



Banff Vascularized Composite Allotransplantation

Linda C. Cendales, M.D.

Associate Professor of Surgery

Duke Health Scholar

Director, Vascularized Composite Allotransplantation

Duke University Medical Center

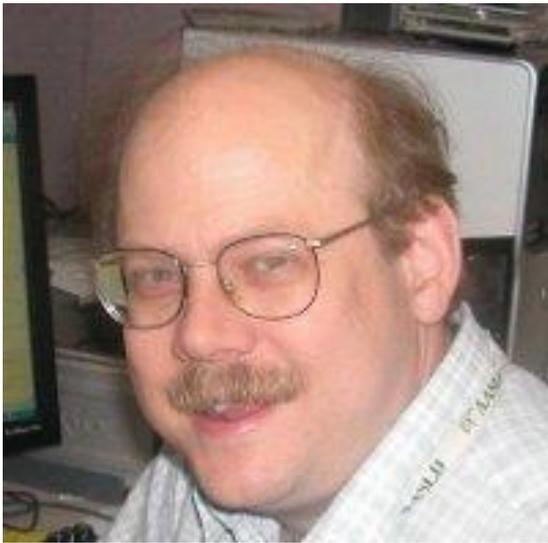
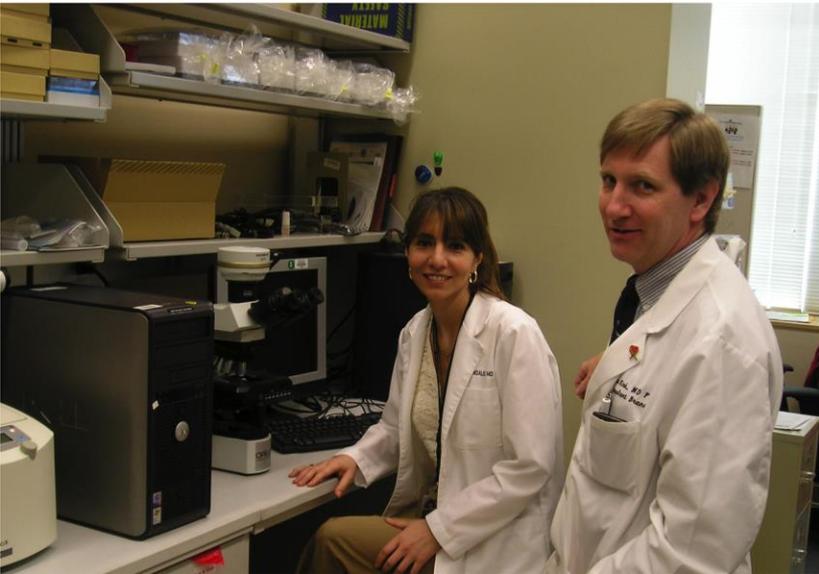
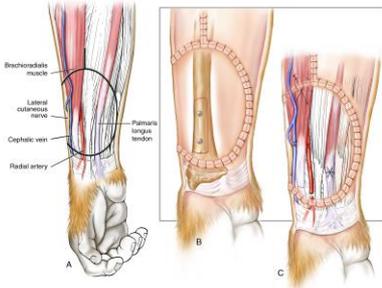
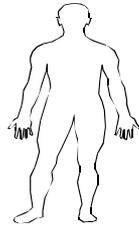
President, International Society of Vascularized Composite
Allotransplantation

Financial Disclosures



None

National Institutes of Health (NIH) 2001





International Collaboration and Objectivity







**Seventh Banff Conference on
Allograft Pathology**

June 14 - 18, 2003
University of Aberdeen
Aberdeen, Scotland

Poster

Cendales L, Kirk AD, Moresi M, Ruiz P, Kleiner D.
Composite Tissue Allotransplantation: Classification of
Clinical Acute Skin Rejection.

2003 - 2007



THE NINTH BANFF CONFERENCE
on
ALLOGRAFT PATHOLOGY

La Coruña, Spain
23 - 29 June 2007

Exposiciones Y Congresos, PALEXCO

Time	23 June 2007 Saturday	24 June 2007 Sunday	25 June 2007 Monday	26 June 2007 Tuesday	27 June 2007 Wednesday	28 June 2007 Thursday	29 June 2007 Friday
Morning	Registration and Opening Reception Followed by Choral Recital	Welcome, Opening Remarks	Heart Symposium	T-Regulatory Cells Symposium	Mechanisms of Rejection Symposium	Liver Symposium	Reports – Consensus statements • Peritubular Capillaries & C4d • EMT, MET • Heart • Pancreas • Liver • Composite tissue Protocol biopsy findings • Liver
		Plenary Session					
		Peritubular Capillaries & C4d					
Lunch		Lunch	Lunch	Lunch	Lunch	Lunch	
Afternoon		EMT, MET & Allografts Symposium	Pancreas Symposium	Composite Tissue Grafts Symposium	Protocol Biopsies & Subclinical Rejection Symposium	Liver Symposium	Departure
		Report of Transcriptome Satellite		Poster Presentations			
Evening		Musical Evening (Philharmonic Orchestra)	City Hall Reception		Gala Dinner Evening		

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

First Author			
Bejarano	Schneeberger	Kanitakis	Cendales
0		0	0
1			
2	1	1	1
3	2	2	2
4	3	3	3
	4a		
	4b	4	4

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)

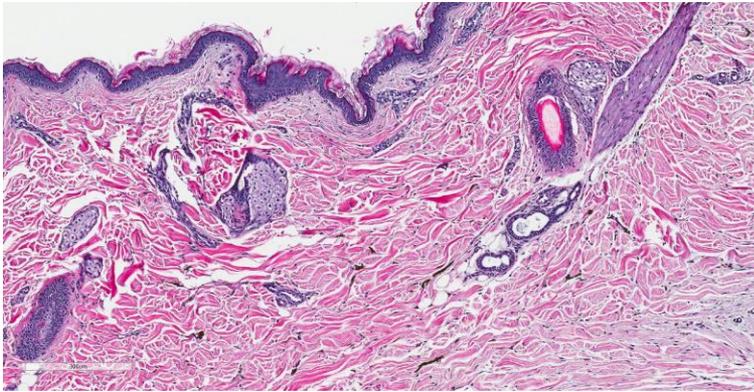
Linda Cendales (USA)

The Banff 2007 Working Classification of Skin-Containing Composite Tissue Allograft Pathology

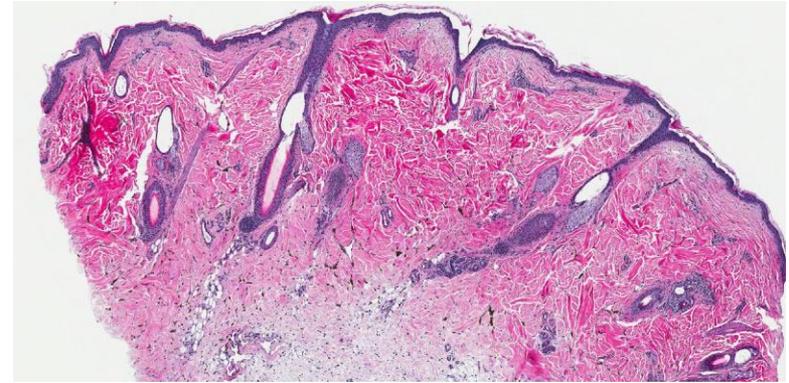
L. C. Cendales^{a,*}, J. Kanitakis^b,
S. Schneeberger^c, C. Burns^d, P. Ruiz^e, L. Landin^f,
M. Remmelink^g, C. W. Hewitt^h, T. Landgrenⁱ,
B. Lyons^j, C. B. Drachenberg^k, K. Solez^l,
A. D. Kirk^m, D. E. Kleinerⁿ and L. Racusen^o

Living Document

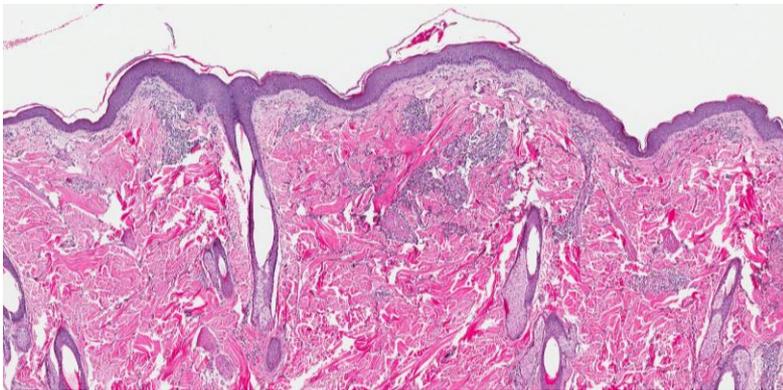
Grade 0



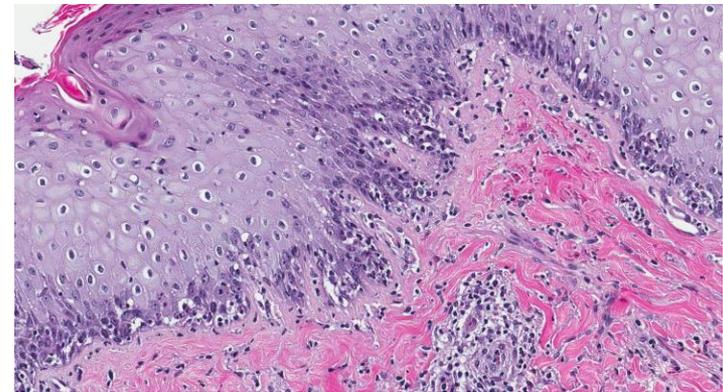
Grade I



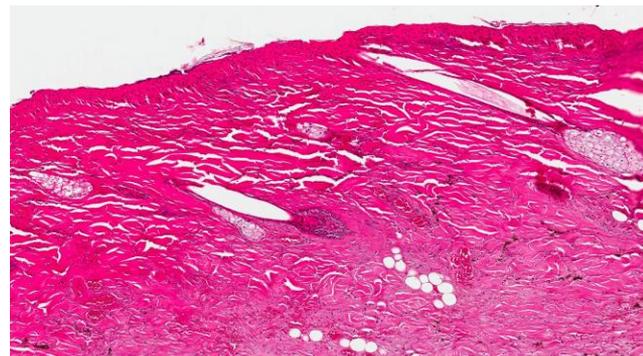
Grade II



Grade III



Grade IV

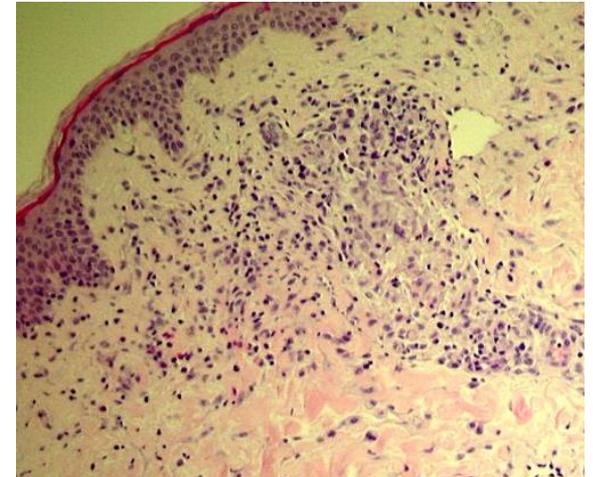
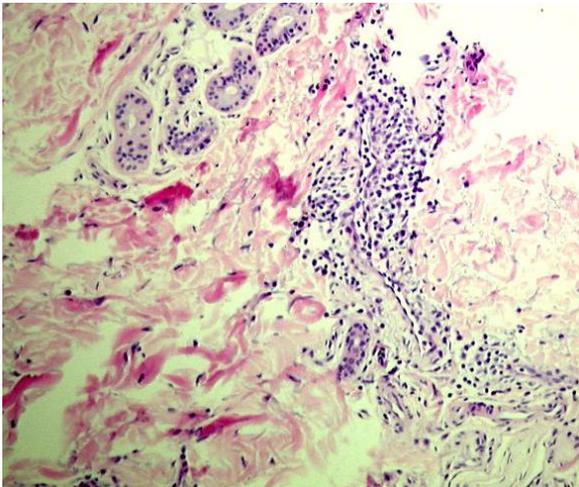
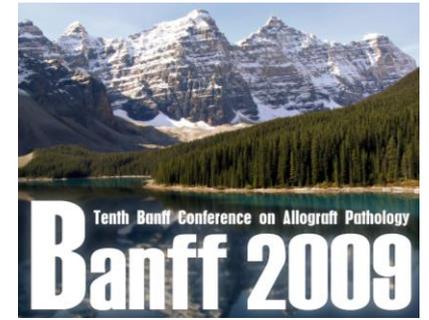


- **Acute Cell-Mediated Rejection**
- **Chronic Rejection**
 - ‘Insufficient data are available to define specific changes of chronic rejection in CTA’
 - Vascular narrowing, loss of adnexa, atrophy, myointimal proliferation, and nail changes
- **Antibody-mediated rejection**
 - ‘there is not enough 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 cellulitides

AJT 2008;8:1396-1400

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AJT 2008;8:1396-1400



Nerlich A, et al. Germany

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Chronic rejection

Nail Changes

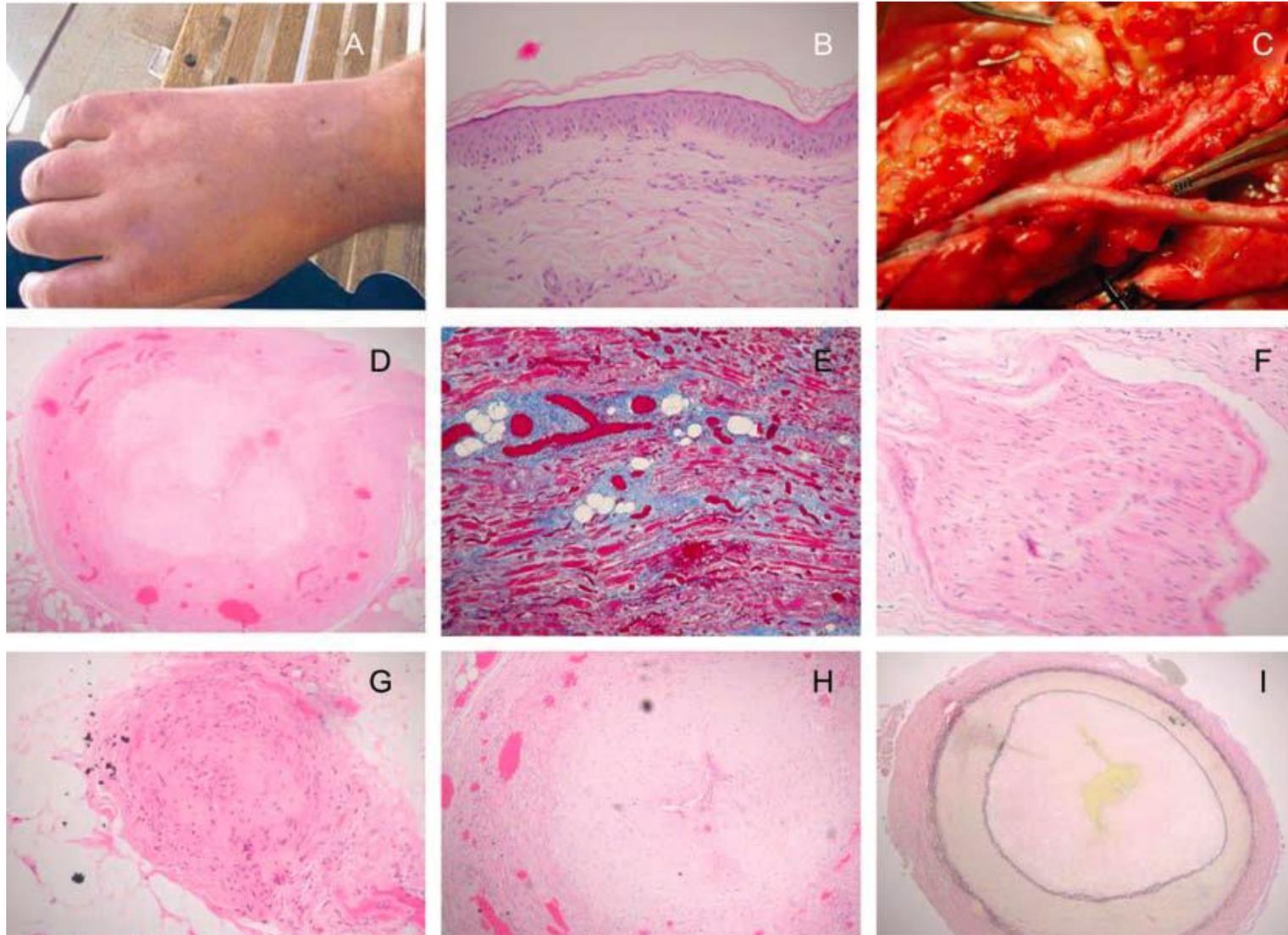


Loss of Adnexa

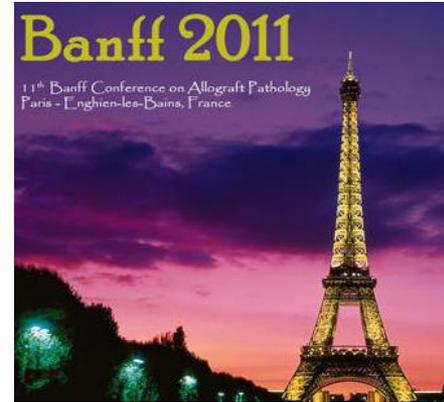


Kaufman C, et al. Louisville, KY

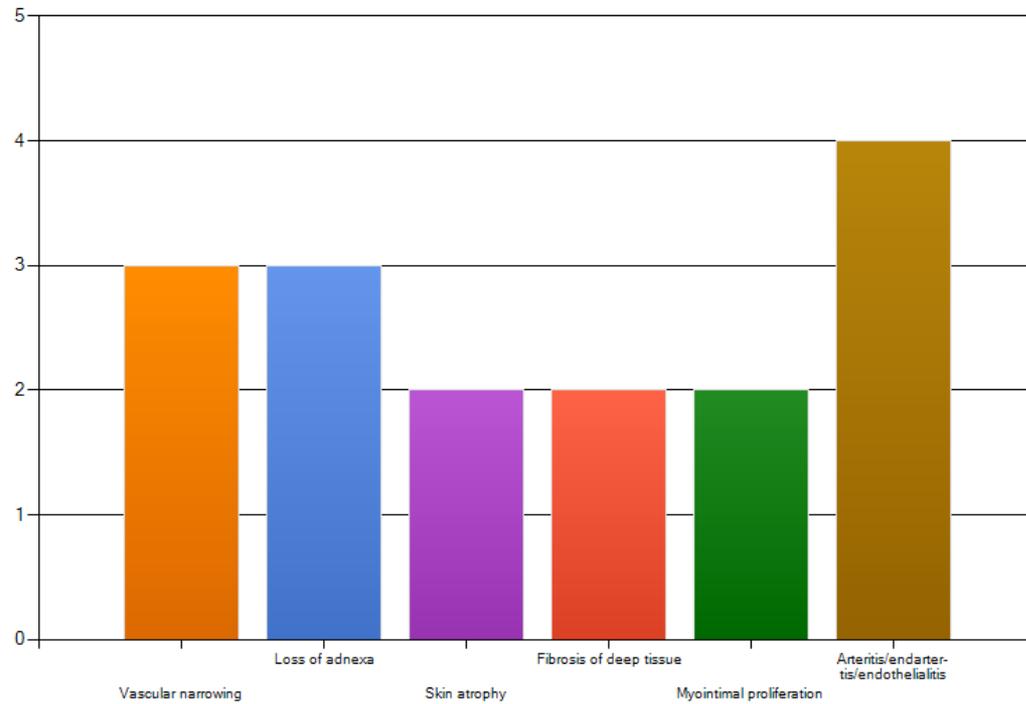
Graft Vasculopathy in Clinical Hand Transplantation



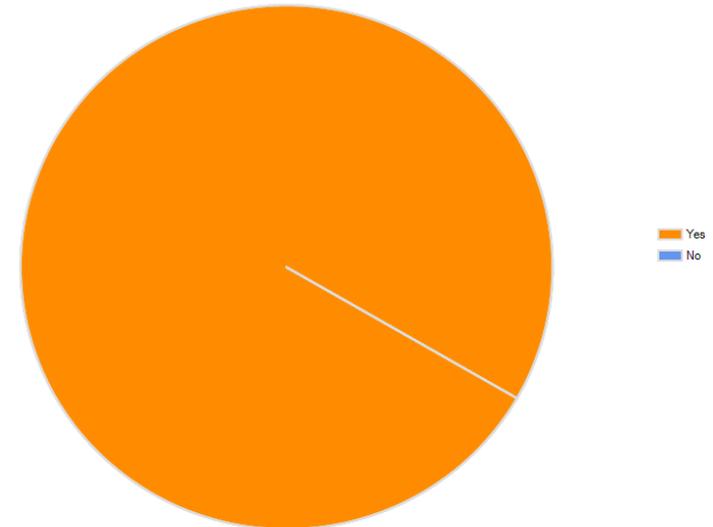
First Banff VCA Survey



Have you observed (check all that apply):



Do you use the VCA Banff system



- Acute Cell-Mediated Rejection
- Chronic Rejection
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Related/nonrejection pathology

12th BANFF CONFERENCE ON ALLOGRAFT PATHOLOGY

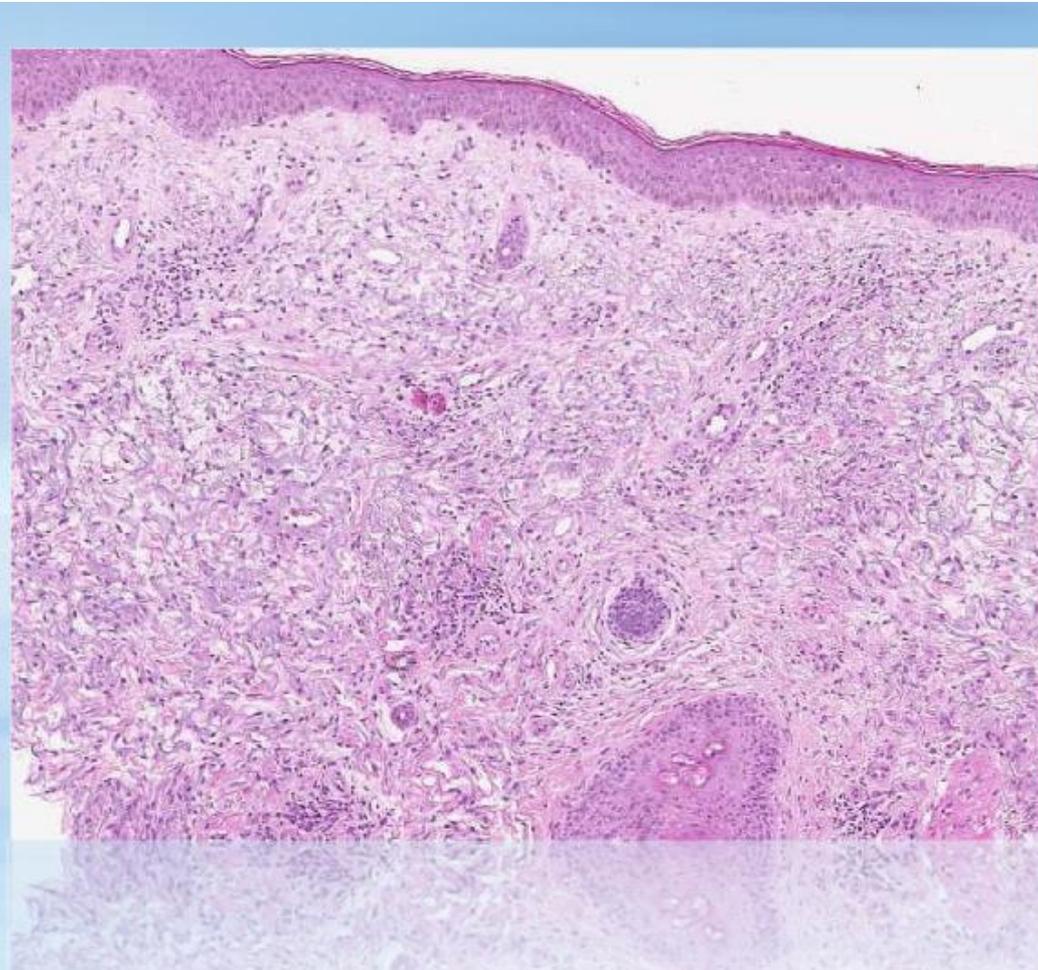
Pre-Meeting: August 17-18, 2013, Conference: August, 19-23, 2013
Comandatuba-Bahia, Brazil



Demetris J, Gorantla V, et al.

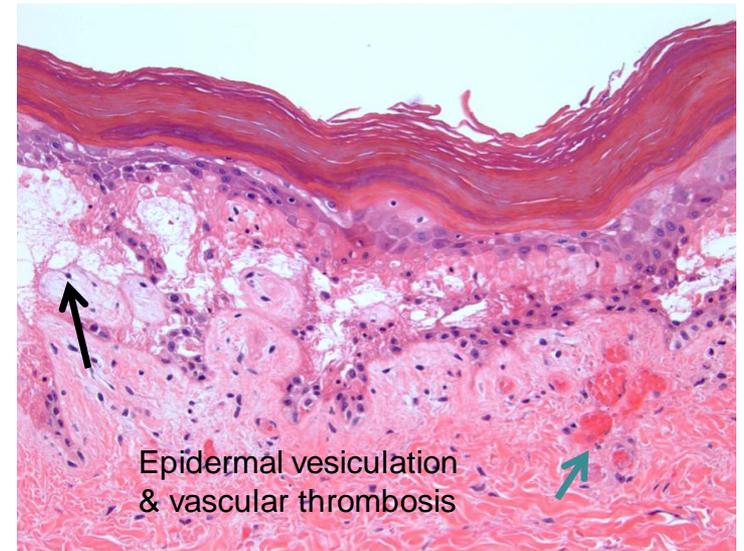
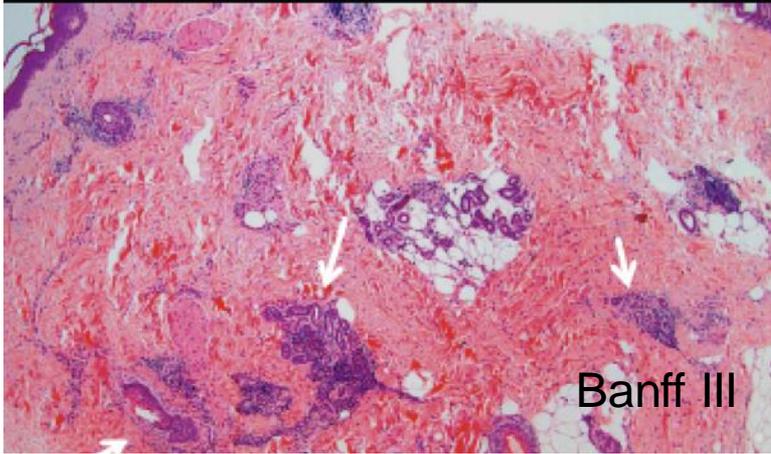
12th BANFF CONFERENCE ON ALLOGRAFT PATHOLOGY

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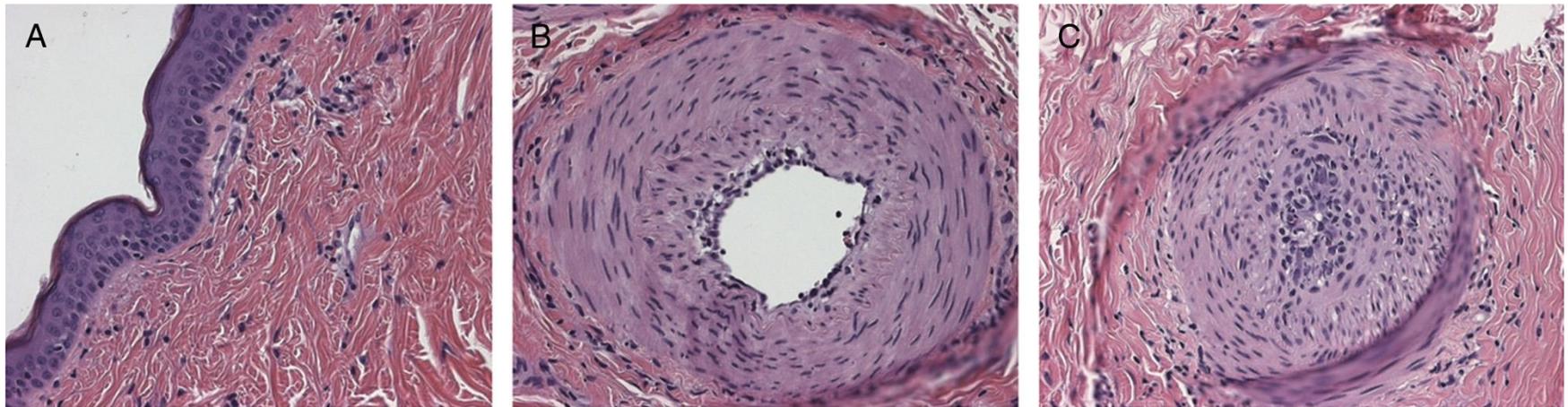
Related/nonrejection pathology



Demetris J, et al., Banff 2013

Gorantla V, et al. VCA Histopathology Workshop 2016

Chronic Rejection (preclinical model)



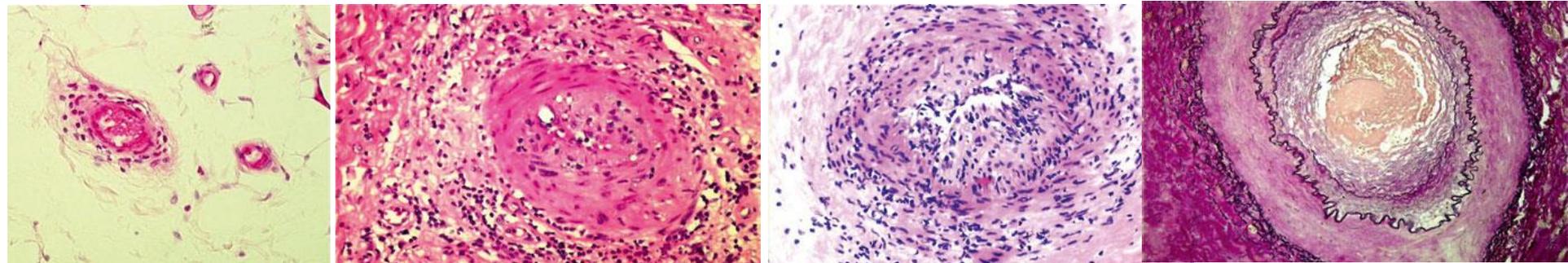
*Munding G, et al. Transplantation 2013
Chronic Rejection in non-human primates*

Drachenberg C, et al

Chronic changes (Clinical)

12th BANFF CONFERENCE ON
ALLOGRAFT PATHOLOGY

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Comandatuba-Bahia, Brazil

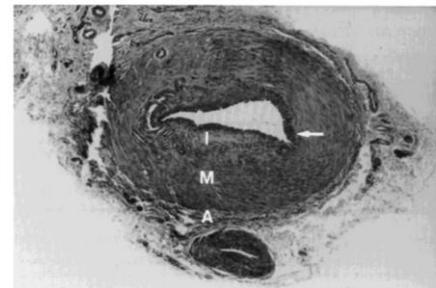


Diefenbeck M, et al Transplant Int. 2011

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

Meuli-Simmen et al.



Drachenberg C,

- Acute Cell-Mediated Rejection
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Antibody-mediated rejection

Case report

Vancouver, British Columbia Canada

13th Banff Conference on Allograft Pathology

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- Sponsors
- Contact Us
- Abstracts
- Programme
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- Registration
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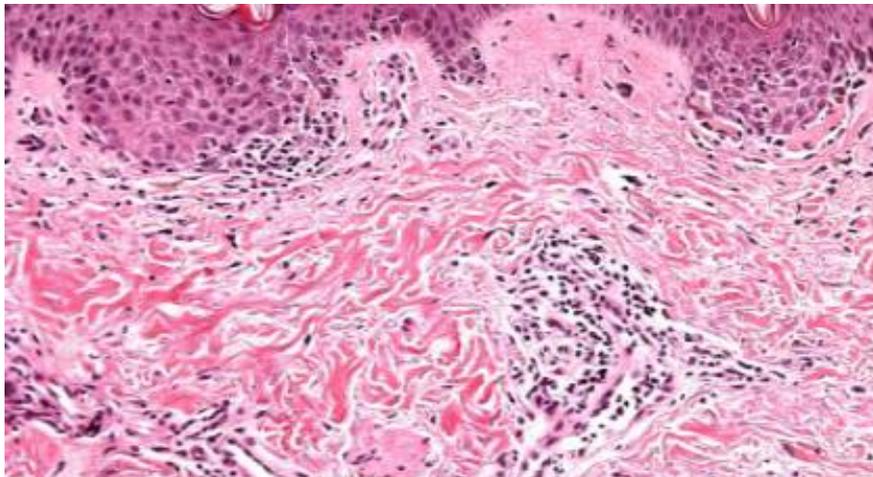


POD 5

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.

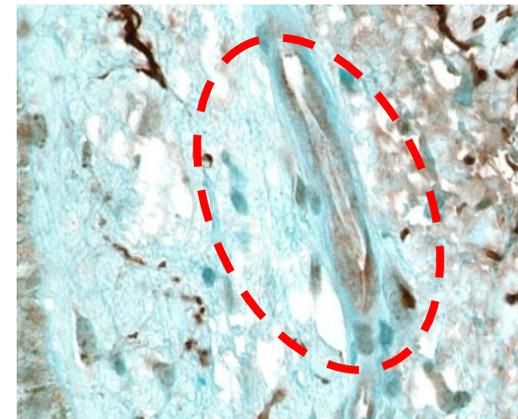
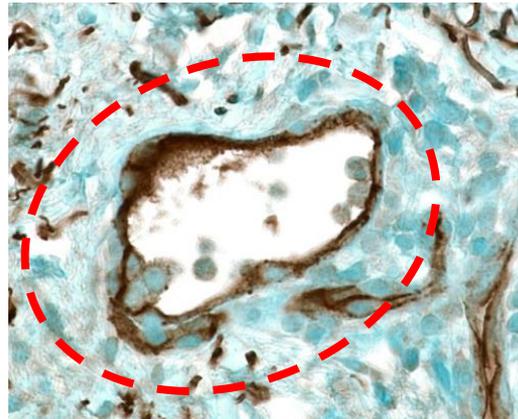
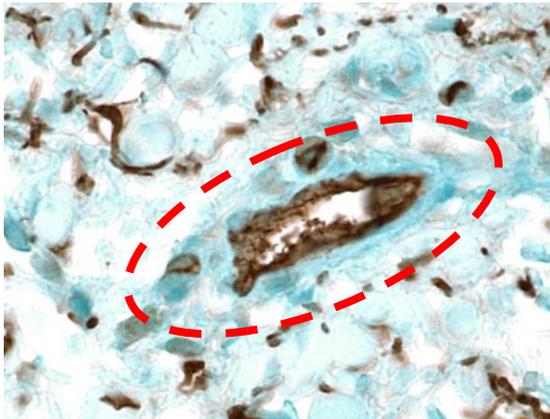
Complement Deposition (C4d)

Pre- cellular rejection

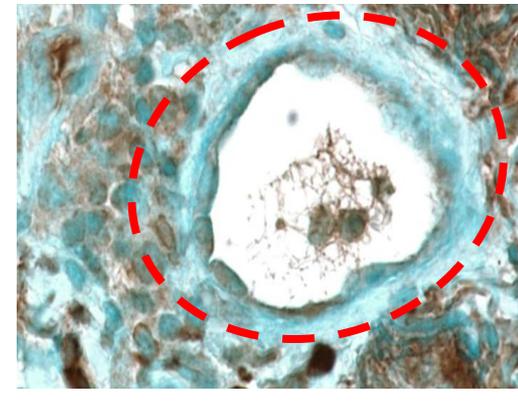
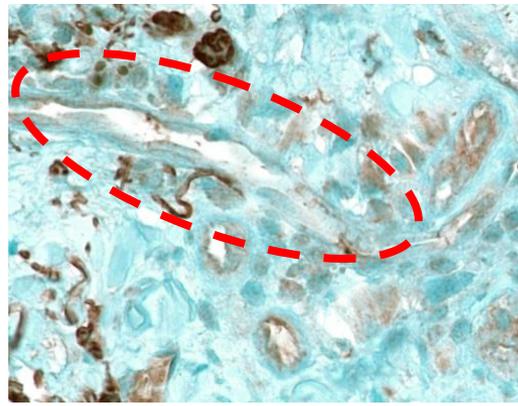
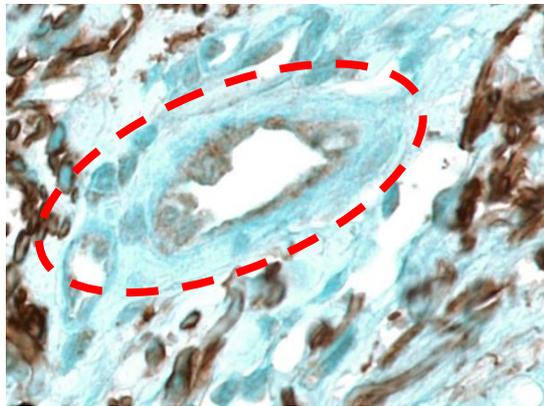
Cellular rejection

Post-treatment

Pre-sensitized patient



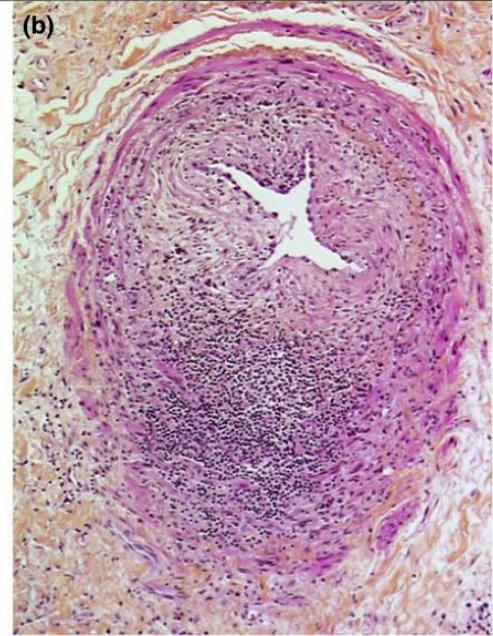
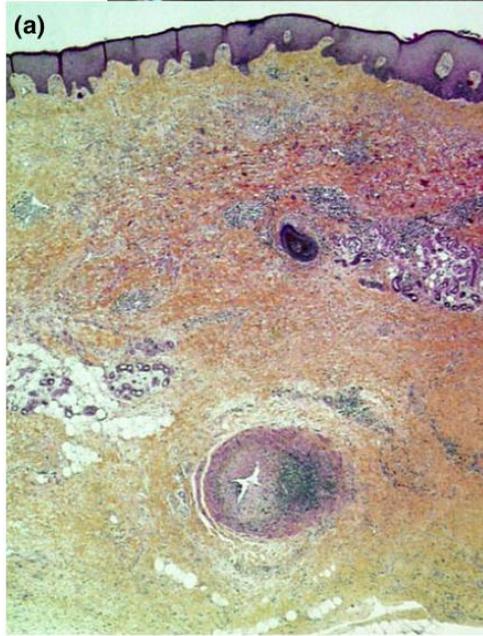
Not pre-sensitized patient



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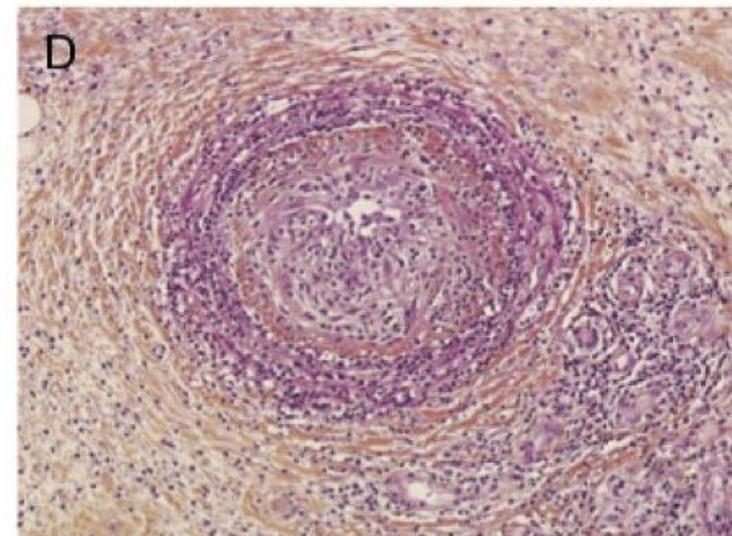
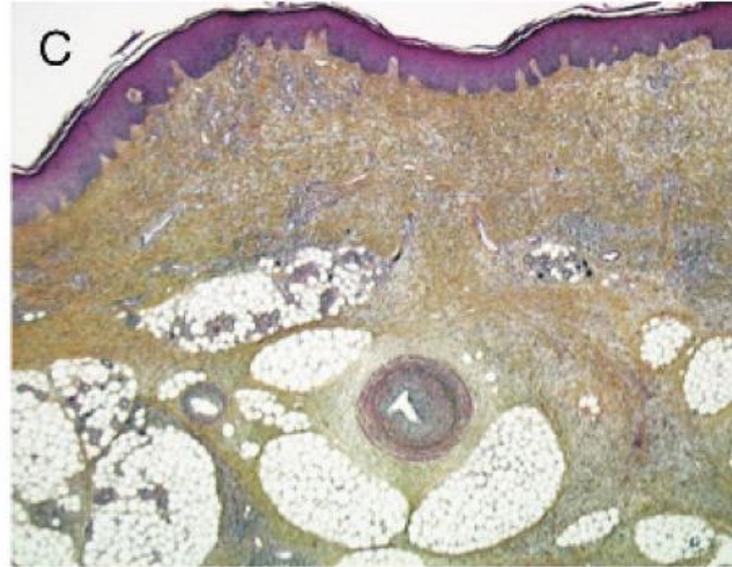


Graft Vasculopathy in the skin



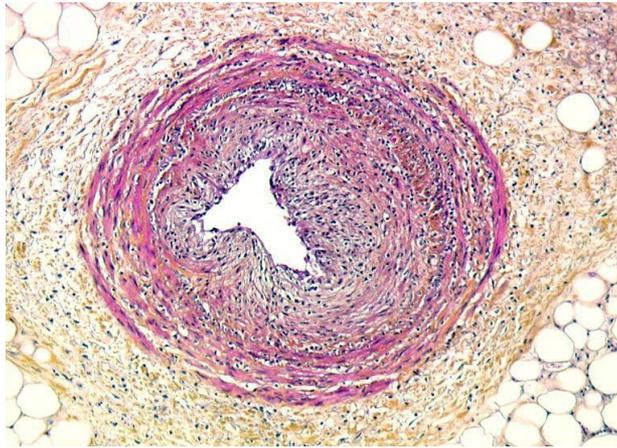
*Kanitakis J, et al.
Transplant Int 2014*

Vasculopathy in the skin

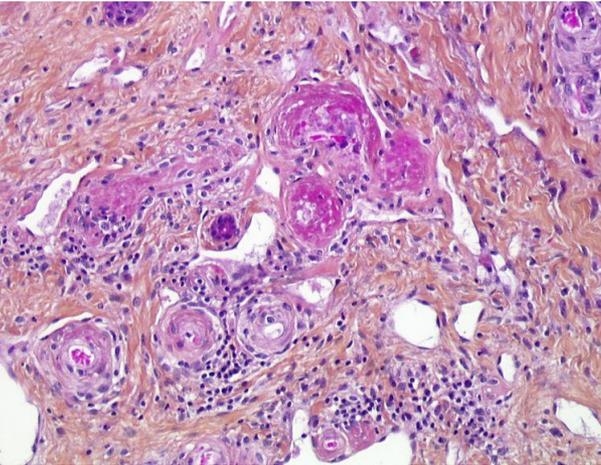


Allograft vasculopathy - Finger amputation

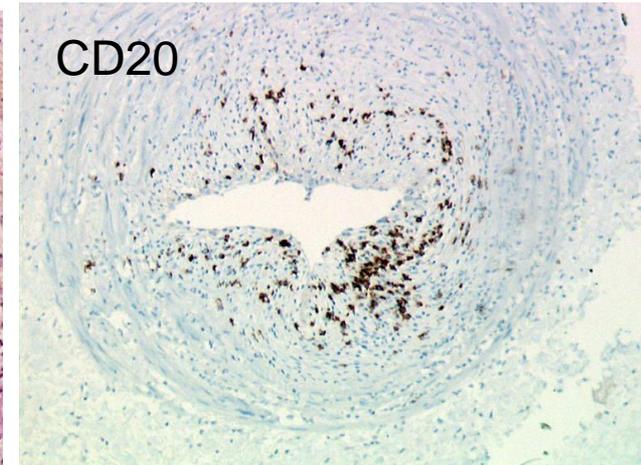
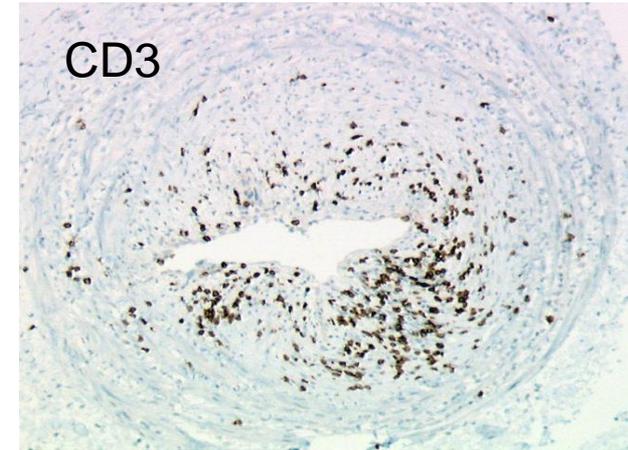
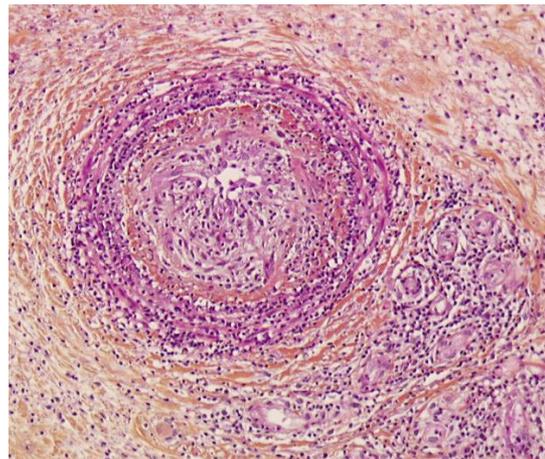
Intimal thickening
myointimal proliferation



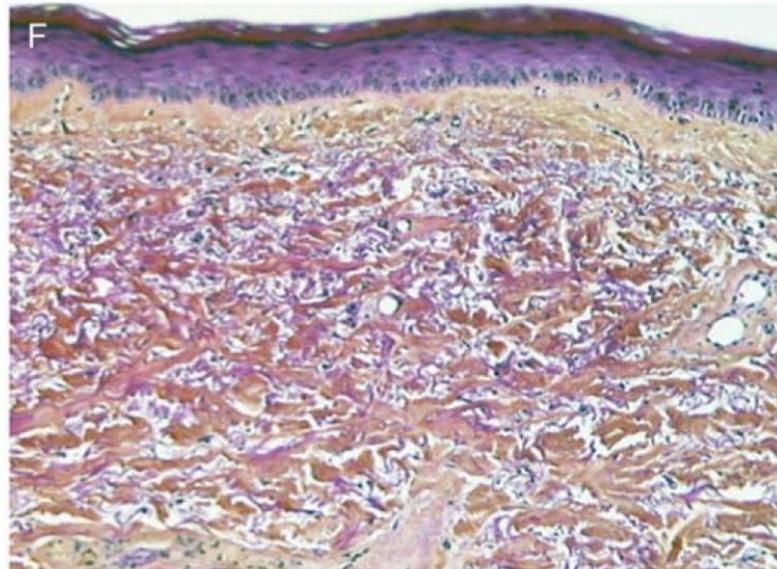
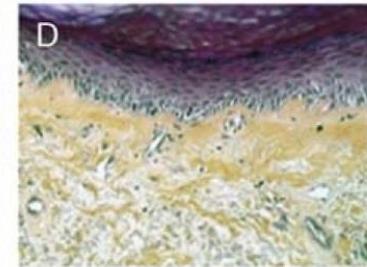
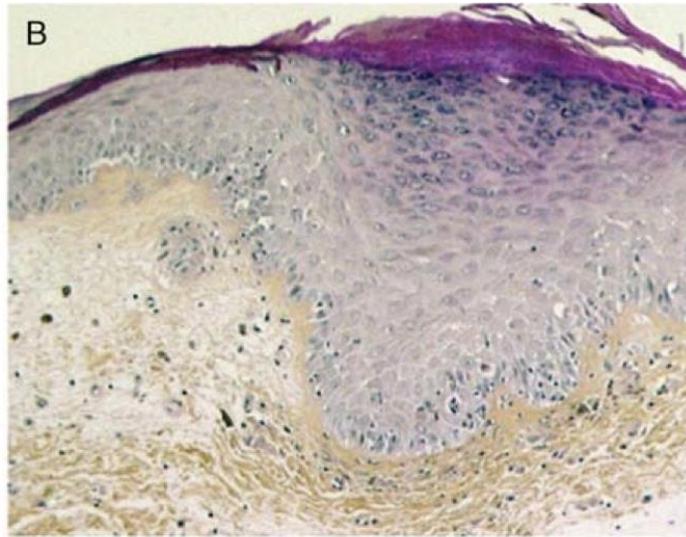
Arteritis



Capillary thrombosis



Chronic changes in face transplantation



Banff VCA Biopsy Form

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- Sponsors
- Contact Us
- Abstracts
- Programme
- Faculty
- Registration
- Accommodation
- Travel
- General Info
- FAQ



Consensus

CUTANEOUS

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

Thickness _____ Normal Atrophic Hypertrophic

Basilar Vacuolopathy Yes No

Dyskeratotic cells Yes No

Spongiosis Yes No

Keratinocytic Atypia Yes No

Exocytosis

Lymphocytes Yes No

Other Inflamm Cells Yes No

Follicular Sebaceous Unit

Extent of involvement **Upper half** **Lower half**

Basilar Vacuolopathy Yes No

Apoptosis Yes No

Exocytosis

Lymphocytes Yes No

Other Inflammatory Cells Yes No

Ecrrine Glands

Extent of involvement **Duct** **Gland** **Both**

Basilar Vacuolopathy Yes No

Apoptosis Yes No

Exocytosis

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 Yes No

Periadnexal Yes No

Interstitial Yes No

Band-like Yes No

Sclerosis

Papillary Dermis only Yes No

Reticular Dermis only Yes No

Both Yes No

Vascular Changes

Arteriopathy Yes No

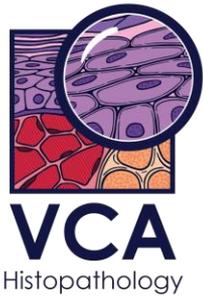
% narrowing of the lumen <25% 25-50%, _____

NIH Consensus Development Program

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- 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'



Duke SCORES
Surgical Center for Outcomes Research

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

Consensus

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

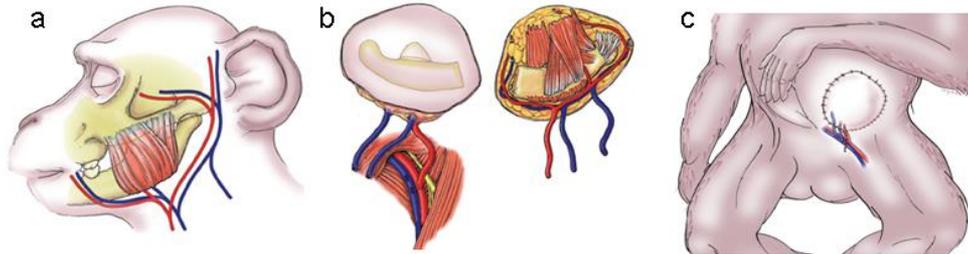
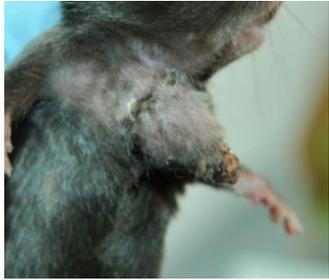
VCA Biorepository

- 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



Hanconck W, Levin S,
Levine M, et al.
CHOP/U Penn

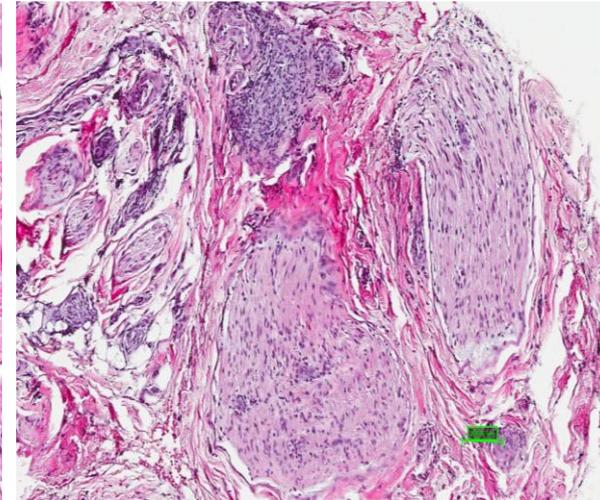
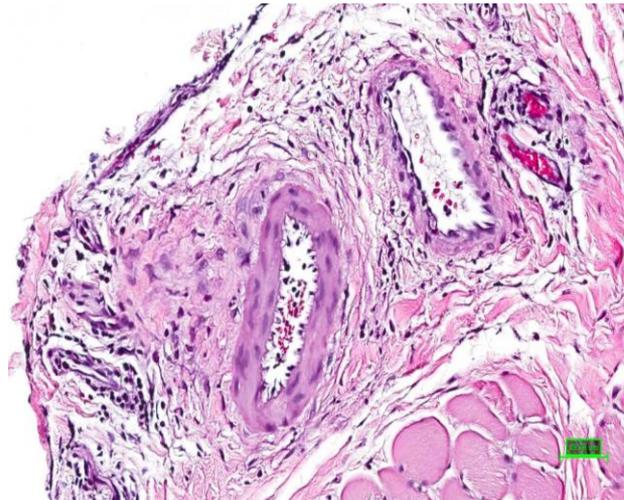
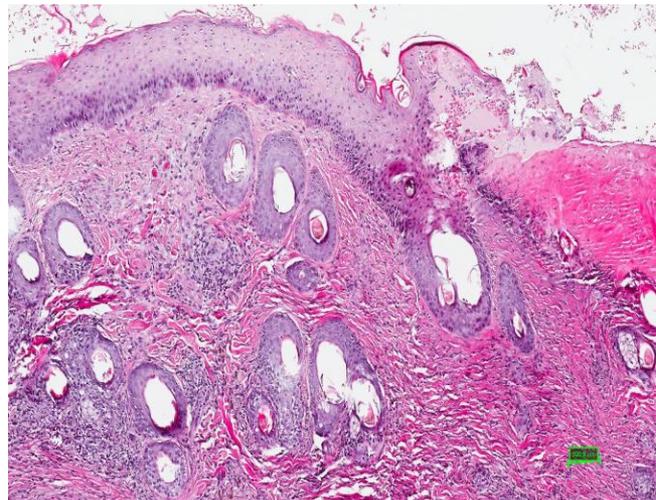
Bartlett S, Barth R, et al.
University of Marland



Skin

Vessels

Nerve



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

E- Survey

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

WebScope-05 **Pathology_Cendales** [\(Clear Server Cache\)](#) [XML](#) [RSS](#) thumbnails

 (return to previous directory)	 DF1C	 DF31	 DF7N	 DFW1	 DM31
 DN7R	 DW07	 EASM	 G03A	 G099	 G693
 G698	 QJ5	 RCH9	 RDN11	 RGC15	 RUi 11
 RVT7					



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
- ✓ • 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 cellulitides

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*



Evolution of the Banff Kidney Scoring System

Pre-Banff[1]	1 st Banff[2]	Banff'97[3]	Banff'97 Update[4]	Banff'051[5]	Banff'07[6]
1. Normal	1. Normal	1. Normal	1. Normal	1. Normal	1. Normal
2. Hyperacute	2. Hyperacute	2. Antibody-mediated rejection immediate – Hyperacute Delayed – accelerated acute	2. Antibody-mediated rejection Type I: C4d+, ATN, min. inflamm Type II: C4d+, leukocytes in ptc Type III: C4d+, transmural arteritis	2. Antibody-mediated rejection Acute AMR Type I: C4d+, ATN, min. inflamm Type II: C4d+, leukocytes in ptc Type III: C4d+, Transmural arteritis Chronic active AMR	2. Antibody-mediated rejection Acute AMR Type I: C4d+, ATN, min. inflamm Type II: C4d+, leukocytes in ptc Type III: C4d+, transmural arteritis Chronic active AMR
3. Accelerated acute	3. Borderline Mild tubulitis: t0, t1 interstitial inflamm: i0, i1	3. Borderline Mild tubulitis: t0, t1 interstitial inflamm: i0, i1	3. Borderline Mild tubulitis: t0, t1 interstitial inflamm: i0, i1	3. Borderline Mild tubulitis: t0, t1 interstitial inflamm: i0, i1	3. Borderline Mild tubulitis: t0, t1 interstitial inflamm: i0, i1
4. Acute rejection	4. Acute rejection Grade I: i2–i3 and/ or t2 Grade II: t3 and/or intimal arteritis: v1, v2 Grade III: transmural arteritis v3	4. Acute/Active rejection Type IA: i2, i3 & t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3	4. Acute/Active cellular rejection Type IA: i2, i3 & t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3	4. T-cell-mediated rejection Acute TCR Type IA: i2, i3 & t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3 Chronic active TCR	4. T-cell-mediated rejection Acute TCR Type IA: i2, i3 & t2 Type IB: severe tubulitis t3 Type IIA: mild-mod intimal arteritis v1 Type IIB: severe intimal arteritis v2 Type III: transmural arteritis v3 Chronic active TCR
5. Chronic rejection	5. Chronic allograft nephropathy Grade I: mild Grade II: moderate Grade III: severe	5. Chronic allograft nephropathy Grade I: mild Grade II: moderate Grade III: severe	5. Chronic allograft nephropathy Grade I: mild Grade II: moderate Grade III: severe	5. Interstitial fibrosis and tubular atrophy (IFTA) Grade I: mild Grade II: moderate Grade III: severe	5. Interstitial fibrosis and tubular atrophy (IFTA) Grade I: mild Grade II: moderate Grade III: severe
	6. Other: Changes not due to rejection	6. Other: Changes not due to rejection	6. Other: Changes not due to rejection	6. Other: Changes not due to rejection	6. Other: Changes not due to rejection

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