Pulm.

SELECTED SYNDROMES OF PULMONARY VASCULITIS

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INTRODUCTION

Vasculitis is defined as an inflammation of blood vessel walls (1, 2). The inflammatory infiltrate may consist predominately of neutrophils, lymphocytes, eosinophils or macrophages with or without a granulomatous response. If the inflammation leads to destruction of vascular walls, the process is termed necrotizing vasculitis (2).

Vasculitis was first identified as a distinct clinical and pathologic entity in 1837 by Schonlein in association with anaphylactoid purpura (3). In 1866 Kussmaul and Maier broadened the spectrum to include lesions of necrotizing vasculitis when they described the syndrome now called polyarteritis nodosa (4). In the ensuing years it has become clear that vasculitis causes diverse clinical syndromes with an extraordinary degree of heterogenity. The respiratory manifestations of this clinicopathologic process are the topic of the discussion today.

CLASSIFICATION

The classification of the vasculitides will remain arbitrary until the etiologic factors involved in their genesis are defined. However, for the purposes of orderly discussion, they may be considered in the categories of Zeek as modified by Dreisin (5). This schema groups syndromes according to both clinical and histologic similarities and thus permits useful comparisons (Table 1).

Table 1

Classification of the Pulmonary Vasculitides

I. Hypersensitivity Vasculitis
   - Anaphylactoid purpura
   - Essential mixed cryoglobulinemia with leukocytoclastic vasculitis
   - Vasculitis associated with malignancy, infection or drugs

II. Vasculitis Associated with Connective Tissue Diseases
   - Rheumatoid disease
   - Systemic lupus erythematosis
   - Progressive systemic sclerosis
   - Dermatomyositis-polymyositis
   - Mixed connective tissue disease

III. Granulomatous Vasculitis

The vasculitides include hypersensitivity vasculitis, vasculitis associated with connective tissue diseases and granulomatous vasculitis. In the first two categories the lung is only secondarily involved with a generalized process. Time constraints prevent a discussion of these entities. Rather, this presentation will consider only granulomatous vasculitis.

Table 2

Granulomatous Vasculitides

Classic Wegener's granulomatosis
  Limited Wegener's
Allergic angiitis and granulomatosis
  Churg-Strauss
  Polyarteritis overlap syndrome
Lymphomatoid granulomatosis
Necrotizing sarcoidal angiitis and granulomatosis
Bronchocentric angiitis and granulomatosis

The granulomatous vasculitides indicated in Table 2 may be considered a separate group of diseases based on three characteristics. First, each has a granulomatous component histopathologically. Second, in each the lung is the primary focus of the disease process clinically. Third, in each cytotoxic chemotherapy must now be considered (6).

PATHOGENESIS

Vasculitic syndromes are the clinical expression of an inflammatory and necrotic process which involves blood vessels. Histological manifestation of vasculitis are listed in Table 3.

Table 3

Histologic Manifestations of Vasculitis

PMN invasion of vessel wall
Fibrinoid deposits in or adjacent to the vessel wall
Vessel wall necrosis
Thrombosis
Perivascular hemorrhage
Granulomatous inflammation and fibrosis in perivascular areas

Current data suggest that the histological changes indicated are induced by immunopathogenic mechanisms. This assumption is based on three observations: First, systemic vasculitis occurs in association with clinical conditions known to be caused by immune complexes such as serum sickness and hepatitis-B related arteritis (1, 2, 7). Second, vasculitis occurs in association with collagen-vascular diseases such as rheumatoid arthritis and systemic lupus erythematosis, diseases in which an immunopathogenesis is generally accepted (1, 8, 9). Third, patients with various forms of systemic vasculitis of unknown etiology frequently have serologic abnormalities associated with immune-mediated diseases such as rheumatoid factor, cryoglobulinemia,

circulating immune complexes, hypocomplementemia, and hypergammaglobulinemia (1, 2). By analogy with systemic vasculitides, the pulmonary vasculitides are thought to be caused by an altered immune response which results in immune-mediated inflammation.

Table 4

Types of Immune Mediated Inflammation

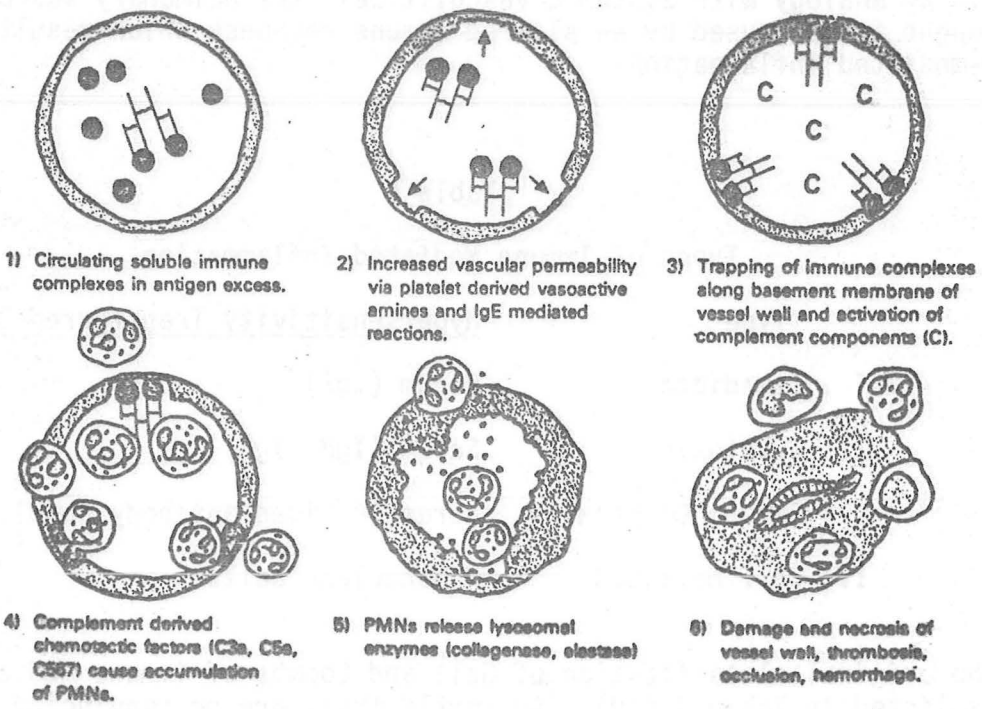
	Type	Hypersensitivity Transferred By
I	Immediate	Serum (IgE)
II	Cytotoxic	Serum (IgM, IgG)
III	Immune Complex	Serum (Antigen-antibody complexes)
IV	Cell Mediated	Mononuclear cells

The original classification of Gell and Coombs of immune mediated inflammation is listed in Table 4 (10). Currently there are no convincing data that IgE mediated response (Type I) or antibodies directed against vessel wall antigens (Type II) play a direct role in the development of pulmonary vasculitis. However, immune complex deposition (Type III) and classic delayed hypersensitivity, cell-mediated immunity (Type IV), have been extensively implicated (11).

Serum sickness reactions have provided the model for immune-complex vascular damage. If a single dose of heterologous serum protein such as bovine serum albumin is injected into an animal, this antigen disappears in seven to ten days. The disappearance of the circulating antigen corresponds to the development of antibodies to bovine serum albumin and the circulation of immune complexes containing both antigen and antibody. These complexes deposit in blood vessel walls and fix complement. The activated late components of complement C_5, C_6 and C_7 have chemotactic activity and lead to leukocyte infiltration (12-14). When smaller doses of antigen are administered daily for eight to fourteen days, the subsequent injury is related to the quantity and size of the complexes. The initial slow disappearance of the antigen is followed by a rapid clearance phase which is associated with clinical symptoms and complement consumption. Large quantities of intermediate complexes formed in antigen excess are the most toxic and can be demonstrated by immunofluoresences to be in vascular lesions (11, 15, 16).

The proposed immunopathogenic mechanism for immune-complex vasculitis is detailed in Figure 1 (1).

Figure 1

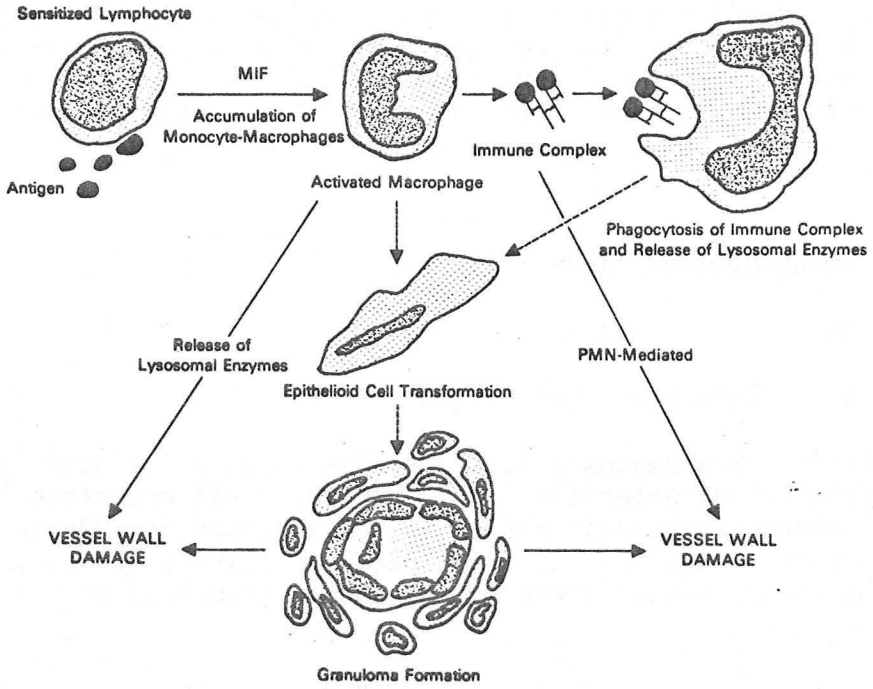


Following exposure to an antigen, soluble antigen-antibody complexes formed in antigen excess may be cleared by the reticuloendothelial system. Immune complexes remaining in the circulation cause increased vascular permeability as a result of vasoactive amines released from platelets and concurrent IgE mediated reactions (13, 17-22). The complexes are then trapped in vessel walls. Following deposition of the immune complexes the inflammatory response is complement and neutrophil dependent (23, 24).

After immune complexes are deposited in vessel walls complement is activated resulting in the generation of potent chemotactic factors for polymorphonuclear leukocytes such as the anaphylatoxin chemotactic factor $C5_a$. These cells become activated and infiltrate vessel walls. Activated neutrophils ingest immune complexes and initiate and perpetuate injury through the release of free oxygen radicals, prostaglandins, vasoactive peptides, and macrophage chemotactic factor. Neutrophils also mediate the resultant tissue necrosis through the release of the neutral proteases collagenase and elastase. The ultimate clinical expression of disease produced by this mechanism is related to the concentration of immune complexes in the circulation, the duration of their circulating half-life and the physical characteristics of the antibody molecule (1, 25-31).

While the sequence of events leading to acute necrotizing vasculitis as a result of immune complex formation and deposition is reasonably well understood, the pathogenesis of granulomatous vasculitis as a result of cell mediated immunity is less well delineated. Potential mechanisms for noninfectious pulmonary granulomatous reactions as described by Fauci are outlined in Figure 2.

Figure 2



Sensitized lymphocytes react with circulating antigen to release a variety of lymphokines including macrophage migration inhibitory factor that causes activated monocyte-macrophage accumulation around blood vessels (32). These cells release their lysosomal enzymes, causing effects similar to neutrophil-mediated vascular damage. Granulomatous reaction also develops directly by transformation of monocytes to activated macrophages and subsequently to the epitheloid and multinucleated giant cells of classic granulomata (33). Alternately, phagocytosis of certain types of immune complexes by macrophages may result in vascular damage by release of lysosomal enzymes or by direct initiation of a granulomatous reaction. In the model of Arthus vasculitis, antigenic material has been identified in the monocytes (34). In addition, immune complexes may activate macrophages by interaction of the F_C portion of the immunoglobulin molecule in the complex and the F_C receptor on the surface of the macrophage. These mechanisms could explain the mononuclear cell infiltration seen in certain types of cutaneous vasculitis as well as the intravascular-extravascular granulomata characteristically seen in the granulomatous vasculitides (35, 36). Furthermore, immune complex-mediated granulomata formation could explain the presence of granulomata in allergic angiitis and granulomatous where there is also evidence of Type IV induced disease.

Since the original description of Hepatitis B antigen associated vasculitis, it has been appreciated that an offending antigen may induce an entire spectrum of diseases from localized hypersensitivity to a polyarteritis nodosa-like systemic vasculitis resulting in a fatal multiorgan system disease (7). This variable outcome suggests that the individual response of the host to the antigenic challenge determines the presence, type and extent of the vasculitic process. In some hosts substantial immune complexes will not be formed; in others they will form and be harmlessly cleared by an intact reticuloendothelial system. However, in still others factors such as genetically determined immune reactivity, immunoregulatory mechanisms, integrity of the reticuloendothelial system and physical characteristics of the antigen-antibody complex most likely determine the variable expression of disease despite a similar sensitizing antigen (37). Until greater insight into the mechanisms responsible for aberrant immunologic reactivity is available, an appreciation of the incidence, variability of symptoms and therapeutic responses of the syndromes of pulmonary granulomatous vasculitis should be useful to the clinician.

PULMONARY GRANULOMATOUS VASCULITIS

A. Wegener's Granulomatosis

1. History and Definition

Wegener's granulomatosis was first described by Klinger in 1931 as an atypical form of polyarteritis (38). Wegener first described the disease as a distinct clinicopathologic entity in publications in 1936 and 1939 (39, 40). It was not until 1954, however, that detailed clinical and pathologic descriptions defined the diagnostic criteria for Wegener's granulomatosis presented in Table 5 (41, 42).

Table 5

Wegener's Granulomatosis

Necrotizing granulomas of upper and lower respiratory tract
Focal, segmental glomerulonephritis
Dissiminated small vessel vasculitis with lung involvement

Although multiple organ systems may be involved, the diagnoses of generalized Wegeners requires the demonstration of necrotizing granulomas in either the upper or lower respiratory tracts. In those patients with renal disease there is an associated focal glomerulonephritis. Dissiminated vasculitis involving small arteries and veins may occur in multiple organs but is usually seen in the lung in association with granuloma (43).

2. Incidence and Demographics

Wegener's granulomatosis remains an uncommon disease, although the exact incidence is difficult to determine. The two series presented in Table 6 encompass a twenty year period and are taken from the otorhinolaryngological experience and from the referral center at the National Institutes of Health (44, 45).

Table 6

Demographics of Patients With Wegener's Granulomatosis

	NIH	ENT
Patients	85	75
Male	48	41
Female	37	34
Age (years)	41	65
Range	14-75	8-75
Race		
White	82	-
Black	2	-
Hispanic	1	-

Wegener's granulomatosis is primarily a disease of whites with a peak incidence in the fourth and fifth decades, although any age group may be affected. There is a slight male preponderance with a ratio of approximately 3:2.

3. Clinical Manifestations

Wegener's original report still provides a clear description of the manifestations of this syndrome. "This sickness develops as a creeping, septic disease with a persistant snuff at the beginning. Thereafter develops granulomatous, ulcerating, necrotizing and destructive rhinitis involving also the adjacent sinuses. In addition to this, there are ulcerous, necrotizing and granulomatous alterations in the mouth, pharynx, larynx and trachea as well as infiltrating lung processes. Later, renal symptoms appear, which end in uremia and deadly renal failure. Primary are the lesions of the respiratory tract after which the diffuse angiitis develops" (46).

The presenting complaints of 85 patients with Wegener's granulomatosis are listed in Table 7 and support Wegener's description of a predominatly upper airways disease followed by systemic manifestations (46).

Table 7

Presenting Complaints in 85 Patients with Wegener's Granulomatosis

	Patients	
	Number	Percent
Upper Airway, Eye and Ear		
Sinusitis	57	67
Otitis	21	25
Rhinitis	19	22
Ocular inflammation	14	16
Epistaxis	9	11
Proptosis	6	7
Oral ulceration	5	6
Hearing loss	5	6
Lower Airway		
Cough	29	34
Hemoptysis	15	18
Chest Discomfort	7	8
Dyspnea	6	7
Pleuritis or effusion	5	6
Systemic and Constitutional		
Arthralgias, arthritis	37	44
Fever	20	34
Weight loss	14	16
Skin rash	11	13
Renal failure	9	11
Anorexia malaise	7	8

The great majority of patients present with problems related to the upper airways, eyes and ears. Sinusitis, otitis and rhinitis are common. Symptoms frequently begin as intractable rhinitis that progresses to sinusitis, most commonly involving the maxillary sinuses (47). Ocular inflammation or epistaxis are each the presenting complaint in 10-15 percent of patients. Less common complaints are proptosis, oral ulceration and hearing loss.

Presenting signs and symptoms referable to the lower respiratory tract occur in one-third of patients with cough and hemoptysis the most frequent. Chest discomfort, dyspnea and pleuritis are less common.

Systemic and constitutional symptoms may cause the patient to seek medical care. Arthralgias, arthritis and fever are particularly consistent. Weight loss and skin rash are less frequent but not uncommon. Skin ulcerations characteristic of pyoderma gangrenosum may predate by months other manifestations of the disease (48). Renal failure as a presenting symptom occurs in only 10 percent of patients.

In this large series the mean duration from the time of onset of symptoms to the diagnosis of Wegener's was 8.3 months with a range of 2 weeks to 10 years. The difficulty in diagnosis reflects both the indolence of the disease and a lack of correlation of symptoms with organ involvement. The frequency of organ involvement is listed in Table 8.

Table 8

Organ System Involvement in 85 Patients with Wegener's Granulomatosis

	Patients	
Organ System	Number	Percent
Lung	80	94
Paranasal sinuses	77	91
Kidney	72	85
Joints	57	67
Nose or nasopharynx	54	64
Ear	52	61
Eye	49	58
Skin	38	45
Nervous system	19	22
Heart	10	12

Although only one-third of patients present because of pulmonary symptoms, almost all have lung disease. In more recent series 100 percent of patients had either lung or upper airway involvement, and most had both. Renal disease, although uncommon as a presenting symptom, develops during the course of the disease in 85 percent. Joints, nose or nasopharynx, ear and eye involvement develop in up to two-thirds of patients and skin lesions in 45 percent. The nervous system and heart are involved in a minority.

a. Respiratory Disease

Pulmonary manifestations of Wegener's granulomatosis occur in almost all patients and are sufficiently characteristic to make the diagnosis highly suspicious. The pulmonary symptoms which occur during the illness are listed in Table 9 (43, 49, 50).

Table 9

Pulmonary Signs and Symptoms Associated with Wegener's Granulomatosis

Finding	Percent
Dyspnea	80
Cough	61
Chest pain	56
Hemoptysis	22-44

Although only one-third of patients describe pulmonary symptoms as a reason for presentation, the majority become symptomatic with dyspnea, cough and chest pain. Dyspnea, while unusual at the outset, develops in up to 80 percent of patients. Productive cough and chest pain occur in approximately 60 percent. The reported incidence of hemoptysis varies depending on severity of disease. Blood streaking is most common; however, life-threatening hemorrhage is reported.

Radiographic changes occur in over 70 percent of patients and provide important diagnostic information. The findings are summarized in Table 10 (51-53).

Table 10

Roentgenographic Findings of the Chest in 41 Patients with Wegener's Granulomatosis

Finding	Percent
Distribution	
Bilateral	54
Unilateral	46
Lesion	
Infiltrate	52
cavitation	10
Nodule	27
cavitation	10
Pleural effusion	20
Bronchial narrowing	13

The typical roentgenographic pattern is that of multiple bilateral infiltrates; however, the spectrum of findings are quite varied. Unilateral lesions are reported in about 45 percent of cases. Infiltrates without sharply defined borders are more frequent than discrete nodules. Cavitation occurs in both types of lesions. Infiltrates may be transient and have no prediction for upper or lower lung fields. Cavities are usually thick walled with a shaggy inner margin, but thin walled cavitation similar to coccidiomycosis is also reported. Pleural disease is less common, but pleural effusions occur in up to 20 percent. In some patients the effusions are massive. Fifteen percent of patients have been reported to have endobronchial involvement during the course of the disease (45) which correlates well with the finding of bronchial narrowing and atelectasis in 13 percent of cases (53). Unusual radiographic manifestations include a retrotracheal mass, paratracheal mass, calcified nodules and a pattern suggestive of miliary tuberculosis (53). Hilar or mediastinal adenopathy has not been reported.

Ulceration, necrosis and airway narrowing are usually found in association with pulmonary disease. The frequency of the sites of respiratory involvement are detailed in Table 11 (54).

Table 11

Sites of Respiratory Involvement in 56 Patients with Wegener's Granulomatosis

	Number	Percent
Nose and nasal sinuses	34	61
Mouth, gingiva and pharynx	21	37
Tongue	7	12
Larynx	14	25
Trachea	17	30
Bronchi	23	41

Involvement of the nose and nasal sinuses varies from uncomplicated sinusitis with local discomfort and rhinorrhea to nasal mucosal ulceration and destructive sinusitis involving the bony walls. The most frequently involved sinuses are maxillary (68 percent), sphenoid (28 percent) and ethmoid (14 percent) (55). Virtually all patients with sinus involvement develop secondary infection, most commonly with *Staphylococcus aureus*. Destruction of cartilage of the nose may result in a saddle nose deformity. Oral lesions tend to be shallow ulcers with sharp margins, and perforation of the hard or soft palate does not develop (56). The absence of erosion through the palate or the skin of the face or nose helps differentiate Wegener's granulomatosis from lethal midline granuloma which frequently causes such lesions (45). This differentiation is important, because lethal midline granuloma, unlike Wegener's, responds to radiation therapy without the need for chemotherapeutic agents.

Gingivitis with granulomatous inflammation may precede other symptoms of Wegener's by several months. Gingival bleeding with loss of teeth, resorption of alveolar bone and delayed healing following an extraction may be associated with gingivitis (57-60). Largyngeal, tracheal and bronchial ulceration occurs in one-third of cases and, when associated with proliferative lesions, can result in airway obstruction.

Pulmonary functional changes secondary to respiratory tract involvement are given in Table 12.

Table 12

Pulmonary Functional Abnormalities in 22 Patients with Wegener's Granulomatosis

Test	Number Decreased	Percent
FVC	9	41
DLCO	8	36
$FEV_{1.0}$	11	50
FEV_{25-75}	14	63

The vital capacity and diffusing capacity are usually mildly reduced, averaging 80 percent of predicted values. These measurements do not correlate with the type or extent of radiographic changes. Reductions in measurements of air flow are present in over one-half of patients, and values average 58 percent of predicted. Significant air flow obstruction correlates well with focal large airway narrowing as detected by bronchoscopy and chest tomography (61). Successful therapy is associated with marked improvement in air flow but with a further reduction in diffusing capacity. In occasional patients upper airway obstruction develops secondary to subglottic lesions; characteristic reductions in the FEV1.0 and FEV25-75 may predict this lesion (61). Thus, pulmonary function tests are some times helpful in diagnosis and management of patients with Wegener's granulomatosis.

b. Renal Disease

Over 85 percent of patients diagnosed as Wegener's granulomatosis have renal lesions. The clinical characteristics of this involvement are presented in Table 13.

Table 13

Clinical Characteristics of Renal Disease in 18 Patients with Wegener's Granulomatosis

	Number	Percent
Renal disease on initial evaluation	14	78
Serum creatinine > 1.2	10	55
Serum creatinine > 10	3	16
Hematuria	11	61
Sterile pyuria	9	50
RBC casts	7	39
Proteinuria	6	33

Renal disease is present on initial evaluation in about 80 percent of patients. Minor elevation of the serum creatinine is common, but overt uremia is less likely. Urinary sediment abnormalities are frequent and associated with moderate levels of proteinuria (62). Extrarenal manifestations almost always precede renal disease. Symptoms of Wegener's granulomatosis have been present an average of 7.5 months before the development of renal failure (49). However, once present, renal disease may progress to severe glomerulonephritis within days or weeks. Results of renal biopsy in 29 patients are given in Table 14 (49, 62).

Table 14

Renal Biopsy Findings in 29 Patients with Wegener's Granulomatosis

	Number	Percent
Focal, segmental glomerulonephritis	27	93
Granulomatous vasculitis	4	14

Focal, segmental, necrotizing glomerulonephritis, frequently with cresent formation, is the pathologic finding in 93 percent of patients. Small vessel vasculitis or granuloma formation around glomeruli is present in only a minority of patients. These findings indicate that renal biopsy is usually not useful in the initial diagnosis (45).

c. Joint Disease

Joint involvement in Wegener's granulomatosis is more common than originally reported. Characteristics of joint involvement are listed in Table 15.

Table 15

Clinical Characteristics of Joint Disease in 85 Patients with Wegener's Granulomatosis

	Number	Percent
Incidence	57	67
Arthralgias	33	39
Arthritis	24	28

Arthralgias without frank arthritis is most common. The arthralgias are polyarticular and symmetrically involve small and large joints. Arthritis affects particularly the knees and ankles; it is not deforming. Joint involvement usually parallels activity in other organ systems, although it some times precedes the onset of other symptoms (63).

d. Ear Disease

Ear involvement has now been reported in 60 percent of patients with Wegener's granulomatosis. The characteristics are listed in Table 16.

Table 16

Clinical Characteristics of Ear Disease in 21 Patients with Wegener's Granulomatosis

Finding	Number	Percent
Serous otitis media	19	90
Unilateral	12	57
Bilateral	7	33
Sensorineural hearing loss	9	43
Chronic otitis or mastoiditis	5	24

The most common otologic finding is either unilateral or bilateral serous otitis media. The symptoms are indistinguishable from simple serous otitis media associated with respiratory tract infection but are refractory to standard therapy. Sensorineural hearing deficits are associated with conductive loss due to serous otitis or tympanic membrane perforation. Vasculitis of the cochlear vessel is the presumed etiology. Chronic otitis and mastoiditis are manifested by active suppuration and necrotizing granuloma in the middle ear (64, 65).

e. Eye Disease

The ocular manifestations of Wegener's granulomatosis have been reviewed in detail and are summarized in Table 17 (55).

Table 17

Ocular Manifestations in 300 Patients with Wegener's Granulomatosis

Manifestation	Number	Percent
Ocular involvement	144	48
Proptosis, conjunctivitis, scleritis, corneo scleral ulcer	54	18
Optic nerve vasculitis	28	9
Nasolacrimal disease	9	3
Uveitis	6	2

Ocular involvement occurs in approximately 48 percent of patients. Proptosis is the most common complaint followed by inflammation of the anterior structures of the eye. Vasculitis of the optic nerve vessels is present in about 10 percent of cases and may result in rapid functional impairment if untreated. Corneal degeneration secondary to occlusive vasculitis can be corrected by corneal transplant after the underlying inflammatory response has been controlled (66, 67).

f. Skin Disease

The cutaneous manifestations of Wegener's granulomatosis are summarized in Table 18.

Table 18

Cutaneous Manifestations in 18 Patients with Wegener's Granulomatosis

Manifestation	Number	Percent
Ulceration	14	78
Papules	7	39
Vesicles	2	11
Subcutaneous nodules	2	11

Cutaneous lesions are found in 45 percent of patients (43). When they occur, the most common lesions are ulcerative and papular. Vesicles and subcutaneous nodules are infrequent (43, 54, 68). Unusual cutaneous manifestations include non-healing of surgical wounds and necrosis of the penis (69, 70).

g. Nervous System Disease

Contrary to early reports, the nervous system is involved in only 22 percent of patients with Wegener's granulomatosis (45). The nervous system lesions are indicated in Table 19.

Table 19

Clinical Characteristics of Nervous System Involvement in 19 Patients with Wegener's Granulomatous

Manifestation	Number	Percent
Cranial nerve involvement	10	53
Mononeuritis multiplex	9	47
Diabetes insipidus	1	5

Cranial nerve dysfunction and peripheral mononeuritis multiplex occur with equal frequency. Diabetes insipidus secondary to central nervous system involvement has been reported (71). Central nervous system vasculitis with or without associated subarachnoid or intracerebral hemorrhage has also been reported (72).

h. Heart Disease

Cardiac involvement is infrequent with an incidence of 12 percent (45). Although pericarditis is the most common cardiac manifestation, involvement of diffuse structures in the heart has been reported (73, 74). Intractable cardiac arrythmias, pancarditis and coronary artery vasculitis are more unusual findings (43, 54, 73, 74).

4. Laboratory Manifestations

There are no laboratory findings that are diagnostic of Wegener's granulomatosis. The more common non-specific findings are listed in Table 20 (45, 54).

Table 20

Laboratory Findings in Patients with Wegener's Granulomatosis

Finding	Number Number/Observations	Percent
Anemia	42/85	50
Leukocytosis	26/85	30
Thrombocytosis >400/000 platelets/mm	33/85	39
Elevated ESR	85/85	100
Rheumatoid factor	27/44	61
Positive ANA, LE factor	0/85	0

Anemia prior to therapy occurs in one-half of patients and is typically normocytic and normochronic. Leukocytosis of greater than 10,000/mm^3 is present in 30 percent of patients; leukopenia of less than 4,000/mm^3 has not been reported. Thrombocytosis of greater than 400,000/mm^3 is reported in 39 percent of patients; there are no reports of thrombocytopenia prior to therapy. Elevation of the erythrocyte sedimentation rate has occurred in every patient reported with a mean level of 93 mm/h. The ESR may be used as an index of disease activity. Rheumatoid factor with a mean titer of 1:128 is found in 61 percent of patients, but a positive ANA or LE prep has not been reported.

Abnormalities of immunologic parameters are listed in Table 21 (45).

Table 21

Abnormalities in Tests of Immunologic Function in Patients with Wegener's Granulomatosis

Finding	Number Number/Observations	Percent
Elevated serum immunoglobulins (IgA, IgG, IgM, IgE)	7/32	22
Immune complexes	16/34	47
Delayed hypersensitivity present	31/32	97

Elevations of serum immunoglobulins occurs in 22 percent of patients with elevations of IgA and IgM most frequent. Immune complexes are present in the sera of 47 percent and have been reported to correlate with activity of disease (75-78). Cutaneous delayed hypersensitivity is not impaired (79).

5. Limited Wegener's

The concept of limited Wegener's granulomatosis was initially suggested by Carrington and Liebow (80). Table 22 lists the clinical characteristics of the patients they described.

Table 22

Clinical Characteristics of Patients with Limited Wegener's Granulomatosis

Kidney and upper respiratory tract not involved
Women affected more than men
Increased incidence of skin lesions
Occasional progression to classic Wegener's
Response to corticosteroids

The presenting signs and symptoms are related to the lower respiratory tract. Abnormalities of renal function are not present, and there are no signs or symptoms of upper respiratory tract disease. There is a female predominance and frequent cutaneous involvement with ulceration and subcutaneous nodules. The overall prognosis is better but occasional progression to fatal classic Wegener's occurs. Responsiveness to corticosteroids was initially reported, but this observation has not been confirmed by subsequent authors (81, 82). Systematic renal biopsies have not been performed on patients with "limited Wegener's", and asymptomatic renal involvement may be present. Therapeutic considerations are not sufficiently different to warrant considering limited Wegener's as a distinct clinical entity.

6. Pathology and Diagnoses

The hallmark of Wegener's granulomatosis is a necrotizing vasculitis. The vasculitis is predominately a fibrinoid necrosis of small arteries and veins with early infiltration of polymorphonuclear leukocytes followed by mononuclear cells and ultimate healing by fibrosis. All stages of lesions may be present at a given time. Granulomata are usually well formed with large numbers of giant cells. The granuloma may be within, adjacent to, or spatially dissociated from vascular lesions. In the lung, large areas of necrosis may be present (42, 83).

7. Diagnosis

The diagnosis of Wegener's granulomatosis is made by demonstrating a necrotizing granulomatous vasculitis by histopathology. The incidence of obtaining this diagnosis from organ biopsies of affected tissue is listed in Table 23.

Table 23

Incidence of Necrotizing Granulomatous Vasculitis
in Various Organs in Patients with Wegener's Granulomatosis

Site	Number Number/Observations	Percent
Renal	4/29	14
Skin	2/8	25
Sinus	5/18	28
Nasal	6/18	33
Lung	10/18	56

Renal biopsies have previously been discussed. Skin biopsies frequently show necrotizing vasculitis, which finding only suggests the diagnosis (84). Sinus and nasal biopsies are diagnostic in approximately one-third of patients. Lung biopsy is definitive in over 50 percent of cases (85). Although endobronchial involvement is common, fiberoptic bronchoscopy with biopsy of endobronchial lesions has not been successful. Likewise, fiberoptic bronchoscopy with transbronchial biopsy is rarely positive due to the small sample size. Open lung biopsy remains the procedure of choice.

8. Treatment

Untreated Wegener's granulomatosis has a mean survival of 5 months from time of diagnosis with a 90 percent mortality at 2 years (54). Treatment with corticosteroids increases mean survival time to 12.5 months but has no effect on significant renal or pulmonary disease (86). Since the first recorded use of cytoxic agents, clinical remissions have been induced in a large fraction of patients (41, 43, 87-89). Cyclophosphamide has emerged as the agent of choice following reports of long term complete clinical remission (45, 90, 91). Current recommendations for treatment of patients with slowly progressive disease is presented in Table 24.

Table 24

Treatment of Slowly Progressive Wegener's Granulomatosis

Cytoxan 2 mgm/kg/day
Prednisone 1 mgm/kg/day

Adjust to keep leukocytes >3,000
neutrophils >1,500

Therapy is initiated with cyclophosphamide at 2 mgm/kg per day and prednisone 1 mgm/kg/day. The prednisone administration is converted to an alternate day regimen over a one to two month period and then gradually tapered over a year. Cyclophosphamide is adjusted to maintain a leukocyte count of >3,000 and a total neutrophil count of >1,500. If the initial response is poor, cytoxan is increased by 25 mgm/day every two weeks until leukopenia develops. Cyclophosphamide is continued for at least one year following complete clinical remission.

Treatment recommendations for patients with fulminate, rapidly progressive disease are presented in Table 25.

Table 25

Treatment of Fulminant Wegener's Granulomatosis

Cytoxan 4-5 mgm/kg/day for 3 days then decrease to 2 mgm/kg/day

Prednisone 2 mgm/kg/day for 3 days then decrease to 1 mgm/kg/day

In fulminant disease cyclophosphamide is initiated at 4-5 mgm/kg/day for 3 days and then decreased to 2 mgm/kg/day. Prednisone is given at 2 mgm/kg/day for 3 days and then decreased to 1 mgm/kg/day.

The results of therapy employing these regimens are presented in Table 26.

Table 26

Results of Therapy in 85 Patients with Wegener's Granulomatosis

	Patients	Percent
Complete remission	79	93
Treatment failure	6	7
Mean duration of remission (months)		48.2

Of 85 patients treated with this regimen, 79 have been in complete remission for more than 48 months. Six died due to progression of disease, a mortality of 7 percent. At last report there were 23 patients off of all treatment for greater than 35 months. Fifty two patients were still receiving therapy, and all were in complete remission (45).

Chlorambucil and azathioprine have both been investigated in the therapy of Wegener's granulomatosis, but they were not as effective in induction of clinical remissions. Azathioprine may be effective in maintaining clincal remission in patients who cannot tolerate cyclophosphamide (45). Plasmapheresis as an adjunct to cytotoxic therapy has also been employed in patients with fulminate nephritis in association with immune complex disease. Results are difficult to evaluate, and the technique remains investigational (92).

B. Allergic Angiitis and Granulomatosis - Churg-Strauss Syndrome

1. History and Definition

Following the initial report of classic polyarteritis nodosa by Kussmal and Maier, several cases were reported with vascular lesions similar to those of polyarteritis nodosa but with involvement of the pulmonary artery (4, 93, 94). Rackeman and Green first noted that patients with allergic disease manifest by asthma, eosinophila and pulmonary infiltrates formed a distinct subset of patients with polyarteritis nodosa (95). The clinicopathologic parameters that define allergic angiitis and granulomatosis were established by Churg and Strauss in 1951 and included the demonstration of both vasculitis and granulomas on histopathology (96). Subsequent reviews have emphasized the difficulty of demonstrating granulomas either on tissue biopsy specimens or at autopsy (97). The pattern of disease, however, is sufficiently distinctive to justify the recognition of the Churg-Strauss syndrome on clinical grounds.

Patients included for discussion in this review meet the three criteria established by Lanham and presented in Table 27 (98).

Table 27

Clinicopathologic Parameters of the Churg-Strauss Syndrome

Asthma
Eosinophil counts in excess of 1,500 mm^3
Systemic vasculitis involving two or more extra-pulmonary organs

The disease occurs in three distinctive phases. The prodromal phase may persist for years and consists of allergic symptoms. Allergic rhinitis and asthma develop in adult patients with no family history of atopy. The second phase is characterized by a total peripheral blood eosinophilia in excess of 1,500 mm^3 and eosinophilic tissue infiltrates in the lung or gastrointestinal tract. Infiltrates are recurrent over a period of years and are ultimately followed by a life-threatening vasculitic phase (98).

2. Incidence and Demographics

Allergic angiitis and granulomatosis or the Churg-Strauss syndrome is a rare disease. There have been 138 cases reported in the English literature.

Table 28

Characteristics of 138 Patients with Churg-Strauss Syndrome

Category	Result
Sex ratio (male to female)	1:1
Mean age of onset	
Allergic rhinitis	28 yrs.
Asthma	35 yrs.
Vasculitis	38 yrs.
Duration of pulmonary symptoms prior to systemic symptoms	2-5 yrs.

The incidence of the disease is equal in men and women. Racial characteristics have not been reported. Mean age of onset of the symptoms of rhinitis, asthma and vasculitis progressively increase from 28 to 38 years. There is a typically 2 to 5 year interval from onset of pulmonary symptoms to systemic symptoms. Patients surviving greater than one year following onset of vasculitis have a interval of 5 years or more; those with early mortality have an interval of 2 years (98-101).

3. Clinical Manifestations

Frequency of organ involvement in the Churg-Strauss syndrome is summarized in Table 29 (100-102).

Table 29

Organ System Involvement in 75 Patients with Churg-Strauss Syndrome

Organ System	Patients	Percent
Lung	75	100
Nose and nasopharynx	53	70
Skin	50	67
Nervous system	47	63
Cardiovascular	50	67
Gastrointestinal	32	42
Renal	29	38

Lung involvement manifest by asthma is present in all patients, and upper respiratory disease with allergic rhinitis and nasal polyposis occurs in a majority. The skin, nervous and cardiovascular systems are involved in about two-thirds of cases. Gastrointestinal and renal lesions occur in at least one-third. This pattern of organ involvement is sufficiently distinctive to separate this syndrome from patients with classic polyartheritis nodosa.

a. Respiratory Disease

Signs and symptoms of respiratory disease are prominent in patients with the Churg-Strauss syndrome. Table 30 lists the important respiratory manifestations.

Table 30

Respiratory Manifestations of the Churg-Strauss Syndrome

Asthma
Pulmonary infiltrates
Allergic rhinitis
Nasal polyposis

Asthma has been reported to precede the development of vasculitis by 30 years, although the majority of patients have symptomatic bronchospasm for only about 3 years (101). Asthmatic exacerbation are initially mild but increase in severity and frequency until the onset of vasculitis (103, 104). Greater than 50 percent of patients have a remission of asthma with the onset of vasculitis, but worsening has also been reported (105).

Radiographic pulmonary infiltrates are a central feature of the Churg-Strauss syndrome and occur in 90 percent of patients. Infiltrates are generally transient and patchy without lobar or segmental distribution and have no predilection for upper or lower lobes (99). Infiltrates frequently radiate from the hilum, and associated hilar adenopathy has been reported (106, 107). Diffuse interstitial infiltratives and a miliary pattern have also been reported. Nodular infiltrates occasionally occur, but in contrast to Wegener's they rarely cavitate (108). Pleural effusions occur in 20 percent of cases and contain large numbers of eosinophils (109).

Allergic rhinitis commonly represents the initial phase of the syndrome and leads to nasal obstruction, recurrent sinusitis and nasal polyposis. Nasal manifestations occur in 70 percent of cases with evidence of pansinusitis in 88 percent. Necrotizing nasal disease with septal perforation has been reported but is much less common than in Wegener's (110).

b. Skin Disease

A skin rash occurs in the vasculitic phase of the Churg-Strauss syndrome and reflects small vessel involvement. Types of skin involvement are summarized in Table 31.

Table 31

Characteristics of Cutaneous Involvement in 138 Patients with the Churg-Strauss Syndrome

Type	Patients	Percent
Purpura	66	48
Nodules	41	30
Erythema, urticaria	35	25

Purpura, which is most often palpable, occurs on the extremities in 48 percent of patients. Subcutaneous nodules are the most distinctive skin lesions in this syndrome. The lesions are tender and occur in the scalp and symmetrically on the extremities. Biopsy of nodular lesions frequently reveals granulomas, whereas other skin lesions are more likely to demonstrate a non-specific vasculitis. A macular or papular erythematous rash or urticaria occurs in 25 percent of cases. Cutaneous infarction, ulceration of nodules and livido reticularis have also been reported (111).

c. Nervous System

Nervous system involvement occurs in 60 percent of cases and have the characteristics listed in Table 32.

Table 32

Characteristics of Nervous System Disease in 138 Patients with the Churg-Strauss Syndrome

Type	Patients	Percent
Mononeuritis multiplex	87	63
CNS involvement, cranial nerve hemorrhage, infarction	37	27

Peripheral neuropathy occurs in 63 percent of cases, and typical lesions of mononeuritis multiplex can be demonstrated. The incidence of central nervous system manifestations are variable; however, cranial nerve involvement and cerebral hemorrhage and infarction has been reported in up to 27 percent of cases (98).

d. Cardiovascular Disease

Cardiovascular manifestations of Churg-Strauss syndrome include hypertension, pericarditis, myocardial infarction and cardiac failure. Hypertension occurs in greater than 60 percent of cases. Histologically numerous granulomas

e. Gastrointestinal Disease

Eosinophilic infiltrates of the bowel wall indistinguishable from other forms of eosinophilic gastrointeritis occurs in 40 percent of patients with the Churg-Strauss syndrome. The infiltrate may precede or coincide with the vasculitic phase. Features of the gastrointestinal disease are summarized in Table 33.

Table 33

Characteristics of Gastrointestinal Disease in 138 Patients with the Churg-Strauss Syndrome

Manifestation	Patients	Percent
Abdominal pain	81	59
Diarrhea	46	33
Bleeding	25	18
Colitis	14	10

Abdominal pain is common and may reflect bowel perforation, peritonitis, intestinal obstruction, mesenteric vasculitis or cholicystitis. Diarrhea occurs in 33 percent of cases, and 18 percent of patients have gastrointestinal bleeding at some time in their course. Colitis is uncommon but may have a relapsing course (113).

f. Renal Disease

Renal disease occurs in 40 percent of patients with the Churg-Strauss syndrome but is generally benign. Renal failure is distinctly uncommon, although reversible changes of focal glomerulonephritis with eosinophilic infiltrates have been demonstrated (114).

4. Laboratory Abnormalities

Although there are no diagnostic laboratory abnormalities, peripheral and tissue eosinophilia are necessary to make the diagnosis of the Churg-Strauss syndrome. The clinical characteristics of hypereosinophilia are listed in Table 34.

Table 34

Characteristics of Eosinophilia in Churg-Strauss Syndrome

Mean peak eosinophil count 5,000 mm^3

Eosinophilic tissue infiltrates
- Lung
- Bone marrow
- Skin
- Kidney
- Gastrointestinal tract
- Upper respiratory tract

Eosinophil degranulation not present

Excessive numbers of eosinophils may appear in the blood at any stage of the illness, although there is frequently an association between the degree of eosinophilia and vasculitis (106). The mean peak blood eosinophil count in this syndrome is 5,000 mm^3, but marked variability in any given patient is common. Although peak eosinophila has been associated with the vasculitic phase, it may occur very early in association with asthma and tissue infiltrates. The lung, bone marrow, skin, kidney, gastrointestinal and upper respiratory tracts are the most frequent sites of eosinophilic infiltrates (98). Increased eosinophil degranulation has not been found (98).

Non-specific laboratory abnormalities are summarized in Table 35.

Table 35

Laboratory Abnormalities in Patients with Churg-Strauss Syndrome

Finding	Number Positive / Number Tested	Percent
Anemia	13/16	81
Leukocytosis	14/16	87
Elevated ESR	30/30	100
Rheumatoid factor	15/29	52
Elevated IgE	15/20	75
Elevated IgG	10/21	48

Normocytic, normochronic anemia and leukocytosis occur in a majority of patients. Elevation of the erythrocyte sedimentation rate is a consistent finding, and rheumatoid factor is present in half of the patients. Immunologic parameters have not been extensively investigated; however, elevations of IgE, and less commonly IgG, have been reported. Immune complexes were found in 2 of 6 patients evaluated (98).

5. Diagnosis

The Churg-Strauss syndrome is most often diagnosed by the clinical manifestations. The constellation of rhinitis, asthma, pulmonary infiltrates, significant peripheral eosinophilia followed by any of the described manifestations of systemic vasculitis is sufficient to make a diagnoses of the Churg-Strauss syndrome. Histologic confirmation should be attempted, but demonstration of a granulomatous vasculitis is more difficult than in Wegener's granulomatosis.

Histologically a necrotizing vasculitis effects small and medium size arteries and veins. Infiltrates consist of mononuclear cells and eosinophils that may obstruct the lumen. Charcot-Leyden crystals are prominent in areas of necrosis. Eosinophils and extravascular granulomas are the most common finding in nodular skin lesions. Fibrinoid necrosis, thrombosis, infarction and aneurysm formation are less frequent but consistent manifestations. The histologic findings from autopies and tissue biopsies from all sites are summarized in Table 36.

Table 36

Histologic Findings in Patients with the Churg-Strauss Syndrome

	Autopsy	Percent	Tissue Biopsy	Percent
Granuloma	18/45	40	14/37	38
Eosinophil infiltrate	19/45	42	21/37	57
Vasculitis	43/45	96	26/37	70
Granuloma eosinophil infiltrate vasculitis	11/45	24	5/37	13

A non-specific vasculitis is the most frequent finding, and eosinophilic filtrates occur in approximately one-half of patients. Granuloma are found in autopsy and biopsy specimens in only approximately 40 percent of cases. Vasculitis, eosinophilic infiltrates and granuloma were found in only 24 percent of autopsies and 13 percent of tissues biopsied.

Table 37 summarizes the reported histologic findings from various tissue biopsy sites.

Table 37

Histologic Findings in Biopsy Specimens in 14 Patients with the Churg-Strauss Syndrome

	Nose	Skin	Kidney
Granuloma	8	9	1
Eosinophilic infiltrate	8	6	3
Vasculitis	0	5	3

Of the reported biopsy sites, granulomas and eosinophilic infiltrates are most likely to be found in nasal and skin biopsies. Histologic findings of renal biopsies commonly demonstrate a non-specific segmental glomerulonephritis, usually without eosinophilic infiltrate (98, 110). I could find only a single series of 3 patients with pre-mortum lung biopsies. All had vasculitis, granuloma and eosinophilic infiltrates, which was similar to autopsy data (102, 115).

Based on available data biopsy sites should include nasal nucosa and skin. If findings are non-specific and pulmonary infiltrates are present, open lung biopsy should be performed if cytoxic therapy is contemplated.

6. Treatment

Untreated patients with the Churg-Strauss syndrome have a 2 year survival of 16 percent and 5 year survival of 4 percent (102). Treatment with corticosteroid increases the 5 year survival to 62 percent (99). A suggested treatment regimen is presented in Table 38.

Table 38

Suggested Treatment for Patients with the Churg-Strauss Syndrome

Prednisone 1 mgm/kg/day
If no response, add
Cytoxan 2 mgm/kg/day

Adjust dose to keep leukocytes >3,000
neutrophils >1,500

Response to steroids is often dramatic within 1 to 2 weeks and includes improvement of allergic symptoms, reduction in eosinophila and remission of symptoms of vasculitis. Lack of response, however, is probably an indication for the use of cytotoxic agents. Efficacy of cytoxic agents can not be well evaluated due to the small numbers of patients reported in the literature. It is clear, however, that remissions have occurred in patients who did not respond to steroids. Thus, it seems reasonable to use these agents in seriously ill patients who have not responded to steroids. Two mgm/kg/day of cyclophosphamide, with adjustment for leukopenia, is extrapolated from successful treatment regimens for Wegener's granulomatosis. Benefit from plasmaphersis has been described, but its use remains investigational (98).

7. Polyarteritis overlap Syndrome

Classic polyarteritis nodosa is a systemic necrotizing vasculitic disease of medium size arteries that results in aneurysm formation and spares the pulmonary circulation. Churg-Strauss syndrome is a systemic necrotizing granulomatous vasculitis that primarily involves the lung and is associated with a distinct clinical syndrome of asthma and eosinophilia. Fauci has described an overlap syndrome in patients who manifest clinical and pathologic features characteristic of both syndromes (1). The potential for fatal disease is similar to both of these diseases in patients in this atypical group. Diagnostic and therapeutic considerations are the same as in the well defined clinical entities and thus a separate consideration is not warranted.

C. Lymphomatoid Granulomatosis

1. History and Definition

Lymphomatoid granulomatosis is an unusual granulomatous vasculitis that was first described by Liebow, Carrington and Friedman in 1972 (116). It is best defined by the clinical and histopathologic characteristics listed in Table 39.

Table 39

Lymphomatoid Granulomatous

Multisystem
Malignant potential
Pulmonary nodules
Perivascular destructive infiltrates with lymphocytes, plasma cells and atypical lymphocytes

Lymphomatoid granulomatosis is a multisystem vasculitis with the potential to develop into a lymphoid malignancy. The malignant potential distinguishes this entity from the other pulmonary vasculitis. Pulmonary nodules are invariably present and have a unique histopathology. Perivascular angiodestructive infiltrates with lymphocytes, plasma cells and atypical lymphocytes with frequent mitoses are characteristic (117).

2. Incidence and Demographics

Lymphomatoid granulomatosis is a rare disease; approximately 200 cases have been reported since it was first established as a distinct entity. Demographics of 152 patients are summarized in Table 40 (118).

Table 40

Demographics of 152 Patients with Lymphomatoid Granulomatosis

Patients	152
Male	95
Female	57
Age (years)	48
Range	7-85

Racial characteristics are not well reported, but there is a male predominance with a male to female ratio of 1.7 to 1. The mean age at onset is 48 years with a range of 7 to 85 years.

3. Clinical Manifestations

Non-specific complaints are the most common presenting symptoms in patients with lymphomatoid granulomatosis. The presenting signs and symptoms of 142 patients are summarized in Table 41.

Table 41

Presenting Sign and Symptoms in 142 Patients with Lymphomatoid Granulomatosis

Finding	Total	Percent
Fever	82	58
Cough	79	56
Malaise	50	35
Weight loss	49	35
Dyspnea	41	29
Neurological	30	21
Chest pain	19	13
Arthralgias	9	6
Myalgias	4	3
Gastrointestinal	4	3
Asymptomatic	4	3

Systemic symptoms such as fever, malaise and weight loss are frequently present. Respiratory symptoms of cough, shortness of breath and chest pain are the most common focal findings. Neurologic dysfunction including both peripheral neuropathies and CNS abnormalities are found in 20 percent of patients. Less common presenting symptoms include cutaneous lesions, arthralgias, myalgias and gastrointestinal distress. Three percent of patients are asymptomatic with pulmonary lesions on routine chest film (118). The time from the onset of symptoms until diagnosis ranges from one month to three years with a mean of 8.5 month. Most frequently the course is chronic and indolent but acute fulminant presentations have been described (119-120).

The frequency of organ involvement is listed in Table 42 (118).

Table 42

Frequency of Organ System Involvement in 152 Patients with Lymphomatoid Granulomatosis

Category	Number	Percent
Lung	152	100
Cutaneous	60	39
Nervous system	45	30
CNS	29	19
Cranial neuropathy	17	11
Peripheral neuropathy	11	7
Splenomegaly	27	18
Hepatomegaly	18	12
Lymphadenopathy	12	8

a. Respiratory Disease

Lung involvement is characteristic of lymphomatoid granulomatosis. Symptoms suggestive of respiratory infection with fever, productive cough, dyspnea and pleuritic chest pain are present in a majority of patients. This constellation of symptoms cause most patients to receive various courses of antibiotics. Hemoptysis is rare but when present may be life-threatening. Upper airway involvement with a prodrome of recurrent sinusitis has been reported but is much less frequent than in Wegener's granulomatosis (118-120).

b. Skin Disease

Skin is the extrapulmonary organ most commonly involved in lymphomatoid granulomatosis. Lesions include subcutaneous and dermal nodules, maculopapular eruptions and ulcerations. The cutaneous involvement may be generalized but has a predilection for the lower extremities and is most often symmetrical. Lesions are generally asymptomatic and resolve spontaneously without treatment in 20 percent. Skin lesions precede, appear simultaneously or appear following pulmonary involvement with equal frequency (121).

c. Nervous System Disease

The nervous system is involved in one-third of patients and may precede or follow lung involvement. The majority of patients with neurologic symptoms have cerebral lesions manifested by mental confusion, ataxia, hemiparesis, or seizures. Cranial nerve involvement is less frequent and includes facial paresis, diplopia, decreased vision or deafness. Peripheral neuropathy with paresthesia, numbness and weakness is rarely encountered (118-122).

d. Visceral Disease

Splenomegaly is found in a minority of patients, although there is one report of massive splenomegaly with leukopenia due to extensive infiltration with lymphomatoid granulomatosis (123). Hepatomegaly is also uncommon, but progressive hepatitic failure due to extensive infiltration and necrosis has been reported (124, 125). Initially lymphadenopathy was reported to rarely occur; however, in a recent series 40 percent of patients had evidence of nodal enlargement which was frequently hilar or periaortic (119). Involvement of the heart, adrenal glands, pancreas and gastrointestinal tract has been documented in 7 to 9 percent of cases at necropsy, but clinical manifestations are absent or rare (118).

e. Renal Disease

In contrast to Wegener's granulomatosis, clinically evident renal disease is rare in lymphomatoid granulomatosis (118). However, histologic involvement with nodular, atypical lymphoreticular infiltrates with necrosis and angiitis occurs in approximately 40 percent of cases at autopsy and on renal biopsy (116, 118, 119). Focal glomerulonephritis has now been reported but the significance of the observation is unclear (119). Renal manifestations are clinically insignificant.

4. Radiographic Abnormalities

A board spectrum of radiographic abnormalities have been reported in lymphomatoid granulomatosis, but several features are characteristic. The radiographic abnormalities are summarized in Table 43 (116).

Table 43

Chest Radiographic Abnormalities in 40 Patients with Lymphomatoid Granulomatosis

	Number	Percent
Lower lobe nodular lesions	38	95
Upper lobe nodular lesions	2	5
Bilateral nodular lesions	28	70
Cavitation	12	30
Atelectasis	12	30
Unilateral mass	12	30
Pleural disease	10	25
Reticulonodular pattern	8	20

Lower and peripheral lung fields are predominately involved with a relative sparing of the apices. Multiple, bilateral nodules that can not be differentiated from pulmonary metastases occur in the majority of patients. Cavitations, atelectasis and a unilateral mass occur in one-third of cases. Pleural disease with small effusions is seen in a minority of cases, and a diffuse reticulonodular pattern is not common.

One of the more characteristic roentgenographic features of lymphomatoid granulomatosis is the tendency for the pulmonary lesions to wax and wane either spontaneously or in response to therapy. Typically some pulmonary lesions regress while new lung lesions or central nervous system signs appear or progress (116, 118, 126).

5. Laboratory Abnormalities

There are no consistent laboratory abnormalities. The non-specific findings are summarized in Table 44.

Table 44

Laboratory Abnormalities in Patients with Lymphomatoid Granulomatosis

	Number Number/Observations	Percent
Anemia Hgb <11	0/40	0
Leukocytosis	27/91	30
Lymphopenia	31/91	34
Elevated ESR	6/40	15

Unlike the findings in patients with other vasculitides, anemia is rare. A normal WBC count, leukocytosis and leukopenia occur with equal frequency. Lymphopenia is more common than lymphocytosis, occurring in 34 percent. The erythrocyte sedimentation rate is frequently normal even with extensive disease, and striking elevations are rare (118, 119, 127). Tests of antinuclear antibody and rheumatoid factor have been reported to be positive in some patients, but no consistent pattern has emerged.

The small number of patients in whom immunologic parameters have been investigated make evaluation difficult. Elevation of immunoglobulins and detection of immune complexes in blood have been inconsistent and are not useful determinations for clinical evaluation (128, 129). However, defects in cell mediated immunity are consistently demonstrated both *in vivo* and *in vitro*. Most patients have been reported to be anergic to various skin tests; lymphocyte stimulation is impaired *in vitro*, and changes in T cell subsets are reported (130-133). These findings have led some investigators to conclude that lymphomatoid granulomatosis is a T cell disorder (129). In view of these findings, tests of delayed hypersensitivity should be included in a clinical evaluation.

6. Diagnosis and Pathology

The diagnosis of lymphomatoid granulomatosis requires the histopathologic confirmation of a pleomorphic mononuclear cell infiltration around and within blood vessels. When nodular skin lesions are present, biopsy may reveal this characteristic infiltration. However, open lung biopsy is required for sufficient tissue to evaluate for the presence of malignancy.

The characteristic histologic pattern seen in both arteries and veins is an angiocentric, angiodestructive inflammatory infiltrate of predominately pleomorphic mononuclear cells with sparse granuloma formation (116). The mononuclear infiltrate is composed of mature lymphocytes, plasma cells, histiocytes, and atypical lymphoreticular cells. The latter cells are larger and contain more cytoplasm than mature lymphocytes and have plasmacytoid features (118). Necrosis and mitotic figures are present to a variable degree. Architectural destruction may be so severe that elastin stains may be required to demonstrate the remnants of a vessel in the center of the inflammatory mass (118).

7. Course and Prognosis

The natural history of lymphomatoid granulomatosis is unclear, but overall mortality remains high. Table 45 indicates the mortality and malignant potential of this disease.

Table 45

Mortality and Malignant Potential in Patients with Lymphomatoid Granulomatosis

	Number Number/Observations	Percent
Mortality	102/163	63
Lymphoproliferative Disease		
Liebow	6/40	15
Katzenstein	18/152	12
Fauci	7/15	46

An overall five year survival of approximately 40 percent has remained consistent since lymphomatoid granulomatosis was established as a clinicopathologic entity. The mean survival of patients who die is 14 months with 94 percent of deaths occurring in 36 months. Deaths are secondary to destruction of pulmonary parenchyma, massive hemoptysis, involvement of the central nervous system and conversion to lymphoproliferative disease. The incidence of lymphoproliferative disease, most commonly non-Hodgkins lymphoma, is less clear. Older series showed only a 15 percent incidence, whereas in a recent 10 year follow-up it was 46 percent.

8. Pathogenesis

The malignant potential of lymphomatoid granulomatosis has therapeutic implications and has led to a controversy as to whether this entity should be considered a primary neoplastic process. A more benign form of lymphomatoid granulomatosis has also been described and labelled "benign lymphocytic angiitis and granulomatosis" (134). The simultaneous histological finding of benign angiitis and lymphomatoid granulomatosis has been reported in the same person (119). Thus, at our current stage of understanding it is appropriate to regard these syndromes as a continuum from benign appearing lymphocytic angiitis through more aggressive lymphomatoid granulomatosis to overt malignant lymphoma. It is unclear whether lymphomatoid granulomatosis is a neoplastic process at onset and gradually expresses its full evolution or whether it evolves into lymphoma from an aberrant immunologic response as had been suggested for immunoblastic lymphadenopathy (118, 135, 136).

9. Treatment

The 60 percent mortality of untreated patients with lymphomatoid granulomatosis is unaltered by treatment with prednisone alone (118). Cyclophosphamide has induced remission in small numbers of patients, and the suggested regimen in Table 46 is similar to that of the other pulmonary vasculitides.

Table 46

Suggested Treatment Regimen for Patients with Lymphomatoid Granulomatosis

Cytoxan 2 mgm/kg/day
Prednisone 1 mgm/kg/day

Adjust dose to keep leukocytes >3,000
neutrophils >7,500

Radiation Therapy

Cyclophosphamide is started at a dose of 2 mgm/kg/day and adjusted for leukopenia. Prednisone is initiated at a dose of 1 mgm/kg/day and converted to an alternate day regimen after 2 months. The induction of a remission has been only 50 percent in patients with lymphomatoid granulomatosis and multiorgan involvement. Patients in whom this regimen does not induce remission invariably develop a lymphoma that is usually refractory to therapy. In unresponsive patients aggressive re-evaluation for lymphoma may be indicated. An appropriate chemotherapeutic protocol should be initiated in patients developing a histologic lymphoproliferative disease (119). Radiation therapy is recommended for cerebral mass disease.

D. Necrotizing Sarcoidal Granulomatosis

1. History and Definition

Necrotizing sarcoidal granulomatosis was first described as a distinct clinicopathologic entity by Liebow in 1973 (6). The syndrome was separated from sarcoidosis by the histologic appearance, but it was found to include the 3 characteristics listed in Table 47.

Table 47

Clinicopathologic Features of Necrotizing Sarcoidal Granulomatosis

Pulmonary nodules without adenopathy

Benign course without therapy

Sarcoid-like granuloma, necrotizing granulomatous vasculitis, confluent granulomas

The initial description included eleven patients who had radiographic evidence of pulmonary nodules without hilar or mediastinal adenopathy. Follow-up of up to fourteen years documented a benign course even without therapy. The distinctive histopathology included sarcoid-like granulomas associated with prominent necrotizing granulomatous vasculitis. Masses of confluent granulomas with necrosis were also present (6).

2. Incidence and Demographics

Since the initial report a total of 60 cases have been described with the characteristics summarized in Table 48.

Table 48

Demographics in 60 Patients with Necrotizing Sarcoidal Granulomatosis

Category	Result
Sex ratio (female to male)	3.3:1
Mean age at onset (yrs.)	48
Race (black to caucasian)	1:1

As in classic sarcoidosis, the disease predominately affects women. It is a disease of middle age with a mean onset of 48 years. Unlike classic sarcoidosis there is no racial predilection (6, 137-140).

3. Clinical Manifestations

Presenting signs and symptoms of necrotizing sarcoidal granulomatosis are summarized in Table 49.

Table 49

Presenting Signs and Symptoms in 49 Patients with Necrotizing Sarcoidal Granulomatosis

Finding	Number Observations	Percent
Respiratory Symptoms	26	53
Systemic Symptoms	13	27
Asymptomatic	21	43

Presenting signs and symptoms are related to the lower respiratory tract in over half of patients. Non-specific chest pain, non-productive cough and dyspnea are the most frequent. Systemic symptoms of fever, weight loss, anorexia, night sweats and malaise occur less often. About 40 percent of patients are asymptomatic but have radiographic lesions. Extrapulmonary lesions similar to those in classic sarcoidosis have been described in only 2 patients (139-141).

4. Laboratory Manifestations

Results of laboratory investigations are summarized in Table 50.

Table 50

Laboratory Findings in Patients with
Necrotizing Sarcoidal Granulomatosis

CBC, ESR, BUN, Creatinine - WNL

Rheumatoid factor, ANA, LE cells - NEG

Delayed hypersensitivity - ABSENT

The complete blood count, erythrocyte sedimentation rate and tests of renal function are normal, although a cellular urinary sediment has been reported in a minority of cases. Cell mediated immunity is lacking in virtually all patients tested for delayed hypersensitivity (137, 139, 140). Additional immunologic parameters have not been evaluated.

5. Radiographic Manifestations

Bilateral pulmonary nodules superimposed on lower lobe interstitial infiltrates are present in over 90 percent of cases. When unilateral nodules have been reported, they have always been solitary. Cavitation, miliary infiltrates, and pleural effusions have been reported but are not characteristic (140). Initially, the absence of hilar adenopathy was considered a unique radiographic manifestation of necrotizing sarcoidal granulomatosis (6, 140). Recently, however, bilateral hilar adenopathy has been reported in one-third of cases (139). Nodules may progressively increase in number and size associated with the development of adenopathy. When growth occurs a histologic diagnoses is required to differentiate the lesions from a malignancy.

6. Diagnosis and Pathology

In patients subsequently diagnosed as necrotizing sarcoidal granulomatosis, transbronchial and liver biopsies demonstrated only non-caseating granuloma. Open lung biopsy is required for adequate histologic evaluation which must by definition demonstrate granulomas, necrosis and angiitis (139). Large nodular lesions with extensive central necrosis have at their margins a band of confluent granulomas. Granulomas are composed of giant cells and eptheliod histiocytes interspersed with chronic inflammatory cells and proliferating fibroblasts. Granulomatous necrosis of both arteries and veins is prominent with both large and small vessel involvement (139).

7. Course, Prognosis and Treatment

All reports have confirmed the benign course reported in Liebow's original description. Table 51 summarizes the course of necrotizing sarcoidal granulomatosis regardless of therapy.

Table 51

Course and Prognosis in 25 Patients
with Necrotizing Sarcoidal Granulomatosis

Category	Number	Percent
Asymptomatic	23	92
Infiltrate stable	13	52
Infiltrate regressed	10	40
Mortality	2	8

Patients have been followed up to eleven years post diagnosis. All surviving patients are reported to be asymptomatic with stable or diminished infiltrates. Two patients have died, one secondary to bacterial infection while being treated with cyclophosphamide and one during resectional surgery.

From this review I conclude that therapy for necrotizing sarcoidal granulomatosis should not be instituted unless lung function deteriorates. Prednisone has been administered to some patients with resultant regression of infiltrates and resolution of symptoms. However, it is not clear if the response was drug induced or secondary to the natural history of the disease. Unilateral mass disease may require resectional surgery, since transbronchial biopsy has been unsuccessful in making a histologic diagnosis. There has been no recurrence following resection of lesions (140).

8. Relationship to Classic Sarcoidosis

Bilateral pulmonary nodules as the sole radiograph abnormality have been reported in 2 to 4 percent of patients with classic sarcoidosis (141, 142). Most classic cases do not have extrapulmonary involvement, and cavitation of pulmonary lesions has been reported in nodular sarcoidosis (143). A benign course usually ensues with radiographic clearing, but there may be residual pulmonary functional abnormalities (144). Thus, the clinical course of many patients with classic sarcoidos is similar those with necrotizing sarcoidal granulomatosis. Minimal histologic granulomatous angiitis and necrosis has also been reported in 69 percent of patients with classic sarcoidosis. The only separation from necrotizing sarcoidal granulomatosis was the lack of confluent granuloma and necrosis of arteries (145). Thus, I agree with Churg and Carrington who have suggested that necrotizing sarcoidal granulomatosis is a histological variant of classic sarcoidosis (139).

E. Bronchocentric Granulomatosis

1. History and Definition

Bronchocentric granulomatosis is the third clinicopathologic entity that was described by Liebow in 1973 (6). Features of the disease are summarized in Table 52.

Table 52

Clinicopathologic Features in Patients with Bronchocentric Granulomatosis

Benign course
No extrapulmonary involvement
Necrotizing granulomatous reaction around airways with secondary arteritis

Bronchocentric granulomatosis can be distinguished from Wegener's granulomatosis, the Churg-Strauss Syndrome and lymphomatoid granulomatosis by its benign course, absence of extrapulmonary involvement and by the pathologic manifestations which are primarily bronchocentric. Necrotizing granulomas are found predominately around airways with only secondary angiitis (146).

2. Incidence and Demographics

Eighty cases of bronchocentric granulomatosis have been reported. The disease is somewhat different in patients with asthma. Demographics of patients with and without asthma are summarized in Table 53.

Table 53

Demographics of 23 Patients with Bronchocentric Granulomatosis

Asthma (10)	
Sex (male to female)	2:1
Mean age (years)	22
Range (years)	9-48
No asthma (13)	
Sex (male to female)	1:1
Mean age (years)	50
Range (years)	32-76

Asthmatic patients with bronchocentric granulomatosis are more frequently young men. In the absence of asthma the disease affects men and women equally, and the onset is typically later in life (146).

3. Clinical and Laboratory Manifestations

The asthmatic patient usually presents with an exacerbation of asthma associated with cough and chest pain, whereas patients without asthma have non-specific symptoms of nasal congestion, malaise and fever. Laboratory findings are summarized in Table 54 (147).

Table 54

Laboratory Abnormalities in 33 Patients with Bronchocentric Granulomatosis

	Number Number/Observations	Percent
Asthmatic		
Eosinophilia	10/12	83
Elevated ESR	4/12	33
Aspergillus precipitins	3/7	43
Non-asthmatics		
Eosinophilia	2/13	15
Elevated ESR	4/13	30
Aspergillus precipitins	0/4	0

Asthmatic patients usually have significant peripheral blood eosinophilia and frequently have aspergillus precipitins in the serum. Elevated IgE levels and reactions to aspergillus antigen skin test are also reported. Non-asthmatics usually do not have eosinophilia, aspergillus precipitins or aspergillus skin test reactivity. An elevated erythrocyte sedimentation rate occurs with equal frequency (148).

4. Radiographic Manifestations

There is no correlation between the radiographic abnormality and the clinical presentation of this disease. Table 55 summarizes the radiographic findings in bronchocentric granulomatosis.

Table 55

Radiographic Findings in 15 Patients
with Bronchocentric Granulomatosis

Finding		Number	Percent
Mass lesion		9	60
Single	7		47
Multiple	2		13
Alveolar infiltrate		4	27
Single lobe	3		20
Multi lobe	1		7
Diffuse Reticulonodular		2	13

The usual three radiographic findings in bronchocentric granulomatosis are mass lesions, alveolar infiltrates or diffuse reticulonodular infiltrates. Solitary mass lesions are located predominately in the upper lobes and are the most common radiographic presentation. Mass lesions may be associated with mucoid impaction and atelectasis. When an alveolar infiltrate is present it is usually localized to a single lobe. A diffuse reticulonodular pattern is the least common form of presentation. Cavitation and hilar adenopathy have not been reported (149).

5. Diagnosis and Pathology

The clinical, laboratory and radiographic characteristics of bronchocentric granulomatosis are not sufficiently unique to differentiate it from bronchogenic carcinoma. Further, the small biopsy sample obtained by fiberoptic bronchocopy is rarely diagnostic. Thus, most patients with this entity are diagnosed at thoracotomy.

Necrotizing granulomas involving small bronchi and bronchioles occur in all cases. However, cellular infiltrates differ in the asthmatic and non-asthmatic patients. Asthmatics demonstrate mucous plugging of small bronchi, eosinophilic infiltrates and hyphae. Non-asthmatics have predominately polymorphonuclear infiltrates with rare eosinophiles. Both groups have only a mild pulmonary arteritis (148, 150).

6. Treatment

Although there are rare cases reported of extrapulmonary or progressive pulmonary bronchocentric granulomatosis, the prognosis even without therapy is good (151-155). Spontaneous remissions occur in the majority of cases. When lesions are resected there is not reoccurrence. Occasional patients with progressive lobar infiltrates and increasing asthmatic or constitutional symptoms require treatment with prednisone (146, 148). A good response to prednisone has occurred in these isolated case reports (146).

SUMMARY

Pulmonary vasculitides that are not merely secondary to a systemic vasculitis include Wegener's granulomatosis, allergic angiitis and granulomatosis (Churg-Strauss syndrome), lymphomatoid granulomatosis, and bronchocentric granulomatosis. The polyarteritis overlap syndrome and necrotizing sarcoidal granulomatosis are not sufficiently different from the Churg-Strauss syndrome and classic sarcoidosis to be considered as distinct entities. Wegener's granulomatosis and the Churg-Strauss syndrome are important pulmonary vasculitic processes for which there is effective therapy. Lymphomatoid granulomatosis is potentially malignant, and therapy is most often ineffective. Bronchocentric granulomatosis is not a true vasculitis and is important only in the differential diagnosis of malignancy.

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