Relevant or Red Herring?

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Registrar

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‘Moving on Up Together’ Study Day
31.01.20
Case

- EJW
- 16y
- Creatinine 120micromol/l - incidental finding
- Repeat 144 micromol/l
- NFAW
November 2017
- Phone call from local hospital
- **Creatinine rising - 200micromol/l**
- Normal Autoimmune screen locally
- Urgent Outpatient review arranged

March 2018
- Review in OP
- **Creatinine improved 150micromol/l**
- Autoimmune screen:
  - **Bordeline CTD**
  - Complement screen normal
- **Nucleosome antibodies – ‘positive’ -106 U/ml**
- Discussion with immunologist and MDT - ?non specific advise to repeat

Late March 2018
UpperGI endoscopy
- **Creatinine 195micromol/l**
- Renal team not aware

August 2018:
- **Creatinine 145micromol/l**
- microalbuminuria – enalapril commenced

November 2018:
- **Creatinine 186 micromol/l**
- **Nucleosome antibodies 138.4U/ml**
- Renal Biopsy
- MMF and prednisolone commenced

Urinalysis: no haematuria, no proteinuria on dipstick
<table>
<thead>
<tr>
<th>Month</th>
<th>Creatinine</th>
<th>Nucleosome Antibodies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2019</td>
<td>168 micromol/l</td>
<td>Negative</td>
<td>Creatinine 168 micromol/l CTD negative Nucleosome 45.5U/ml Enalapril for proteinuria Continuing on MMF and Prednisolone weaning regimen</td>
</tr>
<tr>
<td>April 2019</td>
<td>155 micromol/l</td>
<td>44.54U/ml</td>
<td>Creatinine 155 micromol/l Nucleosome antibodies 44.54U/ml Enalapril for proteinuria Continues on MMF Enalapril for proteinuria</td>
</tr>
<tr>
<td>July 2019</td>
<td>200 micromol/l</td>
<td>11.5U/ml</td>
<td>Creatinine 200 micromol/l Nucleosome antibodies 11.5U/ml ?compliance issues</td>
</tr>
<tr>
<td>Nov 2019</td>
<td>193 micromol/l</td>
<td>15.5U/ml</td>
<td>Creatinine 193 micromol/l Nucleosome antibodies 15.5U/ml MMF</td>
</tr>
<tr>
<td>Jan 2020</td>
<td>171 micromol/l</td>
<td>MMF</td>
<td>Creatinine 171 micromol/l MMF</td>
</tr>
</tbody>
</table>

Urinalysis: no haematuria, no proteinuria on dipstick
Renal function and Antibody Titres

- **Renal Biopsy --> MMF+Pred**
- **Compliance issues**

- **Nucleosome Antibody titres (U/mL)**
  - Normal range 20 - 40 U/mL

- **Serum Creatinine (micromol/L)**

- **eGFR (ml/min/1.3m²)**
Other relevant investigations

- Urine dipstick – no blood, no protein
- Renal ultrasound scans – normal
- Complement screen – normal
- ESR 30-50; normal CRPs
- dsDNA negative
- Upper GI endoscopy – normal
Histopathology

November 2018

VESSELS: Arteries and arterioles are normal.

IH: There is granular staining in the mesangium and focally in the capillary loops for Clq, IgG and C3. IgA is negative.

SUMMARY

RENAL BIOPSY: IN KEEPING WITH CLASS III LUPUS NEPHRITIS. EM TO FOLLOW.
EM Results

Glomerular basement membranes show normal thickness and trilaminar substructure, but for an area of multilamellation. Electron dense deposits are found in the mesangium and focally in subendothelial areas. A few partially resorbed, electron lucent subepithelial deposits are seen.

The findings are in keeping with a immune complex mediated glomerulonephritis, favouring a lupus nephritis.
RENAI BIOPSY.

CLINICAL HISTORY:

Previous biopsy - immune complex GN - ?SLE. Also 2 heterozygous variants of NPH4 - 1 pathogenic, 1 VUS. Rising plasma creatinine: anything reversible.

MACROSCOPIC:

TUBULES AND INTERSTITIUM: There is severe chronic damage with 60% of the cortex showing interstitial fibrosis and tubular atrophy. There are no casts other than uromodulin in atrophic tubules. There is no active tubulointerstitial nephritis.

VESSELS: A small artery present appears normal. There is focal fibroproliferative intimal thickening of arterioles.

IH: There is coarse granular mesangial and capillary wall positivity for IgM and Clq with more focal weaker staining for IgG, IgA and C3.

COMMENT: There is extensive global glomerulosclerosis with severe chronic tubulointerstitial damage. The glomerulomegaly and perihilar sclerosis are indicative of hyperfiltration changes. The IH is in keeping with an immune complex mediated glomerulonephritis but there is no evidence of an active proliferative disease. EM to follow.

SUMMARY

RENAI BIOPSY - IMMUNE COMPLEX GLOMERULONEPHRITIS WITH SEVERE CHRONIC DAMAGE.
Genetics

*NPHP4 c.3368_3369del p.(Val1123Glyfs*43); heterozygous*
- Likely pathogenic
- Predicted to cause premature termination of NPHP4 protein

*NPHP4 c.3920T>C p.(Leu1307Pro)*
- VUS but *in silico* predicts pathogenic
- Uncertain clinical significance

• Results from parents
• RELEVANT or RED HERRING?
Antinuclear Antibody with Full House Nephritis: A Review of the Literature

Sierra C. Simmons a, Maxwell B.Young a,b,c

aDepartment of Internal Medicine, bDepartment of Pediatrics, cDivision of Nephrology and Hypertension, and dDivision of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, USA

Renal-Limited “Lupus-Like” Nephritis: How Much of a Lupus?


Renal-limited 'lupus-like' nephritis.

Huerta A¹, Bomback AS, Liakopoulos V, Palanisamy A, Stokes MB, D’Agati VD, Radhakrishnan J, Markowitz GS, Appel GB.
Anti-nucleosome antibodies as a disease marker in systemic lupus erythematosus and its correlation with disease activity and other autoantibodies.


Anti-nucleosome antibody: significance in lupus patients lacking anti-double-stranded DNA antibody.

An Update on Antibodies to Necleosome Components as Biomarkers of Sistemic Lupus Erythematosis and of Lupus Flares

Gian Marco Ghiggeri 1,2,*, Matteo D’Alessandro 1, Domenico Bartolomeo 1, Maria Ludovica Degl’Innocenti 1, Alberto Magnasco 1, Francesca Lugani 2, Marco Prunotto 3 and Maurizio Bruschi 2,4

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Received: 29 September 2019; Accepted: 11 November 2019; Published: 18 November 2019
“determining circulating anti-nucleosome antibody levels has higher sensitivity for lupus flares than other markers such as anti-dsDNA and can be detected in serum of SLE patients in strict concomitance with the abrupt onset of the disease”
Are anti-nucleosome antibodies a better diagnostic marker than anti-dsDNA antibodies for systemic lupus erythematosus? A systematic review and a study of metanalysis

Nicola Bizzaro, Danilo Villalta, Davide Giavarina, Renato Tozzoli

- Systematic review
- 1 x metanalysis
- Anti- nucleosome antibodies, in Dx of SLE
  - Sensitivity 61%
  - Specificity of 94%
Differential Diagnoses

- Nephronophthisis
- Lupus Nephritis
- Ig-G4 related renal disease
Red Herring or Relevant?

Nucleosome antibodies – initial positivity-negative after MMF Rx

Renal biopsy - immune complex mediated GN

CTD screen – ANA initially ‘borderline’ + positive

NPHP4 mutation X2 variants

cyclical vomiting; polyuria; headaches;
Further biopsy staining for IgG4 – outcome? negative IH not IgG4-related renal disease

MMF and weaning course
Prednisolone commenced (16/01/2019)
d/w vasculitis expert and rheumatologist
Since commencing MMF – repeat nucleosome antibody screen negative continues on MMF

Albuminuria ongoing, continues on enalapril

NPHP4 mutation ? Significance? proteinuria parents tested -

Psychosocial support ongoing cyclical vomiting, polyuria compliance transition to adult care 2020
Apart from her kidneys...

<table>
<thead>
<tr>
<th>Episodic vomiting</th>
<th>Discharged from gastroenterology, no cause found specifically</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches</td>
<td>No organic cause found</td>
</tr>
<tr>
<td>?seizures</td>
<td>EEG normal , MRI normal</td>
</tr>
<tr>
<td>Compliance with medications</td>
<td></td>
</tr>
<tr>
<td>Polyuria &gt; Polydipsia</td>
<td>Endocrine referral to exclude all organic causes;</td>
</tr>
<tr>
<td>No joint pain/swellings</td>
<td></td>
</tr>
<tr>
<td>No rashes</td>
<td></td>
</tr>
</tbody>
</table>
MDT

- Youth Workers – psychosocial support and help with transition
- Paediatric Nephrologist
- Adult Nephrologist
- Immunologist
- Rheumatology
- Endocrinology
- CAHMS
- Counselling from Bernados
Learning Points

Renal limited lupus: In CKD cases with borderline/positive CTD screen – anti-nucleosome antibodies may be ‘relevant’

- in the absence of systemic features
- dsDNA negative

Nucleosome antibodies - Not widely used

- not available in all labs
- not a routine test

When treatment commenced, Nucleosome antibody levels decrease

- ?significance
Relevant?.. Or Red herring?

<table>
<thead>
<tr>
<th>Nephronophthisis</th>
<th>Lupus nephritis</th>
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<tbody>
<tr>
<td>Genetics</td>
<td>Nucleosome antibodies</td>
</tr>
<tr>
<td>Polyuria, Vomiting - episodic IV rehydration</td>
<td>Initially borderline CTD screen</td>
</tr>
<tr>
<td>Albuminuria but &lt;30mg/mmol</td>
<td>Immune complex process on biopsy</td>
</tr>
<tr>
<td>Presentation</td>
<td>Presentation</td>
</tr>
</tbody>
</table>

Psychological overlay:
- Polyuria
- Cyclical nature of vomiting episodes
- Compliance issues
Nephronophthisis  
Differential diagnoses  
Lupus Nephritis  
Ig-G4 related renal disease
References


EYES UP HERE, PLEASE!!! PAY NO ATTENTION TO THE FISH BEHIND THE CURTAIN!!!