A Position Paper on Standardizing the Nonneoplastic Kidney Biopsy Report

Anthony Chang,[*] Ian W. Gibson,[†] Arthur H. Cohen,[‡] Jan J. Weening,[§] J. Charles Jennette,[‖] and Agnes B. Fogo[¶]

Summary

The biopsy report for nonneoplastic kidney diseases represents a complex integration of clinical data with light, immunofluorescence, and electron microscopic findings. Practice guidelines for the handling and processing of the renal biopsy have previously been created. However, specific guidelines for essential pathologic parameters that should be included in these pathology reports do not exist. The Renal Pathology Society has coordinated an effort through the formation of an ad hoc committee to enumerate the essential elements and pathologic parameters that should be reported for every biopsy specimen. This endeavor aims to establish a minimum reporting standard and to improve communication between pathologists and other physicians. This document represents the collective effort and consensus opinions of this ad hoc committee of the Renal Pathology Society.

Clin J Am Soc Nephrol 7: 1365–1368, 2012. doi: 10.1016/j.humpath.2012.04.009

[*]Department of Pathology, University of Chicago Medical Center, Chicago, Illinois; [†]Department of Pathology, University of Manitoba, Winnipeg, Canada; [‡]Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California; [§]Department of Pathology, Erasmus Medical Center Rotterdam, Tergooiziekenhuizen, Hilversum, The Netherlands; [‖]Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, North Carolina; and [¶]Department of Pathology, Microbiology and Immunology, Vanderbilt University, Nashville, Tennessee

Correspondence:
Dr. Anthony Chang, Department of Pathology, University of Chicago Medical Center, Chicago, IL 60607. Email: anthony.chang@uchospitals.edu

Introduction

The biopsy report for nonneoplastic kidney diseases represents a complex integration of clinical data with light microscopy (LM), immunofluorescence (IF), and electron microscopic (EM) findings. In 2004, the Renal Pathology Society (RPS) published practice guidelines for the medical renal biopsy, which primarily addressed specimen handling and processing. These guidelines enumerated many important aspects of the renal biopsy but did not include recommendations for specific elements that should be stated in the final pathology report (1). Multiple classification schemes for specific renal diseases, such as focal segmental glomerulosclerosis (FSGS) (2), lupus nephritis (3), immunoglobulin A (IgA) nephropathy (4), diabetic nephropathy (5), and pauci-immune crescentic glomerulonephritis (6), have been recently established. Although these classifications give nephropathologists guidance with categorization issues, they do not generally enumerate specific pathologic elements that should be reported. In addition, guidelines that may be broadly applied beyond these specific diagnostic entities do not currently exist.

Standardizing nonneoplastic kidney biopsy pathology reports is desirable to improve communication between the pathologist and clinician or clinical team and to minimize the omission of pathologic parameters that may have therapeutic or prognostic importance (7). The reporting guidelines established in this article are applicable for both native and transplant kidney biopsies, but specific requirements that pertain only to the transplant setting have been explicitly stated in the appropriate sections below. It is important to acknowledge that prior efforts by renowned nephropathologists in several renal pathology textbooks have delineated many of the items that should be addressed within the kidney biopsy report (8–11). This position paper builds upon these prior contributions and represents the collective effort and consensus opinions of the RPS ad hoc committee.

We thus recommend that the following headings should be present in all renal biopsy reports. The essential reporting elements are explained within each section and also summarized in the Table.

Clinical History or Data

All relevant clinical history that is provided by the clinician or obtained from an authoritative source should be reported in this section. These data include but are not limited to relevant underlying medical diseases (eg, diabetes and hypertension), therapeutic or medication history, and test results. In particular, the presence and severity of proteinuria and/or hematuria, serum creatinine, and other relevant serologic or laboratory test results should be reported. For allograft biopsies, the date of transplant, cause of end-stage renal disease, and pertinent data of the donor should be stated, if known. The reason for an allograft biopsy, protocol versus clinically indicated, should be given.

Gross Description

The number and length of tissue cores that are submitted for LM, IF, and EM, appropriate fixatives/transport media, should be recorded upon receipt of the biopsy specimen.

Microscopic Description

Light Microscopy

Histochemical stains (eg, periodic acid-Schiff, Jones methenamine silver, Masson trichrome, Congo red) or

Table. Essential pathologic parameters for reporting

- Clinical history/data
  - Brief summary of history provided by clinician or obtained from another authoritative source
- Gross description
  - No. of tissue core(s) for light microscopy and core length(s)
  - No. of tissue core(s) for immunofluorescence microscopy and core length(s)
  - No. of tissue core(s) for electron microscopy and core length(s)
- Microscopic description
  - Light microscopy
    - Histochemical stains (eg, periodic acid-Schiff, Jones methenamine silver, Masson trichrome, Congo red) or IHC performed
    - Presence of cortex/medulla/capsule/calyceal mucosa
    - Glomeruli
      - No. of glomeruli
        - No. of (%) global sclerosis (if present)
        - No. of (%) segmental sclerosis (if present)
        - No. of (%) crescents, cellular to fibrocellular (if present)
        - No. of (%) fibrinoid necrosis (if present)
      - Additional abnormalities (eg, hypercellularity, deposits, thrombosis, double contours, spikes)
    - Tubulointerstitium
      - Extent of interstitial fibrosis/tubular atrophy, at least semiquantitative
      - Interstitial inflammation, tubular injury, crystals
    - Arteries/arterioles
      - Intimal fibrosis (absent/present/severity)
      - Arteriolar hyalinosis (absent/present/severity)
  - Immunofluorescence microscopy
    - No. of glomeruli present
    - No. of globally sclerosed glomeruli
    - Staining intensity, location/pattern of staining for each antibody, and specify intensity scale (0–3+ or 0–4+)
    - Relative intensity of κ/λ staining of tubular casts
    - State when IF performed on paraffin sections
  - Electron microscopy
    - State when EM performed on tissue processed from paraffin sections
    - State whether a sample or all of the submitted tissue examined by toluidine or methylene blue stain
    - No. of glomeruli present in toluidine blue thick sections,
    - No. of globally or segmentally sclerosed glomeruli
    - No. of glomeruli with crescents or necrosis or proliferation
    - No. of glomeruli evaluated by EM
      - Absence or extent of podocyte foot process effacement
      - Absence or presence and location of electron dense deposits
      - GBM thickness (normal, thin, thick) and appearance (eg, layered)
        - If abnormal, state reference range of GBM thickness for age and sex
      - Additional abnormalities (eg, infiltrates, deposit substructure, fibrillary deposits, cellular interposition, tubuloreticular inclusions, fibrin tactoids)
      - Indicate tubulointerstitium was evaluated, specify if tubulointerstitial deposits present
      - Indicate peritubular capillary basement membrane was evaluated (for transplant biopsies), specify if multilayering present (focal *vs* diffuse)

immunohistochemistry (IHC) used for evaluation should be enumerated. Additional step or level sections when obtained to search for focal lesions (eg, FSGS, intimal arteritis) should be reported. The absence or presence of renal cortex and/or medulla and, when appropriate, the presence of surface capsule (particularly relevant to renal allograft biopsy interpretation) and presence of calyceal mucosa should be documented. The rare finding of extrarenal organ-specific tissue, such as liver, pancreas, spleen, or small or large bowel mucosa, should be both documented and treated as a critical value with immediate notification of the clinician.

The report should provide the total number of glomeruli, number of glomeruli that are globally sclerosed (percentages optional), number of glomeruli that are segmentally sclerosed (percentages optional), number of glomeruli with crescents (cellular to fibrocellular, percentages optional), and number of glomeruli with segmental fibrinoid necrosis. Location and nature of glomerular segmental sclerosing lesions (eg, tip, perihilar, cellular, collapsing) should be stated. Additional glomerular abnormalities, such as obvious enlargement, mesangial hypercellularity, mesangial matrix expansion and nodularity, lobulation of the glomerular tuft, diffuse or segmental endocapillary proliferation, duplication or double contours of the glomerular basement membranes (GBMs), epimembranous "spike" formation, or thrombi, should be noted.

The extent and pattern of interstitial fibrosis and tubular atrophy are important pathologic prognostic parameters, and a semiquantitative (or quantitative) assessment (mild [<25%], moderate [26%-50%], severe [>50%]) should be

reported. The extent, distribution, and character of interstitial inflammation and interstitial edema should be reported. Tubular epithelial injury should be recorded, including features such as cytoplasmic vacuolization, sloughing of cells, or loss of brush borders. The presence and character of tubular casts (proteinaceous, Tamm-Horsfall protein casts, "myeloma" casts, red blood cell, or white blood cell casts) should be documented. Tubular or interstitial crystalline deposits should be determined. In renal allograft biopsies, interstitial inflammation, interstitial edema, interstitial hemorrhage, viral inclusions, microvascular inflammation (glomerulitis and peritubular capillaritis), and severity of lymphocytic tubulitis should be documented.

The absence or presence of arteriolar hyalinosis and its pattern (nodular versus circumferential) should be stated. Presence of arteritis (intimal versus transmural) and vascular fibrinoid necrosis should be reported. The severity of arterial intimal fibrosis (arteriosclerosis) in the most affected vessel and overall severity should be assessed semi-quantitatively as mild (<25% narrowing), moderate (26%-50% narrowing), or severe (>50% narrowing). The findings of a Congo red stain for amyloid should be documented, including the specific location of amyloid deposits. Photomicrographs when used should supplement but not replace the microscopic description.

Immunofluorescence Microscopy

The use of frozen tissue or fixed tissue from the paraffin block for IF or IHC microscopy should be specified. Of note, although most laboratories in the United States perform IF from frozen tissue, when no glomeruli are available in this tissue sample, additional IF may be performed on paraffin tissue sections, and this should be explicitly stated, given that this technique is typically less sensitive compared with the use of frozen tissue (12).

A histologic description of the IF specimen, detailing any lesions, sclerosis, and others, is of particular importance when a small portion of cortex or only renal medulla is available in the sample submitted for LM. Histochemical stains (eg, periodic-acid Schiff, Jones methenamine silver, Congo red) may be used under these circumstances to better assess lesions and should be enumerated. The number of glomeruli, number of globally sclerotic glomeruli (percentages optional), and additional pathologic features, such as segmental sclerosis or crescentic or necrotizing injury, should be documented.

The panel of antibodies that is assessed and staining distribution (glomerular mesangial and/or capillary loop, Bowman capsule, tubular basement membrane, interstitial, and vascular), pattern (finely granular versus coarsely granular versus linear), and intensity should be reported. The IF scoring scale (0-3+ or 0-4+) should be explicitly stated for every report. Any extraglomerular staining distribution should be noted. In allograft biopsies, peritubular capillary staining for C4d is particularly relevant to the diagnosis of antibody-mediated rejection, and diffuse (>50%) versus focal (<50%) staining should be documented. Photomicrographs when used should supplement but not replace the microscopic description.

The results of pertinent positive internal controls should be stated. Internal controls include C3 staining of arterioles, tubular reabsorption droplets staining for κ and λ light chains, and albumin; tubular protein casts staining for IgA; and κ and λ light chains and mesangial C4d staining in allograft biopsies. The relative staining intensity of κ versus λ light chains should be specified, as the diagnoses of monoclonal immunoglobulin deposition disease, light chain–restricted cast nephropathy, or light chain proximal tubulopathy are heavily dependent on this pathologic parameter.

Electron Microscopy

Whether a sample or the entire specimen is evaluated under a light microscope with toluidine or methylene blue–stained sections of the tissue submitted for EM should be noted. The total number of glomeruli present and number of globally sclerotic glomeruli should be stated.

A histologic description of the renal compartments should be included, when the LM is suboptimal, but this description may be abbreviated if the findings are similar to those of the samples submitted for LM and IF. If the paraffin-embedded tissue block is processed for EM study, this should be recorded.

For ultrastructural evaluation, the following features should be stated: number of evaluated glomeruli; the extent, if any, of podocyte foot process effacement; absence or presence and location of electron dense deposits; and GBM thickness (normal, thin, and thick) and appearance (eg, duplication and layered). If the GBM thickness is abnormal, then appropriate measurements (average and range) should be made at high magnification, and reference ranges for age and sex should be stated (and/or may be included in the comment section). For fibrillary deposits, thickness or diameter of fibrils, orientation (random versus organized), and presence of hollow cores should be documented. Presence of endothelial tubuloreticular inclusions should be noted. Evaluation of the tubulointerstitium and any pertinent abnormal findings should be stated. Peritubular capillary basement membranes should be assessed in allograft biopsies. If present, the focal or diffuse nature of multilayering should be noted. Photomicrographs when used should supplement but not replace the microscopic description.

Final Diagnosis

A clear and concise final diagnosis is recommended. Multiple diagnoses may be present simultaneously and should be listed separately. The final diagnosis is the most important aspect of the pathology report, but this is the most difficult to standardize, as pathologists have different styles and preferences.

Diagnostic Comment

This section provides the opportunity for the pathologist to address specific clinical concerns or explain any limitations of the evaluation due to sampling or technical issues. Comparisons with prior kidney biopsy specimens should be stated. The application of any classification scheme (Oxford IgA nephropathy classification, ISN/RPS lupus nephritis, Columbia focal segmental glomerulosclerosis, etc) or use of relevant references (eg, reference ranges for GBM thickness for age and sex) should be cited in this section. For allograft biopsies, the Banff classification lesion

scores can be provided to summarize the important features for diagnosis of graft rejection (13).

Discussion

The pathology report represents a permanent document in the patient's medical record with important therapeutic and prognostic implications. A kidney biopsy report with the essential elements of the microscopic descriptions that have been enumerated in this article should allow the reader to understand fully how the final diagnosis was established. Optimal evaluation relies on interpretation in light of the clinical context, and the pathologist reporting a kidney biopsy is encouraged to discuss the findings with the treating physician. The pathologist is ideally situated to integrate complex morphologic findings, shed light on likely etiology of morphological lesions, and also give important information regarding active or chronic lesions. In patients with sequential biopsies, such as often encountered in patients with lupus nephritis and in the transplant setting or following a course of therapeutic intervention, comparison to previous biopsy material is essential and should also be part of the ideal interpretative biopsy report. Follow-up biopsies after aggressive interventions may require specific analysis of changes in extent and severity of active (eg, proliferative, necrotizing, cellular crescentic lesions) versus chronic lesions (eg, sclerosis, fibrous and fibrocellular crescents, interstitial fibrosis) less apt to respond to further immunosuppression. When individual glomeruli are affected by multiple lesions, it is particularly important to communicate the lesional distribution, so that the extent of unaffected glomeruli is clearly communicated. For instance, in a biopsy with 12 glomeruli, of which 4 have cellular crescents and these same 4 glomeruli also have necrosis and segmental proliferation, care must be taken to communicate that the total number of glomeruli affected with active lesions is 4 and not 12.

Standardization of the biopsy report reinforces the systematic approach to the evaluation of the biopsy and may occasionally increase diagnostic accuracy. For example, when FSGS is a diagnostic consideration for a patient with nephrotic syndrome, the LM description should indicate that additional level sections were performed to exclude FSGS, which may not be present in the initial slides that are processed. All of the glomeruli in the IF specimen should be evaluated under a light microscope with a note of the absence or presence of FSGS lesions. For most EM specimens, only a sample of the submitted tissue is initially processed. Before the diagnosis of minimal change disease is established, the remaining tissue should ideally be stained with toluidine or methylene blue for histologic evaluation. Clinical suspicion of any other focal pathologic lesions (eg, intimal arteritis in an allograft biopsy) should be handled in the same manner. Some of these parameters may also serve as quality indicators. For example, the total length of the specimen for LM that is recorded in the gross description should be similar in the tissue sections on the glass slides. Any significant difference may warrant that additional sections be cut from the paraffin tissue blocks or other additional investigation to resolve the discrepancy.

The College of American Pathologists has established cancer protocols and checklists for every organ system to standardize the evaluation of clinically relevant pathologic parameters in the final pathology report. Within the oncology community, these required reporting elements have important clinical implications regarding therapy and prognosis and potentially are used for inclusion or exclusion in clinical trials. These synoptic reports encourage systematic evaluation and minimize omissions. Therefore, the endeavor to standardize the medical renal biopsy report is of interest to both the nephropathology and nephrology communities. Although this position paper could be transformed into a checklist, we recommend that the essential parameters within the microscopic description be stated in prose rather than as individual bullet points. Standardized reporting elements will facilitate optimal communication and stratification of patients for clinical trials and enhance both current and future care of patients with kidney disease.

Acknowledgments

The authors thank David Salant, MD, and Roger Wiggins, MBBCh, for their suggestions and input as members of the American Society of Nephrology Glomerular Disease Advisory Group.

References

1. Walker PD, Cavallo T, Bonsib SM. Practice guidelines for the renal biopsy. Mod Pathol 2004;17:1555-63.
2. D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. Am J Kidney Dis 2004;43:368-82.
3. Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241-50.
4. Cattran DC, Coppo R, Cook HT, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Kidney Int 2009;76:534-45.
5. Tervaert TW, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010;21:556-63.
6. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol 2010;21:1628-36.
7. Nakhleh RE. Quality in surgical pathology communication and reporting. Arch Pathol Lab Med 2011;135:1394-97.
8. Pirani CL. Evaluation of kidney biopsy specimens. In: Tisher CC, Brenner BM, editors. Renal pathology: with clinical and functional correlations. Philadelphia: J.B. Lippincott; 1994. p. 112-13.
9. Colvin RB. Introduction to renal pathology. In: Colvin RB, editor. Diagnostic pathology: kidney disease. Salt Lake City: Amirsys Publishing; 2011. p. 3-4.
10. Zhou XJ, Laszik Z, Silva FG. Algorithmic approach to the interpretation of renal biopsy. In: Zhou XJ, Laszik Z, Nadasdy T, D'Agati VD, Silva FG, editors. Silva's diagnostic renal pathology. New York: Cambridge University Press; 2009. p. 77-8.
11. Salama AD, Cook HT. The renal biopsy. In: Taal MW, Chertow GM, Marsden PA, Skorecki K, Yu AS, Brenner BM, editors. Brenner and Rector's The Kidney. Philadelphia: Elsevier Saunders; 2012. p. 1006-15.
12. Nasr SH, Galgano SJ, Markowitz GS, Stokes MB, D'Agati VD. Immunofluorescence on pronase-digested paraffin sections: a valuable salvage technique for renal biopsies. Kidney Int 2006; 70:2148-51.
13. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. Kidney Int 1999;55:713-23.

Received: March 2, 2012 **Accepted:** April 11, 2012

Published online ahead of print. Publication date available at www.cjasn.org.

This article is being published cooperatively in the *Clinical Journal of the American Society of Nephrology* and *Human Pathology*.

Correction

Di Iorio B, Di Micco L, Torraca S, Sirico ML, Russo L, Pota A, Mirenghi F, Russo D: Acute Effects of Very-Low-Protein Diet on FGF23 Levels: A Randomized Study. *Clin J Am Soc Nephrol* 7: 581–587, 2012; published ahead of print February 23, 2012, doi:10.2215/CJN.07640711.

The authors would like to report an error in their manuscript. On page 585, line 2, we wrote (using reference 35 as the reference) that beer contains 254 mg/100 ml, Coca-Cola contains 277 mg/100 ml, and red wine contains 848 mg/100 ml of phosphorus. The correct concentrations are as follows: beer, 110 mg/L; cola beverages, 171 mg/L; and red wine, 303 mg/L.

We apologize to the readers for the mistake.

Erratum

Correction

Di Iorio B, Bellasi A, Russo D, on behalf of the INDEPENDENT Study Investigators: Mortality in Kidney Disease Patients Treated with Phosphate Binders: A Randomized Study. *Clin J Am Soc Nephrol* 7: 487–493, 2012; published ahead of print January 12, 2012, doi:10.2215/CJN.03820411. In the Methods section, the following statement should have been included, "We performed a *per protocol* analysis". Figures 2–4 contained incorrect numbers of at-risk individuals at each time period that have been corrected here (see revised figures). However, the results of the Cox regression analyses and the Kaplan-Mayer curves reported in the published paper are correct. In addition, the title to Figure 2 should have more specifically indicated that it illustrates all-cause mortality prior to dialysis initiation because patients were censored from the analysis at the time of dialysis initiation; the revised title is "All-cause mortality **prior to dialysis inception** in patients randomized either to sevelamer or calcium carbonate." In addition, the following statement about the study funding was inadvertently omitted from the published manuscript: This study was not supported by industry and did not receive a grant from any institution. Finally, although the study was a clinical trial, it was not registered in any trial registry.

The authors and editors regret any confusion that might have resulted from these errors.

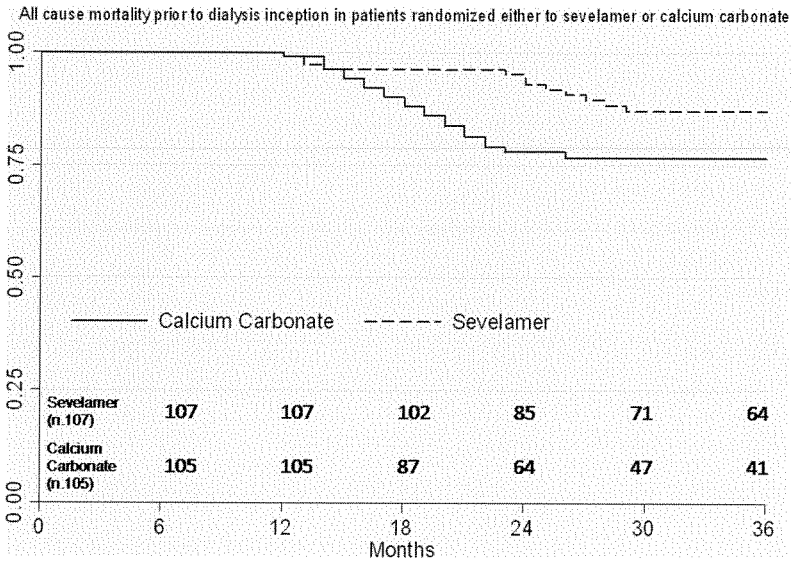

Figure 2. |

