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Abstract

A 13-year-old girl presented with proteinuria and acute kidney failure. She was born at full term \textit{via} cesarean delivery (due to nuchal cord), but there were no other prenatal or perinatal complications. In early childhood, the patient had two hospitalizations at ages 4.5 and 9 years, respectively, the latter for pneumonia. She had no history of symptoms of kidney disease. She came to the hospital at age 12 years for routine bilateral molar extractions. She was treated with oral antibiotics and discharged after the procedure without complications. At age 13 years, 10 months after the molar extraction, she was seen by a pediatrician because of puffiness and increased BP. She had had respiratory symptoms 2 weeks before presentation. The pediatrician prescribed furosemide and amlodipine. A few days later, the patient returned to the pediatrician's office because of hand, ankle, and facial swelling and malaise. The pediatrician recommended hospitalization and the patient was admitted at this time.


Introduction

A 13-year-old girl presented with proteinuria and acute kidney failure. She was born at full term \textit{via} cesarean delivery (due to nuchal cord), but there were no other prenatal or perinatal complications. In early childhood, the patient had two hospitalizations at ages 4.5 and 9 years, respectively, the latter for pneumonia. She had no history of symptoms of kidney disease. She came to the hospital at age 12 years for routine bilateral molar extractions. She was treated with oral antibiotics and discharged after the procedure without complications. At age 13 years, 10 months after the molar extraction, she was seen by a pediatrician because of puffiness and increased BP. She had had respiratory symptoms 2 weeks before presentation. The pediatrician prescribed furosemide and amlodipine. A few days later she returned to the pediatrician's office because of hand, ankle, and facial swelling and malaise. The pediatrician recommended hospitalization and the patient was admitted at this time.

The patient reported no recent infections, including pharyngitis and skin infection. She had no family history of renal disease, although a sibling has type 1 diabetes, and no personal history of hematuria or proteinuria noted previously. Physical examination revealed a well developed, well-nourished female. On admission, her temperature was 36.8°C, heart rate of 84 beats/min, respiratory rate of 14 breaths/min, and BP of 128/84 mmHg. Her weight was 61.4 kg (25th percentile), and her height was 149 cm (25th percentile). She had erythema of the oropharynx, but no exudate. Auscultation revealed decreased breath sounds at the lung bases. Cardiac examination showed regular rate and rhythm without murmur or S4. The abdomen was soft, with no fluid detected. Extremities were remarkable for 2–3+ pretibial pitting edema to the knee.

Her urinalysis revealed 3+ protein, 4+ blood, and 2+ leukocyte esterase but was negative for glucose, bilirubin, nitrite, and ketones. Urine specific gravity was 1.030 with a pH of 5.0. Microscopic examination revealed 21–50 red blood cells/high-power field (hpf), 21–50 white blood cells/hpf, 2+ bacteria, <5 epithelial cells/hpf, and 1–5 hyaline casts; no cellular casts were seen. Initial laboratory studies are summarized in Table 1. The first eGFR, calculated using the Schwartz equation (1), was 102 ml/min per 1.73 m². Chest radiography revealed a small bilateral pleural effusion but no focal or diffuse parenchymal infiltrates.

The patient was restarted on diuretic therapy with 30 mg of furosemide given intravenously twice daily, and she was prescribed a low-sodium diet; normal BP was maintained with 5 mg amlodipine per day. During her hospitalization, her creatinine rose to 1.5 mg/dl and her BUN to 37 mg/dl. By day 4 after admission, the patient was hypertensive, necessitating an increase of amlodipine to 10 mg/d. Her creatinine increased to 2.5 mg/dl, her white blood cell count rose to 10,000 cells/ml, and her temperature increased to 38.4°C. Blood and urine cultures were performed. Systolic BP continued to rise to >140 mmHg, and creatinine peaked at 3.3 mg/dl.

A kidney biopsy was performed, which was well tolerated, and the patient was followed in the outpatient setting pending the results.

Clinical Discussant: Dr. Kevin E. Meyers

In summary, this 13-year-old girl presented with nephritic-nephrotic syndrome and a fairly rapid rise in the serum creatinine concentration. Two to three weeks before clinical presentation, she had an upper
respiratory tract infection. She seems to have no systemic findings other than those related to renal dysfunction. She is hypertensive with azotemia and has a low serum C3 concentration. The red blood cell morphology is normal.

### Differential Diagnosis

Several disorders can be considered in a young girl presenting with proteinuria, a rapid decline in renal function, and isolated hypocomplementemia. The history of an upper respiratory tract infection is compatible with her having had pharyngitis caused by Lancefield group A *Streptococcus* and may suggest an underlying acute post-infectious GN. Of note, “strep” throat infections may be subclinical or even silent. However, the antistreptolysin o titer done at the time of the sore throat was normal, suggesting that she has not had recent exposure to *Streptococcus*. To be certain, however, one would like to know about the streptozyme test results and throat swab rapid strep antigen test or throat culture results. There is growing recognition that upper respiratory tract infection that includes “strep” throat infection may act as a trigger or second hit precipitating a more chronic glomerulopathy (2,3).

The onset of systemic lupus erythematosus (SLE) should always be a consideration in a peripubertal girl. The presentation is compatible with that of SLE nephritis because there may be no extrarenal manifestations (4). Two factors arguing against the diagnosis of SLE as presented in the above case are the negative antinuclear antibody result and the normal C4 level. Activation of SLE nephritis usually occurs through the classic pathway unless pure membranous nephropathy is present; this is an unusual presentation for a child (5). As presented, then, a diagnosis of SLE nephritis is unlikely but still a possibility.

Subacute bacterial endocarditis and shunt nephritis with associated proliferative GN are rarely seen in children (6,7). When present, they occur in the specific context of a child with underlying cardiac disease or in the presence of cerebroventricle-to-atrium shunt placement. Activation is through the classic pathway, and the serum C4 and C3 concentrations are usually decreased.

Viral nephropathies can present with proteinuria and acute kidney failure. In the United States, there is almost universal coverage of children with hepatitis B vaccine, resulting in greatly decreased incidence and prevalence of hepatitis B–associated disease. Hepatitis B causes disease in the context of chronic antigenemia and most often presents with nephrotic syndrome, with histology showing a secondary membranous picture (8,9). Although we are not told about liver enzyme concentrations, this is an unlikely diagnosis, specifically because results of serologic testing for hepatitis B were negative (presumably s and e antigens).

Similarly, the patient has history of drug abuse, sexual intercourse, or blood transfusion to suggest hepatitis C. In the absence of these risk factors, hepatitis C is exceedingly unlikely in this patient. On the whole, it is most uncommon to see a proliferative GN in children with hepatitis C. When it does occur, it is usually in the context of readily identifiable chronic liver disease (10).

### Table 1. Laboratory test results and normal values

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient Results</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum sodium (mmol/L)</td>
<td>139</td>
<td>135–145</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.5</td>
<td>3.3–4.9</td>
</tr>
<tr>
<td>Serum chloride (mmol/L)</td>
<td>98</td>
<td>97–110</td>
</tr>
<tr>
<td>Serum carbon dioxide (mmol/L)</td>
<td>28</td>
<td>20–28</td>
</tr>
<tr>
<td>Serum urea (mg/dl)</td>
<td>16</td>
<td>9–18</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.8</td>
<td>0.2–1.2</td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>7.8</td>
<td>8.6–10.3</td>
</tr>
<tr>
<td>Serum glucose (mg/dl)</td>
<td>101</td>
<td>65–199</td>
</tr>
<tr>
<td>Plasma protein (mg/dl)</td>
<td>5.6</td>
<td>6.5–8.5</td>
</tr>
<tr>
<td>Plasma albumin (mg/dl)</td>
<td>2.3</td>
<td>3.2–5.9</td>
</tr>
<tr>
<td>LDH (mg/dl)</td>
<td>292</td>
<td>0–129</td>
</tr>
<tr>
<td>ALP (IU/ml)</td>
<td>142</td>
<td>44–147</td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood count (K/ml)</td>
<td>10.5</td>
<td>3.8–9.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.0</td>
<td>12.1–15.1</td>
</tr>
<tr>
<td>Platelets (K/ml)</td>
<td>493</td>
<td>140–440</td>
</tr>
<tr>
<td>Red blood cell morphology</td>
<td>Normal, no schistocytes</td>
<td>Normal</td>
</tr>
<tr>
<td>Complement C3 (mg/dl)</td>
<td>39</td>
<td>83–185</td>
</tr>
<tr>
<td>Complement C4 (mg/dl)</td>
<td>28</td>
<td>12–54</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASO titer (IU/ml)</td>
<td>38</td>
<td>0–200</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Anti-GBM antibody</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Hepatitis B serology</td>
<td>Negative</td>
<td>Negative for e and s antigen</td>
</tr>
</tbody>
</table>

LDH, lactate dehydrogenase; ALP, alkaline phosphate; ASO, antistreptolysin o; GBM, glomerular basement membrane.
As for possible HIV-associated kidney disease, her age, absence of history of early sexual contact, and lack of recurrent severe infection make this an unlikely diagnosis. Parvovirus has been associated with collapsing glomerulopathy (normal complement), and a proliferative form of GN (low complement) can present with a nephritic-nephrotic picture. However, activation of the complement cascade, when present, is through the classic pathway and is associated with a decrease in the serum C4 and C3 concentrations (11,12).

Another cause of isolated low C3 with proteinuria and AKI that needs to be strongly considered is membranoproliferative GN (MPGN), including MPGN II (also known as dense deposit disease [DDD]) (Figure 1). The classification and understanding of what was called MPGN types I, II, and III have changed rapidly (13–16). As found on immunofluorescence staining of the biopsy, we now think of “Ig-positive MPGN” where there is classic pathway activation and in which context a concerted effort should be made to identify the underlying cause of antigenemia. This includes evaluation for infections, autoimmune diseases, and monoclonal gammopathies (in adults) (Figure 2). This patient has no evidence for classic pathway activation, making this diagnosis unlikely. Ig-negative C3-positive MPGN is due to dysregulation of the alternative pathway and terminal complement complex. Depending on the relative degree of dysregulation, the electron microscopic picture can resemble DDD or C3 glomerulopathy (C3GN). Ig-negative MPGN I and MPGN III are well recognized; they fall under the umbrella of C3GN and are often called C3GN. DDD is now the preferred name for MPGN II and is another type of C3G. Extrarenal manifestations that may suggest DDD include partial lipodystrophy, both acquired and familial, as well as Drusen (17). Acquired partial lipodystrophy is associated with loss of subcutaneous fat in the upper half of the body in a cephalo-caudal sequence, with sparing of the legs (18). Drusen are whitish-yellow deposits within the Bruch membrane of the retina that develop from the second decade of life; about one tenth of affected persons later have visual problems through formation of subretinal neovascular membranes, macular detachment, and central serous retinopathy (19).

On the basis of immunofluorescence findings, MPGN is then broadly divided into Ig-positive, complement-positive MPGN and Ig-negative, complement-positive MPGN. Ig-negative, complement-positive MPGN is further divided into DDD and C3GN. This division is somewhat artificial and depends on electron microscopic findings. It is very likely that this patient has a C3GN. In light of the rapid increase in the serum creatinine concentration, she might well have the more unusual form of MPGN/C3GN that is associated with presence of crescents (20–22). The C3GNs are associated with disorders of the alternate complement regulatory pathway (13). The presentation is consistent with that of a rapidly progressive GN with glomerular crescent formation, which can be seen with many forms of glomerular disease, including MPGN. Atypical hemolytic uremic syndrome (aHUS) associated with complement abnormalities can have an MPGN-like picture by

**Abbreviations:** ANCA - antineutrophil cytoplasmic antibodies; APIGN - acute post infectious glomerulonephritis; HEP B – hepatitis B; HEP C – hepatitis C; HIVICK – human immunodeficiency virus associated immune complex disease; C3GN – complement 3 associated glomerulonephritis; DDD – dense deposit disease; aHUS – atypical hemolytic uremic syndrome; SLE – systemic lupus nephritis; SBE – subacute bacterial endocarditis.
light microscopy. However, microthrombi in the capillary loops and endothelial damage with subendothelial accumulation are expected. There should be a hemolytic anemia in association with a thrombocytopenia and evidence for intravascular hemolysis. We are not told about any of the hematologic measures except that the red blood cell morphology was normal. In other words, there were no schistocytes on the peripheral blood smear, which argues against an intravascular hemolytic process. Of note, complement factor H protein mutations that have given rise to C3GN and to aHUS in the same patient have been reported (23).

Acute interstitial nephritis or acute tubular necrosis with an underlying chronic GN is unlikely given the negative patient history, negative family history, normal growth, and absence of an immediate proximate cause.

**Clinical Diagnosis**
The most likely diagnosis is a C3GN, possibly DDD with crescents. aHUS is possible but unlikely in the absence of schistocytes.

**Pathology Discussant: Dr. Helen Liapis**
The kidney biopsy specimen contained 20 glomeruli, 18 of which had cellular crescents (90%); crescents were composed of epithelial cells and focal lymphocytes, but there were no fibrin deposits (Figure 3). The noncrescent glomeruli showed mild mesangial hypercellularity and irregular thickening of the capillary loops. On hematoxylin and eosin staining, the capillary loops appeared glassy and hypereosinophilic; they were strongly positive with periodic acid–Schiff staining (Figure 4), but did not stain with Jones silver stain (Figure 5). No globally sclerosed glomeruli were seen. The tubules were back to back, with minimal epithelial injury and no evidence of acute tubular necrosis. The interstitium contained mild, focal chronic inflammation, but there was no significant fibrosis. Small arteries and arterioles were intact, without wall thickening or luminal thrombi.

Immunofluorescence was negative for IgG, IgA, C1q, and \( \kappa \) and \( \lambda \) chains in the glomeruli and tubules. Strong C3 (3+ on a scale of 0–4) granular deposits were present in the capillary loops and focally in the mesangium (Figure 6); mild IgM+ (1+) was present; fibrinogen and albumin were equivocal.

The findings on light microscopy and immunofluorescence raised the differential diagnosis of (1) vasculitis, because of the presence of crescents in >50% of the glomeruli; (2) postinfectious GN, because of the predominance of granular C3 deposits; (3) C3GN; and (4) rare disease presenting as crescentic GN.

Electron microscopy revealed linear osmiophilic (ink black) intramembranous deposits and small granular mesangial deposits (Figure 7, A and B). The deposits were focally interrupted with a “sausage string” appearance. There were no deposits in the Bowman capsule; subepithelial, hump-like deposits were not seen. Taken together, the findings were diagnostic of DDD presenting as crescentic GN.

**What Are the Pathologic Findings of DDD?**
DDD is a rare disease affecting two to three children and adults per 1 million of population. Because of its rarity, histopathologic studies in large patient cohorts were not available in the literature until recently. Older studies considered DDD a type of MPGN and classified it as type II. However, an MPGN pattern is found in <50% of DDD cases (21,24). The light microscopic findings of DDD vary, ranging from minimal glomerular hypercellularity to mesangial proliferation in 25% of cases (24), and acute
proliferative GN with or without exudative lesions (neutrophil infiltrates) in some cases. Crescentic DDD is less frequent, occurring in 4%–10% of cases. Furthermore, DDD may mimic postinfectious GN both clinically and histopathologically, with some patients reported to have bell-shaped subepithelial glomerular deposits on electron microscopy. Histopathologic findings are the same in both children and adults, and no correlation is found with age, sex, ethnicity, or the level of C3 depression; degree of proteinuria; or creatinine level. MPGN pattern and crescents correlate with progressive disease but not with the percentage of global or segmental sclerosis. In children, girls are more frequently affected than boys, while in adults the reverse was reported (occurrence more frequent in men than in women) (21).

Immunofluorescence findings are consistently predominant C3 deposits, found in 100% of cases. Typically, Igs are absent. C3 deposits without Igs suggest activation of complement by antibody-independent pathways, typically the alternative pathway. The pattern of C3 deposits ranges
from linear to granular, the latter mimicking postinfectious GN. Both glomerular and tubular staining may be present. The predominance of C3 deposits has prompted investigators to currently classify DDD under C3 glomerulopathy, an entity defined by exclusive C3 deposits without other Ig and without dense intramembranous glomerular or tubular deposits. The term “C3 glomerulopathy” is gaining popularity because of the unraveled mechanisms underscoring both MPGN and DDD, which implicate abnormalities in the alternative complement cascade. Therefore, DDD is currently viewed in the spectrum of C3GN. Furthermore, the electron-dense deposits that characterize DDD are shown to contain components of the alternative pathway, including C3b and its breakdown products iC3b, C3dg, or C3c, and terminal complement complex. Glomeruli of DDD contain components of the alternative and terminal complement (25).

Abnormalities in the Alternative Complement Pathway in DDD

Following the kidney biopsy diagnosis of DDD, C3Nef, an autoantibody that stabilizes the alternative complement pathway C3 convertase, was ordered. The result was...
positive, confirming the diagnosis of DDD. C3Nef and depressed C3 serum levels, while characteristic and more frequently found in patients with DDD, are not exclusive; they are also found in 45% of C3 glomerulopathy cases. This patient underwent genetic analysis and was found to carry three copies of DDD-associated CFH allele variants in addition to C3Nef activity. No mutations were found in CFH, CFI, MCP, or CFH-CFHR5 genes (Table 2). Abnormalities in the alternative complement pathway are identified in as many as 80% of patients with DDD (26) and include the following: autoantibodies (C3Nef, CFB, C3b); allele variants (17%); homozygous loss-of-function CFH mutations; heterozygous CFH mutations; and mutations in CFI, CFB, and MCP.

C3Nef is present in most cases of DDD (80%) (27). However, other autoantibodies against CFB or specifically against C3b are also reported. Homozygous, loss-of-function CFH mutations are rare. Heterozygous CFH mutations are also infrequent, but CFH allele variants are detected in 17% of DDD cases. Particular variants of CFH (H402Y) and of CFHR5 may preferentially be associated with DDD (28–30). Similar abnormalities are detected in patients diagnosed with MPGN type I and C3 glomerulopathy defined by the pathologic findings as described above. Therefore, these entities are increasingly found to have overlapping abnormalities in the alternative complement pathway and are considered C3-mediated diseases (Tables 3 and 4).

The histopathologic spectrum of diseases due to alternative complement pathway abnormalities was recently expanded to include entities beyond MPGN and C3 glomerulopathy. For example, FSGS was found in a 60-year-old woman with a novel polymorphism (SCR) 12 of CFH (CFH; c.2195C>T, p.Thr732Met and factor C3 (c.463A>C, p.Lys155Gln) (31). Furthermore, the incidence

Figure 7. | Electron microscopy revealed linear, osmiophilic deposits in (A) the capillary loops (white arrow) and (B) the mesangium (black arrow). The deposits were discontinuous and focally were “sausage” shaped (electron microscopy; original magnification, ×8000).
of concurrent aHUS with DDD or aHUS preceding or following DDD is recognized (26). In adults, age-related macular degeneration is linked to CFH mutations. Other entities include mutations in CFH-related proteins (CFHR) 5 and 3.

The CFH gene structure has been studied in detail, and some understanding of how specific mutations in the same gene may cause a histopathologically and clinically different disease is emerging. For example, mutations in DDD are near the C terminus (32).

However, the question of how the same CFH mutation may lead to two different renal diseases in the same patient (e.g., DDD and aHUS) is not currently clear.

### DDD Is Frequently Associated with Infection: Is Infection a Cause or Coincidence?

The relationship between infection and kidney disease, particularly C3-mediated entities, is well documented. This patient had a remote history of pneumonia and a vague history of respiratory infection 2 weeks before symptoms that lead to hospitalization. Others have reported urinary tract infections in association with symptomatic DDD (21). MPGN is well known to be secondary to infectious microorganisms, such as hepatitis C virus. Classic HUS associated with Shiga toxin–producing bacteria is another example of infection causing direct kidney injury. Atypical HUS is associated with genetic mutations coding for complement factors H and I, MCP, C3, and factor B (33) and is linked to genetic mutations and an autoimmune form, including a special form, (deficiency of CFHR plasma proteins and autoantibody-positive form of HUS) (34–37). Recently, aHUS due to mutations or variants of noncomplement-related genes was also reported (38,39). Therefore, both DDD and aHUS are now understood as complement-mediated diseases resulting from abnormalities in the alternative pathway.

### Complement Dysregulation in DDD, MPGN, and Mesangiproliferative and Crescentic GN

The alternative pathway is constantly activated at low levels physiologically and plays a central role in immune surveillance as a first line of defense. This suggests that C5b-9 is activated and deposited in a constitutive manner at a low level even in normal kidney tissue by a “tick-over” mechanism, which leads to C5 recruitment in the fluid phase (40). Activation is tightly regulated by factor H and complement factor I, the two most important inhibitory proteins of the alternative pathway. Soluble as well as membrane-bound complement regulators control complement activation at the cell surface at different activation phases and sites of action (41). Complement dysregulation is frequent in kidney disease, and peripheral markers of complement activation (e.g., serum levels of C3 and C4) are routinely tested in acquired glomerular diseases, including postinfectious GN, lupus nephritis, cryoglobulinemia, and cholesterol embolism. Bacteria are known to use complement to their advantage. Therefore, infection may trigger complement consumption and precipitate symptoms in a preexisting disease, but most investigators believe that infection is not a cause of DDD.

As mentioned under the clinical discussion, both DDD and Ig-negative MPGN are characterized by isolated C3 deposits on immunofluorescence, and both are categorized under the umbrella of C3 glomerulopathies. Subclassification of DDD as MPGN II has created unnecessary confusion. DDD is a better term instead of MPGN II simply because in about 50% of cases DDD has no MPGN pattern but may present as mesangial proliferative GN or crescentic GN, exemplified by the case under discussion. DDD and

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**Table 2. Genetic analysis results**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Single-Nucleotide Polymorphism Reference ID</th>
<th>Risk Allele</th>
<th>Nucleotide</th>
<th>Copies in Patient (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>rs800292</td>
<td>p.Val62</td>
<td>c.184G</td>
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<tr>
<td>CFH</td>
<td>rs1061170</td>
<td>p.His402</td>
<td>c.1204C</td>
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<tr>
<td>C3</td>
<td>rs2330199</td>
<td>p.Gly102</td>
<td>c.304G</td>
<td>Not done</td>
</tr>
<tr>
<td>C3</td>
<td>rs1047286</td>
<td>p.Leu314</td>
<td>c.941T</td>
<td>Not done</td>
</tr>
</tbody>
</table>

**Table 3. Mutations in the complement genes and C3Nef in C3-mediated diseases by histologic type in adults and children**

<table>
<thead>
<tr>
<th>Gene</th>
<th>All (n=134)</th>
<th>MPGN (n=48)</th>
<th>DDD (n=29)</th>
<th>C3GN (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFH</td>
<td>17 (12.7)</td>
<td>5 (10.4)</td>
<td>5 (17.2)</td>
<td>7 (12.4)</td>
</tr>
<tr>
<td>CHI</td>
<td>6 (4.5)</td>
<td>3 (6.2)</td>
<td>0</td>
<td>3 (5.3)</td>
</tr>
<tr>
<td>MCP</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%). Modified from Servais et al. (26). MPGN, membranoproliferative GN; DDD, dense deposit disease; C3GN, C3 glomerulopathy.

**Table 4. C3-mediated diseases**

<table>
<thead>
<tr>
<th>DDD</th>
<th>C3 glomerulonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Familial C3 Complement factor H-related due to rearrangements affecting the CFHR genes (52,53)</td>
</tr>
<tr>
<td></td>
<td>Secondary FSGS associated with single-nucleotide polymorphisms in genes encoding complement factors H and C3 (31)</td>
</tr>
<tr>
<td></td>
<td>Atypical hemolytic uremic syndrome</td>
</tr>
<tr>
<td></td>
<td>Age-related macular degeneration (54)</td>
</tr>
</tbody>
</table>

Values in parentheses are reference citations.
C3 glomerulopathies, including Ig-negative MPGN, have common pathogenic alternative pathway protein abnormalities, as shown in Figure 8.

### Table 5. Summary of dense deposit disease

| DDD is histologically and molecularly heterogeneous |
| Allele polymorphisms are frequent |
| C3Nef more frequent than in MPGN I, C3GN |
| Recurrence about 50% |
| DDD is closely related to C3GN |
| DDD is also related to aHUS, and they may represent extremes in a continuous spectrum of complement-related diseases |
| Symptoms may be triggered by infection |

C3 glomerulopathies, including Ig-negative MPGN, have common pathogenic alternative pathway protein abnormalities, as shown in Figure 8.

### DDD Progression to ESRD and Recurrence After Transplantation

Approximately 50% of patients with DDD progress to ESRD and require dialysis within 10 years of diagnosis. Factors predictive of progression to renal failure include younger age at diagnosis, increased serum creatinine concentrations, and proteinuria at the time of diagnosis, initial presentation with nephrotic and nephritic syndromes, and >20% chronic renal damage. Crescents are also a bad prognostic finding. Servais et al. reported a 63.5% 10-year survival rate in patients with DDD (26). Renal survival was similar to that seen with MPGN I and C3GN and somewhat worse than that in DDD (Table 5).

### Final Pathologic Diagnosis

Crescentic DDD with presence of C3Nef autoantibody.

### Treatment

This patient, who initially presented >10 years ago, was treated with pulsed intravenous methylprednisolone and intravenous cyclophosphamide without good effect. She became dialysis dependent within 3 weeks of presentation and failed to recover renal function. She ultimately underwent cadaveric kidney transplantation without complications and has been stable with normal kidney function without recurrence of the DDD.

Previous treatment of DDD has traditionally included immune suppression targeting T cells and/or B cells (glucocorticoids, cyclophosphamide, mycophenolate mofetil, rituximab) and plasma therapy or plasmapheresis (42). There is no good evidence that any of these therapies reliably alters renal survival in most patients with DDD, even when used for prolonged periods (26,43,44). The Kidney Disease Improving Global Outcomes clinical guidelines to treat children and adults with idiopathic MPGN accompanied by nephritis and progression of disease with “oral cyclophosphamide or MMF [mycophenolate mofetil] plus low dose daily or alternate day corticosteroids with initial therapy limited to less than 6 months” is based on insubstantial evidence and is not supported by recent experience (45–47).

### Treatment Today and into the Future

A growing number of case reports have detailed the use of anti–complement C5 therapy, specifically eculizumab, as treatment for DDD both before and after transplantation (44,47–50).

Bomback et al. performed a trial of eculizumab in C3 glomerulopathy (46). This open-label, proof-of-concept, efficacy, and safety study evaluated three patients with DDD (one with a renal transplant) and three patients with C3GN (two with a renal transplant). The patients received eculizumab every other week for 1 year. Genetic
testing revealed a mutation in CFH and CD46 in one patient each. Complement function testing revealed C3NeF in three patients. There was a mixed response after 12 months of therapy: Two patients (one with DDD and one with C3GN) showed significantly reduced serum creatinine, one patient (with DDD) had marked reduction in proteinuria, and one (with C3GN) had only histologic improvement without biochemical change. The response to eculizumab varied. The authors suggested that an elevation of sC5b-9 was potentially a marker of responsiveness to eculizumab. A recent case published by Gurkan et al. details the temporary response of a child with DDD whose disease progressed during eculizumab treatment (51).

On the basis of our current understanding of the pathogenesis of DDD, targeted anticomplement therapy warrants further consideration. This could be directed at C3 convertase inhibition to limit C3 breakdown product deposition on basement membranes and/or C5 or terminal complement pathway inhibition. The evidence to date, combined with our current understanding of the pathophysiology of C3GN, suggests that a formal trial of eculizumab in many well-characterized patients is indicated.

Disclosures
None.

References
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