Skin Containing VCA as a Monitoring Tool for Intestinal Transplantation

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Intestinal Transplants

- Isolated Intestine
- Liver, intestine and pancreas
- Liver and intestine
- Multivisceral
- Modified MVT
Abdominal Wall Transplant

Transplantation of the abdominal wall.
Sentinel Skin Graft Rejection
Punch Biopsy of Skin
Interface Spongiosis
Histology of Bowel
Sentinel Skin Graft after Treatment
A Case of Intrigue

- Presented with acute bowel dysfunction 25 days after the last pulse of steroids
- Stoma output > 40mls/kg/24 hours
- Abdominal wall graft was normal
- Endoscopy revealed flattening and patchy loss of villi architecture
- Histology was reported as moderate rejection
Abdominal Wall - visual
CMV Inclusion Bodies
CMV Immunohistochemistry
On-going Rejection?

- Not treated with increased immunosuppression based only on the appearance of the abdominal wall skin
- Subsequent immunohistochemistry on the bowel mucosa highly positive for CMV
- No evidence of CMV viremia
- Treated for CMV disease
- Resolution of bowel dysfunction
Lesson Learned

• The skin of the abdominal wall graft was an accurate indicator of immunologic activity in the bowel graft

• Appropriate antiviral therapy was directed after the immunohistochemistry report

• Original diagnosis of rejection was overturned by the pathologist

• Increase in immunosuppression in this case potentially would have led to either graft loss or death due to CMV
Analysis of Oxford ITx and VCA Patients

• Does the addition of a VCA increase the immunological burden?

• Does VCA increase the incidence of de novo DSA?

• Do de novo DSA have an impact on graft survival?
# Pre-Transplant Nationally agreed Risk Stratification

Based on results from most recent sample

<table>
<thead>
<tr>
<th>Risk level</th>
<th>cMFI</th>
<th>Risk of rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1</strong></td>
<td>No detectable DSA</td>
<td><strong>Standard risk</strong></td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>&lt; 2,000</td>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum risk of hyperacute rejection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; Standard risk of rejection</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>2,000 - 8,000</td>
<td><strong>Medium risk</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flow cytometry crossmatch likely to be positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low risk of hyperacute rejection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermediate risk of humoral rejection</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>&gt; 8,000</td>
<td><strong>High risk</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDC crossmatch likely to be positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High risk of humoral rejection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transplant veto, except for exceptional cases</td>
</tr>
</tbody>
</table>
Laboratory Investigations

Pre-transplant HLA antibody profile
• 3 monthly or monthly if sensitised
  – Antibody screening and specificity analysis: Luminex technology
  – Identify unacceptable HLA antigens pre-transplant
  – Calculated HLA antibody Reaction Frequency (cRF%):
    % HLA incompatible, blood group compatible, UK donors in a pool of 10,000

Time of transplant: Crossmatch
  – Complement dependant cytotoxicity (CDC) and flow cytometry (FC)

Post-transplant HLA antibody monitoring
• 1,3,6,9,12 months post transplant, annually and at clinical events
  – Antibody screening and specificity analysis: Luminex technology
Oxford Transplant Cohort

• 2008 – 2015

  – 32 patients
    • 14 ITx without a VCA
    • 18 ITx with a VCA

  – Overall Graft Survival
    • 1 year: 86%
    • 5 years: 49%
Oxford Transplant Cohort n=32

- Sensitisation status pre transplant
  - 19 Unsensitised patients
  - 11 Standard risk, no DSA, crossmatch negative
  - 2 Higher Risk Transplants, DSA +ve
    - 1 -High risk: Bw4, DR16, DQ5, cMFI 19.000
      - CDC-ve, FCXM +ve, SPA +ve
    - 1 -Medium risk: DP*04:01, cMFI 3.200
      - CDC and FCXM -ve, SPA +ve
Post-transplant HLA Sensitisation Status
29 patients monitored

SENSITISATION STATUS

- Increased dnDSA: 48%
- Increased no DSA: 24%
- Unchanged: 28%
Transplanted Cohort

DBD

- **24 SBTx** → VCA n=12 (50%)
- **8 MMVTx** → VCA n=6 (75%)
Rejection

- **5 ITx rejection** episodes in ITx only
  
  \((5/14, 35.7\%)\)

- **3 ITx rejection** episodes in ITx+VCA
  
  \((3/18, 16.7\%)\)

- **7 Skin rejection** episodes in ITx+VCA
  
  \((7/18, 38.9\%)\)

- **NO bowel rejection** without skin rejection!
Donor Specific Antibodies

• Pre Tx DSA 2/32 (6.3%)

• Post Tx 14/29 (48%) developed dnDSA
  – 4 class I alone
  – 3 class II alone
  – 7 class I & class II
  – Mean MFI of class I dnDSA: 7628±10661 SD
  – Mean MFI of class II dnDSA: 10721±18657 SD
Post Transplant Sensitisation

De novo DSA post transplant

8/13 (61.5%) 6/16 (37.5%)

- No VCA
  - Increased dnDSA: 8
  - Increased No DSA: 2
  - Unchanged: 3

- VCA
  - Increased dnDSA: 6
  - Increased No DSA: 5
  - Unchanged: 5

Oxford University Hospitals
NHS Foundation Trust
Graft Survival stratified for de novo DSA

- 89.2%
- 82.3%
- 90.9%
- 45.5%

\[ p = 0.183 \]
Results of the univariate Cox regression analysis to evaluate predictors for graft survival

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wald</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at Tx</td>
<td>4.766</td>
<td>1.061</td>
<td>1.006 - 1.118</td>
<td>0.029</td>
</tr>
<tr>
<td><strong>Donor Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI donor</td>
<td>4.864</td>
<td>1.568</td>
<td>1.051 - 2.338</td>
<td>0.027</td>
</tr>
<tr>
<td><strong>Transplant Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCA included</td>
<td>0.178</td>
<td>1.331</td>
<td>0.352 - 5.036</td>
<td>0.673</td>
</tr>
<tr>
<td><strong>Existence of dnDSA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dnDSA class I</td>
<td>0.240</td>
<td>0.577</td>
<td>0.064 - 5.200</td>
<td>0.624</td>
</tr>
<tr>
<td>dnDSA class II</td>
<td>3.263</td>
<td>4.247</td>
<td>0.884 - 20.391</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>dnDSA class I+II</strong></td>
<td><strong>7.877</strong></td>
<td><strong>14.839</strong></td>
<td><strong>1.016 - 22.362</strong></td>
<td><strong>0.048</strong></td>
</tr>
<tr>
<td>dnDSA max MFI levels</td>
<td>3.384</td>
<td>1.000</td>
<td>1.000 - 1.000</td>
<td>0.066</td>
</tr>
<tr>
<td>dnDSA class I MFI levels</td>
<td>0.849</td>
<td>1.000</td>
<td>1.000 - 1.000</td>
<td>0.357</td>
</tr>
<tr>
<td>dnDSA class II MFI levels</td>
<td><strong>3.487</strong></td>
<td><strong>1.000</strong></td>
<td><strong>1.000 - 1.001</strong></td>
<td>0.062</td>
</tr>
</tbody>
</table>
## Results of the multivariate Cox regression analysis to evaluate independent predictors for long term graft survival

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<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Recipient age at Tx</td>
<td>7.668</td>
<td>1.189</td>
<td>1.052 - 1.344</td>
<td>0.006</td>
</tr>
<tr>
<td>Existence of dnDSA</td>
<td>8.135</td>
<td></td>
<td></td>
<td>0.043</td>
</tr>
<tr>
<td>dnDSA class I</td>
<td>2.207</td>
<td>6.107</td>
<td>0.300 - 124.326</td>
<td>0.137</td>
</tr>
<tr>
<td>dnDSA class II</td>
<td>1.705</td>
<td>7.028</td>
<td>0.376 – 131.216</td>
<td>0.192</td>
</tr>
<tr>
<td>dnDSA class I+II</td>
<td>7.912</td>
<td>45.306</td>
<td>3.178 – 645.875</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Summary

Skin containing VCA seems to be a future leader for diagnosis of rejection – sentinel skin

Combining an intestinal transplant with an abdominal wall VCA does not increase the incidence of de novo DSA

Multivariate analysis showed that the development of de novo DSA in intestinal transplantation is detrimental to the long-term survival of the graft
Questions

What are the next steps?
Do we have to treat as soon as we diagnose de novo DSA?
Which organ leads the decision?
What are the treatment options?
Thank You

Oxford Transplant Centre – Prof. Peter Friend

Transplant Immunology Laboratory – Prof. Susan Fuggle

Plastic, Reconstructive and Hand Surgery – Mr Henk Giele