Classification Systems in Renal Pathology
Promises and Problems

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KEYWORDS
• Kidney disease • Renal biopsy • Pathologic classification

ABSTRACT

Kidney diseases are morphologically heterogeneous. Pathologic classifications of renal disease permit standardization of diagnosis and may identify clinical-pathologic subgroups with different outcomes and/or responses to treatment. To date, classifications have been proposed for lupus nephritis, allograft rejection, IgA nephropathy, focal segmental glomerulosclerosis, antineutrophil cytoplasmic antibody -related glomerulonephritis, and diabetic glomerulosclerosis. These classifications share several limitations related to lack of specificity, reproducibility, validation, and relevance to clinical practice. They offer a standardized approach to diagnosis, however, which should facilitate communication and clinical research.

OVERVIEW

Since the introduction of the kidney biopsy to nephrology practice in the 1950s, pathologic diagnosis has played a central role in defining the spectrum of medical kidney diseases and guiding patient management. It was quickly noted that kidney diseases are morphologically heterogeneous, with variable acute (inflammatory) and chronic (fibrosing and sclerosing) lesions that might contribute to the diverse clinical manifestations and variable outcomes in individual patients with the same disease. This observation led to the introduction of semiquantitative grading of pathologic findings and the development of morphologic classifications of renal disease, beginning with the original World Health Organization (WHO) classification of LN in 1974.[1] Morphologic classifications have since been proposed for renal allograft rejection,[2] IgA nephropathy,[3,4] FSGS,[5] diabetic nephropathy,[6] and pauci-immune glomerulonephritis.[7] This review considers the strengths and weaknesses of these pathologic classifications in relationship to clinical practice.

PATHOLOGIC CLASSIFICATION: GOALS AND GENERAL LIMITATIONS

Key Features
GENERAL PROBLEMS WITH RENAL PATHOLOGIC CLASSIFICATIONS

- Pathologic criteria based on expert opinion, not empiric evidence.
- Independence of clinical variables not demonstrated
- Nonspecificity of pathologic findings
- Variable reproducibility
- Imperfect validation studies

The primary goal of any pathologic classification is to identify subgroups of disease that have different natural histories and/or responses to therapy.

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Standardization of pathologic diagnosis is also important for communication and research. An ideal pathologic classification should be biologically plausible and clinically relevant, applicable to all subjects with the disease, reproducible and easy to use, and validated in independent studies. For kidney diseases, morphologic categories should predict clinical outcomes independently of other variables that are known to influence outcome, such as age, race, disease severity, and therapy. Finally, the classification system should be updated periodically, to incorporate new discoveries from clinical and experimental research.

All of the current pathologic classifications of kidney disease suffer from several limitations, including nonspecificity of pathologic findings, inconsistent reproducibility, lack of an external standard to verify pathologic diagnoses, and validation problems. The causes and pathogenesis of most renal diseases are poorly understood but are clearly multifactorial, involving a host of genetic predisposing factors and environmental triggers, which are not the same in all populations. The reproducibility of pathologic classifications is less than perfect,[8–11] reflecting the subjectivity of pathologic diagnosis, even for clearly defined pathologic variables. Sampling error is a problem in small biopsy specimens, and many disease processes have focal or patchy tissue involvement. In addition, segmental lesions (involving less than the entire glomerular tuft) may be missed due to the random orientation of the glomerulus in individual tissue sections. Moreover, exhaustive tissue sectioning is not feasible in routine diagnostic practice. Most pathologic classifications are heuristic, relying on expert opinion rather than empiric or experimental evidence. With the notable exception of the Oxford classification of IgA nephropathy,[3,4] the prognostic significance of pathologic variables has not been shown independent of clinical covariates. In addition, the Oxford classification is the only glomerular disease classification that scores tubulointerstitial lesions, which, together with vascular lesions, have been shown to have predictive value.[12–14] Lastly, morphologic classifications do not include information from genetic, transcriptomosal, and proteomic studies, which might better illuminate the underlying pathogenetic mechanisms.[15]

Glomerular diseases are uncommon and progress slowly and the development of end-stage renal disease (ESRD) is influenced by multiple variables, including demographic and socioeconomic factors (reflecting genetic risk factors and access to medical care), clinical disease severity, presence of comorbid conditions (eg, diabetes and hypertension), and choice of treatment. Therefore, studies with sufficient power to identify the prognostic significance of pathologic variants are difficult to accomplish. In addition, retrospective validation studies are subject to biases, including case selection criteria and choice of therapy, and which limits their generalizability. For individual patients with glomerular disease, morphologic variants have limited relevance to clinical management, with the exception of broad categories, such as proliferative LN.

With these caveats in mind, the individual pathologic classifications of renal disease are reviewed.

LUPUS NEPHRITIS

Key Features

International Society of Nephrology/Renal Pathology Society Lupus Nephritis Classification

- Definitions are not evidence based
- Improved reproducibility compared with earlier classifications
- Definition of segmental lesions requires further study
- Tubulointerstitial and vascular lesions are not incorporated
- Does not include nonimmune complex–mediated glomerular disease

The 2003 International Society of Nephrology (ISN)/Renal Pathology Society (RPS) classification of LN[16] is based on the original 1974 WHO classification,[1] which was previously updated in 1982[17] and 1995.[18] This classification is predicated on the presence of glomerular immune deposits by immunofluorescence microscopy and is categorized based on the light microscopic findings, with a minimum sample size of 10 glomeruli (**Table 1**). Mesangial LN is subdivided into class I (minimal mesangial) and class II (mesangial), depending on the absence or presence of histologically identifiable mesangial expansion. Class III (focal) and IV (diffuse) LN are distinguished based on the percentage of glomeruli demonstrating endocapillary and/or extracapillary proliferative lesions (<50% or $\geq$50%, respectively). Sclerotic glomeruli representing scarred LN are included in the count of proliferative lesions. Class III and class IV are categorized as purely active (A), mixed (A + C), or purely chronic (C). Class IV is further subclassified into segmental (S) or global categories (G), based