The spectrum of granulomatous vasculitides

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Granulomatous vasculitides include some primary systemic vasculitides, but can also be secondary to other systemic diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis), other granulomatous diseases (Crohn's disease, sarcoidosis or lymphomatoid granulomatosis), and infections (tuberculosis or fungal infections) or lymphoma or lymphoproliferative hemopathic diseases. Wegener's granulomatosis and Churg–Strauss syndrome are the two main primary granulomatous vasculitides that affect small vessels. Granulomatous vasculitis can also be observed on histology in giant cell (temporal) arteritis and, more occasionally, in Takayasu's arteritis (the two primary large-vessel vasculitides), but only very rarely in polyarteritis nodosa, a medium-sized vessel vasculitis. Treatment for primary necrotizing vasculitides is now fairly well established, although there remain some issues to be clarified, such as the optimal maintenance therapy in Wegener's granulomatosis or the exact indications of biotherapy, for example, with anti-CD20 monoclonal antibodies.

Keywords: Churg–Strauss syndrome, corticosteroids, cyclophosphamide, giant cell arteritis, granulomatous vasculitis, immunosuppressant, systemic necrotizing vasculitides, Wegener's granulomatosis

The spectrum of granulomatous vasculitides encompasses different diseases and/or conditions, such as primary systemic vasculitides, but also those that are secondary to autoimmune and/or systemic inflammatory diseases, lymphoproliferative disorders or infections (Box 1) [1–3]. Since the lung is one of the most frequently affected organs in granulomatous vasculitides, a classification of pulmonary granulomatous vasculitides has been proposed (Box 2) [4]. However, no classification has been devised to include all the different entities characterized by, or associated with, granulomatous vasculitis in one or several organ(s) or system(s). Therefore, we attempted to list and briefly describe each of these diseases, with particular emphasis on primary small-vessel granulomatous vasculitides, especially Wegener's granulomatosis (WG) and Churg–Strauss syndrome (CSS), with which we have conducted several therapeutic studies on behalf of the French Vasculitis Study Group over the past several years.

Primary systemic vasculitides

Definition & classification

Systemic vasculitides are characterized by inflammation within the blood vessel walls, potentially resulting in vascular obstruction and ischemia of the affected tissues or organs. They can be classified according to the criteria established in 1990 by the American College of Rheumatology (ACR) [5–10] or the Chapel Hill Nomenclature [11], which appears to be more pragmatic as it distinguishes vasculitides according to the size and type of vessels affected, the target end organs and whether vessel-wall necrosis and/or granulomatous inflammatory infiltration exists. Moreover, the nomenclature also introduces the diagnostic value of the detection in sera of antineutrophil cytoplasmic autoantibodies (ANCAs) in the diagnosis of WG, CSS and microscopic polyangiitis (MPA) [12]. According to this Chapel Hill nomenclature, large-vessel vasculitides include giant cell (temporal) arteritis (GCA) and Takayasu's arteritis, whereas medium-sized vessel vasculitides include Kawasaki disease and polyarteritis nodosa (PAN). WG and CSS are the two small-vessel vasculitides characterized histologically by the combination of necrosis and granulomatous inflammation within or near the vessel walls. The other small-vessel vasculitides are nongranulomatous and include cutaneous leukocytoclastic angiitis, MPA, Henoch–Schönlein purpura and mixed essential cryoglobulinemic vasculitis.

In most cases, clinical manifestations are suggestive of the vasculitis. However, diagnosis should ideally be confirmed histologically or proven on biopsy of an affected organ or tissue; although biopsy sensitivity is highly variable and depends on the localization.

Wegener's granulomatosis

WG was first described in 1931 [13]. WG is characterized by granulomatous necrotizing inflammatory lesions of the upper and/or lower respiratory tract, usually associated with rapidly progressing glomerulonephritis (Table 1) [1,14–23]. The ACR classification criteria for WG were established in 1990 (Box 3) [9]. The reported incidence of WG varies from 2 to 12 per million people and the prevalence from 24 to 157 per million people [24,25]. Epidemiological studies

revealed that exposure to some environmental agents, such as silica, dust, cattle, hard metals or organic solvents, was noted prior to diagnosis in some WG patients, but represented less than 10% of all cases [25,26]. Hence, the precise cause(s) of WG remain(s) unknown.

Granulomatous ear, nose and throat (ENT) lesions are the most typical manifestations of the disease, noted in 75–99% of patients at diagnosis, with crusting rhinitis, sinusitis, chronic otitis media, saddle-nose deformity and/or nasal septum perforation (Figure 1) [14,20].

Box 1. Differential diagnosis of granulomatous vasculitis .

Primary systemic vasculitides

Large-vessel vasculitides
- Giant cell arteritis
- Takayasu's arteritis

Medium-sized vessel vasculitides
- Polyarteritis nodosa*

Small-vessel vasculitides
- Wegener's granulomatosis
- Churg–Strauss syndrome

Systemic granulomatosis with vasculitis

- Lymphomatoid granulomatosis
- Sarcoidosis
- Crohn's disease

Lymphoproliferative diseases with possible (mainly cutaneous) granulomatous vasculitis

- Lymphoma
- Follicle center cell lymphoma
- Large B-cell lymphoma
- Secondary cutaneous T-cell lymphoma
- Mycosis fungoides
- Subcutaneous panniculitis-like T-cell lymphoma
- Small/medium pleomorphic T-cell lymphoma
- Cryoglobulinemia due to either lymphocytic lymphoma or Waldenström's macroglobulinemia

Inflammatory & autoimmune disorders

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjögren's syndrome

***Infections with possible granulomatous vasculitis*‡**

Virus
- Herpes simplex virus
- Varicella zoster virus
- Hepatitis C virus
- HIV

Bacteria
- Tuberculosis
- *Mycobacterium avium* intracellulare
- Leprosy of tuberculoid type
- *Staphylococcus aureus* (role in Wegener's granulomatosis?)
- *Streptococcus* spp.

**For some authors, and probably in the next classification criteria for vasculitides, the presence of granulomatous lesions should be considered as an excluding criterion for polyarteritis nodosa.*
‡Other infections that may induce or be associated with granulomatous lesions, but without vasculitis, are not mentioned here.

Box 1. Differential diagnosis of granulomatous vasculitis (cont.).

Fungal infections

Fungal infections
- Bronchopulmonary aspergillosis (bronchocentric granulomatosis)
- Mucormycosis (rhino-cerebritis)
- Coccidioidomycosis

Miscellanous

- Cerebral primary (granulomatous) angiitis
- Drugs (carbimazole, phenytoin, propylthiouracil, potassium iodide and leukotriene modifiers induced Churg–Strauss syndrome)
- Toxic (cocaine and insoluble cellulose particles)
- Type 1 BARE lymphocyte syndrome (transporter for antigen presentation deficiency)
- Mediterranean fever

**For some authors, and probably in the next classification criteria for vasculitides, the presence of granulomatous lesions should be considered as an excluding criterion for polyarteritis nodosa.*
‡Other infections that may induce or be associated with granulomatous lesions, but without vasculitis, are not mentioned here.

Two thirds of patients have pulmonary involvement. Bilateral parenchymal nodules, excavated in half of cases (Figure 2), and/or alveolar hemorrhage in 8–12% of patients are the more characteristic manifestations [19,22]. Rapidly progressive glomerulonephritis, also termed necrotizing crescentic glomerulonephritis, is the third main manifestation of WG, noted in 40–100% of patients, depending on the series [16,27]. Neurological involvement occurs in 11–64% of cases [19,28], and is mainly represented by mononeuritis multiplex (79% of the patients with peripheral neuropathy), then sensorimotor polyneuropathy [27,28]. CNS involvement is rare and can be found in 6–13% of patients, and usually occurs later in the course of the disease [29]. Cardiac involvement is reported with a frequency varying between 0–12% [14,19]. Skin lesions occur in 10–50% of patients, with palpable purpura of the legs and feet being the most frequent manifestation [3,30]. Necrotic papules on the extensor surfaces of the limbs, nodules or extensive and painful cutaneous ulcerations are less frequent, but sometimes more suggestive of disease.

Box 2. Pulmonary granulomatous vasculitis.

- Wegener's granulomatosis
- Churg–Strauss syndrome (allergic angiitis and granulomatosis)
- Lymphomatoid granulomatosis
- Benign lymphocytic angiitis and granulomatosis
- Granulomatous vasculitis associated with sarcoidosis and necrotizing sarcoid granulomatosis
- Bronchocentric granulomatosis
- Granulomatous vasculitis-associated infectious granulomas (tuberculosis and fungal infections)

Taken from Dreisin [4].

Although their precise definitions and appellation are not widely accepted at present, at least two different forms of WG may be distinguished: systemic/generalized/severe forms and localized/limited forms. Systemic WG is represented by kidney involvement, alveolar hemorrhage, involvement of one or more other vital organ(s), or less severe manifestation(s), but with general systemic symptoms such as fever and/or weight loss. Limited disease corresponds to WG whose manifestations remain limited mostly to the upper respiratory tract or, more rarely, the skin (i.e., are not life threatening) [31]. These latter limited/localized forms represent less than a third of all WG cases and occur mostly in women who are slightly younger than those with systemic WG [2,20,22,32]. The detection of ANCA in sera can help in the diagnosis of WG [33]. Indeed, 90% of patients with systemic WG have cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA), with a diffuse cytoplasmic immunofluorescence pattern, and antiproteinase 3 (PR3) specificity, but only 50–78% of the limited forms present with these antibodies [22,34]. These forms also appear to differ histologically; systemic WG is associated more with predominant vasculitic lesions and localized WG with marked granulomatous features; possibly due to the more central role of T-helper (Th)2 T-lymphocytes in the former and Th1 T-lymphocytes in the latter [22,35–39].

Table 1. Frequencies of organ/system involvement in, or manifestations of, Wegener's granulomatosis.

n	Organ/system involved or manifestation (%)								Ref.
	ENT	*Lung*	*Kidney*	*Heart*	*GI*	*Skin*	*CNS*	*PNS*	
18	94	100	100	44		67	44	67	[16]
50	56/38/16*	38/24/6‡	74	4		30		14	[17]
56	89/52/26	48/81/78	25/67/78	11/28	24	46/17	7	29/7	[1]
56§	80	61	80	20	5	34	13	23	[18]
85	91	94	85	12		45			[19]
155	93.5	55	53.5	12.9		23.2		20.6	[20]
158	92	85	72	6		46	8	15	[2]
180	77	60	54	1.7	1.7	20	8.9	8.9	[22]
216	87	69	48	2.8	6.5	12	8.3		[23]
265	75	63	60	<4		25			[14]
701	51/68/43*	62	38			27			[15]

**Patients with rhinitis/sinusitis/otitis (%).*

‡*Patients with lung nodules/alveolar hemorrhage/pleuritis (%).*

§*Autopsy study (autopsy was performed on 54 of the 56 patients). Percentages refer to: clinical manifestations noted prior to death/presence of granulomas/arteritis observed during post-mortem histological examination.*

ENT: Ear, nose and throat; GI: Gastrointestinal tract; PNS: Peripheral nervous system.

Despite this, localized WG is not easier to treat than systemic WG [40]. It is marked by frequent relapses and can evolve at any time into a more systemic disease. Conversely, once life-threatening manifestations have been treated and controlled, systemic WG can further evolve as a localized, but often persistent, form, as demonstrated with crusting rhinitis or subglottic stenosis [41]. Voswinkel and colleagues found some structural homologies to PR3–ANCA-encoding genes in *VH* genes of immunoglobulin heavy chains from granulomatous lesions [42]. These results suggest that selection and affinity maturation of potentially ANCA-producing autoreactive B cells may start in granulomatous lesions, favoring disease progression from ANCA-negative localized to ANCA-positive generalized WG.

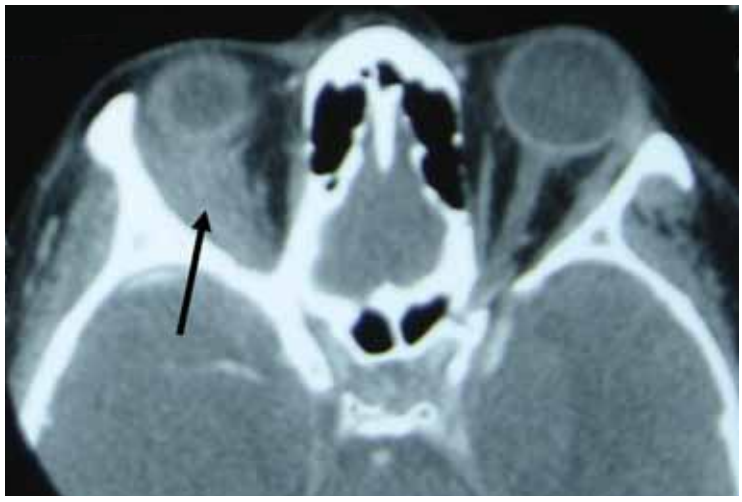
Box 3. Wegener's granulomatosis: American College of Rheumatology Criteria (1990) [9].

For purposes of classification, a patient shall be said to have Wegener's granulomatosis if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 88.2% and a specificity of 92%.

- Nasal or oral inflammation: development of painful or painless oral ulcers, or purulent or bloody nasal discharge
- Abnormal chest radiograph: chest radiograph showing the presence of nodules, fixed infiltrates or cavities
- Urinary sediment: microhematuria (more than five red blood cells per high-power field) or red cell casts in urine sediment
- Granulomatous inflammation on biopsy: histological changes demonstrating granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)

Nasal and/or sinus biopsy is easy to perform, but only 20 and 50% of the results, respectively, contribute to diagnosis [43]. Tracheal biopsy in cases of subglottic lesions with stenosis contribute to diagnosis in less than 18% of the cases [44]. Cutaneous biopsy often reveals small-vessel leukocytoclastic vasculitis, which is unfortunately nonspecific. Skin nodules coincide with necrotizing or granulomatous vasculitis of medium-sized arterioles or, most often, with extravascular granulomas [3,45,46]. Biopsy of lung nodules contributes more often to diagnosis, demonstrating necrotizing vasculitis in up to 60% of cases, sometimes in association with vascular or extravascular granuloma (Figure 3), but these biopsies are sometimes only feasible on open-lung surgery. Mark and colleagues described three different and timely consecutive types of lung lesions in WG [47]: micronecrosis (microabscesses) in areas of necrosis with surrounding giant cells and neutrophils; macronecrosis (widespread necrosis), corresponding to the progression of necrosis in a diffuse geographic pattern with more consistent giant cell and neutrophilic infiltrates; and, finally, fibrosis at the healing stage. In cases of alveolar hemorrhage, a lung biopsy may demonstrate diffuse alveolar infiltrate and hemorrhage, with varying degrees of necrotizing capillaritis and some granulomatous inflammation.

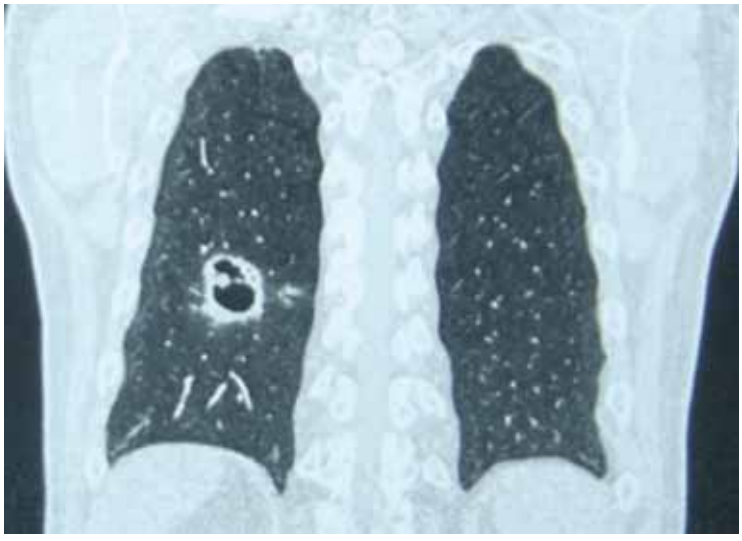
Figure 1. Granulomatous orbital pseudo-tumor in a patient with Wegener's granulomatosis (orbital-computed tomography scan).



Neuromuscular biopsy, especially of the peroneal muscle and nerve branches, yields a diagnostic sensitivity of 60%, but is limited by the potential definitive sensitive sequella of the procedure [48].

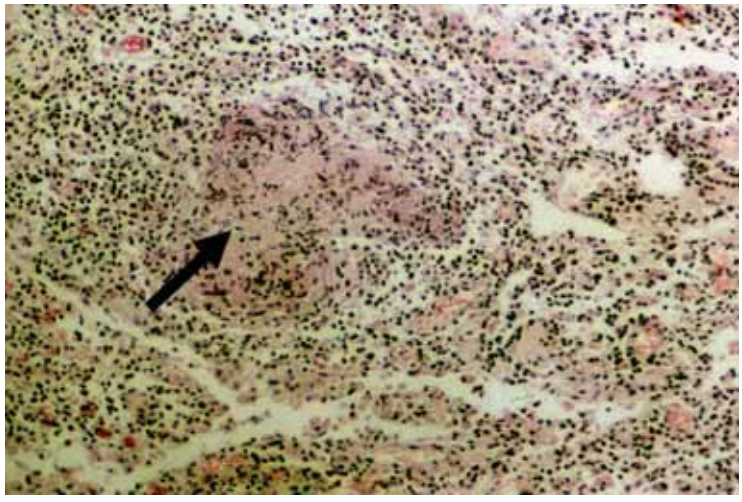
Although the precise cause of WG remains unknown, ANCAs are considered to be a useful immunological marker for WG diagnosis. Over the last decade, some *in vitro* data and animal models have supported their possible direct pathogenic role in disease. PR3 is a 29-kDa neutrophil serine protease, encoded by a single gene, located in chromosome 19p13.3. This protein is stored physiologically in granules of human neutrophils and monocytes. Following tumor necrosis factor (TNF)-α priming, neutrophils express the ANCA target antigen on their cell membrane, making it accessible for interaction with ANCA [49]. Thereafter, ANCAs promote neutrophil adhesion to endothelial cells and their lysis. Furthermore, ANCAs can also activate monocytes, which results in enhanced production of reactive oxygen species [50]. Pfister and colleagues demonstrated that local inflammation, induced by intradermal injection of TNF-α into mice, triggered a stronger subcutaneous panniculitis in the presence of passively transferred systemic PR3-ANCA [51]. Anti-endothelial cell antibodies in WG might also play a pathogenic role [52,53].

Figure 2. Lung-cavitated nodule in a patient with Wegener's granulomatosis (thoracic computed tomography scan 2D reconstruction).



However, the primary mechanisms leading to the synthesis of ANCA and the stimulus leading to the formation of granulomas in WG are not fully understood. Pendergraft and colleagues demonstrated in mice that immunization with the middle region of the protein derived from the antisense DNA strand of PR3 (cPR3) resulted in production of antibodies not only to cPR-3, but also to PR3 [54], binding to each other, thus, indicating idiotypic relationships. By comparing protein gene sequences, the authors suggested that these anti-cPR3 antibodies might be produced *in vivo* as a response to various microbials, such as *Staphyloccus aureus*, which would cross-react with the autoantigen (cPR3). Recently published data by Csernok and colleagues demonstrated that PR3 can induce the maturation of dendritic cells via the protease-activated receptor-2 pathway *in vitro* [55]. These dendritic cells thereby become fully competent antigen-presenting cells and can induce the stimulation of PR3-specific $CD4^+$ T cells, which produce interferon-γ, as a Th1-like autoimmune response, potentially favoring granuloma formation. Hypothetically, the activation of $CD4^+$ T cells via this pathway could also be the initial step towards ANCA production by plasma cells. In WG lesions and granulomas, Mackiewicz and colleagues observed that local tissue macrophages are driven to perfusion cells and foreign-body giant cells owing to an unknown stimulus, and that, despite macrophage activation and continuing maturation to professional scavenger receptor (MARCO) and meltrin-positive multinuclear giant cells, macrophages still contain partially undigested cell and tissue debris [56]. These results suggest that, in the absence of any identified exogenous foreign bodies or evidence of microbes,

Figure 3. Granulomatous inflammation on a lung biopsy in a patient with Wegener's granulomatosis.



an overwhelming production of endogenous tissue debris may act as an inducing stimulus for granuloma formation, and/or that macrophage ability to clear apoptotic neutrophils and debris is altered, as in patients with systemic lupus erythematosus [57].

Churg–Strauss syndrome

The terms allergic and granulomatous angiitis are sometimes used to describe conditions suggesting CSS. The disorder is characterized by pulmonary and systemic small-vessel necrotizing vasculitis, vascular and/or extravascular granulomas, hypereosinophilia and tissue infiltration by eosinophils, occurring in individuals with asthma and allergic rhinitis [58,59]. The annual incidence ranges between 0.9 and 4 per million inhabitants, according to location and the classification criteria used, whereas its prevalence ranges between 10.7 and 13 per million [24,60]. Various triggering and/or precipitating factors, such as inhaled allergens, vaccinations, desensitization, drugs or infections (parasitic or bacterial), have been suspected in the etiology of some cases [36].

Box 4. Churg–Strauss syndrome: American College of Rheumatology criteria (1990) [10].

In a patient with vasculitis, four of these six criteria permit a grading of Churg–Strauss syndrome, with 85% sensitivity and 99.7% specificity.

- Asthma
- Blood eosinophilia >10%
- Mono or polyneuropathy
- Moving pulmonary infiltrations
- Sinus pain or opacity
- Extravascular eosinophils on biopsy

The ACR published its classification criteria for CSS (Box 4) [10]. The mean age at the time of diagnosis is 48 years, with a sex ratio of approximately 1:1. General symptoms, such as fever or weight loss, are present in most patients. Asthma is the central clinical feature (Table 2) [61–66], whereas 38–77% of patients have transient and patchy pulmonary infiltrates. A more diffuse interstitial infiltrative pattern or bilateral nodular infiltrates without cavitation are seen rarely; 70% of the patients have a history of allergic rhinitis or sinus polyposis, and 50–78% present with peripheral neuropathy, essentially mononeuritis multiplex [67,68]. Heart involvement is noted in up to 60% of patients [58], and represents the major cause of mortality, accounting for 48% of all deaths [69,70]. Skin lesions occur in 40–75% of patients. Palpable purpura (often necrotic) on the legs and feet is the most frequent of these manifestations and is observed in half of patients with skin involvement. Cutaneous nodules (a third of patients) or papules, sometimes with an urticarial appearance, are also common and are localized mostly on the limbs or fingers. Various other skin lesions have been reported: maculopapules resembling erythema multiforme, ulcerations, livedo reticularis, patchy and migratory urticarial rashes, nail-fold infarctions, deep pannicular vasculitis and facial edema [3,71]. Digestive tract symptoms, including abdominal pain, diarrhea and bleeding, have been reported in 37–62% of CSS patients [72], and kidney disease in 16–49%, usually presenting as a focal segmental glomerulonephritis with necrotizing features including crescents [73–75].

Biologically, CSS is characterized by elevated serum immunoglobulin (Ig)E and peripheral blood eosinophilia, with various degrees of activation [76] thought to be hallmarks of Th2 lymphocyte responses (characterized by interleukin [IL]-4, -5 and -13 production). In addition, ANCAs are detected in 38–50% of patients and usually generate a perinuclear immunofluorescent labeling pattern, termed to P-ANCA, that is most frequently specific to myeloperoxidase (MPO) [74,75]. According to Lanham, the pathophysiology of CSS can be divided into three aspects corresponding to the three main phases of the natural history of the disease [65]:

- Pathogenesis of asthma, involving Th2 lymphocytes [77–79];
- Pathogenic role of P-ANCA anti-MPO in the occurrence of vasculitis lesions;
- Finally, potential pathogenetic role of eosinophils infiltrating tissues.

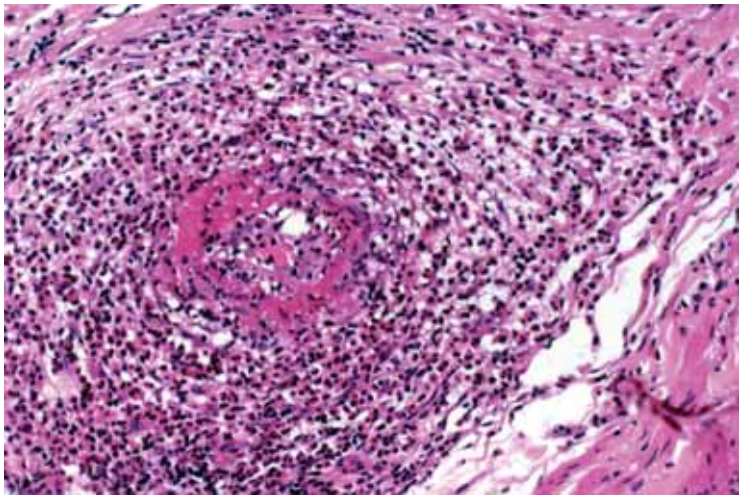
Table 2. Frequencies of organ/system involvement in, or manifestations of, Churg–Strauss syndrome.

n	Organ/system involved or manifestation (%)								Ref.
	Asthma	*Kidney*	*Heart*	*Skin*	*GI*	*ENT*	*CNS*	*PNS*	
12	100	8	42	67	8	83	8	92	[61]
16	100	49	47	48	59	70		66	[65]
20	100	35	50	75	50	45		65	[63]
30	100	20	16	67	17	70		63	[62]
32	100	12.5	37.5	81	44		6	28	[66]
96	100	26	14 (Myocarditis) 23 (Pericarditis)	51	33	61	8.3	78	[64]

ENT: Ear, nose and throat; GI: Gastrointestinal tract; PNS: Peripheral nervous system.

P-ANCA anti-MPO have been shown to activate TNF-α-primed neutrophils *in vitro*, leading to the production of reactive oxygen metabolites and the release of lysosomal proteolytic enzymes, including MPO, thereby permitting the cascade of events that lead to vasculitis [80]. However, a potential role of P-ANCA has mostly been demonstrated for MPA, which is also strongly associated with the presence of anti-MPO. Autoimmune manifestations with or without necrotizing vasculitis and extracapillary glomerular lesions can be induced by the passive transfer of anti-MPO in experimental models [81,82]. However, none of these models have features suggestive of CSS, such as tissue eosinophilia. Eosinophil granules contain major basic protein (MBP), eosinophilic cationic protein (ECP) and eosinophil-derived neurotoxins that can cause direct tissue damage. ECP has been found to be elevated in serum and bronchoalveolar lavage fluid of CSS patients [83], and extracellular deposits of ECP and MBP have been detected in damaged tissues at sites of active disease [84,85].

Figure 4. Florid necrotizing medium-sized vessel vasculitis with eosinophil infiltration in a patient with Churg–Strauss syndrome (muscle biopsy).



Histologically, the two characteristic lesions of CSS are angiitis and extravascular necrotizing granulomas, usually with eosinophilic infiltrates (Figure 4), contrasting with the polymorphous infiltrate of neutrophils, plasma cells and histiocyte observed in WG. The vasculitis may be granulomatous or nongranulomatous and typically involve both arteries and veins in pulmonary and systemic vessels. Granulomas are typically approximately 1 mm or more in diameter and are commonly located near small arteries or veins. They are characterized by palisading epithelioid histiocytes arranged around central necrotic zones in which eosinophils are prominent. In practice, necrotizing vasculitis, tissue infiltration by eosinophils and extravascular granulomas rarely coexist temporally or spatially, and are found together in only a minority of cases. In the lungs, the histological features of CSS combine necrotizing vasculitis and areas resembling eosinophilic pneumonia. Extrapulmonary lesions are more commonly found in the gastrointestinal tract, spleen and heart than in the kidney. Muscle biopsy, ideally combined with nerve biopsy, might also be very informative, especially in cases of neuropathic features observed on electromyography, but can itself, as aforementioned, be responsible for persistent and disabling sensory and/or motor sequelae at the biopsy site. Although highly suggestive of disease, cutaneous and subcutaneous lesions, so-called Churg–Strauss granulomas, lack diagnostic specificity and are detected in less than half of the patients with skin lesions [3,71]. Purpuric lesions usually correspond to inflammatory infiltrates which are rich in eosinophils, whereas nodules may correspond to granulomatous

Box 5. Giant-cell (temporal) arteritis: American College of Rheumatology criteria (1990) [7].

In a patient with vasculitis, three of these five criteria permit a grading of giant cell (temporal) arteritis, with 93.5% sensitivity and 91.2% specificity.

- ≥50 years of age at disease onset
- New onset of localized headache
- Temporal artery abnormalities (tenderness or decreased temporal artery pulse)
- Temporal artery biopsy, characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells
- Elevated erythrocyte sedimentation rate (Westergren) ≥50 mm/h

vasculitis, necrotizing vasculitis or extravascular granulomas. Temporal artery involvement in CSS has been reported anecdotally [86].

Other primary systemic vasculitides

GCA and Takayasu's arteritis are large-vessel vasculitides also associated with granulomatous inflammation. PAN, the main adult primary medium-sized vessel necrotizing vasculitis, is not characteristically associated with granulomatous inflammation, but can occasionally be observed.

Giant cell arteritis

GCA is a chronic vasculitis of large, predominantly, and medium-sized vessels that occurs in people over 50 years of age [87]. The incidence increases with age and is alsohigher in people of northern European origin; for example, in Iceland the incidence is 50 cases per year per 100,000 in people over 50 years of age [88]. The mean age at onset is approximately 70 years, with women being approximately twice as frequently affected as men (male/female ratio 7:3) [89]. Classification criteria proposed by the ACR published in 1990 are listed in Box 5 [7]. Headache is the most frequent symptom (Table 4) , noted in two thirds of patients and often localized to the temporal areas, with evocative artery induration in some patients [7,88,90,91]. Intermittent jaw claudication is frequent as well as scalp or tongue necrosis at a later stage (Figure 5). Loss of vision may occur, caused by ischemia of the optic nerve secondary to arteritis of the branches of the ophthalmologic or posterior ciliary arteries, or more rarely of retinal arterioles. Stroke or transient ischemic attacks are also common. In approximately 10–15% of cases, the branches of the aortic arch, particularly the subclavian and axillary arteries, become narrowed and produce upper extremity claudication [92]. Thoracic aortic aneurysm is 17-times more likely to develop, usually as a late event, in patients with GCA [93]. Pericardial effusion, coronary ischemia and occlusion are rare manifestations of GCA [94].

Temporal artery biopsy is the easiest and most frequently biopsied artery to confirm GCA. Lesions are segmental and irregularly sparse, warranting large biopsy and often bilateral samples. Histological characteristics include the infiltration of the vessel wall, especially the inner media, with lymphocytes, macrophages and multinucleated giant cells [95]. The internal elastic membrane is fragmented, with frequently associated intimal thickening. Most of the skin lesions described are due to ischemia, as in scalp necrosis. Few cases with granulomatous skin vasculitis have been reported, sometimes mimicking WG at the onset of the disease [96,97].

Takayasu's arteritis

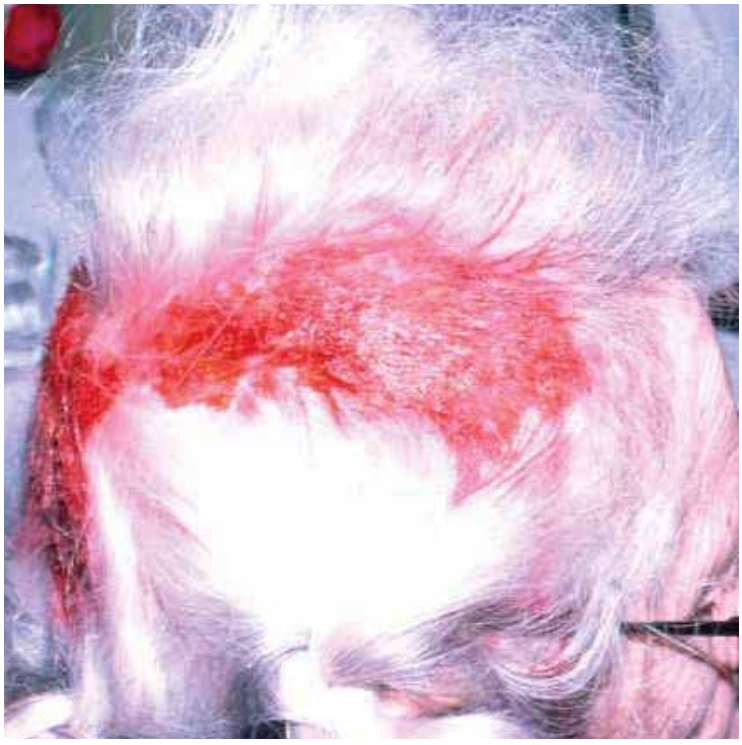
Takayasu's arteritis is an obliterative giant cell arteritis, most frequently observed in young women aged 15–25 years, and in Asian countries, India, South America and Africa, rather than in Europe or the USA. Classification criteria of the ACR published in 1990 are listed in Box 6 [5]. The disease affects the aortic arch and its proximal branches. Distribution of the arteries involved also varies according to geography, since abdominal branch involvement is mostly seen in patients in Europe, India and the USA. The disease characteristically evolves in three phases [98]. Systemic symptoms develop and then

Table 4. Frequencies of manifestations of giant-cell arteritis.

n	Manifestations							Ref.
	Fever >38°C	*Headache*	*Temporal artery tenderness/stiffness*	*Jaw claudication*	*Transient amaurosis*	*Definitive blindness*	*Polymyalgia/ arthralgia**	
133		63	44	11	14	1	48	[88]
191		87	75	40			49	[90]
214		64	57	8	28	10	83	[7]
240	10	85	73	41	23	13	40	[91]

**Diagnosed or considered as polymyalgia rheumatica.*

Figure 5. Scalp necrosis in a patient with giant cell (temporal) arteritis.



resolve over several weeks, while arteritis takes root. This arteritis also resolves, with an ensuing asymptomatic period (mean duration of 8 years) before vaso-occlusive signs and symptoms develop. During the initial phase, systemic symptoms are noted in less than half of cases, especially in European patients, whereas these are rare in Japanese patients. The disease is monophasic and self-limiting for 20% of patients.

Severe cardiovascular complications of Takayasu's arteritis are caused by fibrotic thickening of the aortic arch and its branches and, more rarely, are complicated by thromboembolic events. Aortic regurgitation and aneurysm formation, particularly in descending thoracic aorta have been described [99].

More common histological findings are granulomatous inflammation and adventitial sclerosis, predominantly at the adventia–media junction, but necrosis is unusual. Occasionally, vascular inflammation spreads from the aorta to the proximal epicardial coronary arteries and may cause coronary insufficiency and myocardial infarction. Of white patients with Takayasu's arteritis, 8–28% may have cutaneous manifestations, mostly with erythematous nodules of the lower limbs. Skin biopsy usually demonstrates large vessel affectation with necrotizing vasculitis [100,101]. Indeed, granulomatous vasculitis, panniculitis associated with vasculitis, lobular and septal panniculitis (sometimes with granulomas) can also be observed. Pulmonary nodular infiltrates with extravascular granulomas on lung biopsy have also been reported [102].

Polyarteritis nodosa

First described by Küssmaul and Maier, PAN is a necrotizing angiitis, predominantly involving medium-sized arteries [103]. Granulomatous vasculitis is definitely not the hallmark of PAN, but has been reported and can be observed in some rare cases [104]. Such findings warrant the exclusion, or at least the discussion, of other diagnoses, such as WG, CSS or GCA when granulomatous vasculitis is found on temporal artery biopsy. For some authors, and probably in the next classifications for vasculitides, the presence of granulomatous lesions should even be considered as an excluding criteria for PAN.

Extensive description of PAN can be found elsewhere [105–118]. PAN can be the consequence of hepatitis B virus (HBV) infection [119,120], as mentioned in the 1990 classification criteria of the ACR (Box 7) [8], and is sometimes the consequence of other viral agents, such as Parvovirus B19 or HIV [121,122]. The mechanism of vascular inflammation implicated in PAN is most often immune complex-mediated [123,124]. The characteristic histological lesions defining PAN are focal segmental necrotizing vasculitis of medium-sized arteries, less commonly, arterioles and, only rarely, capillaries and venules. The acute phase of arterial wall inflammation is characterized by fibrinoid necrosis of the media and intense infiltration of pleomorphic cells, predominantly neutrophils and variable numbers of lymphocytes and eosinophils. Arterial microaneurysms, which can be observed on angiography, are highly suggestive of PAN.

Other entities possibly associated with granulomatous vasculitis

Secondary granulomatous vasculitides

Rheumatoid arthritis

Rheumatoid vasculitis (RV) is a rare event in the course of rheumatoid arthritis, occurring in less than 10% of patients [125] and exhibiting poor prognosis, with a mortality rate of between 16 and 46% at 2 years after disease onset [126]. All types of vessels and every organ can be affected, although small- and medium-sized

Box 6. Takayasu's arteritis: American College of Rheumatology criteria (1990) [5].

In a patient with vasculitis, three of these six criteria permit a grading like Takayasu's arteritis, with 90.5% sensitivity and 97.8% specificity.

- Age of onset ≤40 years
- Decreased brachial artery pulse
- >10 mmHg difference in systolic blood pressure between arms
- A bruit over the subclavian arteries or the aorta
- Claudication of an extremity
- Arteriographic evidence of narrowing or occlusion of the entire aorta, its primary branches or large arteries in the proximal upper or lower extremities

arteries are predominantly concerned, with clinical presentations consisting mainly of skin lesions and/or peripheral neuropathy. All the different types of vasculitis, such as leukocytoclastic vasculitis, PAN-like necrotizing vasculitis, scleroderma-like obliterating arteritis with fibrosis or granulomatous aortitis, have been described [127].

Clinical manifestations of RV are highly variable. However, two main forms can be distinguished: chronic cutaneous and acute/subacute systemic. RV occurs mostly in male patients, with seropositive rheumatoid arthritis, after many years of evolution, marked by destructive joint progression and rheumatoid nodules [126]. Cutaneous manifestations of rheumatoid arthritis range from nodules to digital micro-infarction, ulcers, gangrene, rheumatoid neutrophilic dermatosis, diffuse interstitial and palisading granulomatous dermatitis or pyoderma gangrenosum, and occasionally granulomatous vasculitis, potentially with mixed features [128]. From 43 skin-lesion biopsy results of rheumatoid arthritis patients, Magro described only one patient with isolated granulomatous vasculitis who had a purpuric rash over the thighs and legs [128]. A total of 21 (49%) had palisading granulomatous inflammation, mostly presenting as painful violaceous plaques, nodules and/or papules located on the hands/fingers, elbows and legs and associated with vasculitis in 38% of the patients. Peripheral neuropathy most often presents as mononeuritis multiplex, but also presents as sensitive polyneuropathy [129]. Gastrointestinal, CNS and cardiac involvement are rarer, but carry poor prognosis.

Box 7. Polyarteritis nodosa: American College of Rheumatology criteria (1990) [8].

In a patient with vasculitis, three of these ten criteria permit a grading of a polyarteritis nodosa with 82.2% sensitivity and 86.6% specificity.

- Weight loss >4 kg
- Livedo reticularis
- Testicular pain
- Diffuse myalgia, muscular weakness or inferior limbs sensibility
- Mono- or polyneuropathy
- Diastolic arterial pressure >90 mmHg
- Renal insufficiency (urea >400 mg/l or creatininemia >15 mg/l)
- Plasma hepatitis B (HB) marker (HBs antigen or anti-HBs antibody)
- Arteriographic abnormalities (aneurysms and/or visceral artery occlusions)
- Polynuclear in arterial wall on a biopsy of a small- or medium-sized calibre artery

Systemic lupus erythematosus

Vasculitis can occur in approximately a third of patients with systemic lupus erythematosus [130]. Skin manifestations are the most frequent clinical features, primarily due to cutaneous leukocytoclastic small-vessel vasculitis, which can be observed in approximately 14% of the lupus skin lesions [131]. Cerebral or coronary artery vasculitis is rare and has poor prognostic value. Indeed, granulomatous vasculitis has been infrequently reported with systemic lupus erythematosus, but is possible [132–134].

Sjögren's syndrome

Although vasculitis, especially skin vasculitis (9–32% of patients with a predominance of small then medium-sized vessel vasculitis) [135] and/or nervous system vasculitis, can occur in Sjögren's syndrome, reports of granulomatous vasculitis are purely anecdotal in this setting [136,137].

Crohn's disease

Rare associations between cutaneous vasculitis, sometimes with granulomatous inflammation, and Crohn's disease have been reported [138,139], as well as some cases with proven intestinal granulomatous vasculitis [140,141].

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease that may be complicated by systemic vasculitis, affecting small to large vessels. Sarcoid vasculitis can mimic systemic granulomatous angiitis, such as CSS or Takayasu's arteritis, but can also mimic PAN or MPA. Furthermore, granulomatous angiitis and/or microangiopathy may be present in up to 31% of the sarcoid skin lesions, with no correlation between the latter and the clinical presentation of cutaneous sarcoidosis [142,143]. Lung-necrotizing sarcoid granulomatosis is probably a variant of sarcoidosis, in which angiitis is a prominent feature.

Lymphomatoid granulomatosis

Liebow's disease, or lymphomatoid granulomatosis, is a systemic granulomatous disease with vasculitic features and is caused by Epstein–Barr virus (EBV) infection [144]. EBV is supposed to induce the transformation and clonal proliferation of B cells in an angiocentric T-cell-rich infiltrate. Notably, systemic vasculitis has also been reported as a manifestation of EBV infection in patients with X-linked lymphoproliferative disorders [145].

The disease may affect patients of all ages, but usually occurs in those aged between 40 and 60 years, with a slight male predilection (male/female ratio 2.5:1). Clinical expression of lymphomatoid granulomatosis can resemble WG or tuberculosis [146,147]. Clinical presentation can be confined to the respiratory system (presenting with a cough in 60%, chest pain in 10% and dyspnea in 30–45% of patients), or associated with constitutional symptoms (occurring in 80% of patients, including fever, weight loss, fatigue and/or night sweats), nervous system involvement (CNS in 35%, seizures in 10% and peripheral neuropathy in 20% of patients) and/or cutaneous involvement (40–50%) [146,148], chronic sinusitis (20%), arthralgias or arthritis (5%), anemia (5%) and/or skin lesions (16–33%) that can occur a few months before the pulmonary lesions [146,149]. Notably, lymphoid tissues are usually spared [146].

The outcome is poor for patients with constitutional symptoms or multiple organ involvement, with approximately two thirds dying within the year following diagnosis, usually due to extensive pulmonary disease with respiratory failure. Resolution can sometimes occur spontaneously without treatment (7%) or with chemo/immunomodulatory therapy (62%), but disease may progress to aggressive lymphoma in some patients (18–31%) [148,149]. No standard therapy exists for relapsed or refractory disease.

The diagnosis relies on the biopsy demonstrating nodular lesions with angiocentric and angiodestructive polymorphous lymphohistiocytic infiltrate, and sometimes lymphoma infiltrates. EBV infection can sometimes be detected in pulmonary lesions [150].

Lymphoproliferative diseases & other malignant hemopathic disorders

Granulomatous vasculitis may occur, although rarely, with lymphoproliferative diseases, primarily lymphoma [151,152]. Indeed, every patient with vasculitis should theoretically be screened for lymphoproliferative diseases, because vasculitis may be a revealing manifestation [153]. The most common systemic (but rarely granulomatous) vasculitis is caused by cryoglobulinemia, due to either lymphocytic lymphoma or Waldenström's macroglobulinemia. Some association has also been reported between systemic vasculitides and other malignant hemopathic diseases: PAN and hairy-cell leukemia; WG and Hodgkin's disease; and CNS granulomatous angiitis, GCA or Henoch–Schönlein purpura and lymphoma [152,154]. A prominent granulomatous reaction may be observed in approximately less than 2% of all patients with cutaneous lymphoma (primary or secondary), especially mycosis fungoides. More rarely, this reaction may occur in subcutaneous panniculitis-like T-cell lymphoma, small/medium pleomorphic T-cell lymphoma, follicle center-cell lymphoma, large B-cell lymphoma or secondary cutaneous T-cell lymphoma [151].

Infections

Viral infections which trigger small- or medium-sized vessel granulomatous vasculitis have been described, as for example, an uncommon post-herpetic reaction or a delayed complication of varicella-zoster virus infection [155,156]. Granulomatous vasculitis has been also found in a few patients with dermatopathologic manifestations of HCV infection [157], whereas necrotizing cutaneous vasculitis is more characteristic of cryoglobulinemic patients with cutaneous vasculitis infected with this virus [158]. Viral agents, such as HBV (compared with PAN), HIV [159], cytomegalovirus or parvovirus B19 [160], have also been reported as potential causes of vasculitis but not usually of granulomatous vasculitis.

Bacterial infections with *Mycobacterium tuberculosis*, *M. avium intracellulare* or other *Mycobacterium* spp., as well as leprosy of the tuberculoid type are classic granulomatous infections. However, histological evidence of granulomatous vasculitis is not frequently observed in these cases. For example, in tuberculosis aortitis, inflammatory vessel wall lesions usually lack granuloma. Conversely, granulomatous phlebitis (also named lobular granulomatous panniculitis or erythema induratum-nodular vasculitis) can be considered a venous granulomatous vasculitis occurring in the setting of tuberculosis. A role for *S. aureus* in the pathogenesis of WG has been suggested, and for *Streptococccus pneumoniae* in PAN, especially in children. However, in WG, *S. aureus* might act as a triggering factor for the onset of the disease or, at least, for some of the flares and/or relapses [161,162].

Granulomatous vasculitis has also been described in some fungal infections, such as bronchopulmonary aspergillosis (bronchocentric granulomatosis), mucormycosis (rhino-cerebritis) or coccidioidomycosis, and is more often limited and localized to one organ or region [163–166].

Miscellaneous

Besides the potential triggering factors for WG (dust, silica, organic solvants and cattle) or CSS (vaccinations, desensitization, leukotrienes modifiers, such as montelukast, and macrolides) [167–169], some drugs (e.g., carbimazole, propylthiouracil [170,171], phenytoin [172] or potassium iodide [173]) have been reported as causing occasional cases of granulomatous vasculitis, as well as some toxics, such as cocaine [174,175], or environmental exposure to insoluble cellulose particles [176]. Berryliosis is caused by the inhalation of insoluble beryllium dust and characterized by granuloma formation in the lung, and, eventually, fibrosis. The disease may mimic WG in the lung but is not associated with vasculitis [177].

Granulomatous vasculitides is also one of the possible features of type 1 BARE lymphocyte syndrome, caused by a deficiency in transport of antigenic peptides, resulting in human leukocyte antigen (HLA) Class I molecule deficiency [178], which is characterized by frequent granulomatous infections that can clinically mimic WG, at least for ENT and cutaneous manifestations.

Anecdotal reports exist of the association of granulomatous vasculitis and Mediterranean fever [179] or Sweet syndrome [173].

Finally, primary isolated angiitis of the CNS, also termed granulomatous angiitis of the CNS, can be considered granulomatous vasculitis, because granulomas can sometimes be observed on histology [180,181]. This is an extremely rare disease, with less than 100 reported cases [182,183]. Symptoms are restricted to the CNS and include headaches, confusion, seizures, stroke and cerebral hemorrhage [184,185]. The disease must be distinguished from other primary systemic vasculitides with CNS involvement, such as those cited above, but also from cerebral vasculitis secondary to infections, drug exposure, lymphoma and lymphoproliferative disorders, systemic lupus erythematosus, Sjögren's syndrome, neurosarcoidosis or amyloid cerebral angiopathy [186]. Left untreated, the disease is usually fatal within 1–2 years. Treatment with corticosteroids, alone or in combination with cyclophosphamide, has considerably lowered the mortality rate, and thus 50% of the patients improve clinically and 70% survive [187].

Diagnostic considerations

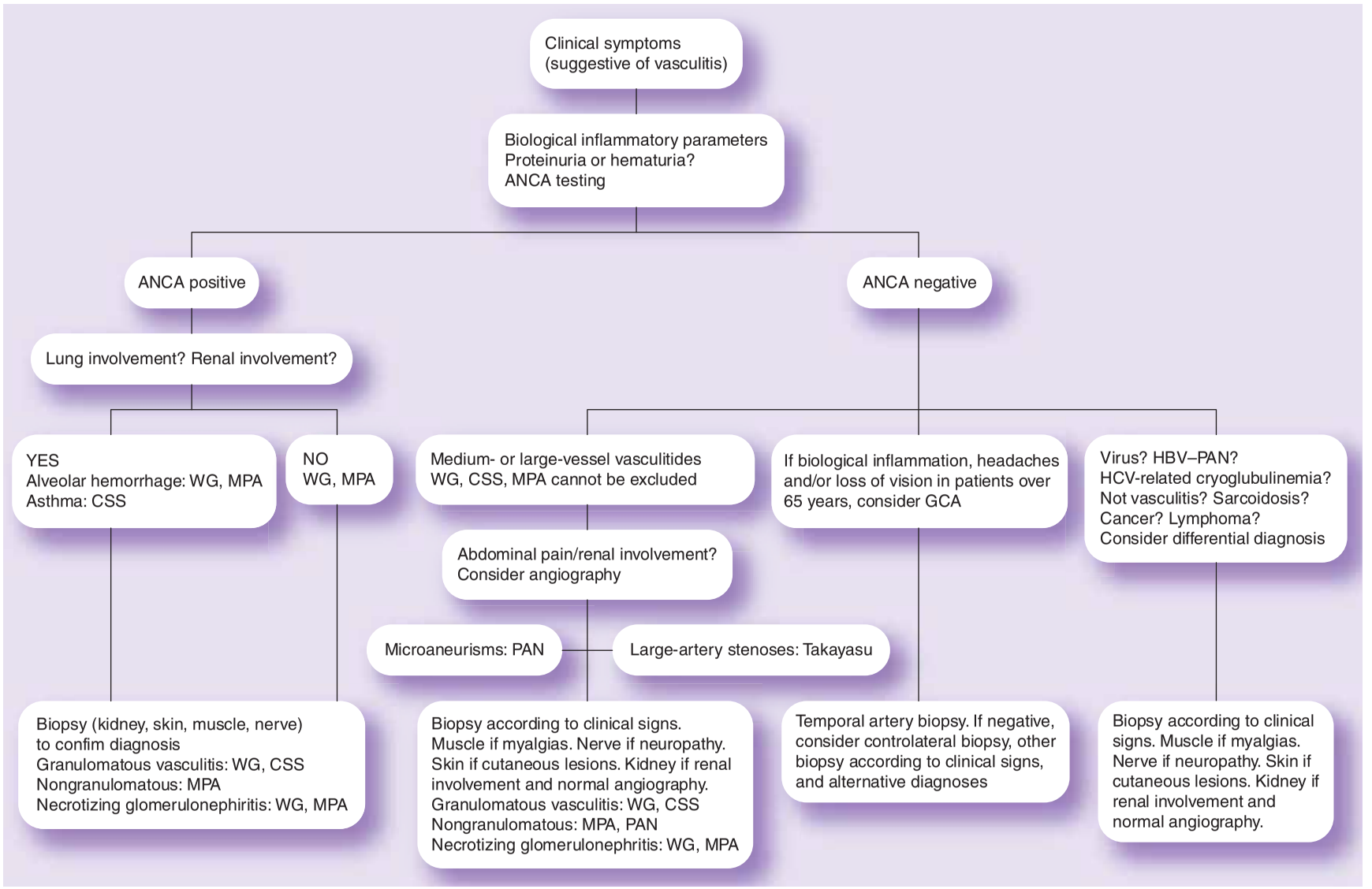
In most cases, the finding of granulomatous vasculitis on a biopsy confirms a clinically presumed diagnosis of WG, CSS or GCA (Figure 6). However, in some circumstances, granulomatous vasculitis can be an unexpected histological finding; for example, in a patient being investigated for myalgias and/or inflammatory syndrome. In such cases, the diagnostic approach can be more challenging.

First, classification criteria established in 1990 by the ACR [5–10] and the Chapel Hill Nomenclature [11] must not be used as diagnostic tools for vasculitis. Their purpose and use is for classifying (mainly in clinical trials) disease in patients who already have a definite diagnosis of primary vasculitis.

Second, even vasculitis found on biopsy does not provide a definite diagnosis. The results demonstrate vasculitis, but do not distinguish between the primary systemic vasculitides. Peripheral nerve biopsy usually demonstrates necrotizing vasculitis affecting the small epineurial vessels and their branches, but in medium-sized as well as in small-vessel vasculitides. Therefore, the presence of vasculitis on biopsy must always be interpreted with consideration of the patient's clinical and biological features. For instance, any clinical manifestation(s) suggesting WG or CSS should be investigated, while ruling out some infections. Laboratory results, such as the detection of ANCA, can also have strong diagnostic value.

Third, the location of the biopsy is a major element in diagnosis in this setting. Biopsy should be performed primarily in an affected organ or site such as the temporal artery in suspected GCA cases or the paranasal mucosa in patients with crusting rhinitis suggestive of WG. In the absence of overt clinical manifestations to guide the choice of biopsy site, muscle or both nerve and muscle can be proposed first. Nerve and muscle biopsy is often more contributive, but can lead to sensitive disabling dysesthesia. When vasculitis is suspected, a distal biopsy, particularly of the peroneal nerve and peroneus brevis muscle, should be performed, since vasculitis mostly affects small and distal parts of the vessels and nerves [48,188]. Granulomatous vasculitis observed on temporal artery biopsy is usually related to GCA or may represent specific involvement in some WG [189] or CSS cases [56]. When observed on muscle biopsy, WG and CSS should primarily

Figure 6. Algorithm for diagnosing a patient with suspected vasculitis.



ANCA: Antineutrophil cytoplasmic autoantibodies; CSS: Churg–Strauss syndrome; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MPA: Microscopic polyangiitis; PAN: Polyarteritis nodosa; WG: Wegener's granulomatosis.

be considered and occasionally sarcoidosis or PAN. Granulomatous vasculitis on lung nodule biopsy is most commonly observed in WG, but can also reveal lymphomatoid granulomatosis, tuberculosis, sarcoidosis or other infections.

Notably, some researchers have reported that ANCA might be detected in some of these infections, especially tuberculosis [190], even with PR3 specificity. However, we did not confirm this finding [191]. Conversely, in ANCA-negative patients with lung nodules (even when cavitating, and granulomatous vasculitis observed on histology, the absence of extrapulmonary manifestations of WG, such as necrotizing glomerulonephritis and/or crusting destructive rhinitis) should be a concern. In this instance, lymphomatoid granulomatosis, lymphoma or infections should be strongly considered, thus, requiring every part of the biopsy block to be studied.

Principles of treatment for primary systemic vasculitides

The treatment of secondary granulomatous vasculitis targets its etiological cause (i.e., antimicrobial agents in the case of infection or chemotherapy in the case of lymphoma).

Corticosteroids are mandatory for patients with GCA (prednisone 0.7–1 mg/kg/day initially, progressively tapered in dosage over 12–18 months). To date, no consensual or worldwide accepted therapeutic scheme has been defined. The combination of corticosteroids and an immunosuppressant as first-line therapy for GCA, to further limit the low rate of progression despite corticosteroids, or relapse under or just after cessation of corticosteroids alone, is also controversial [192].

CSS and PAN patients without any of the factors identified as demonstrative of a poor prognosis (five factor score [FFS]; Table 4) can be treated with corticosteroids alone [105,118], reserving the adjunction of immunosuppressants in case of treatment failure [193]. However, even with no marker of poor prognosis, CSS patients may become corticoid dependent to control their asthma, although corticosteroids alone are sufficient to cure vasculitis.

By contrast, the association of corticosteroids and immunosuppressants, mainly cyclophosphamide, is mandatory for all patients with WG or severe forms of PAN or CSS (i.e., when FFS ≥1) [194,195]. As induction treatment, cyclophosphamide pulse therapy acts at least as rapidly as, and engenders fewer side effects than, oral administration [17,196]. A cyclophosphamide pulse (0.5–0.7 g/m²) is administered every 15 days for the first three doses, then every 3 weeks (or monthly for PAN and CSS) until remission is achieved (or sustained for a total of 12 pulses for PAN and CSS). When preferred or required (e.g., after failure of intravenous pulse cyclophosphamide), oral cyclophosphamide should be prescribed at 2 mg/kg/day. Once remission is achieved [197], induction therapy must be switched to maintenance therapy with a less toxic immunosuppressant, such as azathioprine, methotrexate or mycophenolate mofetil, for at least 12 additional months (total treatment duration should be ≥18 months). Long-term maintenance treatment with cyclophosphamide must not be prescribed, as it is associated with an unacceptable risk of adverse events, especially infections or late development of cancers (bladder cancer and hematologic malignancies) [2,198].

Before the introduction of corticosteroids in the 1970s, no more than 10–15% of patients with untreated PAN or WG survived [113,199]. Survival has now increased to 55% with the use of corticosteroids alone and to 75–90% at 5 years with the use of combined corticosteroids and immunosuppressants therapy [112,200,201]. However, the relapse rate varies, from less than 10–20% for HBV-related PAN [106], to 23.4% for CSS [64], and approximately 50% for WG, despite maintenance therapy [2,201].

Alternatively, in less severe or localized forms of WG, other induction treatments have been demonstrated to be as effective as cyclophosphamide in achieving remission, with less toxicity: methotrexate in WG [202]; sulfamethoxazole/trimethoprim used alone in some patients with minor, nondestructive and nonprogressing ENT-localized WG [161,203,204]; and interferon-α in CSS [205,206].

Other treatments, such as intravenous immunoglobulin therapy or plasma exchange as adjuvant therapy, can be prescribed for disease relapse and/or ANCA-associated vasculitis which does not respond to conventional regimens or with severe kidney disease, for plasma exchange. Another promising treatment is biotherapy with, for example, monoclonal anti-CD20 antibodies (rituximab, ocrelizumab) [207,208] or anti-TNFα antibodies (infliximab or adalimumab) [209,210]. These antibodies are currently being evaluated in international prospective trials [194,211,212]. At present, such treatments should be prescribed only after patients are referred to known treatment centers for vasculitides.

Future perspective

This review summarizes the current clinical knowledge of granulomatous vasculitides. It is more than doubtful that issues regarding diagnosis will change over the next 5–10 years. In most of the cases, finding granulomatous vasculitis on histology is the final step in confirming a diagnosis that was clinically and/or biologically presumed. However, differential diagnoses, such as lymphomatoid granulomatosis or lymphoma-mimicking vasculitis, should not be discounted.

GCA, CSS and WG are the main primary systemic disorders with histological features of granulomatous vasculitis in the current classification of systemic vasculitides. Clinical characteristics of these diseases have been well described in earlier series, but the possible existence of different subgroups of patients has emerged in the last few years. Clinical and physiopathogenetic differences between ANCA-positive and -negative CSS patients on the one hand and systemic/generalized/severe and localized/limited WG on the other, as well as the mechanisms for switching from one WG form to the other, should be further elucidated. Indeed, patients may benefit from different therapeutic regimens individually tailored according to the precise form and/or phase of their WG or CSS.

Furthermore, biological therapies, such as the use of anti-CD20 or anti-TNFα, may benefit some patients with ANCA-associated vasculitides. Indeed, differences may occur in the therapeutic response to these agents, depending on the form of the disease, but also on their exact mechanisms of action and kinetics. For example, the effect of etanercept, an anti-TNFα agent, was found to be disappointing in a recent trial in both limited and severe WG [210]. However, other anti-TNFα agents, infliximab or adalimumab, might be effective, at least in some subgroups of WG patients [209,213]. Similar differences in efficacy were observed for Crohn's disease, another granulomatous disease. Indeed, contrary to etanercept, infliximab and adalimumab are associated with antibody-mediated cell lysis, have a longer elimination half-life, and were shown to induce apoptosis in lamina propria-activated T lymphocytes [214,215].

Newer biologics, such as anti-CD22 or cytotoxic T-lymphocyte-associated antigen 4-Ig, are under investigation. To date, all the available biological therapies are prescribed mainly for patients with refractory disease or in whom disease has relapsed despite conventional and first-line treatment and who are in referral centers for vasculitides.

Conclusion

Diagnoses of primary systemic vasculitis, such as GCA, PAN, WG or CSS, have been facilitated due to an increased awareness of these diseases among physicians. However, differential diagnoses of granulomatous vasculitis must also be recognised and evoked, at diagnosis and in cases of disease refractory to conventional therapy. For primary systemic vasculitides, corticosteroids alone are effective as first-line therapy for GCA, CSS or PAN without poor prognosis factors. Conversely, the indication and efficacy of induction therapy with pulse intravenous cyclophosphamide and corticosteroids has definitively been proven for WG and poor-prognosis CSS, PAN and MPA. The mortality rate for systemic WG has been reduced to less than 15%, as compared with almost 95% in the 1970s. However, physicians should always keep in mind that long-term immunosuppression carries a risk of adverse events, especially infections or delayed malignancy. Finally, some promising drugs, such as monoclonal antibodies, are currently being tested for disease-relapse patients and disease refractory to treatment.

Executive summary

Primary systemic vasculitides

- According to the Chapel Hill Nomenclature, Wegener's granulomatosis (WG) and Churg–Strauss syndrome (CSS) are the two main granulomatous systemic necrotizing vasculitides affecting small vessels.
- Granulomatous vasculitis can also be seen in giant cell (temporal) arteritis (GCA) and Takayasu's arteritis, the two primary systemic large-vessel vasculitides, but rarely in polyarteritis nodosa (PAN).

Other diseases possibly associated with granulomatous vasculitis

- Granulomatous vasculitis can also be observed in some other disorders, such as lymphomatoid granulomatosis, sarcoidosis-associated vasculitis, vasculitides secondary to lymphoproliferative hemopathy, systemic inflammatory diseases, such as rheumatoid arthritis or lupus, or infection with *Mycobacterium* spp. or fungi.

Executive summary

Diagnostic considerations

- In most cases, granulomatous vasculitis on histology is an expected, but important, finding in a patient with clinical manifestations and/or biological abnormalities, such as the presence of antineutrophil cytoplasmic autoantibodies (ANCA), and can confirm the presumed diagnosis of primary systemic vasculitis, specifically WG or CSS.
- However, alternative diagnoses should be considered in cases in which all the characteristic manifestations of one of these primary vasculitides are lacking and/or conventional therapy for what has been initially diagnosed as primary vasculitis is not effective.

Principles of treatment for primary systemic vasculitides

- The treatment of secondary granulomatous vasculitis relates to its cause (i.e., antimicrobial agents for infection or chemotherapy for lymphoma).
- Corticosteroids are mandatory for patients with GCA, but a consensual or worldwide accepted therapeutic scheme is currently lacking. First-line adjuvant therapy with immunosuppressants is also controversial.
- Patients with CSS and PAN, without any indication of poor prognosis, can be treated with corticosteroids alone, and with adjuvant immunosuppressant therapy in the case of treatment failure or in severe forms.
- All patients with WG should receive a combination of corticosteroids and immunosuppressants, mainly cyclophosphamide, for systemic forms.
- Other treatments, such as intravenous immunoglobulin therapy, can be prescribed for disease relapse and/or ANCA-associated vasculitis that does not respond to conventional regimens.
- Biologics, such as monoclonal anti-CD20 antibodies or antitumor necrosis factor-α antibodies, are promising therapy, but are still under evaluation in international trials.

Conclusion

- With granulomatous vasculitis observed on histology, a diagnosis of primary systemic vasculitis, such as GCA, PAN, WG or CSS is not usually difficult.
- However, differential diagnoses must be considered, especially in cases of unusual clinical manifestations or treatment failure.
- The exact cause(s) and all the mechanisms leading to granulomatous inflammation in these primary systemic vasculitides have only been partly elucidated, but their closer identification in the future will provide clues to the development of other more specific and targeted therapies.

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