

IMAGE QUIZ 5

CLINICAL HISTORY:

A 10 year old boy presented with anasarca and oliguria since 6 weeks. There was no history of preceding upper respiratory infections or gross hematuria.

INVESTIGATIONS:

Urine albumin 3+, RBC 8-10/hpf (25% dysmorphic), WBC 4-6 /hpf

Urea 34 mg% (12.1 $\mu\text{mol/L}$), Creatinine 1.4 mg% (123.7 $\mu\text{mol/L}$)

HBsAg/HCV/HIV- negative, Cholesterol 158 mg% (4.09 mmol/L)

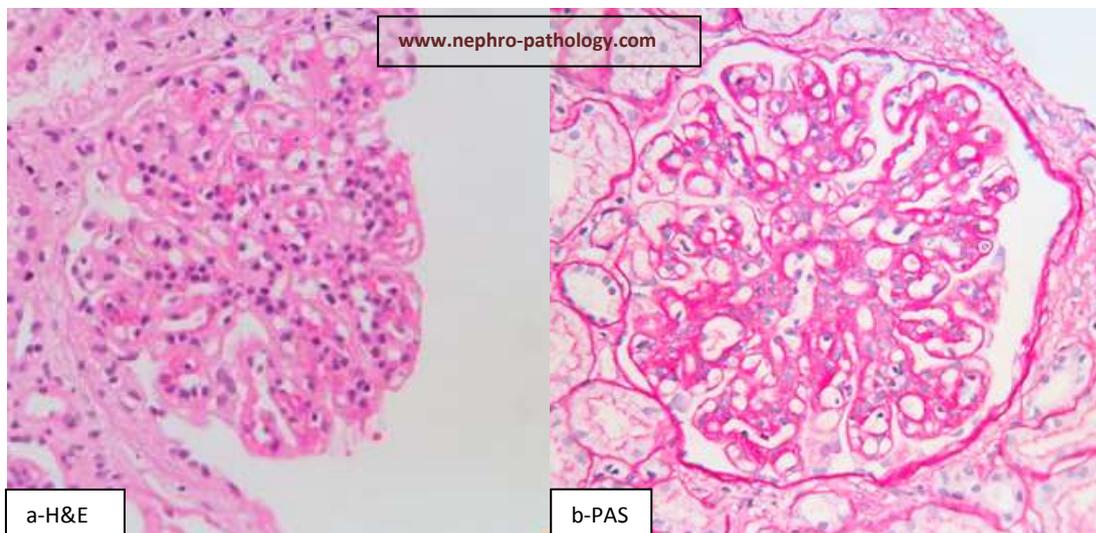
C3 18 mg% (0.18 g/L), C4 36 mg% (0.36 g/l)

ANA/ANCA/anti GBM antibodies/anti dsDNA- negative

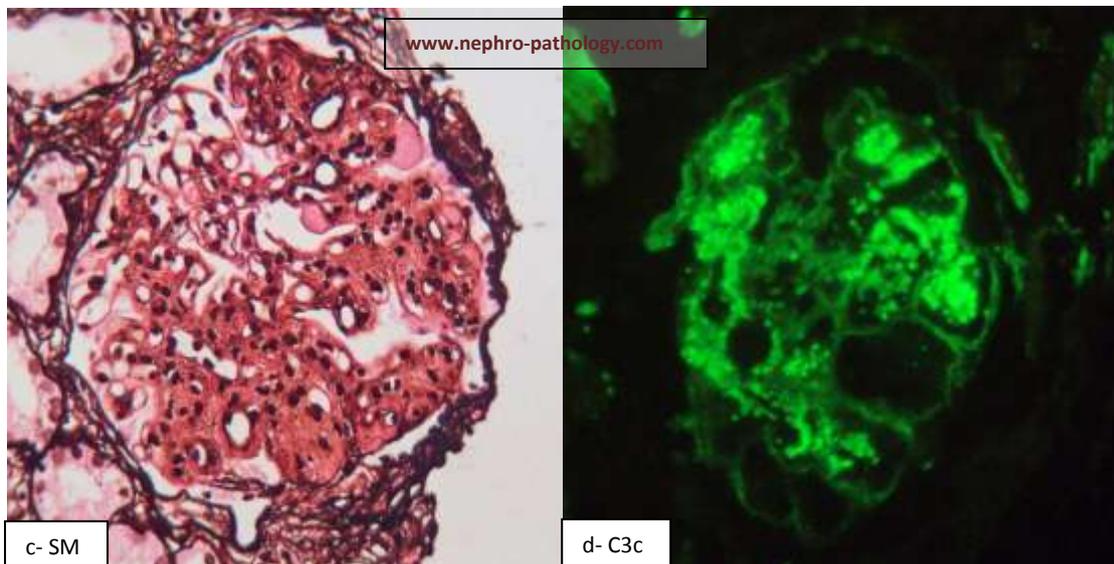
In view of non-resolving nephrotic-nephritic syndrome with severe hypocomplementemia, a renal biopsy was performed.

Representative light microscopic images and DIF image of C3 stained section is provided. The glomeruli were negative for IgA, IgG, IgM, C1q and kappa and lambda light chains in DIF studies

MICROSCOPY



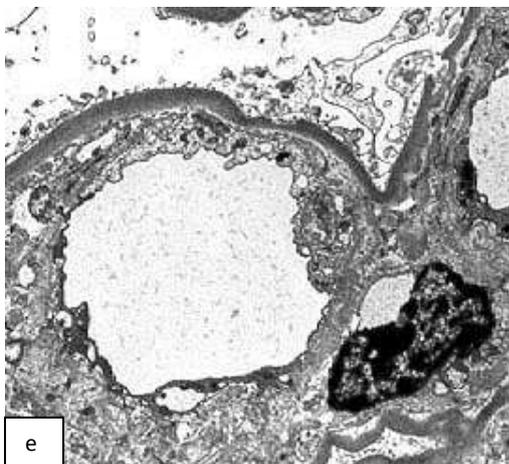
Light microscopic studies revealed a membranoproliferative injury pattern with mesangial proliferation, matrix expansion and diffuse thickening of glomerular capillaries (a). The mesangium and thickened capillaries are PAS positive (b).



Silver methenamine stained sections (c) show argyrophilic periphery of capillaries and negative/weakly positive internal staining, corresponding to capillary wall (and mesangial) deposits.

DIF studies show exclusive/isolated staining for C3 with a characteristic pattern of “band like” staining in peripheral capillaries and coarse granular positivity in central mesangial areas with few “ring like” forms.

Based on serological features (severe hypocomplementemia: low C3 with normal C4 levels), membranoproliferative glomerular injury pattern, and exclusive/ isolated deposits of C3 in a characteristic pattern, possibilities of Dense Deposit Disease and C3 glomerulonephritis were considered.



Ultrastructural examination confirmed the intense “ribbon like” confluent electron dense deposits in capillary walls and mesangial areas (e).

DIAGNOSIS:

Dense Deposit Disease (DDD)

DISCUSSION:

Dense Deposit Disease (DDD) or Membranoproliferative glomerulonephritis Type 2, MPGN II is rare disease, accounting for less than 20% of cases of MPGN in children and only a small proportion of cases in adults. Its morphologic hallmark is the presence of dense, often ribbon like continuous or discontinuous deposits within the lamina densa of glomerular basement membrane (GBM) and less often in mesangial areas seen by electron microscopy. The entity was first described in 1975 by Habib et. al [1] as a variant of Membranoproliferative glomerulonephritis, and since then great strides have made in understanding the pathogenesis and pathophysiology of the disease. MPGN II affects both genders equally and is usually diagnosed in children between 5 and 15 years of age and may present with one of five findings: Hematuria, proteinuria, hematuria and proteinuria, acute nephritic syndrome, or nephrotic syndrome. Although these findings are nonspecific, about 80% of patients with MPGN II are positive for serum C3 nephritic factor (C3NeF), an autoantibody directed against C3bBb, the convertase of the alternative pathway (AP) of the complement cascade [2].

Patients with MPGN II can develop drusen, which are whitish-yellow deposits within the ocular Bruch's membrane, beneath the retinal pigment epithelium. Over long time, these may affect vision due to formation of neovascular membranes, macular detachment, and central serous retinopathy in approximately 10% of the patients [3]. MPGN II can be associated with acquired partial lipodystrophy (APL). This manifests as loss of subcutaneous fat in the upper half of the body and usually precedes the onset of kidney disease by several years [4-5]

Spontaneous remissions of MPGN II are uncommon and most patients suffer from chronic deterioration of renal function leading to ESRD in approximately half of patients within 10 yr of diagnosis [6-8].

The pathophysiologic basis for MPGN II seems to be the uncontrolled systemic activation of the alternative pathway of the complement cascade. There are different triggers that result in complement system dysfunction, including mutations in fH, antibodies directed against fH, and an autoantibody directed against C3bBb called C3NeF that is present in most people with MPGN II.

It is thought that dense deposit disease is a more accurate descriptive name than MPGN II because dense deposits are diagnostic and are not invariably associated with prominent capillary wall thickening or hypercellularity [9]. On light microscopy, the dense deposits associated with DDD are eosinophilic and refractile, stain brightly with periodic acid-Schiff, and are highly osmophilic, explaining their electron-dense appearance [10]. Often, they are present in the mesangial matrix, along the basement membranes of tubules and Bowman's capsule, and around small vessels.

The characteristic immunopathological finding in MPGN II is intense and exclusive (usually no immunoglobulins are seen while the glomeruli may show variable staining for C1q) deposition of C3 along the glomerular capillary walls in a ribbon-like pattern and in the mesangial regions as coarse granules, "rings" or "spherules" [11]. Recent studies using laser capture microdissection and mass spectrophotometric analysis of proteins has shown that in addition to fluid-phase dysregulation of the alternative pathway (C3), soluble components of the terminal complement complex (clusterin and vitronectin) also contribute significantly to glomerular lesions found in DDD [12].

Most treatments for MPGN II are ineffective. Although only a few patients will have fH mutations, genetic screening of fH should be completed on all patients with MPGN II. Treatments to remove or suppress C3NeF activity include plasmapheresis, IVIg, and B cell suppression [13]. Recent reports have documented utility of eculizumab in DDD [14-16].

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