THE BL/TCMR WORKING GROUP

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OUTLINE TALK

- Current problems with the BL category
- Prospects of refining this diagnosis with MDx
- Continued importance of TCMR in the current practice of kidney transplantation
- Suitability of i-IFTA as a possible criterion c-TCMR

BORDERLINE DEFINITION BANFF 1991

- Coined in 1991 for TCMR <1A
- Intent was to avoid over Dx & gratuitous Rx
- Entity was described as (“very mild rejection)”
- Defined as i1 or i2 mono inflamm with foci t1 tubulitis
- Grade i1 inflamm intended to be ‘more than trivial’

EVOLUTION OF THE DEFINTION OF BL

- 1997: BL change "suspicious for Ac rejection"
  "More than trivial i" defined: "at least i1" (>10%)

- 2005: phrase ACR changed to AC T-cell-MR
  -May coexist with other dx: ABMR, IFTA
  -Grade i0 became acceptable but table 2≠3
  - t2 & t3 was included as long as i score 0 or 1

- 2007: i3 endorsed if tubulitis 0 or 1
- 2015: ruled on i0/i1 issue: either OK if specified

RESPONSE TO STEROID TREATMENT IN BL BIOPSIES IS VERY HETEROGENEOUS

- Scheweitzer et al. 58% CR, 30% PR
- Saad et al. 63% CR, 13% PR
- Dooper et al. 24% CR
- Gaber et al. 8/8 (100%) CR

Not all BL biopsies get treated

REASONS FOR VARIABLE RESPONSE TO TREATMENT

No Response

- Rise of creatinine due to pre-renal factors
- Non-immune injury (ATN, CNI, infection)
- Antibody mediated injury
- IFT A underlying either TCMR or ABMR

Good Response:

- BL biopsy represents an early stage TCMR
- Underestimated i &/or t due to sampling error

POTENTIAL USE OF MDX FOR BETTER CATEGORIZATION OF BL BIOPSIES

40 BL, 35 H-TCMR, 116 non-rejection biopsies

- 13/40 (33%) BL re-assigned as TCMR after analysis using Affymetrix microarrays
  - Histologic undercall: many had i-IFTA

- 27/40 (67%) BL not M-TCMR
  - Deemed non immune injury but upto 40% molec. undercall (analysis of different less affected core)

de Freitas et al. 2012: 12: 191

STUDY DESIGN TO FURTHER EVALUATE THE ROLE OF MDX IN BL BIOPSIES

- Control for i, t, Ti, i-IFTA, ci, ct, scores
- i0t1ci1 biopsy ≠ with an i3t1ci3 specimen
- Morphometric scoring ideal (area & density)
- Add edema, eosinophils, tub injury (60%, 44%)
- Exclude C4d + & DSA + biopsies
- Avoid sampling issues by using the same core
- FFPE processed by Nanostring, MA, RNA-seq
- Pathologists must work in cooperation with MDX

WILL MDX ELIMINATE BL?

- Includes immune and non-immune pathology
- Useful term to trigger more clinical evaluation
- Apply modern tools to reach specific Dx keeping in mind MDx is not fool proof: Bxs with TCMR score 0.2 = only a 20% probability of being correct
- Learn to accept the term, while making every effort to minimize the frequency of its use

THOUGHTS ON THE RELEVANCE OF TCMR IN THE ERA OF ANTIBODY DOMINANCE

TCMR HAS NOT DISAPPEARED

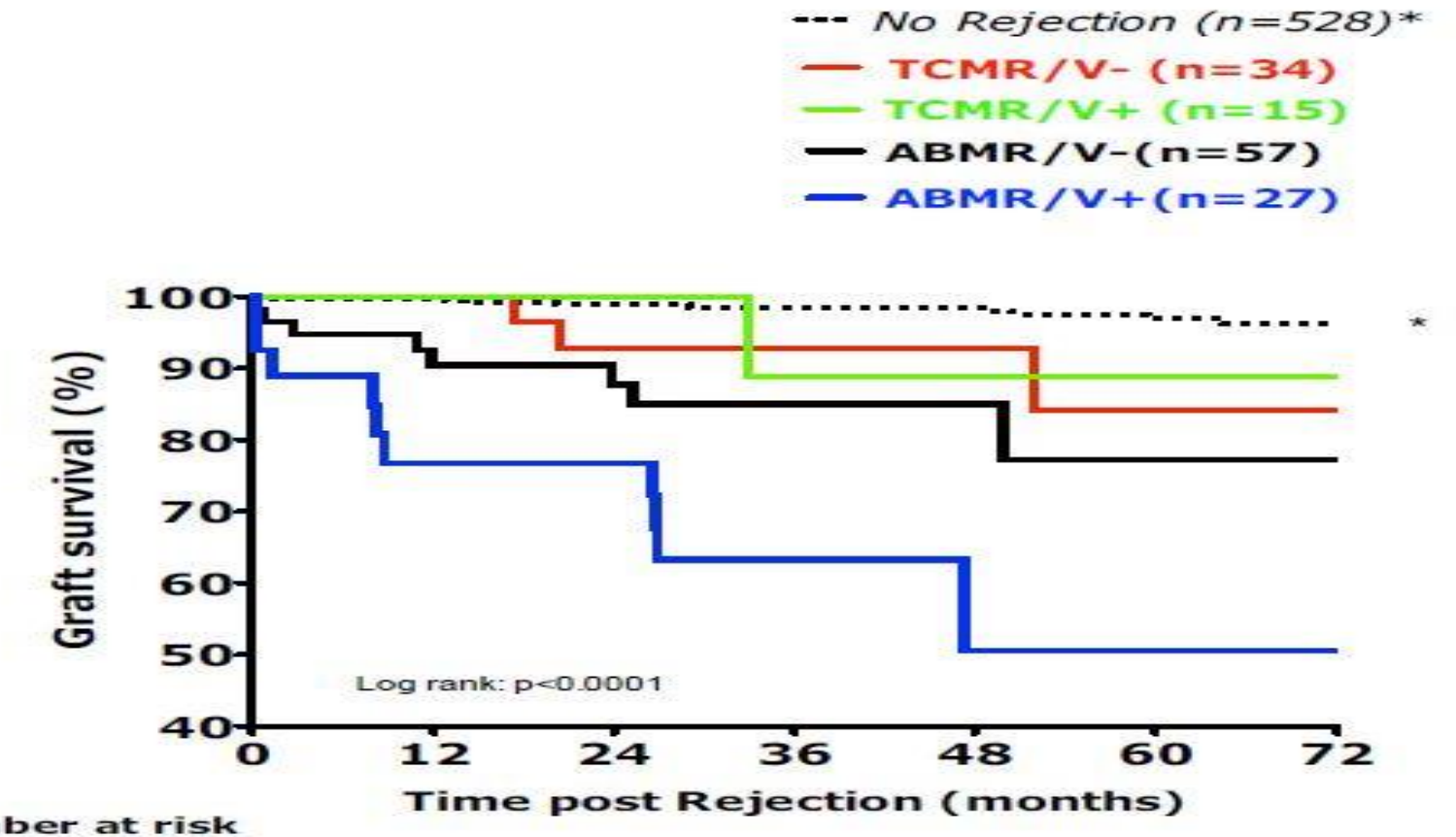
-302 BPARs 1998 to 2008

-C4d status & DSA at bx available in all

TCMR-V0 (139)	46%	Commonest type rejection
TCMR-V (26)	9%	
ABMR–V0 (73)	24%	
ABMR-V (64)	21%	
	26/90 = 28% VRs TCMR	2/3 VRs mixed i+t > 3

Lefaucheur et al. Lancet 2013: 381: 313

Graft Survival in TCMR without V-Lesions



Number at risk

No rejection	528	499	354	277	212	152	102
TCMR/V-	34	31	23	20	14	7	6
TCMR/V+	15	15	12	8	5	4	3

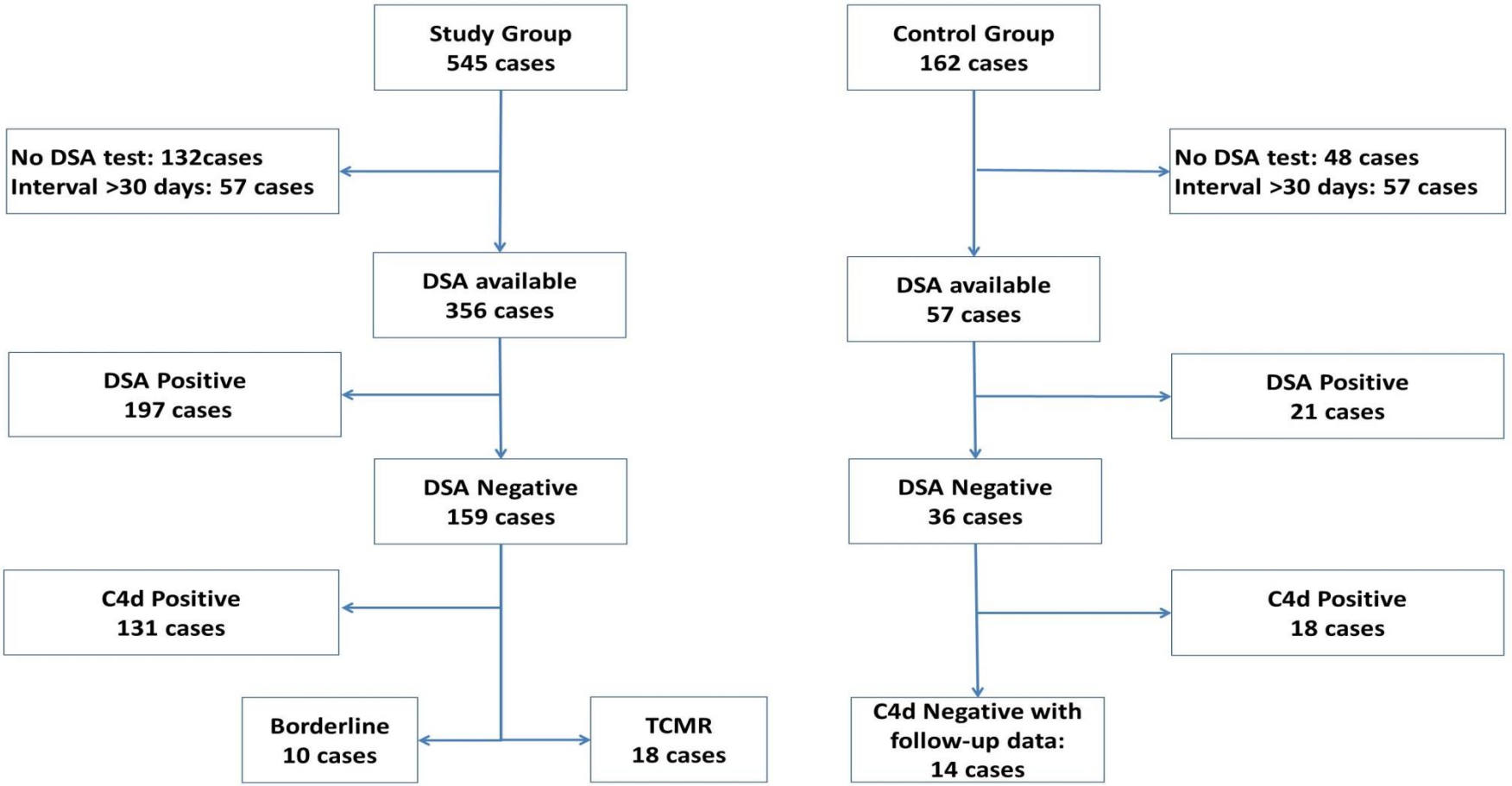
Response to Therapy

	Steroids	Steroids + anti-T	HR
TCMR-V0 (139)	100%	0%	1.0
TCMR-V (26)	73%	19%	1.5 = NS
ABMR–V0 (73)	0%	0%	2.93
ABMR-V (64)	Only 28%	Only 17%	9.07
	2/3rd i+t >3		

Lefaucheur et al. Lancet 2013: 381: 313

Pure TCMR – University of Pittsburgh (Jan 2010-Dec 2012)

Figure 1



Zhao & Randhawa, Transplantation 2017: 101: 395

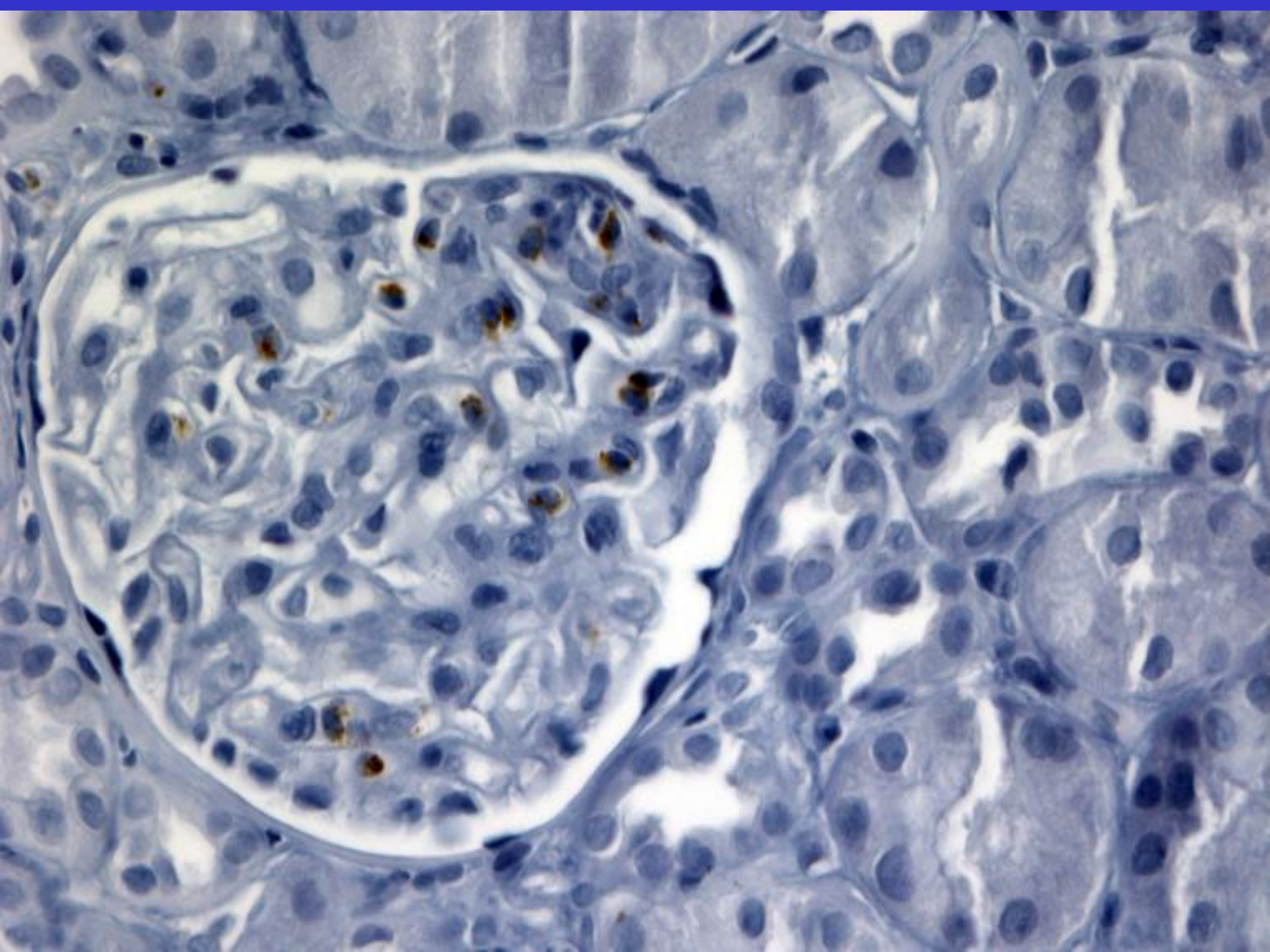
LONG TERM OUTCOME

	Last Av Scr	% rise baseline
BL	3.87+/-3.84	124+/-195
TCMR	2.94+/-2.34	100.8+/-189
Control	1.51+/-0.83	-6.2+/-36.2

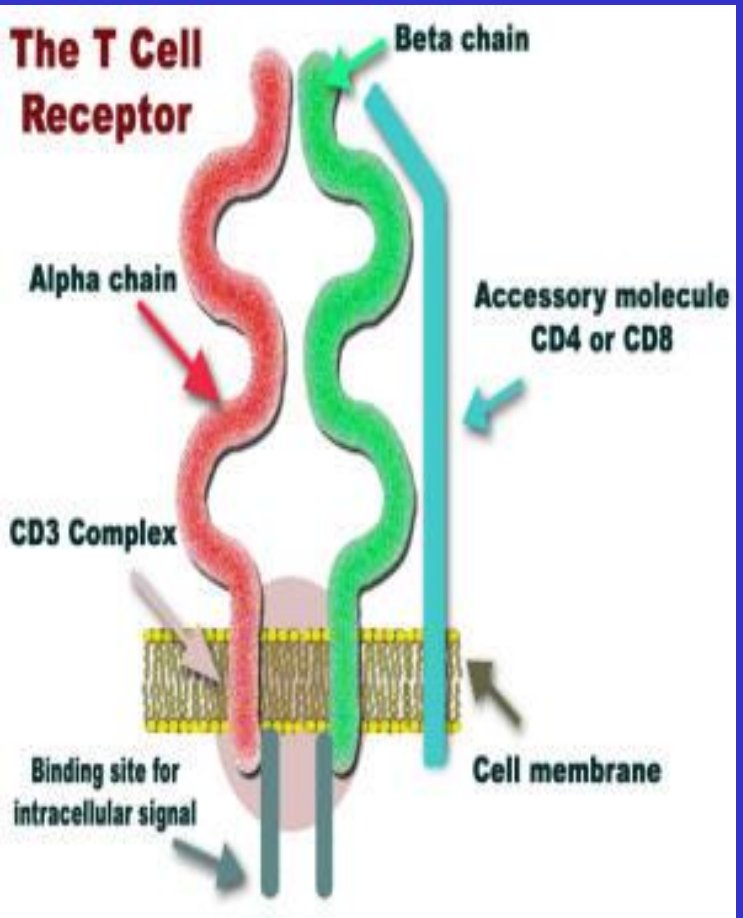
MICROVASCULAR LESIONS IN DSA NEGATIVE C4d NEGATIVE

	BL	TCMR	Control
g	1/10	5/18 g=1	0
cg	1/10)	3/18 (one cg=3)	0
PTC	(1/10)	8/18 (ptc2= 5)	0

- cg could potentially be due to past DSA
- active lesions not readily explained thus (C4d –ve & DSA test –ve within 30 d of biopsy)

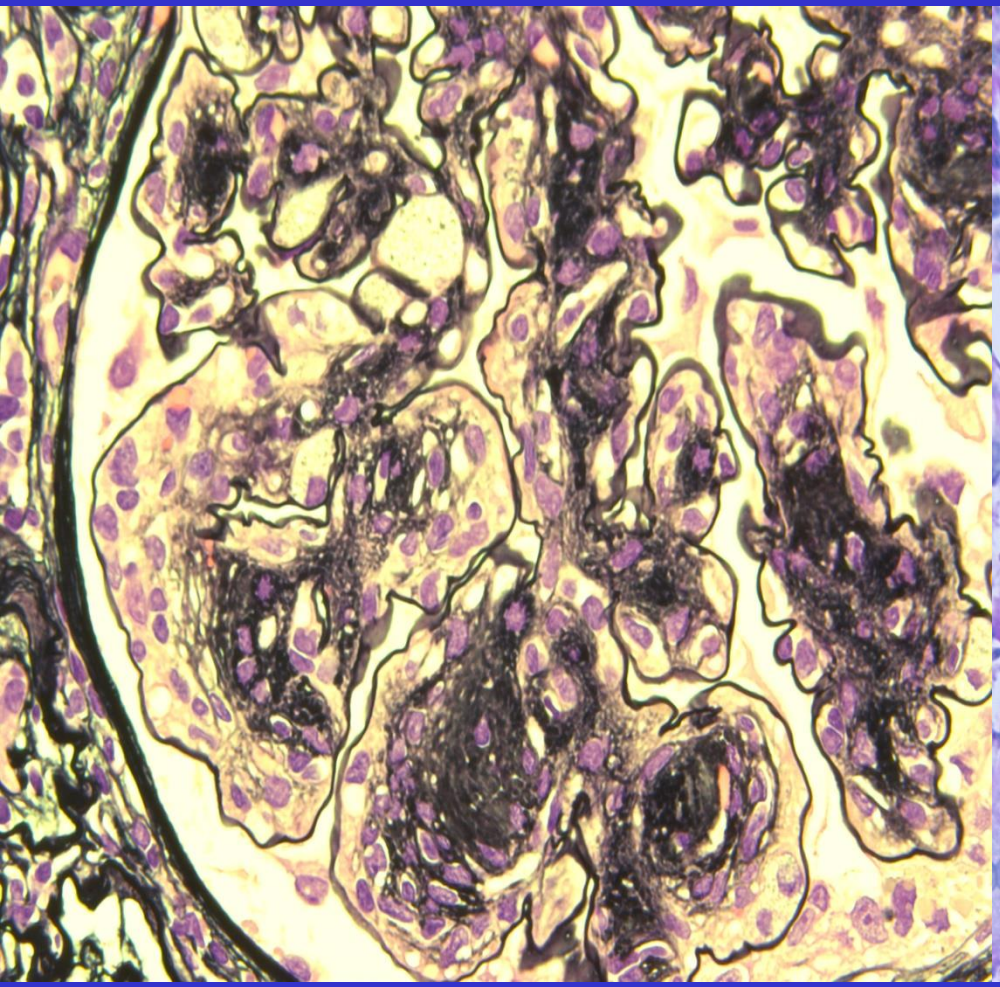


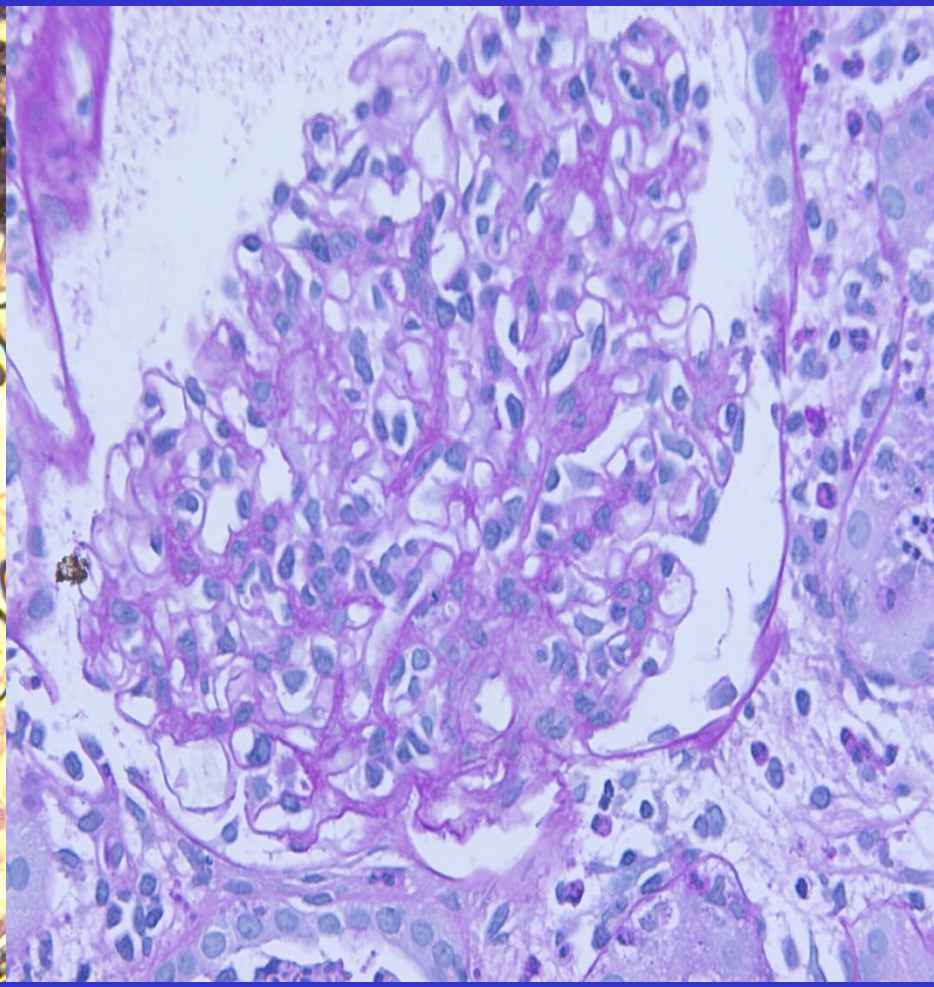
Biologic Plausibilty of T-cell Mediated Glomerulitis



- Ag recognition repertoire of T-cell pool corresponds to 10^{16} unique TCRs
- It is expected that endothelial cells will bear antigens that can be recognized by T-cells
- Claims of C4d-DSA- molecular ABMR are mostly TCMR
- G accepted as TCMR lesion 48% E & 44% NE pathologists

SOME CASES OF GLOMERULITIS ARE NON-IMMUNE





Such biopsies should be examined for presence of ENDATs and DSATs

Further Studies Needed on Mixed ABMR-TCMR in the context of

(a) Preformed and

(b)Denovo DSA

(Not yet specifically requested by the WG)

INCIDENCE OF MIXED TCMR-ABMR

- Lower end estimates mixed rejection: 6%
- Higher end: 43% early, 48% late ABMR

  63% & 96% BL

- Demographics, immunosuppression.

  -i-IFTA not reported by pathologists leads to undercalling TCMR in late biopsies

- Predicts graft loss C4d/DSA-ve Bxs

Pathogenesis of Mixed TCMR-ABMR

- Bidirectional relationship
- ABMR→secondary influx T-cells
- TCMR→21% DSA mean 4.4 m later
  (Loupy: Tx 2015: 99: 965)
- Relative frequency unknown
  (ABMR→AB-associated-AR)
- Actual sequence of events not relevant
- Combined T-cell/Ab Rx may improve outcomes in pts simply labeled ABMR

CHRONIC ACTIVE TCMR

BANFF 2015: CHRONIC ACTIVE TCMR

- Chronic allograft arteriopathy
  - arterial intimal fibrosis, mononuclear inflammation in fibrosis, formation of neointima
  - can represent chronic active ABMR as well as TCMR
- Latest version 2015: c-TCMR may also be manifest in the tubulo-interstitial compartment.
- Corresponding dx criteria are not defined

Loupy et a. Am J Tx 2017: 17: 28

i-IFTA is the Best Candidate Lesion for Defining c-TCMR

Main objections for accepting this idea:

1. Seen in native biopsies with ci-ct
2. Hence not a specific response to alloantigens
3. Accepting it as a criterion & treating it as such may not result in therapeutic responses
4. Put the patient at risk for complications of over-immunosuppression

Most Biopsies with i-IFTA Share GE Profiles with Indicative of Immunologic Injury

Shown in 3 independent studies from respected labs

- Halloran Lab. Am J Tx 2012: 12: 191 (TCMR score)
- Salomon Lab. AJT, 2016:16:1982 (GE-AR, ≠C4d/DSA)
- Sarwal Lab. Kid Int 2011:80: 1364 (↑acquired/innate genes: T/B-cell proliferation & NK/Mac activation

Proposal: i-IFTA be accepted as a criterion for chronic T-cell &/or Ab rejection& called ALLOIMMUNE-IFTA, if other causes are reasonably excluded

Non-immune Causes of i-IFTA

- Chronic BKVN
- Chronic pyelonephritis/obstruction
- Recurrent disease, Donor disease
- CNI toxicity, Uncontrolled hypertension

i-IFTA should refer to a pattern of injury ----like MPGN or FSGS---- the d/d of which requires clinicopathologic correlation

Sub-classfication Alloimmune-IFTA

- Chronic ABMR or Chronic TCMR if relevant criteria satisfied
- Probable Chr ABMR/TCMR: pathology ≠ diagnostic; prior episodes ABMR/TCMR documented
- Retain the term i-IFTA NOS for biopsies where sufficient information not available at signout

Utility of Alloimmune IFTA

- Formally recognize subtle & indolent T-cell & Ab injury as a factor in graft loss
- Facilitate dx of late rej in setting of tissue scarring, non-compliance & infection (URIs)
- Encourage adjustment of I.S. on case by case basis, including use of steroids, as needed

SUMMARY – A Proposed Roadmap to Better Understand T-cell Mediated Injury

- Conduct well designed histologic & molecular studies to better classify bxs with BL change
- Further define the clinicopathologic characteristics of Pure TCMR and Mixed T-cell/ABMR
- Formal studies comparing the clinical outcome in i-IFTA associated with c-TCMR, c-ABMR, c-mixed rejection & chronic non-immune IFTA