Review

Unclassified vasculitis

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Received on February 8, 2011; accepted in revised form on February 25, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 64): S81-S85.

Key words: vasculitis, Chapel Hill classification, primary angiitis of the central nervous system, acral necrosis, Behçet's disease

Competing interests: none declared.

ABSTRACT

Vasculitides are a heterogeneous group of inflammatory disorders of the blood vessels. The etiology and pathogenesis of vasculitides is incompletely understood, and the nomenclature and classification of vasculitides remains a challenge. A number of vasculitides were not included in the Chapel Hill Consensus (CHC) Conference definitions, thus, have remained "unclassified", but may be included in a revised version of the nomenclature, e.g. Goodpasture's syndrome. In other cases the term "unclassified" implies "unclassifiable", i.e. a vasculitis cannot be assigned to any of the known entities. Vasculitis-induced acral necrosis including giant cell arteritis of small arteries as well as isolated forms of intestinal vasculitis including granulomatous giant cell polyphlebitis may belong to this category of rare "unclassified" vasculitides. In some entities the relationship between vasculitis and other manifestations remains unclear, e.g. in Behçet's disease and IgG4-related systemic disease. In this review the clinical and pathological aspects of "unclassified" vasculitides are briefly discussed.

Classified and unclassified vasculitides

Vasculitides are a heterogeneous group of inflammatory disorders affecting the blood vessels. To date, the etiology and pathogenesis of vasculitides is only incompletely understood. They are characterised by both diversity and considerable overlap of clinical and pathological findings. Therefore, the nomenclature and classification of vasculitides remains a challenge for pathologists and clinicians. The now routinely used Chapel Hill Consensus (CHC) Conference nomenclature provides names and definitions of 10 primary systemic vasculitides based on well-recognised clinical and pathological features (Table I) (1). Some vasculitides were not included in the CHC definitions, and thus, have remained "unclassified", but may be included in a revised version of the nomenclature (*e.g.* Goodpasture's syndrome). In other cases the term "unclassified" implies "unclassifiable", *i.e.* the vasculitis cannot be clearly assigned to one of the known entities (*e.g.* vasculitis characterised by acral necrosis or granulomatous giant cell polyphlebitis). Of note, the relationship between vasculitis and other clinical manifestations is still rather obscure in some entities *e.g.* Behçet's disease. Vasculitis could be a secondary event rather than an obligatory manifestation of the disorder. It may be difficult to prove in routine biopsies and/or truly affect only a subset of patients with the disorder. The term "primary" systemic vasculitis itself may undergo changes as etiological agents or underlying genetic traits will be demonstrated to be involved in the pathogenesis of vasculitis. Herein, we will briefly discuss some of the clinical and pathological aspects of "unclassified" vasculitides in the following sections.

"Unclassified" systemic vasculitides

Anti-glomerular basement membrane disease and Goodpasture's syndrome

Anti-glomerular basement membrane (Anti-GBM) disease is a systemic autoimmune disorder caused by antibodies directed to the noncollagenous-1 (NC-1) domain of α3- and α5-chains of type IV collagen in the glomerular and alveolar basement membrane. The pulmonary-renal syndrome due to anti-GBM disease and diffuse alveolar haemorrhage is referred to as Goodpasture's syndrome. Renal vasculitis in anti-GBM disease presents as rapidly progressive glomerulonephritis (RPGN) with hematuria, proteinuria, and renal failure. Environmental factors such as tobacco smoking are associated with the induction of alveolar haemorrhage in Goodpasture's syndrome (2, 3).

Histological examination of the kidney in anti-GBM disease reveals severe inflammation with crescent formation and glomerular necrosis, *i.e.* focal segmental necrotising and crescentic intra- and extracapillary glomerulonephritis. Vasculitis of small- and medium-sized vessels may be present. Anti-GBM antibodies induce linear immunoglobulin (Ig)G and C3 complement deposits along the glomerula basement membrane and the walls of pulmonary capillaries. Diffuse alveolar haemorrhage with hemosiderin-laden macrophages is the dominant pathologic finding in the lungs. Fibrin exsudates may indicate microvascular injury. Pulmonary capillaritis is common in patients with Goodpasture's syndrome (3, 4).

Behçet's disease

Behçet's disease is characterised by recurrent oral and genital ulcerations, ocular disease, a variety of skin lesions, and less often by arthritis and neurological features. As yet, the etiology and pathogenesis of Behçet's disease remains obscure. Vasculitis apparently underlies many of the clinical manifestations of Behçet's disease. However, demonstration of true vasculitis on biopsies is often not possible and perivascular inflammatory infiltrates ("perivasculitis") are seen, especially in mucocutaneous lesions (5). Vasculitis may affect both arteries and veins of all sizes in Behçet's disease. Aortitis with or without aneurysm formation has also been reported. Aneurysm formation may be a consequence of vasculitis in the adventitial *vasa vasorum* of the aorta and large arteries. Pulmonary artery vasculitis and aneurysms confined to the main pulmonary arteries and their lobar branches may complicate the course. Fatal rupture of aneurysms may occur. Skin biopsy may reveal leukocytoclastic vasculitis. Inflammatory venous vascular involvement may cause thrombosis including portal vein thrombosis, deep venous thrombosis, and migratory superficial thrombophlebitis (6-9).

IgG4-related systemic disease

IgG4-related systemic disease (IgG4-RSD) is a recently recognised systemic disorder which may present with autoimmune pancreatitis, chronic sclerosing sialadenitis, orbital inflammatory pseudotumour, and retroperitoneal fibrosis (10). Elevated serum IgG4 concentrations are often detected in the serum. Diffuse lymphoplasmacytic infiltration with abundant IgG4-positive plasma cells and fibrosis are the hallmark of histological findings in IgG4-RSD. Aortitis and lymphoplasmacytic vasculitis with interstitial infiltration and fibrosis of the lung have been reported in patients with IgG4-RSD. The relationship between vasculitic and other inflammatory lesions has to be further elucidated in IgG4-RSD (11, 12).

Table I. Names and definitions of vasculitides adopted by the Chapel Hill Consensus Conference on the nomenclature of systemic vasculitis (1).

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

Cogan's syndrome

Interstitial keratitis and vestibuloauditory symptoms are the cardinal features of Cogan's syndrome. The disease may be associated with systemic vasculitis, in particular aortitis with involvement of the aortic valve. The etiology and pathogenesis of this syndrome remains unclear (13).

"Unclassified" non-systemic vasculitides

Non-systemic vasculitides were not included in the CHC definitions (1). An isolated vasculitis may represent a limited variant ("*forme fruste*") of a defined

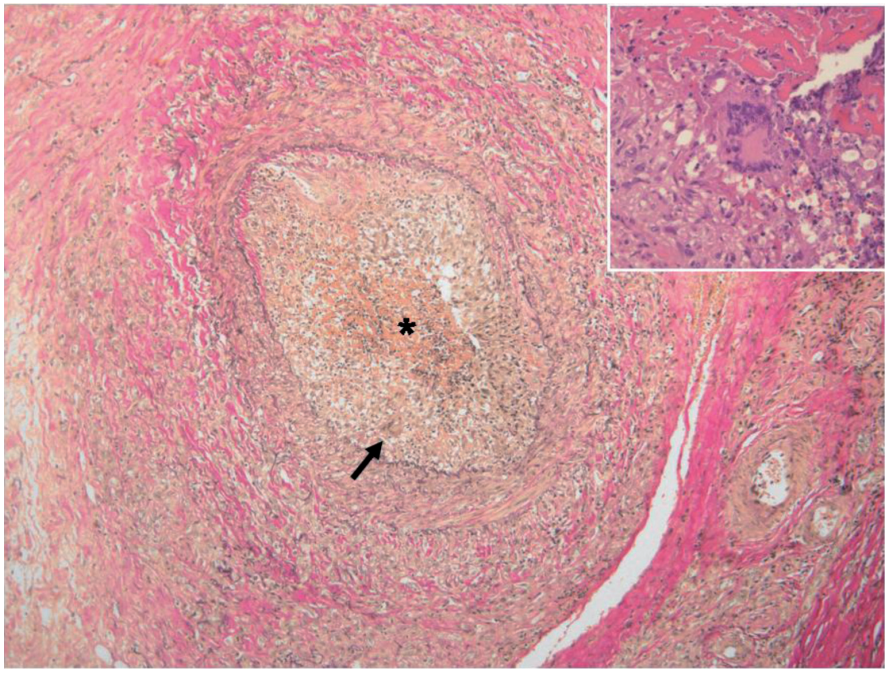

Fig. 1. Giant cell arteritis of a small digital artery. The arterial wall shows onion-skin splitting and partial destruction of elastic fibres, transmural inflammatory infiltrates including numerous epitheloid cells and giant cells (arrow and inset) and complete occlusion of the lumen (*) by organised thrombotic material (with permission from: (20)).

vasculitis, *e.g.* polyarteritis nodosa of the gastrointestinal tract. Follow-up of the patient will show whether the vasculitis remains limited to the organ or becomes systemic after some time. Apart from limited variants of systemic vasculitides, it seems that some distinctive non-systemic vasculitides can be recognised.

Primary angiitis of the central nervous system

Primary angiitis of the central nervous system (PACNS) is a rare vasculitis of unknown etiology solely confined to the vessels of the CNS. Patients typically suffer from severe headache and various neurological deficits. Cerebrospinal fluid (CSF) is abnormal with mild lymphcytic pleocytosis and elevated protein in 80–90% of PACNS cases, while magnetic resonance imaging of the CNS has a diagnostic sensitivity approaching 100%, although it is not specific (14). Magnetic resonance, computerised tomography, or digital subtraction angiography is altered in approximately 50% of cases. Typical changes are multifocal, alternating and segmental stenoses and/or irregularities of several intracranial arteries (15). Of note, solely angiographically documented cases of so-called "benign angiopathy of the CNS" (BACNS) are part of the large spectrum of reversible cerebral vasoconstriction syndromes (16).

In 1988, diagnostic criteria were proposed including a) a history or clinical findings of an acquired neurologic deficit unexplained after a thorough initial basic evaluation, b) cerebral angiography with classic features of vasculitis, or a CNS biopsy showing vasculitis, and, c) no evidence of systemic vasculitis or of any other condition to which the angiographic or pathologic features could be attributed (17). Histological confirmation remains the gold standard for confirming the diagnosis. However, the focal and segmental distribution of the vasculitic lesions constrains the diagnostic yield of biopsies to 66–75%. PACNS appears to consist of several subsets of heterogeneous diseases. PACNS predominantly affects small- to medium-sized leptomenigeal and/or cortical and subcortical intraparenchymal vessels. The surrounding brain may show haemorrhage, infarction, loss of myelin, and axonal degeneration. Large vessels are sometimes involved. Large vessel involvement is associated with a higher mortality rate and greater disability. Veins and venules may be affected to a lesser degree. The vasculitis may occasionally involve the spinal cord. Three main histopathological patterns are found in PACNS: granulomatous, lymphocytic, and necrotising vasculitis. As a rule, these patterns are not associated with specific clinical manifestations, course, or outcomes. However, only granulomatous and/or necrotising histopathological patterns of vasculitis have been found in rapidly progressive disease. The histopathological pattern apparently remains stable over time excluding a staged development from one lesion to another in most cases (14-19).

Vasculitis-induced acral necrosis

Acral ischaemia and necrosis are a common problem in connective tissue diseases such as systemic sclerosis. They are also occasionally encountered in primary or secondary systemic vasculitides, *e.g.* polyarteritis nodosa, cryoglobulinemic vasculitis, and rheumatoid vasculitis. Acral ischaemic lesions may be found as the only hallmark manifestation of an otherwise unclassified vasculitis in rare cases. Raynaud's phenomenon is common, but other symptoms suggestive of a defined and/or classified vasculitis are absent and do not develop in the further course of the patients disease. Histopathological findings in those patients include necrotising and leukocytoclastic vasculitis. In one patient giant cell arteritis of small arteries was found as the cause of acral ischaemic lesions with necrosis necessitating digit amputation (Fig. 1) (20).

Intestinal vasculitis

Isolated intestinal vasculitis is rare condition. It may either represent a genuine entity or a *"forme fruste"* of a defined vasculitic entity such as polyarteritis nodosa. Vasculitis may affect all intestinal organs including the stomach, duodenum, small intestine, colon, appendix, pancreas, omentum, and the gall-bladder. Abdominal pain, gastrointestinal bleeding, bowel obstruction, and acute abdomen are encountered as a consequence of intestinal vasculitis. Patients frequently present with an acute abdomen requiring surgical intervention. Abdominal CT scan findings

may show bowel wall thickening, bowel infarction, and solid organ infarcts. Abdominal angiography may suggest vasculitis of medium-sized vessels. Various histological findings have been reported in isolated intestinal vasculitis such as granulomatous or non-granulomatous arteritis, necrotising vasculitis, and leukocytoclastic vasculitis (21-23). In rare cases a vasculitis solely confined to the veins has been reported. Biopsies disclosed granulomatous giant cell polyphlebitis of the visceral veins in one of those patients (24).

Chronic periaortitis

Chronic periaortitis is characterised by a fibro-inflammatory process spreading from the abdominal aorta and the iliac arteries into the retroperitoneum. Other vascular segments such as thoracic aorta and coronary, renal, and mesenteric arteries may be involved as well. Formation of aneurysms may be a consequence of chronic periaortitis. Histopathologic studies show adventitial inflammation and fibrosis extending to the retroperitoneum. Vasculitis of the vasa vasorum within the inflamed adventitial layer of the aorta suggests that chronic periaortitis may be considered to be a primary large-vessel vasculitis (25). On the same line, a study using ^{18}F-FDG PET (^{18}F-fluorodeoxyglucose positron emission tomography) has provided evidence that approximately one third of the patients with chronic periaortitis have diffuse large-vessel involvement (26).

Thromboangiitis obliterans (Winiwarter-Bürger's disease)

Endangiitis or thromboangiitis obliterans is a vasculitis involving small and medium-sized arteries and veins preferentially in the distal upper and lower extremities. Cerebral, intestinal, or coronary vessels may also be affected. The disease is typically found in men younger than 40 years, and is highly associated with tobacco smoking. Patients suffer from Raynaud's phenomenon, claudication of the affected extremity, a migratory phlebitis of superficial veins, trophic skin and nail changes, and ulcers and acral necrosis. Angiography shows tapering segmental lesions, "corkscrew" appearance of arteries and/or microaneurysms. Thromboangiitis obliterans is characterised by a highly cellular and inflammatory thrombus with relative sparing of the vessel wall. However, vasculitis of vasa vasorum in the arterial wall is also present. Although thrombosis of the arteries and veins has been suggested to be the primary event, thromboangiitis obliterans is considered among the vasculitides because of the highly inflammatory response within the thrombus and affected vessel walls (27).

Other non-systemic vasculitides

Other non-systemic vasculitic conditions include isolated vasculitis of the peripheral nervous system, retinal vasculitis (Eales' disease), and vasculitis of the urogenital tract (28-30). Although often idiopathic, these vasculitides have to be distinguished from initial manifestations or limited variants of primary or secondary systemic vasculitides, *e.g.* retinal vasculitis in sarcoidosis (29).

References

1. JENNETTE JC, FALK RJ, ANDRASSY K *et al.*: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
2. PEDCHENKO V, BONDAR O, FOGO AB *et al.*: Molecular architecture of the Goodpasture autoantigen in anti-GBM nephritis. *N Engl J Med* 2010; 363: 343-54.
3. CHAN AL, LOUIE S, LESLIE KO, JUAREZ MM, ALBERTSON TE: Cutting Edge Issues in Goodpasture's Disease. *Clin Rev Allergy Immunol* 2011 Jan 5; (Epub ahead of print).
4. LOMBARD CM, COLBY TV, ELLIOTT CG: Surgical pathology of the lung in anti-basement membrane antibody-associated Goodpasture's syndrome. *Hum Pathol* 1989; 20: 445-51.
5. BALABANOVA M, CALAMIA KT, PERNICIARO C, O'DUFFY JD: A study of the cutaneous manifestations of Behcet's disease in patients from the United States. *J Am Acad Dermatol* 1999; 41: 540-5.
6. ARIDA A, VAIOPOULOS G, MARKOMICHELAKIS N, KAKLAMANIS P, SFIKAKIS PP: Are clusters of patients with distinct clinical expression present in Behçet's disease? *Clin Exp Rheumatol* 2009; (Suppl. 53): S48-51.
7. MELIKOGLU M, KURAL-SEYAHI E, TASCILAR K, YAZICI H: The unique features of vasculitis in Behcet's syndrome. *Clin Rev Allergy Immunol* 2008; 35: 40-6.
8. HIROHATA S, KIKUCHI H: Histopathology of the ruptured pulmonary artery aneurysm in a patient with Behçet's disease. *Clin Exp Rheumatol* 2009; 27 (Suppl. 53): S48-51.
9. CALAMIA KT, SCHIRMER M, MELIKOGLU M: Major vessel involvement in Behcet's disease: an update. *Curr Opin Rheumatol* 2011; 23: 24-31.
10. KAMISAWA T, FUNATA N, HAYASHI Y *et al.*: A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38: 982-4.
11. KHOSROSHAHI A, STONE JH: A clinical overview of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011; 23: 57-66.
12. YAMASHITA K, HAGA H, KOBASHI Y, MIYAGAWA-HAYASHINO A, YOSHIZAWA A, MANABE T: Lung involvement in IgG4-related lymphoplasmacytic vasculitis and interstitial fibrosis: report of 3 cases and review of the literature. *Am J Surg Pathol* 2008; 32: 1620-6.
13. MAZLUMZADEH M, MATTESON EL: Cogan's syndrome: an audiovestibular, ocular, and systemic autoimmune disease. *Rheum Dis Clin North Am* 2007; 33: 855-74.
14. SIVA A: Vasculitis of the nervous system. *J Neurol* 2001; 248: 451-68.
15. NEEL A, PAGNOUX C: Primary angiitis of the central nervous system. *Clin Exp Rheumatol* 2009; 27 (Suppl, 52): S95-107.
16. CALABRESE LH, DODICK DW, SCHWEDT TJ, SINGHAL AB: Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med* 2007; 146: 34-44.
17. CALABRESE LH, MALLEK JA: Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine* (Baltimore) 1988; 67: 20-39.
18. SALVARANI C, BROWN RD JR, CALAMIA KT *et al.*: Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62: 442-51.
19. SALVARANI C, BROWN RD JR., CALAMIA KT *et al.*: Rapidly progressive primary central nervous system vasculitis. *Rheumatology* (Oxford) 2011; 50: 349-58.
20. PIPITONE N, HOLL-ULRICH K, GROSS WL, LAMPRECHT P: Unclassified vasculitis with acral ischemic lesions: "forme fruste" or idiopathic vasculitis? *Clin Exp Rheumatol* 2008; 26 (Suppl. 49): S41-S46.
21. KALLA AH, LEE KU, VOSS EC JR: The dilemma of colonic vasculitis: report of a unique case. *Dis Colon Rectum* 1980; 23: 590-6.
22. GARCIA-PORRUA C, GUTIERREZ-DUQUE O, SOTO S, GARCIA-RODEJA E, GONZALEZ-GAY MA: Localised vasculitis of the gastrointestinal tract. *Semin Arthritis Rheum* 2006; 35: 403-6.
23. SALVARANI C, CALAMIA KT, CROWSON CS *et al.*: Localized vasculitis of the gastrointestinal tract: a case series. *Rheumatology* (Oxford) 2010; 49: 1326-35.
24. LEU HJ, BRINNINGER G, PERNEGGER C, ODERMATT B: Primary granulomatous giant cell polyphlebitis of visceral veins. *Virchows Arch A Pathol Anat Histopathol* 1993; 423: 519-21.
25. VAGLIO A, PIPITONE N, SALVARANI C: Chronic periaortitis: a large-vessel vasculitis? *Curr Opin Rheumatol* 2011; 23: 1-6.
26. SALVARANI C, PIPITONE N, VERSARI A *et al.*: Positron emission tomography (PET): evaluation of chronic periaortitis. *Arthritis Rheum* 2005; 53: 298-303.

27. PIAZZA G, CREAGER MA: Thromboangiitis obliterans. *Circulation* 2010; 121: 1858-61.
28. COLLINS MP, PERIQUET MI: Isolated vasculitis of the peripheral nervous system. *Clin Exp Rheumatol* 2008; 26 (Suppl. 49): S118-30.
29. HUGHES EH, DICK AD: The pathology and pathogenesis of retinal vasculitis. *Neuropathol Appl Neurobiol* 2003; 29: 325-40.
30. HERNANDEZ-RODRIGUEZ J, MOLLOY ES, HOFMAN GS: Single-organ vasculitis. *Curr Opin Rheumatol* 2008; 20: 40-6.