DÍFFUSE EXTENT OF PERITUBULAR CAPILLARITIS INDEPENDENTLY RELATED TO MORE SEVERE CHRONIC ALLOGRAFT DAMAGE

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Background:

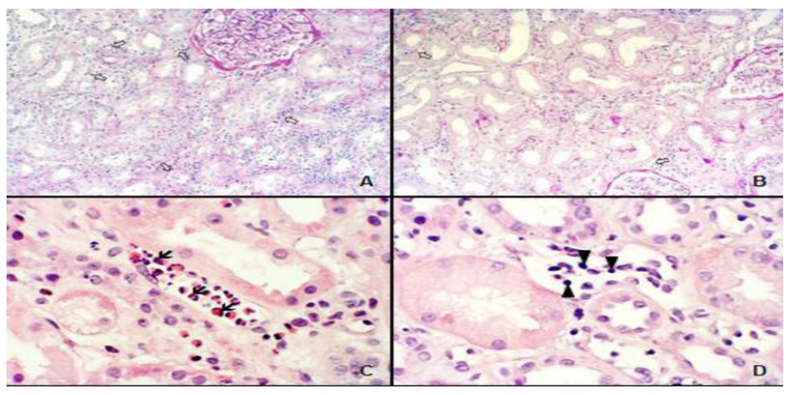
Peritubular capillaritis (ptc) as a lesion of microcirculatory damage has been recognised as an important rejection feature, due associations with circulating anti HLA antibodies, histological features of ABMR[2,3,4], and associations with chronic allograft lesions including basal membrane multilayering of PTC, subclinical chronic ABMR and chronic rejection.

Current recommendation for histological reporting[2,5]: include information on the

- •ptc score:1, 2 or 3 (depending on the severity of leukocytic infiltration),
- •ptc extent: diffuse (>50% of the cortex) or focal (10-50% of the cortex), and
- •leukocytic composition (neutrophilic granulocytes, lymphocytes and monocytes).

While the ptc score has been shown to a significant indicator of clinical outcomes,

We recently have demonstrated that diffuse extent of ptc is an independent risk factor for graft loss, features suggestive of cABMR and higher eGFR slopes [1].



Histological features of peritubular capillaritis: diffuse (A), focal (B), granulocytic (C) and mononuclear ptc (D).

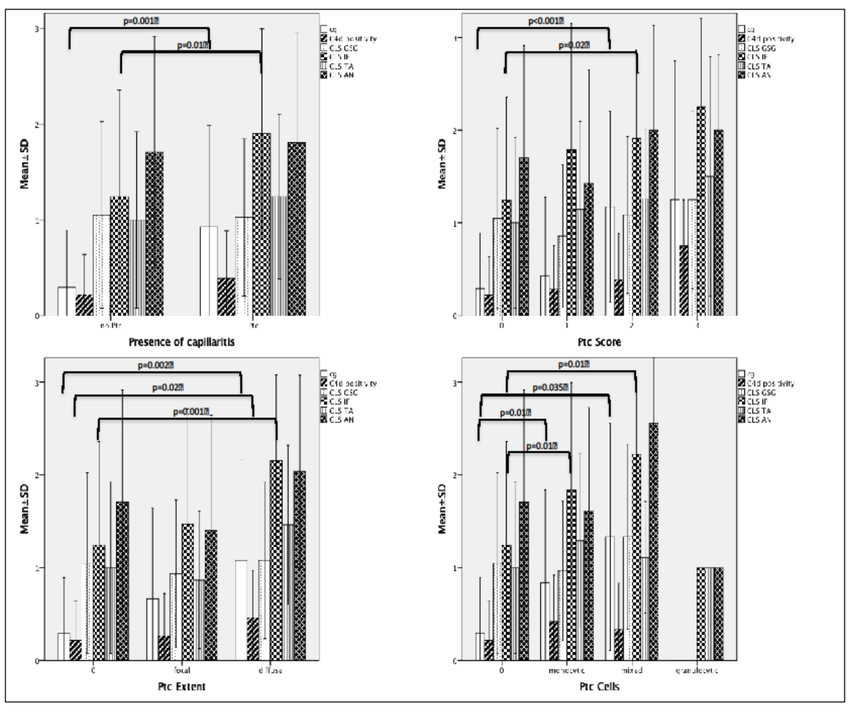
Aim of the study and design of the study

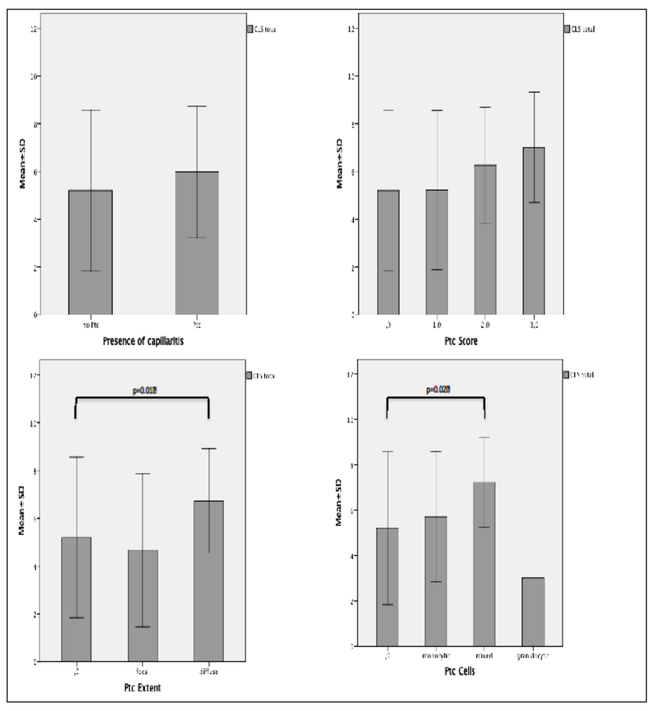
- Determine the association of ptc subcharacterisations with alloimmunity and DSA quality in late ABMR.
- Examine the influence of the ptc subclassifications and histologic lesions on transplant glomerulopathy and chronic lesions as assesed by the CLS Score by Remuzzi et al.
- **Prospective crossectional study and reevaluation of 85 kidney allograft biopsies from 741 recipients subjected to DSA screening for late ABMR (BORTEJECT Trial)**
- •Semiquantitative evaluation of ptc: **cellular composition** (lymphocytic (≥75%), mixed or granulocytic (≥75%), **extent** (diffuse or focal) and **intensity** (according to the "ptc-score")
- **Endpoints:** serological (MFI max, HLA MM quality) and clinical (TG and chronic lesions, chronic lesion score as defined by Remuzzi et al.)

Results: **Study Population**

	Cohort (85)	Capillaritis		P Value
		Ptc=0 (43)	Ptc>0 (42)	
Recipient related				
Age at biopsy (yrs), mean±s.d.	53.3±13	53.6±13.2	53.2±12.9	0,87
Female sex (%)	39 (45.9)	16 (37.2)	23 (54.8)	0.13
Previous NTX (%)	24 (28.2)	11 (25.6)	13 (31)	0.63
Biopsy time post TX, months, mean±s.d.	88.9±80.7	102±76.1	75.3±83.9	0.12
Serum Creatinine (mg/dL) at biopsy, mean±s.d.	1.7±0.7	1.57±0.62	1.84±0.75	0.07
Proteinuria (Prot/Krea, mg/g) at biopsy, mean±s.d.	572±1111	438±902	709±1287	0.27
Cyclosporine at biopsy (%)	29 (34.1)	15 (34.9)	14 (33.3)	1
Tacrolimus at biopsy (%)	51 (60)	24 (55.8)	27 (64.3)	0.51
Donor related				
Age (yrs), mean±s.d.	47.3±16.6	46.1±15.8	48.6±17.5	0.53
Living donor (%)	13 (15.3)	7 (16.3)	6 (14.3)	1
Immunological				
Previous ABMR (%)	19 (22.4)	5 (11.6)	14 (33.3)	0.02
Previous TCMR (%)	22 (25.9)	11 (25.6)	11 (26.2)	1
ABMR at biopsy (%)	47 (55.3)	11 (25.6)	36 (85.7)	<0.001
Banff Borderline at biopsy (%)	9 (10.6)	4 (9.3)	5 (11.9)	0.74
MFI max IgG, median (IQR)	2896 (1475-6441)	1946 (1272-4562)	3571 (1957-7454)	0.018
MFI sum, median (IQR)	3312 (1679-9066)	2444 (1355-7873)	3878 (2452-10647)	0.046
DSA, HLA Class I only (%)	44 (51.8)	22 (51.2)	22 (52.4)	1
DSA, HLA Class II only (%)	58 (68.2)	28 (65.1)	30 (71.4)	0.64
DSA, HLA Class I and II (%)	17 (20)	7 (16.3)	10 (23.8)	0.43
Transplant related				
HLA missmatch, median (IQR)	1.5 (1-2)	1 (1-2)	1 (1-2)	0.58
CDC XM pre Tx (%)	8 (9.4)	2 (4.7)	6 (14.3)	0.16
ABO incompatibility (%)	2 (3)	2 (6.1)	0 (0)	0.49
DSA pre TX (%) (n=42)	25 (59.5)	5 (33.3)	20 (74.1)	0.02
Sensitized (%) (n=76)	32 (42.1)	10 (25)	22 (61.1)	0.002
Cold ischaemia time (hrs), median (IQR)	11 (8-16)	11 (6.2-15.5)	12.9 (10-16.5)	0.22
Delayed graft function (%) (n=72)	7 (9.7)	3 (7.9)	4 (11.8)	0.7

Endpoints, diffuse ptc extent is related to cg and more severe chronic damage





Baseline variables in relation to ptc subcharacterisations

		Ptc Extent			
	0 (43)	focal (15)	p value	diffuse (27)	p value
Recipient related					
Age at biopsy (yrs), mean±s.d.	53.6±13.2	55.5±10.5	0.57	51.8±14.1	0.6
Female sex (%)	16 (37.2)	8 (53.3)	0.36	15 (55.6)	0.15
Previous NTX (%)	11 (25.6)	5 (33.3)	0.74	8 (29.6)	0.78
Biopsy time post TX, months, mean±s.d.	102±76.1	76.4±84.7	0.31	74.6±85	0.17
Serum Creatinine (mg/dL) at biopsy, mean±s.d.	1.57±0.62	1.65±0.72	0.7	1.95±0.76	0.034
Proteinuria (Prot/Krea, mg/g) at biopsy, mean±s.d.	438±902	736±1924	0.57	694±788	0.22
Cyclosporine at biopsy (%)	15 (34.9)	4 (26.7)	0.75	10 (37)	1
Tacrolimus at biopsy (%)	24 (55.8)	10 (66.7)	0.55	17 (63)	0.62
Donor related					
Age (yrs), mean±s.d.	46.1±15.8	45.3±20.1	0.9	50.5±15.9	0.31
Living donor (%)	7 (16.3)	2 (13.3)	1	4 (14.8)	1
Immunological					
Previous ABMR (%)	5 (11.6)	4 (26.7)	0.22	10 (37)	0.017
Previous TCMR (%)	11 (25.6)	4 (26.7)	1	7 (25.9)	1
ABMR at biopsy (%)	11 (25.6)	12 (80)	<0.001	24 (88.9)	<0.001
Banff Borderline at biopsy (%)	4 (9.3)	0 (0)	0.56	5 (18.5)	0.3
DSA number, median (IQR)	1 (1-2)	1 (1-2)	0.7	1 (1-2)	0.44
MFI sum, median (IQR)	2444 (1355-7873)	2718 (1639-4755)	0.87	5172 (3007-13783)	0.019
DSA, HLA Class I only (%)	22 (51.2)	8 (53.3)	1	14 (51.9)	1
DSA, HLA Class II only (%)	28 (65.1)	9 (60)	0.76	21 (77.8)	0.3
DSA, HLA Class I and II (%)	7 (16.3)	2 (13.3)	1	8 (29.6)	0.24
Transplant related					
HLA missmatch, median (IQR)	1 (1-4)	1 (1-2)	0.7	1 (1-2)	0.44
CDC XM pre Tx (%)	2 (4.7)	2 (13.3)	0.27	4 (14.8)	0.2
ABO incompatibility (%)	2 (6.1)	0 (0)	1	0 (0)	0.52
DSA pre TX (%) (n=42)	5 (33.3)	7 (70)	0.11	13 (76.5)	0.03
Sensitized (%) (n=76)	10 (25)	7 (50)	0.1	15 (68.2)	0.001
Cold ischaemia time (hrs), median (IQR)	11 (6.2-15.5)	12 (10-15.5)	0.4	13.5 (8.5-19.2)	0.46
Delayed graft function (%) (n=72)	3 (7.9)	0 (0)	0.55	4 (20)	0.22

		Ptc Score					
	0 (43)	1 (15)	p value	2 (23)	p value	3 (4)	p value
Recipient related							
Age at biopsy (yrs), mean±s.d.	53.6±13.2	54.2±11.7	0.88	53.3±14	0.92	48.6±13.1	0.51
Female sex (%)	16 (37.2)	7 (46.7)	0.55	12 (52.2)	0.3	4 (100)	0.027
Previous NTX (%)	11 (25.6)	5 (33.3)	0.74	7 (30.4)	0.77	1 (25)	1
Biopsy time post TX, months, mean±s.d.	102±76.1	71.5±87.8	0.24	74.5±78.9	0.17	93.7±117.9	0.9
Serum Creatinine (mg/dL) at biopsy, mean±s.d.	1.57±0.62	1.74±0.75	0.44	1.88±0.8	0.11	1.98±0.46	0.18
Proteinuria (Prot/Krea, mg/g) at biopsy, mean±s.d.	438±902	713±1935	0.6	665±773	0.29	952±832	0.31
Cyclosporine at biopsy (%)	15 (34.9)	6 (40)	0.76	6 (26.1)	0.58	2 (50)	0.61
Tacrolimus at biopsy (%)	24 (55.8)	8 (53.3)	1	17 (73.9)	0.19	2 (50)	1
Donor related							
Age (yrs), mean±s.d.	46.1±15.8	52.2±20.1	0.34	44.6±16.1	0.74	58.3±7.2	0.07
Living donor (%)	7 (16.3)	3 (20)	0.71	3 (13)	1	0 (0)	1
Immunological							
Previous ABMR (%)	5 (11.6)	4 (26.7)	0.22	8 (34.8)	0.048	2 (50)	0.1
Previous TCMR (%)	11 (25.6)	4 (26.7)	1	5 (21.7)	1	2 (50)	0.3
ABMR at biopsy (%)	11 (25.6)	12 (80)	<0.001	21 (91.3)	<0.001	3 (75)	0.073
Banff Borderline at biopsy (%)	4 (9.3)	2 (13.3)	0.64	3 (13)	0.69	0 (0)	1
DSA number, median (IQR)	1 (1-2)	1 (1-1)	0.41	1 (1-2)	0.43	3 (1.25-4)	0.087
MFI sum, median (IQR)	2444 (1355-7873)	2718 (1757-3986)	0.84	5760 (2501-13783)	0.037	5027 (3506-12717)	0.044
DSA, HLA Class I only (%)	22 (51.2)	9 (60)	0.76	10 (43.5)	0.61	3 (75)	0.61
DSA, HLA Class II only (%)	28 (65.1)	8 (53.3)	0.54	19 (82.6)	0.16	3 (75)	1
DSA, HLA Class I and II (%)	7 (16.3)	2 (13.3)	1	6 (26.1)	0.35	2 (50)	0.16
Transplant related							
HLA missmatch, median (IQR)	1 (1-4)	1 (1-1)	0.41	1 (1-2)	0.94	3 (1.25-4)	0.09
CDC XM pre Tx (%)	2 (4.7)	2 (13.3)	0.27	3 (13)	0.43	1 (25)	0.24
ABO incompatibility (%)	2 (6.1)	0 (0)	1	0 (0)	0.53	0 (0)	1
DSA pre TX (%) (n=42)	5 (33.3)	7 (70)	11	11 (78.6)	0.025	2 (66.7)	0.53
Sensitized (%) (n=76)	10 (25)	8 (57.1)	0.047	12 (63.2)	0.009	2 (66.7)	0.18
Cold ischaemia time (hrs), median (IQR)	11 (6.2-15.5)	12.3±5.4	0.42	12.5±6.6	0.63	18±6.9	0.44
Delayed graft function (%) (n=72)	3 (7.9)	0 (0)	0.56	4 (22.2)	0.19	0 (0)	1

		Ptc Cells				
	0 (43)	monocytic (32)	p value	mixed (9)	p value	neutrophilic (1)	p value
Recipient related							
Age at biopsy (yrs), mean±s.d.	53.6±13.2	51.9±13.5	0.57	56.2±10.5	0.53	66.8±0	0.33
Female sex (%)	16 (37.2)	17 (53.1)	0.24	5 (55.6)	0.46	1 (100)	0.39
Previous NTX (%)	11 (25.6)	10 (31.3)	0.61	2 (22.2)	1	1 (100)	0.27
Biopsy time post TX, months, mean±s.d.	102±76.1	68.4±76.3	0.06	106.1±108.7	0.92	17.9±0	0.28
Serum Creatinine (mg/dL) at biopsy, mean±s.d.	1.57±0.62	1.81±0.75	0.13	2.04±0.71	0.09	0.84±0	0.25
Proteinuria (Prot/Krea, mg/g) at biopsy, mean±s.d.	438±902	738±1430	0.3	687±706	0.38	0	0.63
Cyclosporine at biopsy (%)	15 (34.9)	10 (31.3)	0.81	4 (44.4)	0.71	0	1
Tacrolimus at biopsy (%)	24 (55.8)	21 (65.6)	0.48	5 (55.6)	1	1 (100)	1
Donor related							
Age (yrs), mean±s.d.	46.1±15.8	48.3±17.5	0.6	45.6±16.4	0.94	76±0	0.07
Living donor (%)	7 (16.3)	6 (18.8)	1	0 (0)	0.33	0 (0)	1
Immunological							
Previous ABMR (%)	5 (11.6)	10 (31.3)	0.045	3 (33.3)	0.13	1 (100)	0.14
Previous TCMR (%)	11 (25.6)	8 (25)	1	3 (33.3)	0.69	0 (0)	1
ABMR at biopsy (%)	11 (25.6)	27 (84.4)	<0.001	8 (88.9)	0.001	1 (100)	0.27
Banff Borderline at biopsy (%)	4 (9.3)	3 (9.4)	1	2 (22.2)	0.27	0 (0)	1
DSA number, median (IQR)	1 (1-2)	1 (1-2)	0.43	1 (1-2)	0.68	1 (1-1)	0.74
MFI sum, median (IQR)	2444 (1355-7873)	3747 (2223-9045)	0.097	3771 (2482-13854)	0.14	5172 (5172-5172)	0.24
DSA, HLA Class I only (%)	22 (51.2)	19 (59.4)	0.49	3 (33.3)	0.47	0 (0)	1
DSA, HLA Class II only (%)	28 (65.1)	21 (65.6)	1	8 (88.9)	0.24	1 (100)	1
DSA, HLA Class I and II (%)	7 (16.3)	8 (25)	0.39	2 (22.2)	0.64	0 (0)	1
Transplant related							
HLA missmatch, median (IQR)	1 (1-4)	1 (1-2)	0.43	1 (1-2)	0.68	1 (1-1)	0.74
CDC XM pre Tx (%)	2 (4.7)	5 (15.6)	0.13	1 (11.1)	0.44	0 (0)	1
ABO incompatibility (%)	2 (6.1)	0 (0)	0.5	0 (0)	1	0 (0)	1
DSA pre TX (%) (n=42)	5 (33.3)	15 (71.4)	0.041	4 (80)	0.13	1 (100)	0.37
Sensitized (%) (n=76)	10 (25)	17 (60.7)	0.005	4 (57.1)	0.17	1 (100)	0.27
Cold ischaemia time (hrs), median (IQR)	11 (6.2-15.5)	11.6±5.7	0.63	18.6 (12.5-24)	0.09	17 (17-17)	0.12
Delayed graft function (%) (n=72)	3 (7.9)	2 (8)	1	2 (25)	0.2	0 (0)	1

Conclusion

- Diffuse extent of ptc is significantly associated to recipient pre-sensitization, higher DSA MFI max and previous ABMR. Therefore diffuse ptc extent is a significant surrogate of ongoing ABMR.
- •Diffuse extent of ptc is independently related to more frequent transplant glomerulopathy in late ABMR.
- Diffuse ptc is an independent risk factor for more severe chronic allograft damage even after adjustment for MFI max, C4d, and timing of the biopsy
- Our results argue strong for the routine diagnostic and prognostic use of diffuse ptc extent as a rejection criterion

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