Churg-Strauss Syndrome

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ABSTRACT

First described in 1951 as an allergic and granulomatous angiitis, Churg-Strauss syndrome (CSS) is a small-vessel vasculitis. Mean age at the time of diagnosis is ~50 years, with a sex ratio around 1. Asthma is the central feature of CSS and precedes the systemic manifestations in almost all cases, whereas 70% of the patients have maxillary sinusitis, allergic rhinitis, and/or sinus polyposis. General symptoms are frequent, and associated with pulmonary infiltrates in 38 to 77% of the patients; peripheral neuropathy, usually mononeuritis multiplex, in 64 to 75%; skin involvement in 40 to 70%; and gastrointestinal tract symptoms in 37 to 62%. Cardiac involvement is common, with pericarditis in 23% of the patients and myocarditis in 13%, and represents the primary cause of mortality. Hypereosinophilia is the main biological feature of CSS, whereas antineutrophil cytoplasm antibodies (ANCA), especially anti-myeloperoxidase (MPO), are found in one third to one half of the patients. Triggering factors, such as vaccination, desensitization, or exposure to leukotriene-receptor antagonists, have been suspected as contributing to the development of CSS, but its etiology has not yet been fully elucidated. T-helper type 2 (Th2) lymphocytes, by analogy with the pathogenesis of asthma, eosinophils infiltrating tissues, and anti-MPO ANCA are probably implicated in the pathogenesis of vasculitic lesions. CSS usually responds rapidly to corticosteroids. Adjunction of cyclophosphamide is indicated when at least one factor of poor prognosis is present. With treatment, remission is obtained in more than 80% of the patients, but it is often impossible to withdraw corticosteroids completely because of residual asthma. Relapses occur in 25% of the patients, half during the first year. The 10-year survival rate was 79% for our patients, with 73% of them requiring low-dose prednisone maintenance therapy for persistent asthma.

KEYWORDS: Churg-Strauss syndrome, primary systemic necrotizing vasculitis, asthma

Objectives: Upon completion of this article, readers should be able to: (1) list the main clinical features of Churg-Strauss syndrome (CSS); (2) identify among CSS patients those with poor prognostic factor(s); and (3) choose the most appropriate therapeutic management.

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KEY POINTS

- Churg-Strauss syndrome (CSS) is a primary small-vessel systemic necrotizing vasculitis, strongly associated with antineutrophil cytoplasm antibodies (ANCA), especially anti-myeloperoxidase (MPO).
- Triggering factors may be implicated in the development of some cases [leukotriene-receptor antagonists (LTRA), vaccinations, desensitization].
- Asthma, lung infiltrates, extravascular necrotizing granulomas and hypereosinophilia are the hallmarks of the disease.
- Cardiomyopathy is common and represents the major cause of mortality, just before gastrointestinal (GI) tract involvement with bowel perforation(s).
- First-line therapy consists of high doses of corticosteroids.
- Cyclophosphamide is added only when one or more factors of poor prognosis are present.
- With treatment, remission is obtained in more than 80% of the patients but it is often impossible to discontinue corticosteroids because of residual asthma.

DEFINITION

The syndrome of allergic granulomatosis and angiitis is a disorder characterized by pulmonary and systemic small-vessel vasculitis, extravascular granulomas, and hypereosinophilia, that occurs in individuals with asthma and allergic rhinitis. It bears the name Churg-Strauss syndrome (CSS) in reference to the two pathologists, J. Churg and L. Strauss,[1] who first described it, in 1951, as a disease that is similar to but clearly distinct from polyarteritis nodosa (PAN). Churg and Strauss established three major criteria based on histological examination and postmortem studies: tissue infiltration by eosinophils, necrotizing vasculitis, and extravascular granulomas. CSS is strongly associated with antineutrophil cytoplasm antibodies (ANCA), especially anti-myeloperoxidase (MPO) ANCA.

CLASSIFICATION

CSS is characterized by the presence of asthma, eosinophilia, and granuloma(s). It is a distinct entity, as indicated in all classifications of systemic vasculitides.[2–4] In 1990, the American College of Rheumatology (ACR) proposed six classification criteria for CSS (Table 1), with four being necessary for CSS to be diagnosed with 85% sensitivity and 99.7% specificity.[2] In the classification of vasculitides formulated by the Chapel Hill Consensus Conference,[3] CSS is included in the group of small-sized vessel vasculitides. Lanham et al[5] proposed clinical criteria that are very useful for the diagnosis of CSS: the association of asthma, blood eosinophil count $>1500/mm^3$, and symptoms of systemic vasculitis involving at least two extrapulmonary sites yields 95% sensitivity and 95% specificity for the diagnosis. CSS is an ANCA-associated vasculitis, like Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA), and clearly distinct from classic PAN, a disease involving medium-sized arteries and usually not associated with ANCA.

HISTOLOGY

The two characteristic lesions for the diagnosis of CSS[6] are angiitis and extravascular necrotizing granulomas, usually associated with eosinophilic infiltrates. Vasculitic lesions may be granulomatous or nongranulomatous and typically involve both arteries and veins, as well as pulmonary and systemic vessels. Temporal artery involvement in CSS has been reported anecdotally.[7] Granulomas usually measure 1 mm or more in diameter and are commonly located close to small arteries or veins; they are characterized by palisading epithelioid histiocytes arranged around central necrotic zones in which eosinophils are prominent. Necrotizing vasculitis, eosinophilic infiltration of tissues, and extravascular granulomas rarely coexist temporally or spatially, and are only found together in a minority of cases.

Table 1 1990 American College of Rheumatology Criteria for the Classification of Churg-Strauss Syndrome

Criterion	Definition
1. Asthma	History of wheezing or diffuse, high-pitched rales on expiration
2. Eosinophilia	Eosinophilia > 10% of white blood cell differential count
3. Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy (i.e., glove/stocking distribution) attributable to vasculitis
4. Pulmonary infiltrates, nonfixed	Migratory or transitory pulmonary infiltrates on radiographs (not including fixed infiltrates), attributable to systemic vasculitis
5. Paranasal sinus abnormality	History of acute or chronic paranasal sinus pain or tenderness, or radiographic opacification of the paranasal sinuses
6. Extravascular eosinophils	Biopsy including artery, arteriole or venule, showing accumulations of eosinophils in extravascular areas

For classification purposes, a patient with vasculitis shall be said to have Churg-Strauss syndrome if at least four of these six criteria are present. The presence of any four or more criteria yields a sensitivity of 85% and a specificity of 99.7%. (Adapted from Masi et al.[2])

In the lungs, the histological features of CSS combine necrotizing vasculitis and areas resembling eosinophilic pneumonia. Vasculitis affects both arteries and veins. It is characterized by granulomatous inflammation or giant-cell infiltration of vessel walls. In some cases, transmural eosinophil and histiocyte infiltrates with fibrinoid necrosis may be seen. Small extravascular granulomas are also common.

Extrapulmonary lesions are more frequently found in the gastrointestinal (GI) tract, spleen, and heart than in the kidney. Cutaneous and subcutaneous lesions, so-called Churg-Strauss granulomas, lack diagnostic specificity and half of these lesions are seen in a variety of systemic diseases other than CSS.

EPIDEMIOLOGY

CSS is a rare disease. Since its first description, a few series have been published in the English and French literature.[5,8–10] The annual incidence of CSS in Olmstead County, Minnesota, was estimated to be 4/1,000,000 inhabitants,[11] based on a single case seen during the period from 1976 to 1979. From 1988 to 1998, 14 cases of CSS were diagnosed in the Norwich Health Authority,[12] where the annual incidence of CSS using Lanham's[5] criteria was 3.1/1,000,000 inhabitants, much higher than in Lugo, Spain, where CSS is extremely rare, with an annual incidence of 0.9/1,000,000 inhabitants.[13] Twelve of the 14 CSS patients diagnosed at the Norwich Health Authority were living in a rural area, which suggested the role of environmental factors, such as pesticides or pollens. More recently, Gonzalez-Gay et al identified only 4/54 patients with CSS in the Lugo province of Spain, none of whom were living in a rural area.[14] In the county of Seine–Saint-Denis, a suburban area of northern Paris, France, the prevalence of CSS was of 11/1,000,000 inhabitants.[15]

PATHOGENESIS

Limited data are available regarding the immunopathogenesis of CSS. Biologically, CSS is characterized by elevated serum immunoglobulin E (IgE) and eosinophilia that are thought to be hallmarks of T-helper type 2 (Th2) responses. The pathophysiology of CSS can be considered to have three facets, corresponding to the three main phases of the natural history of CSS: development of asthma, involving Th2 lymphocytes; potential role of eosinophils infiltrating tissues; contribution of MPO ANCA to the formation of vasculitic lesions.

Allergic asthma is characterized by airway hyperreactivity to a variety of specific and nonspecific stimuli, chronic airway inflammation, and elevated serum IgE levels. The inflammatory process is thought to be a consequence of inappropriate immune responses to common airborne allergens in genetically susceptible individuals.[16] Hence, the $CD4^+$ T cells that produce Th2 cytokines seem to play a pivotal role in the pathogenesis of asthma.[17] Th2 cells orchestrate the recruitment and activation of the primary effectors of the allergic response—mast cells and eosinophils—through the release of cytokines, such as interleukin (IL)-4, IL-5, and IL-13. Activation of these cells results in the release of a plethora of inflammatory mediators that individually or in concert contribute to causing asthma.[18] IL-4 is required for class-switching from IgG to IgE, and IL-5, in association with IL-3 and granulocyte/macrophage–colony-stimulating factor (GM–CSF), is particularly important in regulating eosinophil proliferation. During the pathogenesis of asthma, proinflammatory cytokines, such as IL-1β and tumor necrosis factor-α (TNFα), interact with vascular endothelial cells to induce the expression of intercellular adhesion molecules (ICAM-1), which allow the egress of eosinophils from vessels into inflammatory loci and, in turn, further promote the expression of adhesion molecules.

Only a few studies specifically addressed the involvement of cytokines in the pathogenesis of CSS. Grau et al[19] reported that TNFα and IL-1β serum levels were elevated in CSS patients. Tsukadaira et al obtained similar results and also reported high IL-5 levels in the sera of five CSS patients.[20]

Although their exact role in the control of allergic immune responses remains to be determined, T-helper type 1 (Th1) cytokines, such as interferon-gamma (IFNγ), can inhibit Th2-cell development in vitro and antagonize the actions of Th2 cytokines in vivo in animal models of asthma.[21] In addition, $CD4^+$ regulatory T cells, which synthesize transforming growth factor-β (TGFβ), have been identified in the respiratory mucosa. These cells seem to play an important role in asthma by regulating Th2-induced airway hyperreactivity and inflammation.[22] Using short-term cultures of polyclonal T cell lines derived from the peripheral blood of CSS patients, Kiene et al[23] provided evidence for the presence of both $CD4^+$ Th1 cells (IFNγ) and Th2-cell responses. However, more Th2 (IL-4, IL-5, and IL-13) than Th1 cytokines were detected. No data are yet available concerning the potential role of TGFβ-producing T cells in the pathogenesis of CSS. The hypothesis that inhaled allergens, vaccinations, desensitization, drugs, or infections (parasitic or bacterial) might trigger $CD4^+$ Th2 cells to secrete cytokines and thereby induce massive expansion of eosinophils needs to be confirmed.

Patients with CSS often show marked peripheral blood eosinophilia, with these cells exhibiting various degrees of activation, but only a few studies evaluated eosinophil involvement in tissue lesions. Conditions secondary to eosinophil infiltration of tissues, such as eosinophilic endomyocarditis, are rarely reported.[1,16] Activated eosinophils are able to induce vascular endothelial cell activation and may be directly responsible

for some of the classical features of CSS, by virtue of the release of their stored cationic proteins, which are implicated in the cardiotoxicity.[24] Eosinophil granules contain major basic protein (MBP), eosinophilic cationic protein (ECP), and eosinophil-derived neurotoxins. ECP has been found to be elevated in the sera and bronchoalveolar lavage fluids of CSS patients.[25] Extracellular ECP and MBP deposits have also been detected in damaged tissues at sites of active CSS.[26,27]

ANCA, in most cases directed against MPO, are found in ~50% of CSS patients and might play a role in the development of endothelial damage in systemic vasculitides, like in WG and MPA. ANCA titers may correlate with disease activity, and patients who are persistently ANCA-positive during remission are prone to developing relapses.[28] Although the specific pathogenetic role of ANCA has not been demonstrated in CSS, recent evidence for their role in the pathogenesis of systemic vasculitis has been obtained.[29]

In vitro, ANCA activate TNFα-primed neutrophils generating oxygen radicals and the release of lysosomal proteolytic enzymes, including the ANCA antigens themselves. ANCA-mediated activation of neutrophils also results, in part, from their binding to the low-affinity receptors for the Fc fragment of IgG (FcγRII).[30] TNFα-priming induces the expression of ANCA target antigens on the surface of the neutrophils, thereby making these cells accessible for interaction with anti-MPO antibodies.[31] ANCA interact with primed neutrophils adhering to vascular endothelium, particularly via β-integrins. In addition, ANCA can stimulate neutrophil cytotoxicity toward activated endothelial cells in culture. The coexistence of cytokine-primed neutrophils, endothelium, and circulating ANCA may permit ANCA to trigger the cascade of events leading to vasculitis, especially in small vessels where neutrophils are in close contact with vessel walls.

The role of ANCA in the pathogenesis of systemic vasculitides was demonstrated in experimental models. Genetically susceptible rats develop autoimmune manifestations after injection of mercury chloride. These animals synthesized antibodies to MPO, but also to other proteins and nuclear antigens,[32] but none of them developed glomerulonephritis. In another model, SCG/Kj mice produced anti-MPO antibodies and developed necrotizing vasculitis and extracapillary glomerular lesions.[33] However, it must be kept in mind that anti-MPO antibodies are also observed in the context of a polyclonal immune response, thus limiting the potential contribution of that model. In addition, two models of anti-MPO–induced necrotizing glomerulonephritis that require an initial infusion of antiglomerular basement membrane antibodies have been created.[34]

Recent input in the field came from a new experimental murine model. MPO-knockout mice immunized with murine MPO developed anti-MPO antibodies.[29] These antibodies were then purified and transferred into RAG2-knockout mice, which developed crescentic necrotizing glomerulonephritis.[29] These observations suggest that anti-MPO antibodies alone are able to induce necrotizing glomerulonephritis lesions.

The role of circulating IgE-containing immune complexes also has to be considered. Manger et al[35] found the levels of these complexes to be elevated in the sera of five CSS patients, and their renal biopsies contained deposits of various immunoglobulin classes and C3.

TRIGGERING FACTORS

Although triggering factors have been identified in CSS, its etiology has not been elucidated. The development of vascular inflammatory infiltrates relies on dynamic interactions among neutrophils, endothelial cells, and extracellular matrix proteins. These interactions, which are mediated by adhesion molecules, are part of the physiological inflammatory response to injury.

Desensitization and vaccinations have been implicated as potential triggering factors for the development of CSS.[9,36] Suspected precipitating factors were identified in 24/96 of our patients.[9] CSS cases have been sporadically reported in relationship with the use of different drugs, such as macrolides, carbamazepine, or quinine.[37–39] More recently, the possible contribution of leukotriene-receptor antagonists (LTRA) (zafirlukast, montelukast, pranlukast) to the development of CSS has been highlighted, with more than 100 cases reported to the U.S. Food and Drug Administration.[40–43] A temporal relationship with their use has been suggested for almost all cases, but without demonstrating or excluding a direct role. LTRA therapy usually provides the opportunity for substantial tapering or withdrawal of corticosteroids, which in turn may unmask an underlying and previously incomplete disease, named forme fruste, and allow it to fully develop.[44–48] Indeed, CSS has also been reported, but much less frequently, with the use of other systemic corticosteroid-sparing therapies, such as the long-acting β_2-agonist salmeterol,[49] disodium cromoglycate,[50,51] inhaled fluticasone,[44] and even just after the onset of tapering of inhaled or oral corticosteroids,[47,52] without the combination or the introduction of any other anti-asthma drug. However, a direct causative role of LTRA cannot be excluded because LTRA only block the actions of LT(leukotriene)C4, LTD4, and LTE4, thereby provoking a potential imbalance of leukotrienes with an LTB4 predominance,[53] which is a potent chemoattractant and activating factor for eosinophils and neutrophils. Although these points remain controversial, physicians should be aware of the potential risk of CSS-worsening associated with the use of these drugs, desensitization, or vaccinations.

The estimated incidences of CSS in the asthmatic population treated or not with an LTRA are strikingly similar, ~60/million asthmatics/year. In comparison with the CSS incidence in the general population, these rates observed in association with leukotriene modifiers appear to represent a marked increase, but the CSS incidence[54] in a cohort of asthmatics receiving non-leukotriene-modifying asthma drugs was very similar (64.4/million asthmatics/year), suggesting that CSS was not directly due to zafirlukast or montelukast, but rather to an underlying systemic eosinophilic disorder that was chronically masked by systemic or high-dose inhaled corticosteroids for what was perceived to be severe asthma.

CLINICAL FEATURES

Natural History of CSS

Lanham[55] identified three phases of the disease. The prodromal period may last for years (up to 30 or even more) and consists of asthma and other allergic manifestations (allergic rhinitis and nasal polyposis). A systematic inquiry[9] showed that 63.8% of the patients had a personal history of allergy and 25% had a familial history of allergy.[36] The second phase of the disease is characterized by the onset of peripheral blood and tissue eosinophilia with Löffler's syndrome, chronic eosinophilic pneumonia, or eosinophilic gastroenteritis; the eosinophilic infiltrative disease may enter remission and recur over the years before the systemic vasculitis appears and defines the third phase of CSS, although these three phases do not necessarily have to follow one another in this order. Systemic vasculitis emerges within a mean time of 8.86 ± 10 years after the onset of asthma and a shorter duration of asthma prior to the onset of vasculitis is associated with a poorer prognosis.

Clinical features of CSS[5,8,9,36,56–58] are summarized in Table 2.[5,8,9,56–58] The mean age of our patients at the time of CSS diagnosis was 48.2 ± 14.6 years; the sex ratio was ~1, with 47% males.[9] Most patients had general symptoms, such as fever or weight loss, and their development in asthmatic patients is suggestive of the diagnosis.

Pulmonary Manifestations

ASTHMA

Asthma is the central feature of CSS and precedes the systemic manifestations in almost all cases. Unlike common asthma, it appears relatively late, around the

Table 2 Frequencies (%) of Clinical Features of Churg-Straus Syndrome in 191 Patients Reported in the Literature

Features		Chumbley et al[8] 1977	Lanham et al[5] 1984	Gaskin et al[56] 1991	Haas et al[57] 1991	Abu-Shakra et al[58] 1994	Guillevin et al[9] 1999
DEMOGRAPHIC							
n		30	16	21	16	12	96
Sex	M	21	12	14	12	6	45
	F	9	4	7	4	6	51
Mean age (yr)		47	38	46.5	42.5	48	48.2
Range		(15–69)	—	(23–69)	(17–74)	(28–70)	(17–74)
CLINICAL							
Asthma		100	100	100	100	100	100
General symptoms		—	—	—	100	100	70
Pulmonary infiltrates		27	72	43	62	58	38
Allergic rhinitis and ENT involvement		70	70	—	10	83	47
Mononeuritis multiplex		63	66	70	75	92	78
CNS involvement		—	27	—	—	8	8
GI involvement		17	59	58	56	8	33
CV involvement		16	47	15	56	42	30
Arthritis, arthralgias		20	51	43	31	42	41
Myalgias		—	68	—	43	33	54
Skin involvement		67	—	50	68	67	51
	Purpura		48	—	25	—	31
	Nodules	27	30	—	25	—	19
Renal involvement		20	49	80	31	8	16
Pleural effusion		—	29	—	25	—	—

[a]Nephrology patients.
CNS, central nervous system; CV, cardiovascular; ENT, ear, nose and throat; GI, gastrointestinal.

age of 35 years.[9] Severity and frequency of the asthmatic attacks usually increase until the onset of vasculitis and half of the patients require at least inhaled but more often oral steroids. Although asthma may regress dramatically when vasculitis emerges, it usually becomes more severe during the weeks preceding vasculitis, becoming corticosteroid dependent, and patients must often be hospitalized to treat asthma attacks or respiratory failure. The severity of asthma justified the use of steroids in 77% of the patients in one study.[36] Upper airway findings can include sinusitis, allergic rhinitis, and nasal polyps.

PULMONARY INFILTRATES

Chest radiographs are often abnormal and 38 to 77%[5,8,9,56–58] (Table 2) of the patients have pulmonary infiltrates. These infiltrates, when present during the second phase of the disease, and in association with asthma and hypereosinophilia, may mimic chronic eosinophilic pneumonia. The radiological features of pulmonary infiltrates are diverse: transient and patchy infiltrates with an alveolar pattern without lobar or segmental distribution are the most typical findings, although a diffuse interstitial infiltrative pattern or massive bilateral nodular infiltrates without cavitation may be seen. The most common computed tomographic (CT) finding is nonspecific and consists of areas of parenchymal opacification that may be random or peripheral in distribution. Their significance is not univocal: pulmonary eosinophilic infiltration or more rarely alveolar hemorrhage.

PLEURAL EFFUSION

Pleural effusion is rarely present at the time of diagnosis and was observed in only 3% of our patients.[9] The effusion can be unilateral or bilateral and is often asymptomatic. The fluid is an eosinophil-rich exudate and its glucose concentration can be low. Vasculitis and eosinophil infiltration of the pleura can be seen and CSS can, on rare occasions, be diagnosed by pleural biopsy.

Neurological Involvement

NEUROPATHY

Peripheral neuropathy, usually mononeuritis multiplex, is found in 64 to 75% of our patients, and its occurrence is highly suggestive of the diagnosis. Motor and sensory signs are asymmetric, predominantly affecting the lower limbs, especially the sciatic nerve and its peroneal and tibial branches. Radial, cubital, and median nerves are involved less frequently. Motor deficit appears abruptly. Sensory signs are responsible for hypo- or hyperesthesia and pain in the area of the motor deficit, which is sometimes present before the sensory loss. Peripheral neuropathy is typically mononeuritis multiplex or multiple mononeuropathy but can sometimes take on the appearance of bilateral distal sensory neuropathy. Electromyography shows axonal nerve involvement and often detects more extensive involvement than the clinical symptoms would indicate. When performed, neuromuscular biopsies often (63%) showed epineurial vessel involvement[9] and they are a good tool for diagnosing vasculitis. Under treatment, mononeuritis multiplex regresses progressively and patients can recover without sequelae. However, when the latter are present, they are more sensory than motor. Cranial nerve palsy is infrequent and the most common cranial nerve lesion is ischemic optic neuritis.

CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT

CNS involvement is relatively rare. It occurred in 8.3% of our patients.[9] Clinical manifestations are nonspecific (strokes with motor or sensory deficit, meningeal or brain hemorrhage, cognitive dysfunction, or epilepsy) and reflect the presence of brain vasculitis. CT scans and magnetic resonance images are useful for diagnosis. CNS involvement has been demonstrated to be one of the factors of poor prognosis.[59]

Cutaneous Lesions

Skin involvement occurs in 50 to 68% (Table 2) of the patients and reflects the predilection for small vessels. Purpura is seen in 25% to half (Table 2) of the patients and subcutaneous nodules in 30%. Skin biopsies can show extravascular granulomas. These nodules are the most distinctive skin lesions of CSS but are not pathognomonic and have been described in other vasculitides, autoimmune diseases, and non-Hodgkin's lymphoma. They are red or violaceous and occur primarily on the scalp and the limbs or hands and feet. They are often bilateral and symmetric. Other cutaneous manifestations have been reported, including Raynaud's phenomenon; livedo reticularis (6.2%); urticarial lesions (9.3%); patchy skin necrosis; infiltrated papules, vesicles, or bullae; and toe or finger ischemia.

Cardiac Involvement

Cardiac involvement is common in CSS and represents the major cause of mortality. Among our patients,[9] 22.9% had pericarditis and 13.4% had myocardial involvement. Histologically, granulomatous infiltration of the myocardium and coronary vessel vasculitis are the most common lesions. Endomyocardial fibrosis is very rarely found.[60] Congestive heart disease develops rapidly and is often severe; it was responsible for the death of five of our 96 patients.[9] Angina pectoris and myocardial infarction are rare, despite frequent coronary vasculitis. Electrocardiograms show abnormalities due to ischemia or cardiomyopathy. Echocardiography shows

diminished contractile parameters that are not specific to vasculitis. Cardiac involvement has been demonstrated to be one of the factors of poor prognosis.[59]

Gastrointestinal Involvement

Digestive tract symptoms, including abdominal pain, diarrhea, and bleeding, occur in 8 to 59% (Table 2) of the patients. Two different mechanisms of involvement are possible: mesenteric vasculitis is the most common and shares the GI location of PAN with the risk of bowel perforation; bowel-wall infiltration by eosinophils is rare and may be responsible for obstructive symptoms or diarrhea and bleeding. Bowel perforation is the most severe manifestation and is one of the major causes of death.[9] Vasculitis and granulomas can be present throughout the GI tract, but more frequently in the small intestine or colon. Endoscopic detection of several duodenal and jejunal ulcers may evoke the diagnosis. The sensitivity of angiography to detect microaneurysms appears to be low. GI manifestations have been demonstrated to be one of the factors of poor prognosis.[59]

Renal Involvement

Kidney disease is present in 16 to 49% (8–80%, Table 2) of the patients. The glomerular lesion that typifies CSS is focal segmental glomerulonephritis with necrotizing crescents, often associated with a perinuclear ANCA-labeling pattern.[56] Other lesions are possible: vasculitis, eosinophilic interstitial infiltrates, and granuloma(s). Although renal involvement in CSS is generally considered to be mild, seven of the 17 nephrology patients reported by Gaskin et al[56] had severe renal impairment (creatinine >150 μmol/L or 1.7 mg/dL) and two required dialysis. Renal involvement has been demonstrated to be one of the factors of poor prognosis.[59]

Musculoskeletal Involvement

Arthralgias are frequent and often occur during the first days or weeks. Arthritis with local inflammatory findings is rare, and joint deformity and radiographic erosions are not seen. Although arthralgias can affect all joints, they predominate in the larger articulations. Myalgias are frequent (33–68%, Table 2) and usually regress quickly under treatment. However, sometimes they are so intense that they mimic polymyositis[5,9] but usually regress quickly under treatment.

ENT and Ophthalmologic Symptoms

Maxillary sinusitis is frequent and 70% of the patients have allergic rhinitis and/or sinus polyposis. A history of chronic sinusitis preceded CSS in 62.5% of our patients.[9] The eye can also be involved, and uveitis, retinal vasculitis, episcleritis, and conjunctival nodules have been described.[61]

COMPLEMENTARY EXAMINATIONS

Anemia and elevated parameters of inflammation such as erythrocyte sedimentation rate (ESR) 1st/h and C-reactive protein are common and were present in 80% of our patients. Eosinophilia is constant and often $>1500/mm^3$ (97%). The absence of eosinophilia may be explained by prior steroid administration for asthma. The mean eosinophil count in our patients was $7{,}193 \pm 6706/mm^3$[320] but the eosinophil count can exceed $50{,}000/mm^3$. The association of eosinophilia $>1000/mm^3$ with asthma is highly suggestive of the diagnosis of CSS. Corticosteroids promptly reduce the eosinophil count to within the normal range in most patients and the eosinophil count usually rises prior to a relapse of the vasculitis. Serum IgE is elevated in 75% of the patients.

CSS is strongly associated with ANCA,[62] being detected in one third to one half of the patients, especially anti-MPO. The value of serial ANCA determinations to monitor disease activity in CSS has not been determined. Rheumatoid factor is also detected in half of the patients.

Abdominal and renal angiographies are usually normal.

DIAGNOSIS

CSS is diagnosed based on clinical and histological features. Patients are usually middle-aged and have a history of asthma that has been present for several years. In addition to the latter, allergic rhinitis and eosinophilia, the appearance of a systemic illness characterized by mononeuritis multiplex, pulmonary infiltrates, cardiomyopathy, or calf pain or cramps should lead the physician to consider the diagnosis of CSS. Among the patients with mononeuritis multiplex, asthma, and eosinophilia, the frequency of vasculitis is high. As much as possible, the diagnosis should be substantiated by biopsy of one of the involved tissues. Placing CSS within the spectrum of ANCA-associated vasculitides is based on the frequency of ANCA in patients with CSS; however, the contribution of ANCA positivity to the diagnosis of this vasculitis must always be interpreted in light of the patient's clinical condition. For patients with asthma, eosinophilia, and mononeuritis multiplex, a positive anti-MPO ANCA titer is highly indicative of the diagnosis of CSS.

The differential diagnosis of CSS includes PAN, WG, chronic eosinophilic pneumonia, and the idiopathic hypereosinophilic syndrome.

Many similarities exist between PAN and CSS, and the systemic vasculitis characteristic of the third

phase of CSS shares numerous clinical aspects of PAN. Pulmonary involvement and asthma are usually absent in PAN. Renal involvement in CSS is characterized by necrotizing glomerulonephritis that is not observed in PAN. In CSS, the vasculitis involves small vessels, and microaneurysms like those observed in PAN are rare. ANCAs are rarely found in PAN, whereas they are present in one third to one half of the patients with CSS.

Differentiation from WG on clinical grounds is usually not difficult. Asthma and a history of allergy are not prominent features of WG, in which eosinophilia is only an occasional and minor finding. Upper respiratory tract involvement in CSS is not associated with the necrotizing lesions characteristically seen in WG. Renal involvement in CSS is less severe and prominent than in WG. Histopathologic features of the granulomatous lesions of CSS and WG are very different. ANCA are frequently found in both diseases and may provide another tool for the differential diagnosis: anti-proteinase 3 (PR3) ANCA are characteristic of WG, whereas most of the ANCA found in CSS patients are anti-MPO.

Chronic eosinophilic pneumonia usually affects women and generally does not involve extrapulmonary organs. Granuloma and vasculitis are not among its histological features.

Idiopathic hypereosinophilic syndrome is a condition characterized by persistent, marked blood and bone-marrow eosinophilia associated with diffuse organ infiltration by eosinophils. Although many similarities exist between idiopathic hypereosinophilic syndrome and CSS, the higher mean peak eosinophil count, typical endomyocardial fibrosis, absence of asthma and history of allergy, absence of vasculitis and granuloma at biopsy, and resistance to steroids observed in the former usually make its differentiation from CSS easy.

OUTCOME

The prognosis of CSS has improved dramatically since the introduction of corticosteroids and, when indicated, cytotoxic drugs. With treatment, remission is rapidly obtained in more than 80% of the patients (88.6% of ours).[9] During follow-up and after a mean follow-up of 69.3 months, 25.5% suffered relapses, half during the first year and later for the others. The clinical symptoms of relapse differed from the initial manifestations of CSS in half of the patients, and can be severe and sometimes responsible for death. Some patients experience several relapses. The 10-year survival rate was 79.4% for our patients.[9] Approximately 75% of the deaths are directly attributable to vasculitis. Cardiac involvement is the primary cause of death of CSS patients. Congestive heart failure is also a major concern in the long term and some patients may require cardiac transplantation. Asthma usually persists after recovery from vasculitis. In our patients, 82.2% of the survivors in long-term remission of CSS had persistent asthma and 72.6% of them required maintenance treatment with low doses of prednisone (mean dose: 8.85 $\pm$ 6.8 mg/d) and/or inhaled corticosteroids (12% of our patients).[9] Permanent morbidity due to vasculitis sequelae can be neurological, such as the consequence of severe peripheral neuropathy or cerebral ischemia. Renal failure may lead to chronic dialysis.

TREATMENT

CSS responds quickly to corticosteroids but sometimes they must be associated with cytotoxic agents, which are useful in the most severe forms of the disease. The initial management of CSS should include high doses of corticosteroids: 1 mg/kg/day of prednisone or its equivalent of methylprednisolone. The administration of methylprednisolone pulses, usually 15 mg/kg intravenously (IV) over 60 minutes repeated at 24-hour intervals for 1 to 3 days, can be used at the initiation of therapy for the most severe forms because of its rapid action and relative safety. The response to corticosteroids is often dramatic; clinical symptoms and eosinophilia regress quickly and vasculitis remission is obtained in most cases. As the patient's clinical status improves and as the ESR returns to normal, usually within 3 weeks to 1 month, tapering of the prednisone dose can begin, but it is often impossible to discontinue corticosteroids because of the residual asthma, which requires low doses of prednisone (mean dose: 8.85 $\pm$ 6.8 mg/d[9]) and/or inhaled corticosteroids (12%[9]).

The outcome of CSS and other systemic vasculitides depends upon the extent of disease dissemination and the severity of visceral involvement.[63] The choice of first-line treatment may be helped by using well-established severity indicators and prognostic factors.[59,64] Based on a prospective study on 337 patients,[59] we determined the clinical, biological, immunological, and therapeutic factors that are associated with the prognosis of PAN and CSS. Among all the parameters evaluated, the following five, which had significant prognostic value and were responsible for higher mortality, became the basis of the five-factor score (FFS)[59]: proteinuria >1 g/day, renal insufficiency (creatininemia >140 µmol/L or 1.58 mg/dL), cardiomyopathy, GI tract involvement, and CNS involvement. Cyclophosphamide is indicated in the first-line regimen when one or more factors of poor prognosis are present. The majority of CSS patients do not have these factors of poor prognosis. Thus, for patients without poor prognosis factors, cyclophosphamide should be prescribed only as second-line treatment, in the case of corticosteroid failure or relapse.

The oral cyclophosphamide dose has conventionally been defined as 2 mg/kg/day or less for 1 year and, in combination with corticosteroids, represented the

traditional treatment of systemic vasculitides, but we prefer IV pulses, which effectively induce remission and are less toxic. Major side effects associated with daily cyclophosphamide administration include hemorrhagic cystitis, bone-marrow suppression, ovarian failure, neoplasm (bladder cancer and hematologic malignancies), and severe infections.[65]

In an attempt to decrease the morbidity associated with daily cyclophosphamide administration, pulse cyclophosphamide therapy is now being used increasingly to treat systemic necrotizing vasculitis. In the protocols of the French Vasculitis Study Group, the recommended cyclophosphamide-pulse dose is 0.6 g/m^2, given at 2-week intervals for 1 month, then every 4 weeks. Intense hydration and the use of sodium 2-mercaptoethanesulfonate (mesna) are strongly recommended during pulse therapy. Cyclophosphamide pulses allow a lower cumulative dose to be given and expose the patient to less potential toxicity for shorter periods. Oral cyclophosphamide has been successfully introduced when IV administration failed to control disease activity or when a relapse occurred within the first 6 months of therapy.[66] Treatment duration with corticosteroids and cyclophosphamide should not be too short. In a prospective study, we showed that 15/16 patients who received six pulses of cyclophosphamide relapsed versus 7/17 of the patients receiving 12 pulses ($p < 0.005$).[67] At present, based on other studies on the treatment of ANCA-related vasculitides, we recommend treating poor-prognosis patients with six cyclophosphamide pulses followed by 6 to 12 months of maintenance treatment with azathioprine or other less toxic drugs.

Plasma exchanges might be useful in ANCA-related vasculitides associated with renal insufficiency due to extracapillary glomerulonephritis. In a prospective study, Gaskin[68] found that, when evaluated at 3 months, the adjunction of plasma exchanges to corticosteroids and cyclophosphamide was associated with improved renal function and fewer patients requiring dialysis compared with those given no exchanges. At 12 months, no difference was observed between these groups, thereby confirming that plasma exchanges are only indicated in the short term. Plasma exchanges could also be useful to treat alveolar hemorrhage, or as second-line treatment for CSS refractory to conventional therapy.

IV immunoglobulins, 2 g/kg over 2 days, can also be prescribed as has been done for other ANCA-related vasculitides.[69] They are not recommended as first-line therapy but may be useful for patients refractory to conventional treatments.

IFNα may represent a therapeutic option in asthma and CSS because it is reported to have a beneficial effect on patients with idiopathic hypereosinophilic syndrome. IFNα promotes the differentiation of Th1 cells in vitro[70] and inhibits the degranulation and effector function of eosinophils. Clinical responses to high doses of IFNα (9–63 million units/wk) were obtained in four patients with biopsy-proven CSS refractory to steroids plus cyclophosphamide, with their blood eosinophil count declining in a dose-dependent manner under treatment, but most of them relapsed at the end of the therapy.[71] Simon et al[72] administered IFNα to 10 patients with corticosteroid-resistant asthma, including three CSS patients; all of them showed early clinical improvement of pulmonary function tests and their prednisone dose could be tapered.[72] Cutaneous lesions have also been treated successfully with IFNα.[73] However, IFNα should be used cautiously in patients with congestive heart failure.

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