Vasculitis—when can biopsy be avoided?

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INTRODUCTION

Vasculitis is a potentially avoidable and reversible cause of endstage renal disease (ESRD), and small-vessel vasculitis is the most common cause of the syndrome of rapidly progressive glomerulonephritis. Delayed diagnosis or inadequate treatment fails the vasculitis patient and greatly increases their risk of ESRD and premature death. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is the major subgroup,with immunoglobulin A (IgA) vasculitis (Henoch–Schonlein purpura), cryoglobulinaemia and anti-glomerular basement membrane (GBM) disease being less frequent [1]. Haematuria with proteinuria is universal, but proteinuria can be low level; red cell casts, if seen, are strongly suggestive for vasculitis

and rapidly declining renal function is often present. Renal biopsy remains the definitive investigation and should always be considered in the diagnostic workup. However, shortly after the introduction of widespread ANCA testing a debate began as to whether biopsy can be avoided in AAV. The arguments underlying this decision are reviewed and opinion-based rather than evidence-driven advice is given.

CAN YOU TRUST THE SEROLOGY?

The integration of serologic testing with the clinical presentation provides the basis for a biopsy decision.With thier improved performance, proteinase 3 (PR3) and myeloperoxidase (MPO)-ANCA assays are replacing the indirect immunofluorescence (IFF) test (gives a cytoplasmic ANCA or perinuclear ANCA result), which has a low specificity for an AAV diagnosis when used alone [2]. A positive PR3 or MPO-ANCA in a patient with suspected nephritis has a>95% association with histology revealing necrotizing, crescentic glomerulonephritis, usually with few or no immune deposits. But positive ANCA, usually MPO-ANCA, occurs in a wide range of other inflammatory settings, e.g. lupus nephritis, endocarditis, other chronic infection, malignancy and

drugs. ANCA may be a ‘false’ positive, i.e. there is no vasculitis on biopsy, or a ‘true’ positive but a secondary vasculitis is present that is driven by another illness. Low-level positive or borderline false positive values can be seen with hypergammaglobulinaemia, myeloma and in other settings and the cut-off between positive

and negative is arbitrary. Unfortunately, current assays do not compare well in the quantification of the ANCA result—a strong positive in one can be a weak positive in another [3]. In 5–10% of cases of pauci-immune crescentic nephritis, ANCA is absent, although these cases are included within the ‘AAV’ subgroup [4].

The anti-GBM test tends to be more reliable, although occasional false positives and false negative results are seen. An antinuclear antibody (ANA) test is usually requested at the same time and MPO-ANCA can cause a false positive ANA in some assays, while anti-double-stranded DNA antibodies can cause a false positive MPO-ANCA. Rheumatoid factor can be positive in an AAV patient but would suggest a secondary infective cause or cryoglobulinaemia, and there has been increasing focus on complement C3 levels in AAV, although traditional teaching would associate hypocomplementaemia with an immune complex nephritis [5]. The nephrologist needs to understand the performance of local serology assays and have experience in evaluating the clinical presentation and integrating his/her findings with the serology to minimize the risk of error with a decision not to biopsy.

WHAT CAN A BIOPSY TELL YOU?

The primary role of the biopsy is to provide diagnostic information. The glomerular pathology in AAV has been subclassified (the ‘Berden classification’) into categories that have prognostic importance [6]. However, even the most severe subgroups can respond to therapy and maintain dialysis independence. In current practice there are no biopsy features that guide the choice or duration of therapy [7]. Rarely, in addition to confirming AAV histology, unexpected diagnostic information of a parallel or related pathology is seen, such as tuberculosis, malignancy or IgA nephropathy. A repeat or delayed biopsy provides information on ongoing activity and treatment response that may influence treatment decisions. If a diagnostic biopsy is felt to be unnecessary in AAV, a delayed biopsy after 4–6 weeks should be considered if the clinical course is worse than expected. This

has not been widely studied in vasculitis, but the concept of biopsy after induction treatment is well developed in lupus nephririts: ‘if you are only going to do one biopsy, do the second’ (Gary Hill) [8].

WHEN IS BIOPSY INDICATED?

Biopsy is indicated if vasculitis is suspected but the serology is inconclusive or the clinical presentation is not typical. For a suspected AAV, this could be when the PR3 and MPO-ANCA assays are negative or borderline, when there are circumstances to suspect the reliability of the assay or when a secondary vasculitis is present. Examples would be a suspicion of infective endocarditis or tuberculosis, if IgA vasculitis is suspected and there is renal dysfunction or persistent urinary abnormalities regardless of how ‘classic’ the presentation and in most cases of anti-GBM disease and cryoglobulinaemia.

WHEN IS A BIOPSY CONTRAINDICATED?

There are few absolute contraindications, but a single kidney, bleeding diathesis, advanced uraemia, concurrent plasma exchange, the presence of anti-phospholipid antibodies or lupus anticoagulant or respiratory failure due to alveolar haemorrhage all increase the risk of the procedure [9]. Biopsy is not indicated in suspected polyarteritis nodosa or large-vessel vasculitis affecting the kidney, when angiography is more appropriate. Mimics of vasculitis, including severe left ventricular failure, atheroembolic disease or atypical pneumonia, are other scenarios that need to be considered by the physician.

WHEN CAN BIOPSY BE AVOIDED?

Renal biopsy remains the default option for confirming a diagnosis of renal vasculitis. Avoiding a biopsy risks an incomplete evaluation and incorrect diagnosis. But this can be considered when there is a typical presentation of a renal vasculitis with a positive PR3 or MPO ANCA and the centre is experienced in vasculitis management. Also, that the patient will receive appropriate treatment and follow-up and there is a low suspicion for a secondary vasculitis, vasculitis mimic or false positive ANCA (Figure 1).

Clinicians and patients should be prepared for a delayed biopsy for progressive disease, an inadequate treatment response or the detection of new diagnostic information. The value of this approach remains to be confirmed by

prospective studies. Scenarios where there is an increased risk of haemorrhage after renal biopsy. Again a delayed biopsy is indicated where concerns over disease control remain and bleeding risks have been addressed.

REFERENCES

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2. Damoiseaux J, Csernok E, Rasmussen N. Detection of antineutrophil cytoplasmic antibodies (ANCAs): a multicentre European Vasculitis Study Group (EUVAS) evaluation of the value of indirect immunofluorescence (IIF) versus antigen-specific immunoassays. Ann Rheum Dis 2017; 76: 647–653

Table 1. Primary small-vessel vasculitis syndromes affecting the kidney

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| --- | --- | --- |
| Diagnosis | Serology | Immunohistology |
| AAV type* Granulomatosis with

Polyangiitis (Wegener’s) * Microscopic polyangiitis
* Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
 | All syndromes: Pauci-immune (one thirdhave granular deposits)PR3-ANCA, MPOANCAorANCA negative | Pauci-immune (one thirdhave granulardeposits) |
| Immune complex type* IgA vasculitis (Henoch–Schonlein)
 | Negative | Granular IgA andcomplement |
| Cryoglobulinemia | Rheumatoid factor, lowcomplement, paraprotein,cryoglobulins | Granular immunoglobulin,complementandcryoglobulins |
| Anti-GBM disease | Anti-GBM  | Linear IgG andcomplement |

FIGURE 1: Biopsy algorithm for a patient with suspected renal

vasculitis.

