### Review

**Unclassified vasculitis**

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**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. the vasculitis cannot be clearly 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 1) (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 haematuria, 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 (IgG) 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 ulcers, 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. Arthritis 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 confine 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).

**Cogan’s syndrome**
Interstitial keratitis and vestibulolatory 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
It seems that some distinctive non-systemic variants of systemic vasculitides, systemic after some time. Apart from remains limited to the organ or becomes gastrointestinal tract. Follow-up of the CNS has a diagnostic sensitivity approaching 100%, although it is not specific. Magnetic resonance, computed 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. 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 leptomeningeal 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.

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 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 necrosis 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).

**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 18F-FDG PET (18F-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


