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Editorial

Antiphospholipid Antibodies (aPL) and Thrombotic Microangiopathy for the Diagnosis of aPL Nephropathy: You Can't Have One Without the Other

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In 2003, the title of a paper by Rollino et al asked the following question: "Is it possible to diagnose primary anti-phospholipid syndrome (PAPS) on the basis of renal thrombotic microangiopathy (PAPS nephropathy) in the absence of other thrombotic process?"[1] The authors concluded, in essence, based on their experience with 3 patients and a literature review, that thrombotic microangiopathy (TMA) in the kidney in a patient with antiphospholipid antibodies (aPL) constituted a distinct clinicopathologic entity falling within the spectrum of PAPS. Twenty years later, the study by Barbhaiya et al,[2] in this issue of *The Journal of Rheumatology*, has encompassed this in the term *aPL nephropathy* [*aPL-N*] and makes it evident that, in some ways, the question posed by Rollino et al[1] is still with us.

The study of Rollino et al[1] followed a succession of case reports published through the 1980s and 1990s describing renal microvascular injuries involving glomeruli and terminal portions of the arterial vasculature and arterioles characteristic of TMA in patients with aPL. The article by Rollino et al[1] also followed a landmark study by Nochy et al in 1999 that described a range of acute and chronic pathologic manifestations of TMA in the kidneys of 16 patients with circulating aPL.[3] Many, but not all, of the patients included in the study by Nochy and in the multiple case reports from around that time occurred in patients with systemic lupus erythematosus (SLE), and there remained some consideration of whether there was a separate aPL-mediated TMA distinct from SLE in these earlier studies. In 2006, as part of what has become known as the Sapporo consensus classification, many of these previously reported cases were codified into a proposed diagnostic entity within the broad category of systemic antiphospholipid syndrome (APS).[4] Nephropathy was defined by features of acute and chronic TMA as well as some features of chronic kidney scarring that represent nonspecific sequela of acute and chronic microvascular injury, which may occur as a result of a multiplicity of vascular and nonvascular mechanisms. These latter features indicated focal cortical atrophy and a type of severe tubular atrophy with a particular histologic appearance that pathologists refer to as "thyroidization." These chronic changes in the tubulointerstitium have no direct pathogenic link to aPL and are not currently used as criteria for the pathologic diagnosis of TMA. It became commonly accepted practice to otherwise follow the Sapporo consensus classification[4] and diagnose aPL-N when a renal biopsy demonstrates any of the well-recognized pathologic features of acute or chronic TMA in a patient with circulating aPL, in the absence of clinical data indicative of another superseding etiology.

This definition aligns with the aPL-N characterized in the current study by Barbhaiya et al[2] and with numerous subsequent depictions of TMA in general and aPL-N specifically.[2,4-9] Subsequent to the Sapporo consensus classification,[4] there have been no validated reports of biomarkers that might clinically refine the diagnosis of aPL-N nor have more specific pathologic criteria emerged that would consistently distinguish TMA occurring in patients with aPL from TMA resulting from other etiologies.

With this historical background, an international group of rheumatologists, nephrologists, and a renal pathologist have recently revisited and refined criteria for APS classification, and as part of that effort, a subcommittee was formed with the aim of better and more standardized characterization of aPL-N.[2] Their methodology included a literature review to assess how commonly used descriptors of pathology are applied in practice in making the diagnosis of aPL-N, a review of 23 renal biopsy reports from the international APS Alliance for Clinical Trials and International Networking (APS ACTION) registry, and a

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survey of members of the Renal Pathology Society as to whether these descriptors are sufficient to define aPL-N.[2] It is reasonable to ask what gaps in our understanding have been addressed by this exercise, and how this effort advances our understanding of aPL-mediated kidney disease and/or improves patient care.

At the outset, we must be clear that this study does not break new ground by expanding or altering currently accepted diagnostic criteria for aPL-N. It does not identify new histopathologic features that distinguish aPL-N from those of TMA resulting from multiple other etiologies. It does not change or challenge conventional pathology practice with respect to the diagnosis of aPL-N. The renal pathologists participating in this survey emphasized the importance of knowing recent aPL results to confidently diagnose aPL-N.[2] The majority of the survey respondents were equivocal or lacked confidence in identifying lesions suspicious for aPL-N (ie, TMA) and in making a renal biopsy diagnosis of aPL-N in the absence of a serologic evidence of circulating aPL. Accordingly, the accepted practice for the diagnosis of aPL-N essentially remains unchanged from what it has been for the past 2 decades.

Nonetheless, this study is useful on several levels. The authors provide a carefully assembled list of the important histopathologic descriptors (Table 3 and Table 4 of Barbhaiya et al[2]) that characterize both acute and chronic manifestations of TMA. This list is well detailed, illustrated, and complete, and is likely to be a helpful guide to individuals who have reason to better understand this entity, either for direct patient care or for research endeavors. These descriptors have been endorsed by the survey of a large number of practicing renal pathologists, and this aspect of the study provides a level of validation and robustness to these diagnostic criteria that had not been available previously.

There are some limitations to this study. The classification is exclusively reliant on histologic appearances. As a result, some pathologic features that are commonly encountered in renal biopsies demonstrating TMA and that can be suggestive of this type of injury are not included in this proposed classification of acute and chronic TMA. Examples include the histologic and ultrastructural appearance of glomerular mesangiolysis and the ultrastructural findings of endothelial injury and subendothelial swelling and widening in glomerular capillaries and in arterioles. These features may not have been considered because the authors reviewed renal biopsy reports and not actual biopsies. The conclusions that can be drawn from this approach may be limited in the identification of relevant descriptors because the reporting pathologists either may not have recognized such lesions or may have differed in the amount of descriptive detail routinely included in their biopsy reports. Hence, the 23 biopsy reports may not have been consistent in their description or in the use of terminology. The accuracy of the descriptions was not assessed. It is unknown how many of the pathology evaluations included ultrastructural study of the pathogenic lesions, and whether these were considered helpful or essential in making the diagnosis of aPL-N.

The study by Barbhaiya et al[2] invites consideration of opportunities for future investigations. The features of TMA considered for this study are exclusively those of histologic morphology. That leaves an obvious gap that may be addressed by rapidly evolving technologies focused on the extraction of information present in a renal biopsy that may not be recognizable with traditional light microscopy alone. With the rapid advent of digital pathology and machine learning algorithms, it may be possible to uncover earlier stages of endothelial cell injury in both glomeruli and blood vessels; this may allow earlier or improved diagnosis, or more specific diagnosis among the many causes of TMA. As technologies such as spatial transcriptomics and proteomics evolve, we may be able to uncover molecular signatures within a kidney biopsy that are distinctive and separate one form of TMA from another. These technologies also may allow the identification and distinction of other concurrent injury processes that are contributing to or exacerbating aPL-N in individual patients, such as hypertension or prior existing microvascular disease, in ways not currently possible by histopathologic examination alone. Such precision diagnostics offer the promise of more precisely targeted therapeutic options for individual patients with aPL-N. Examples of omics extraction of potentially important clinical and pathophysiologic information that remains hidden in histologic evaluation of commonly encountered kidney diseases, such as diabetic nephropathy, hypertension-associated nephropathy, and collapsing glomerulopathy, have been reported recently.[10,11]

In summary, the diagnosis of aPL-N continues to rest on the demonstration of features of acute or chronic TMA in patients with aPL. On the basis of these features, we are not yet able to distinguish aPL-N from other forms of TMA in patients without aPL or in patients for whom a serologic test for circulating aPL may be equivocal. The goal of identifying a defined entity of aPL-N that can be recognized by histopathologic features alone still eludes us, but it is a reasonable expectation that this may change in the foreseeable future with the advent of technological advances applicable to precision pathology diagnostics.

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