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Pathological classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis

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Summary

What drives human beings to classify? It seems as if it is within our nature to do so. Clinical classification systems for the systemic vasculitides were composed a long time ago, and they are constantly being revised and altered. The histopathological features of many diseases are so diverse that classification is called for. The histopathological classification for anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis was the culmination of results produced from a number of clinicopathological studies conducted within the European Vasculitis Study Group (EUVAS). The classification scheme has four general categories, named focal, crescentic, sclerotic and mixed. The first three categories are based on the predominance of normal glomeruli, glomeruli with cellular crescents and globally sclerotic glomeruli. The mixed category represents a heterogeneous phenotype of biopsies in which none of the aforementioned features is dominant. Results from a validation study incorporating 100 patients with at least 1-year follow-up showed that the phenotypical order of the four classes corresponded to the severity of renal function impairment. The new histopathological classification for ANCA-associated glomerulonephritis provides a logical structure for the categorization of patients into four subgroups defined according to glomerular features. This classification will be of use for future studies, such as clinical trials.

Keywords: ANCA-associated glomerulonephritis, classification, renal biopsy, systemic vasculitis

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Introduction

> Classification = The act of forming into a class or classes; a distribution into groups, as classes, orders, families, etc., according to some common relations or attributes (http://www.wiktionary.org).

What drives human beings to classify? It seems as if it is within our nature to do so. There are classifications for just about everything: wines (Bordeaux wines, Saint-Emilion wines, Champagne), folk songs (see, for instance, *The Problem of Classification in Folksong Research* by Marcello Sorce Keller [1] and dinosaurs (my 3-year-old son who sets apart the carnivores and the herbivores). Given this drive to classify, one may wonder why we did not devise a histopathological classification for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis earlier. Clinical classification systems for the systemic vasculitides were composed a long time ago, and they are being revised and altered constantly. Their great benefits outweigh their shortcomings, and they come forward to the goals for which all medical classification systems are aiming, carefully summarized by Glassock in 2004 [2]. He proposed that any classification system should be devised such as to: (i) enhance the quality of communication between experts involved in the field; (ii) provide a logical structure for the categorization of groups of patients for epidemiological, prognostic (outcome) or interventional studies (clinical trials); and (iii) assist in the clinical management of individual patients and that, to this extent, categories should be mutually exclusive and predictive of the subsequent behaviour of the disease (prognosis).

Histopathological classifications

The histopathological features of many disease entities are so diverse that classification is called for. In pathology, almost all oncological entities are classified and their classification schemes are related closely to prognosis and clinical

decision-making. Well-known immunopathological classifications are, for instance, the Marsh classification for duodenitis in coeliakie and the classification for labial salivary gland biopsies in Sjögren's disease. Renal diseases were initially lacking behind, but over the past decade a number of classifications have seen the light, which are currently being used in clinical practice. The classification for lupus nephritis is probably the most widely used classification system that, since its first appearance, has undergone several modifications [3]. Other classification systems have been developed recently; for instance, for immunoglobulin (Ig)A nephropathy [4] and diabetic nephropathy [5]. All of them hinge greatly on glomerular features – which is evident given the glomerular nature of these diseases. Proposals for histopathological classification systems were, in some instances, launched by a group of experts who devised the system on the basis of their long-standing experience. In other instances, classification systems emerged together with a clinical validation, as was the case for the new histopathological classification for ANCA-associated glomerulonephritis [6].

Histopathological classification for ANCA-associated glomerulonephritis

The new histopathological classification for ANCA-associated glomerulonephritis was the culmination of results which emerged from a number of clinicopathological studies conducted within the European Vasculitis Study Group (EUVAS). In 1994, an expert panel of renal pathologists was established to evaluate renal biopsies in EUVAS trials. This panel is known as the RENHIS (RENal HIStology) group, and consists of renal pathologists from European centres in France, Italy, Germany and the Netherlands. After the establishment of a scoring protocol containing all relevant lesions which may be encountered in renal biopsies of patients with ANCA-associated glomerulonephritis, this group has worked together for many years in the evaluation of renal biopsies. In all EUVAS trials, renal biopsies were scored independently by two pathologists, and discrepancies were resolved during consensus meetings, allowing for an optimal evaluation to be used in the final analyses of the clinical trials.

Clinicopathological studies evolved from the EUVAS studies through the years have generated a number of consistent findings. In many studies, the number of normal glomeruli emerged as an important parameter related to renal outcome, both at the time of renal biopsy and during follow-up [7–9]. In 2003, an index for the GFR at 1 year after the renal biopsy in ANCA-associated glomerulonephritis was presented, which included the presence of normal glomeruli and of fibrinoid necrosis as the main histological features [8]. Active lesions such as cellular crescents and fibrinoid necrosis were associated with renal function at recovery, in such a way that it was suggested that these lesions

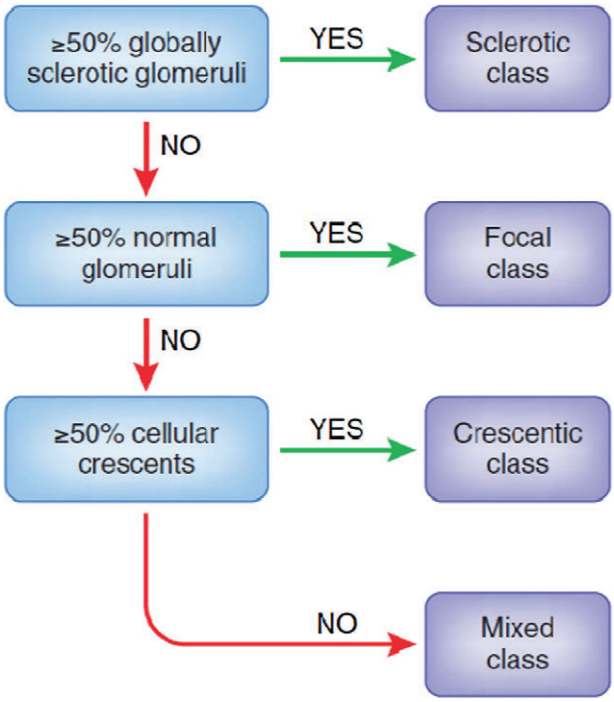

Fig. 1. Classification flowchart. Biopsies should be scored for glomerular lesions in the following order: globally sclerotic glomeruli, normal glomeruli and cellular crescentic glomeruli. Any biopsies that do not fit into one of the categories on the basis of a predominant glomerular phenotype will automatically be included in the mixed category.

may partially recover [10]. These results came from the CYCAZAREM study [11], in which patients with a moderately disturbed renal function at entry were included. In patients with severely disturbed renal function at entry, included in the MEPEX-trial [12], normal glomeruli were a positive predictor of dialysis independence and improved renal function after 12 months, indicative of the unaffected part of the kidney being vital in determining renal outcome [9].

Based on the findings of the previously mentioned studies and others, as well as the knowledge and expertise of an international collaboration of pathologists and clinicians, a classification system for ANCA-associated glomerulonephritis was launched in 2010 [6]. The classification scheme has four general categories, named focal, crescentic, sclerotic and mixed. The first three categories are based on the predominance of normal glomeruli, glomeruli with cellular crescents and globally sclerotic glomeruli, respectively. The mixed category represents a heterogeneous phenotype, and comprises those biopsies in which none of the aforementioned features is dominant. Figure 1 shows a flowchart through which renal biopsies with ANCA-associated glomerulonephritis can be evaluated according to this classification system. Results from a validation study incorporating 100 patients with a minimum of 1-year follow-up showed that the phenotypical

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order of the four classes corresponded to the order of severity of renal function impairment during follow-up. Relatively preserved renal function and favourable renal outcome was found in patients whose biopsy showed a focal class. Biopsies of patients with the highest risk for not recovering renal function typically showed a sclerotic class. A crescentic class was associated with severely reduced renal function but a good chance of recovery. Patients with a mixed phenotype had an intermediate outcome profile.

Conclusion

The new histopathological classification for ANCA-associated glomerulonephritis provides a logical structure for the categorization of patients into four subgroups, which are defined according to glomerular features. This classification may be of use for future studies such as clinical trials. The classification system may enhance the communication between experts in the field, in particular because it is easy to use and its clinical impact has been validated. At present, it cannot be used to assist in the clinical management of individual patients. Hopefully, future studies in different cohorts throughout the world will lead to further refinement of the system.

Disclosure

None.

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