

15. Vasculitis

Carol A. Langford, MD, MHS *Bethesda, Md*

Vasculitis is histologically defined by the presence of blood vessel inflammation. It can be observed in a wide variety of settings, either occurring secondarily to another process or as the pathologic foundation of a primary vasculitic disease. The primary systemic vasculitides comprise a broad group of disease entities that are uniquely identified by the nature of their clinical, histopathologic, or therapeutic characteristics. Individual diseases often predominantly affect blood vessels of a particular size, the pattern of which influences their clinical manifestations and has been used in their classification. The vasculitides span a wide range of disease severity, extending from illnesses that rarely produce death to those almost universally fatal before the introduction of effective therapy. Immunosuppressive and cytotoxic agents are used to treat many vasculitic diseases. Although such approaches can be effective, long-term treatment may be complicated by chronic sequelae from organ damage, disease relapses, and medication side effects. Recent investigations have focused on understanding the pathophysiology of these diseases, which may lead to more efficacious and less toxic therapeutic options. (*J Allergy Clin Immunol* 2003;111:S602-12.)

Key words: *Vasculitis, arteritis, ANCA, granuloma, glucocorticoid, cyclophosphamide*

Vasculitis is characterized by histologic evidence of blood vessel inflammation. When such inflammation occurs, it can lead to thinning or rupture of the blood vessel, resulting in aneurysms or hemorrhage, or blood vessel stenosis with resultant tissue ischemia. Vasculitis can be thought of in two broad groups: secondary vasculitides in which blood vessel inflammation is occurring in the setting of an underlying disease or exposure, or primary vasculitides whereby vasculitis occurs in the absence of any known cause. This review will focus on the clinical features, diagnosis, and treatment of the primary vasculitic diseases.

CLASSIFICATION

The first account of a systemic vasculitic disease was made in 1866 when Kussmaul and Maier published a detailed report of a disorder, characterized by nodular inflammation of the muscular arteries, that they named periarteritis nodosa (later referred to as polyarteritis nodosa [PAN]). The description of other necrotizing vasculitides followed, and in 1952, Zeek proposed the first

Abbreviations used

ANCA:	Antineutrophil cytoplasmic antibody
BACNS:	Benign angiitis of the central nervous system
CHCC:	Chapel Hill Consensus Conference
CNS:	Central nervous system
CSS:	Churg-Strauss syndrome
ESR:	Erythrocyte sedimentation rate
GACNS:	Granulomatous angiitis of the central nervous system
GCA:	Giant cell arteritis
HCV:	Hepatitis C virus
HSP:	Henoch-Schönlein purpura
IVIg:	Intravenous immunoglobulin
MPA:	Microscopic polyangiitis
MPO:	Myeloperoxidase
PACNS:	Primary angiitis of the central nervous system
PAN:	Polyarteritis nodosa
PR 3:	Proteinase 3
WG:	Wegener granulomatosis

classification system. The nomenclature and classification of the vasculitides has remained an evolving process, as we have continued to learn about these diseases. In 1990, the American College of Rheumatology introduced classification criteria for 7 forms of vasculitis to provide a standard way to evaluate and describe groups of patients in therapeutic, epidemiologic, or other studies.¹ This was followed in 1994 by a proposal of uniform diagnostic terms and definitions for the most common forms of vasculitis at the Chapel Hill Consensus Conference (CHCC)² (Table I). Although these both represent significant advancements in standardization for the vasculitic diseases, they were not intended and should not be used for the purposes of diagnosing the individual patient.

PATHOPHYSIOLOGY AND ANCA

The pathophysiology of the vasculitides remains poorly understood and may vary between different diseases.³ For each disease, however, immunologic mechanisms appear to play an active role in mediating the necrotizing inflammation of blood vessels. Based on current understanding of the inflammatory response, it can be hypothesized that cytokine-mediated changes in the expression and function of adhesion molecules together with inappropriate activation of leukocytes and endothelial cells are key factors influencing vessel inflammation and damage. Although the primary events that initiate this process remain largely unknown, recent advances have begun to allow investigators to examine the effector mechanisms involved in disease pathogenesis (Table II).

From the Immunologic Diseases Section, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.

Reprint requests: Carol A. Langford, MD, MHS, Immunologic Diseases Section, National Institutes of Health, Bldg 10, Room 11B-13, Bethesda, MD 20892.

© 2003, by Mosby, Inc. All rights reserved.

0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.80

TABLE I. Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

Large-vessel vasculitis	
Giant cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 and often is associated with polymyalgia rheumatica.
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.
Medium-sized vessel vasculitis	
Polyarteritis nodosa (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries, and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.
Small-vessel vasculitis	
Wegener granulomatosis	Granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels (eg, capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common.
Churg-Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia.
Microscopic polyangiitis (microscopic polyarteritis)	Necrotizing vasculitis, with few or no immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs.
Henoch-Schönlein purpura	Vasculitis, with Ig-A dominant immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles). Typically involves skin, gut, and glomeruli, and is associated with arthralgias or arthritis.
Essential cryoglobulinemic vasculitis	Vasculitis, with cryoglobulin immune deposits, affecting small vessels (ie, capillaries, venules, or arterioles), and associated with cryoglobulins in serum. Skin and glomeruli are often involved.
Cutaneous leukocytoclastic vasculitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis.

From Reference 2.

Antineutrophil cytoplasmic antibodies (ANCA) have become a prominent focus in the study of vasculitides, not only for their possible influence in disease pathogenesis but also for their clinical applications. Two types of ANCA have been identified in patients with vasculitis: ANCA directed against the neutrophil serine protease proteinase 3 (PR3), which causes a cytoplasmic immunofluorescence pattern (cANCA) on ethanol-fixed neutrophils, and ANCA directed against the neutrophil enzyme myeloperoxidase (MPO), which generates a perinuclear immunofluorescence pattern (pANCA).⁴ Because the methodology of testing can influence the interpretation, ANCA positivity determined by indirect immunofluorescence should be corroborated with antigen-specific testing for PR3 and MPO.

The strongest association of a disease with ANCA has been that between Wegener granulomatosis (WG) and PR3/cANCA.⁴ ANCA have been described with variable frequency in other vasculitic diseases (Table III), and some forms of vasculitis, in particular giant cell arteritis, Takayasu arteritis, and Behçet disease, are not ANCA-associated.

In WG, the sensitivity of PR3/cANCA has been reported to be 28% to 92%, whereas specificity has been reproducibly high, ranging from 80% to 100%.^{5,6} This has raised the question as to whether ANCA can be used in place of tissue biopsy for diagnosing WG. In patients with sinusitis, an active urine sediment, and pulmonary nod-

TABLE II. Potential mechanisms of vessel damage in selected primary vasculitis syndromes

Immune complex formation
Hepatitis B-associated polyarteritis nodosa
Henoch-Schönlein purpura
Essential mixed cryoglobulinemia
Production of antineutrophil cytoplasmic antibodies
Wegener granulomatosis
Microscopic polyangiitis
Churg-Strauss syndrome
Pathogenic T-lymphocyte responses and granuloma formation
Giant cell (temporal) arteritis
Takayasu arteritis
Wegener granulomatosis
Churg-Strauss syndrome

ules and/or infiltrates in which infection has been excluded, the predictive value of PR3/cANCA for WG may exceed 90%.⁷ However, for other clinical presentations in which the prevalence of WG would be low, the predictive value of ANCA is insufficient to justify the initiation of toxic therapy in the absence of a tissue diagnosis.

ANCA levels will vary during the course of WG, and from cohort studies it was observed that patients with active disease had higher levels of ANCA compared with those who were in remission.^{5,6} However, changes in sequential ANCA measurement in an individual patient

TABLE III. Clinical comparison of four forms of systemic vasculitis affecting small and/or medium-sized vessels*

Characteristic	Wegener granulomatosis	Microscopic polyangiitis	Polyarteritis nodosa	Churg-Strauss syndrome
Upper airways disease	95%	No	No	50% to 60%
Pulmonary disease				
Asthma	No	No	No	90% to 100%
Radiographic nodule/infiltrates	70% to 85%	15% to 70%	No	40% to 70%
Alveolar hemorrhage	5% to 15%	10% to 50%	No	<5%
Glomerulonephritis	70% to 80%	75% to 90%	No	10% to 40%
Gastrointestinal	<5%	30%	14% to 53%	30% to 50%
Nervous system				
Peripheral	40% to 50%	60% to 70%	38% to 72%	70% to 80%
Central	5% to 10%	10% to 15%	3% to 30%	5% to 30%
Cardiac	10% to 25%	10% to 15%	5% to 30%	10% to 40%
Ocular	50% to 60%	<5%	<5%	<5%
Arthralgia/arthritis	60% to 70%	40% to 60%	50% to 75%	40% to 50%
Genitourinary	<2%	<5%	5% to 10%	<2%
Skin	40% to 50%	50% to 65%	28% to 60%	50% to 55%
ANCA				
PR3/cANCA	75% to 90%	10% to 50%	Rare	3% to 35%
MPO/pANCA	5% to 20%	50% to 80%	Rare	2% to 50%

*Frequencies reflect data compiled from different series.

has not been found to be universally reliable for assessing disease activity or predicting relapse. In one series, 44% of patients who had a 4-fold rise in titer did not go on to relapse.⁸ Given the toxicity of therapy, a rising ANCA titer should not be used as the basis to start or increase immunosuppressive therapy but should prompt a careful evaluation for objective evidence of active disease and frequent patient monitoring.

INDIVIDUAL VASCULITIC DISEASES

Takayasu arteritis

Takayasu arteritis is a granulomatous vasculitis that affects the aorta, its main branches, and the pulmonary arteries. Although it has been characterized as a disease affecting young women of Eastern ethnicity, Takayasu arteritis has been observed throughout the world and may have varying clinical spectrums in different populations.

Patients with Takayasu arteritis have systemic symptoms and/or features of vascular compromise. Systemic symptoms include fatigue, malaise, weight loss, night sweats, fever, arthralgias, or myalgias, but these may be absent in 13% to 80% of patients. Vascular ischemic symptoms are related to the location of the lesion(s), the degree of vessel narrowing, and the collateral blood flow (Table IV). Physical examination may reveal bruits, diminished pulses, asymmetrical blood pressure measurements, valvular regurgitation, and arterial tenderness, particularly over the carotid vessels. Hypertension occurs in 32% to 93% of patients and contributes to renal, cardiac, and cerebral injury. Takayasu arteritis is a chronic disease in which 45% of patients relapse and 23% never achieve remission regardless of therapy.⁹ The estimated 15-year survival rate is 83%, with mortality rate being influenced by the presence of a progressive course, Takayasu retinopathy, hypertension, aortic regurgitation, and aneurysms.¹⁰

A complete aortic arteriogram with visualization of all major branches is important in diagnosis and in determining the extent of disease. Findings include vessel stenosis, occlusion, or aneurysm (Fig 1). Disease activity is typically assessed by using clinical symptoms, erythrocyte sedimentation rate (ESR), and arteriographic changes. However, these are not always reliable and in one surgical series, active arteritis was observed in 44% of patients who had been judged to be quiescent.⁹

Initial treatment of Takayasu arteritis usually consists of prednisone 1 mg/kg per day given for the first 1 to 3 months and then tapered on an alternate-day schedule to discontinuation. Glucocorticoids relieve systemic symptoms in 25% to 100% of patients and may bring about an improvement in blood flow. First-time therapy has been found to result in remission in 52% of patients, and 60% treated with glucocorticoids alone achieve remission at least once.⁹

Cytotoxic therapy is primarily used in patients who have persistent disease activity, despite glucocorticoid treatment, or in whom glucocorticoids cannot be tapered.⁹ Methotrexate at 15 to 25 mg/wk in combination with glucocorticoids has been found to induce remission and minimize glucocorticoid therapy and toxicity.¹¹ Cyclophosphamide should be reserved for patients with active inflammatory disease who cannot taper glucocorticoids and are unresponsive, intolerant, or unable to take methotrexate.¹²

Surgical therapy has an important role in treating fixed vascular lesions that are producing significant ischemia.¹³ The most frequent indications for surgery include cerebral hypoperfusion, renovascular hypertension, limb claudication, repair of aneurysms, or valvular insufficiency. Percutaneous transluminal angioplasty can be effective to control hypertension related to renal artery stenosis and may also be considered in treating short stenotic segments of other aortic branches.

GIANT CELL ARTERITIS

Giant cell (temporal) arteritis (GCA) is a granulomatous, large-vessel vasculitis that preferentially affects the extracranial branches of the carotid artery. It is the most common form of systemic vasculitis, with an incidence of 17.8 new cases per 100,000 person-years in Olmsted County, Minnesota.¹⁴ GCA occurs almost exclusively in people over 50 years of age, at a female/male ratio of up to 2:1, and is observed predominantly in persons of European ancestry.

Symptoms of GCA include headache, jaw or tongue claudication, scalp tenderness, constitutional features, or fever (Table V).¹⁵ Involvement of the primary branches of the aorta occurs in 15% of cases and can present with limb claudication.¹⁶ Polymyalgia rheumatica, which is characterized by aching and morning stiffness in the proximal muscles of the shoulder and hip girdles, occurs in 40% to 50% of patients with GCA. Findings on physical examination include nodularity, tenderness, or absent pulsations of the temporal arteries or other involved vessels. The most dreaded complication of GCA is vision loss caused by optic nerve ischemia from arteritis involving vessels of the ocular circulation. Visual features may include diplopia, ptosis, and transient or permanent blindness. Although GCA is characteristically self-limited, the course can span from months to years. Acute death from GCA is uncommon, although thoracic aortic aneurysms may occur as a late complication of disease and can be associated with rupture and death.¹⁷

The suspicion of GCA is raised by clinical features together with the demonstration of an elevated ESR, which occurs in >80% of patients. The diagnosis is confirmed by temporal artery biopsy, which demonstrates a panmural mononuclear cell infiltration that can be granulomatous with histiocytes and giant cells (Fig 2). To increase yield, the length of biopsy specimen should be at least 3 to 5 cm and sampled at multiple levels. Results of biopsy are positive in 50% to 80% of cases, and if the first biopsy is negative, consideration should be given to a biopsy of the contralateral artery. In patients strongly suspected of having GCA, treatment should be instituted immediately to protect vision while a prompt temporal artery biopsy is being arranged.

Glucocorticoids bring about a rapid improvement in cranial and systemic symptoms and prevent visual complications in GCA. In one study, the probability of loss of vision was calculated to be only 1% after starting glucocorticoids.¹⁸ Prednisone is usually initiated at a dose of 40 to 60 mg/d. If the initial dose was 60 mg/d, this can usually be reduced to 50 mg/d after 2 weeks and to 40 mg/d after 4 weeks. After that time, the dose is decreased by approximately 10% of the total daily dose every 1 to 2 weeks.¹⁴ Although the reduction of ESR generally occurs within the first month, it remains elevated in some patients and is not consistently reliable in assessing disease activity or guiding therapy. Relapses requiring increase or reinstitution of prednisone occur in 26% to 90% of patients. Most patients require glucocorticoids for >2 years with



FIG 1. Takayasu arteritis: Arteriogram. There is irregularity of renal arteries and abdominal aorta, with stenosis of iliac arteries.

many receiving over 4 years of treatment. In patients with acute visual loss, solumedrol 1 g/d for 3 to 5 days is frequently given to protect remaining vision.¹⁸

Although glucocorticoids are effective, it has been estimated that 36% to 65% of patients have one or more side effects from this therapy. The ability of methotrexate to decrease relapses and lessen glucocorticoids was examined in two randomized studies that yielded conflicting results.^{19,20} At this time, neither the addition of methotrexate nor any other cytotoxic agent has been found uniformly effective in reducing the use of prednisone sufficiently to lower its risk of side effects.

WEGENER GRANULOMATOSIS

WG is a necrotizing, granulomatous vasculitis that affects small to medium-sized vessels. The disease can occur at any age and appears to affect men and women in equal proportions.

WG is a multisystem disease that has a predilection to involve the upper and lower respiratory tract and kidneys (Table III).^{21,22} More than 90% of patients first seek medical attention for symptoms related to the upper and/or lower airways. Nasal and sinus mucosal inflammation may result in cartilaginous ischemia with perforation of the nasal septum and/or saddlenose deformity. Pulmonary

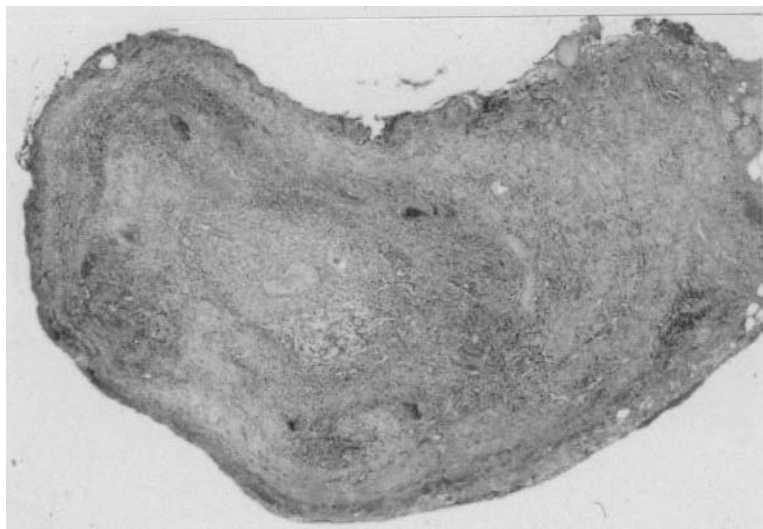


FIG 2. Giant cell arteritis. Temporal artery biopsy specimen shows occlusion of vessel lumen, giant cells, and panmural inflammatory infiltrate.



FIG 3. Computed tomography of the chest in a patient with Wegener granulomatosis revealing a nodular infiltrate and cavitary lesion.

radiographic abnormalities can include single or multiple nodules or infiltrates, cavities (Fig 3), and ground glass infiltrates (Fig 4). Glomerulonephritis is present in 20% of patients at the time of diagnosis but develops in 80% at some point during the disease course. Renal involvement is detected by the presence of an active urine sediment with microscopic hematuria and red blood cell casts and has the potential to be rapidly progressive and asymptomatic. Before the development of treatment, patients with WG had a mean survival time of 5 months, with death occurring from pulmonary or renal failure. Although effective therapy has brought the potential for long-term survival, relapse occurs in at least 50% of patients.^{21,22}

The diagnosis of WG is made by biopsy, with non-renal tissues demonstrating the presence of granulomatous inflammation, necrosis, often with aggregates of neutrophils, and necrotizing or granulomatous vasculitis.²¹ Surgically obtained biopsy specimens of abnormal pulmonary parenchyma demonstrate diagnostic changes in 91% of cases. Biopsy of the upper airways is less invasive but demonstrates diagnostic features only 21% of the time. The characteristic renal histology is that of a focal, segmental, necrotizing, crescentic glomerulonephritis with few to no immune complexes. The clinical applications of ANCA in WG are discussed in a separate section of this review.

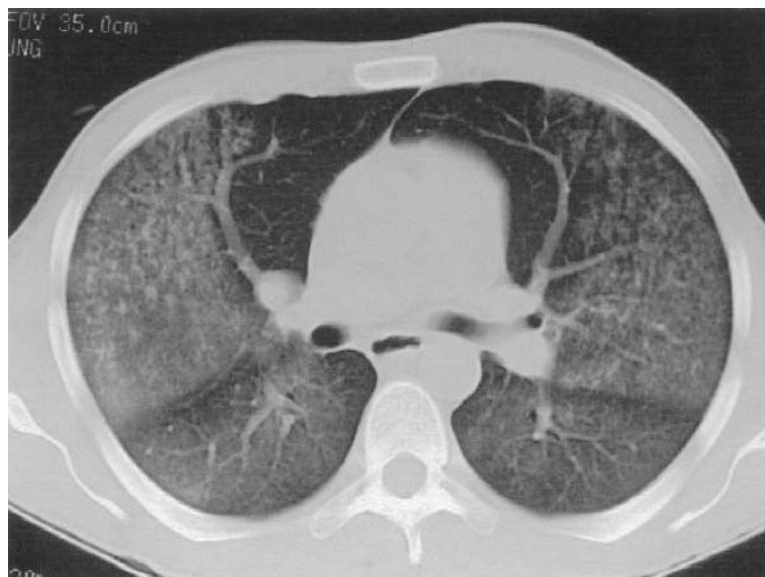


FIG 4. Computed tomography of the chest with ground glass infiltrates suggestive of alveolar hemorrhage, as can be seen in Wegener granulomatosis or microscopic polyangiitis.

TABLE IV. Frequency of arteriographic abnormalities and potential symptomatic manifestations of arterial involvement in Takayasu arteritis

Artery	Frequency of arteriographic abnormalities	Potential symptomatic manifestations
Subclavian	93%	Arm claudication, Raynaud
Common carotid	58%	Visual changes, syncope, transient ischemic attacks, stroke
Abdominal aorta	47%	Abdominal pain, nausea, vomiting, (often asymptomatic)
Renal	38%	Hypertension, renal failure
Aortic arch or root	35%	Aortic insufficiency, congestive heart failure
Vertebral	35%	Visual changes, dizziness
Celiac axis	18%	Abdominal pain, nausea, vomiting, (often asymptomatic)
Superior mesenteric	18%	Abdominal pain, nausea, vomiting, (often asymptomatic)
Iliac	17%	Leg claudication
Pulmonary	10% to 40%	Atypical chest pain, dyspnea
Coronary	<10%	Chest pain, myocardial infarction

Glucocorticoids alone are ineffective in the setting of active WG affecting a major organ such as the lung, kidney, nerve, or eye and must be combined with a cytotoxic agent.²¹ Patients who have active WG immediately threatening to life should be treated with cyclophosphamide at 2 mg/kg per day in combination with prednisone at 1 mg/kg per day.^{21,23,24} With the use of such therapy, 91% of patients have had marked improvement, 75% achieved a complete remission, and an 80% survival rate has been observed.²¹ In the setting of fulminant disease, 1 g/d solumedrol may be given in divided doses over a period of 3 days, in combination with 3 to 4 mg/kg per day cyclophosphamide for 3 days, after which time it is reduced to 2 mg/kg per day.²³ After the first 4 weeks of treatment, if there is evidence of improvement, the prednisone is tapered on an alternate day schedule and discontinued by 6 to 12 months. In the first studied regimen, cyclophosphamide was given for 1 year past remission,

after which time it was tapered and discontinued.²³ Although cyclophosphamide is very effective, it is associated with substantial toxicity including bone marrow suppression, bladder injury, infertility, myeloproliferative disease, and transitional cell carcinoma of the bladder.

Recent studies have examined a staged approach whereby cyclophosphamide is given until remission, which usually occurs at about 3 to 6 months, at which time it is switched to a less toxic medication for remission maintenance. The two maintenance agents with which there has been the greatest body of experience have been methotrexate at 20 to 25 mg/wk²⁵ or azathioprine at 2 mg/kg per day.²⁶ These are given for 1 to 2 years, after which time if patients remain in remission, they are tapered and discontinued.

In patients who have active but non-life-threatening disease or patients who are unable to tolerate cyclophosphamide, prednisone given together with 20 to 25 mg/wk

TABLE V. Clinical manifestations of giant cell (temporal) arteritis

Manifestation	% of Patients affected
Headache	68
Weight loss/anorexia	50
Jaw claudication	45
Fever	42
Malaise/fatigue/weakness	40
Polymyalgia rheumatica	39
Other musculoskeletal pain	30
Transient visual symptoms	16
Synovitis	15
Central nervous system abnormalities	15
Fixed visual symptoms	14
Sore throat	9
Swallowing claudication/dysphagia	8
Tongue claudication	6
Limb claudication	4

From Reference 15.

methotrexate has also been found to be efficacious at inducing remission.²⁷ Methotrexate should not be given to patients with impaired renal function (creatinine clearance of <35 mL/min) or chronic liver disease.

MICROSCOPIC POLYANGIITIS

As defined by the CHCC, microscopic polyangiitis (MPA) is characterized by necrotizing vasculitis with few or no immune deposits affecting small vessels. Because of its recent distinction from PAN, there remain limited data on MPA as a specific disease entity.²⁸ MPA has many similarities to WG, which has provided useful insights regarding diagnosis and management pending further studies.

The cardinal features of MPA include glomerulonephritis, pulmonary hemorrhage (Fig 4), mononeuritis multiplex, and fever (Table III).²⁸ The presentation of MPA can be acute and severe, and in one series, the estimated 5-year survival rate was 74%.²⁸ Current data suggest that relapses occur in at least 34% of patients.

The diagnosis of MPA is made by biopsy demonstration of necrotizing vasculitis of the small vessels or small to medium-sized arteries in which granulomatous inflammation is absent. Biopsy specimens of lung tissue in the setting of pulmonary hemorrhage reveal capillaritis, hemorrhage into the alveolar space, and the absence of linear immunofluorescence, as would be seen in antiglomerular basement membrane antibody disease (Goodpasture syndrome). The renal histology is similar to that observed in WG in being a focal segmental necrotizing glomerulonephritis with few to no immune complexes.

Patients with life-threatening disease involving the lung, kidney, or nerve^{29,30} should be treated with 2 mg/kg per day cyclophosphamide and 1 mg/kg per day prednisone, according to the schedule outlined for WG. Evidence in support of such treatment has come from its known efficacy in WG and retrospective data demon-

strating a reduced mortality rate in patients with MPA treated with a cytotoxic agent.^{28,30}

POLYARTERITIS NODOSA

Although PAN was the first described form of systemic vasculitis, changes in nomenclature have impacted our understanding of the nature and treatment of this disease. In examining the characteristics of patients included in prior PAN series, some would now be considered to have MPA under the definitions of the CHCC.

The most common clinical manifestations of PAN include hypertension, fever, musculoskeletal symptoms, and vasculitis involving the nerve, gastrointestinal tract, skin, heart, and nonglomerular renal vessels³¹ (Table III). The estimated 5-year survival rate with treatment is 80%, with death being influenced by disease severity.³² Relapses are infrequent and have been observed in <10% of patients.³²

PAN is diagnosed by biopsy or arteriography. Biopsy specimens reveal necrotizing inflammation involving the medium-sized or small arteries with abundant neutrophils, fibrinoid changes, and disruption of the internal elastic lamina. Arteriography is most often performed to study the visceral and renal circulation, in which the diagnosis is suggested by the presence of microaneurysms, stenoses, or a beaded pattern brought about by sequential areas of arterial narrowing and dilation (Fig 5).

Patients with immediately life-threatening disease affecting the gastrointestinal system, heart, or central nervous system (CNS) should be treated with 2 mg/kg per day cyclophosphamide and glucocorticoids.^{29,32} In patients in whom the disease manifestations do not pose an immediate threat to life or major organ function, glucocorticoids alone can be considered as initial therapy, with cyclophosphamide being added in patients who continue to have evidence of active disease or who are unable to taper prednisone.

PAN can also be seen in patients infected with hepatitis B, hepatitis C, or the human immunodeficiency virus.³³⁻³⁵ In the setting of hepatitis B or C, an antiviral agent should be part of the treatment regimen, with the goal being to contain viral replication and favor seroconversion. Some investigators also advocate the use of plasmapheresis.^{33,34} To initially gain control of the active vasculitis, patients may require glucocorticoids, alone or combined with cyclophosphamide, depending on the disease severity. Once clinical improvement is observed, these therapies should be rapidly withdrawn while antiviral treatment is continued because the virus will persist and replicate in the setting of immunosuppression.

CHURG-STRAUSS SYNDROME

Churg-Strauss syndrome (CSS) is a rare disease characterized by asthma, fever, hypereosinophilia, and systemic vasculitis.³⁶⁻³⁸ It has been estimated to affect about 3 people per million and has been observed in all ages equally between sexes.

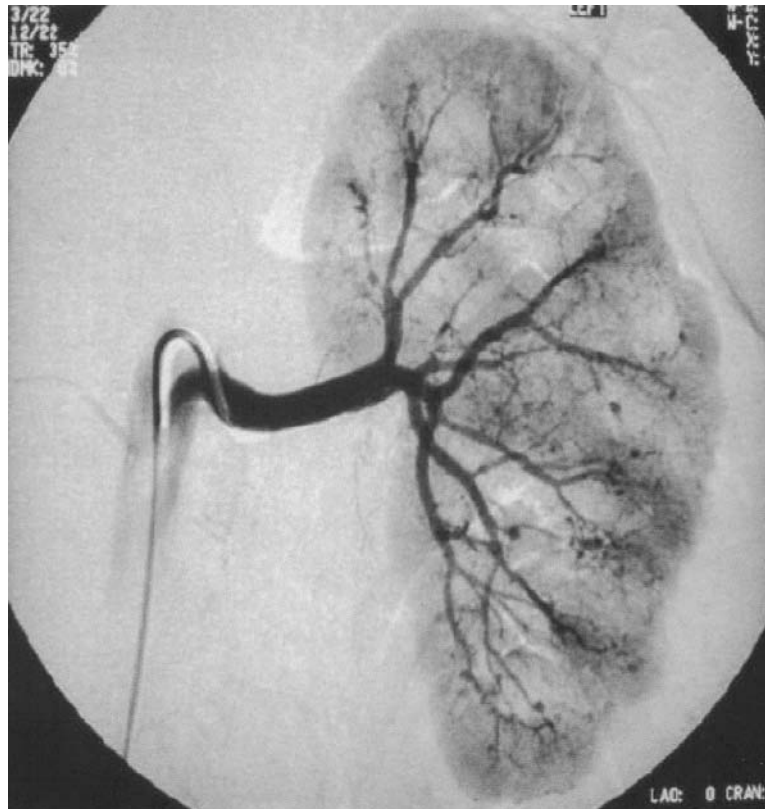


FIG 5. Renal arteriogram in a patient with polyarteritis nodosa. Microaneurysms and vessel stenoses are present.

CSS has been thought of as having three phases: a prodromal phase, with allergic rhinitis and asthma, a phase characterized by peripheral eosinophilia and eosinophilic tissue infiltrates, and, ultimately, vasculitic disease that can involve the nerve, lung, heart, gastrointestinal tract, and kidney³⁶⁻³⁸ (Table III). Although these phases help to conceptualize the disease, they may not be clinically identifiable in all patients and they often do not occur in sequence. CSS is characterized by frequent exacerbations of asthma, and relapses of vasculitic disease occur in at least 26%.³⁸ Prognosis is influenced by the presence of severe factors of disease involving sites such as the heart, gastrointestinal tract, CNS, and kidney. In one study, survival was found to be 63% in those who had ≥ 2 factors of severe disease as compared with 88% in those who had none.³⁸ Cardiac involvement is the main cause of patient death and is a poor prognostic sign.

The histologic features of CSS include eosinophilic tissue infiltrates, extravascular "allergic" granuloma, and small-vessel necrotizing vasculitis. Vasculitis can be difficult to definitively establish, making clinical manifestations of particular importance in the diagnosis of CSS.

Prednisone (1 mg/kg per day) is effective for many manifestations of CSS. Asthma often persists after remission of the vasculitis and may limit the ability for prednisone to be tapered to complete discontinuation. The use of combined therapy with glucocorticoids and cyclophosphamide (2 mg/kg/day) is reserved for patients with life-threatening disease.

CUTANEOUS LEUKOCYTOCLASTIC VASCULITIS

Cutaneous vasculitis is the most commonly encountered vasculitic manifestation in clinical practice. Lesions have the appearance of palpable purpura, although necrotic papules and ulcerative lesions are also seen. Cutaneous vasculitis is histologically characterized by the presence of small-vessel inflammation within the dermis, often with leukocytoclasia. Involvement of medium-sized vessels may be seen in cutaneous PAN.

In more than 70% of cases, cutaneous vasculitis occurs in the setting of an underlying process such as a medication exposure, infection, malignancy, connective tissue disease, or as a manifestation of a primary systemic vasculitis.^{39,40} A diagnosis of idiopathic cutaneous vasculitis should only be made after other causes have been ruled out. The course of idiopathic cutaneous vasculitis ranges anywhere from a single brief episode to multiple protracted recurrences. Progression to a systemic vasculitis occurs infrequently.

If an underlying disease or exposure is identified, management of this process forms the initial basis for treating the cutaneous vasculitis. The therapeutic principle for idiopathic cutaneous vasculitis should be to use the least toxic yet effective regimen. Glucocorticoids are frequently used, but there remains no optimal dosage schedule. Other agents that have been applied include nonsteroidal anti-inflammatory agents, antihistamines, dapsone, and

colchicine. Cytotoxic agents should be reserved for very select cases in which patients have severe disease that is unresponsive to other measures or when glucocorticoids cannot be tapered. Cyclophosphamide should rarely, if ever, be used to treat isolated cutaneous vasculitis.⁴¹

CRYOGLOBULINEMIC VASCULITIS

Cryoglobulins are cold-precipitable monoclonal or polyclonal immunoglobulins that can occur in conjunction with a variety of disease processes, including plasma cell or lymphoid neoplasms, chronic infection, and inflammatory diseases.⁴² In historic series, 34% to 71% of patients had circulating cryoglobulins in the absence of a well-defined disease, which became termed essential mixed cryoglobulinemia. With the discovery of the hepatitis C virus (HCV), it became established that the majority of cases of essential mixed cryoglobulinemia are related to HCV infection.

Cryoglobulinemia can be associated with a vasculitic illness characterized by palpable purpura, arthritis, weakness, neuropathy, and glomerulonephritis.^{42,43} Although the presence of glomerulonephritis is associated with an overall poor prognosis, progression to end-stage renal failure is uncommon.

Combined therapy with interferon- α and ribavirin provide the best opportunity for improvement of HCV-associated cryoglobulinemic vasculitis, but long-term resolution is confined to patients who have a sustained virologic response.⁴⁴ Plasmapheresis has been used with brief responses but is not practical for long-term management. Glucocorticoids, cyclophosphamide, azathioprine, and methotrexate have been applied, particularly in the case of severe disease.⁴⁵ Although treatment with immunosuppressive drugs may transiently improve the inflammatory manifestations of cryoglobulinemic vasculitis, these agents may lead to an increase in HCV viremia.

HENOCH-SCHÖNLEIN PURPURA

Henoch-Schönlein purpura (HSP) is a small-vessel vasculitis that predominantly affects children.⁴⁶ Although adults can have HSP, 75% of cases occur before the age of 8 years. Two thirds of patients report an antecedent upper respiratory tract infection although no predominant organism has been identified.

The four cardinal manifestations of HSP are palpable purpura, arthritis, gastrointestinal involvement, and glomerulonephritis. Gastrointestinal symptoms include colicky abdominal pain, vomiting, and potentially intussusception. Renal disease, most often characterized by hematuria and proteinuria, is seen in 20% to 50% of affected children with 2% to 5% progressing to end-stage renal failure. Recurrence occurs in up to 40% of cases, often within the first 3 months after the initial episode. Outcome is usually excellent, with disease-related death occurring in 1% to 3%. Less is known about HSP in adults, although several studies suggest that glomerulonephritis may be more severe and lead to renal insufficiency in up to 13% of cases.

The diagnosis of HSP is established by the characteristic pattern of clinical manifestations but can be less certain when other features precede the skin lesions. Skin biopsy reveals leukocytoclastic vasculitis with IgA deposition in blood vessel walls but is not required in most instances. Renal biopsy is rarely necessary for diagnosis but may have prognostic utility.

HSP is typically a self-limited condition that rarely requires treatment.⁴⁷ Glucocorticoids may lessen tissue edema, arthritis, and abdominal discomfort and decrease the rate of intussusception. However, they are of no proven benefit in skin or renal disease and do not appear to shorten duration or lessen the likelihood of relapse.⁴⁸ Uncontrolled studies suggest that glucocorticoids in combination with a cytotoxic agent may be beneficial in patients with active glomerulonephritis and progressive renal insufficiency.

KAWASAKI DISEASE

Kawasaki disease is an acute vasculitis of childhood and represents the primary cause of acquired heart disease in children from the United States and Japan.⁴⁹ Eighty percent occurs before the age of 5 years, and boys are affected 1.5 times more often than girls.

Kawasaki disease begins as an acute febrile illness that is followed within the first 1 to 3 days by rash, conjunctival injection, and oral mucosal changes. Extremity changes characterized by brawny induration occur early in the disease, and 50% to 75% have cervical adenopathy. Together with fever, these 5 features constitute the criteria on which the diagnosis is based.⁵⁰ Coronary artery lesions are responsible for most of the disease-related morbidity and mortality that occurs in Kawasaki disease. Aneurysms appear 1 to 4 weeks after the onset of fever and develop in 15% to 25% of affected children who do not receive intravenous immunoglobulin (IVIg).

IVIg (2 g/kg) as a single infusion has been shown to prevent coronary aneurysm formation, lessen fever, and reduce myocardial inflammation.⁵¹ Aspirin (80 to 100 mg/kg per day) is given concurrently. To monitor for the development of coronary aneurysms, an electrocardiogram is recommended in the first week of illness and a 2-dimensional echocardiogram should be obtained at diagnosis and at 2 and 4 weeks after disease onset. Children with multiple aneurysms, giant aneurysms, or coronary artery obstruction require close follow-up and possible long-term anticoagulation.

BEHÇET DISEASE

Behçet disease is a multisystem inflammatory disease with vascular manifestations that can affect vessels of all sizes.⁵² It is most prevalent in 20- to 35-year-old people of Asian and Eastern Mediterranean descent, with sex pattern being influenced by ethnic background.

Behçet disease is characterized by recurrent aphthous oral ulcers and at least two or more of the following: recurrent genital ulceration, eye lesions, cutaneous lesions, or a

positive pathergy test.⁵³ Among the most severe manifestations are gastrointestinal inflammation and ulceration, ocular inflammation that may lead to blindness, and CNS disease with meningoencephalitis. Large venous or arterial lesions occur in 7% to 38% of patients and may include vessel thrombosis and occlusion, as well as pulmonary or peripheral artery aneurysms. Behçet disease has the ability to remit and relapse frequently. Death occurs in 4% of cases, generally as the result of gastrointestinal perforation, vascular rupture, and CNS disease.

Treatment is based on the disease manifestations. Aphthous lesions and mucocutaneous disease may be treated with topical or intralesional glucocorticoids, dapsone, or colchicine. Thalidomide has also been beneficial although serious concerns with teratogenicity and neurotoxicity have limited its use. Ocular and CNS disease requires aggressive immunosuppression, with cyclosporine, azathioprine, and chlorambucil being the most commonly utilized agents.

PRIMARY ANGIITIS OF THE CNS

Primary angiitis of the CNS (PACNS) is an uncommon disease in which patients have clinical disease isolated to the CNS and there are minimal to no signs of systemic vasculitis. Two variants have been suggested: granulomatous angiitis of the CNS (GACNS) and benign angiitis of the CNS (BACNS).^{54,55} BACNS appears to have a monophasic course and is usually observed in young women who have an acute severe headache or focal neurologic deficit with an abnormal arteriogram. In contrast, GACNS is a slowly progressive disease characterized by focal neurological deficits, chronic headache, alterations in higher cortical function, or inflammatory spinal cord lesions.

More than 90% of patients with GACNS will have an abnormal cerebrospinal fluid with mononuclear pleocytosis and elevated protein with normal glucose. Magnetic resonance imaging is almost always abnormal, reflecting multifocal vascular insults of different ages. Cerebral arteriogram may reveal stenoses and ectasia in up to 40% of patients. In all instances, a careful search must be made for processes of similar appearance including vascular spasm, atherosclerosis, infection, neoplasms, and drug-induced changes. Biopsy of tissue from the CNS is the diagnostic modality of choice, but results can be falsely negative in up to one fifth of patients. The diagnostic yield may be increased by taking biopsy specimens of both the leptomeninges and the underlying cortex.

GACNS is characteristically a fatal and progressive disorder but can respond to 1 mg/kg per day prednisone and 2 mg/kg per day cyclophosphamide. In BACNS, 1 mg/kg per day prednisone for 2 to 3 months may be sufficient. For the 50% of patients with PACNS who do not fit into the categories of BACNS or GACNS, treatment is based on the severity of disease manifestations and rate of progression.

COGAN SYNDROME

Cogan syndrome is a rare disease that occurs in young adults, without sex predominance.⁵⁶ Features include

interstitial keratitis and vestibuloauditory dysfunction that may result in permanent hearing loss. Patients can also have aortitis or other features of large-vessel vasculitis. Prednisone (1 mg/kg per day) is indicated for severe ocular disease, vestibuloauditory disease, and vasculitis. Initiation of treatment at the first indication of hearing loss provides the best opportunity for prevention of further loss and potential return of auditory function.

REFERENCES

1. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell (temporal) arteritis. *Arthritis Rheum* 1990;33:1122-8.
2. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994;37:187-92.
3. Sneller MC, Fauci AS. Pathogenesis of vasculitis syndromes. *Med Clin North Am* 1997;81:221-42.
4. Hoffman GS, Specks U. Antineutrophil cytoplasmic antibodies. *Arthritis Rheum* 1998;41:1521-37.
5. Van der Woude FJ, Lobatto S, Permin H, Giessen MvD, Rasmussen N, Wiik A. Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985;1:425-9.
6. Rao JK, Weinberger M, Oddone EZ, Allen NB, Landsman P, Feussner JR. The role of antineutrophil cytoplasmic antibody (c-ANCA) testing in the diagnosis of Wegener granulomatosis: a literature review and meta-analysis. *Ann Intern Med* 1995;123:925-32.
7. Langford CA. The diagnostic utility of c-ANCA in Wegener's granulomatosis. *Cleve Clin J Med* 1998;65:135-40.
8. Kerr GS, Fleisher TA, Hallahan CW, Leavitt RY, Fauci AS, Hoffman GS. Limited prognostic value of changes in antineutrophil cytoplasmic antibody titer in patients with Wegener's granulomatosis. *Arthritis Rheum* 1993;36:365-71.
9. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. *Ann Intern Med* 1994;120:919-29.
10. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's disease: clinical and statistical analyses of related prognostic factors. *Circulation* 1994;90:1855-60.
11. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, Fauci AS. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. *Arthritis Rheum* 1994;37:578-82.
12. Shelhamer JH, Volkman DJ, Parillo JE, Lawley TJ, Johnston MR, Fauci AS. Takayasu's arteritis and its therapy. *Ann Intern Med* 1985;103:121-6.
13. Giordano JM, Leavitt RY, Hoffman GS, Fauci AS. Experience with surgical treatment for Takayasu's disease. *Surgery* 1991;109:252-8.
14. Hunder GG. Giant cell arteritis and polymyalgia rheumatica. *Med Clin North Am* 1997;81:195-219.
15. Calamia KT, Hunder GG. Clinical manifestations of giant cell (temporal) arteritis. *Clin Rheum Dis* 1980;6:389-403.
16. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum* 1999;42:311-7.
17. Evans JM, Bowles CA, Bjornsson J, Mullany CJ, Hunder GG. Thoracic aortic aneurysm and rupture in giant cell arteritis: a descriptive study of 41 cases. *Arthritis Rheum* 1994;37:1539-47.
18. Aiello PD, Trautmann JC, McPhee TJ, Kunselman AR, Hunder GG. Visual prognosis in giant cell arteritis. *Ophthalmology* 1993;100:550-5.
19. Jover JA, Hernandez-Garcia C, Morado IC, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2001;134:106-14.
20. Hoffman GS, Cid MC, Hellman DB, Guillemin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002;46:1309-18.
21. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992;116:488-94.

22. Reinhold-Keller E, Beuge N, Latza U, de Groot K, Rudert H, Nolle B, et al. An interdisciplinary approach to the care of patients with Wegener's granulomatosis: long-term outcome in 155 patients. *Arthritis Rheum* 2000;43:1021-32.
23. Fauci A, Haynes B, Katz P, Wolff S. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983;98:76-85.
24. Langford CA, Sneller MC. Update on the diagnosis and treatment of Wegener's granulomatosis. *Adv Intern Med* 2001;46:177-206.
25. Langford CA, Talar-Williams C, Barron KS, Sneller MC. A staged approach to the treatment of Wegener's granulomatosis: induction of remission with glucocorticoids and daily cyclophosphamide switching to methotrexate for remission maintenance. *Arthritis Rheum* 1999;42:2666-73.
26. Jayne D. Update on the European Vasculitis Study Group trials. *Curr Opin Rheumatol* 2001;13:48-55.
27. Sneller MC, Hoffman GS, Talar-Williams C, Kerr GS, Hallahan CW, Fauci AS. An analysis of forty-two Wegener's granulomatosis patients treated with methotrexate and prednisone. *Arthritis Rheum* 1995;38:608-13.
28. Guillevin L, Durand-Gasselin B, Cevallos R, Gayraud M, Lhote F, Callard P, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. *Arthritis Rheum* 1999;42:421-30.
29. Langford CA. Treatment of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: where do we stand? *Arthritis Rheum* 2001;44:508-12.
30. Hogan SL, Nachman PH, Wilkman AS, Jennette JC, Falk RJ. Prognostic markers in patients with antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996;7:23-32.
31. Lhote F, Guillevin L. Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: clinical aspects and treatment. *Rheum Dis Clin North Am* 1995;21:911-47.
32. Gayraud M, Guillevin L, le Toumelin P, Cohen P, Lhote F, Casassus P, et al. Long-term follow-up of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: analysis of four prospective trials including 278 patients. *Arthritis Rheum* 2001;44:666-75.
33. Guillevin L, Lhote F, Cohen P, Sauvaget F, Jarrousse B, Lortholary O, et al. Polyarteritis nodosa related to hepatitis B virus: a prospective study with long-term observation of 41 patients. *Medicine* 1995;74:238-53.
34. Guillevin L, Lhote F, Gherardi R. The spectrum and treatment of virus-associated vasculitides. *Curr Opin Rheumatol* 1997;9:31-6.
35. Cacoub P, Maisonneuve T, Thibault V, Gatel A, Servan J, Musset L, et al. Systemic vasculitis in patients with hepatitis C. *J Rheumatol* 2001;28:109-18.
36. Lanham JG, Elkon KB, Pusey CD, Hughes GR. Systemic vasculitis with asthma and eosinophilia: a clinical approach to Churg-Strauss syndrome. *Medicine* 1984;63:65-81.
37. Chumbley LC, Harrison EG, DeRemee RA. Allergic granulomatosis and angiitis (Churg-Strauss Syndrome): report and analysis of 30 cases. *Mayo Clin Proc* 1977;52:477-84.
38. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg-Strauss syndrome: clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999;78:26-37.
39. Gibson LE. Cutaneous vasculitis: approach to diagnosis and systemic associations. *Mayo Clin Proc* 1990;65:221-9.
40. Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol* 1998;39:667-87.
41. Cupps TR, Springer RM, Fauci AS. Chronic, recurrent small-vessel cutaneous vasculitis: clinical experience in 13 patients. *JAMA* 1982;247:1994-8.
42. Lamprecht P, Gause A, Gross WL. Cryoglobulinemic vasculitis. *Arthritis Rheum* 1999;42:2507-16.
43. Agnello V, Romain PL. Mixed cryoglobulinemia secondary to hepatitis C virus infection. *Rheum Dis Clin North Am* 1996;22:1-21.
44. Ferri C, Marzo E, Longombardo G, Lombardini F, La Civita L, Vanacore R, et al. Interferon-alpha in mixed cryoglobulinemia patients: a randomized, crossover-controlled trial. *Blood* 1993;81:1132-6.
45. Vassilopoulos D, Calabrese LH. Hepatitis C virus infection and vasculitis: implications of antiviral and immunosuppressive therapies. *Arthritis Rheum* 2002;46:585-97.
46. Saulsbury FT. Henoch-Schönlein purpura in children. Report of 100 patients and review of the literature. *Medicine (Baltimore)* 1999;78:395-409.
47. Allen DM, Diamond LK, Howell DA. Anaphylactoid purpura in children (Schönlein-Henoch syndrome). *Am J Dis Child* 1960;99:833-54.
48. Meadow SR, Glasgow EF, White RHR, Moncrieff MW, Cameron JS, Ogg CS. Schönlein-Henoch nephritis. *Q J Med* 1972;41:241-58.
49. Barron KS, Shulman ST, Rowley A, Taubert K, Myones BL, Meissner HC, et al. Report of the National Institutes of Health Workshop on Kawasaki Disease. *J Rheumatol* 1999;26:170-90.
50. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974;54:271-6.
51. Newburger JW, Takahashi M, Beiser AS, Burns JC, Bastian J, Chung KJ, et al. A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. *N Engl J Med* 1991;324:1633-9.
52. Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. *N Engl J Med* 1999;341:1284-91.
53. International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. *Lancet* 1990;335:1078-80.
54. Calabrese LH, Duna GF, Lie JT. Vasculitis in the central nervous system. *Arthritis Rheum* 1997;40:1189-201.
55. Hajj-Ali R, Furlan A, Abou-Chebel A, Calabrese L. Benign angiopathy of the central nervous system (BACNS): cohort of 16 patients with clinical course and long-term follow-up. *Arthritis Rheum* 2002;47:662-9.
56. St Clair EW, McCallum RM. Cogan's syndrome. *Curr Opin Rheumatol* 1999;11:47-52.