Medical Renal Pathology

Knowledge and Skills Competency Expectations for Anatomic Pathology Residents

Table of Contents

Medical Renal Pathology 1
Knowledge and Skills Expectations for Anatomic Pathology Residents 1
1. Basic Technical Knowledge and Skills Requirements 3
A. Renal Biopsy Adequacy Assessment 3
B. Operation of a Fluorescent Microscope with Interpretation 3
C. Transmission Electron Microscopy (TEM): Specimen Preparations and Interpretation 4
D. Operation of a microscope-associated digital camera and image storage 5
E. Technical Knowledge and Skills Summary 5
2. Medical Renal Biopsies 7
A. Triage for External Interpretation (i.e., Send-Out) 8
B. Assessment of medical renal biopsies: In-House Assessment 9
3. Renal Biopsy Assessments Associated with Renal Transplantation 10
A. Transplant Adequacy Assessment 12
B. Post-Transplantation Assessment 13
4. Assessment of the Non-Neoplastic Portion of a Renal Excision 14
5. Assessment of the Kidneys at Autopsy 16
A. Medical Record Review and Clinicopathologic Correlation 18
B. Grossing 18
C. Microscopic Evaluation 19
D. Autopsy Reporting 21

1. Basic Technical Knowledge and Skills Requirements

A. Renal Biopsy Adequacy Assessment

The practitioner should be able to assess the adequacy of the biopsy while preserving the integrity of the specimen. A variety of methods may be used including the use of a dissecting microscope, traditional microscope or hand lens, with attention given to not drying the specimen or introducing artifacts.

Knowledge and Competency Targets:

- To understand what constitutes an adequate renal biopsy
- To recognize the medulla and cortex in a renal biopsy
- To determine if a renal biopsy is adequate.

Rationale: The magnified visualization of a renal biopsy is important for determining adequacy. This is particularly important if the biopsy is not going to be processed and assessed on site but rather sent to an external laboratory for interpretation. This may be accomplished by various methods, as denoted above, with attention given to maintaining the integrity of the specimen.

B. Operation of a Fluorescent Microscope with Interpretation

Knowledge and Competency Targets:

- To understand the operations of a fluorescent microscope
- To appropriately operate a fluorescent microscope

- To recognize and localize basic immunofluorescent patterns associated with renal diseases
- To differentiate background and non-specific staining from disease-associated immunofluorescence.

Rationale: Fluorescent microscopy uses modifications of the skill sets employed in light microscopy. Fluorescent microscopy is selectively used in the assessment of kidney biopsies, skin biopsies, ANCA and similar tests, and microbiology, so it is a skill set that pathology residents should gain.

C. Transmission Electron Microscopy (TEM): Specimen Preparations and Interpretation

Knowledge and Competency Targets:

- To understand when TEM should be used in the assessment of kidney tissue.
- To understand the fixative(s) to preserve tissue for TEM.
- To understand the importance of screening thick (also referred to as 'semi-thin', 'survey' or 'scout') sections prior to TEM.
- To screen thick sections for adequacy for TEM.
- To recognize the basic ultrastructural anatomy and pathologic findings present in transmission electron micrographs

Rationale: TEM is an important technique used for the assessment of a variety of diseases that involve the kidneys. Although residents and fellows usually do not need to perform the TEM, it is important that they understand how to fix tissues appropriately for TEM, review thick sections for adequacy to determine the optimal areas for TEM analysis, and to recognize basic ultrastructural microanatomy and the ultrastructural features associated with the diseases for which this methodology is employed.

D. Operation of a microscope-associated digital camera and image storage

Knowledge and Competency Targets:

- To understand the functions of the microscope-associated digital camera, including ways to optimize image capture, adjust image quality, and store images.
- To obtain high-quality digital images with light microscopy and immunofluorescence
- To adjust, label, store, and retrieve digital images from a database

Rationale: The capture of digital images is important for a variety of applications. These images may be incorporated into patient reports, used for interdepartmental conference presentations, and for needed for publications.

E. Technical Knowledge and Skills Summary

1. The trainee should first understand which portions of a renal biopsy or excision, and the quantity thereof, that are necessary for an adequate evaluation. This is important regardless of whether the specimen will be processed and evaluated onsite or sent to a reference laboratory. The importance, however, is elevated if the specimen is to be evaluated in a remote laboratory, since the sending of an inadequate specimen will cause a delay in the diagnosis. In some instances, the suboptimal assessment can make a complete and accurate diagnosis difficult or impossible to achieve.

The ability (i.e., skill) to gross renal biopsies and excision specimens follows an understanding of the issues important for the pathologic assessment of these specimens. An understanding of the fixatives that should be used to preserve renal tissue for subsequent studies is critical, which includes immunofluorescence and TEM studies, since inappropriate fixation can lead to suboptimal or uninterpretable results.

The pathologist-in-training who is evaluating renal biopsies or tissues from excision specimens should recognize the basic renal morphologic patterns by light microscopy. They should also recognize basic renal morphologic features by immunofluorescence and become familiar with basic ultrastructural anatomy and pathologic findings present in transmission electron micrographs that correlate with important renal diseases.

The sections that follow include specific material that covers four very important areas in renal pathology. These are 1) The handling of Medical Renal Biopsies, 2) Renal Biopsy Assessments associated with Renal Transplantation, 3) Assessment of the Non-Neoplastic Portion of a Renal Excision, and 4) Assessment of the Kidneys at Autopsy. The pathologist-in-training should use the overview provided here in conjunction with renal pathology texts and other high-quality study materials in preparation for the appropriate handling of renal tissues in practice, as well as in preparation for their certification examinations.

2. Medical Renal Biopsies

Introduction:

Medical renal biopsies are obtained to evaluate intrinsic (i.e., non-transplant, non-neoplastic) renal diseases and are often pursued in the setting of unexplained acute or chronic kidney dysfunction, proteinuria, hematuria, or systemic diseases with known renal involvement. These biopsies are essential for establishing a definitive diagnosis, guiding management, and contribute to the determination of prognosis. Proper handling and triage of renal biopsy tissue are critical to ensure that adequate material is submitted for light microscopy, immunofluorescence, and transmission electron microscopy. Pathologists must integrate microscopic findings with clinical and laboratory data to provide a comprehensive interpretation. Given the complexity and diversity of medical renal diseases, a systematic approach to biopsy evaluation—

emphasizing pattern recognition and clinicopathologic correlation—is essential for accurate diagnosis and effective communication with the clinical team.

Knowledge and Competency Targets:

A. Triage for External Interpretation (i.e., Send-Out)

- To understand the importance of specimen adequacy for external interpretation
- To determine the adequacy of the specimen for send-out interpretation
- To understand how to gross a specimen(s) to be sent for external interpretation
- To gross a specimen(s) to be sent for external interpretation
- To understand the appropriate fixative for a specimen to be sent for external interpretation according to the test(s) ordered.
- To appropriately fix the specimen to be sent for external interpretation according to the test(s) ordered.

Note: Trainees who train in programs without on-site renal biopsy assessment are required to have the same knowledge and skills as trainees with on-site renal biopsy assessment.

- To study and understand the pathogenic mechanisms of diseases of the kidney
- To understand the microscopic findings possible in the renal biopsy/biopsies

- To describe the microscopic findings in the renal biopsy/biopsies, which include immunofluorescence and transmission electron microscopy findings, if these studies are performed.
- To correlate relevant clinical laboratory findings with renal pathology
- To provide a differential diagnosis based on clinical, laboratory, and pathologic findings
- To describe/follow an algorithmic pathway to secure a diagnosis
- To understand the necessary components of a renal pathology report.

B. Assessment of medical renal biopsies: In-House Assessment

- To study and understand the pathogenic mechanisms of diseases of the kidney
- To understand the importance of a renal biopsy specimen(s) adequacy
- To determine the adequacy of a renal biopsy specimen(s) for interpretation
- To understand how to gross a renal biopsy specimen(s)
- To gross the renal biopsy specimen(s)
- To understand the microscopic findings possible in the renal biopsy/biopsies
- To describe the microscopic findings in the renal biopsy/biopsies, which include immunofluorescence and transmission electron microscopy findings, if these studies are performed.
- To correlate relevant clinical laboratory findings with renal pathology

- To provide a differential diagnosis based on clinical, laboratory, and pathologic findings
- To describe/follow an algorithmic pathway to secure a diagnosis
- To understand the necessary components of a renal pathology report.
- To create a renal biopsy report

3. Renal Biopsy Assessments Associated with Renal Transplantation

Introduction:

The kidney is the most commonly transplanted organ [1]. For patients with end-stage renal disease, a kidney transplant can reduce their risk of mortality and improve their quality of life [2]. A person can choose to donate their kidney after their death (i.e., deceased-donor) or during their lifetime (i.e., living-donor). The recipient of the allograft will benefit tremendously from either type of donation, but histologic evaluation of the allograft prior to or at the time of transplant differs between the two types.

For a deceased-donor kidney transplant (DDKT), an intraoperative interpretation (i.e., frozen section) with H&E-stained slides may be performed prior to transplantation for immediate interpretation to aid in the decision to determine if the kidney is suitable for transplantation. Factors assessed include the extent of glomerulosclerosis, interstitial fibrosis and tubular atrophy (IFTA), vascular disease, or the presence of other pathologic findings (e.g., diabetic glomerulopathy) that could impact graft function and survival. Areas of necrosis or possible neoplasia should also be recognized and reported.

Living-donor kidney transplants (LDKT) may be biopsied at the time of transplant (i.e.,"time-zero biopsy") to assess the "baseline" status of the transplant; in this situation, the decision to use the organ for transplantation has already been made. The evaluation of these biopsies is similar to that of DDKT specimens but usually without intraoperative consultation (i.e., frozen sectioning). Exceptional care should be taken during evaluation of LDKT specimens to exclude subtle or early pathologic processes that may not have been detected during pre-transplant donor evaluations but could impact the donor and/or recipient. Additional studies such as special stains, immunofluorescence, and transmission electron microscopy should be performed on LDKT specimens if the concern for a medical renal condition arises.

Once the allograft has been successfully transplanted, the clinical team will continue to monitor the patient's progress and graft function through regular visits and laboratory testing. An allograft biopsy may be performed if the clinical history and laboratory values suggest allograft dysfunction. These values may include elevated serum creatinine, the development of donor specific antibodies (DSA), an increase in circulating allogeneic (i.e., donor-derived) cell-free DNA, and urine abnormalities. Depending on the clinical presentation and time from transplantation, a limited (i.e., "C4d-only") or full medical renal (i.e., full immunofluorescence panel and electron microscopy) evaluation can be performed. A "C4d-only" work-up consists of H&E and special stained slides along with C4d immunofluorescence performed on frozen tissue. This work-up is used primarily to exclude rejection and can usually be performed on allografts that were transplanted less than one year ago, have no significant proteinuria,

and there is no concern for a recurrence of native disease. This work-up requires most of the glomeruli identified under the gross dissecting microscope to be triaged for light microscopy. A small amount of cortex with a few glomeruli can be submitted for frozen sectioning and C4d immunofluorescence staining. Cases that do not meet these clinical criteria should be handled (including gross examination and triage) as native kidney specimens with the addition of C4d staining on the immunofluorescence panel. Once the tissue has been appropriately triaged and processed, the biopsy should be evaluated to determine the cause of renal dysfunction.

In allografts, rejection is usually the primary concern and the presence or absence of acute cellular and/or antibody mediated rejection should be determined based on the most recent grading criteria (i.e., Banff Classification). Additional causes of renal injury including infections, recurrence of native disease, de-novo renal diseases, and medication-associated changes should also be excluded. The extent of chronic injury, including features of chronic rejection, IFTA, vascular changes, should also be documented.

Knowledge and Competency Targets:

A. Transplant Adequacy Assessment

- To study and understand the pathogenic findings that may preclude kidney transplantation
- To understand the importance of a renal biopsy specimen(s) adequacy
- To determine the adequacy of a renal biopsy specimen(s) for interpretation
- To understand how to gross a renal biopsy specimen(s)

- To gross the renal biopsy specimen(s)
- To prepare the specimen for the requested assessment, including intraoperative consultation and appropriate fixation.
- To describe the microscopic finding in the renal biopsy/biopsies

B. Post-Transplantation Assessment

- To study and understand the pathogenic findings associated with kidney transplantation
- To understand the importance of a renal biopsy specimen(s) adequacy
- To determine the adequacy of a renal biopsy specimen(s) for interpretation
- To understand how to gross a renal biopsy specimen(s)
- To gross the renal biopsy specimen(s)
- To understand which histochemical, immunohistochemical, molecular, and other studies are necessary to achieve the diagnosis.
- To order the appropriate histochemical, immunohistochemical, molecular, and other studies necessary to achieve the diagnosis.
- To accurately interpret the histochemical, immunohistochemical, molecular and other studies used to achieve the diagnosis.
- To understand the classification of rejection patterns in kidney transplant biopsies
- To recognize and appropriately classify rejection patterns in kidney transplant biopsies

- To understand the types of infections and other diseases common in renal biopsies from kidney transplant recipients.
- To recognize and characterize infections and other diseases common in renal biopsies from kidney transplant recipients.

4. Assessment of the Non-Neoplastic Portion of a Renal Excision

Introduction:

The preservation of renal function is critical in optimizing clinical outcomes for patients with renal masses. Advances in nephron-sparing surgical techniques have resulted in a 5-year survival for T1 tumors that approaches 100%. Evaluation of the non-neoplastic kidney parenchyma is important in the management of patients with renal masses. It is important to thoroughly characterize the non-neoplastic portion of a renal excision, as up to 25% of tumor nephrectomies contain benign neoplasms (e.g., oncocytoma, angiomyolipoma, etc.). This assessment should also denote various non-neoplastic kidney diseases, such as evidence of diabetes, arterial hypertension, nephrotoxic substances, tubulo-interstitial nephritis, amongst others.

The resident should also be able to distinguish these abnormalities from damage to non-neoplastic parenchyma by direct pressure from adjacent tumor (particularly for partial nephrectomies, where non-neoplastic tissue distant from tumor may be limited) or hydronephrosis due to obstruction of urinary outflow by tumor (most common with urothelial carcinomas involving the renal pelvis or ureter).

Knowledge and Competency Targets:

- To understand how to gross an excised kidney
- To gross an excised kidney and obtain and process tissue for appropriate evaluation
- To study and understand the features of the major diseases that may be present in an excised kidney.
- To describe the microscopic finding in the non-neoplastic portions of the kidney
- To correlate the microscopic findings in the renal tissue with clinical history and relevant clinical laboratory findings
- To provide a differential diagnosis based on clinical, laboratory, and histopathologic findings
- To describe/follow an algorithmic pathway to secure a diagnosis, to include appropriately ordered histochemical, immunohistochemical, molecular, and other studies necessary to achieve the diagnosis.
- To order the appropriate histochemical, immunohistochemical, molecular, and other studies necessary to achieve the diagnosis.
- To accurately interpret the histochemical, immunohistochemical, molecular and other studies used to achieve the diagnosis.
- To integrate the non-neoplastic renal pathology findings into the surgical pathology report

The resident should be able to identify and quantify common abnormalities and know when to advise urologists to seek additional consultation with nephrology, since this is not a routine aspect of renal mass management. These include:

A. Diabetic nephropathy

(e.g., diffuse/nodular mesangial sclerosis, arteriolar hyalinosis)

B. Crescentic and immune complex-mediated glomerulonephritis

C. Segmental or global sclerosis

D. Tubulo-interstitial disease

(e.g., to include the evaluation of interstitial fibrosis with tubular atrophy)

E. Vascular disease

(e.g., arterio- and arteriolosclerosis, thrombotic microangiopathy (TMA), vasculitis, atheroemboli)

F. Ischemic glomeruli

5. Assessment of the Kidneys at Autopsy

Introduction:

The review of the premortem clinical evaluation of the kidney function of the patient is imperative. This is accomplished through review, at a minimum, of creatinine, urea

nitrogen, electrolytes, complete blood count and urinalysis both prior to death and at a point of prior health, to understand any trend in renal function. In certain clinical scenarios, other laboratory findings may be relevant, in particular autoantibody serologies and serum/urine protein electrophoresis.

The gross and microscopic evaluation of the kidneys examined during a hospital autopsy is critically important to understanding the comprehensive medical condition of the patient at the time of death. The objective is to determine baseline renal function through a microscopic analysis and clinical correlation, and to search for overlying acute kidney injury patterns brought about during the illness and treatment prior to death. Frequently the kidney suffers chronic injury from systemic diseases such as arterio/atherosclerosis, diabetes mellitus, collecting system dysfunction from tumor, nephrolithiasis, infections, and autoimmune diseases. Kidney failure, in some instances, due to another specific underlying etiology may be the cause of death.

The kidney should be examined grossly with attention to the four major compartments – the vascular supply, the urinary collecting system, and the renal cortex and medulla. The findings within each compartment should be descriptively documented and any lesions should be sampled for microscopic analysis utilizing digital photography. Sections of the cortex and medulla should be routinely submitted. The microscopic examination of the kidney similarly involves assessment of these compartments with further subclassification into the examination of glomeruli, tubules, interstitium, vasculature and collecting system. This is best performed with the addition of the Periodic acid-Schiff (PAS), Jones methenamine silver, and Masson trichrome

histochemical stains. The result of the gross, microscopic and clinical examination will determine if ancillary renal pathology studies are relevant, such as immunofluorescence and electron microscopy.

Knowledge and Competency Targets:

A. Medical Record Review and Clinicopathologic Correlation

- To understand the salient features to extract from a medical history review.
- To perform a medical record review to evaluate kidney function
- To document the baseline renal function throughout the clinical course of the patient.
- If applicable, to establish a hypothesis for underlying chronic kidney disease and to document most likely etiology.
- If applicable, to establish a hypothesis for acute injury and document the most likely etiology. These include, but are not limited to:
    - Periods of hypotension / resuscitation
    - Issues related to sepsis or other infections
    - Medications administered and changes in renal function

B. Grossing

- To study and understand the anatomy of the kidney, including the vascular supply, and collecting system.
- To review and understand the implications of allograft anatomy, ureteral stents / nephrostomy tubes, Ileal bladder conduit, etc.

- To perform a thorough gross examination following comprehensive dissection of the kidneys, bladder and collecting system
- To recommend the best autopsy technique for the comprehensive postmortem examination, which, if applicable, will include examination of the allograft
- Recognize, at minimum, the following specific gross examination of autopsy kidney
    - Cysts (location, size, number, inner contour / contents)
    - Vascular stenosis / thrombosis
    - Ureteral caliber, hydroureter/hydronephrosis / renal papillae / nephroliths
    - Cortex thickness
        - Surface color (pale/congested/flea bitten);
        - contour (granular / pitted)
    - Bladder/prostate (if applicable) examination may be relevant to ureteral issues (e.g., infection, neoplasia, etc).

C. Microscopic Evaluation

- To study and understand the microscopic components of the kidney that should be evaluated.
- To perform a thorough microscopic examination of the microscopic compartments of the kidney.
- To determine if ancillary studies are needed

- If applicable, order, interpret, and document of the finding of ancillary studies.
- Microscopic analysis should include:
    - Vascular compartment examination at the arterial and arteriolar level (e.g., stenosis, fibrinoid necrosis, atheroemboli clefts, amyloid, hyalinosis)
    - Cortex
        - Glomeruli – Number of globally sclerosed, nodular glomerulopathy, fibrin microthrombi, glomerulitis
        - Tubular compartment – autolysis vs true tubular injury, cast description (hyaline/granular/paraprotein/red cell) vacuolar changes (hypokalemia, hyperglycemia, osmotic states), proteinuria, chronicity of tubular atrophy, signs of ascending infection, tubulitis (transplant), opportunistic infections, calcifications/crystals (phosphate/oxalate)
        - Interstitium – chronicity of fibrosis, microvasculature (transplant), amyloid, interstitial inflammation
    - Medulla
        - Tubules
        - Interstitium
        - Transition to collecting system
    - Collecting system

- Epithelium for infection/neoplasia/reactivity

D. Autopsy Reporting

1. Provisionals Anatomic Diagnosis Documentation

Knowledge and Competency Targets:

- To document the gross pathologic diagnoses in the provisional anatomic diagnosis of the autopsy report, which includes gross findings pertaining to the kidneys.

2. Final Anatomic Diagnosis Documentation

Knowledge and Competency Targets:

- To document the final gross and microscopic findings in the autopsy report, which includes findings pertaining to the kidneys.
- To provide a *Clinicopathological Correlation and Appropriate Diagnosis and Designation of Renal Disease in Final Anatomic Diagnoses*, within Outline format linkage/hierarchy
    - Cause and effect should be explained (e.g., Each line in the outline linkage should be “due to” something else).
    - Regarding renal pathology, the comprehensive gross, microscopic and clinical correlation should lead to appropriately referencing the kidney disease under the specific disease process (chronic

disease) and potentially separately (acute disease) if renal findings are the result of another body system failure.

Recommended Readings

1) National Institutes of Health, News in Health, monthly newsletter.

https://newsinhealth.nih.gov/2011/03/organ-donation-pass-it

2) Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol. 1998 Nov;9(11):2135-41. doi: 10.1681/ASN.V9112135. PMID: 9808102.

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Working Group Members: Drs. Lois Arend, Anthony Chang, Vivek Charu, Lynn Cornell, Alana Dasgupta, Maura DeJoseph, Mohiedean Ghofrani, David Howell, Nicolas Kozakowski, Gary W. Procop