CASE REPORT

Dense deposit disease in an adolescent male mimicking acute post-streptococcal glomerulonephritis

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Abstract

Background: Dense deposit disease (DDD), a subtype of complement factor 3 glomerulopathy (C3G), is a rare entity associated with dysregulation of the alternative complement pathway. It usually affects children, with a 50% likelihood of progression to end-stage renal disease within ten years of diagnosis.

Description of the case: We report the case of an adolescent male with acute nephritic syndrome and nephrotic range proteinuria, initially diagnosed as acute post-streptococcal glomerulonephritis (APSGN). Despite his spontaneous improvement, renal biopsy, performed due to a persistently low C3 level for over 18 weeks, confirmed the diagnosis of DDD. Complement and genetic studies showed high levels of C3-nephritic factor and risk polymorphisms for developing the disease. He was treated with prednisolone and mycophenolate mofetil (MMF). At the last follow-up, 15 months from onset, the serum creatinine level and 24h-hour total protein excretion were normal.

Conclusion: C3G (including the DDD subtype) should be suspected in apparent APSGN with atypical clinical features at presentation/follow-up, even in the case of spontaneous improvement. Timely and accurate diagnosis, based on histopathological, complement, and genetic studies, is important to initiate the appropriate treatment aimed at preventing or slowing the disease progression. HIPPOKRATIA 2020, 24(4): 191-193.

Keywords: Complement factor 3 glomerulopathy, dense deposit disease, post-streptococcal glomerulonephritis, child, adolescent

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Introduction

Acute post-streptococcal glomerulonephritis (APSGN) is an immunologically mediated disease characterized by a decrease in serum complement factor 3 (C3) due to complement activation[1], which usually normalizes within eight weeks[2]. In the case of APSGN with a low C3 level persisting after a period of eight weeks, renal biopsy should be performed to rule out idiopathic membranoproliferative GN (MPGN), which may be immunoglobulin-mediated or non-immunoglobulin-mediated. Non-immunoglobulin MPGN and other proliferative patterns of GN with dominant C3 expression are currently classified as C3 glomerulopathy (C3G)[3,4].

Dense deposit disease (DDD), a subtype of C3 glomerulopathy (C3G)[5], is a rare entity, affecting 2-3 people per 1,000,000. It presents mainly in childhood, with 50 % progression to end-stage renal disease (ESRD) within ten years of diagnosis. It is more frequently encountered in younger children (<10 years) and females[6].

We report the case of an adolescent male with acute nephritic syndrome and nephrotic range proteinuria, initially diagnosed as APSGN, but renal biopsy confirmed the diagnosis of DDD.

Case presentation

A previously healthy 14-year-old boy was admitted to the Pediatric Nephrology Department to investigate Coca-Cola-colored urine of one week's duration. Multiple episodes of streptococcal tonsillitis were reported, the last of which was three months before the onset of urinary discoloration. He had mild hypertension (140/90 mmHg, 95th centile: 132/84 mmHg), serum creatinine 0.9 mg/dl [normal range (NR): 0.5-1.0 mg/dl], estimated glomerular filtration rate (e-GFR) 70 ml/min/1.73m^2, nephrotic range proteinuria (2,346 mg/m^2/24h), dysmorphic erythrocytes, antistreptolysin O antibodies (ASTO) titer 1,840 IU/ml, and C3 complement fragment 17 mg/dl (NR: 79-152 mg/dl). Throat swab culture showed normal bacterial flora. Other causes of post-infectious GN were ruled out (i.e., negative IgM/IgG antibodies for Cyto-

megalovirus, Epstein-Barr virus, Mycoplasma, hepatitis C, and HbsAg). Antinuclear antibody, antineutrophil cytoplasmic antibodies, and double stranded-DNA were all within the normal range.

He had no oliguria or edema. He was treated with a low salt diet and cefuroxime for ten days. His blood pressure normalized on the 9th day, and the serum creatinine level decreased to 0.6 mg/dl on the 10th day. The proteinuria gradually decreased to 330 mg/m^2/24h, ten weeks from onset. A renal biopsy was decided on when the C3 level remained low (35.6 mg/dl) at 18 weeks from onset, and the diagnosis of DDD was made (Figure 1, Figure 2, Figure 3).

Following the biopsy findings, he was treated with prednisolone 60 mg/m^2/day for four weeks, followed by 40 mg/m^2 on alternate days for four weeks. Complement studies revealed the presence of C3-nephritic factor[7]: 16.8 %, (NR: <10 %), and an increase in terminal complement pathway activation marker, serum C5b-9: 436 ng/mL (NR: 110-252 ng/mL). C1q, C4, and complement factor H, I, B (FH, FI, FB) antigens were within the normal range. Anti-factor H IgG and anti-C1q IgG autoantibodies were negative. Genetic studies showed no mutations in the *FH*, *FI*, *FB*, membrane cofactor protein, *C3*, thrombomodulin (*THBD*), or factor H-related protein 5 (*CFHR5*) genes. The patient was homozygous for the rare allele of the Y402H polymorphism of the *FH* gene (and the H1 haplotype containing this allele), and heterozygous for the R102G and P314L polymorphisms of the *C3* gene. Following the complement study, mycophenolate mofetil (MMF) was prescribed (550 mg/m^2 twice daily).

At his last follow-up (15 months from onset, at which point he had been on MMF for ten months), the 24h-hour urine total protein excretion, serum creatinine, and C3 levels were all normal (147 mg/m^2/24h, 0.6 mg/dl, 80.1 mg/dl, respectively).

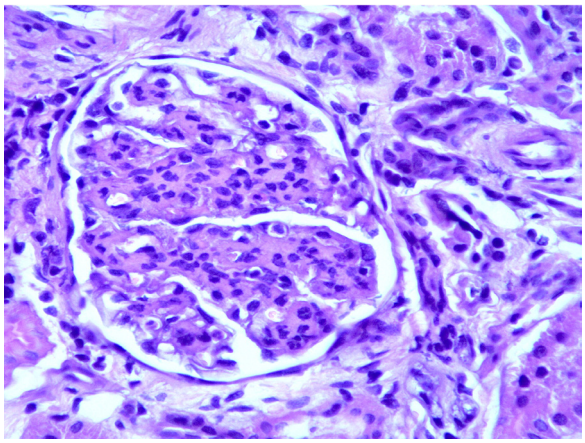

Figure 1: Light microscopy image (hematoxylin and eosin stain, x 400) showing a glomerulus with endocapillary proliferation and exudative features, with numerous neutrophils in the glomerular lumen and thickening of the glomerular basement membrane, and segmental lobular architecture (a sign of membranoproliferative glomerulonephritis).

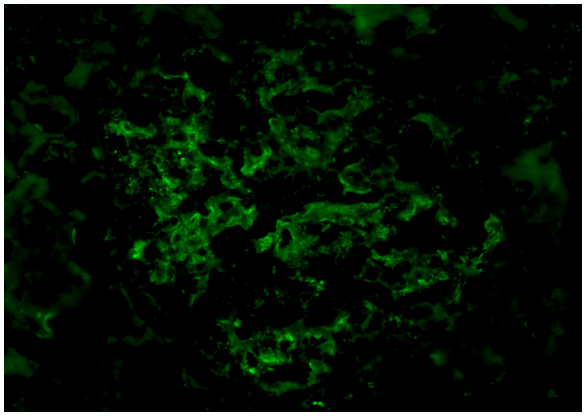

Figure 2: Immunofluorescence image (C3, x 400) showing staining of the glomerular capillary walls and the mesangium in a discontinuous pattern, with some spherical structures.

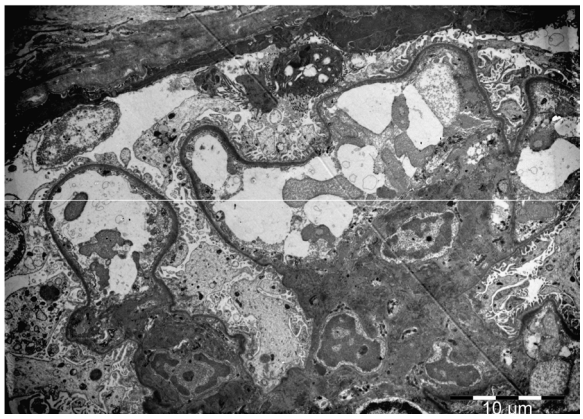

Figure 3: Electron microscopy image (Uranyl acetate and lead citrate, x 2200) showing a segment of a large glomerulus with intramembranous and mesangial electron-dense deposits, unevenly distributed in a ribbon-like fashion, among the glomerular base membranes, with mild to moderate glomerular involvement.

Discussion

The case of an adolescent male with DDD and complete recovery is described here. This patient was initially diagnosed as suffering from severe PSGN. However, despite his marked clinical/laboratory improvement, the serum C3 level remained low beyond eight weeks, leading to the need for renal biopsy, which showed findings compatible with DDD[5].

C3G (C3GN and DDD) is frequently associated with autoantibodies directed against C3 or C5 convertases, which cause complement dysregulation by increasing the half-life of these normally short-lived enzymes[8]. Mutations in the *FH*, *FI*, and *C3* genes have been identified in several patients with DDD associated with a C3 nephritic factor[9]. Our patient had a C3-nephritic factor and was homozygous for the rare allele of Y402H polymorphism of the complement *FH* gene and heterozygous for the R102G, P314L polymorphisms of the *C3* gene, all reported as risk factors for the development of DDD[9,10].

DDD usually affects children, more frequently fe-

males, and at a younger age (<10 years), with a 50 % rate of progression to ESRD within ten years of diagnosis[6]. Our patient experienced marked spontaneous clinical and laboratory improvement. The absence of crescents in renal biopsy and the relatively low levels of C3-nephritic factor may have contributed to his favorable outcome. A similar spontaneous resolution with no immunosuppressive treatment was reported for the first time in an 11-year-old girl with DDD and nephrotic syndrome[11].

Recently, a retrospective case series of four children with DDD was published. At their last follow-up (ranging from 2-120 months), all the children had persistent proteinuria and hematuria, and two showed progressive renal dysfunction, with one requiring a kidney transplant[12]. Steroids were used in all four patients and MMF in three of them[12]. The above cases, and ours, highlight the variable outcomes of DDD, ranging from complete recovery to ESRD.

Conclusion

C3G should be suspected in apparent PSGN with atypical clinical/laboratory features at presentation or follow-up, even in the case of spontaneous improvement, in order to initiate appropriate treatment aimed at preventing or slowing the progression of the disease.

Conflict of interest

The authors declare that they have no conflict of interest relevant to the material discussed in this article.

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