Immune cell infiltration in pediatric renal allografts: mononuclear phagocytes correlate with rejection, re-transplantation and fibrosis in a retrospective study

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# Characterization of retrospective pediatric KTx cohort

## Recipient characteristics (n=58)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>9.71 ± 5.19</td>
</tr>
<tr>
<td>Sex</td>
<td>37.9% (22) female</td>
</tr>
</tbody>
</table>

## Primary disease (cause of renal failure)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal dysplasia</td>
<td>22.4% (13)</td>
</tr>
<tr>
<td>CAKUT (urinary tract)</td>
<td>15.5% (9)</td>
</tr>
<tr>
<td>Cystic disease</td>
<td>17.2% (10)</td>
</tr>
<tr>
<td>Congenital FSGS</td>
<td>15.5% (9)</td>
</tr>
<tr>
<td>Nephronophtisis</td>
<td>8.6% (5)</td>
</tr>
<tr>
<td>aHUS</td>
<td>6.9% (4)</td>
</tr>
<tr>
<td>HUS</td>
<td>3.4% (2)</td>
</tr>
<tr>
<td>RPGN</td>
<td>5.2% (3)</td>
</tr>
<tr>
<td>Mitochondriopathy</td>
<td>1.7% (1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3.4% (2)</td>
</tr>
</tbody>
</table>

## Values are % (N), mean ± SEM or mean (minimum/maximum).

## Biopsy characteristics (n=200)

<table>
<thead>
<tr>
<th>Biopsy Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-transplantation</td>
<td>27.0% (54)</td>
</tr>
<tr>
<td>Days post KTx</td>
<td>1054 (1/4759)</td>
</tr>
<tr>
<td>Protocol (control) biopsy</td>
<td>30.3% (82)</td>
</tr>
<tr>
<td>Indication biopsy (for cause)</td>
<td>69.7% (189)</td>
</tr>
</tbody>
</table>

## Reevaluation according to Banff 2017

- no rejection: 49.0% (94)
- Polyoma nephropathy: 2.6% (5)
- borderline rejection: 19.8% (38)
- TCMR (T cell-mediated): 17.2% (33)
- ABMR (humoral rejection): 4.2% (8)
- TCMR + ABMR: 9.9% (19)
male, 13 yrs, protocol bx, 6 months, borderline

CD68 / cortex: 0.6%

**Digital Image Analysis:** Scan (Leica) of a stained biopsy (A) and result of semi-automatic segmentation (B) into cortex, medulla and extrarenal tissue. Macrophages in a pediatric renal graft biopsy stained for CD68 (brown, C) and positively stained area labelled red with QuPath after interactive setting of threshold (D).
Indication (iBx) vs. control (cBx; protocol) biopsies

- CD68: macrophages
- CD206: M2 (alternatively activated macrophages)
- CD3: T-cells
- CD20: B-cells

Non-parametric Mann-Whitney U test, mean with SEM (*p<0.05)
Immune cell infiltration and fibrosis / IFTA

markers: CD209: dendritic cells; CD206: M2 (alternatively activated macrophages); CD3: T-cells; CD20: B-cells

non-parametric Mann-Whitney U test, mean with SEM (*p<0.05, **p<0.01, ***p<0.001)
Immune cells and rejection

- CD68: macrophages
- CD206: M2 (alternatively activated macrophages)
- CD3: T-cells
- CD20: B-cells

Non-parametric Kruskal-Wallis test for 5 groups $p<0.0001$ (between 2 groups $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$)
Rejection: children vs. adults

Pediatric immune response:
- naive adaptive immune system
- fewer antigen-specific T-cell precursors
- reduced T-cell effector function
- more tolerogenic DCs

markers: CD68: macrophages
Macrophage infiltration correlates negatively with kidney function – independent of timepoint after KTx. Accordingly, correlation with creatinine is positive (not shown). Hidden functional decline by size mismatch!

markers: CD68: macrophages; CD206: M2 (alternatively activated macrophages); CD3: T-cells; CD20: B-cells
Re-KTx and macrophages

Mann-Whitney U test, mean with SEM (*p<0.05, ***p<0.001)

markers: CD68: macrophages; CD206: M2 (alternatively activated macrophages)

(Graves RC & Fine RN, Pediatr Nephrol 2016)
Conclusion and future

Innate immune cell rejection: **poorly understood but may be as crucial for long-term graft survival** as adaptive responses.

Macrophages in pediatric KTx might use independent innate (+ memory) mechanisms of allore cognition as already described for defense against pathogens.

Our ongoing research:
Thank you!

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M. Verboom

MHH-Surgery:
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Immune cells / macrophages in adult KTx:


Casper J, Schmitz J et al. Increased urinary tract infection rate and altered medullary macrophage polarization marker expression in renal transplant recipients receiving loop diuretic therapy. Kidney Int. 2018