Banff VCA Summary Session

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Duke University Medical Center

On behalf of the Banff VCA Working Group

VCA Banff

Trachea Transplantation – Eric Genden, M.D.

Phallus Transplantation- Curtis Cetrulo, M.D.

The Dallas Uterus Transplant Study: Histological and Clinical Update – Jake Demetris, M.D.

Update on Uterus Transplantation Pathology – Verena Brocker, M.D.

Non-invasive biomarkers of rejection in VCA – Leo Riella, M.D.

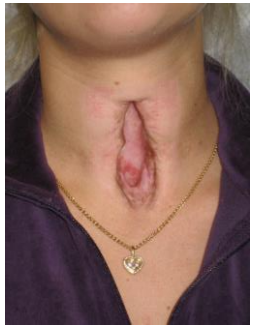
Vascular Changes in VCA – Jean Kanitakis, M.D.

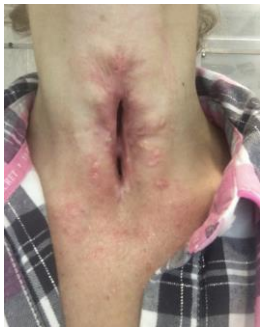
Treatment of acute rejection in VCA – Simon Talbot, M.D.

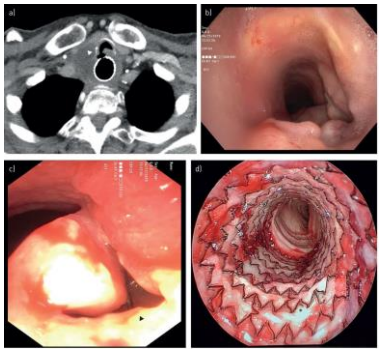
Revision of the VCA-Banff scoring system – Group Discussion

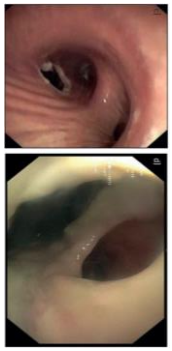
Trachea Transplantation –
Eric Genden, M.D. Mount Sinai Medical Center

Stent – esophageal fistula

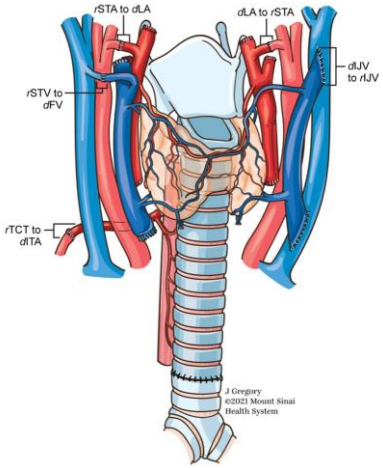


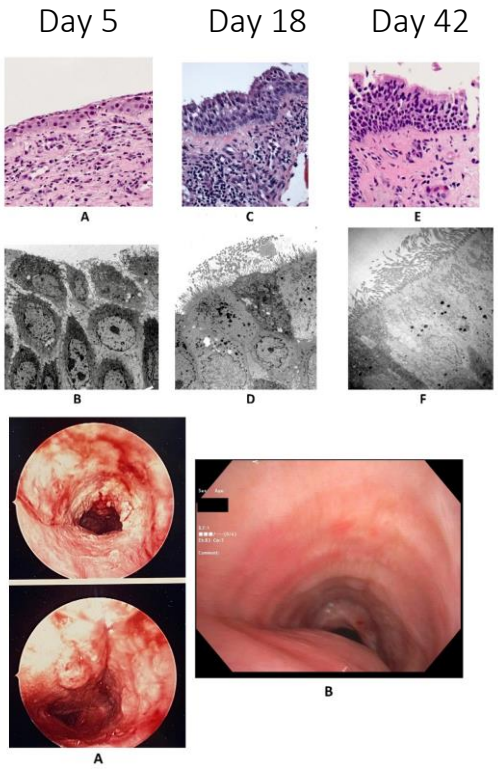






Long segment reconstruction





<u>What have we learned?</u>

Single stage vascularized tracheal transplantation is possible

Standard immunosuppression appears effective.

The graft initially sloughs epithelium

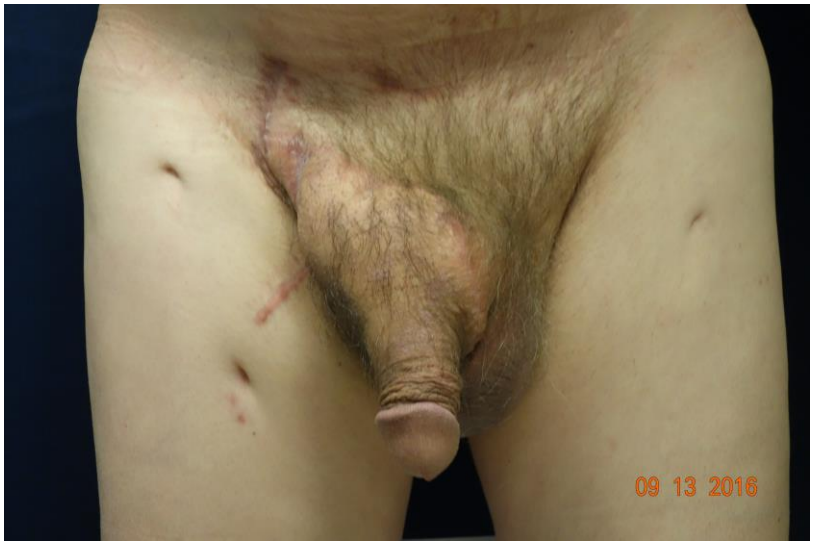
The allograft undergoes re-epithelialization in a chimeric fashion

Phallus Transplantation
Curtis Cetrulo, M.D. Massachusetts General Hospital

6 Years Post Op

Successful Aesthetic Outcome

Successful Urinary Function Outcome (no complications)



Sensory return at 2 years

Successful Sexual Function Returned at 3 years

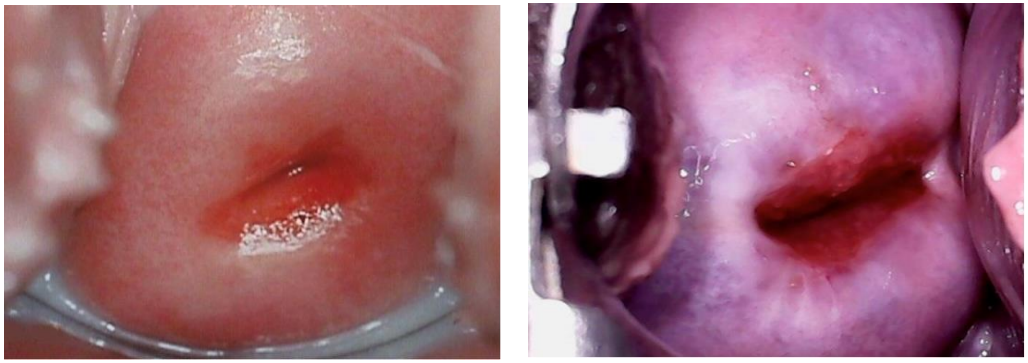
Sexually active patient

Able to maintain erections and ejaculate

Uterus Allograft Rejection after Immunosuppression Withdrawal an observational study

Jake Demetris, M.D.
Baylor University Medical Center, University of Pittsburgh Medical Center

Gross Appearance of Cervix



Cervix at day 0 (a) and 29 (b) after withdrawal of immunosuppression. Discoloration is shown at day 29.

Conclusions

Orderly progression of gross and histopathological findings of rejection but pace of evolution differs

More severe forms of rejection

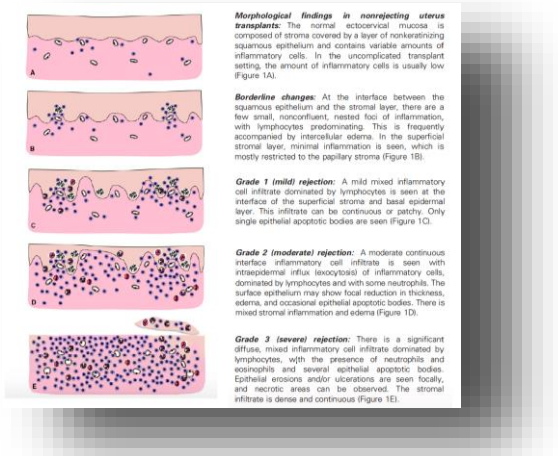
- cervical cyanosis with/out altered flora and vaginal discharge
- as severity increased signs of mixed rejection appears
- C4d staining often first detected in lamina propria capillaries

Antibody sensitization: DSA > PSA

Update on Uterus Transplantation Pathology
Verena Brocker, M.D. University of Gothenburg

163 biopsies in 7 patients, 36 months follow up

Grading	Biopsies	Patients (n)
Rejection G1 G2 G3	13/163 (8%) 7 3 3	5/7
Borderline	15/163 (9%)	5/7
Normal	135/163 (83%)	



Molne, J., V. Broecker, … M. Brannstrom
AJT 2017

Conclusions from transplant hysterectomies

- Rejection (mild) occurs but without clear association to outcome
- Inflammation in the cervix mirrors inflammation in the myometrium and arteries
- ”Borderline” is not specific for transplants, although more frequent
- Endocervical inflammation is not diagnostic
- Morphological spectrum of rejection includes,
- Linear subepithelial stromal inflammation, interface inflammation
- Perivascular stromal inflammation (?)
- Inflammatory foci in the myometrium
- Endarteritis in larger arteries

Broecker V, et al. AJT 2021

Non-invasive biomarkers of rejection in VCA – Leo Riella, M.D.
Massachusetts General Hospital

Th17 and Th1 cells peak during rejection both in the blood and in the allograft of face transplant recipients

Borges et al. AJT 2016

Many similarities in human VCA and solid organ transplant rejection
Significant overlap of signals:
leukocyte trafficking, T cell activation, antigen processing and presentation, and effector molecules

Win et al. JCI 2020

Serum MMP3 is a marker of severity of VCA rejection

Multicenter study – 140 serum samples (both face and limb recipients)

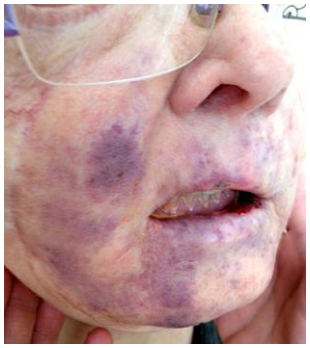
Collaboration with Emmanuel Morelon
Kollar et al. Frontiers Imm 2019

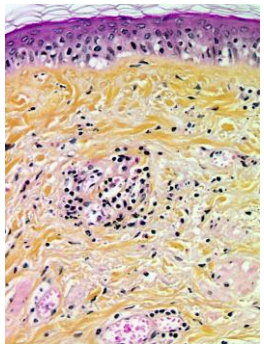
Conclusions

- Th17 and Th1 cells peak during rejection both in the blood and in the allograft of VCA recipients
- Serum MMP3 protein is a promising marker for stratifying patients according to severity of rejection, complementary to biopsy findings.
- DSA are the best transplant-specific biomarkers to monitor post-transplant
- Non-HLA antibody levels seem to correlate with severity of injury. Though the role on nonHLA antibodies in the pathogenesis is unclear.

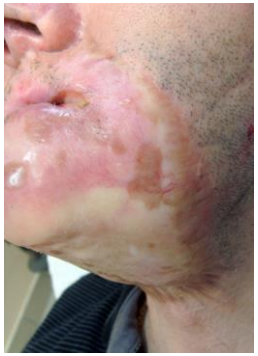
Vascular Changes in VCA - Personal experience– Jean Kanitakis, M.D.

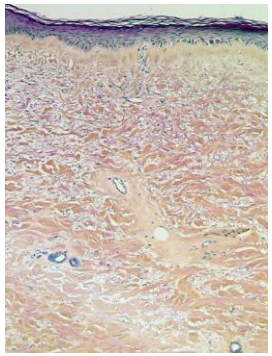
Ed. Herriot Hospital



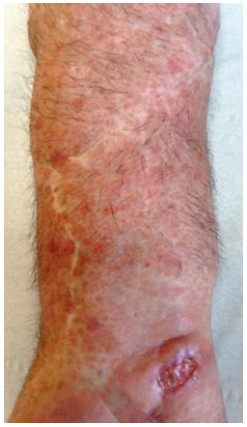


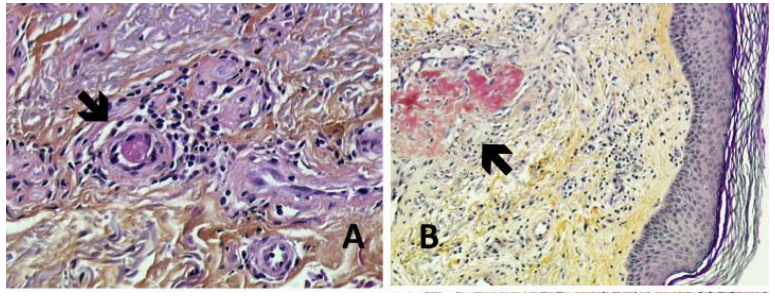
Small vessel skin (leukocytoclastic ±) vasculitis in face VCA during severe rejection



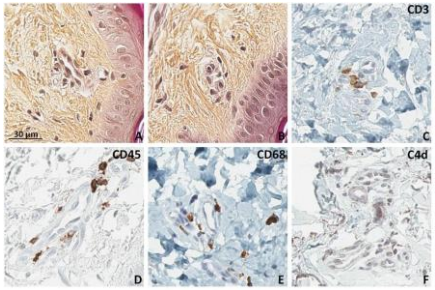


Chronic rejection in face VCA

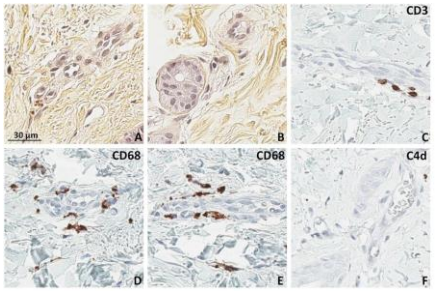




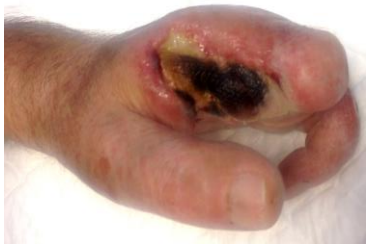
Skin capillary thromboses in hand transplantation

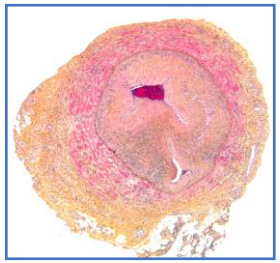


Pre-DSA



Post-DSA



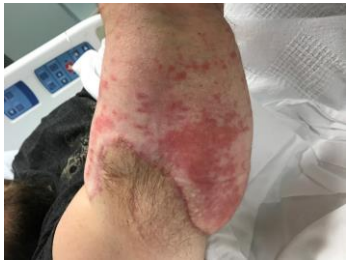


Graft vasculopathy - ischemic graft necrosis

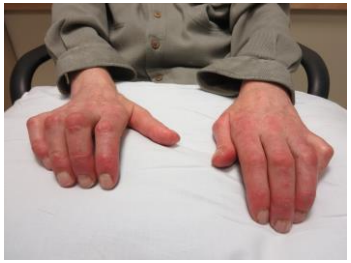
Treatment of acute rejection in VCA – Simon Talbot, M.D.

Brigham and Women's Hospital

- Typical
  - Maculopapular rash (diffuse, patchy, or focal)
  - Sparing palmar skin and nails
  - Possible pain
- Atypical
  - Palmar skin and nail involvement
  - Desquamation with red papules, scaling, lichenification of the palm
  - Nail dystrophy, degeneration, deformation



- Overlapping clinical presentation of chronic rejection and anti-body-mediated rejection – still to be defined



Future directions

- Unique advantages of VCA
  - Continuous monitoring is possible
  - Topical application
  - Biopsies are minimally morbid
- Local/targeted drug delivery systems (steroids, tacrolumus, cyclosporine)
  - Thermoresponsive nanogels
  - PLC microfilms
  - PLGA plugs/microspheres
  - Macroporous scaffolds
  - Suspensions
  - Hydrogels

The VCA Banff Working Group Discussion

First Revision of the Classification

Banff VCA
NIH Consensus Development Program

- Broad based, non advocacy independent panel
- Freedom from scientific or financial conflict of interest
- Systematic literature review
- Invited speakers
- Predetermined questions defining the scope and direction of the conference
- Conclusions summarized as Consensus Report and submitted for peer review publication
- Reconvene to evaluate how the classification is working

The VCA Banff Working Classification of Allograft Pathology Common Language

American Journal of Transplantation 2008; 8: 1–5
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2008.02243.x

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. Landgren[i], B. Lyons[j], C. B. Drachenberg[k], K. Solez[l], A. D. Kirk[m], D. E. Kleiner[n] and L. Racusen[o]

Skin containing VCA

N= < 300 recipients reported worldwide

Kidney

N= > 200,000 recipients reported worldwide

Timeline for the First Revision of the Scoring System

May 2016

- Survey # 1
- I International Workshop on VCA

May 2022

- Survey #2
- Pathologists
- Clinicians

July 2022

- Virtual Consensus Discussion

August 2022

- Survey #3
- Pathologists

September 12, 2022

- Virtual Consensus Discussion
- Pathologists

September 22, 2022

- Final Consensus Discussion
- Consensus achieved

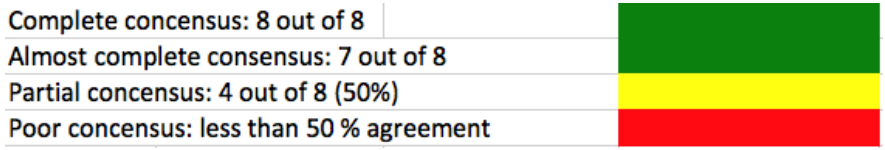
October 2022

- Manuscript preparation

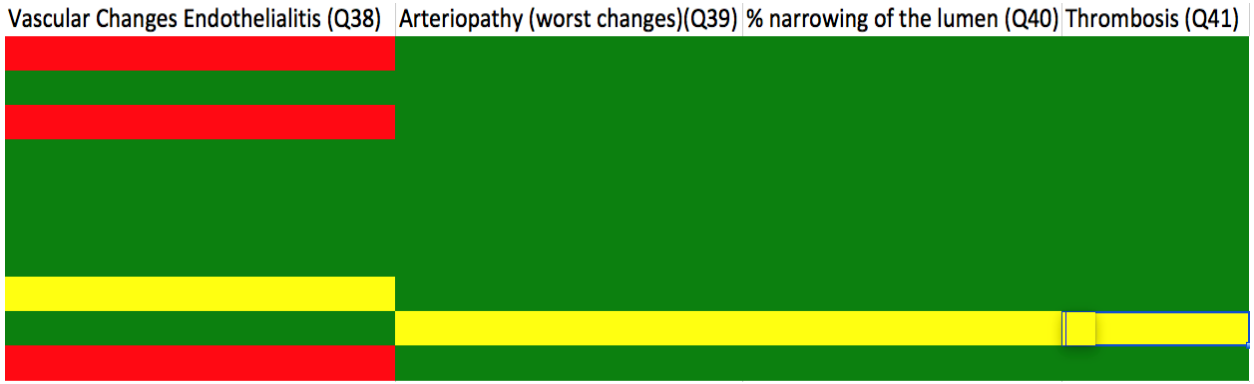
Timeline for the First Revision of the Scoring System

May 2016

- Survey # 1
- I International Workshop on VCA



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



Duke SCORES
Surgical Center for Outcomes Research

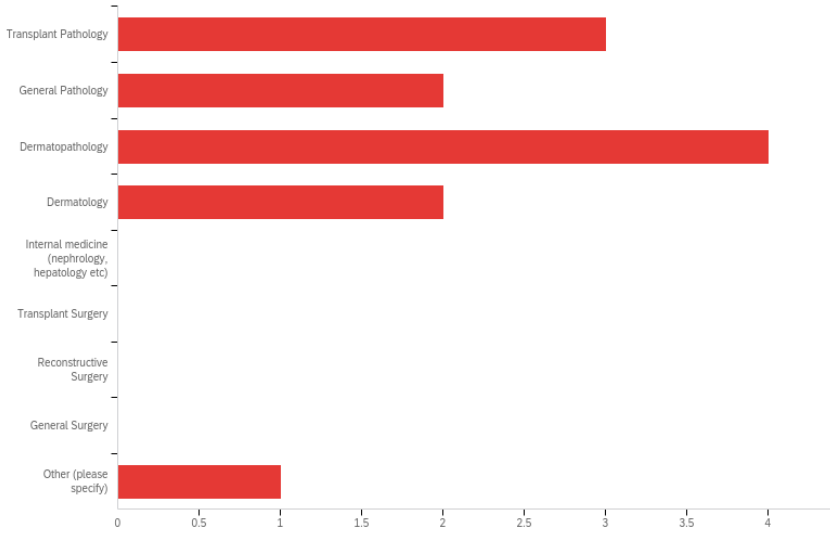
VCA
Histopathology

Timeline for the First Revision of the Scoring System

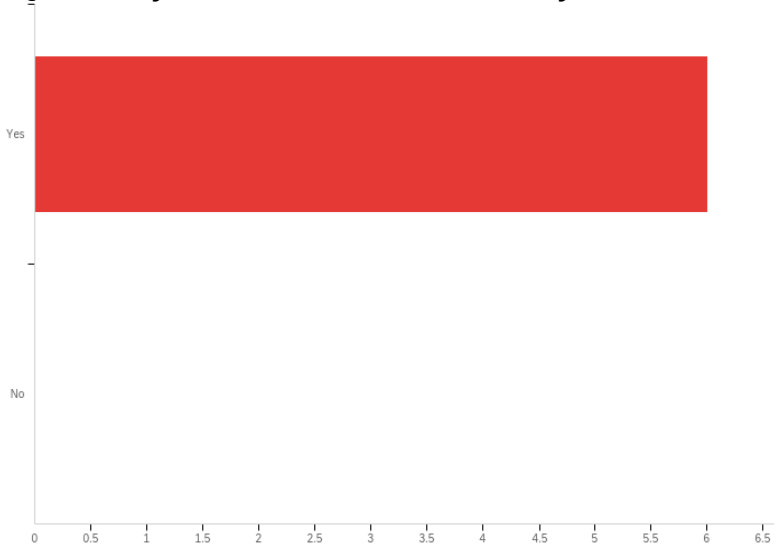
May 2022 → July 2022

- Survey #2
- Pathologists
- Clinicians

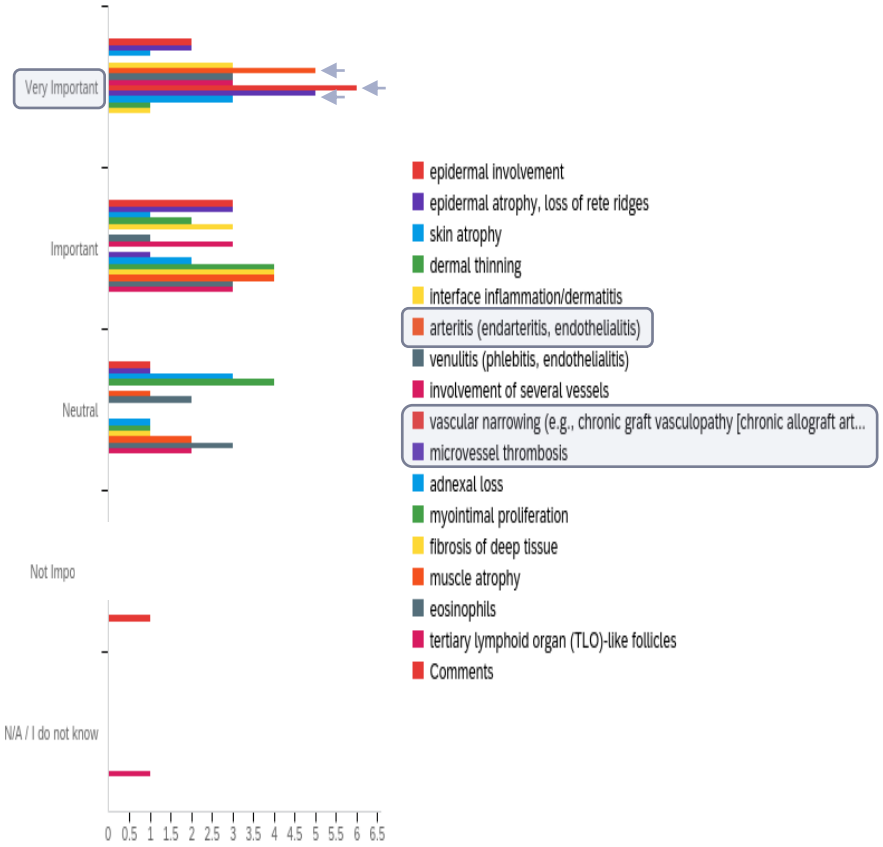
- Virtual Consensus Discussion

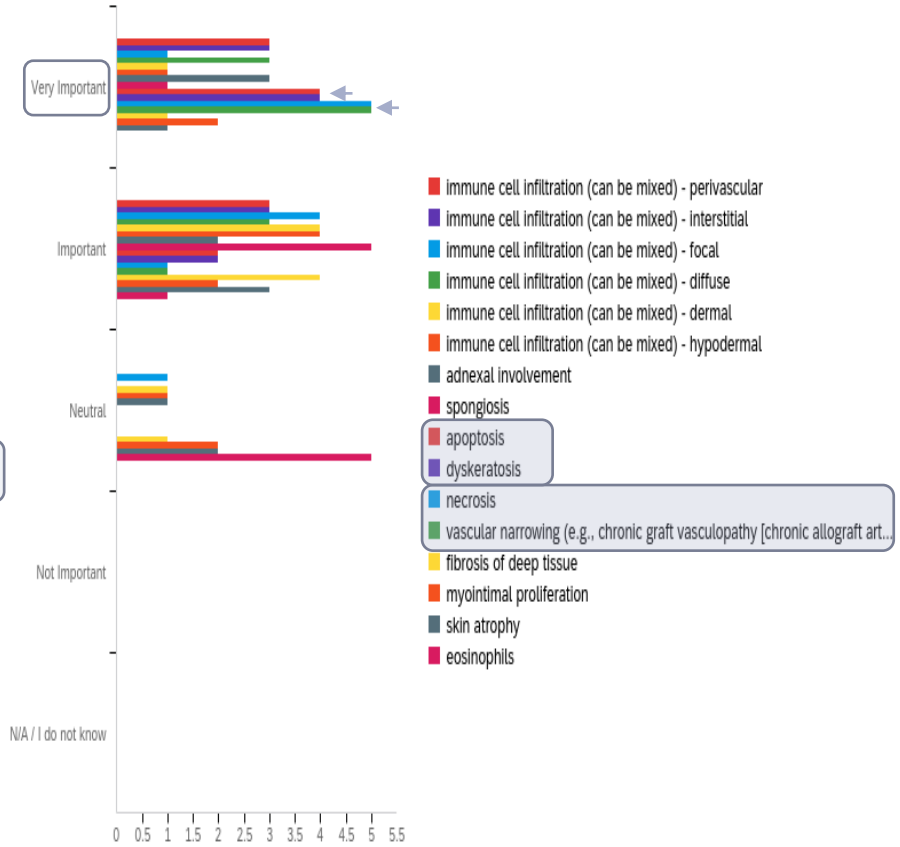


Q6 - Do you use the VCA Banff system?



Criteria to evaluate rejection severity and monitoring





- Arteritis (endarteritis, endothelialitis)
- Vascular narrowing (e.g. Chronic graft Vasculopathy)
- Microvessel thrombosis

VASCULARIZED COMPOSITE ALLOTRANSPLANTATION
2017, VOL. 3, NOS. 1–2, 62–74
https://doi.org/10.1080/23723505.2017.1318200

Taylor & Francis
Taylor & Francis Group

RESEARCH PAPER

OPEN ACCESS Check for updates

Systematic pathological component scores for skin-containing vascularized composite allografts

Ivy A. Rosales[a], Ruth K. Foreman[a], Matthew DeFazio[b], David H. Sachs[c], Curtis L. Cetrulo, Jr.[b,c], David A. Leonard[b,c,d], and Robert B. Colvin[a]

[a]Department of Pathology, Massachusetts General Hospital, Massachusettts General Hospital, Boston, MA, USA; [b]VCA Laboratory, Center for Transplantation Sciences, Massachusetts General Hospital, Charlestown, MA, USA; [c]TBRC Laboratories Center for Transplantation Sciences, Massachusetts General Hospital, Charlestown, MA, USA; [d]Canniesburn Plastic Surgery Unit, Glasgow Royal Infirmary, Glasgow, Scotland, UK

Systematic scoring system developed from MHC-mismatched porcine skin-containing VCA.

Biopsies from 20 VCA, 9 autologous skin flaps and 9 normal skin were analyzed to optimize the methodology and set thresholds.

A 2018 Reference Guide to the Banff Classification of Renal Allograft Pathology

Candice Roufosse, MD, PhD, Naomi Simmonds, MD, [...], and Jan U. Becker, MD

- Arteritis (endarteritis, endothelialitis)
- Vascular narrowing (e.g. Chronic graft Vasculopathy)
- Microvessel thrombosis

Transplant Arteriopathy

Transplant Arteriopathy is defined as arterial fibrointimal thickening, also referred to as vascular fibrous intimal thickening.

It is graded based on the extent of luminal occlusion in the most severely affected artery.

It does not discriminate between bland arterial intimal fibrosis and fibrosis containing leuko- cytes

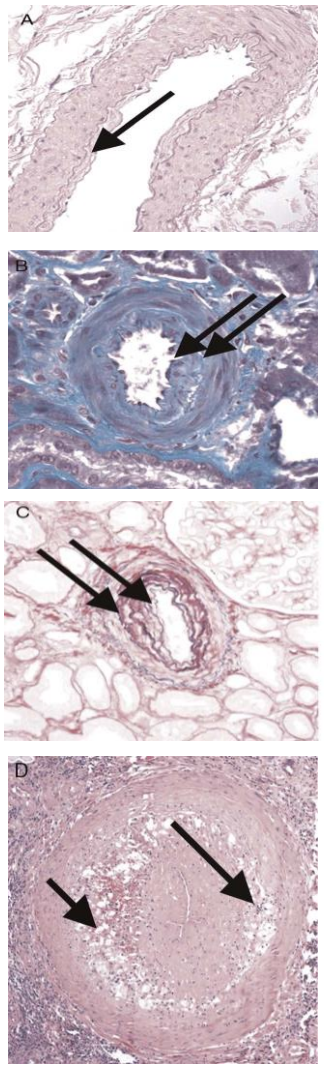
Transplant arteriopathy is scored with the Banff Lesion Score *cv*.

cv0—No chronic vascular changes.

cv1—Vascular narrowing of up to 25% luminal area by fibrointimal thickening.

cv2—Vascular narrowing of 26 to 50% luminal area by fibrointimal thickening.

cv3—Vascular narrowing of more than 50% luminal area by fibrointimal thickening.[11]



Transplantation 2018;102: 1795–1814

Arteritis

	VCA	KIDNEY	Similarities	Differences
Definition	**Endarteritis**: Mononuclear cells underneath arterial endothelium, scored on the most involved artery, arterioles not scored	**Arteritis, Intimal**: Synonymous with endarteritis or arterial endothelialitis. Banff 2015: defined as mononuclear cell infiltration beneath the arterial endothelium. Arterioles are not scored. Total number of arteries in the biopsy and the number of arteries affected should be noted.	✓ . (mononuclear cells underneath the endothelium)	----
Score				
V0	None	No arteritis	✓ .	----
V1	<25% of lumen/vessel	Mild to moderate intimal arteritis in at least 1 arterial cross section		Use degree of inflammation
V2	>25% of lumen/vessel	Severe intimal arteritis with at least 25% luminal area lost in at least 1 arterial cross section	✓ .	----
V3	Fibrinoid necrosis/transmural involvement	Transmural arteritis and/or arterial fibrinoid changes and medial smooth muscle necrosis with lymphocytic infiltrate in vessel	✓ .	----
Vx	No arteries			Based on biopsy requirements

Vasculopathy

	VCA	KIDNEY	Similarities	Differences
Definition	**Chronic allograft vasculopathy**: intimal thickening with luminal reduction, scored as percent luminal reduction	**Chronic allograft arteriopathy:** Arterial intimal fibrosis with mononuclear cell infiltration in fibrosis and/or formation of neointima.	✓ . (intimal thickening)	----
Score				
CAV0	None	CV0—No chronic vascular changes	✓ .	----
CAV1	<25% luminal reduction	CV1—Vascular narrowing of up to 25% luminal area by fibrointimal thickening.	✓ .	----
CAV2	>25-50 % luminal reduction	CV2—Vascular narrowing of 26 to 50% luminal area by fibrointimal thickening.	✓ .	----
CAV3	>50% luminal reduction	CV3—Vascular narrowing of more than 50% luminal area by fibrointimal thickening.	✓ .	----
CAVx	No arteries			Based on biopsy requirements

Timeline for the First Revision of the Scoring System

August 2022

- Survey #3
- Pathologists

September 12, 2022

- Virtual Consensus Discussions

Arteritis, Vasculopathy, Microvessel thrombosis

Terminology
Definition
Scoring System
Reporting System

Timeline for the First Revision of the Scoring System

September 22, 2022

- Final Discussion
- **Consensus achieved**

First Revision of the Banff VCA skin-containing classification system

Table 1: The Banff 2007 working classification of skin-containing composite tissue allograft pathology

Grade 0. No or rare inflammatory infiltrates.
Grade I. Mild. Mild perivascular infiltration. No involvement of the overlying epidermis.
Grade II. Moderate. Moderate-to-severe perivascular inflammation with or without mild epidermal and/or adnexal involvement (limited to spongiosis and exocytosis). No epidermal dyskeratosis or apoptosis.
Grade III. Severe. Dense inflammation and epidermal involvement with epithelial apoptosis, dyskeratosis and/or keratinolysis.
Grade IV. Necrotizing acute rejection. Frank necrosis of epidermis or other skin structures.

American Journal of Transplantation 2008; 8: 1396–1400

DRAFT- Vascular Changes

Vasculitis/Arteritis

Def-. Mononuclear cells underneath vessel endothelium, scored on the most involved vessel, including capillaries, arterioles, venules, veins, arteries. The number of involved arteries and the total number of arteries to be scored.
Scoring-
V0 No arteritis.
V1 Mild to moderate intimal arteritis in at least 1 arterial cross section.
V2 Severe intimal arteritis with at least 25% luminal area lost in at least 1 arterial cross section.
V3 Transmural arteritis and/or arterial fibrinoid change and medial smooth muscle necrosis with lymphocytic infiltrate in vessel.
Vx no arterie

Reporting Modifier

Allograft Vasculopathy

Def- combination of option 1 and option 2

Scoring-
CAV0 None
CAV1 25-50 % luminal reduction
CAV3 >50% luminal reduction
CAVx No arteries

Reporting Modifier

Small vessel thrombosis

Def- small vessel thrombosis

Scoring- Present/absent

Reporting Modifier ”t”

Timeline for the First Revision of the Scoring System

October 2022

- Manuscript preparation

Summary

- Common language
- International Collaboration
- Consensus discussions
- *Refined the universally accepted criteria for VCA rejection reporting*
  - *Addition of vascular changes*
- Living document
- Working classification for dissemination to the healthcare practice and transplant community

Thank you

Angelica Selim, M.D. - Duke University

Armando Gamboa Dominguez, M.D. - Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Brad Farris, M.D. - Emory University

Cynthia Drachenberg, M.D. - University of Maryland

David Elder, M.D. - University of Pennsylvania

Ivy Rosales, M.D. - Massachusetts General Hospital

Jean Kanitakis, M.D. - Ed. Herriot Hospital

Xiaowei (George) Xu, M.D. University of Pennsylvania

Simon Talbot, M.D. Brigham and Women's Hospital

Bruce Gelb, M.D. NYU

Brian Nankivell, M.D. Westmead Hospital

All attendees of the VCA Banff Consensus Discussion Working Group Sessions