

Banff 2013 Update on renal allograft pathology

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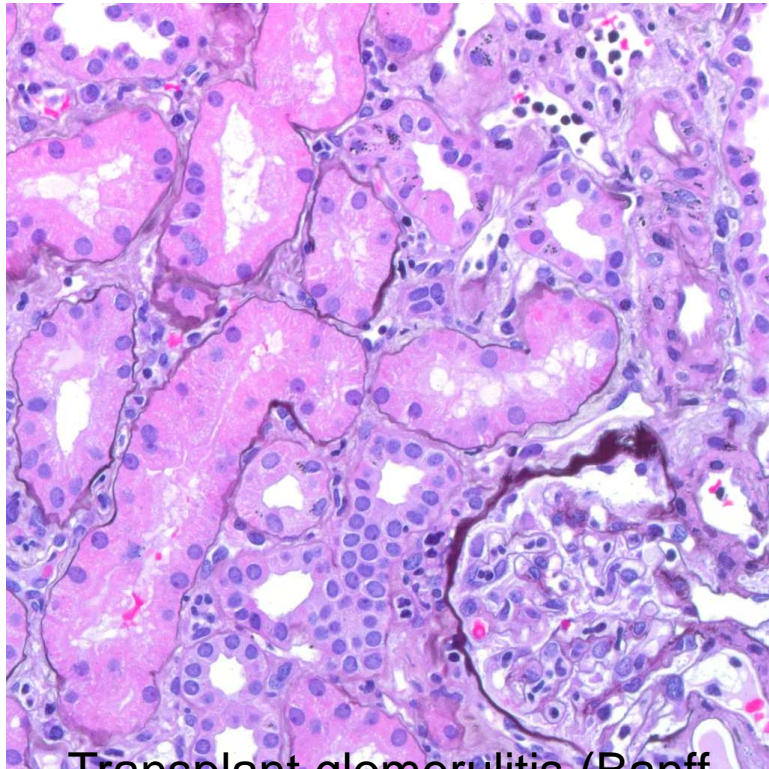
Report of working groups

- Isolated v-lesion (B. Sis):
acute cellular rejection, some even with acute humoral component
- Fibrosis (B. Farris):
improve interobserver agreement in IFTA-scoring
- Implant biopsy (H. Liapis):
reproducible results on wedge biopsies with frozen sections, scoring only percentage of globally sclerosed glomeruli and arterial intimal fibrosis (cv)
- Polyoma (V. Nickleit):
new score based on extent of infected tubuli and Banff ci
- C4d-BIFQUIT trial (M. Mengel):
significant interinstitutional differences

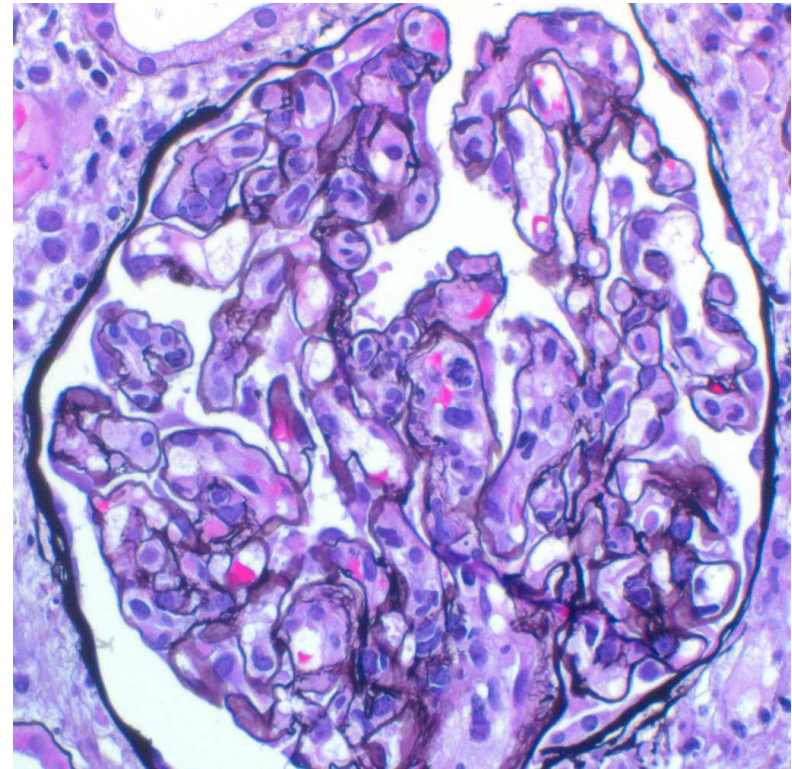
Updates of importance

- Antibody-mediated rejection (ABMR)
- acute and chronic
- C4d-negative

Updates of importance: microvascular inflammation

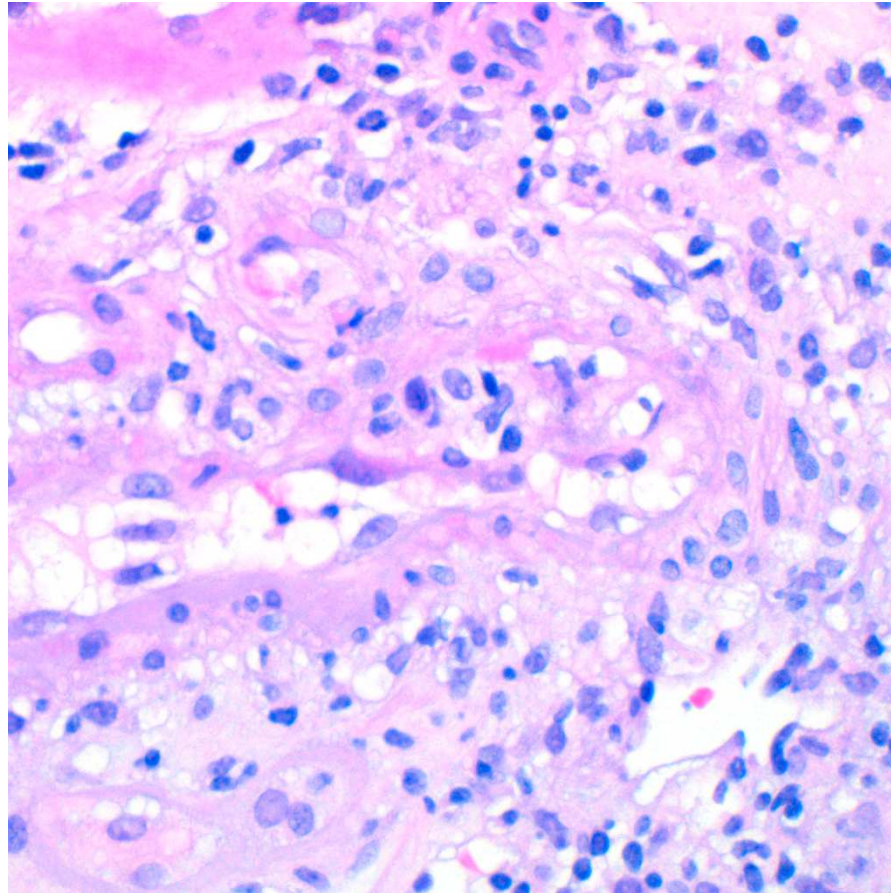


Transplant glomerulitis (Banff
g)
peritubular capillaritis (Banff
ptc)



Transplant glomerulitis (Banff
g)

Updates of importance: arterial endothelialitis (Banff v)



Redefinition of glomerular lesions Banff g and cg

- Two series of virtual slides (total n=47)
- PAS and silver stains
- examined by pathologists of various experience
- after first circulation elimination of definitions with low interobserver reproducibility
- goal of indentifying reproducible, diagnostically and prognostically significant lesions

Redefinition of Banff α (glomerulitis)

- Definition of basic lesion with highest interobserver reproducibility and best correlation with C4d, mRNA transcription profiles (ENDAT, DSASTs):

≥ 1 complete or partial occlusion of glomerular capillary with endothelial enlargement and leukocyte

- Banff α ≥ 3 : $\geq 50\%$ of glomeruli

Thresholds used to be 0%, 25%, 75% in Banff 1997

What about association with outcome or DSA? Definition may now be better reproducible but just based on only n=47 cases

Redefinition of Banff cg

- Same procedure and set of slides as with Banff g
- Best interobserver agreement, better correlation with HLA class II DSAs and ENDATS with threshold for cg1 of at least one capillary loop with splitting/double contour instead of $\geq 10\%$
- Definitions of cg2 and cg3 shall remain

Electron microscopy (EM)

and Banff cg

- Banff advises to use EM more than 6 months after transplantation and on indication biopsies more than 3 months after transplantation
- if cg present (according to redefinition), then test for DSAs
- Banff recommends EM for all patients with histologic signs of humoral rejection

Massive increase in cost and workload, but what do we gain?
Splitting of GBM just by EM is not a well established outcome parameter.

Would recommend DSA testing with all transplant biopsies.

Redefinition of Banff cg

- cg0: no GBM double contours by light microscopy or EM
- cg1a: no GBM double contours by light microscopy but by EM in at least 3 glomerular capillaries with associated endothelial swelling and/or subendothelial electron-dense widening
- cg1b: one or more glomerular capillary with double contour
EM confirmation recommended

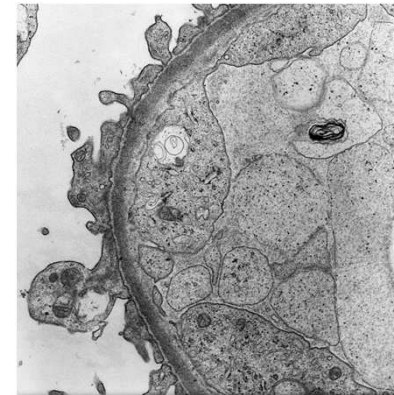
Weak parameters, weak definitions, cumbersome to determine.

Study Design

- Light microscopy and ultrastructural examination
 - 20 iAB0 C4d+ grafts (57 biopsies) with presumed good prognosis
 - 20 cAB0 C4d+ grafts (31 biopsies) with presumed bad prognosis
 - 15 controls (15 biopsies of „stable“ grafts)
- Means of all parameters of all biopsies from a single graft analyzed.

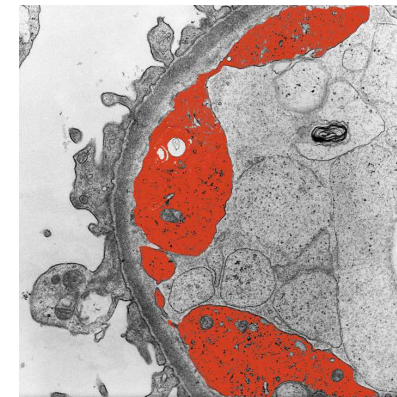
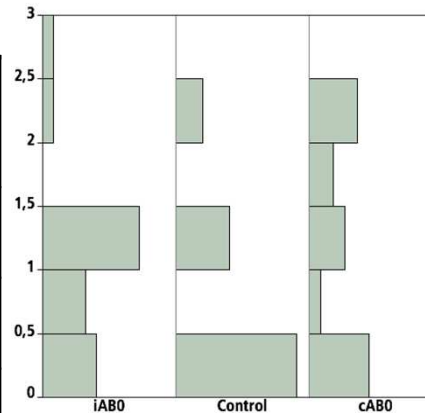
Ultrastructural changes

	all C4d+	iAB0 vs. cAB0	iAB0 vs. Control	cAB0 vs. Control
Glomerulus	Foot Process Effacement	ns	ns	ns
	GEC Swelling	ns	ns	ns
	GEC Loss of Fenestration	cAB0 > iAB0	ns	cAB0 > Control
	Lamina rara interna Expansion	cAB0 > iAB0	ns	cAB0 > Control
	Lamina densa Duplication	ns	ns	ns
PTC	PTC Endothelial Swelling	cAB0 > iAB0	ns	ns
	BM Lamellation	cAB0 > iAB0	ns	cAB0 > Control



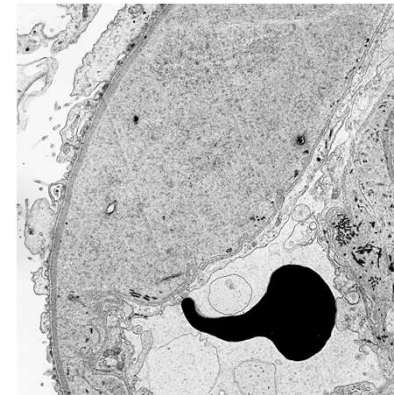
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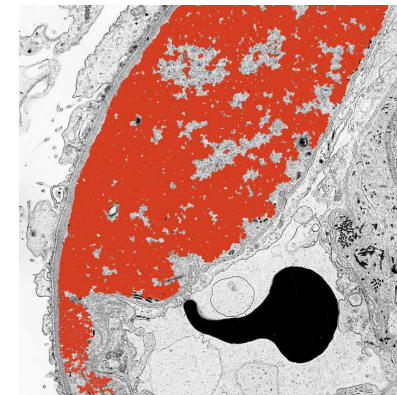
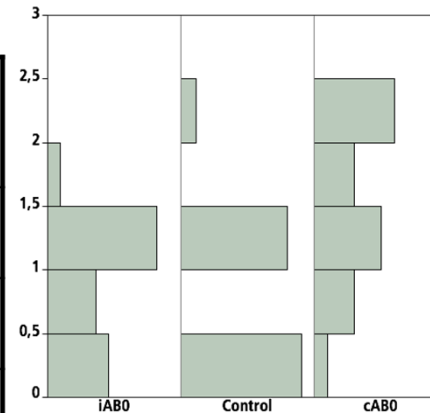
New definition of Banff cg

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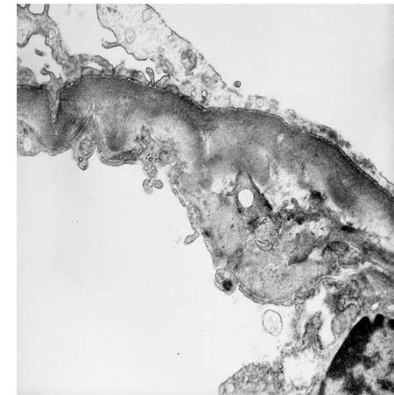
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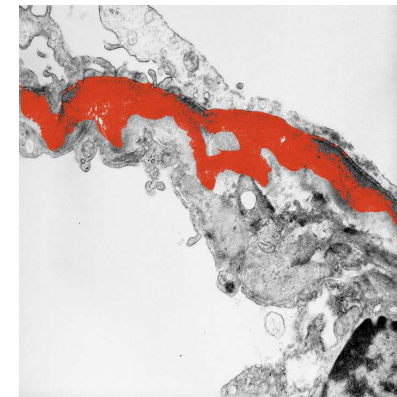
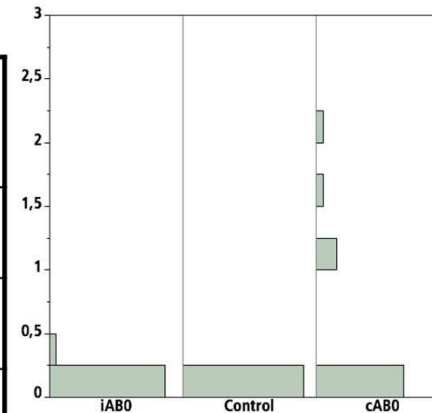
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Redefinition of Banff cg

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- cg1a: no GBM double contours by light microscopy but by EM in at least 3 glomerular capillaries with associated endothelial swelling and/or subendothelial electron lucency and/or endothelial redensification
- cg1b: one or more glomerular capillary with double contour by light microscopy; EM confirmation recommended
- cg2: $\geq 25\%$ double contours by LM in most severely affected glomerulus
- cg3: $\geq 75\%$ double contours by LM in most severely affected glomerulus

Confirmation is almost always positive, should be primarily used to exclude glomerulonephritis.

Acute/Active AB

Microvascular inflammation is contained in two different categories.

3/3 criteria diagnostic, criterion 1. or 3. missing:

Usually hierarchical exclusion:
Recurrence, ABMR, CNI

- 1. Histologic evidence of acute tissue injury, including one or more of the following:
 - microvascular inflammation (Banff $g > 0$ and/or $ptc > 0$)
 - intimal or transmural arteritis (Banff $v > 0$)
 - acute thrombotic microangiopathy, in the absence of any other cause
- 2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
 - linear C4d staining in PTC
 - at least moderate microvascular inflammation ($[g+ptc] \geq 2$)
 - increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury if thoroughly validated
- 3. Serologic evidence of donor-specific antibodies (HLA or other antigen)

Lower threshold of g and ptc
notoriously low reproducibility.

Chronic, active ABMR

3/3 criteria diagnostic, criterion 1. or 3. missing:
just chronic

- 1. Morphologic evidence of chronic tissue injury, including at least one of the following:
 - transplant glomerulopathy (cg>0), if no evidence of chronic TMA
 - severe peritubular capillary basement membrane multilayering (≥ 7 plus 2 ≥ 5)
 - arterial intimal fibrosis of new onset, excluding other causes
- 2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one of the following:
 - linear C4d staining in peritubular capillaries (C4d2 or C4d3 on frozen or C4d>0 on paraffin)
 - at least moderate microvascular inflammation ($[g+ptc] \geq 2$)
 - increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly validated
- 3. Serologic evidence of DSA (HLA or other antigen)

chronic TMA may be due to ABMR

Poor definition.

Conclusion: Banff 2013

● Arterial endothelialitis now criterion for update
ABMR. good!

- Expect massive reclassification from „active“ to „chronic, active ABMR“ based on EM findings
- Massively increased workload and cost, if compliance with Banff recommendations
- Counseling of individual centers and their nephropathologists recommended whether Banff 2013 Update should be implemented

Thank you!

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