DÍFFUSE EXTENT OF PERITUBULAR CAPILLARITIS – AN INDEPENDENT RISK FACTOR FOR GRAFT LOSS[1]

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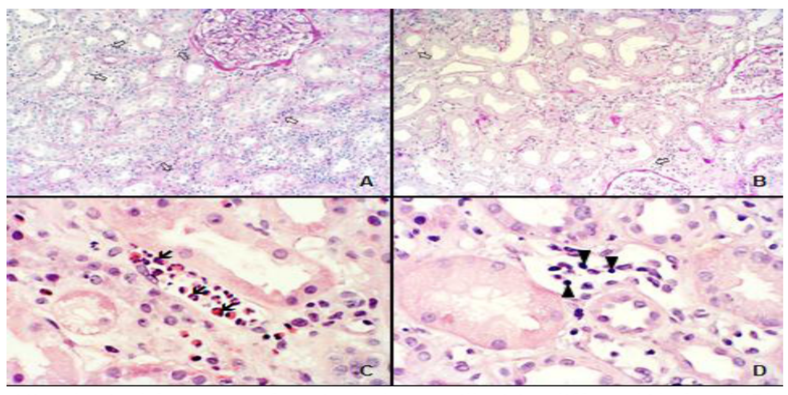
Background:
Peritubular capillaritis (ptc) as a lesion of microcirculatory damage has been recognised as an important rejection feature, due associations with circulating anti HLA antibodies, histological features of ABMR[2,3,4], and associations with chronic allograft lesions including basal membrane 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, the clinical relevance of scoring ptc extent or leukocytic subpopulations in ptc has been poorly examined .



Histological features of peritubular capillaritis: diffuse (A), focal (B), granulocytic (C) and mononuclear ptc (D).
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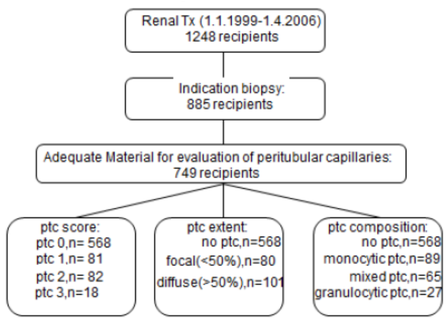
Aim of the study and design of the study
- Determine the exact subclassification and prevalence of ptc in a large cohort of allograft kidney biopsies
- Examine the influence of the ptc subclassifications and histologic lesions
- **Retrospective study and reevaluation of 1322 kidney allograft biopsies for cause (99-06) from 749 patients**
- Semiquantitative evaluation of ptc: **cellular composition** (lymphocytic (≥75%), mixed or granulocytic (≥75%), **extent** (diffuse or focal) and **intensity** (according to the "ptc-score")
- **Endpoints:** death-censored graft loss (mean follow-up after first indication biopsy: 60.39 ±36.30 months) and eGFR slope (ΔeGFR) after 3 years according to the Mayo-Equation (n=476 recipients).
- Confounders: (baseline immunosuppression, C4d positive graft dysfunction, TCMR= Banff≥Ia, re-transplantation, HLA mismatch (MM) and pre-sensitization (CDC PRA >10%)

Results: **Study Population**

	Study population (749)	ptc=0 (568)	ptc>0 (181)	p value
Donor related				
Donor age, years, mean+/-SD	49.1+/-14.9	49.5+/-14.9	47.8+/-15	0.21
Living donor (%)	95 (12.7)	69 (12.1)	26(14.4)	0.44
HLA MM, mean+/-SD	2.9+/-1.4	2.9+/-1.5	3.1+/-1.3	0.07
CIT, hours, mean+/-SD	13.6+/-7.4	13.4+/-7.2	14+/-7.9	0.39
Recipient related				
Female (%)	254 (33.9)	187 (32.9)	67 (37)	0.31
Biopsy time post TX, months, mean+/-SD	2.4+/-8	2.2+/-7.2	3.33+/-10.1	0.09
Number of biopsy, mean+/-SD	1.8+/-1.1	1.7+/-1	1.8+/-1.1	0.28
Age at biopsy, years, mean+/-SD	50.6+/-13.7	51.7+/-13.5	47.1+/-14	<0.001
TCMR=Banff≥1 (%)	224 (29.9)	137 (24.1)	87 (48.1)	<0.001
C4d positive graft dysfunction (%)	77 (10.3)	41(7.2)	36 (19.9)	<0.001
Pre sensitization (CDC-PRA>10%) (%)	156 (20.8)	109 (19.2)	47 (26)	0.055
Re-transplantation	130 (17.4)	85 (15)	45 (24.9)	0.002
Graft loss (%)	167 (22.3)	115 (20.2)	52 (28.7)	0.017
Serum creatinine, mg/dl,at 3 years, mean+/-SD	2.2+/-1.3	2.1+/-1.2	2.4+/-1.5	0.04
Estimated GFR- Mayo at 3 years, ml/min/m2, mean+/-SD	49.1+/-27.4	50+/-26.9	46.8+/-28.7	0.26
Baseline Immunosuppression				
Cyclosporine A (%)	556 (74.2)	405 (71.3)	151 (83.4)	0.001
Tacrolimus (%)	112 (15)	96 (16.9)	16 (8.8)	0.008
mToR inhibitor (%)	20 (2.7)	15 (2.6)	5 (2.8)	0.93
Depleting antibodies (%)	52 (6.9)	45 (7.9)	7 (3.9)	0.06
IL-2 inhibitor (%)	9 (1.2)	7 (1.2)	2 (1.1)	0.88

Study flow chart



Cox regression analysis, Censored graft loss

	ptc score			ptc extent			ptc leukocytic composition	
	HR	p value		HR	p value		HR	p value
0	Reference	-	0	Reference	-	0	Reference	-
1	0.91 (0.54-1.54)	0.73	focal	0.65 (0.36-1.17)	0.15	monocytic	1.06 (0.66-1.71)	0.8
2	1.14 (0.70-1.87)	0.58	diffuse	1.67 (1.1-2.54)	0.015	mixed	1.31 (0.63-2.71)	0.47
3	2.57 (1.25-5.28)	0.01				granulocytic	1.22 (0.72-2.06)	0.47
TCMR (Banff≥1)	1.02 (0.71-1.46)	0.9		1.01 (0.71-1.43)	0.97		1.12 (0.79-1.57)	0.53
C4d+ dysfunction	1.42 (0.87-2.27)	0.14		1.35 (0.85-2.15)	0.2		1.37 (0.86-2.19)	0.18
Re-transplantation	1.58 (1.02-2.45)	0.04		1.52 (0.99-2.33)	0.06		1.51 (0.98-2.33)	0.93
HLA MM	1.19 (1.06-1.35)	0.004		1.20 (1.07-1.36)	0.002		1.20 (1.06-1.35)	0.004
Sensitization	1.06 (0.70-1.62)	0.76		1.10 (0.73-1.66)	0.64		1.09 (0.72-1.66)	0.68
Cyclosporine A	Reference	-		Reference	-		Reference	-
Tacrolimus	0.95 (0.56-1.59)	0.84		0.87 (0.52-1.46)	0.6		0.93 (0.56-1.57)	0.79
mTor inhibitor	1.88 (0.86-4.10)	0.11		1.81 (0.83-3.93)	0.13		1.84 (0.84-4.00)	0.13
Depleting Ab	1.05 (0.52-2.11)	0.88		0.99 (0.49-1.99)	0.98		1.03 (0.51-2.07)	0.93
IL-2 inhibitor	0.44 (0.06-3.16)	0.41		0.45 (0.06-3.27)	0.43		0.43 (0.06-3.09)	0.4

ptc score, ptc extent, ptc leukocytic composition and Banff single lesions

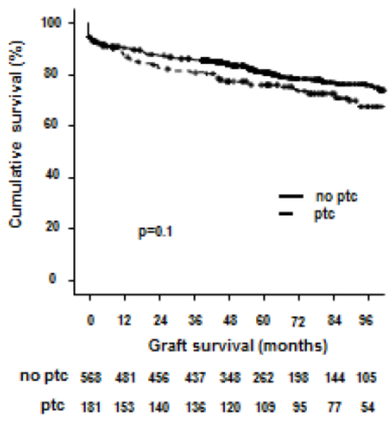
	ptc		p value	ptc score			p value	ptc extent		p value	ptc leukocytic composition			p value
	0	>0		1	2	3		focal	diffuse		mono-nuclear	granulo-cytic	mixed	
Number of cases + (%)	993 (75.11)	329 (24.88)		141 (10.66)	154 (11.65)	34 (2.57)		139 (10.5)	190 (14.4)		173 (13.1)	43 (3.3)	113 (8.5)	
g>0 (%)	6.54	18.84	<0.001	19.51	16.49	27.99	<0.001	13.92	22.39	0.047	23.37	13.95	12.39	0.093
cg>0 (%)	2.32	6.00	0.004	2.42	8.39	11.50	<0.001	3.48	7.71	0.11	7.49	6.98	0	0.22
i>0 (%)	44.81	85.71	<0.001	78.29	91.53	89.71	<0.001	89.41	80.18	0.02	83.58	86.04	92.03	0.37
ci>0 (%)	26.28	37.39	<0.001	32.83	41.00	40.01	0.002*	31.01	41.53	0.046	39.48	39.53	23.01	0.14
t>0 (%)	30.00	72.34	<0.001	63.76	78.89	79.27	<0.001	65.58	77.08	0.02	70.57	76.7	69.02	0.52
ct>0 (%)	21.45	33.13	<0.001	28.89	37.82	30.41	<0.001	25.87	38.20	0.019	36.23	34.88	15.93	0.049
v>0 (%)	10.00	24.62	<0.001	22.76	23.37	39.33	<0.001	19.21	28.52	0.045	26.02	25.58	15.04	0.35
cv>0 (%)	17.82	24.62	0.01	22.76	25.56	27.99	0.09	20.20	27.53	0.1	27.91	20.93	20.35	0.39
ah>0 (%)	12.00	16.72	0.024	13.31	16.41	34.49	0.003	13.99	18.83	0.18	19.59	16.28	5.31	0.1
C4d+	9.00	25.40	<0.001	23.52	26.17	30.03	<0.001	21.58	28.20	0.18	25.43	25.58	27.43	0.95

Allograft function, eGFR slope after 3 years

ΔeGfR, mL/min/ 1.73m2/year 1-3yr	ptc		ptc extent			
	>0	p value	focal	p value	diffuse	p value
Coef. + SE	-1.91 +/- 0.84	0.023	-1.49 +/- 1.2	0.21	-2.21 +/- 1.03	0.033
	ptc score					
	1	p value	2	p value	3	p value
Coef. + SE	-0.81 +/- 1.17	0.49	-3.22 +/- 1.15	0.005	-0.96 +/- 2.15	0.66
	ptc leukocytic composition					
	mononuclear	p value	granulocytic	p value	mixed	p value
Coef. + SE	-0.91 +/- 1.1	0.41	-3.06 +/- 1.3	0.02	-2.67 +/- 1.84	0.15

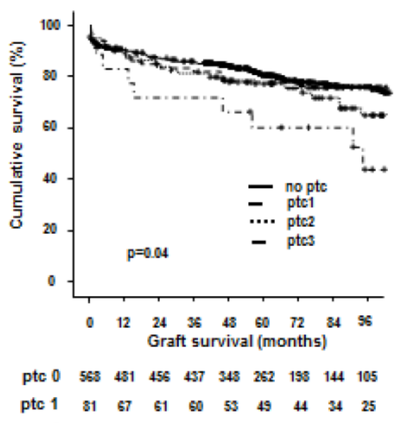
Death censored graft loss, Kaplan Meier Analysis

ptc



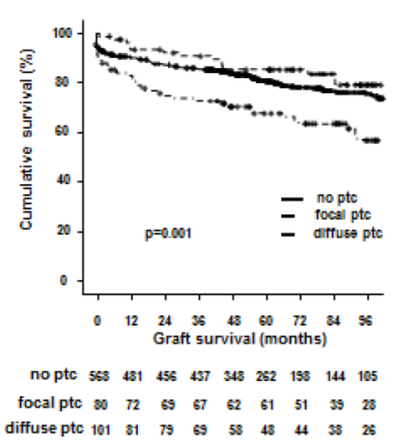
	0	12	24	36	48	60	72	84	96
no ptc	568	481	456	437	348	262	198	144	105
ptc	181	153	140	136	120	109	95	77	54

ptc score



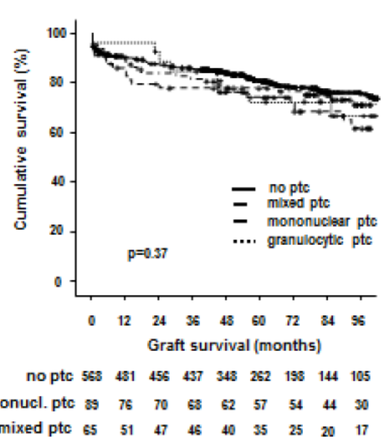
	0	12	24	36	48	60	72	84	96
ptc 0	568	481	456	437	348	262	198	144	105
ptc 1	81	67	61	60	53	49	44	34	25
ptc 2	82	71	66	63	55	50	42	35	25
ptc 3	18	15	13	13	12	10	9	8	4

ptc extent



	0	12	24	36	48	60	72	84	96
no ptc	568	481	456	437	348	262	198	144	105
focal ptc	80	72	69	67	62	61	51	39	28
diffuse ptc	101	81	79	69	58	48	44	38	26

ptc leukocytic composition



	0	12	24	36	48	60	72	84	96
no ptc	568	481	456	437	348	262	198	144	105
mononucl. ptc	89	76	70	68	62	57	54	44	30
mixed ptc	65	51	47	46	40	35	25	20	17
granulocyt. ptc	27	26	23	22	18	17	16	13	7

For univariable analyses we used the Fisher's exact test or Chi squared test.
The association of ptc with graft loss were estimated using regression models +/- potential confounders for uni- and multivariate analyses.

Conclusion

- Peritubular capillaritis is observed in both cellular and humoral rejection.
- •Diffuse ptc and ptc 3 are independent risk factors for allograft loss in indication biopsies.
- Diffuse ptc is an independent risk factor for graft loss even after adjustment for ptc score, glomerulitis and multiple rejection episodes while ptc 3 loses this independent association
- •Diffuse ptc is associated with a steeper eGFR decline
- In contrast reporting the leukocytic composition of ptc is not associated with graft loss risk.

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