Do Anti-Phospholipase A2 Receptor Antibodies Predict Recurrence of Membranous Nephropathy After Transplantation?

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Idiopathic Membranous Nephropathy

- One of the most common causes of nephrotic syndrome in adults
- MN can also be secondary to: infections, drugs, toxins, autoimmune disease, and cancer
- Idiopathic (primary) MN is the most common form (2/3 of biopsy-proven cases of MN)
- Current diagnosis of IMN relies exclusively on kidney biopsy
- IMN progresses to ESRD in 15-30%
M-Type Phospholipase A₂ Receptor as Target Antigen in Idiopathic Membranous Nephropathy

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Idiopathic Membranous Nephropathy

- Growing data from American, European and Chinese cohorts show high prevalence (above 70%) of anti-PLA2R antibodies among patients with idiopathic MN while nearly all subjects with secondary MN were negative.
- IgG4 is the dominant subclass in the majority of patients.
  - IgG4 has been linked to “tolerogenic” immune responses
  - IgG4 does not activate complement in the same way that other subclasses do
Presence of anti-PLA2R antibody correlates with clinical disease

Recurrent MN

- Incidence of recurrence: 10 to 45%
- Centers performing protocol biopsy report higher incidence and earlier recurrence
- Assessment of incidence rate is imperfect:
  - Patients who lose their allograft to rejection before developing rMN
  - Subclinical disease without substantial proteinuria
- The mean time for overt recurrence is 13-15 months
  - Kidney biopsy may show recurrence as soon as one week after transplantation*

Anti-PLA2R and rMN

- The occasionally rapid recurrence of MN following transplantation suggests the presence of a circulating factor that may be present at the time of transplantation and raises 2 important questions:
  1. Does a positive anti-PLA2R at or just before transplantation predict recurrence?
  2. Can one use anti-PLA2R seropositivity post-transplant instead of surveillance biopsies to diagnose early recurrence?
Our Study

- We examined the relationship between anti-PLA2R antibodies and recurrence of MN in the allograft
- Retrospective analysis of anti-PLA2R by western blotting of sera from 70 patients
- To date we have obtained and analyzed pre-TP serum from 34 patients
- 25/34 are from the Mayo protocol biopsy group and 9/34 sporadic patients
Pre-TP PLA2R as a predictor of recurrence

<table>
<thead>
<tr>
<th></th>
<th>Recurrence (+) n=25</th>
<th>Recurrence (-) n=9</th>
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</thead>
<tbody>
<tr>
<td>PLA2R Ab (+) n=23</td>
<td>17</td>
<td>6</td>
<td>Positive predictive value 74%</td>
</tr>
<tr>
<td>PLA2R Ab (-) n=11</td>
<td>8</td>
<td>3</td>
<td>Negative predictive value 27%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>68%</td>
<td></td>
<td>Specificity 33%</td>
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<tr>
<td>Specificity</td>
<td>33%</td>
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Pre-TP PLA2R as a predictor of recurrence among the Mayo protocol biopsy group

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<tr>
<th>PLA2R Ab</th>
<th>Recurrence (+) n=16</th>
<th>Recurrence (-) n=9</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tr>
<td>(+)</td>
<td>12</td>
<td>4</td>
<td>67%</td>
<td>43%</td>
</tr>
<tr>
<td>(-)</td>
<td>6</td>
<td>3</td>
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Positive predictive value: 75%

Negative predictive value: 33%
PLA2R-Ab within 4 month of recurrence as evident by biopsy/proteinuria

- 5 subjects with PLA2R-AB negative (31%)
- 11 subjects with PLA2R-AB positive (69%)
Time to recurrence (in weeks) by PLA2R-Ab titer

Significant by two-tailed U test (Mann-Whitney)

\[ p = 0.0127 \]
Time to recurrence (in weeks) by type of transplant

Non-significant by two-tailed U test (Mann-Whitney)

$\text{p} = 0.14$

$DDKT = \text{Deceased Kidney Transplant}$

$LKT = \text{Living Kidney Transplant (Related + Un-Related)}$
Conclusions

- This study does not represent the true incidence of rMN.
- Positive anti-PLA2R pre-TP predicts a high risk for recurrence but not all seropositive cases have recurred to date.
- The absence of pre-TP anti-PLA2R does not rule out future recurrence, which might be explained by post-TP reappearance of anti-PLA2R or other as yet unidentified antibodies.
Conclusions

- The prevalence of anti-PLA2R at the time of recurrence is similar to that seen in primary MN.

- Our results suggest that high pre-TP anti-PLA2R levels predict early recurrence.

- We propose that the presence of anti-PLA2R before or after transplantation merits close monitoring for recurrent MN.
Last Slide

It's not over...

THANK YOU
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