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Crescentic C3 glomerulopathy with acquired partial lipodystrophy: An unusual cause of rapidly progressive renal failure

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Complement component C3 glomerulopathy (C3GP) is a recently defined entity characterized by predominant glomerular C3 fragment deposition with absent or scanty immunoglobulin deposition due to abnormal control of complement activation, deposition, or degradation.[1] C3GP is subcategorized morphologically into dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) based on electron microscopic (EM) findings. DDD previously called membranoproliferative glomerulonephritis Type II refers to cases with hyperosmiophilic, dense transformation of glomerular basement membranes (GBM) on EM[2] and other cases of C3GP without the pathognomonic ultrastructural findings are designated C3GN. DDD has an estimated prevalence of 2–3/million population[3] and traditionally presents with nephritic-nephrotic syndrome in children or young adults.[4] We describe a rare case of DDD with crescentic glomerulonephritis, presenting as rapidly progressive renal failure (RPRF) in an adult female patient, associated with acquired partial lipodystrophy (Barraquer Simons' or Dunnigan-Koeberling syndrome).[5]

A 26-year-old female presented with RPRF. She had prominent loss of subcutaneous adipose tissue around cheeks suggestive of acquired partial lipodystrophy [Figure 1a]. Investigations showed proteinuria (3.5 g/400 ml urine/day) with active urine sediments (red blood cell 19, white blood cell 63/HPF), serum creatinine 6.64 mg/dL, low complement component C3 (16.9 mg/dL [normal range >90]) and normal C4 (28 mg/dL). ANA, DsDNA, ASO, and ADNaseB levels were within normal limits. Serology for hepatitis viruses and HIV was negative. Renal biopsy showed cellular and fibrocellular crescents in 8 of 10 glomeruli with mesangial expansion, proliferation, and thickened capillary walls [Figure 1b-d]. Immunofluorescence showed isolated coarsely granular deposits of only C3. EM showed dense transformation of GBMs in all glomeruli due to hyperosmiophilic, ribbon-like intramembranous deposits [Figure 2a and b] and similar deposits in tubular basement membranes [Figure 2c] confirming the diagnosis of DDD/C3GP with crescentic glomerulonephritis.

She received steroids and plasmapheresis. On the last follow-up at 3 months, she was dialysis dependent.

In a recent study of clinicopathological features of C3GP by Terence Cook *et al.*, patients with DDD were found to be younger, more likely to have low serum C3 levels, and more likely to have crescentic GN than patients with C3GN.[1] However, in the largest study from India to date, none of the biopsies diagnosed with DDD had crescentic glomerulonephritis.[2] Our patient was 26-year-old, presenting with RPRF and renal biopsy demonstrated crescentic GN by light microscopy and ultrastructural examination revealed DDD. This being the first case of DDD with crescentic GN and acquired partial lipodystrophy reported from the Indian population may be reflective of existing ethnic diversity within India.

Acquired partial lipodystrophy (Barraquer Simons' or Dunnigan-Koeberling syndrome) in which subcutaneous fat is lost from the face and upper body, has a well-established association with DDD[3] and was present in this patient also. It often predates the onset of renal clinical manifestations of DDD. Other reported associations include ocular drusen,[4] monoclonal gammopathy in older patients[5] and increased risk of diabetes mellitus type I in families with DDD. We investigated our patient for these associations also which yielded negative results.

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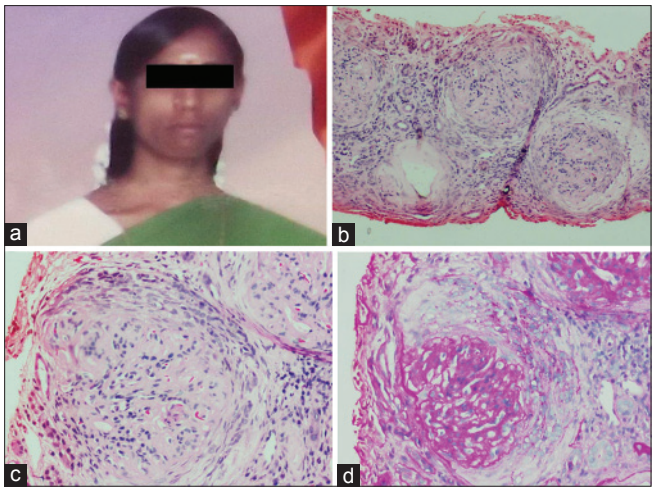

Figure 1: (a) Acquired partial lipodystrophy of face. (b) Crescentic glomerulonephritis with marked thickening of capillary walls and narrowed capillary lumina (H and E, ×200). (c) Fibrocellular crescent with mesangial proliferation and narrowed capillary lumina (H and E, ×400). (d) Fibrocellular crescent and glomerular capillary wall thickening due to deposits (PAS, ×400)

The presence of C3 in the absence of immunoglobulins in C3GP suggests activation of complement by antibody-independent pathways, typically the alternative pathway, and many patients have evidence of genetic or acquired alternative pathway dysregulation. The absence of Complement factor B from glomerular tissue on laser microdissection is consistent with alternate pathway C3 convertase formation leading to excessive C3 activation in the fluid phase, with subsequent deposition of C3 breakdown products.

RPRF defined as decline in renal function of >50% over days to weeks, almost always presents to a nephrologist as a clinical emergency. Accurate diagnosis of etiology by renal biopsy is crucial in management and prognostication of patients with RPRF. The diagnosis of DDD rests on EM, and it may be worthwhile to include ultrastructural examination of renal biopsies in such scenarios for accurate subcategorization.

It is important to diagnose and segregate patients of C3GP from other glomerular diseases with similar morphological patterns as targets for therapy are different. Immune complex-mediated disease needs targeting primary infection, relevant autoantibodies, or clonal light chains according to the diagnosis. In C3GP, plasmapheresis for removal of autoantibodies and use of ecluzimab targeted against C5 component are the only potential available therapies. Variants of C3GP are also important from renal transplantation perspective as rate of recurrences are variable with different subtypes of C3GP.

This case highlights an unusual presentation of a rare disease along with its uncommon clinical associations. A comprehensive renal biopsy examination inclusive of EM is essential for diagnosis and contributes to patient management and prognostication.

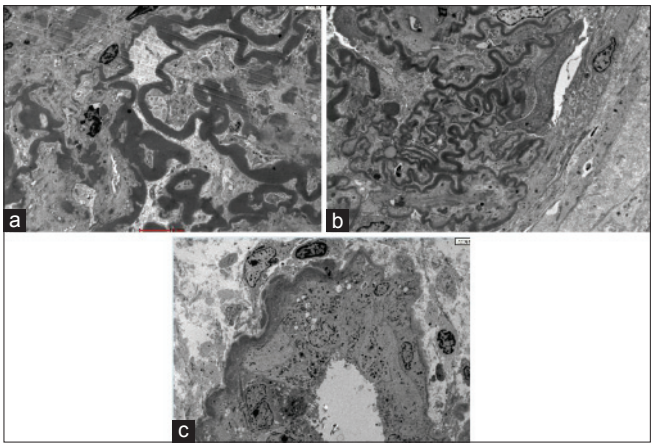

Figure 2: (a) Dense, osmiophilic, ribbon like transformation of glomerular basement membranes in dense deposit disease, transmission electron microscopy (×1700). (b) Ischemic collapse of glomerular tuft with dense deposit disease, transmission electron microscopy (×2550). (c) Tubular basement membrane dense deposits, transmission electron microscopy (×1700)

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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