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NEWSLETTER

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What's new in medical renal pathology 2025: Updates on podocytopathy and immunofluorescence staining in medical kidney

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Abstract

Diffuse podocytopathy, including minimal change disease and primary focal segmental glomerulosclerosis, is a common cause of nephrotic syndrome in adults and children. It is increasingly recognized to be autoimmune-mediated associated with anti-nephrin and other emerging anti-slit diaphragm antibodies, and can recur in the kidney allograft. Immunofluorescence is routinely used in evaluation of kidney biopsies, and updates include those on fibrillar diseases, monoclonal staining, lupus-like staining, and use of antibody KM55 in IgA-dominant glomerulonephritis.

UPDATE ON PODOCYTOPATHY

Anti-nephrin mediated podocytopathy in the native kidney

- A major subset of diffuse podocytopathy manifesting as acute nephrotic syndrome in children and adults is mediated by autoantibodies against nephrin. This causation has been proven in a rodent immunization model as well as a passive transfer model. This form of acquired podocytopathy is now classified as an antibody-mediated autoimmune disease [1-3].
- In native kidney biopsies, light microscopic patterns of glomerular injury in this subset include minimal change disease and primary focal segmental glomerulosclerosis (FSGS) with predominance of the tip lesion variant. Typically, fine punctate staining for IgG is seen in podocytes, most often colocalizing

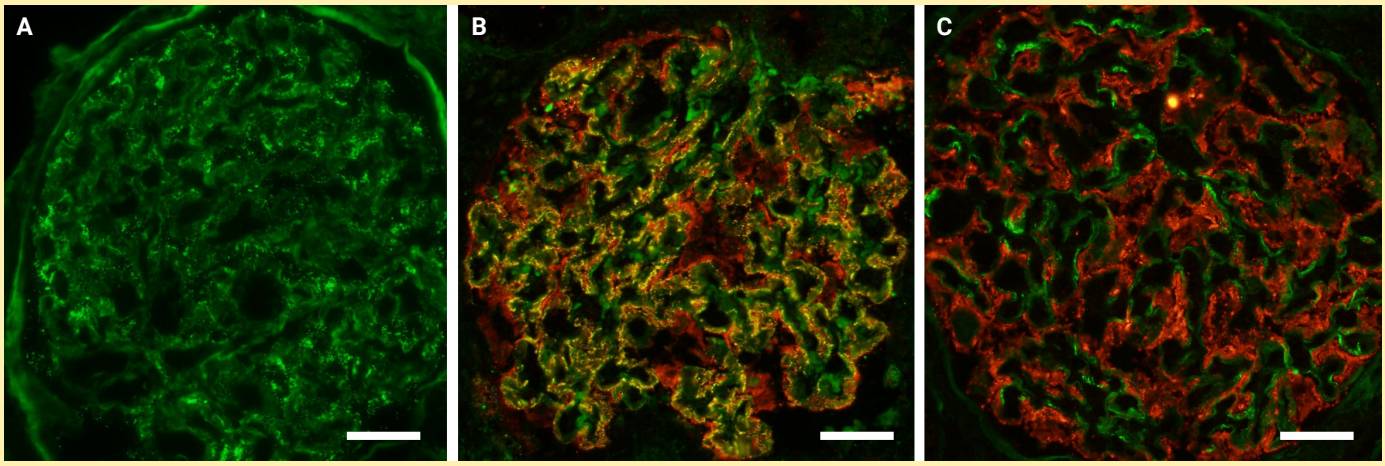

Fig. 1. Immunofluorescence staining in diffuse podocytopathy (DP) (Scale bars 20um) (contributed by Dr. Weins). (A) Fine punctate podocyte IgG in autoimmune DP. (B) Overlap of IgG and nephrin in anti-nephrin DP. (C) DP lacking overlap of background IgG with nephrin.

with clustered nephrin (Fig. 1). By electron microscopy, diffuse podocyte foot process effacement is accompanied by a loss of slit diaphragms.

- Testing for nephrin autoantibodies may predict disease course and inform therapeutic strategy. However, availability of an additional cross-validated and clinically approved serological assay will be crucial for wide clinical application as a minimally invasive diagnostic.
- Co-existence of autoimmune causes and genetic podocyte vulnerabilities are possible in rare cases; therefore, genetic testing is recommended to inform about risk of glomerular disease progression.

Podocytopathies in the kidney transplant

- Anti-nephrin antibodies and likely other permeability factors are important in recurrent diffuse podocytopathy [4,5].
- Genome-wide association studies are important to enhance our understanding of the pathogenesis of recurrent diffuse podocytopathy.
- Recipients of kidneys from Black donors have increased probability of developing collapsing glomerulopathy, which negatively impacts allograft outcome. In these patients, collapsing glomerulopathy is often associated with donor *APOL1* kidney risk variants and with a "second hit" [6,7].
- Identification of immune and genomic risk factors for collapsing glomerulopathy may improve utilization of kidneys from Black donors.

Mechanisms of podocytopathies

- Podocytopathies arise from diverse mechanisms, including autoimmune responses, genetic mutations, toxic or infectious agents, and adaptive responses to stressors such as obesity or low nephron number. Accurate diagnosis requires a personalized and integrative approach involving not only detailed clinical history and kidney biopsy but also genetic testing, serological profiling, and high-resolution microscopy [8].
- The extent and timing of podocyte loss, together with the renal progenitor cell response, shape podocytopathy patterns. Minimal change disease involves minimal podocyte loss or effective renal progenitor cell replacement. FSGS results from chronic injury with >20% podocyte loss and failed renal progenitor cell repair, leading to scarring. Collapsing glomerulopathy reflects sudden, massive podocyte loss that prevents renal progenitor cell differentiation. Diffuse mesangial sclerosis, seen in children under 5, arises from chronic loss during a phase of high regenerative activity [9].
- Autoantibodies targeting slit diaphragm proteins have been identified in subsets of patients with nephrotic syndrome, particularly those with minimal change disease or FSGS [1,10]. These antibodies colocalize with slit diaphragm proteins directly disrupting the filtration barrier and can be assessed in the serum of patients in active phases of the disease [10].
- Detection of anti-slit diaphragm antibodies in kidney biopsies enables stratification of pediatric patients with steroid-resistant nephrotic syndrome, identifying those more likely to benefit from second-line immunosuppressive therapies; this is associated with better clinical outcomes [10].
- Some patients with anti-slit diaphragm antibodies do not show reactivity to nephrin, but instead target other slit diaphragm proteins such as podocin or Kirrel1 [11], highlighting the heterogeneity of autoimmune targets in podocytopathies.

INTRICACIES AND COMPLEXITIES ON IMMUNOFLUORESCENCE STAINING IN MEDICAL KIDNEY

Updates on immunofluorescence staining in fibrillary diseases

- Fibrillary glomerulonephritis is most commonly defined by a smudgy staining of glomeruli with polyclonal IgG and C3. Sometimes, the immunofluorescence (IF) pattern can be pseudo-linear, which can mimic anti-glomerular basement membrane antibody disease, although rarely they may co-exist (Fig. 2). Extraglomerular staining is seen in up to 70% of cases.
- Among the IgG subtypes, IgG4 is most commonly found in fibrillary glomerulonephritis deposits.
- DNAJB9-positive FGN with apparent light chain restriction on frozen tissue should prompt IgG subclass studies, as well as paraffin based IF. True monotypic FGN, confirmed by paraffin IF and IgG subclass restriction, is extremely rare — 0.7% [12].
- Unusual patterns of FGN based on IF studies include immunoglobulin-negative variant, heavy chain FGN, and a DNAJB9-positive tubulointerstitital predominant FGN [13,14].
- Mimics of FGN include immunotactoid glomerulopathy, immunoglobulin type amyloid, and diabetes [15].

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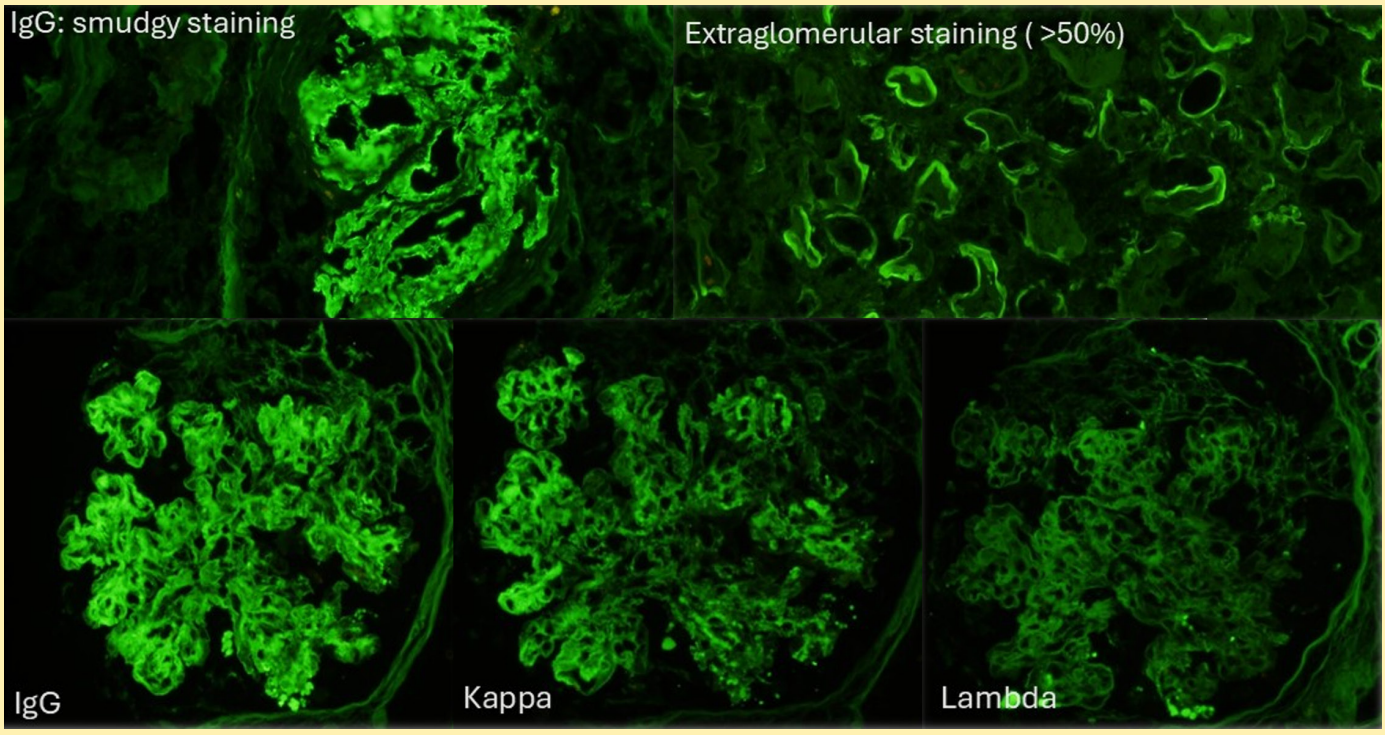

Fig. 2. Immunofluorescence features of fibrillary glomerulonephritis (contributed by Dr. Alexander). Monotypic staining on fibrillary glomerulonephritis on routine immunofluorescence microscopy should prompt paraffin IF, IgG subclass, and DNAJB9 staining.

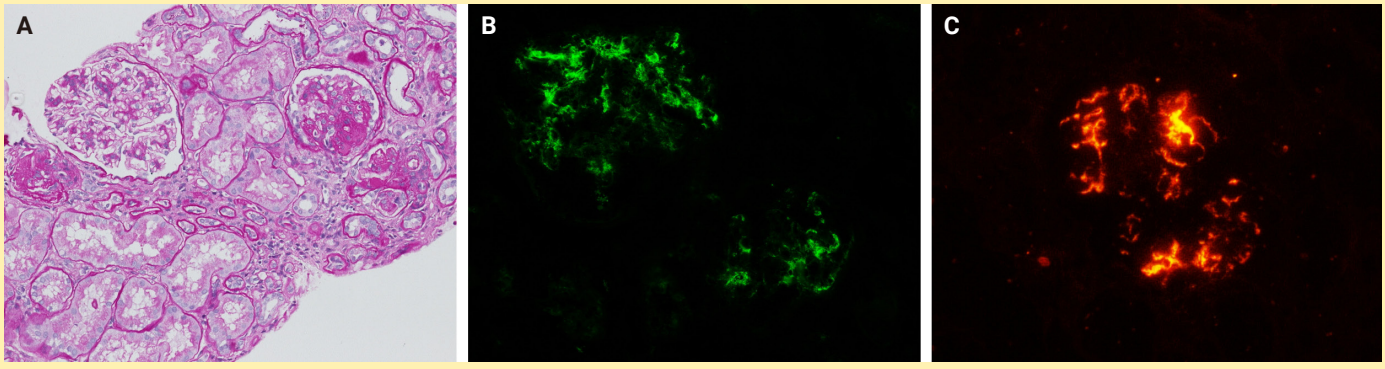

Fig. 3. KM55 staining in primary and secondary forms of IgA nephropathy. Renal biopsy from a 28-year-old male who had previously undergone right hemicolectomy for Crohn's disease, presenting with elevated creatinine, subnephrotic proteinuria, hematuria, and negative serologies. (A) Mesangioproliferative pattern of glomerular injury with segmental sclerosis (PAS, 200×). (B) 3+ mesangial granular staining for IgA, and (C) 3+ mesangial granular staining for KM55 (contributed by Drs. Singh and Raj).

Monoclonal background staining without electron dense deposits

- Kidney biopsy diagnosis of monoclonal gammopathy of renal significance (MGRS)-associated lesion requires three important features for diagnosis: (1) organizing or non-organizing deposits in one or more renal compartments; (2) corresponding monoclonal light chain (with/without heavy chain) staining; (3) characteristic light microscopy features.
- Occasionally, only diffuse background monoclonal light chain staining is seen on direct IF without specific electron dense deposits, cast nephropathy or light microscopy features of MGRS. This may be more common in patients with diabetes.
- This background light chain staining cannot be considered an "MGRS lesion" by itself; however, it can provide an important clue to the possibility of underlying monoclonal gammopathy and, thus, warrants a thorough hematological work-up [16]. With time, these and similar changes might potentially progress to an overt MGRS [17], smoldering myeloma or even active myeloma.

Updates in immunofluorescence staining mimicking lupus nephritis

- A full-house pattern is defined as a concurrent positive staining for IgA, IgG, IgM, C3, and C1q at IF or immunohistochemistry on kidney biopsy.
- The full-house pattern has always been considered as most characteristic of lupus nephritis. However, it may also be found in patients who do not fulfill the criteria for systemic lupus erythematosus, leading to the designation non-lupus full house nephropathy (NLFHN).

- NLFHN is a rare, complex entity: confusion arises from the low-quality evidence available, the low grade of accuracy and reproducibility in the full-house pattern evaluation and the lack of consensus on nomenclature [18].
- The development of a full-house pattern may be explained by a process of immunity overload, where circulating immune complexes deposit in the kidney. If a clear causative agent is identified (infectious diseases, drugs, concurrent glomerulopathies), we classify NLFHN as "secondary;" otherwise we call it "idiopathic." A third category of patients classified as NLFHN who develop diagnostic criteria for lupus nephritis during follow-up has been rarely described [18,19].

Updates in staining for IgA nephropathy: KM55

- KM55, an antibody that detects galactose-deficient IgA1 (Gd-IgA1), has utility in the classification of IgA containing glomerular diseases [20]. This is based on our understanding that mucosal plasma cell-derived IgA is galactose-deficient dimeric IgA, unlike bone marrow plasma cell derived IgA, which is monomeric and galactosylated [21].
- Utilizing KM55, it has been demonstrated that IgA nephropathy, IgA vasculitis and secondary IgA nephropathy (with chronic liver disease, inflammatory bowel disease, etc.) share a common pathogenesis and are driven by mucosal plasma cell-derived IgA (KM55 positive), regardless of the pattern of glomerular injury (Fig. 3) [22,23].
- KM55 is negative in glomerular IgA deposits in other settings such as lupus and cryoglobulinemia, suggesting bone marrow-derived plasma cell origin of the IgA [22,23].
- Monotypic IgA containing glomerular diseases can also be investigated with KM55, as most are positive and represent IgA nephropathy; KM55 negativity suggests IgA proliferative glomerulonephritis with monoclonal immunoglobulin deposits (IgA PGNMID) [24].
- IgA-dominant infection-related and *Staphylococcus*-associated glomerulonephritis remain grey areas requiring further investigation as to the source of the IgA [23,25].

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Meet the Authors

The authors are members of the Renal Pathology Society (RPS) and leaders in their field. Drs. Jonathan Zuckerman and Nicole Andeen are Editorial Board Members for PathologyOutlines.com. These educational updates were presented at the Renal Pathology Society Satellite and Companion Society meetings at the U.S. and Canadian Academy of Pathology (USCAP) meeting in 2025.

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