Case Report

Dense Deposit Disease: An Ultra-Rare C3 Glomerulopathy in Children

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Abstract

Dense deposit disease (DDD), previously known as membranoproliferative glomerulonephritis type 2, is an extremely rare disease affecting two to three people per million. The rarity of this disease makes it difficult for clinicians to establish evidence-based clinical practices for its management. Here, we report a case of DDD who presented with features of acute nephritic syndrome and did not respond to most of the treatment options available in literature.

Key words: C3 glomerulopathy, children, dense deposit disease, membranoproliferative

INTRODUCTION

Dense deposit disease (DDD), previously known as membranoproliferative glomerulonephritis type 2 (MPGN type 2), is an extremely rare renal disease affecting only 2–3 people per million and leads to renal failure within 10 years in 50% of affected children. It accounts for <20% of all cases of MPGN in children and only a fractional percentage of cases in adults.[1] DDD is a glomerular disease characterized by electron-dense deposits (EDDs) in the lamina densa of the glomerular basement membrane (GBM). Here, we report a case of DDD that presented with features of acute nephritic syndrome and remained unresponsive even after utilizing most of the treatment options described in recent literature.

CASE REPORT

A 12-year-old male child presented with a 2-month history of periorbital puffiness and decreased urine output for 15 days. There was no history of hematuria, hypertension, poor urinary stream, recurrent urinary tract infection, polyuria, joint pain, rashes, or growth retardation. Pallor was present and there were facial puffiness, pedal edema, and marked ascites. His vitals were pulse 96/min, blood pressure (BP) 150/90 mmHg, respiratory rate 24/min, and SpO_2 98% on room air. Routine hematological evaluation showed a hemoglobin of 9.8 g/dL, total leukocyte count of 18,170/mm^3 (64% polymorphs and 30% lymphocytes), and platelet count of 1.8 lakh/mm^3. Urinalysis revealed 3+ protein, 80–100 red blood cell, and 50–80 pus cells/hpf. Urine culture showed growth of *Enterococcus faecium*. Based on these findings, presumptive diagnosis of complicated nephrotic syndrome with urinary tract infection was made. He was started on parenteral antibiotic based on cultural sensitivity and oral antihypertensives (amlodipine, labetalol, and clonidine) with a target BP of <95th percentile. On the 5th day of hospitalization, his edema increased significantly and urine output decreased to 0.8 mL/kg/h. There was marked hypoalbuminemia (with a serum albumin level of 1.9 g/dL), and UPr/U_{cr} ratio was 13.63. Renal functions were mildly deranged with a blood urea of 40 mg/dL and serum creatinine of 1.2 mg/dL. Serum electrolytes

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and liver function tests were within normal limits. Repeat urine culture after 7 days of antibiotics showed no growth. Serial urinalysis showed persistent microscopic hematuria and nephrotic-range proteinuria. His blood pressure remained >99th percentile on 3 anti-hypertensive medications and renal function tests showed further derangement (blood urea of 97 mg/dL and serum creatinine of 1.5 mg/dL). Diagnosis was modified to acute nephritic syndrome, and further workup was planned accordingly. Antistreptolysin titer was 50 IU/mL (normal reference range <200 IU/mL). Serum C3 was 115 mg/dl (reference range of 90–180 mg/dL) while serum C4 was 54 mg/dL (reference range 12–72 mg/dL). Viral markers (hepatitis B surface antigen, HIV, and IgM antihepatitis C virus) were nonreactive. Antinuclear antibody, antidouble-stranded DNA antibody, and antineutrophil cytoplasmic antibody were negative. Oral prednisolone was started at 60 mg/m^2/day, and edema was managed with 20% albumin and furosemide infusions. Percutaneous renal biopsy under real-time ultrasonography was performed in view of persistent microscopic hematuria, nephrotic-range proteinuria, hypertension, and rising creatinine. Empirically, he was started on methylprednisolone pulses as final renal biopsy results were expected only after a week. A total of three pulses of methylprednisolone were given, but urinalysis did not show any considerable improvement. Renal biopsy showed mesangiocapillary/ membranoproliferative glomerulonephritis (MPGN) injury pattern on light microscopy [LM] on light microscopy (LM) [Figure 1]. There were crescents over 16/32 (50%) glomeruli (3 cellular crescents and 13 fibrocellular crescents). Direct immunofluorescence study [Figure 2] revealed glomerular C3 staining (3+ capillary wall and mesangial, granular) without staining for immunoglobulins or light chains (IgA negative, IgG negative, IgM segmental entrapment, C1q negative, kappa negative, and lambda negative). Electron microscopy (EM) [Figure 3] revealed GBM thickening ranging from 348.5 to 748.3 mm (mean 511.4 mm). There was a significant effacement of visceral epithelial cell foot processes. Many extremely electron dense deposits (EDDs) were seen in linear/continuous fashion along glomerular capillaries, mesangial areas, and focally along tubular basement membrane. Overall biopsy features were consistent with DDD. Further workup was required to ascertain hereditary and acquired factors responsible for the dysregulation of alternative complement pathway. Genetic analysis for several mutations including CFH, CFHR, CFI, CFB, and MCP was planned. Similarly, for acquired factors, anti-CFH antibody and C3 nephritic factors (C3Nef) estimations were required. However, these investigations were not available at our center, and outsourcing was too costly to be afforded by the index case. Following the biopsy confirmation of DDD, the patient

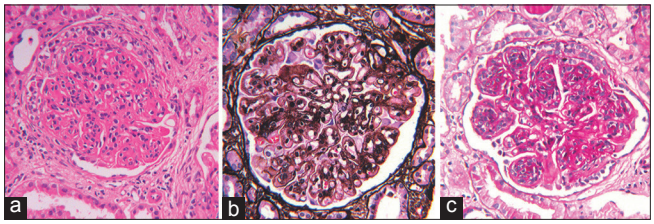

Figure 1: Light microscopy (a) H and E (b) silver methenamine and (c) PAS images showing mesangioproliferative (membranoproliferative glomerulonephritis) injury pattern with crescents (H and E, silver methenamine, PAS, ×250)

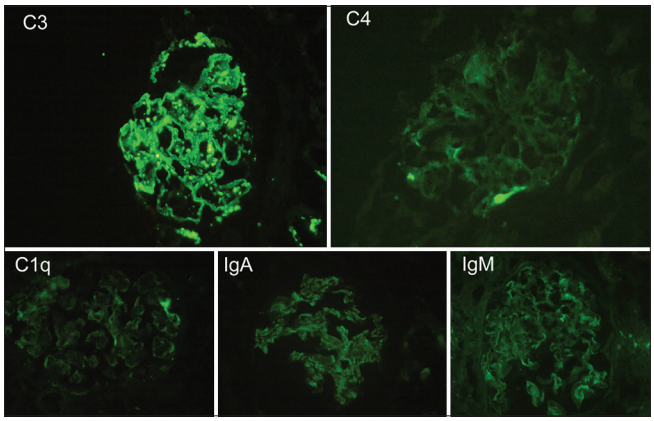

Figure 2: Direct immunofluorescence image showing exclusive glomerular C3 staining with negative staining for C4, C1q, IgA, and IgM (FITC, ×400)

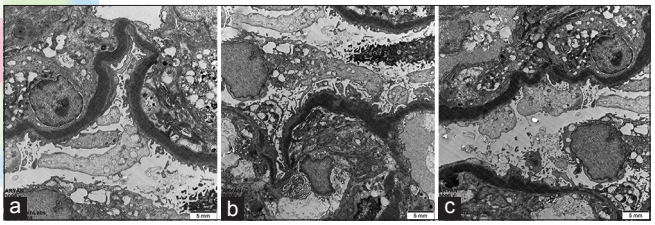

Figure 3: Electron microscopy images (a-c) showing electron-dense deposits along glomerular capillaries, mesangial areas, and tubular basement membrane

was put on alternate day prednisolone and mycophenolate mofetil (MMF). As his renal function (serum creatinine of 1.3 mg/dL) and blood gasses (PH 7.35, PCO_2 24, PO_2 83, and HCO_3 18.5) were under control, he did not require renal replacement therapy throughout the hospital stay. However, edema and ascites used to reappear and multiple albumin transfusions were required. Daily plasma exchange with fresh frozen plasma (FFP) was done for five sessions, but there was no improvement in proteinuria and microscopic hematuria. One pulse of cyclophosphamide with mesna was also given, but it could not change the outcome. As further treatment options were too costly to afford and no conclusive evidences were available for their efficacy in DDD, he was referred to a tertiary care pediatric nephrology center.

DISCUSSION

DDD is a glomerular disease characterized by EDDs in the

lamina densa of the GBM (seen also within the mesangium, tubular basement membrane, and Bowman's capsule). These deposits arise secondary to dysregulation of the alternative pathway of the complement cascade. Dysregulation occurs at the level of the C3 convertase and involves a variety of factors, such as C3Nefs, genetic mutations in complement genes, and autoantibodies to complement proteins, such as complement factor H.[2] The modern approach to classification distinguishes those forms of MPGN with deposits of C3 only (known as C3 glomerulopathy) from MPGN with deposits of immunoglobulin and complement. C3 glomerulopathy is a newly recognized subgroup encompassing DDD and those subclass of type I and type III (now termed "C3 glomerulonephritis") in which immunofluorescence reveals isolated deposits of C3, underscoring the pathogenetic importance of dysregulation of the alternative complement pathway.[3] DDD is most often diagnosed in children between the ages of 5 and 15 years and does not show a sex bias.[4] Although LM and immunofluorescence findings can be suggestive of the diagnosis, EM is required and will show ribbon-like dense deposits in the GBM. The presence of C3Nefs in the serum is supportive of the diagnosis although it is not conclusive.[5] Nonspecific symptoms of renal insufficiency, such as hypertension, hematuria, proteinuria, and nephrotic syndrome, are frequently present in DDD patients. Acquired partial lipodystrophy and drusen (tiny yellow or white accumulations of extracellular material that build up in Bruch's membrane of the eye) are associated with DDD.[6] Nonspecific measures such as use of angiotensin-converting-enzyme inhibitors I have been useful in controlling hypertension and proteinuria. Steroids have not been found effective in DDD, and strategies to reduce C3NeF in DDD using mycophenolate mofetil have not been studied.[1] In patients with defined pathologic mutations of CFH, infusion of FFP or plasma exchange to provide functionally intact factor H has been associated with favorable outcome. Eculizumab (anti-C5 antibody) has been used at few centers around the world to treat small groups of DDD patients. Huge cost and poor availability of this drug has been a limiting factor for conducting a quality research for its efficacy in DDD. Sulodexide (a combination of low-molecular-weight heparin and dermatan sulfate) is another treatment that may slow disease progression in DDD.[1] The long-term renal prognosis of C3G is generally unfavorable. It was reported in a study that 47% of patients with DDD and 23% of patients with C3GN progressed to end-stage renal disease (ESRD) during a median follow-up period of 28 months.[7] Roughly, 50% of DDD patients progress to ESRD and require dialysis within 10 years of diagnosis. Factors predictive for progression to renal failure include younger age at diagnosis, elevated serum creatinine levels and proteinuria at diagnosis, initial presentation with nephrotic and nephritic syndromes, and >20% chronic renal damage on initial biopsy. Renal transplantation is not a reliable treatment option because up to 50% of recipients eventually lose their graft within 5 years of transplantation as a result of disease recurrence.[8]

CONCLUSION

One-fifth of DDD patients have silent symptoms which are detected on routine physical examinations. Therefore, screening for hematuria, proteinuria, and hypertension should be stressed upon even in routine physical checkups for children. Since progression to ESRD and posttransplant recurrence is common in all forms of C3 glomerulopathy, therapies that target underlying disease mechanisms are urgently required. There is a need to increase health-care provider awareness of DDD to optimize best care practices for such children.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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