НИРКИ KIDNEYS

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Diagnostic and therapeutic challenges in dense deposit disease: case report

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Abstract. *We report a complex case of a 15-year-old girl initially diagnosed with post-streptococcal glomerulonephritis (PSGN) but later identified as having dense deposit disease, which was initially classified as type 2 membranoproliferative glomerulonephritis. PSGN and C3 glomerulopathy present overlapping clinical and histological features, complicating diagnosis and treatment. This report highlights the case of a young patient whose initial presentation and management for PSGN transitioned to a complex diagnosis of dense deposit disease, necessitating tailored therapeutic interventions.*

Keywords: *post-streptococcal glomerulonephritis; dense deposit disease; C3 glomerulopathy; membranoproliferative glomerulonephritis; glomerular basement membrane*

Introduction

Post-infectious glomerulonephritis (PIGN) follows infections and manifests as nephritic syndrome within 1–3 weeks. Diagnostic hallmarks include proliferative glomerulonephritis on light microscopy, bright C3 staining on immunofluorescence (IF) microscopy, and subepithelial "humps" on electron microscopy. While most cases resolve spontaneously, some patients endure persistent hematuria and proteinuria or advance to end-stage kidney disease [1]. Persistent hematuria and proteinuria in individuals previously diagnosed with post-infectious glomerulonephritis warrant consideration for a kidney biopsy. If atypical clinical or histological features are observed in a case initially presumed to be PIGN, particularly in the presence of subepithelial humps, suspicion for C3 glomerulopathy should be heightened [2].

C3 glomerulopathies encompass a rare spectrum of kidney disorders characterized by dysregulated complement activity both in the systemic circulation and within the glomerular microenvironment. This dysregulation leads to significant deposition of complement C3 in kidney. The primary subgroups within C3G are dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) (Fig. 1) [3]. C3 glomerulopathy is characterized histopathologically by accumulation of the C3 component of complement in renal tissue. This finding, in the absence or near-absence of immunoglobulin deposits in a patient with the classic clinical features of glomerulonephritis, is the single diagnostic criterion [3]. DDD, also known as MPGN type II, is a rare disease. DDD is a negative immunoglobulin and positive C3 glomerulopathy. It is mostly characterized by MPGN pattern of injury, C3 deposits on IF microscopy and characteristic sausage-shaped, wavy deposits by electron microscopy inside the glomerular basement membrane (GBM) and mesangium [4, 5].

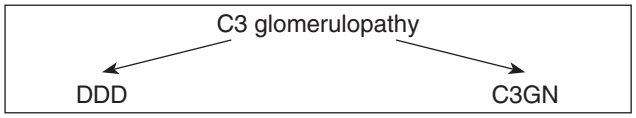

Figure 1. Interaction between C3 glomerulopathy, C3GN and DDD

Case report

A 14-year-old female presented to the outpatient department with hematuria. She reported having had a throat infection two weeks prior to the onset of hematuria. Initial laboratory tests indicated sub-nephrotic range proteinuria, hematuria, and hypertension. The clinical diagnosis of post-streptococcal glomerulonephritis (PSGN) was made based on her recent streptococcal infection and the urinary findings. The patient was managed conservatively with adequate hydration to support kidney function, antibiotics (beta-lactams) to address the streptococcal infection, antihypertensives (RAS inhibitors) to manage blood pressure. The patient was scheduled for regular follow-up to monitor renal function and urinary parameters.

Despite the initial treatment, hematuria persisted three months post-diagnosis. The patient developed bilateral lower limb swelling and decreased urine output, prompting further evaluation and renal biopsy.

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Laboratory findings at this stage showed: urine protein 1.2 g/day, albumin 3+, pus cells 4–6, RBC 16–18 and ASO titer of > 200.

A renal cortex sample containing 21 glomeruli was examined, revealing endocapillary proliferation, patchy capillary wall thickening, increased mesangial cellularity, and the presence of neutrophils in the glomerular tuft. A fibrocellular crescent was observed in one glomerulus, with mild tubular atrophy and interstitial fibrosis (5–10 %), and neutrophils and occasional eosinophils in the interstitium. Direct immunofluorescence was negative for IgA, IgG, C4, and C1q but showed 1+ positivity for IgM and C3 in the mesangium and along the capillary membrane. The findings are indicative of diffuse proliferative glomerulonephritis, consistent with a diagnosis of post-infectious glomerulonephritis.

The patient was managed conservatively following the biopsy. Despite this, her condition deteriorated: sub-nephrotic range proteinuria transformed into nephrotic range proteinuria (3.7 g/day). Hematuria resolved, but hypertension persisted (BP 144/92). Initial immunosuppressive therapy: The patient was started on mycophenolate mofetil for three months, but no significant improvement was observed. Tacrolimus was added along with an angiotensin receptor blocker, but her kidney function worsened, indicated by a rise in serum creatinine levels which led to withdrawal of tacrolimus.

Given the deterioration, a second biopsy was performed which revealed widespread foot process effacement (about 80 %). Extremely electron-dense deposits in a continuous, ribbon-like fashion along glomerular capillaries and mesangial areas. Mesangial interposition, neo basement membrane formation, and intracapillary neutrophils. Tubular basement membranes also showing electron-dense deposits on electron microscopy. The findings were consistent with DDD, a subtype of C3 glomerulopathy (Fig. 2).

Tailored immunosuppressive therapy therapeutic intervention was followed. Based on the diagnosis of DDD, the patient was started on low-dose oral cyclophosphamide 0.5 g/day to suppress immune activity was continued for period of six months. Intravenous methylprednisolone 20 mg/kg/day to reduce inflammation and control the disease process initially followed by transition to oral

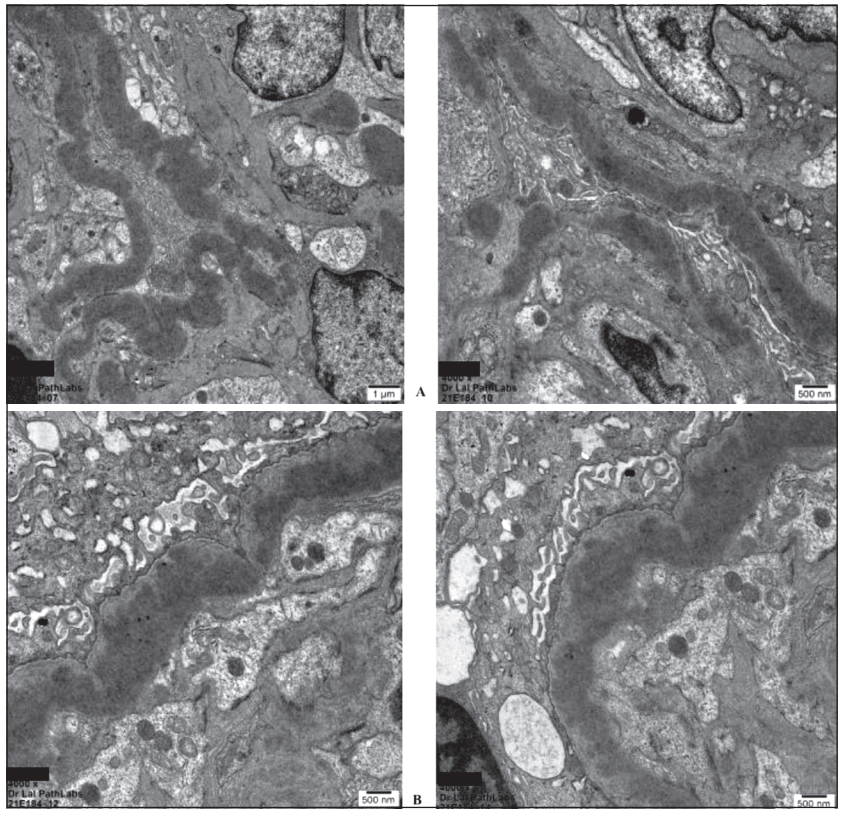

Figure 2. Kidney biopsy on electron microscopy: A) extremely electron dense/hyperosmiophilic deposits in a linear/continuous fashion along glomerular capillaries and focally in mesangial areas, B) widespread effacement of visceral epithelial cell foot processes with mesangial interposition & GBM neo basement membrane formation

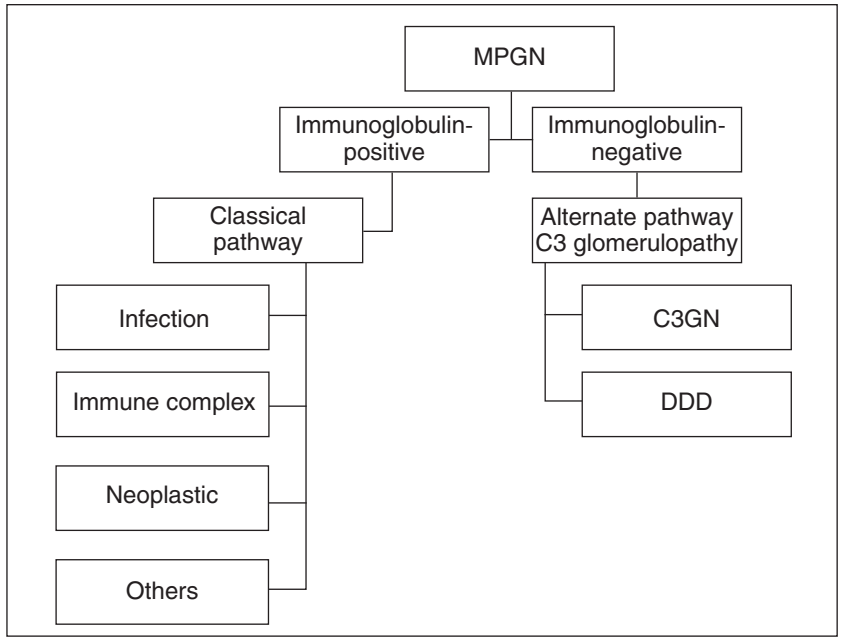

Figure 3. A simple classification of MPGN based on the findings of IF staining and the difference in the state of complement activation. The MPGN pattern detected by light microscopy is divided into immunoglobulin-positive or immunoglobulin-negative on IF staining. It is suspected that immunoglobulin-positive MPGN is induced by classical pathway activation. Immunoglobulin-negative C3-positive MPGN is categorized as C3G due to dysregulation of the alternative pathway. C3G is further subdivided into C3GN and DDD [7]

prednisolone 1 mg/kg/day and tapered over several months based on clinical response.

The patient showed significant clinical improvement. Kidney function improved, with stabilized serum creatinine levels. Treatment duration was individualized based on clinical response, with significant improvement in kidney function and proteinuria control. Proteinuria decreased from nephrotic to sub-nephrotic range, indicating effective disease control.

Discussion

This case of a 14-year-old girl initially diagnosed with PSGN but later identified as having DDD highlights several critical aspects in the diagnostic and therapeutic management of glomerulonephritis. The case underscores the importance of considering alternative diagnoses when clinical presentation deviates from the expected course, emphasizing the need for repeat biopsies and advanced diagnostic techniques.

PSGN and DDD, while both presenting with glomerulonephritis, have distinct pathogenetic mechanisms. PSGN is primarily an immune complex-mediated disease following infection, leading to the deposition of immune complexes and activation of the alternate complement pathway (Fig. 3). This typically results in transient glomerular inflammation and, in most cases, resolves with supportive care.

In contrast, DDD, a form of C3 glomerulopathy, involves dysregulation of the alternative complement pathway. This dysregulation leads to persistent activation of complement and deposition of C3 along the GBM without significant immune complex involvement [6]. The electron-dense deposits (Fig. 2) observed in DDD are a hallmark of this condition and distinguish it from other types of glomerulonephritis. This case highlights the necessity of electron microscopy in identifying these unique deposits, which are not discernible with light microscopy and DIF.

Conclusions

This case underscores the necessity for careful follow-up and comprehensive evaluation in glomerulonephritis patients. Persistent symptoms despite standard treatment should prompt consideration of alternative diagnoses such as C3 glomerulopathy. Accurate diagnosis through repeat biopsies and successful outcome with tailored immunosuppressive therapy emphasizes the importance of comprehensive diagnostic evaluation and individualized treatment approaches. Further research and increased clinical awareness are essential to improve the management and outcomes of patients with DDD.

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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Діагностичні й терапевтичні проблеми при хворобі щільних депозитів: опис випадку

Резюме. Авторами наведено складний випадок у 15-річної дівчини, у якої був діагностований постстрептококовий гломерулонефрит (ПСГН), але пізніше виявлено захворювання щільних депозитів, яке спочатку було класифіковано як мембранопроліферативний гломерулонефрит 2-го типу. ПСГН і С3-гломерулопатія мають схожі клінічні й гістологічні ознаки, що ускладнює діагностику та лікування. У цьому випадку початкова клінічна картина та лікування ПСГН переросли в складну діагностику хвороби щільних депозитів, що потребувало індивідуальних терапевтичних втручань.

Ключові слова: постстрептококовий гломерулонефрит; хвороба щільних депозитів; С3-гломерулопатія; мембранопроліферативний гломерулонефрит; базальна мембрана клубочка