The Continuing Challenge of Anti-Neutrophil Cytoplasm Antibody–Associated Systemic Vasculitis and Glomerulonephritis

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As guest editor for this Frontiers in Nephrology series, it is my job to put the following four articles on small-vessel vasculitis into context for the practicing clinician. I have had an interest in this group of diseases for more than 25 yr, since I first arrived at the Hammersmith Hospital as senior registrar to Keith Peters. At that time, the use of plasma exchange, together with immunosuppressive drugs, was being investigated in Goodpasture syndrome (anti–glomerular basement membrane disease). Because many patients with Wegener granulomatosis (1) and what we then called microscopic polyarteritis (2) also presented with severe crescentic glomerulonephritis, it was argued that a similar therapeutic approach might be effective, even though no circulating autoantibody had been identified. The apparent success of this approach led us to set up one of the first randomized controlled trials of plasma exchange in this condition, which confirmed benefit only in patients who already were on dialysis (3). This led us to develop a treatment protocol involving oral prednisolone, cyclophosphamide (for the first 3 months) then switching to azathioprine and plasma exchange in patients with advanced renal disease or other life-threatening manifestations, such as lung hemorrhage.

So, what has really changed since the early 1980s? At first glance, not enough, because in many cases, we are still using exactly the same treatment. However, in reality, there have been immense advances in almost every aspect of the disease. One of the most important of these was the recognition of anti-neutrophil cytoplasm antibodies (ANCA) as a diagnostic marker. This has been followed by extensive efforts to demonstrate whether ANCA are actually pathogenic. That ANCA were present in some forms of systemic vasculitis, but not others, also has catalyzed approaches to nomenclature and classification. This, in turn, has allowed collaboration among various centers that treat vasculitis, with the development of a series of randomized controlled trials. Although these initially focused on the best way to use existing therapies, better understanding of the pathogenic mechanisms is now leading to the introduction of a number of new therapeutic approaches, including biologic agents. There also is increasing recognition that certain types of small-vessel vasculitis should be regarded as chronic inflammatory disorders and therefore need safe and effective long-term treatment.

A problem that we faced 25 yr ago was that systemic vasculitis often was hard to diagnose because of the varied clinical presentations and the lack of a good diagnostic marker. Diagnosis depended on histology, which was relatively easy to obtain from the kidney but often more difficult from organs such as the lung. The key finding on renal biopsy was a focal segmental and necrotizing glomerulonephritis, usually with crescent formation. Importantly, immune deposits were absent or scanty, thus allowing differentiation from anti–glomerular basement membrane disease or immune complex diseases such as systemic lupus erythematosus. The concept of pauci-immune crescentic glomerulonephritis thus evolved; for nephrologists, this was the hallmark of small-vessel vasculitis.

The report by van der Woude et al. (4) in 1985 of autoantibodies against neutrophils and monocytes in Wegener granulomatosis then changed the landscape. In retrospect, this phenomenon had been described by Davies et al. (5) in 1982, in a report of patients with crescentic nephritis associated with Ross River virus infection. Several other groups rapidly confirmed the presence of ANCA with a granular cytoplasmic staining pattern in patients with Wegener granulomatosis and subsequently identified the main antigen as proteinase 3 (PR3) (6). However, it also was discovered that ANCA were present in other forms of systemic vasculitis and crescentic glomerulonephritis and that these generally showed a perinuclear staining pattern. Notably, Falk and Jennette (7), in 1988, reported the presence of ANCA with specificity for myeloperoxidase (MPO) in these patients.
The discovery of a good biomarker for systemic vasculitis—ANCA—made it easier to diagnose, leading to the possibility of earlier treatment and also to better understanding of the epidemiology (8). However, we still faced the problem that, whereas Wegener granulomatosis was a generally agreed-on diagnosis, other forms of small-vessel vasculitis were less well defined. In Europe, the term “microscopic polyarteritis” often was used for patients with vasculitis but without the granulomatous respiratory tract lesions characteristic of Wegener granulomatosis. However, this term was not universally recognized, even by the American College of Rheumatology. An International Consensus Conference at Chapel Hill provided a much-needed classification, depending on the size of vessel involved and a number of short clinical definitions (9). The term “microscopic polyangitis” was introduced as a more accurate version of the previous term “microscopic polyarteritis.” It was recognized that Wegener granulomatosis, microscopic polyangitis, and, less consistently, Churg-Strauss syndrome were associated with ANCA but that vasculitis of medium and large arteries was not.

There was also great controversy as to whether ANCA were merely a marker of disease, produced as an epiphenomenon of some other process, or were pathogenic in their own right. Falk et al. (10) reported in 1990 that ANCA could induce neutrophils in vitro to degranulate and produce oxygen radicals. This work was rapidly confirmed by other groups and was followed by the demonstration of the importance of Fc γ receptors and the involvement of various downstream signaling pathways (11). However, that ANCA were pathogenic in vivo was hard to demonstrate. The first convincing evidence had to wait until 2002, in a report from Xiao et al. (12), who showed that ANCA specific for MPO could cause glomerulonephritis and vasculitis in mice. More recently, Little et al. (13) in our laboratory reported a rat model of experimental autoimmune vasculitis that is induced by immunization with MPO. They showed that the MPO-ANCA produced might augment leukocyte-microvascular interactions in vivo and lead to microvascular hemorrhage. Although this does not prove that ANCA are the main pathogenic mechanism in human vasculitis, the argument is increasingly strong.

Although the role of ANCA has remained the main focus of laboratory research in vasculitis, a few groups have investigated the role of autoreactive T cells. Because ANCA are class-switched and antigen-specific autoantibodies, it can be inferred that their production involves T cell help. The presence of autoreactive T cells against PR3 or MPO in patients with systemic vasculitis was reported by several groups in the early 1990s (14,15). Because T cells can be detected in affected tissues from patients with vasculitis, including the granulomas in Wegener granulomatosis, they also may be involved in some way in direct tissue injury. Whether and how remain to be determined.

Has all of this new information about ANCA-associated small-vessel vasculitis made any difference in treatment? I believe that it has, although too slowly. The original regimen of prednisolone and cyclophosphamide, pioneered at the National Institutes of Health (16) and then adapted in various ways, has induced remission in >80% of cases in most series (17,18). However, the adverse effects of long-term cyclophosphamide treatment, including development of malignancies, have become clear (19), and a variety of alternative strategies, including the use of azathioprine, have been introduced for maintenance therapy. Others have attempted early withdrawal of treatment, particularly in patients with MPO-ANCA, because they are significantly less likely to relapse. The association of a rising ANCA titer with clinical relapse is widely accepted (20), and there have been a few studies of preemptive treatment in response to a rising titer (21). Most nephrologists, however, still use ANCA levels only as part of their overall clinical decision making.

Of considerable importance in this era of evidence-based medicine has been the implementation of a number of randomized, controlled trials of treatment. Several of these have been performed by the European Vasculitis Study Group (EUVAS), which has taken the lead in this area. This group has taken the approach of categorizing patients according to disease severity, and examining the effectiveness of both initial induction treatment and longer-term maintenance treatment. For example, Jayne et al. (22) reported that switching from cyclophosphamide to azathioprine at 3 mo, for maintenance treatment in generalized disease, resulted in similar rates of remission and relapse to continuing cyclophosphamide for 12 mo. De Groot et al. (23) reported that methotrexate gave similar rates of remission to cyclophosphamide in early systemic disease but with more relapses. Other soon-to-be-reported EUVAS trials include a comparison of oral and intravenous cyclophosphamide in generalized disease and of plasma exchange and methylprednisolone in severe renal disease. Such activity is not exclusive to Europe, and the Wegener Granulomatosis Etanercept Group from the United States recently reported a trial that showed that etanercept was not effective for maintenance of remission in Wegener granulomatosis (24).

The articles that were chosen for this Frontiers in Nephrology series are intended to cover in more detail the tremendous advances that have been made in our understanding of ANCA-associated systemic vasculitis and glomerulonephritis. In the first of these, Morgan et al., from Caroline Savage’s group, provide an outstanding overview of the subject, from our understanding of pathogenesis through to current approaches to treatment. Jennette et al. then consider the role of ANCA in the pathogenesis of vascular inflammation and, to my mind, make an extremely convincing case. Third, Tipping and Holdsworth consider the role of T cells in crescentic glomerulonephritis. Their excellent review draws on information from various experimental models and human diseases and sheds light on how T cells may contribute both to the autoimmune process and to effector mechanisms. Finally, Feldmann and I take a different approach, considering how lessons learned from other chronic inflammatory diseases might be applied to systemic vasculitis. This idea was based, in part, on the plenary session at last year’s meeting of the American Society of Nephrology, at which Marc Feldmann and Ravinder Maini reviewed the role of TNF and the effects of TNF blockade in rheumatoid arthritis. The extent to which this knowledge can be applied in systemic vasculitis remains controversial.

I hope that this Frontiers in Nephrology series on ANCA-associated vasculitis and glomerulonephritis will bring readers up to date on this fascinating condition, which can present with acute life-threatening disease and go on, in some cases, to become a chronic relapsing and remitting inflammatory disorder that re-
quires long-term management. Despite the excellent work described in these reviews, there is no cause for complacency. We clearly need to understand the pathogenesis better and to develop safer and more effective approaches to treatment. I hope that the next generation of nephrologists (and some of the old hands!) will rise to this challenge.

References