P331

P331 -Syndromic C3 glomerulopathy reveals a shared genetic risk factor with age-related macular degeneration

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Introduction
C3 glomerulopathy (C3G) is an ultra-rare kidney disease that can share similar clinical and histopathological findings with post infectious glomerulonephritis (PIGN) at initial presentation. Unlike PIGN, C3G follows a chronic progressive course with 50% of patients progressing to end stage renal disease (ESRD) within 10 years. C3G is usually caused by dysregulation of the alternative pathway of complement, leading to dominant C3 deposition within the glomerulus. This is usually an acquired phenomenon in the setting of C3 Nephritic factor (C3Nef) but rare genetic variants have been described in complement factor H (CFH) and C3. Age-related macular degeneration (AMD), the commonest cause of blindness in the developed world, shares similar genetic risk factors with C3G. We present a case of acute kidney injury (AKI) initially attributed to PIGN which relapsed suggesting a diagnosis of C3G. The confluence of C3G and AMD in the absence of C3Nef led to genetic analysis and identification of a pathogenic mutation in CFH.

Case description
An 82 year old lady presented with a history of polyarthritis and purpuric rash on her legs with a previous diagnosis of AMD. She had an elevated creatinine at presentation, peaking at 380µmol/L, consistent with AKI. Urine dipstick showed blood and protein and urine P:Cr was elevated at 389 mg/mmol. A clinical diagnosis of Henoch-Schönlein Purpura was considered and empirical treatment with high-dose steroid was commenced. A renal biopsy showed acute diffuse endocapillary proliferative glomerulonephritis with coarse C3 deposition on immunofluorescence (IF). The electron microscopy (EM) showed larger and 'hump-like' electron dense deposits in a subepithelial distribution. Her presentation was attributed to PIGN, her prednisolone was tapered and her creatinine improved to her previous baseline (~150 µmol/L) after 5 months.
Two years later at routine renal follow-up, she had a further rise in creatinine to 300 µmol/l. Her urine P:Cr had remained persistently greater than 100mg/mmol since the initial presentation. A renal biopsy was repeated and showed again showed diffuse endocapillary proliferation. There was strong deposition of C3 on IF with no other specific deposition. On this occasion, EM showed electron dense deposits, seen in a subepithelial, subendothelial and intramembranous distribution.
We proceeded to complement profile testing and confirmed low factor H levels (0.25g/L [normal range 0.35-0.59 g/L]). Genetic testing revealed a pathogenic CFH mutation (c.265G>T p.Gly189X). C3Nef was negative.
The underlying renal disease was reclassified as C3G and she was treated with prednisolone and mycophenolate mofetil (MMF). Her renal function returned to baseline again and her urine P:Cr has fallen to 20mg/mmol at latest follow up.

Discussion
Pathologically PIGN and C3G are difficult to distinguish with clinical course and laboratory findings required for a definitive diagnosis. In this case the failure to resolve and the associated AMD led to genetic screening which identified a pathogenic mutation in CFH confirming the diagnosis of C3G. This helped determine optimal treatment options e.g. prednisolone and MMF as defined in KDIGO guidelines.