IgM-dominant Glomerular Immune Complex Deposition in Renal Transplant biopsies

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BACKGROUND

- IgM nephropathy is an uncommon glomerular disease characterised by diffuse mesangial IgM deposition with electron dense deposits (EDDs)[1] often thought to be a bridge between minimal change disease and focal segmental glomeruloscerlosis (FSGS).
- It was first described as a distinct glomerular disease by two independent research groups in 1978, however its definition and clincopathological significance remains controversial.
- IgM nephropathy can be seen in systemic diseases (e.g. SLE, rheumatoid arthritis, vasculitis, paraproteinaemias), as well as in renal transplant biopsies associated with infections, thrombotic microangiopathy and chronic antibody mediated rejection (cAMR); however, its significance in the renal allograft has not been characterised.

METHODS

- We retrospectively identified 16 patients with ≥2 transplant biopsies at least 6 months apart, between 2005 and 2017, where the index biopsy satisfied the following criteria:
  1. dominant or co-dominant mesangial staining for IgM on immunofluorescence (≥ 1+)
  2. mesangial electron dense deposits; and
  3. excluded cases with systemic diseases, infections, thrombotic microangiopathy or cAMR.
- We compared the clinicopathological features associated with transient and persistent IgM deposition in the renal allograft.

RESULTS

Clinical Features

- None of the patients had a native kidney biopsy to confirm underlying cause of ESRD.
- This was the first allograft in all cases with the median age at transplantation being 50 years (range 18-67years).
- The median time from transplant to detection of mesangial IgM deposits was 25.5 months (range 10-78months).
- The indication for biopsy was surveillance (50%), proteinuria and worsening creatinine (25%), worsening creatinine only (19%) and proteinuria only (6%).
- At biopsy, 68.75% had creatinine ≥100umol/L and 43.75% had proteinuria (UPCR ≥100mg/mmol).

Demographic and clinical findings between transient and persistent IgM nephropathy patients	Transient IgM [n=6(%)]	Persistent IgM [n=10(%)]	p-value
Male Gender	5 (83%)	4 (40%)	0.09
Caucasian	3 (50%)	5 (50%)	1.00
Diabetes	2 (33%)	7 (70%)	0.17
Indication biopsy	3 (50%)	6 (60%)	0.72
Mean time to biopsy (months)	28.83	34.70	0.59
Mean creatinine at biopsy (umol/L)	123.50	138.10	0.62
Mean eGFR at biopsy (ml/min/1.73m2)	54.17	49.10	0.61
Mean UPCR at biopsy (mg/mmol)	74.67	110.50	0.51
DSA at biopsy	0 (0%)	1 (10%)	0.46
Rejection at anytime	3 (50%)	2 (20%)	0.24

Pathological Features

- The most common glomerular pattern of injury on light microscopy was mesangial hypercellularity (87.5%) (Figure 1a) with focal segmental glomerulosclerosis in 50% of the cases. The average interstitial fibrosis and tubular atrophy (IFTA) was 16.25%.
- All cases showed diffuse mesangial staining for IgM (≥ 1+) (Figure 1b). 5 cases also had staining for C1q and/or C3.
- All cases showed mesangial EDDs (Figure 1c) with segmental foot process effacement. 75% had a degree of glomerular basement membrane (GBM) thickening.

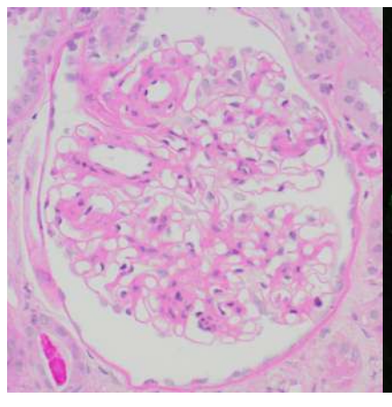

Figure 1a: PAS stain showing mesangial expansion and mild mesangial hypercelluarity

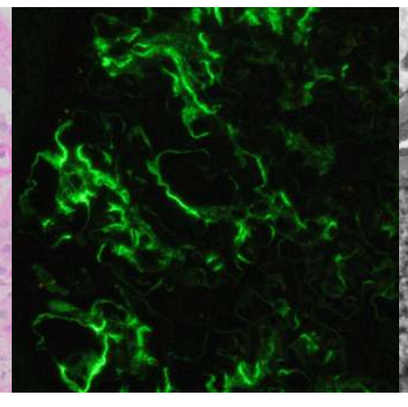

Figure 1b: IF showing granular mesangial IgM 2+

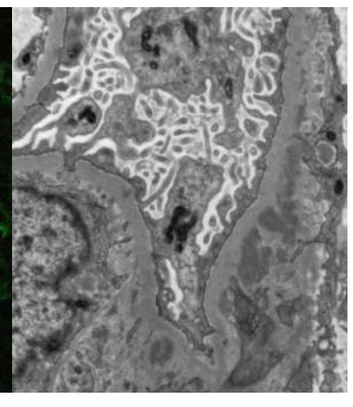

Figure 1c: Electron microscopy showing mesangial electron dense deposits

Renal Biopsy findings between transient and persistent IgM nephropathy patients	Transient IgM [n=6(%)]	Persistent IgM [n=10(%)]	p-value
Mesangial hypercellularity	4 (67%)	10 (100%)	0.18
FSGS	3 (50%)	5 (50%)	1.00
Mean IFTA (%)	18.33%	15%	0.71
GBM thickened	4 (67%)	8 (80%)	0.58

Treatment & Outcomes

- Median clinical follow-up was 87 months.
- At time of the index biopsy, 2 patients were treated for rejection with the addition of mycophenolate mofetil (MMF) and prednisone; 1 patient had MMF added due to a new Class I DSA; and 1 patient had plasma exchange and rituximab as per our local FSGS in transplant protocol with plasma exchange and rituximab.
- Death censored allograft survival was no different between the transient and persistent IgM nephropathy groups, p=0.17.
- There was also no difference in patient survival (p=0.24) nor all cause graft loss (p=0.24).

DISCUSSION

- To the best of our knowledge this is the first case series in literature characterising IgM deposition in the renal allograft.
- We conclude that IgM mesangial deposition in the renal allograft is a morphological pattern that can be transient, and has no apparent clinical significance in the majority of patients.
- It can be detected as early as the first the year of transplant and most cases show mesangial hypercellularity.
- We did not elucidate the aetiology behind the transient nature of IgM nephropathy and a larger cohort study is needed.

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