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Review Article

Small vessel vasculitis

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Abstract

Background: Vasculitis is a primary inflammatory process of large, medium-sized, and small blood vessels. There are multiple entities particularly among small vessel vasculitides. Some are life threatening and require treatment with toxic agents. Diagnostic challenges are posed by low prevalence, controversial classification, inconsistency of clinical and pathological features, and the existence of clinical and pathological "look-alikes". Also, patients may present to a variety of medical specialists, and the diagnosis is often unexpected. The cause often is unknown. **Review:** Classification is by vessel size and then on an immunopathologic basis. Generalised and "organ-limited" forms occur. The principal clinical and pathological features are outlined for each of antibasement membrane disease, immune complex disorders including Henoch–Schönlein purpura and cryoglobulinemic vasculitis and the pauci-immune group, which is often associated with antineutrophil cytoplasmic antibody (ANCA), comprising microscopic polyangiitis, Wegener's granulomatosis, and Churg–Strauss syndrome. A brief account is given of "look-alikes" including microthrombotic conditions, which can confound the diagnosis of small vessel vasculitis. **Conclusion:** Requirements for diagnosis include full disclosure of the past and present medical history with review of laboratory results, especially diagnostic immunology. Histology should be of targeted biopsies of recent active lesions in preference to blind biopsies. Sampling should be extensive using high-quality thin sections. Systematic microscopic evaluation of architectural features and cellular detail is necessary. Tissue immunofluorescence is a useful adjunct. The final opinion must take all available information into account but may ultimately depend on a critical judgement by the pathologist.

Keywords: Small vessel vasculitis; Cytoplasmic ANCA; Perinuclear ANCA

1. Introduction

Fundamentally, vasculitis is a primary inflammatory process beginning in the wall of one or more blood vessels with limited extension into adjacent structures, haemorrhage from the damaged vessel, and ischaemic damage in the distribution of the vessel. Secondary involvement of a vessel in inflammation is not "vasculitis".

Biopsy pathology continues to be important for diagnosis, but greater understanding of the nature and extent of these diseases has in the past come from autopsy. There is, however, now a changing perspective partly from the reduction in numbers of autopsies as a method for their study but also because of improved diagnosis and treatment of vasculitis, so fewer patients now die of untreated disease. Another major element in this changed perspective is a better understanding of their immunopathology, so these disorders are not now defined by morphology alone.

Vasculitis presents a major problem both for diagnosis and treatment. This is because there are multiple entities, and, collectively and individually, they are uncommon. Some are acutely life threatening and require urgent treatment with steroids and cytotoxic drugs for good results. However, others, though morphologically similar, not only do not require treatment with toxic drugs but also patients may be adversely affected by such treatment.

Accurate diagnosis is critical for effective treatment, and histopathologists have a major role in identifying the different entities. This, however, presents several challenges arising from:

- Low prevalence and incidence of vasculitis both collectively and of the constituent entities so personal experience may be limited

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- Difficulties with criteria for classification and diagnosis
- Frequent inconsistency of clinical and pathological features
- Clinical "look-alikes" with different pathologies
- Pathological "look-alikes" with different behaviours
- The disorders commonly ignore the boundaries of different medical specialties
- The diagnosis frequently is unexpected
- Their aetiology and pathogenesis is incompletely understood and a specific causal agent usually has not been identified; if organisms are identified the condition is generally not classed as "vasculitis".

2. Vasculitis—a classification

There have been a number of attempts to classify this group of disorders, but for pathologists the most suitable approach is:

- by anatomy
  - particularly by vessel size into large, medium, small
  - and by location whether generalised or tissue/organ specific
- and by immunopathology especially for small vessel vasculitis

This recommended approach is the system adopted by the International Consensus Conference on Nomenclature of Systemic Vasculitides, Chapel Hill, 1994 [1]. Not all conditions falling into the category of small vessel vasculitis have been defined by this classification, but its principles can be applied generally, and it covers most of the clinically important forms of systemic vasculitis. (Any entity defined at this conference is denoted in this review by *.)

While this review is focussed on small vessel disease, it is useful to place this in the context of vasculitis as a whole. There are three anatomical groups.

3. Large vessel vasculitis

These are diseases of the aorta and its principal branches: Takayasu arteritis*, giant cell (temporal) arteritis*, ankylosing spondylitis/Reiter's syndrome, and Behçets syndrome.

While conventionally classified as large vessel disease, there may be a small vessel constituent in the form of a "vasa vasoritis" [2]. This is not, however, considered conventionally within the spectrum of small vessel vasculitis.

4. Medium-sized vessel vasculitis

This affects small muscular arteries, e.g., temporal artery, arcuate artery, and branches. There are systemic and localised forms. Systemic forms are granulomatous, e.g., giant cell (temporal) arteritis*, and necrotizing, e.g., classic polyarteritis nodosa* and Kawasaki disease*.

Some of these may have an accompanying small vessel component.

5. Small vessel vasculitis

This involves the smallest arteries, arterioles, capillaries, and venules. There may be coexistent medium-vessel disease, but the small vessel component is the determinant of behaviour. Both systemic and localised forms occur, and, in addition to histopathology, immunohistology and autoimmune serology are important for full definition of the disorders in this group.

The three immunopathological types are:

- Antibody mediated
- Immune complex mediated and
- "Pauci-immune" [commonly but not invariably associated with antiproteinase 3 cytoplasmic ANCA (cANCA) or antimyeloperoxidase perinuclear ANCA (pANCA)].

For convenience of description, the features of the principal types of systemic small vasculitis will be first described followed by those in which it is apparently localised. This distinction should, however, be made with some care because in some cases seemingly localised disease may represent an early stage or *forme fruste* of the systemic disorder rather than isolated organ disease and which may subsequently declare itself in full.

5.1. Systemic small vessel vasculitis—antibody mediated

The only antibody identified as having a clear association with small vessel vasculitis is antibody against basement membrane. Although antibodies have been identified against endothelium in the context of ANCA-associated vasculitis [3–5], they have no generally accepted pathogenic role.

Antibasement membrane disease usually presents with lung haemorrhage accompanied by rapidly progressive glomerulonephritis, although renal-limited disease occurs in 30–40% of cases. There may be a background of systemic illness. This classic presentation traditionally has been designated Goodpasture's syndrome, although it is not the most frequent cause of lung haemorrhage and nephritis [6,7]. It is uncommon with an estimated incidence of one patient per million [8].

The pathology has the form of a "capillaritis" producing in the kidney a segmental necrotising glomerulonephritis (Fig. 1A) progressing into crescentic nephritis (Fig. 1B) and in the lungs extensive haemorrhage producing a background against which it may not be easy to identify the underlying