The percutaneous kidney biopsy is a well-established procedure with minimal morbidity and remains the gold standard for diagnosing any renal disease. Approximately 4,000 pediatric native and transplant kidney biopsies are performed in the United States annually. Pathologic evaluation of either native or allograft kidneys requires a complex integration of the clinical and laboratory data with histologic, immunofluorescence (IF), and ultrastructural findings. Pediatric renal diseases can be roughly divided into the four anatomic compartments (glomeruli, tubules, interstitium, and vasculature). However, injuries simultaneously involving several anatomic compartments are common, especially in advanced stages of any single renal disease or possibly due to two or more unrelated diseases. The common pediatric renal pathologic entities that is encountered by the practicing surgical pathologist or nephropathologist is reviewed.

CONGENITAL NEPHROTIC SYNDROME

Nephrotic syndrome in neonates and infants is due to a variety of inherited or sporadic gene mutations involving the podocytes or visceral epithelial cells.\(^1\) The age at presentation of the nephrotic syndrome can narrow the differential diagnosis. Congenital (<3 months) and infantile (3 months to 1 year) nephrotic syndromes are most commonly caused by mutations in the following genes: NPHS1 (congenital nephrotic syndrome of Finnish type), WT1/PLCE1/LAMB2 (diffuse mesangial sclerosis), and NPHS2 (podocin-induced focal segmental glomerulosclerosis) among others. These disease entities typically present with massive proteinuria and are steroid resistant, leading inexorably to end-stage renal disease (ESRD). There is a wide range of overlapping histologic features, so the definitive diagnosis requires molecular genetic testing.

Congenital nephrotic syndrome of Finnish type (CNF or Finnish nephropathy) is an autosomal recessive disease resulting from homozygous mutations in NPHS1, which encodes nephrin, a slit diaphragm protein. CNF accounts for the majority of cases of congenital nephrotic syndrome worldwide (61%), and the incidence is disproportionately high in Finland. Histologically, the glomeruli can be normal or show mild mesangial
hypercellularity with the development of progressive segmental to global glomerulosclerosis in later stages. There is often microcystic dilatation of proximal and distal tubules (Fig. 3.1), with progressive interstitial fibrosis and tubular atrophy. Electron microscopy (EM) reveals extensive podocyte foot process effacement with normal glomerular basement membranes (GBMs).

Podocin deficiency or podocin-induced focal segmental glomerulosclerosis (FSGS) accounts for 10% to 30% of cases of pediatric steroid-resistant nephrotic syndrome. The age of onset ranges from younger than 1 year of age to adult, depending on the type of NPHS2 mutation, which can be familial or sporadic. The histologic appearance ranges from minimal change disease to FSGS with diffuse podocyte foot process effacement seen by EM.

Diffuse mesangial sclerosis (DMS) is the second most common glomerular pathology found in neonates with congenital nephrotic syndrome and also can present as late as 4 years of age. DMS can be idiopathic or caused by a variety of genetic mutations, including WT1 (Wilms tumor-1, a transcription factor involved in gonad and podocyte differentiation), LAMB2 (laminin β2, associated with Pierson syndrome), and PLCE1 (phospholipase C enzyme). WT1 mutations along with the glomerular finding of DMS can be present in Denys-Drash syndrome, which is characterized by male pseudohermaphroditism and increased risk of Wilms tumor. Therefore, the finding of DMS should prompt investigation for associated genetic mutations and clinical/radiologic exclusion of a renal mass (or Wilms tumor).
In early stages of DMS, histology reveals normal glomeruli with prominent podocytes, which is normal for infants and toddlers. The finding of DMS is different from the matrix expansion that is characteristic of diabetic nephropathy. If DMS were described with current terminology, many of the affected glomeruli would satisfy the current criteria for collapsing glomerulopathy or the collapsing variant of FSGS. These glomeruli can eventually undergo global solidification. By EM, the GBMs can appear thickened and lamellated, which can be reminiscent of Alport hereditary nephritis. There is also variable podocyte foot process effacement.

MINIMAL CHANGE DISEASE

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children that usually presents with abrupt onset of nephrotic syndrome, which can be accompanied by microscopic hematuria or renal dysfunction. MCD is characterized by a diffuse podocyte injury, but the pathogenesis of MCD remains poorly understood. Secondary forms of MCD associated with medications or neoplasia are more common in adults. Pediatric nephrotic syndrome is often presumed to be MCD and treated empirically with steroids and generally good response to therapy. Kidney biopsies are performed when a patient is steroid resistant to exclude other diseases.

By histology, the glomeruli are normal with delicate GBMs (Fig. 3.2). Tubular atrophy or interstitial fibrosis also should be absent, and the presence of any tubulointerstitial scarring should raise a suspicion for FSGS,
which may not be present in the biopsy sample. In such cases, additional serial tissue sections should be evaluated by light microscopy to exclude the presence of FSGS. In MCD, no immune complexes are detected by IF or EM. The ultrastructural examination shows extensive effacement of the podocyte foot processes (Fig. 3.3), and the absence of a diffuse podocyte injury is incompatible with a diagnosis of MCD.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS

FSGS is the most common cause of nephrotic syndrome in adults but accounts for 10% to 20% of the nephrotic syndrome in children. FSGS may be primary (idiopathic) or secondary to genetic mutations, viral infections, drugs, or structural–functional adaptations. The clinical presentation of FSGS is similar to MCD with abrupt onset of the nephrotic syndrome, which may be associated with renal insufficiency, hypertension, and/or microscopic hematuria. FSGS is often less responsive to corticosteroid therapy than MCD, and approximately 40% to 60% of patients develop ESRD within 10 to 20 years of disease onset. There is also a high rate of recurrence following transplantation, developing in 30% of allografts.

FSGS is characterized by an increase in matrix, hyaline, or inflammatory cells that obliterate the glomerular capillary lumens, which may have either segmental or global involvement. These lesions are characterized by solidification of the glomerular capillary tuft with hyaline accumulation, sometimes

FIGURE 3.3 Diffuse effacement of the podocyte foot processes (arrows) as seen in EM is characteristic of MCD. The GBMs have normal thickness and architecture, and there are no electron-dense deposits.
with adhesion to Bowman capsule. Intracapillary foam cells within glomeruli may be the predominant lesions in the tip or cellular variant and glomerular sclerosis is not required to establish the diagnosis of the tip or cellular variants of FSGS. Therefore, some FSGS variants are neither segmental (collapsing variant) nor sclerotic (cellular or tip variant), and advanced phases of disease are not limited to being focal (involving <50% of the total glomeruli). Adequate sampling is important because as the name suggests, the glomerular lesions can be very focal; FSGS can be diagnosed based on a single glomerulus. By IF microscopy, nonspecific trapping of immunoglobulin M (IgM) and C3 can be observed in the areas of glomerular sclerosis. This focal or irregular staining distribution argues against an immune complex–mediated injury, which typically has diffuse and global glomerular involvement. EM shows variable but often extensive effacement of the podocyte foot processes.

The Columbia FSGS classification recognizes the following five variants: 1) tip, 2) perihilar, 3) cellular, 4) collapsing, and 5) not otherwise specified (NOS). The tip variant has the best prognosis because it behaves like MCD and is characterized by a cellular lesion (usually with foamy macrophages) involving less than 50% of the glomerulus or a sclerotic lesion involving less than 25% of the glomerulus adjacent to the urinary pole. These lesions show herniation or confluence of the glomerular capillaries with the epithelial cells at the origin of the proximal tubule (Fig. 3.4). The cellular variant shows endocapillary hypercellularity, which can include foam cells, leukocytes, and occasionally pyknotic or karyorrhectic

**FIGURE 3.4** The tip variant of FSGS occurs at the urinary pole (or tip of the glomerulus) with prominence of the podocytes and intracapillary foam cells (white arrow) (Jones methenamine silver).
debris, and has an intermediate prognosis between that of the tip and collapsing variants. The perihilar variant has segmental sclerosis involving the vascular pole and is frequently seen in secondary forms of FSGS. The collapsing variant of FSGS or collapsing glomerulopathy is considered the most aggressive variant with the worst prognosis. This pattern of injury has been variably associated with viral infections, particularly HIV and parvovirus B19; autoimmune diseases including systemic lupus erythematosus; and drugs/medications, specifically pamidronate. At least one glomerulus must show global or segmental collapse of the capillary tuft with overlying podocyte hyperplasia (Fig. 3.5). As previously mentioned, collapsing FSGS is essentially identical to DMS, and this finding in a young pediatric patient should trigger the appropriate genetic and imaging studies.

IgM nephropathy and C1q nephropathy are two additional entities that may be considered variants within the spectrum of podocyte injury seen in MCD and FSGS. Both are associated with steroid resistance and higher risk of disease progression. Either entity can have normal glomeruli (typical of MCD) or segmental glomerulosclerosis (similar to FSGS). IF microscopy reveals dominant or codominant mesangial staining with an intensity of at least 2+.

FIGURE 3.5 There is global collapse of the glomerular capillary tuft with podocyte hyperplasia, which is consistent with the collapsing variant of FSGS. This particular glomerulus is from a patient with CNF, but in the proper context, collapsed glomeruli are identical to DMS and should lead to appropriate genetic testing or exclusion of renal masses.
out of 4+ for IgM or C1q (Fig. 3.6) to diagnose IgM nephropathy or C1q nephropathy, respectively. Ultrastructural evaluation also shows mesangial electron-dense deposits and diffuse effacement of the podocyte foot processes.

**MEMBRANOUS NEPHROPATHY**

Membranous nephropathy (MN) is an uncommon cause of nephrotic syndrome in children, which contrasts with adults. Primary MN in adults (70% of cases) is associated with autoantibodies targeting the M-type phospholipase A₂ receptor (PLA₂R), which is expressed on podocytes and proximal tubules.³ However, pediatric MN may involve other antigens because neutral endopeptidase has been identified in a rare form of neonatal MN⁴ or more recently antibodies to bovine serum albumin, which may be due to an immunologic reaction from ingestion of cow milk.⁵

By light microscopy, the GBMs range from normal to marked thickening (Fig. 3.7) with subepithelial “spike” formation or a vacuolated appearance when visualized with a Jones methenamine silver stain. There is no significant mesangial or endocapillary hypercellularity in cases of primary MN. There is diffuse granular IF staining of the capillary walls for immunoglobulin G (IgG) (Fig. 3.8) and κ and λ light chains with variable C3 deposition. In primary MN, IgG₄ is the dominant subclass present in
FIGURE 3.7  The GBMs are thickened with a rigid appearance in this pediatric patient with MN, but definite subepithelial "spike" formation is not present (PAS).

FIGURE 3.8  Granular IgG IF staining along the glomerular capillary walls correlates with subepithelial immune complex deposition in MN. The presence of mesangial staining should raise suspicion for a secondary type of MN.
FIGURE 3.9 EM of MN demonstrates numerous subepithelial to intramembranous electron-dense deposits (arrows) with basement membrane (“spikes”) material between the deposits. There is also extensive effacement of the podocyte foot processes.

the immune complexes. The presence of mesangial or extraglomerular immune complexes favors a secondary type of MN, which includes, but is not limited to, infections (e.g., hepatitis B or C virus, syphilis), systemic diseases (lupus, sarcoidosis), and malignancy. The EM findings for MN can be categorized into four stages as described by Ehrenreich and Churg, but this has not been shown to be an independent prognostic factor. Ultrastructurally, the deposits have a homogeneous electron-dense appearance with extensive podocyte foot processes effacement (Fig. 3.9), but a microspherular substructure has been described in some cases, including the neonatal form of MN involving neutral endopeptidase. The presence of subendothelial or mesangial deposits should raise the suspicion of a secondary form of MN. The subepithelial deposits in postinfectious glomerulonephritis may mimic MN, but the segmental distribution of subepithelial deposits and presence of large subepithelial “humps” can help favor the former diagnosis.

IMMUNOGLOBULIN A NEPHROPATHY/HENOCH-SCHÖNLEIN PURPURA

Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis (GN) throughout the world and is particularly prevalent in some geographic areas including Southeast Asia. Historically known as Berger disease, IgAN occurs in a wide age range, with a peak incidence between 20
and 30 years of age. The onset of disease is usually insidious with asymptomatic hematuria and proteinuria detected on urinalysis, although patients can manifest with nephrotic syndrome and/or acute kidney injury. The pathogenesis of IgAN involves abnormal glycosylation of IgA1 with subsequent mesangial deposition.\(^8\) There is variable disease progression with many pediatric patients showing spontaneous remission,\(^9\) but there is a substantial risk of progression to ESRD, and IgAN tends to recur in kidney allografts.

Henoch-Schönlein purpura (HSP) is a systemic disease that commonly affects pediatric patients, which is also associated with abnormal glycosylation of immunoglobulin A (IgA),\(^10\) and the pathologic renal findings are indistinguishable from IgAN. HSP and IgAN are likely related diseases, and infections often precede the onset of either HSP or IgAN. The extrarenal manifestations of HSP are secondary to vasculitis, including purpura, diarrhea, and arthritis. HSP is usually an acute and self-limiting injury, so its prognosis is generally very good in children, depending on the extent of renal involvement.

The histologic features are highly variable in IgAN/HSP. In a minority of cases, the glomeruli are histologically normal. The most common glomerular finding is mesangial expansion with mesangial hypercellularity (defined as >3 mesangial cell nuclei per peripheral mesangial area, in a 3 micron-thick section) (Fig. 3.10). IgAN can manifest itself as a proliferative GN, with varying degrees of endocapillary hypercellularity, and occasional crescent formation. Crescent formation involving more than 50% of the glomeruli is very unusual and should raise suspicion for a superimposed

![Image of IgAN/HSP histology](image)

**Figure 3.10** Mild segmental mesangial hypercellularity (>3 mesangial cell nuclei per peripheral mesangial area, in a 3 micron-thick section) is characteristic of IgAN (PAS).
pauci-immune crescentic GN. However, crescent formation is much more common in HSP than IgAN. As these diseases evolve, it is common to encounter segmental and/or global glomerulosclerosis. Interstitial inflammation, if present, is usually mild. In HSP, skin biopsy reveals a leukocytoclastic vasculitis and IgA deposits are present in a patchy distribution.

The diagnostic IF finding is dominant or codominant IgA glomerular deposition of at least 1+ staining intensity that is predominantly mesangial in distribution with variable capillary wall involvement (Fig. 3.11). This is usually mirrored by less intense staining for IgG, C3, and κ and λ light chains (λ usually staining more intensely than κ). Fibrinogen/fibrin often highlights cross-linked fibrin degradation products that colocalize with the immune complex deposits of IgAN/HSP. C1q staining is unusual and raises the possibility of a lupus or “lupus-like” nephritis.

EM shows many electron-dense deposits in mesangial areas (Fig. 3.12), whereas some subepithelial and/or subendothelial deposits can also be present. The presence of subepithelial “hump”-like deposits should raise suspicion for an IgA-dominant postinfectious glomerulonephritis, which is discussed in the following section. Podocytes can show variable effacement, which may correlate with the extent of proteinuria.

Several histologic classification systems exist for IgAN and HSP. The most current and widely validated system is the 2009 Oxford IgAN classification, which factors the presence or absence of mesangial

![FIGURE 3.11](image_url) The defining feature of IgAN is dominant or codominant IgA IF staining that is predominantly in a mesangial distribution. Staining for λ light chain typically is more intense than κ light chain (not shown).
hypercellularity, endocapillary hypercellularity, and segmental glomerulosclerosis, and the extent of tubular atrophy/interstitial fibrosis. For HSP, the 1977 International Study of Kidney Disease in Children histologic classification is preferred, which established categories primarily based on the degree of mesangial proliferation and extent of crescent formation.

**POSTINFECTIOUS GLOMERULONEPHRITIS**

Postinfectious glomerulonephritis (PIGN) is characterized by an immune complex–mediated glomerular injury following a nonrenal infection. The most well-characterized form of this disease, poststreptococcal GN, presents with abrupt onset of gross hematuria and renal insufficiency between 1 and 4 weeks after an infection by group A *Streptococcus pyogenes* pharyngitis or pyoderma. The identity of the nephritogenic antigen has yet to be determined but is postulated to be cationic with capability to cross the GBM.

The disease is generally self-limited in children, with treatment focused on supportive therapy and antibiotics, and more than 90% of children will regain normal renal function. Poststreptococcal GN continues to be a serious health problem in developing countries, but its incidence is on the decline in industrialized nations. Staphylococcal infections are associated with the variant known as IgA-dominant PIGN, which can be mistaken for IgAN.
The classic appearance of acute PIGN is that of a diffuse and global glomerular injury with abundant circulating neutrophils in the glomerular capillaries (Fig. 3.13) and accentuated lobulation of the glomerular capillary tuft. The GBMs are without duplication, although the subepithelial deposits can rarely be detected on trichrome staining. Cellular crescents, if present, are usually focal. The tubulointerstitium often shows prominent neutrophilic inflammation, which can resemble acute pyelonephritis. Many intratubular red blood cells, or possibly red cell casts, can be seen. In later stages of the disease, with resolution of inflammation, the glomerular alterations are subtle and the diagnosis largely depends on IF and EM findings.

By IF, PIGN typically shows coarse, irregular deposits of IgG (Fig. 3.14) and C3 along the capillary walls in the active stage of the disease, arranged in either a “starry sky” or “garland” pattern, depending on the frequency of the deposits. In the past, the presence of only C3 glomerular staining often raised the consideration of a chronic phase of PIGN. These atypical PIGN cases may overlap with the recently described entity of a C3 glomerulonephritis because many have aberrations in the alternative complement pathway.18,19

In the active phase of PIGN, EM typically reveals scattered large electron-dense deposits (humps) along the subepithelial aspect of the GBM (Fig. 3.15), which do not incite a reaction of basement membrane material (or spike formation). If large humps are not apparent, these cases may be difficult to distinguish from an early stage of MN. In PIGN, mesangial and/or subendothelial deposits are also frequently present.
FIGURE 3.14  IF shows coarsely granular and occasionally confluent staining for IgG and C3 (not shown) along the glomerular capillary walls and some mesangial areas. In resolving PIGN, the deposits are predominantly or exclusively mesangial, and C3 may persist longer than immunoglobulin.

FIGURE 3.15  The characteristic ultrastructural feature of PIGN is the subepithelial electron-dense deposit, also termed "hump" (arrows). A neutrophil is in the glomerular capillary lumen.
MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

Membranoproliferative glomerulonephritis (MPGN) is an entity that has greatly evolved since its first description, which was initially thought to represent a discrete clinicopathologic entity. However, improved diagnostic tools allowed further refinement as more causes of secondary MPGN, such as hepatitis B or C viral infection, cryoglobulinemia, or paraprotein-related renal diseases, were subsequently identified. Primary MPGN often presents in older children and young adults and is more common in Caucasians. Nephrotic-range proteinuria, microscopic hematuria, and hypocomplementemia are usual features. The disease tends to have a chronic, slowly progressive course. Based on recent identification of abnormalities in the alternative complement pathway, Sethi and Fervenza propose to subdivide primary MPGN into either immune complex-mediated or complement-mediated categories as the cases of idiopathic MPGN continue to decrease. These discoveries regarding the importance of the alternative complement pathway initially created the encompassing term of C3 glomerulopathy (discussed in the next section), but the significance is spreading into the realm of primary MPGN as well as some atypical PIGN cases, and it is likely that this will continue to evolve as better understanding and knowledge is gained.

The characteristic histologic findings include accentuation of the lobular architecture of the glomerular tufts with endocapillary hypercellularity and frequent duplication of the GBMs (Fig. 3.16). Inflammatory
or mesangial cells may be present or interposed between the duplicated basement membranes. Progressive glomerular injury will eventually lead to interstitial fibrosis and tubular atrophy. Both IgG and C3 (Fig. 3.17) IF studies reveal capillary wall and mesangial staining in a coarsely granular pattern. C3 IF alone in the absence of immunoglobulin staining favors a diagnosis of C3 glomerulopathy, which is discussed next. In MPGN, ultrastructural examination reveals many discrete electron-dense deposits throughout the glomerulus, primarily in subendothelial and mesangial locations, as well as duplication of the GBMs with cellular interposition (type I; Fig. 3.18). In MPGN type III, there are also abundant subepithelial to transmembanous deposits.

C3 GLOMERULOPATHY

C3 glomerulopathy is a recently established term that encompasses the entities of dense deposit disease (DDD, formerly MPGN type II) and C3 glomerulonephritis (C3GN). The hallmark of these diseases is C3 glomerular deposition in the virtual absence of immunoglobulin and both are associated with dysregulation of the alternative complement pathway.21,22 These disease entities are uncommon and tend to present in childhood and young adulthood. There is typically some degree of both proteinuria and hematuria at presentation, with variable renal insufficiency.
Hypocomplementemia, specifically low C3, is present in a majority of cases of DDD and approximately half of cases of C3GN and should raise suspicion for the presence of C3 nephritic factor (C3NeF), an autoantibody against C3 convertase (C3bBb) that prevents its inactivation. The diagnosis of a C3 glomerulopathy should prompt testing for C3NeF or other described mutations of or antibodies to alternative complement pathway components.

The histologic features of these two diseases widely vary from purely mesangial proliferative changes or variable endocapillary hypercellularity to a membranoproliferative pattern of injury, which typically has a worse clinical course. In DDD, the glomerular and tubular basement membranes can show segmental thickening in areas of complement deposition, with an eosinophilic, refractile, and strongly periodic acid–Schiff (PAS)–positive appearance. Focal crescent formation or an exudative GN can also be seen in either disease.

The IF and EM features of DDD are distinct with segmental ribbon-like staining for C3 along the glomerular and frequently tubular basement membranes, along with granular mesangial staining. In rare cases, this can be accompanied by immunoglobulin or C1q staining. Ultrastructural examination reveals highly osmiophilic dense deposits along the lamina densa of the GBMs, resulting in a very electron-dense appearance, typically in a segmental discontinuous distribution. The deposits lack organized...
substructure. Similar deposits can be seen in the mesangium, along Bowman capsule, and in the tubular basement membranes. In a subset of cases, subepithelial deposits resembling subepithelial humps have been described, which are less dense than the intramembranous deposits.

The IF and EM features of C3GN are somewhat variable. The disease is defined by bright granular C3 staining, typically in the mesangium and occasionally along the glomerular capillary walls with no significant immunoglobulin or C1q staining. By EM, there are amorphous to discrete electron-dense deposits in the mesangium and scattered subendothelial and/or subepithelial deposits. These deposits are less dense than those of DDD.

LUPUS NEPHRITIS

Lupus nephritis (LN) is a major cause of morbidity in patients with systemic lupus erythematosus (SLE), occurring in 50% to 80% of patients during their disease course. There is a strong predilection for disease involvement in young females. The presentation ranges from asymptomatic hematuria and/or proteinuria to nephrotic syndrome, nephritic syndrome, and varying degrees of renal insufficiency.

LN is categorized into six classes according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) Classification of Lupus Nephritis.23 In class I (minimal mesangial) LN, the glomeruli are histologically normal, but mesangial immune complex deposition is detectable by IF only or IF and EM. Class II (mesangial proliferative) LN shows varying degrees of mesangial hypercellularity with mesangial immune complexes. Rare subendothelial or subepithelial electron-dense deposits by EM are permissible for class II LN. Class III (focal) or class IV (diffuse) LN are characterized by proliferative (active) and/or sclerosing (chronic) lesions involving less than 50% or 50% or more of the population of glomeruli, respectively. Proliferative or active lesions include prominent subendothelial “wire-loop” deposits, intracapillary deposits (hyaline “thrombi” or pseudothrombi; Fig. 3.19), endocapillary hypercellularity, cellular or fibrocellular crescents, fibrinoid necrosis, GBM rupture, and karyorrhexis. The sclerosing or chronic lesions include segmental or global glomerulosclerosis, fibrous adhesions, and fibrous crescents. For class IV LN, the glomerular injury is further divided into either a segmental (involving <50% of the glomerulus) or global (involving >50% of the glomerulus) designation. Some studies suggest that segmental glomerular injury may be due to a pauci-immune mechanism.24,25 Finally, class III and IV LN are assigned an additional modifier based on whether the lesions are active (A), chronic (C), or mixed (A/C). Class V (membranous) LN is diagnosed when more than 50% of the glomerular capillary loops in greater than 50% of the sampled glomeruli contain subepithelial immune complex deposits as detected by IF and EM. The histologic features are similar to primary MN (discussed earlier) with the additional feature of mesangial hypercellularity and mesangial immune complex deposition. In addition, class V LN can occur concurrently with
class III or IV LN. Class VI (advanced sclerosing) LN is diagnosed when more than 90% of the glomeruli are globally sclerosed.

Although the ISN/RPS LN classification focuses entirely on the glomerular compartment, variable degree of tubulointerstitial (typically lymphoplasmacytic) inflammation is found in approximately 50% of biopsies. We have observed that the extent of interstitial inflammation often correlates with the presence of tubulointerstitial immune complex deposition. Rarely, prominent tubulointerstitial LN can occur in the absence of significant GN. A number of vascular lesions can occur in SLE patients, including vascular immune complex deposition or thrombotic microangiopathy, which often occurs in association with the presence of antiphospholipid antibodies. Vasculitis without immune deposits is rare, and when present, may be due to a pauci-immune mechanism. Other pathologic entities described in kidneys of SLE patients include podocytopathy,\textsuperscript{26} collapsing glomerulopathy,\textsuperscript{27} and antineutrophil cytoplasmic antibodies (ANCA)–associated crescentic GN.\textsuperscript{28}

In LN, there is “full house” IF staining for all classes of immunoglobulins (IgG, IgA, IgM) as well as complement C3 and C1q. If present, extraglomerular immune deposits are very characteristic of LN and usually stain with at least IgG and C1q (Fig. 3.20). These granular deposits can be seen in the tubular basement membranes, arteries, arterioles, and peritubular capillaries. Also, strong nuclear staining in tubular epithelial cells is the equivalent of tissue “antinuclear antibodies.” By EM, electron-dense deposits can be seen in any intraglomerular or extraglomerular

FIGURE 3.19 Segmental mesangial hypercellularity, variably thickened GBMs, and prominent intracapillary immune complex deposits, also known as hyaline “thrombi” (arrow), are present in this pediatric female patient with LN (PAS).
In addition, characteristic tubuloreticular inclusions can be identified in endothelial cell cytoplasm (eFig. 3.1), both in the glomerular and peritubular capillaries.

**Crescentic GN** is the most severe form of glomerular injury and can be caused by the following three main pathogenic mechanisms, in descending order of frequency in the pediatric population: 1) immune complex mediated, which includes LN, MPGN, PIGN, and IgAN/HSP; 2) pauci-immune, which is often associated with ANCA; and 3) anti-GBM disease. Immune complex–mediated GN is the most common cause of crescentic GN in children and is further discussed in their respective sections. Anti-GBM GN is the least common cause of crescentic GN in both children and adults.

Overall, pauci-immune crescentic GN is much more common in adults, and reports in children are limited to small series and case reports.\(^{29-31}\) Disease onset can occur as early as 2 weeks of age, and females are more frequently affected. Most patients present with renal failure and hematuria. Isolated pauci-immune crescentic GN (renal-limited vasculitis) as well as those associated with systemic vasculitis (granulomatosis with polyangiitis/Wegener, microscopic polyangiitis, and Churg-Strauss syndrome) have been
described in the pediatric population. The renal biopsy findings do not distinguish between the various clinicopathologic conditions. Outcomes vary with some children recovering renal function and others progressing to ESRD.

The hallmark finding is crescent formation in Bowman space, composed of proliferating epithelial cells, neutrophils, and/or macrophages, which is often accompanied by fibrinoid necrosis of the glomerular capillary tuft (Fig. 3.21) and disruption of the GBMs and/or Bowman capsules. The crescents can be categorized as cellular, fibrocellular, or fibrous, which roughly indicates the duration of glomerular injury. The unaffected glomeruli are histologically normal without mesangial or endocapillary hypercellularity. The glomerular changes are accompanied by varying degrees of interstitial inflammation, usually occurring adjacent to the affected glomeruli. In the chronic phase, pauci-immune crescentic GN can mimic FSGS, but typically, some activity in the form of cellular crescents or fibrinoid necrosis is focally present. Also, irregular glomerular scarring and disruption of Bowman capsule can support the diagnosis of pauci-immune crescentic GN. Only a minority of cases will show vasculitis (5% to 35%), which can affect small arteries, arterioles, capillaries, and venules.

There is no or minimal immunoglobulin or complement deposition in the glomeruli (<2+ out of 4+ granular IF staining for IgG, IgA, IgM, C3, and C1q), but chronic sclerosing lesions can show entrapment of immunoreactants, particularly IgM and C3. If there is strong linear staining of the GBMs for IgG and κ and λ light chains, a diagnosis of

**FIGURE 3.21** This cellular crescent due to proliferation of epithelial cells (white arrow) is accompanied by fibrinoid necrosis (black arrow) in a patient with pauci-immune crescentic GN with positive ANCA titers (PAS).
anti-GBM GN should be made. Some patients may have positive titers for both anti-GBM and ANCA and these patients have outcomes that are similar to those with pauci-immune crescentic GN.

The ultrastructural examination may show disruption of the GBM in necrotic segments, associated with fibrin tactoids and increased cellularity. The endothelial cells can appear swollen and injured. Typically, there are no detectable electron-dense deposits, but sometimes rare scattered mesangial or capillary wall deposits can be appreciated.

**THIN BASEMENT MEMBRANE NEPHROPATHY**

Thin basement membrane nephropathy (TBMN) or disease (also known as benign familial hematuria) is an abnormality which is present in up to 2% of the population. It commonly presents with persistent microscopic hematuria but can occasionally be associated with gross hematuria or mild proteinuria. It is usually inherited in an autosomal dominant pattern and can be associated with mutations involving the α3 or α4 chains of collagen type IV. There is no specific treatment, and the prognosis is usually excellent.

By light microscopy, the glomeruli are normal. Bowman space and tubular lumina may contain red blood cells. The diagnosis of TBMN is made by EM and requires uniform thinning of the GBMs. There are several methods for GBM morphometry, including the orthogonal intercept/mean harmonic thickness method. In our experience, the simplest method is to perform at least 30 direct measurements of GBM thickness per glomerulus, measuring the distance from base of the podocyte foot process to the endothelial cell membrane in peripheral capillary loops (excluding tangential sections). Calculation of the arithmetic mean yields the average GBM thickness. In children younger than 9 years of age, there is a linear relationship between the thickness of the GBM and age, so age-specific averages should be used in determining whether the average measured thickness meets the lower limit for diagnosis of TBMN; namely, the estimated lower limit for GBM thickness for males aged X years is \((X/9 \times [250 - 135])\) nm + 135 nm, and for females aged Y years is \((Y/9 \times [215 - 137])\) nm + 137 nm. The ultrastructural evaluation in TBMN shows normal architectural organization of the GBMs without any significant irregularities, such as lamellation or “basket weaving.” Of note, female patients with X-linked Alport syndrome may manifest with only thin basement membranes at a young age, so IF staining for the α3 and α5 chains of collagen type IV would reveal segmental staining of the GBMs in Alport patients, but a normal IF staining pattern for these two antibodies does not entirely exclude Alport hereditary nephritis.

**ALPORT SYNDROME**

Alport syndrome, often referred to as “hereditary nephritis,” is an inherited glomerular disease caused by mutations in the α chains of collagen IV. The most common (85% of cases) mutation involves the α5 chain of
collagen IV (COL4A5) gene, which is located on chromosome Xq26-48 and therefore is inherited in an X-linked pattern. Males are most severely affected and often present with hearing and eye abnormalities, as well as hematuria. Female carriers may show mild disease, depending on the degree of mosaicism. The less common forms of Alport hereditary nephritis result from mutations in the α3 (COL4A3) or α4 chains (COL4A4), which are both located on chromosome 2q35-37 and show an autosomal recessive inheritance pattern or rarely autosomal dominant. In addition to gross or microscopic hematuria, patients with Alport syndrome frequently present with subnephrotic proteinuria, particularly in later stages of the disease. The disease is slowly progressive, with the majority of X-linked males developing ESRD by the age of 40 years. Autosomal recessive disease typically shows a more aggressive course.

By light microscopy, the glomeruli may appear normal or show mild mesangial hypercellularity. With disease progression, there is development of segmental and global glomerulosclerosis. Interstitial aggregates of foamy macrophages correlate with a chronic proteinuric state (eFig. 3.2). There is gradual progression of interstitial fibrosis and tubular atrophy.

There is no significant IF staining for the standard panel of immunoglobulins or complement components. Additional indirect IF microscopy for the α3 and α5 chains of collagen IV can establish the diagnosis of X-linked or autosomal inheritance pattern of Alport nephritis (Fig. 3.22). However, a normal staining pattern does not exclude the diagnosis of X-linked Alport syndrome. The inset illustrates typical collagen IV α5 chain staining in a normal glomerulus.
Alport hereditary nephritis because some mutations involve portions of the α chains of collagen IV that do not affect the epitopes that are recognized by the antibodies that are used for the diagnostic testing.

The ultrastructural findings in Alport hereditary nephritis are characterized by alternating thick and thin segments with multilamellation of the GBM, which imparts a “basket-weave” appearance (Fig. 3.23). Of note, female carriers of the X-linked form of Alport syndrome may manifest with only thin GBMs at a young age.

OXALOSIS

Primary oxalosis, or primary hyperoxaluria, is a rare autosomal recessive disease in which inborn errors of glyoxylate metabolism result in increased endogenous oxalate synthesis by the liver. Systemic calcium oxalate deposition can result in retinopathy, cardiomyopathy, neuropathy, osteoarthropathy, and pancytopenia. Type 1 primary oxalosis is due to alanine glyoxylate aminotransferase gene mutations and manifests in childhood with renal colic and renal insufficiency, which frequently progresses to ESRD. Type 2 primary oxalosis is associated with mutations of the glyoxylate reductase gene and typically manifests a milder clinical course with rare progression to ESRD. The diagnosis is made by assay of enzyme activity in liver tissue, and treatment of type 1 primary oxalosis ultimately requires simultaneous liver and kidney transplantation. Secondary oxalosis, which is much less common in pediatric patients, results from increased absorption of dietary oxalate.
oxalic acid and can be seen in association with gastric bypass surgery, inflammatory bowel disease, short bowel syndrome, ethylene glycol toxicity, excess dietary intake, and rarely vitamin C toxicity.

By light microscopy, calcium oxalate deposits are characterized by translucent to faintly yellow fan-shaped crystals, which are birefringent when viewed by polarization microscopy (Fig. 3.24). Early in the disease course, the crystalline deposits are contained within the tubular lumens and can be associated with proximal and distal tubular cell injury and necrosis. Over time, there is tubular rupture with extrusion of crystals, accompanied by giant cell reaction, tubulointerstitial inflammation, and fibrosis. Calcium oxalate crystals may also be observed in the blood vessel walls.

**CYSTINOSIS**

Cystinosis is another rare autosomal recessive disorder due to mutations in the *CTNS* gene that encodes cystinosin, a lysosomal membrane transport protein, which leads to lysosomal accumulation of cystine in all tissues. The infantile and juvenile forms are both nephropathic and account for the vast majority of cases. The infantile form of disease typically presents with Fanconi syndrome between 6 and 12 months of age, and the juvenile form presents a few years later (>3 years), typically with some degree of proteinuria. Other systemic manifestations can be seen in both infantile and juvenile diseases, including growth retardation, hypothyroidism, retinopathy, male
hypogonadism, myopathy, and corneal crystal deposits. Treatment with the cystine-depleting drug, cysteamine, has been shown to significantly delay the progression of kidney disease and other systemic manifestations, but many cases eventually require renal replacement therapy.37,38

Because cystine crystals are water soluble, they dissolve with formalin fixation. Therefore, they are best identified in the frozen tissue and appear as rhomboid or hexagonal polarizable crystals, which are typically located in macrophages in the interstitium but can also be seen in other cell types including endothelial cells and podocytes. Another characteristic finding in cystinosis is podocyte multinucleation, as well as occasional tubular epithelial cell multinucleation. Lesions of FSGS have been described in the juvenile form of disease. EM will show platelike, hexagonal intracellular spaces where the crystals were present before processing.

**TUBULOINTERSTITIAL NEPHRITIS**

Tubulointerstitial nephritis is a common cause of acute kidney injury, which can be associated with systemic manifestations including arthralgias, fever, rash, and eosinophilia. An immunologic reaction to pharmacologic agents, especially nonsteroidal anti-inflammatory drugs and antibiotics, is a common cause of acute interstitial nephritis (AIN) but can also be seen in the context of systemic or direct renal infections, autoimmune diseases (e.g., tubulointerstitial nephritis with uveitis or antitubular basement membrane disease), hereditary and metabolic disorders, and obstruction/reflux, or may accompany the glomerulonephritides, especially LN.39 If a pharmacologic agent is a suspected cause, discontinuation of therapy should lead to recovery of renal function, and additional steroid therapy may be warranted in some situations.

By light microscopy, the interstitial inflammatory infiltrate consists of a mixture of lymphocytes and monocytes with variable numbers of plasma cells and eosinophils (Fig. 3.25). Interstitial edema is usually present, imparting a bluish hue to the expanded interstitium (using the hematoxylin and eosin [H&E] stain), which contrasts with the pale eosinophilic appearance of interstitial fibrosis. Increased number of eosinophils may be more suggestive of a drug-induced injury. Tubulitis provides additional evidence of tubular injury as lymphocytes (usually T cells) breach the tubular basement membranes and can be seen among the tubular epithelial cells. In severe tubulitis, disruption of the tubular basement membranes can lead to formation of interstitial granulomas with epithelioid histiocytes and rarely multinucleated giant cells. Tubulointerstitial nephritis is often associated with acute tubular injury/necrosis, and any degree of sustained or continuous damage can lead to irreversible interstitial fibrosis and tubular atrophy.

It is important to be aware of the syndrome known as tubulointerstitial nephritis with uveitis (TINU) because the presence of uveitis has been reported in up to 46% of pediatric patients with idiopathic AIN.40 The syndrome was initially described in adolescent females in 1975 and
is characterized by AIN with a favorable course and uveitis with a chronic relapsing course. Usually, the onset of AIN precedes the development of uveitis, so close clinical follow-up is important in any child diagnosed with AIN.

**ACUTE PYELONEPHRITIS**

Anatomic abnormalities of the urinary tract can cause urinary obstruction and/or vesicoureteric reflux, predisposing children to the development of ascending pyelonephritis. Gram-negative bacteria from the gastrointestinal tract are the most common offending organism, particularly *Escherichia coli*. Presentation typically involves fever and flank pain, and renal insufficiency may be present. Recurrent episodes can result in chronic pyelonephritis and irreversible renal injury.

In acute pyelonephritis, there are prominent aggregates of neutrophils along with cellular debris within the tubular lumina and neutrophilic tubulitis (Fig. 3.26). There may also be interstitial inflammation with numerous neutrophils that may be intermixed with lymphocytes,
plasma cell, and eosinophils. In chronic pyelonephritis, neutrophilic inflammation may not be prominent, and there are other nonspecific findings, including chronic tubulointerstitial inflammation with progressive interstitial fibrosis and tubular atrophy. The atrophic tubules often show epithelial flattening and luminal hyaline casts which resemble colloid, which has been termed “thyroidization,” but this finding is not specific for chronic pyelonephritis. IF or EM do not reveal additional findings.

THROMBOTIC MICROANGIOPATHY

Thrombotic microangiopathy (TMA) is an important cause of acute kidney injury that is characterized by endothelial cell injury and thrombosis of arteries, arterioles, or glomerular capillaries. TMA can occur in the context of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension, antiphospholipid antibody syndrome, scleroderma, preeclampsia/eclampsia, drug toxicity, postradiation therapy, antibody-mediated rejection, and a few other clinical scenarios. The underlying etiology of TMA cannot be determined based solely on biopsy findings, and additional correlation with clinical information is essential.

In acute TMA, thrombi involve arteries, arterioles, or glomerular capillaries (Fig. 3.27), which are best seen by H&E or Jones silver stains. The thrombi distend the involved vessels and may contain entrapped red blood cells or fragments. Endothelial cell swelling can result in a “bloodless” appearance of the glomeruli. The affected glomeruli can also show
segmental mesangiolysis or dissolution of the mesangial matrix. Mucoid intimal change may be observed in arterioles or arteries, as commonly seen in the context of malignant hypertension or scleroderma, with incorporation of fragmented red blood cells within the thickened intima. By IF, the thrombi stain strongly for fibrin or fibrinogen. Ultrastructural evaluation of glomeruli reveals endothelial cell swelling with subendothelial expansion by electron lucent to flocculent material, and fibrin tactoids can be identified within the glomerular capillaries or incorporated into the subendothelial space.

In long-standing or chronic TMA, repeated endothelial injury results in duplication of the GBMs, which can be appreciated by both light and EM. Variable segmental and global glomerulosclerosis can develop over time. Affected arterioles and arteries may develop luminal narrowing due to concentric smooth muscle cell hyperplasia and intimal fibrosis or “onion skinning.”

**TRANSPLANT PATHOLOGY**

The three most common causes of ESRD in decreasing order among pediatric patients are aplastic/hypoplastic/dysplastic kidneys, obstructive uropathy,
and FSGS. Kidney transplantation is currently the best therapeutic option for children with ESRD. Fewer than 1,000 pediatric kidney transplants are performed annually in the United States. The percutaneous kidney biopsy remains the gold standard for establishing the cause of allograft dysfunction. Evaluation of kidney allograft biopsies can be quite challenging given the many injuries that can occur, which include allograft rejection, opportunistic infections, donor disease, surgical complications, recurrent or de novo renal diseases, drug toxicities, or any combination of these injuries. The minimal criteria for sample adequacy are 7 glomeruli and 1 artery with the ideal sample containing at least 10 glomeruli and 2 arteries. Immunolocalization for C4d should be performed on all allograft biopsies. Additional IF and/or EM can be performed as clinically indicated.

**T CELL–MEDIATED REJECTION**

Allograft rejection is the most common cause of graft loss in pediatric transplant patients. Almost half of pediatric patients will encounter at least one episode of acute rejection during the lifespan of the allograft. Two main mechanisms of immunologically mediated damage in kidney allografts are T cell–mediated rejection (TCMR) and antibody-mediated rejection (AMR). The Banff classification for allograft pathology is the most widely adopted schema by nephropathologists and transplant clinicians, which is the basis of the discussion in this chapter.

TCMR has been separated into the following three types: 1) tubulointerstitial (type I; Fig. 3.28), which requires interstitial

![FIGURE 3.28](image-url) Acute T cell–mediated (type I) rejection consists of a diffuse interstitial mononuclear cell infiltrate and tubulitis involving well-preserved renal tubules (arrow) (PAS).
inflammation involving greater than 25% of the kidney parenchyma AND tubulitis with 5 to 10 lymphocytes (type IA) or greater than 10 lymphocytes (type IB) per tubular cross section; 2) intimal arteritis or endarteritis (type II; Fig. 3.29), which is characterized by infiltration of the intima by leukocytes involving less than 25% (type IIA) or greater than 25% of the arterial lumen (type IIB); and 3) transmural arteritis or fibrinoid necrosis (type III). For the diagnosis of type I TCMR, areas of interstitial fibrosis and tubular atrophy are not assessed because atrophic tubules can demonstrate substantial tubulitis, but this concept is being challenged by recent data. Type I and II can occur simultaneously or in isolation, and there is emerging evidence that isolated intimal arteritis without significant interstitial inflammation may represent AMR rather than TCMR. If the criteria for type I, II, or III rejection are not satisfied, the diagnosis of a “borderline” inflammatory infiltrate can be made if there is 10% to 25% interstitial inflammation AND any amount of tubulitis. The chronic manifestation of type I rejection is interstitial fibrosis and tubular atrophy, whereas foamy macrophages can be observed in the chronic phase of type II rejection, which is also termed chronic transplant arteriopathy.

**ANTIBODY-MEDIATED REJECTION**

AMR has emerged as an important cause of allograft dysfunction and concurrent TCMR can be identified in nearly half of kidney transplant biopsies with evidence of AMR. To establish the diagnosis of AMR, the following
three criteria have to be satisfied: 1) any evidence of tissue injury in the form of acute tubular injury with minimal interstitial inflammation, glomerular and/or peritubular capillaritis (Fig. 3.30) and/or thrombi, or transmural arteritis or fibrinoid necrosis; 2) C4d peritubular capillary deposition (Fig. 3.31), established by either immunohistochemistry (IHC) or IF microscopy; and 3) presence of donor-specific antibodies. Only the first two criteria may be established with a kidney allograft biopsy, but the presence of these two findings alone is highly suggestive of AMR. Chronic AMR manifests in the form of duplication of the GBMs (chronic transplant glomerulopathy; Fig. 3.32) or multilayering of the peritubular capillary basement membranes (eFig. 3.3).

POLYOMAVIRUS NEPHROPATHY AND OTHER VIRAL INFECTIONS

Polyomavirus nephropathy (PVN) is observed in up to 5% of pediatric kidney transplant patients\(^\text{48}\) and can be a rapid cause of allograft loss. BK virus is the main culprit, but JC virus is reportedly identified in approximately 15% of patients. PVN is typically due to reactivation of latent viral infection because the seroprevalence of BK and JC virus are 91% and 14% by the age of 9 years,\(^\text{49}\) but de novo infections are pertinent to the pediatric population given that seronegativity is a risk factor for PVN. PVN can mimic type I TCMR
FIGURE 3.31 Strong and diffuse IF C4d staining of the peritubular capillaries is very suggestive of active AMR in an ABO-compatible kidney transplant patient. Glomerular C4d capillary staining is also present, but this finding by itself is not indicative of AMR. Granular mesangial C4d staining is a nonspecific finding, which can be useful as an internal control.

because both are characterized by prominent interstitial inflammation and tubulitis. Aggregates of plasma cells can be observed in either setting. Viral cytopathic effect with nuclear inclusions and a “ground-glass” appearance (Fig. 3.33) aids the diagnosis of PVN, but JC virus often lacks the viral cytopathic changes. Inflammation involving the renal medulla may be more characteristic of PVN compared with TCMR, which may be due to ascension of the viral infection from the lower urinary tract. In advanced cases of PVN, involvement of parietal epithelial cells can be observed and focal prominence and proliferation of these cells can mimic cellular crescent formation. We recommend that IHC for the simian virus 40 (SV40) large T antigen (eFig. 3.4) should be performed on all “borderline” inflammatory infiltrates to exclude the diagnosis of PVN. The presence of one virally infected epithelial cell is sufficient for the diagnosis of PVN. There is a staging system based on the extent of interstitial fibrosis and tubular atrophy and the severity of interstitial fibrosis/tubular atrophy correlates with clinical outcome. Other differential diagnoses include adenovirus infection and posttransplant lymphoproliferative disorder. Also, concurrent TCMR or AMR can rarely occur with PVN.
Adenovirus infection is rare in renal allografts, but children particularly those younger than 5 years of age are more susceptible than adults. The presence of severe tubular injury or necrosis and interstitial hemorrhage should raise this important diagnostic consideration. Also, a smudged appearance or viral cytopathic changes can be observed in some nuclei and granulomatous inflammation around injury is common. Cytomegalovirus (CMV) is much less frequent, but characteristic “owl-eye” nuclear inclusions are present in the endothelial cells of glomerular and/or peritubular capillaries.

Although viral infections are commonly encountered in kidney allografts, polyomavirus, adenovirus, or CMV infections can occur in the native kidneys of immunocompromised patients, such as other solid organ transplantation, AIDS, or acute leukemia.

**CALCINEURIN INHIBITOR TOXICITY**

Calcineurin inhibitors, which include cyclosporine and tacrolimus (FK506), are common drugs in most immunosuppressive regimens used for kidney transplant patients. Calcineurin inhibitor toxicity (CIT) can contribute to
allograft dysfunction and affects tubular epithelial cells and renal vessels. Isometric vacuolization is characteristic of acute CIT involving the tubules, but this finding can also be seen with mannitol infusion or various preparations of intravenous immune globulin. The finding of glomerular capillary or arteriolar thrombi can be observed with acute CIT, but other causes of TMA, including AMR, should be excluded. Chronic CIT can lead to adventitial hyaline nodules within arterioles, but arteriolar hyalinosis may also be due to diabetic or hypertensive vascular injury. Chronic CIT can result in “striped” interstitial fibrosis and tubular atrophy that initially involves the medullary rays of the cortex prior to diffuse involvement.

**POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER**

Posttransplant lymphoproliferative disorder (PTLD) occurs infrequently in kidney versus other solid organ transplant patients. The vast majority of PTLD is associated with Epstein-Barr virus (EBV), but EBV-negative cases can occur. EBV seronegativity is the most important risk factor for PTLD and likely accounts for the increased incidence in pediatric patients (2.4% compared with 0.5% of adult kidney transplant patients). PTLD consists of either B-, T-, or NK-cell neoplasms with a wide spectrum of entities ranging from plasmacytic hyperplasia to diffuse large B-cell lymphoma, Burkitt lymphoma (Fig. 3.34), or anaplastic large cell lymphoma.
Ancillary tests to aid in the diagnosis of PTLD include in situ hybridization for Epstein-Barr virus–encoded RNA (EBER), gene rearrangement, or cytogenetic studies.

**RECURRENT RENAL DISEASES**

Recurrence of the original renal disease accounts for nearly 7% of pediatric graft failures, and the three most common causes are FSGS, DDD, and hemolytic uremic syndrome. Knowing the original cause of ESRD is essential for clinical management and pathologic evaluation of allograft biopsies because recurrent disease nearly always occurs in the absence of simultaneous liver transplantation for primary hyperoxaluria (type 1) or MPGN due to complement factor H or I mutations.

**REFERENCES**


