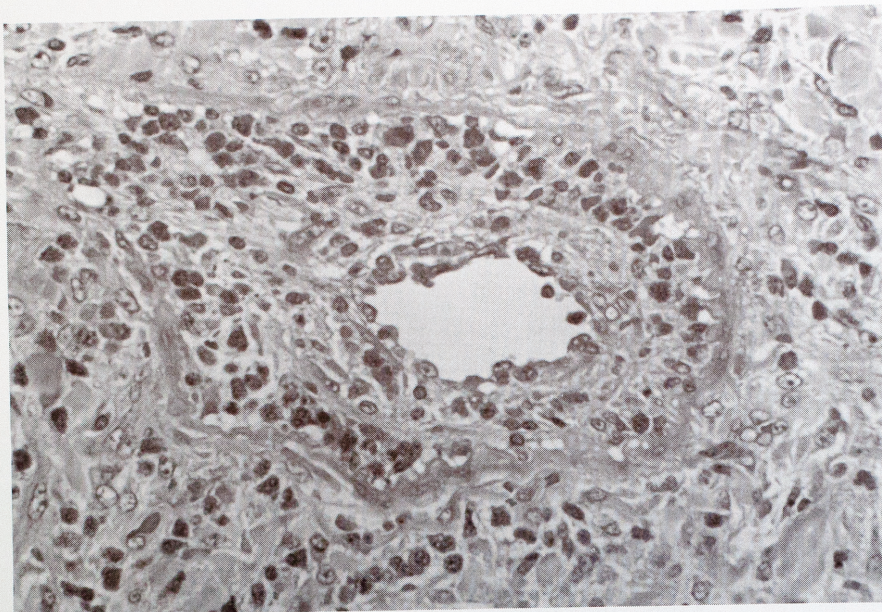
FIGURE 68-8. Eosinophilic vasculitis is a variant of Wegener granulomatosis (see Color Fig. 68-3). (H & E stain; intermediate magnification.)

Although P-ANCA may be seen in patients with WG, it occurs more commonly in other diseases, including idiopathic and vasculitis-associated crescentic glomerulonephritis, classic polyarteritis nodosa, Churg-Strauss syndrome, and microscopic polyarteritis.[47]

An interesting question concerning C-ANCA remains. Is this antibody an epiphenomenon in the disease, or is it of pathogenetic importance? The question is at this time unresolved, as there are valid arguments for both sides of the issue. The following are arguments against C-ANCA being of pathogenetic significance:

As many as 25% of patients with WG lack this antibody.
In early fulminant WG, the antibody may be absent, only to appear later in the course of the disease.
Experimental infusion of this antibody into animals does not result in disease.[43]

The following are points that indicate C-ANCA plays a pathogenetic role:

There is a high degree of specificity of the antibody for the disease.
There is a correlation of antibody titer with clinical activity of disease.
Protease 3 regulates myelomonocytic differentiation and may stimulate neutrophil activation and degranulation.[44]
Protease 3 has elastolytic properties, and it has been suggested that ANCA may bind to both protease 3 and its natural inhibitors and interfere with the function of the inhibitors.[48]

Further research should help clarify the role of this autoantibody in the pathogenesis of WG.

DIFFERENTIAL DIAGNOSIS

The histologic differential diagnosis of WG includes several entities (Display 68-5). Because treatment involves the use of immunosuppressive therapy in most cases, it is imperative to exclude granulomatous infection, particularly of fungal and mycobacterial

etiologies. There is significant overlap between the pathologic findings in fungal and tuberculous pulmonary infection and WG. Examination of special stains for microorganisms is very important in these cases; however, in infections, organisms may not be detectable.

It is important to culture biopsy specimens, but the frequent rapid clinical progression of disease does not always afford the luxury of waiting for results before making therapeutic decisions. Histologic features favoring the diagnosis of WG include vasculitis outside the areas of necrosis and inflammation, the presence of neutrophilic capillaritis, and the absence of sarcoidlike granulomas. Although a rare sarcoidal granuloma has been described, other authors[30] and I consider the presence of sarcoidlike granulomas to be strong evidence against the diagnosis of WG.

The presence of a positive ANCA serologic test provides laboratory support for the diagnosis. The presence of vasculitis in extrapulmonary sites, particularly the upper respiratory tract and kidney, also favors the diagnosis of WG. Necrotizing sarcoid granulomatosis can give rise to some confusion because there are frequently large areas of necrosis surrounded by granulomatous inflammation and an associated granulomatous vasculitis. Yet the presence of large areas of coalescent sarcoidal granulomas helps distinguish necrotizing sarcoid from WG.

Pulmonary lymphoproliferative disease, including lymphomatoid granulomatosis (i.e., angiocentric immunoproliferative le-

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DISPLAY 68-5. DIFFERENTIAL DIAGNOSIS OF WEGENER GRANULOMATOSIS

Granulomatous infection
Necrotizing sarcoid granulomatosis
Lymphomatoid granulomatosis
Pulmonary lymphoma
Rheumatoid nodules
Bronchocentric granulomatosis
Churg-Strauss allergic angiitis
Alveolar hemorrhage syndromes
Drug-associated vasculitis
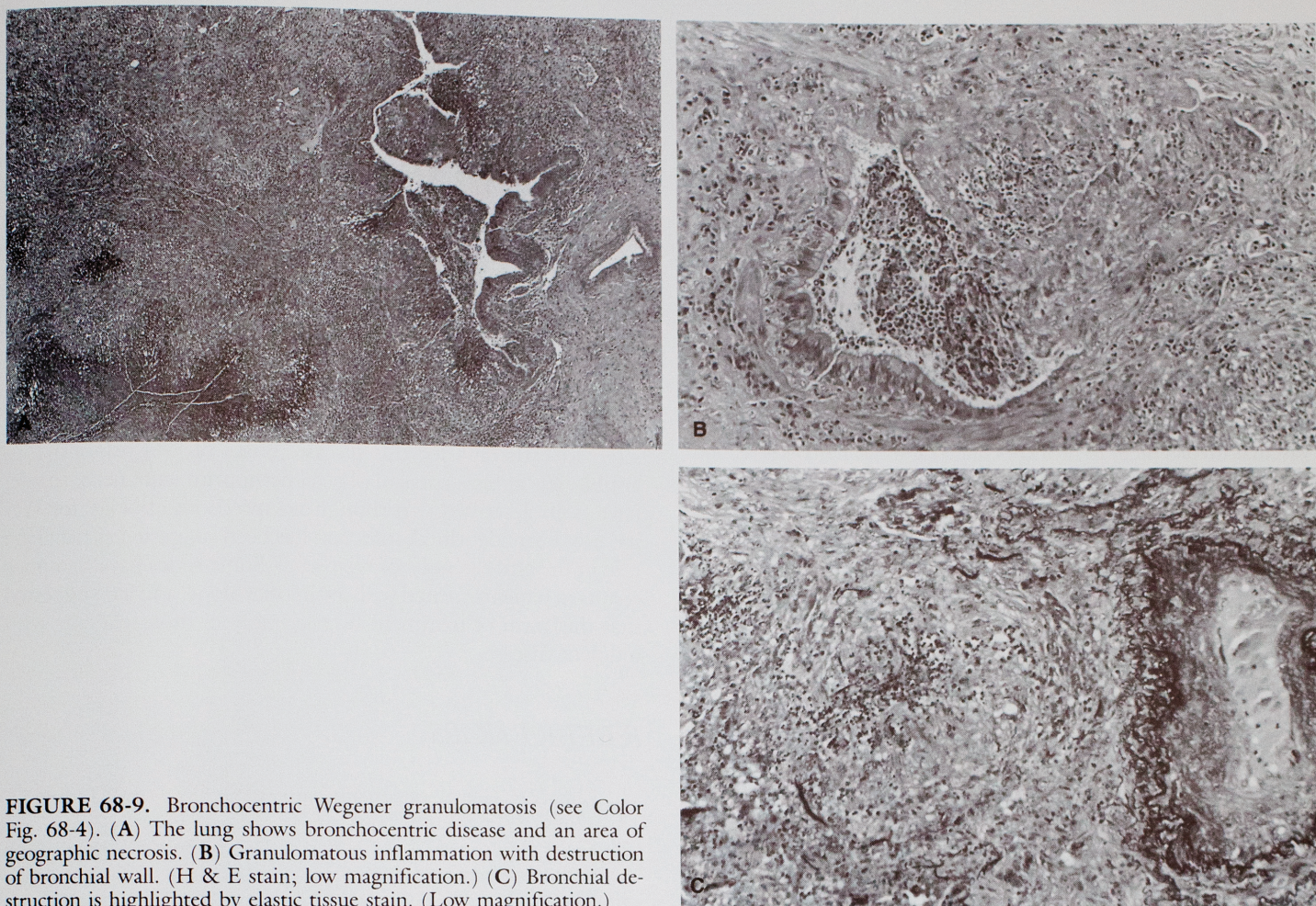
FIGURE 68-9. Bronchocentric Wegener granulomatosis (see Color Fig. 68-4). (**A**) The lung shows bronchocentric disease and an area of geographic necrosis. (**B**) Granulomatous inflammation with destruction of bronchial wall. (H & E stain; low magnification.) (**C**) Bronchial destruction is highlighted by elastic tissue stain. (Low magnification.)

sions) and pulmonary lymphoma, can simulate WG.[49] Helpful features for the diagnosis of a lymphoproliferative disease include the following:

- the presence of dense lymphoid infiltrates without significant neutrophilic inflammation

- presence of atypical lymphoid cells
- absence of granulomatous inflammation
- absence or paucity of vessel wall necrosis in areas of vasculitis
- immunologic or molecular demonstration of a monoclonal proliferation of lymphoid cells.
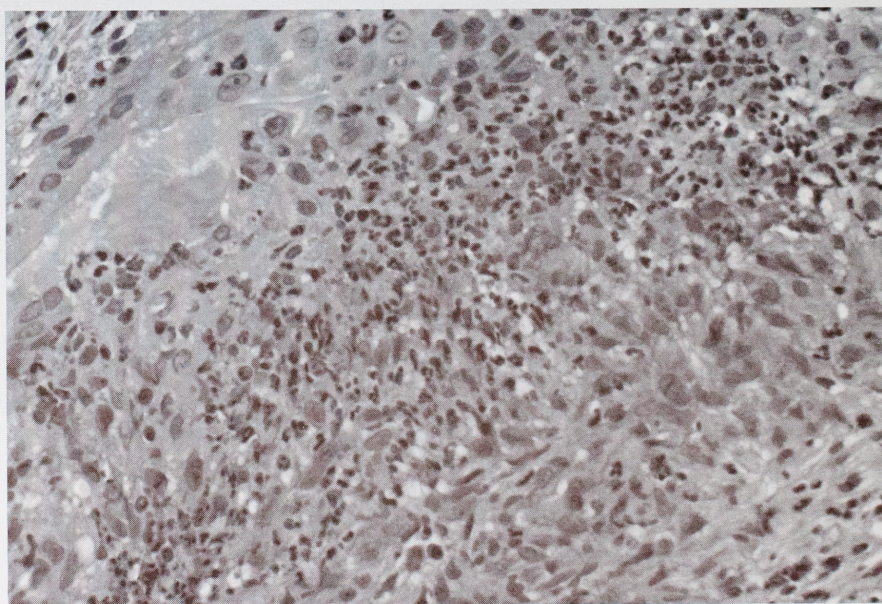
FIGURE 68-10. Nasal biopsy specimen reveals mucosal ulceration and infiltrate composed of mixed neutrophilic and granulomatous inflammation. (H & E stain; intermediate magnification.)

Hodgkin disease may be a particularly difficult differential diagnosis in that the atypical lymphoid cells may be sparse and difficult to identify. In addition, Hodgkin disease commonly has significant associated granulomatous inflammation.

Although rheumatoid nodules may closely resemble WG pathologically, there is rarely any clinical difficulty distinguishing these diseases. Histologic features favoring a rheumatoid nodule include a prominence of plasma cells, a paucity of multinucleate giant cells, and pleural involvement. Although rare cases of rheumatoid arthritis may show a marked necrotizing vasculitis, in general, this feature favors the diagnosis of WG.

In most cases of WG, the bronchial involvement is a minor component of the disease, and distinguishing it from bronchocentric granulomatosis is not difficult. In the cases described as bronchocentric WG, the differential diagnosis is more difficult. Vascular involvement in bronchocentric granulomatosis is secondary to the bronchial inflammation and is restricted to the side of the vessel adjacent to the inflamed airway. The presence of a necrotizing vasculitis also favors the diagnosis of WG.

Distinguishing Churg-Strauss allergic angiitis from the eosinophilic variant of WG requires clinicopathologic correlation. The clinical presence of asthma, peripheral eosinophilia, allergic nasal and sinus polyps, and a chest x-ray film showing transient patchy infiltrates favors Churg-Strauss syndrome. WG is favored in a patient with nasal or oral ulcers and nodular infiltrates on chest x-ray films who does not have asthma or circulating eosinophilia. Although both may show intense tissue eosinophilia on lung biopsy, the findings of large areas of basophilic serpentine necrosis and neutrophilic capillaritis favor the diagnosis of WG.

A number of alveolar hemorrhage syndromes are included in the differential diagnosis of WG presenting with such manifestations. These alveolar hemorrhage syndromes include anti–basement membrane antibody–mediated Goodpasture syndrome; collagen-vascular disease, particularly systemic lupus erythematosus; microscopic polyarteritis; and pulmonary hemorrhage associated with idiopathic glomerulonephritis. Clinicopathologic correlation is essential in elucidating this problem. Examination of fresh frozen or Zeuss-fixed tissue for immune deposits is helpful. This test will aid in the diagnosis of anti–basement membrane–mediated disease because in WG there is generally no specific immune complex deposition in the lung. Cases of systemic lupus and immune complex–mediated glomerulonephritis will commonly show granular deposits of IgG and complement.

Serologic studies useful in the differential diagnosis include antinuclear antibody, RF, ANCA, and anti–basement membrane antibody. Careful examination of specimens showing alveolar hemorrhage with capillaritis may show foci of granulomatous inflammation, and this finding would favor the diagnosis of WG.

There is a significant clinical and pathologic overlap between WG and microscopic polyarteritis.[50] Distinguishing features include the absence of ear, nose, and throat lesions in microscopic polyarteritis and the presence of P-ANCA in microscopic polyarteritis, as opposed to the C-ANCA pattern seen in most cases of WG. Finally, a number of drugs (*i.e.,* retinoids,[51] α-methyldopa,[52] and propylthiouracil)[53] have been reported to cause a disease indistinguishable from WG. Clinical history and temporal association of the disease with administration of the drug are required.

TREATMENT

Standard therapy for WG consists of daily cyclophosphamide and glucocorticoids.[6] On this regimen, partial and complete remission rates are 90% and 75%, respectively. Median time to clinical remission is 12 months. However, one half of patients who achieve a complete remission subsequently suffer one or more relapses of disease. These relapses occur anywhere from 3 months to as long as 16 years following remission of disease. Nevertheless, this represents a significant improvement in survival. The natural history of untreated WG is a mean survival of 5 months with 90% of patients dying of disease within 2 years of presentation.[54]

Because of the high rate of recurrent disease and also because of the numerous complications of prolonged therapy with cyclophosphamide and steroids, there has been an impetus to look for alternative therapy for this disease. Cases of WG responsive to antibiotics alone, particularly trimethoprim-sulfamethoxazole, have been described.[55] Although no infectious etiology for WG has ever been identified, infection has been suggested as playing a role in the pathogenesis of relapses.[56] Some series have had poor results in patients treated with antibiotics alone, and it is suggested that this form of treatment be tried only in those patients with indolent disease.

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