Membranous Nephropathy - A Diagnostic and Therapeutic Challenge

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Lisbon Clinical Nephrology Update
Clinical Case

- ID: 14-year-old Pakistani girl

- Personal antecedents
  - Poorly controlled type 1 diabetes since the age of six (HbA1c >15%)
  - Hashimoto’s thyroiditis with hypothyroidism (verificar terapeutica)
  - Severe dyslipidemia
  - Iron deficiency anemia

- Nephrotic range proteinuria (124mg/m2/hour) without hypoalbuminemia

- Normal blood pressure and renal function; negative immunological study

- Normal renal and abdominal ultrasonography and doppler
Clinical Case

- Decreased proteinuria with ACE inhibitors and metabolic control
- Improvement inconsistent with low adherence to therapeutics
- Ver complemento
- Quadro com evolução resultados
Clinical Case

- Self-limited malar rash coincident with sun exposure
  - Repeat immunological study
- Positive anti-dsDNA
- Positive anti-nuclear antibodies 1/320 – Anti RNP/Sm and Anti RNP-/A+
- No other manifestation of autoimmune disease emerged in the follow-up
Kidney biopsy

- Diabetic nephropathy (DN) IIb
- Type II membranous nephropathy (MN) with a high immunological standard on immunofluorescence (IgG, IgM, K and lambda light chains)
Kidney biopsy:
- DN IIb + Type II MN with a high immunological standard
- Kidney biopsy is the gold standard for diagnosis, prognostic indicator and to guide treatment but in some cases there isn´t a clear association
- Coexistence of histological findings of DN and MN with evidence of immune activity raises doubts about whether it is:
  - One disease (MN secondary to diabetes or Hashimoto’s thyroiditis)
  - Two diseases (diabetic nephropathy and idiopathic MN)
Positive anti-dsDNA and anti-nuclear antibodies 1/320 – Anti RNP/Sm and Anti RNP-/A+
  - These values were not confirmed later

No other manifestation of autoimmune disease emerged in the follow-up

Evolução de C, anemia, creatinina, dislipidemia, tiroide......
Renal Biopsy

- tricromio
- Proliferation mesangial, aumento matriz, sinequias à capsula
- Atrofia tubular
- Espessamento / hialinose arteriolar
- (grandes vasos preservados)
Renal Biopsy

- (PAS) DN
- Hipercelularidade mesangial
- Desarranjo / Espessamento difuso da capsula
- Espassamento MBG
Renal Biopsy

Prata
Renal Biopsy

- (prata) DN
- Gotas hialinas subcapsulares e na matriz com aderências à capsula (esclerose)
- Espessamento difuso da MBG
- Espassamento capsula
Renal Biopsy

- IgG deposition along the glomerular basement membrane
- em parafina
- Phospholipase A2 receptor (PLA2r) negative
Renal Biopsy

- Electron-dense deposits of immune complexes in the sub-epithelial glomerular basement membrane

- Phospholipase A2 receptor (PLA2r) negative
- **Phospholipase A2 receptor (PLA2r) negative**
  - M-type phospholipase A2 receptor are the target antigen of autoantibodies in iMN
  - Type I transmembrane glycoprotein
  - Antibodies are IgG4
  - Lacking in secondary formas og MN
  - Direct pathogenic function and act as sensitive and specific markers for iMN

- **Anti-phospholipase A2 receptor antibody (anti-PLA2r) serum levels**
  - Active disease, risk of declining renal function and benefit from earlier therapeutic intervention
Kidney biopsy is the gold standard for diagnosis, prognostic indicator and to guide treatment but in some cases there isn’t a clear association

Traditional biomarkers: serum creatinine, estimated glomerular filtration, albuminuria and proteinurua (nor specific or sensitive)

“Novel” biomarkers – reproducible, financially within reach, predict clinical and response to treatment….: auto-antibodies, modified serum proteins, cytokines, growth factors, urinary IgG/IgM

MN – anti-PLA2R antibodies:
- Positive in ~70%, correlate with disease activity and response to therapy
- A negative serological test does not rule out PLA2R-mediated MN
- PLA2R cannot replace kidney biopsy as the gold standard for the diagnosis of MN
The main features revealed in renal biopsy → chronicity

Membranous nephropathy (MN)
- Immune-complex mediated disease
- Antibodies react against endogenous antigens in situ.
- In childhood → Secondary to an underlying pathology
- The idiopathic form is a rare cause of asymptomatic proteinuria or nephrotic syndrome and a diagnosis of exclusion
- The diagnostic and therapeutic approach to MN is challenging because of its variable manifestation and inconsistent response to treatment.
- ACE inhibitors, ARBs, corticosteroids and other immunosuppressive therapies such as cyclosporine may be considered.
The coexistence of histological findings of diabetic nephropathy and MN with evidence of autoimmune activity raises doubts about whether it is one disease (MN secondary to diabetes or Hashimoto’s thyroiditis) or two diseases (diabetic nephropathy and MN).

In this case, considering the age, sociocultural context with poor therapeutic adherence and difficult metabolic control, the treatment options are even more limited and under discussion.
MN secondary to infections, autoimmune diseases, drugs and malignancies

iMN – Idiopathic membranous nephropathy
- Immune etiologic basis
- Circulating antibody against antigen presents on podocytes »» Immune complexes deposits
- 20-25% have spontaneous remission
- 40-50% may lead to chronic renal failure
- Majority are partial remissions (median proteinuria may decline or even persist despite the absence of immunological disease - disappearance of anti-PLA2R antibodies)

Biomarkers for disease activity and/or treatment effects?
- Age, renal function, amount of proteinuria, gender
Thank you for your attention