Thrombotic Microangiopathy in the renal allograft: the pathologists' or the nephrologists' view?

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Disclosure

- **No conflict of interest to declare**

Introduction

TMA in the native kidney vs. TMA in the transplanted kidney

A. Native kidney TMA= a typical Hemolytic Uremic Syndrome (HUS)

1. associated with laboratory indicators of microvascular thrombosis
2. Only TMA is present in the Bx

B. Transplant TMA = Typically not clinically apparent

1. Often lacks laboratory indicators of microvascular thrombosis
2. Is associated with confounding factors,
3. Is not a systemic disease: Localized TMA (L-TMA) or renal TMA

Introduction

- Tx-TMA: an endothelial cell injury
- Thrombotic occlusion of vessels
- Clinically: unexpected allograft failure
- Triggers: Immunologic, genetic, hematologic disorders and drugs
- Renal Bx
- Pathologists' problems with diagnosing Tx-TMA
- Nephrologists' problems with diagnosing Tx-TMA

Tx-TMA diagnosis: Pathologist's dilemma

- lack of standardized criteria
- multitude of histopathologic findings (major = thrombi)
- variability in extent and number of reported cases (0.3% - 14%)
- association with confounding lesions
- dependence on the pathologist (!)

Nephrologist's dilemma

- The renal-limited character of Tx-TMA: Localized Tx-TMA

- The extreme breath of differential diagnoses
  - recurrent disease
  - CNI toxicity
  - ABMR
  - infections with CMV, influenza, polyoma etc.

Nephrologist's dilemma

- The underlying cause is often not very clear
  - The lack of a standard to differentiate between different etiologies of Tx-TMA
  - Contradictory treatments (lowering CNIs vs. treatment of rejection)

Nephrologists' questions

- Focal TMA:
  - "The post-Tx Bx finding is focal: Shall I wait and watch, or shall I act?
  - "Focal TMA: What does it mean? Is it serious? Not? What are the long-term consequences of such a finding?"

- "TMA is a challenge for me – when there is DGF/oliguria, and absence of systemic signs of MAHA: When shall I biopsy?"

Nephrologists' questions

- **Platelet count:**
  - **"In the immediate post-Tx period: : Not a good marker for diagnosis of Tx-TMA"**
  - **Specifically, when there has been thymoglobulin induction**
  - **How to tease out low platelets is indicative of Tx-TMA and not the result of ATG, MMF etc.?"**
  - **"Does the platelet level need to be very low? How much?"**

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Banff classification on allograft pathology

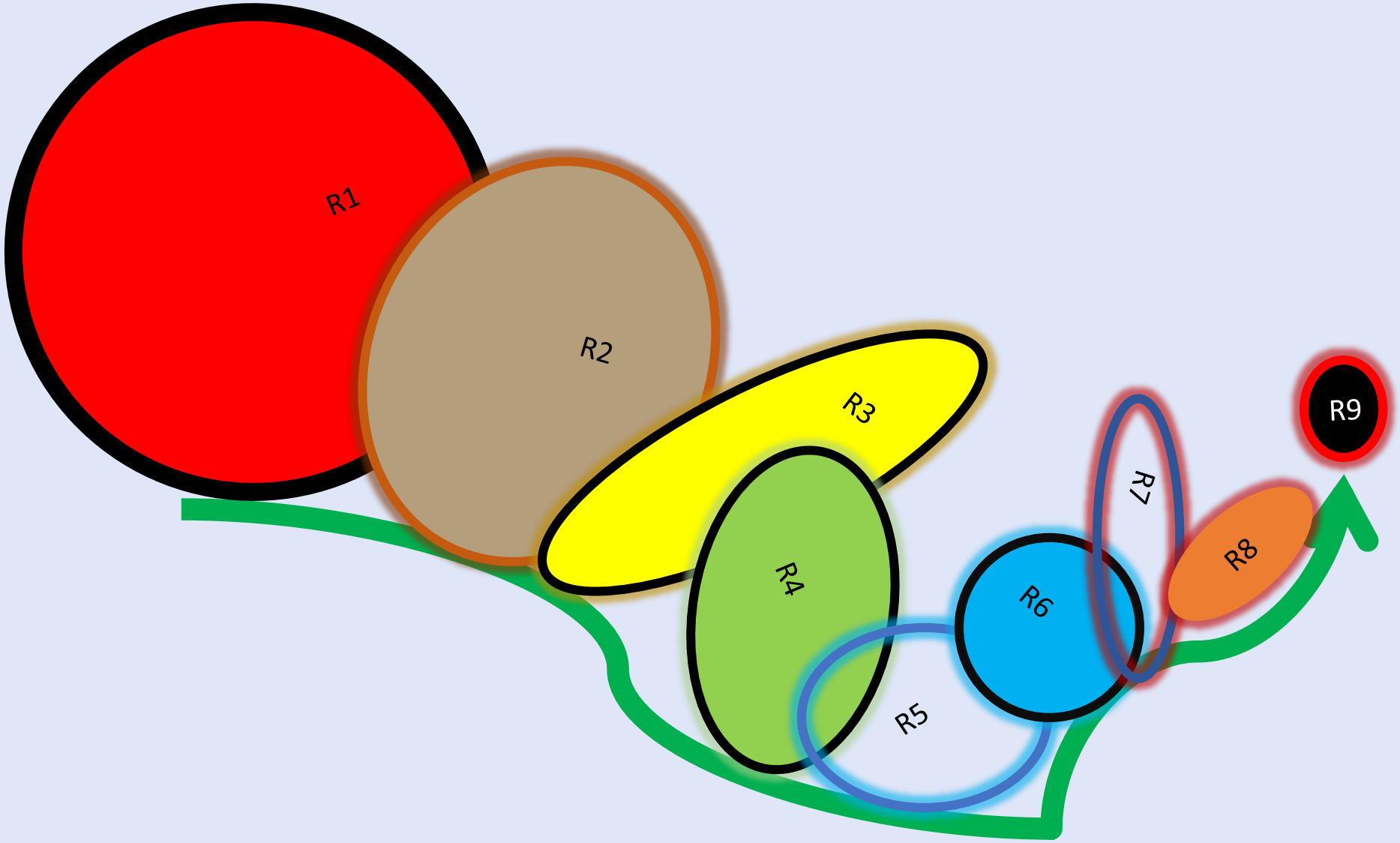
TMA Banff Working Group (BWG) mandate

- The BWG was formed in 2016 under the auspices of the Banff Foundation for Allograft Pathology

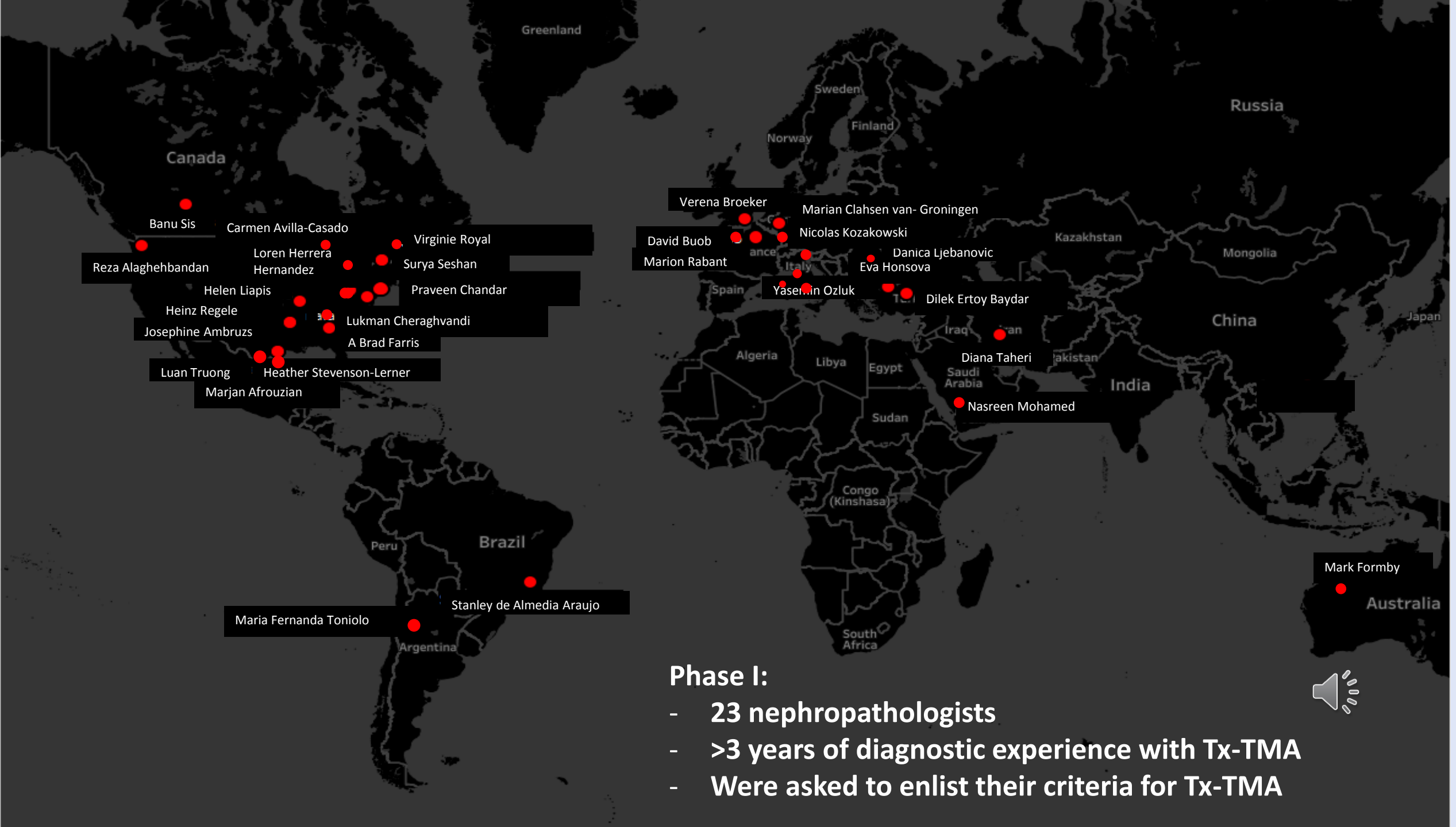
- Mandate: to standardize Tx-TMA diagnostic criteria

- Delphi methodology for consensus generation
  - Phase I: Generating consensus among pathologists
  - Phase II: Generating consensus among nephrologists
  - Phase III: Consensus of the consensus groups

Delphi Methodology



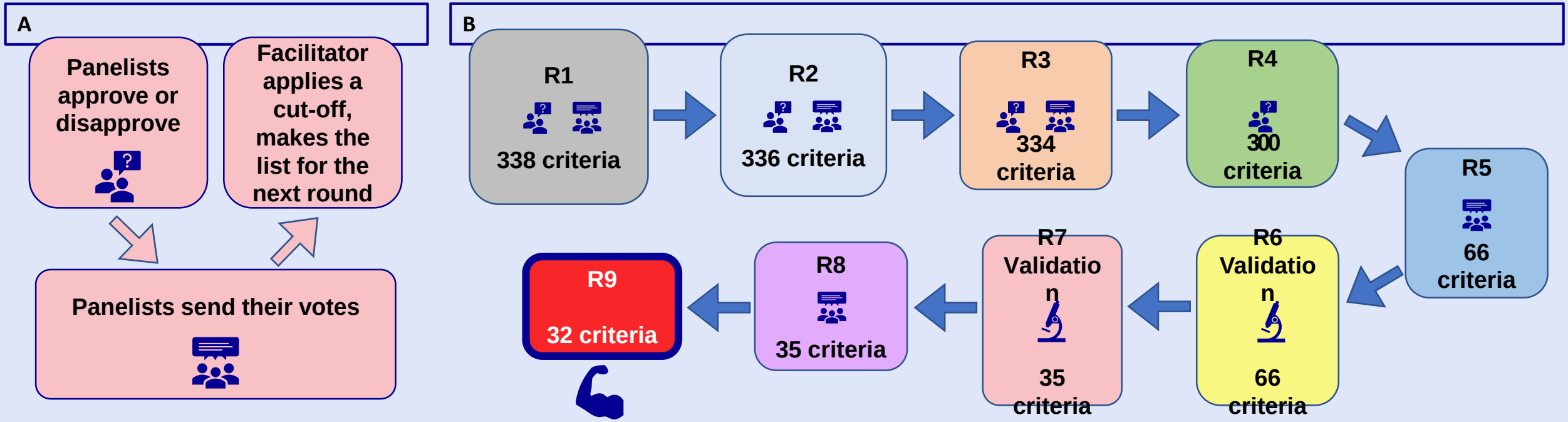
Phase I of the study: Consensus among pathologists



Phase I:

- **23 nephropathologists**
- **>3 years of diagnostic experience with Tx-TMA**
- **Were asked to enlist their criteria for Tx-TMA**

Delphi: A Democratic And Cost-effective Method Of Consensus Generation In Transplantation



A- Interactions between facilitator and 23 panelists in one consensus round (R) of Delphi.

B- The Delphi process started in R1 with 338 criteria (# of criteria at the end of each R is shown in each box); two validation Rs (R6 & R7) including evaluation of whole slide images were carried out; in the final R the criteria were narrowed down to 32.

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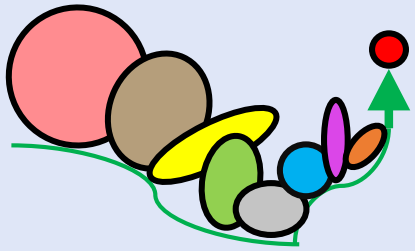
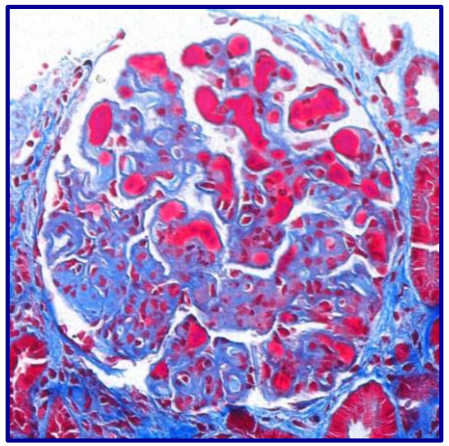
Transplant International

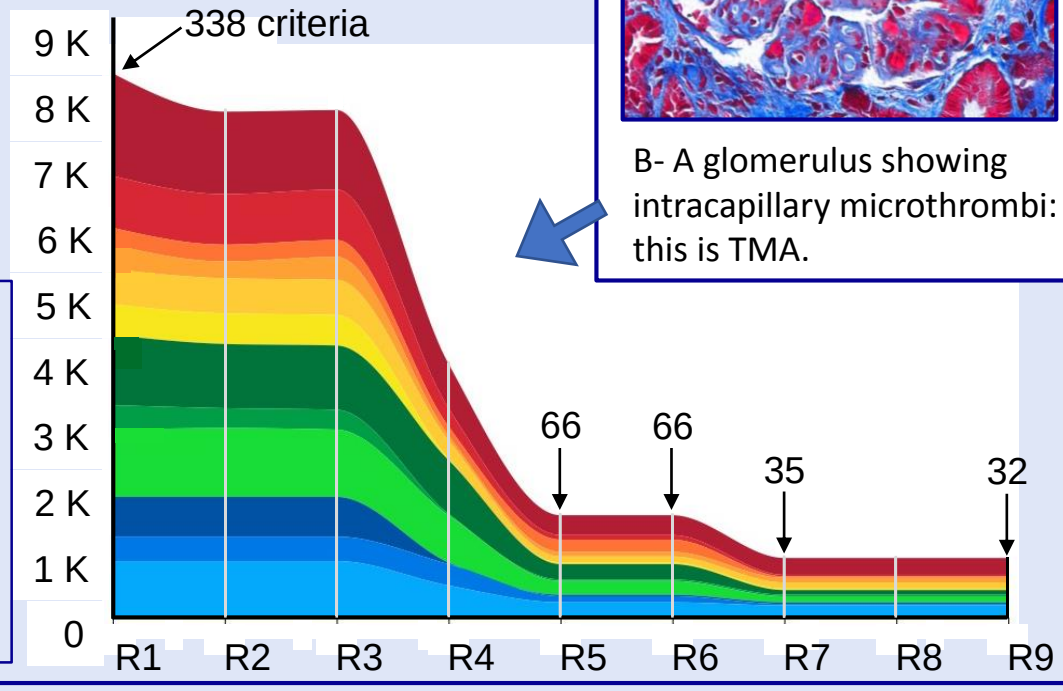
Thrombotic Microangiopathy In The Renal Allograft: Results Of The TMA Banff Working Group Consensus On Pathologic Diagnostic Criteria



A- The process of consensus generation using the Delphi methodology.



B- A glomerulus showing intracapillary microthrombi: this is TMA.



C- Criteria evolution from R1 to R9, starting with 338 criteria and narrowing them down to 32.

Pathology criteria #	Clinical criteria #	Laboratory criteria #	Differential diagnosis #
LM + 11	Clin + 2	Lab + 4	#D 8
LM – 0	Clin – 0	Lab – 0	
IF + 1		Genetics N/A	
IF – 2			
EM + 4			
EM – 0			

D- The final criteria were classified into four major classes: Pathology, Clinical, Laboratory and Differential Diagnosis. Each class was then further split into positive (+) and negative (-) categories, such as LM +, LM - , IF +, IF -, EM +, EM -, … etc.

In conclusion, for the first time in Banff Classification, we were able to create consensus using the Delphi methodology and come up with minimum diagnostic criteria for TMA in the renal allograft. A future phase will generate consensus among nephrologists.

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ESOT Leading the way in transplantation

Transplant International

The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Phase II of the study: Consensus among nephrologists

TEHRAN 2023

Phase II

- 31 nephrologists
- >3 years of diagnostic experience with Tx-TMA
- Were asked to list their criteria for Tx-TMA

Systemic TMA

Criteria ID	Category	Criteria	% response=1 cut-off 5%
S1	S-TMA Def	One or more organ involvement (kidney, liver, GI tract, heart, brain, or skin) evocative of ischemic organ dysfunction.	83.87
S2	S-TMA Path	Fibrin thrombi in microvasculature (arteriolar, glomerular, or capillary) in kidney biopsy and other organs in systemic TMA, in acute or subacute TMA.	32.26
S3	S-TMA Path	Endothelial swelling in microvasculature (arteriolar, glomerular, or capillary), in acute TMA.	32.26
S4	S-TMA Path	Chronic vascular injury, GBM double contours in the absence of immune complexes.	32.26
S5	S-TMA Lab	Elevated serum creatinine	32.26
S6	S-TMA Lab	Elevated LDH + thrombocytopenia	32.26
S7	S-TMA Lab	Hemolytic anemia	32.26
S8	S-TMA Lab	Schistocytes	32.26
S9	S-TMA Lab	Low haptoglobinemia	32.26
S10	S-TMA Lab	Thrombocytopenia	29.03
S11	S-TMA Lab	High, low or normal serum levels of calcineurin inhibitor (Tac, CSA) as effect of drugs on TMA occurrence is not dose/level-related, and susceptibility and thresholds are individualized	29.03
	S-TMA Lab	STEC	29.03
S12	S-TMA Lab	Virology/serology	25.81
S13	S-TMA Lab	ANA	25.81
S14	S-TMA Lab	Low ADAMTS13 (<5% or 10%)	22.58
S15	S-TMA Lab	Although elevated DSAs are seen in ABMR-induced TMA, but they should not be included in the criteria for diagnosis of TMA	22.58
	S-TMA Lab	Elevated DSAs can be a criterion for the diagnosis of ABMR-induced TMA	19.35
	S-TMA Lab	Low C3, C4, C3d (Sys-TMA)	19.35
	S-TMA Lab	Homocystein/MMA	16.13
	S-TMA Lab	Normal C3, C4, C3d	9.68
	S-TMA Lab	High C3, C4, C3d	6.45

Results of Round 5 of the study

Localized TMA

Criteria ID	Criteria	% of answers=1 Cut-off 20%
L1	TMA found only in kidney biopsy, lack of biological signs of systemic TMA including anemia, thrombocytopenia, LDH and haptoglobinemia or lack of symptoms of other organ systems involvement	96.77
L2	Fibrin thrombi in microvasculature (arteriolar, glomerular, or capillary) in kidney biopsy and other organs in systemic TMA, in acute or subacute TMA	96.77
L3	Endothelial swelling in microvasculature (arteriolar, glomerular, or capillary), in acute TMA	96.77
L4	Chronic vascular injury, GBM double contours in the absence of immune complexes	93.55
	Elevated serum creatinine.	87.10
	High, low or normal serum levels of calcineurin inhibitor (Tac, CSA) as effect of drugs on TMA occurrence is not dose/level-related, and susceptibility and thresholds are individualized.	87.10
	Elevated LDH might or might not be present in localized TMA.	77.42
	Although elevated DSAs are seen in ABMR-induced TMA, but they should not be included in the criteria for diagnosis of TMA.	77.42
	Thrombocytopenia might or might not be present in localized TMA.	74.19
	Elevated DSAs can be a criterion for the diagnosis of ABMR-induced TMA.	70.97
	Schistocytes might or might not be present in localized TMA.	70.97
	Low C3, C4, C3d might or might not be present in localized TMA.	67.74
	Virology/serology.	67.74
	Hemolytic anemia might or might not be present in localized TMA.	64.52
	ANA.	64.52
	Low haptoglobinemia might or might not be present in localized TMA.	64.52
	STEC.	54.84
	Elevated LDH only useful when combined with other signs such as thrombocytopenia.	48.39
	Normal C3, C4, C3d might or might not be present in localized TMA.	48.39
	Homocystein/MMA.	35.48
	Low ADAMTS13 (<5% or 10%).	29.03
	High C3, C4, C3d might or might not be present in localized TMA.	25.81

Recommendations

ID	Category	Items or Comments	% of answers=1 Cut off 70%
R1	Recommendations	In case of systemic TMA, other reasons for hemolytic anemia should be ruled out.	100.00
R2	Recommendations	Perform investigations for pre-formed or de novo DSA when ABMR is suspected.	100.00
R3	Recommendations	Genetic testing (CFH, CFI, CFB, MCP, C3, thrombomodulin, DGKE mutation analysis) should be performed prior to transplantation, is required in patients with TMA as original disease and helpful if positive. Negative results (no pathogenic mutation detected or mutation of unknown significance) do not rule out TMA of genetic origin.	100.00
R4	Recommendations	High levels of ADAMTS13 almost excludes TTP.	96.77
R5	Recommendations	In case atypical HUS is suspected, analysis of complement regulatory factors (CFH, CFI, CFB, MCP, C3, thrombomodulin, CFHR1-5, DGKE mutation analysis, FH antibodies) is compulsory.	93.55
R6	Recommendations	CNI toxicity is considered a cause of TMA if after introducing CNI, or having high drug levels, there is improvement of kidney function subsequent of drug withdrawal.	93.55

Notes

ID	Category	Items or Comments	% of answers=1 Cut-off 70%
N1	Etiology	Recurrent aHUS, genetic.	93.55
N2	Etiology	CNI toxicity causing de novo TMA.	93.55
N3	Etiology	ADAMTS13 deficiency.	87.10
N4	Etiology	TTP.	83.87
N5	Etiology and/or mimicker?	ABMR.	87.10
N6	#D	Mimicker: acute ABMR.	74.19

Systemic and Localized TMA criteria

Criteria ID	Category	Criteria	Systemic %A Cut off 5%	Localized %A cut-off 20%
S1	Definition	One or more organ involvements (kidney, liver, GI tract, heart, brain, or skin) evocative of ischemic organ dysfunction.	83.87	
L1	Definition	TMA found only in kidney biopsy, lack of biological signs of systemic TMA including anemia, thrombocytopenia, high LDH and low haptoglobinemia or lack of symptoms of other organ systems involvement		96.77
S2 / L2	Bx	Fibrin thrombi in microvasculature (arteriolar, glomerular, or capillary) in kidney biopsy and other organs in systemic TMA, in acute or subacute TMA.	32.26	96.77
S3 / L3	Bx	Endothelial swelling in microvasculature (arteriolar, glomerular, or capillary), in acute TMA.	32.26	96.77
S4 / L4	Bx	Chronic vascular injury, GBM double contours in the absence of immune complexes.	32.26	93.55

Systemic and Localized TMA criteria

Criteria ID	Category	Criteria	Systemic % A Cut off 5%	Localized % A cut-off 20%
S5 / L5	Lab	Elevated serum creatinine	32.26	87.10
S6 / L6	Lab	High, low or normal serum levels of calcineurin inhibitor (Tac, CSA) as effect of drugs on TMA occurrence is not dose/level-dependant, and susceptibility and thresholds are individualized	29.03	87.10
S7	Lab	Elevated LDH + thrombocytopenia	32.26	
L7	Lab	Elevated LDH might or might not be present in localized TMA.		77.42
S8	Lab	Thrombocytopenia	29.03	
L8	Lab	Thrombocytopenia might or might not be present in localized TMA.		74.19
S9	Lab	Hemolytic anemia	32.26	
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Systemic and Localized TMA criteria

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S11 / L11	Lab	STEC	29.03	54.84
S12 / L12	Lab	Virology/serology	25.81	67.74
S13 / L13	Lab	ANA	25.81	64.52
S14 / L14	Lab	Low ADAMTS13 (<5% or 10%)	22.58	29.03
S15 / L15	Lab	Although elevated DSAs are seen in ABMR-induced TMA, but they should not be included in the criteria for diagnosis of TMA	22.58	67.74
S16 / L16	Lab	Elevated DSAs can be a criterion for the diagnosis of ABMR-induced TMA	19.35	48.39
S17 / L17	Lab	Homocystein/MMA	16.13	35.48
S18 / L18	Lab	Low C3, C4, C3d (Sys-TMA)	19.35	67.74
S19 / L19	Lab	Normal C3, C4, C3d	9.68	48.39
S20 / L20	Lab	High C3, C4, C3d	6.45	25.81

Recommendations

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N6	#D	Mimicker: acute ABMR.	74.19

So, the pathologists’ view or the nephrologists’?

Pathologists	Nephrologists
	Elevated serum creatinine
	High, low or normal serum levels of calcineurin inhibitor (Tac, CSA) as effect of drugs on TMA occurrence is not dose/level-related, and susceptibility and thresholds are individualized
Elevated LDH	Elevated LDH + thrombocytopenia
	Elevated LDH might or might not be present in localized TMA.
thrombocytopenia	Thrombocytopenia
	Thrombocytopenia might or might not be present in localized TMA.
Hemolytic anemia	Hemolytic anemia
	Hemolytic anemia might or might not be present in localized TMA.
Low haptoglobin levels (in the absence of history of transfusion)	Low haptoglobinemia
	Low haptoglobinemia might or might not be present in localized TMA.
Dropping hematocrit	STEC
	Virology/serology
	ANA
	Low ADAMTS13 (<5% or 10%)
	Although elevated DSAs are seen in ABMR-induced TMA, but they should not be included in the criteria for diagnosis of TMA
	Elevated DSAs can be a criterion for the diagnosis of ABMR-induced TMA
	Homocystein/MMA
	Low C3, C4, C3d (Sys-TMA)
	Normal C3, C4, C3d

	Pathologists		Nephrologists
LM	bloodless dilated, congested glomerular capillaries		
LM	Fibrin thrombi in glomerular capillaries/ hilum		Fibrin thrombi in microvasculature (arteriolar, glomerular, or capillary) in kidney biopsy and other organs in systemic TMA, in acute or subacute TMA.
LM	arterial or arteriolar intimal edema/ mucoid changes		
LM	glomerular endothelial swelling (acute changes)		Endothelial swelling in microvasculature (arteriolar, glomerular, or capillary), in acute TMA.
LM	mesangiolysis (acute lesion)		
LM	double contours (chronic changes)		
LM	platelet thrombi in glomerular capillaries (CD61)		
LM	fragmented/ extravasated RBCs		
LM	onion skin changes (chronic lesion)		
LM	collapsed capillaries		
IF	glomerular intraluminal staining with fibrin-related antigens		
IF-	C4d-positivity in peritubular capillaries (favoring ABMR vs TMA)		
IF-	presence of immune complexes		

On electron microscopic criteria

	Pathologists		Nephrologists
EM	Sub-endothelial widening/ rarefaction + accumulation of "fluff"		
EM	fibrin tactoids in the lumen/ widened sub-endothelial space (glomerular or vascular)		
EM	glomerular endothelial swelling, loss of/ decreased fenestration (acute lesion)		
EM	GBM duplication/ lamination/ mutilayering with mesangial (or mesangial cell) interposition (chronic lesion		Chronic vascular injury, GBM double contours in the absence of immune complexes.

On differential diagnoses

#D	Pathologists		Nephrologists
#D	Acute or chronic NT-ABMR		Acute ABMR
#D	TTP/Acquired HUS/aHUS		
#D	Donor TMA: observed in the donor in the first week/ first month post-Tx		
#D	Chronic Tx glomerulopathy		
#D	DIC		
#D	Anti-phospholipid syndrome		
#D	Immune complex-mediated GN (de novo or recurrent, MPGN, IgAN, LN, post-infectious GN)		
#D	accelerated HTN		

On differential diagnoses

#D	Pathologists		Nephrologists
#D	Acute or chronic NT-ABMR		Acute ABMR
#D	TTP/Acquired HUS/aHUS		
#D	Donor TMA: observed in the donor in the first week/ first month post-Tx		
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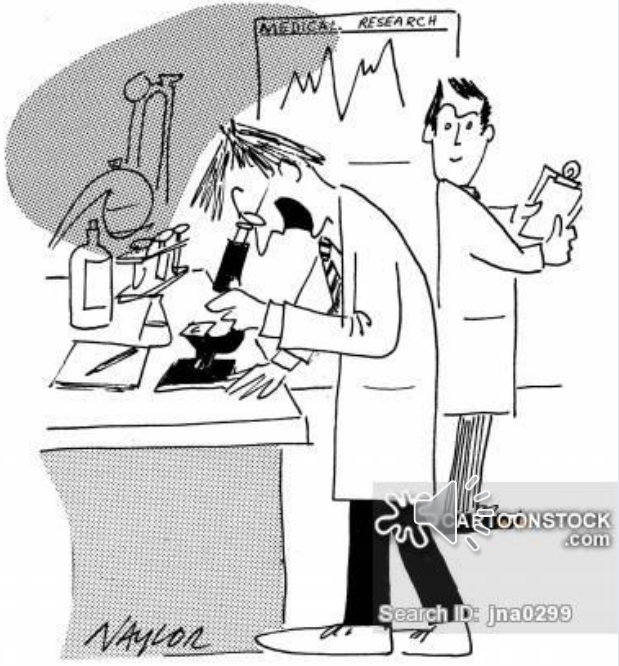
#D	accelerated HTN		



"Good, our side's winning!"

So, the pathologists’ view or the nephrologists’?

So, the pathologists' view or the nephrologists'?

The painful Truth

So, the pathologists' view or the nephrologists'?

The painful Truth

Phase III

The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Fin

TEHRAN 2023