34 male, physician

- Detected with 3+ proteinuria and microscopic hematuria during evaluation of generalized weakness
- No edema, dyslipidaemia, mild hypoalbuminemia
- No family history of renal disease
- 24 hours UP 3.1 gm
- Creatinine 1.1 mg%
- ANA, anti ds DNA – negative, C3 & C4- WNL
- Viral markers- negative
CLINICAL HISTORY

• Unresponsive to steroids

• Renal biopsy performed- reported as MPGN
  • Segmental M,G and C3 in DIF studies (? Immune mediated MPGN)
  • Tubulointerstitium well preserved

• Initiated on MMF, cyclophosphamide and CNI’s at various centres- persistent proteinuria

• Repeat biopsy offered (after 8 months of initial biopsy)
? Diagnosis
Differential diagnosis of MPGN pattern injury

- Membranoproliferative glomerulonephritis (type I, II/DDD/C3 GN, or IIIB/IIIS)
- Diabetic glomerulosclerosis with nodular mesangial expansion (KW nodules)
- Monoclonal immunoglobulin deposition disease with nodular sclerosis
- Lupus nephritis
- Idiopathic (smoking associated) nodular glomerulosclerosis
- Thrombotic microangiopathy (Chronic)
- Transplant glomerulopathy
- Fibrillary glomerulonephritis
- Immunotactoid glomerulopathy
- Fibronectin glomerulopathy
- Type III Collagen glomerulopathy (Collagenofibrotic glomerulopathy)
Salient features in this case

- MPGN pattern injury
- C3 & C4 normal
- DIF negative
- Congo red – negative
- PAS positive (intense) and silver stain negative mesangial areas
- Fuchsinophilic mesangial & capillary wall material
- No definite fibrillary structures/ electron dense deposits in EM
Diagnosis- Fibronectin glomerulopathy
Fibronectin nephropathy/glomerulopathy is a genetically heterogeneous autosomal dominant disorder characterized clinically by proteinuria, microscopic hematuria, and hypertension that leads to end-stage renal failure in the second to fifth decade of life.
• FN is a dimeric glycoprotein with two nearly identical 250 kDa subunits.
• It is a component of several normal matrices, involved in the control of cellular proliferation and cell-to-cell interactions, including platelet adhesion and thrombogenesis.
• Increased FN expression in diabetes or glomerulonephritis usually reflects local mesangial or epithelial cell production of the *insoluble, cellular form*.
• FN glomerulopathy results instead from massive deposition of the *soluble, plasma isoform*.
DISCUSSION

- Clustering of the disease within families indicates a genetic origin, and segregation with disease appearance in successive generations is consistent with an *autosomal dominant* pattern of inheritance with age-related penetrance.

- In 40% of families the disease is caused by heterozygous mutations in the FN1 gene (2q34) encoding fibronectin.

- Whole-genome linkage analysis in a large pedigree showed another disease locus on 1q32.

- No specific candidate genes has been identified so far.
DISCUSSION

• Genetic counseling is useful for children of affected subjects with FN1 mutations to identify carriers that are at risk of developing the disease later in life.

• Monitoring these subjects for proteinuria could allow early treatment with angiotensin inhibitors to delay onset of renal dysfunction.
Lessons learnt.....

• Do not overlook even the rarer causes of MPGN pattern injury

• Closely analyse the differential staining pattern of PAS, Silver methenamine, Masson’s trichrome and Congo red

• Non specific entrapment in DIF studies not to be misinterpreted as true positivity: can lead to incorrect diagnosis and erroneous, harmful therapy