Banff Vascularized Composite Allotransplantation

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Duke Health Scholar
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Duke University Medical Center

President, International Society of Vascularized Composite Allotransplantation
Financial Disclosures

None
International Collaboration
and
Objectivity
Poster

2003 - 2007
# THE NINTH BANFF CONFERENCE on
ALLOGRAFT PATHOLOGY

La Coruña, Spain
23 - 29 June 2007
Exposiciones Y Congresos. PALEXCO

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<td>Morning</td>
<td>Welcome, Opening Remarks</td>
<td>Heart Symposium</td>
<td>T-Regulatory Cells Symposium</td>
<td>Mechanisms of Rejection Symposium</td>
<td>Liver Symposium</td>
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<td>Afternoon</td>
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<td>Registration and Opening Reception Followed by Choral Recital</td>
<td>EMT, MET &amp; Allografts Symposium</td>
<td>Pancreas Symposium</td>
<td>Composite Tissue Grafts Symposium</td>
<td>Protocol Biopsies &amp; Subclinical Rejection Symposium</td>
<td>Liver Symposium</td>
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<td>Evening</td>
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<td>Report of Transcriptome Satellite</td>
<td>Poster Presentations</td>
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<td>Departure</td>
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<td>Evening</td>
<td>Musical Evening (Philharmonic Orchestra)</td>
<td>City Hall Reception</td>
<td>Gala Dinner Evening</td>
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Then...

- 41 patients receiving a skin-containing VCA had been reported worldwide
  - N=28, hands
  - N= 3, face
  - N= 1, knee with a skin island
  - N= 9, abdominal wall
NIH Consensus Development Program

- Broad based, nonadvocacy, independent panel
- Freedom from scientific or financial conflict of interest
- Systematic literature review
- Invited speakers
- Predetermined questions defining scope and direction of the conference
- Conclusions summarized as Consensus Report and submitted for peer-reviewed publication
- Reconvene in 2 years to evaluate how this classification is working
## Approximate Histological Grade Equivalences

<table>
<thead>
<tr>
<th>Bejarano</th>
<th>Schneeberger</th>
<th>Kanitakis</th>
<th>Cendales</th>
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Banff CTA 2007

Jean Kanitakis (France)
Carolyn Burns (USA)
Charles Hewitt (USA)
David Kleiner (USA)
Luis Landín (Spain)
Myriam Remmelink (Belgium)
Phillip Ruiz (USA)
Stefan Schneeberger (Austria)

Gabriela Alarcón-Galvan (Mexico)
Ibrahim Batal (USA)
Fernando Casco (Spain)
Cinthia Drachenberg (USA)
Tomoo Itoh (Japan)
Tony Landgren (Australia)
Bruce Lyons (United Kingdom)
Trinidad Marchal Molina (Spain)
Kim Solez (Canada)
Lorraine Racusen (USA)
Linda Cendales (USA)
The Banff 2007 Working Classification of Skin-Containing Composite Tissue Allograft Pathology

L. C. Cendales\textsuperscript{a,*}, J. Kanitakis\textsuperscript{b},
S. Schneeberger\textsuperscript{c}, C. Burns\textsuperscript{d}, P. Ruiz\textsuperscript{e}, L. Landin\textsuperscript{f},
M. Remmelink\textsuperscript{g}, C. W. Hewitt\textsuperscript{h}, T. Landgren\textsuperscript{i},
B. Lyons\textsuperscript{j}, C. B. Drachenberg\textsuperscript{k}, K. Solez\textsuperscript{l},
A. D. Kirk\textsuperscript{m}, D. E. Kleiner\textsuperscript{n} and L. Racusen\textsuperscript{o}
• **Acute Cell-Mediated Rejection**
• **Chronic Rejection**
  – ‘Insufficient data are available to define specific changes of chronic rejection in CTA’
  – Vascular narrowing, loss of adnexa, atrophy, myointimal proliferation, and nail changes
• **Antibody-mediated rejection**
  – ‘there is not enough information to draw conclusions regarding AMR”… donor-HLA specific antibodies, vasculitis, neutrophilic margination, thrombi, necrosis, history of sensitization,
• **Related/nonrejection pathology**
  – Infection, drug toxicity, PTLD, GVHD, dermatitis, eosinophilic cellulitis

*AJT 2008;8:1396-1400*
• Acute Cell-Mediated Rejection
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AJT 2008;8:1396-1400
Chronic rejection

Nail Changes

Loss of Adnexa

Kaufman C, et al. Louisville, KY
Graft Vasculopathy in Clinical Hand Transplantation
First Banff VCA Survey

Bar chart showing the observations of different conditions:
- Vascular narrowing: 3
- Loss of adnexa: 4
- Fibrosis of deep tissue: 2
- Myointimal proliferation: 2
- Ameloblastic encephalitis: 5

Pie chart showing:
- Yes: 100%
- No: 0%
• Acute Cell-Mediated Rejection

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AJT 2008;8:1396-1400
Demetris J, Gorantla V, et al.
Related/nonrejection pathology

Demetris J, et al., Banff 2013
Gorantla V, et al. VCA Histopathology Workshop 2016
Chronic Rejection (preclinical model)

Chonic Rejection in non-human primates

Drachenberg C, et al
Chronic changes (Clinical)

Diefenbeck M, et al Transplant Int. 2011

FIBROMUSCULAR PROLIFERATION IN FINGER ARTERIES AFTER HAND REPLANTATION: A CASE REPORT

CLAUDIA MEULI-SIMMEN, M.D.,1* THOMAS EIMAN, M.D.,2
BERNARD S. ALPERT, M.D.,3 VIKTOR E. MEYER, M.D.,1
GREGORY M. BUNCKE, M.D.,4 and HARRY J. BUNCKE, M.D.4

Drachenberg C,
• Acute Cell-Mediated Rejection
• Chronic Rejection
  – ‘Insufficient data are available to define specific changes of chronic rejection in CTA’
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Antibody-mediated rejection

Case report

Pre-op

POD 5

POD 12 Banff I

POD 15 Banff II and signs of AMR with capillaries in the papillary dermis, around eccrine glands, small arteries and arterioles with C4d+

Chandraker A, et al.
Complement Deposition (C4d)

Pre-cellular rejection  Cellular rejection  Post-treatment

Pre-sensitized patient

Not pre-sensitized patient

Chandraker A, et al.
• Acute Cell-Mediated Rejection

• Chronic Rejection
  – ‘Insufficient data are available to define specific changes of chronic rejection in CTA’
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AJT 2008;8:1396-1400
Graft Vasculopathy in the skin

Kanitakis J, et al. Transplant Int 2014
Vasculopathy in the skin

Kanitakis J et al, Transplantation 2016
Allograft vasculopathy - Finger amputation

Intimal thickening
myointimal proliferation

Arteritis

Capillary thrombosis

Kanitakis J et al, Transplantation 2016
Chronic changes in face transplantation

Kanitakis J, et al
# Banff VCA Biopsy Form

**Patient’s Surgical Identification # (or Case #):**

**Patient’s Transplant Type:** Limb, face, abdominal wall, etc.

**Physician / Clinician to contact with results:** (If more than one person, please let us know)

**Name:**

**Specialty:**

**Address:**

**Telephone number:** Fax number: __________

**Email Address:**

---

**Protocol Biopsy**

**Other**

Clinical signs and symptoms at the time of the biopsy (check all that apply)

- rash
- sclerosis
- edema
- pain
- erythema
- scale
- blister

Percentage of allograft involved: <10%, __________ 10-50% __________ >50% __________

Immunosuppressive Therapy for the transplant:

---

**Sample Type, Punch** ellipse other

**Other stains**

**Epidermis**

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Normal</th>
<th>Atrophic</th>
<th>Hypertrophic</th>
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<tbody>
<tr>
<td>Basilar Vacuolopathy</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Dyskeratotic cells</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Spongiosis</td>
<td>Yes</td>
<td>No</td>
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<td>Keratinocytic Atypia</td>
<td>Yes</td>
<td>No</td>
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<td>Exocytosis</td>
<td>Yes</td>
<td>No</td>
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<td>Lymphocytes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Other Inflam Cells</td>
<td>Yes</td>
<td>No</td>
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**Follicular Sebaceous Unit**

**Extent of involvement**

| Basilar Vacuolopathy | Yes | No |
| Apoptosis | Yes | No |
| Exocytosis | Yes | No |
| Lymphocytes | Yes | No |
| Other Inflammatory Cells | Yes | No |

**Eccrine Glands**

**Extent of involvement**

| Basilar Vacuolopathy | Yes | No |
| Apoptosis | Yes | No |
| Exocytosis | Yes | No |
| Lymphocytes | Yes | No |
| Other Inflammatory Cells | Yes | No |

**Dermis**

**Extent of Involvement**

- Papillary Dermis only: Yes No
- Reticular Dermis only: Yes No
- Both: Yes No

**Inflammation:**

| Cell Type: |
| Lymphocytes | Yes | No |
| Plasma Cells | Yes | No |
| Eosinophils | Yes | No |
| Neutrophils | Yes | No |

**Distribution:**

| Perivascular |
| Peridendral |
| Interstitial |
| Band-like |

**Sclerosis**

| Papillary Dermis only | Yes | No |
| Reticular Dermis only | Yes | No |
| Both | Yes | No |

**Vascular Changes**

| Arteriopathy |
| % narrowing of the lumen | <25% | 25-50% |
NIH Consensus Development Program

- Broad based, nonadvocacy, independent panel
- Freedom from scientific or financial conflict of interest
- Systematic literature review
- Invited speakers
- Predetermined questions defining scope and direction of the conference
- Conclusions summarized as Consensus Report and submitted for peer-reviewed publication
- Reconvene in 2 years to evaluate how this classification is working
I International Workshop on VCA Histopathology - May 2016

'Grades and Stages of Rejection: Towards Clinical Correlation'

Evaluation of the Classification
Discussion of the first revision
E-Survey to 11 Pathologists
Biopsy Form –
   Consensus
   Banff VCA Vancouver 2015
Case Presentations
   Pathologists
   Treating Physicians

Austria
Brigham and Women Hospital
Johns Hopkins
Louisville
Lyon, France
Massachusetts General Hospital
Mexico City, Mexico
University of Maryland
University of Pennsylvania
University of Pittsburgh
Duke University
Pre-Workshop Survey

Complete consensus: 8 out of 8
Almost complete consensus: 7 out of 8
Partial consensus: 4 out of 8 (50% agreement)
Poor consensus: less than 50% agreement

8/11 responded
41 data points collected

Case #10:

Adnexa

Dermal changes

Vascular changes
Consensus

- Standardize definitions of criteria
- Acute, chronic, AMR
- Meeting report
VCA Biorepository

- Laboratory Information Management System (LIMS) – LabVantage
  - Patient
    - Consents
  - Visits
  - Sample
    - aliquots
  - Track & Store
  - Distribution & Shipping
- REDCap
  - Extracted clinical data
  - Query discrete clinical criteria
- Clinical and Preclinical Histology Immunohistochemistry Core
Pre-clinical models in VCA

CHOP/U Penn

Bartlett S, Barth R, et al.
University of Maryland

Cendales L, Kirk AD, et al.
Duke University
Skin as a Harbinger of Rejection of Underlying Structures in Vascularized Composite Allografts: Concordance or Discordance?

Cendales L¹, Levine M², Bartlett S³, Cheeseman J¹, Drachenberg C³, Hancock W⁴, Joshi M¹, Kirk AD¹, Leopardi F¹, Levin S¹, Uluer M³, Selim A¹, Song M¹, Twaddell W³, Wang L⁴, Wang Z², Barth R³.

¹Duke University,
²University of Pennsylvania,
³University of Maryland
⁴Children's Hospital of Philadelphia

AJT 2016, 16(S3):433
E- Survey

http://aperio.duhs.duke.edu/Pathology_Cendales/view.apml

<table>
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<tr>
<th>WebScope-05</th>
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Now…

• International Collaboration

• Composite Tissue Allotransplantation to Vascularized Composite Allotransplantation
Established a Common Language

- Acute Cell-Mediated Rejection
- Chronic Rejection
  - ‘Insufficient data are available to define specific changes of chronic rejection in CTA’
  - Vascular narrowing, loss of adnexa, atrophy, myointimal proliferation, and nail changes
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- Related/nonrejection pathology
  - Infection, drug toxicity, PTLD, GVHD, dermatitis, eosinophilic cellulitis

AJT 2008;8:1396-1400
Limitations

• Sampling error

• Reproducibility
  – Dependent on the group in which is tested
  – Influenced by biological variability
  – Experience of the pathologist

• Role of immunostaining
  – Not indicated for diagnosis in routine practice
  – May result in overdiagnosis of rejection
Controversies in pathology

- Classification is non-specific
- Presence of histopathological signs of rejection with absence of clinical signs of rejection
- Classification relies on histopathological characterization of rejection and excludes the visual changes
- Classification does not differentiate rejection from other T-cell dominated inflammatory conditions
- Classification is inadequate between intra- and interobserver reproducibility
- Classification is deficient in precision between borderline acute rejection and acute rejection
Skin and non-skin containing VCA

N = < 300 recipients reported worldwide

Kidney

N = > 200,000 recipients reported worldwide
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<tr>
<td>3. Accelerated acute</td>
<td>3. Borderline Mild tubulitis: t0, t1 interstitial inflamm: i0, i1</td>
<td>3. Borderline Mild tubulitis: t0, t1 interstitial inflam: i0, i1</td>
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<td>4. Acute rejection</td>
<td>4. Acute/Active rejection Type IA: i2, i3 &amp; t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3</td>
<td>4. Acute/Active cellular rejection Type IA: i2, i3 &amp; t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3</td>
<td>4. T-cell-mediated rejection Acute TCR Type IA: i2, i3 &amp; t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3</td>
<td>Chronic active AMR</td>
<td>Chronic active AMR</td>
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<td>6. Other: Changes not due to rejection</td>
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Evolution of the Banff Kidney Scoring System

More Unknowns than Knowns

- Grading capillary thrombosis
  - Relationship with chronic rejection
  - Or consequence of AMR
- Diagnosis and Grading chronic lesions
  - Fibrosis:
    - surface extension
    - Deepness in the skin biopsy
- Grading of vasculopathy
  - Involvement, number of arteries
  - Localization
  - Active lesion, arteritis
- Diagnosis of AMR
- Molecular and genomic approaches
- Study of effector functions of antibody and its manifestations in tissues (acute and chronic)
  - Detection of antibody functions
    - Biopsy: histology, genomics
    - Blood: serological, cellular
- Therapeutic options
- Mixed rejection
- Specificity of isolated dyskeratotic/apoptotic keratinocytes
- Does location alter the specificity of isolated dyskeratotic/apoptotic cells?
  - Epidermis
  - Follicular epithelium
  - Sweat gland epithelium
  - Basal vs. suprabasal/at all levels
- Analogy to GVHD
- Value of a numeric threshold
- Role of mast cells in chronic immune injury
- Role of C4d staining and/or DIF staining for C4d in the management of rejection
- Significance of focal epidermal changes (i.e. spongiosis and/or lymphocyte exocytosis) in Banff I, Banff II
- Relationship of graft function vs. rejection
  - Acute and chronic
Coming together and agreeing to systematically study VCA pathology is a significant step.

But the hard work starts now.
We started talking together in a common language

A common language allows for collaboration
We started talking together in a common language

We can now argue