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Soluble CD30 correlates with clinical but not subclinical renal allograft rejection

Patricia Hirt-Minkowski,[1] Michèle Roth,[1] Gideon Hönger,[1] Patrizia Amico,[1] Helmut Hopfer[2] and Stefan Schaub[1]

1 Clinic for Transplantation Immunology and Nephrology, University Hospital Basel, Basel, Switzerland
2 Institute for Pathology, University Hospital Basel, Basel, Switzerland

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Correspondence
Stefan Schaub MD, MSc, Clinic for Transplantation, Immunology and Nephrology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland.
Tel.: +41 61 265 45 33;
fax: +41 61 265 24 10;
e-mail: schaubs@uhbs.ch

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Summary

Soluble CD30 (sCD30) has been proposed as a promising noninvasive biomarker for clinical renal allograft rejection, but its diagnostic characteristics regarding detection of subclinical rejection have not been assessed. We investigated sCD30 in 146 consecutive kidney allograft recipients under tacrolimus–mycophenolate-based immunosuppression having 250 surveillance biopsies at 3 and 6 months as well as 52 indication biopsies within the first year post-transplant. Allograft histology results were classified as (i) acute Banff score zero or interstitial infiltrates only, (ii) tubulitis t1, (iii) tubulitis t2-3 and (iv) isolated vascular compartment inflammation. sCD30 correlated well with the extent of clinical ($P < 0.0001$), but not subclinical tubulointerstitial rejection ($P = 0.06$). To determine diagnostic characteristics of sCD30, histological groups were assigned to two categories: no relevant inflammation (i.e. acute Banff score zero and interstitial infiltrates only) versus all other pathologies (tubulitis t1-3 and isolated vascular compartment inflammation). For clinical allograft inflammation, AUC was 0.87 (sensitivity 89%, specificity 79%; $P = 0.0006$); however, for subclinical inflammation, AUC was only 0.59 (sensitivity 50%, specificity 69%; $P = 0.47$). In conclusion, sCD30 correlated with clinical, but not subclinical renal allograft rejection limiting its clinical utility as a noninvasive rejection screening biomarker in patients with stable allograft function receiving tacrolimus–mycophenolate-based immunosuppression.

Introduction

Despite continuous improvement of immunosuppression, allograft rejection is still the leading cause for renal allograft loss [1]. Thus, the development of reliable biomarkers detecting allograft rejection in kidney transplant patients is an important goal [2]. An ideal rejection biomarker should not only correlate with clinical rejection (i.e. biopsy-proven rejection with allograft dysfunction), but also with subclinical rejection (i.e. biopsy-proven rejection with stable allograft function). Such a rejection biomarker would allow for a noninvasive screening strategy and guidance of surveillance biopsies to detect subclinical rejection and prevent progression to interstitial fibrosis and tubular atrophy [3–7].

Soluble CD30 (sCD30) is released into the bloodstream by activated $CD30^+$ T cells [8,9] and has been proposed as a rejection biomarker. Indeed, an elevated pretransplant concentration of sCD30 has been reported as a predictive factor for acute renal allograft rejection and poor graft outcome in single centre as well as in two large multi-centre studies [10–17]. Furthermore, nondecreasing levels of sCD30 in the early post-transplant period were associated with the occurrence of acute rejection within the first 6–12 months post-transplant and poor graft outcome [17–28]. However, an association of pre and/or post-transplant levels of sCD30 with acute rejection as well as graft function and survival could not be demonstrated in some studies [29–32]. An important limitation of most of the studies is that sCD30 was not measured at

the time of allograft biopsies and therefore a correlation with the histopathological findings was not possible [17–28,32]. In addition, sCD30 has not been evaluated regarding its diagnostic potential to detect subclinical rejection.

The aim of this study was to correlate sCD30 with clinical and especially subclinical allograft rejection in a normal risk population of 146 consecutive kidney allograft recipients treated with current tacrolimus–mycophenolate-based immunosuppression.

Materials and methods

Patient population

From October 2005 to March 2009, 228 consecutive patients received a kidney allograft at our centre. Eighty-two patients were excluded from the analysis for the following reasons: (i) induction therapy with a polyclonal anti T-lymphocyte globulin (i.e. ATG; $n = 46$) because of the presence of donor-specific HLA-antibodies [33], (ii) blood-group incompatibility ($n = 11$), (iii) no tacrolimus-based immunosuppression ($n = 10$) and (iv) no available sera at the time of indication or surveillance biopsies ($n = 15$). Thus, the final population consists of 146 consecutive patients (90% first transplants) treated with a uniform immunosuppressive regimen consisting of an induction therapy with basiliximab (Simulect; Novartis, Basel, Switzerland) and triple therapy either with tacrolimus (Tac; Prograf, Astellas, Wallisellen, Switzerland), mycophenolate-mofetil (MMF; CellCept, Roche, Basel, Switzerland) and prednisone, or a steroid-free regimen consisting of Tac, mycophenolate-sodium (MPS; Myfortic, Novartis) and sirolimus or everolimus (Rapamune, Wyeth or Certican, Novartis).

From these 146 allograft recipients, 250 surveillance biopsies were available at 3 and 6 months post-transplant with corresponding serum samples: 124/146 patients (85%) had a surveillance biopsy at 3 months, 126/146 patients (86%) at 6 months post-transplant and 110/146 patients (75%) had both. In addition, 46/146 patients (32%) had 52 indication biopsies within the first year post-transplant with corresponding serum samples. Thus, the whole study sample collection consists of 302 allograft biopsies with corresponding serum samples from 146 patients. The study was approved by the Ethics committee of the University of Basel and all participating patients gave written informed consent.

Evaluation of allograft biopsies

Clinically indicated allograft biopsies were performed when serum creatinine increased by >20% from baseline. Surveillance biopsies were scheduled at 3 and 6 months post-transplant. All obtained allograft biopsies (two cores obtained with a 16-gauge needle) had been evaluated using light microscopy, immunofluorescence (C4d, HLA-DR) and immunohistochemistry (SV40 large T-antigen). Acute and chronic Banff scores were assessed and biopsies were assigned to four groups according to the acute scores [34]:

Group 1: Acute Banff score zero (i.e. t0 i0 g0 v0 ptc0) or interstitial infiltrates only (i.e. t0 i1-3 g0 v0 ptc0)

Group 2: Tubulitis t1 plus any other inflammation (i.e. t1 i0-3 g0-3 v0-3 ptc0-3)

Group 3: Tubulitis t2-3 plus any other inflammation (i.e. t2-3 i0-3 g0-3 v0-3 ptc0-3)

Group 4: Isolated vascular compartment inflammation (i.e. t0 i0-3 g0-3 v0-3 ptc0-3).

Urine protein analyses

Measurement of total protein (benzethonium chloride method) and creatinine (enzymatic method) were performed on a Modula clinical chemistry analyser (Roche Diagnostics, Roche, Switzerland). Urinary α1-microglobulin (α1m) was determined using nephelometry (Beckman-Coulter nephelometry system, Brea, CA, USA).

Soluble CD30 assay

Serum samples were tested retrospectively for sCD30 using a commercially available ELISA kit (Bender MedSystems, Vienna, Austria). Previously, the concentration values were given in U/ml, whereas in the most recent version of the same ELISA, the values are indicated in ng/ml, whereby 1 ng/ml is considered to be equal to 1 U/ml. Each serum sample was tested in duplicate. Briefly, in 96-well microtitre plates coated with sCD30 antibody, 25 μl of the patient's serum and 75 μl of sample diluent were added. To this mixture, 50 μl of horseradish peroxidase (HRP)-conjugated detection antibody solution was added, and then the plates were subsequently incubated for 3 h in dark at room temperature on a shaker set at 100 rpm. Following incubation, unbound conjugated antibody was removed by three wash steps and 100 μl of tetramethyl benzidine solution, reactive to HRP, was added to each well. The reaction was terminated after 10 min by addition of 100 μl of 1 M phosphoric acid and optical absorption was measured at 450 nm at the spectrophotometer. In each 96-well plate, we included duplicates of a negative control (100 μl of sample diluent, but no serum), seven external human sCD30 standard dilutions, two external (kid components) and one internal control (healthy donor). sCD30 duplicates demonstrated good correlation ($r^2 = 0.9$). In our study, the detection limit was 0.65 ng/ml, and the intra-assay and interassay coefficients of variation were 6.2% and 10.8%, respectively.

Statistical analysis

We used JMP software version 9.0 (SAS Institute Inc., Cary, NC, USA) for statistical analysis. For categorical data, Fisher's exact test or Pearson's chi-squared test was used. Parametric continuous data were analysed using Student's *t*-tests. For nonparametric continuous data, the Wilcoxon rank-sum or Kruskal–Wallis rank-sum tests were used for analysis. Significant results in the Kruskal–Wallis rank-sum test were further analysed using pair-wise nonparametric tests. Receiver-operator characteristic (ROC) analysis was performed to determine the diagnostic characteristics of sCD30 for detection of clinical and subclinical renal allograft rejection. A two-tailed *P*-value <0.05 was considered to indicate statistical significance.

Results

Characteristics of indication biopsies

Among the 52 indication biopsies, only one was classified as an isolated vascular compartment inflammation and therefore excluded. Demographic data of the remaining 51 indications biopsies stratified by the histological results are summarized in Table 1. By definition, the three groups demonstrated significant differences regarding the acute Banff scores (i, t, v, g). Recipient and donor characteristics did not differ among the three histological groups. Furthermore, serum creatinine, estimated glomerular filtration rate (eGFR), total urine protein/creatinine ratio and urinary α1m/creatinine ratio were not different across the three groups ($P \geq 0.21$). The causes for allograft dysfunction in the 33 biopsies with an acute score zero or interstitial infiltrates only were as follows: drug-related toxicity ($n = 15$), acute tubular necrosis ($n = 1$), postrenal obstruction ($n = 2$), infection ($n = 2$), recurrent glomerulonephritis ($n = 1$), thrombotic microangiopathy ($n = 2$), multiple aetiologies ($n = 4$) and unknown ($n = 6$).

sCD30 and correlation with clinical allograft inflammation

Serum sCD30 values were significantly different among the three groups ($P < 0.0001$; Table 1). Median sCD30 concentration was lowest in the acute score zero or interstitial infiltrates only group (18.3 ng/ml) with a stepwise increase to the tubulitis t1 group (29.6 ng/ml; $P = 0.0005$) and the tubulitis t2-3 group (49.4 ng/ml; $P = 0.001$; Fig. 1a). The tubulitis t1 group had a lower median sCD30 concentration (29.6 ng/ml) than the tubulitis t2-3 group (49.4 ng/ml), but this did not reach statistical significance ($P = 0.09$).

Diagnostic characteristics of sCD30 for detection of clinical allograft inflammation

For this analysis, the four histologically classified groups were separated into two categories. Category one contained the acute Banff score zero or interstitial infiltrates only group (i.e. no relevant inflammation category; $n = 33$). The second category comprised the tubulitis t1 and the tubulitis t2-3 group as well as the single indication biopsy with isolated vascular compartment inflammation (i.e. relevant inflammation category; $n = 19$). The prevalence of clinical allograft inflammation was therefore 36.5% (i.e. 19/52 indication biopsies). Recipient and donor characteristics as well as functional parameters (i.e. serum creatinine, eGFR, total urine protein/creatinine ratio, and urinary α1m/creatinine ratio) were not different between the two categories ($P \geq 0.11$; data not shown). However, median serum sCD30 concentration was significantly higher in the inflammation category (median 37.2 ng/ml vs. 18.3 ng/ml; $P < 0.0001$; Fig. 2a). ROC analysis revealed an area under the curve (AUC) of 0.87 for sCD30 for the detection of clinical allograft inflammation ($P = 0.0006$; Fig. 2c). In contrast, eGFR, total urine protein/creatinine ratio and urinary α1m/creatinine ratio had AUC ≤ 0.63 ($P \geq 0.34$). The optimal cut-off for sCD30 was 23.6 ng/ml (sensitivity 89%, specificity 79%).

Characteristics of surveillance biopsies

Among the 250 surveillance biopsies, only six were classified as isolated vascular compartment inflammation and therefore excluded. Demographic data of the remaining 244 indications biopsies stratified by the histological results are summarized in Table 2. By definition, the three groups demonstrated significant differences regarding the acute Banff scores (i, t, v, g, ptc), but not regarding chronic Banff scores, C4d positivity and the presence of BKV-viraemia ($P \geq 0.13$). Furthermore, recipient and donor characteristics (with the exception of total HLA mismatches; $P = 0.04$), immunosuppressive regimens, serum creatinine, eGFR, total urine protein/creatinine ratio and urinary α1m/creatinine ratio were not different across the three groups ($P \geq 0.11$).

sCD30 and correlation with subclinical allograft inflammation

Serum sCD30 values were slightly different among the three groups, but this did not reach statistical significance ($P = 0.06$; Table 2). Although, the median sCD30 concentration was lowest in the acute Banff score zero or interstitial infiltrates only group (21.6 ng/ml) with a stepwise increase to the tubulitis t1 group (26.2 ng/ml) and the tubulitis t2-3 group (30.2 ng/ml), the differences were not

Table 1. Characteristics of 51 indication biopsies obtained within the first year post-transplant, grouped according to histology results. One biopsy with an isolated vascular compartment inflammation was excluded from the total 52 indication biopsies, leaving 51 for the analysis.

	Acute score zero or i only (n = 33)	Tubulitis t1+ any i/g/v/ptc (n = 11)	Tubulitis t2-3+ any i/g/v/ptc (n = 7)	P-level
Recipient				
Age, median (IQR)	56 (41–63)	45 (33–60)	53 (31–60)	0.18
Female, *n* (%)	5 (15)	2 (18)	–	0.51
Primary disease				
ADPKD	6 (18)	2 (18)	2 (29)	0.63
Diabetic	4 (12)	1 (9)	–	
Vascular	4 (12)	1 (9)	–	
Glomerulopathy	6 (18)	5 (46)	3 (42)	
Other	13 (40)	2 (18)	2 (29)	
Baseline IS				
Tac-MMF-P, *n* (%)	8 (24)	2 (18)	2 (29)	0.87
Tac-MPS-mTOR, *n* (%)	25 (76)	9 (82)	5 (71)	
Donor				
Age, median (IQR)	52 (44–63)	48 (38–62)	50 (40–61)	0.61
Deceased donor, *n* (%)	11 (33)	7 (64)	3 (43)	0.21
DGF, *n* (%)	5 (15)	1 (9)	1 (14)	0.88
HLA-A-B-DR MM, mean ± SD	4.1 ± 1.3	4.1 ± 1.1	3.6 ± 1.4	0.60
Allograft histology				
Glomeruli, median (IQR)	18 (12–20)	13 (11–22)	16 (11–20)	0.64
Acute scores, mean ± SD				
i-score	0.2 ± 0.5	0.9 ± 0.5	2.3 ± 0.95	<0.0001
t-score	0	1.0	2.4 ± 0.5	<0.0001
v-score	0	0.3 ± 0.6	0.3 ± 0.5	0.02
g-score	0	0.3 ± 0.6	0.3 ± 0.5	0.02
ptc-score	0	0.3 ± 0.9	0	0.16
Chronic scores, mean ± SD				
i-score	0.2 ± 0.5	0.5 ± 0.5	0.7 ± 0.8	0.03
t-score	0.2 ± 05	0.5 ± 0.5	0.7 ± 0.8	0.03
v-score	0.4 ± 0.6	0.4 ± 0.5	0.3 ± 0.5	0.94
g-score	0	0	0	1.0
C4d positive, *n* (%)	2 (6)	2 (18)	3 (43)	0.04
BKV-viraemia, *n* (%)	1 (3)	1 (9)	0	0.20
Allograft function				
Creatinine [μmol/L], median (IQR)	187 (157–287)	174 (142–351)	235 (198–288)	0.71
eGFR [ml/min], median (IQR)	30 (22–39)	37 (20–52)	25 (24–33)	0.71
Urine protein				
Prot/creat ratio [mg/mmol], median (IQR)	27 (17–44)	16 (9–27)	20 (7–37)	0.21
α1m/creat ratio, [mg/mmol] median (IQR)	9.9 (4.5–17.1)	7.6 (3.3–17.5)	6.8 (5.9–12.2)	0.76
sCD30				
ng/ml, median (IQR)	18.3 (11.3–23.3)	29.6 (24.8–45.4)	49.4 (38.7–60.8)	<0.0001

Tac, tacrolimus; MMF, mycophenolate-mofetil; MPS, mycophenolate-sodium; mTOR, sirolimus or everolimus; P, prednisone; eGFR, estimated glomerular filtration rate calculated by the MDRD formula; sCD30, soluble CD30; DGF, delayed graft function.

statistically significant ($P \geq 0.10$; Fig. 1b). When surveillance biopsies with concomitant BKV-viraemia were excluded from the analysis (n = 20), sCD30 values did only slightly vary, but were still not different across the three groups (P = 0.29; data not shown). We further analysed sCD30 levels among the three main immunosuppressive regimens (i.e. Tac-MMF-P, Tac-MPS-mTOR, Tac-MMF) in surveillance biopsies demonstrating subclinical rejection. We observed no statistically significant differences, although sCD30 levels were numerically higher under Tac-MMF than Tac-MPS-mTOR and Tac-MMF-P (median 41.0 ng/ml vs. 27.1 ng/ml vs. 22.7 ng/ml; P = 0.11).

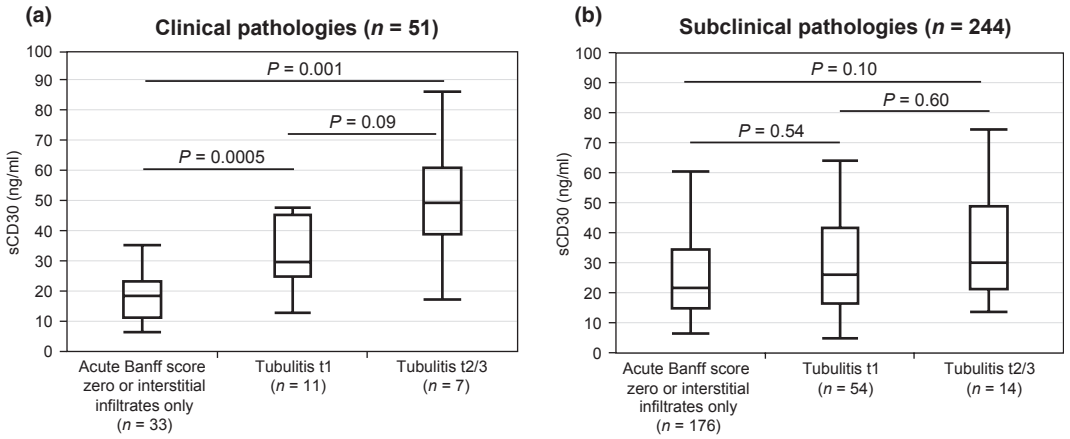

Figure 1 Correlation of serum soluble CD30 levels with allograft histology. (a) Clinical pathologies (n = 51). (b) Subclinical pathologies (n = 244).

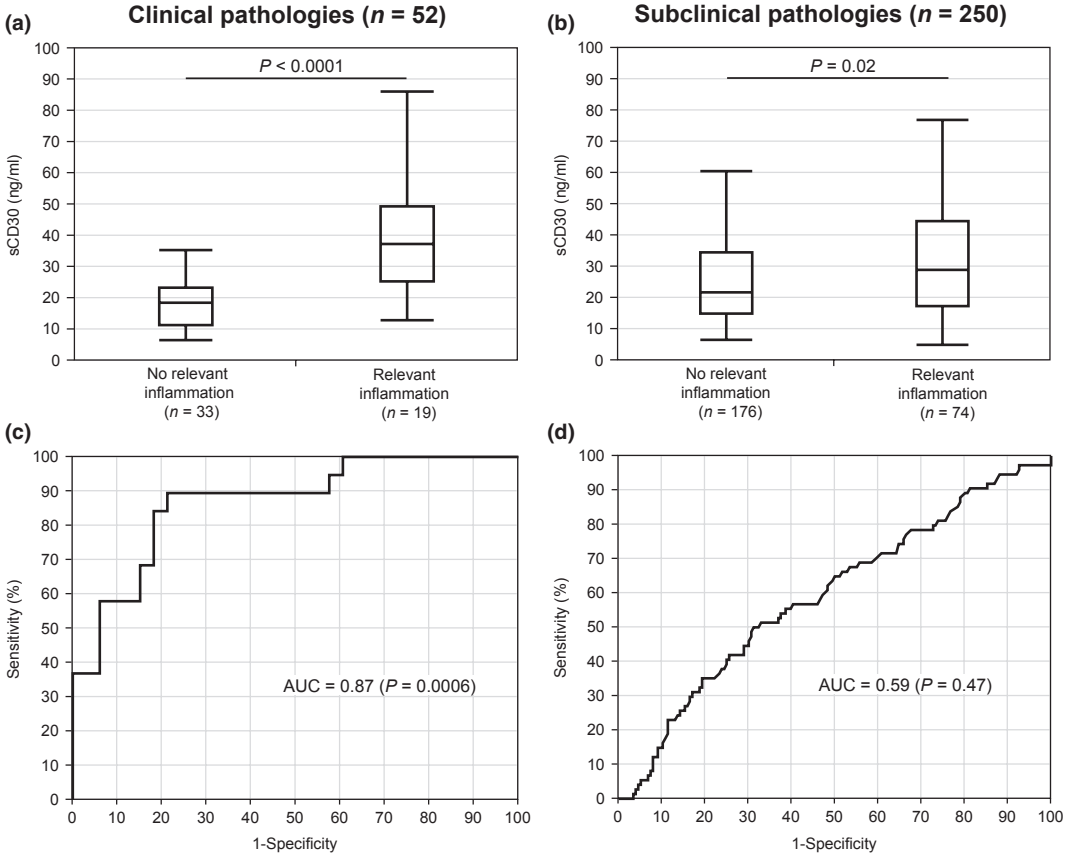

Figure 2 Correlation of serum soluble CD30 levels with allograft inflammation categories and corresponding receiver-operator characteristic (ROC) curves. (a and c) Clinical pathologies (n = 52). (b and d) Subclinical pathologies (n = 250).

Diagnostic characteristics of sCD30 for detection of subclinical allograft inflammation

As for analysis regarding clinical allograft inflammation, the 250 surveillance biopsies (including the six surveillance biopsies with isolated vascular compartment inflammation) were divided into two categories [i.e. no relevant inflammation category (n = 176) and relevant inflammation category (n = 74)]. The prevalence of subclinical allograft inflammation was therefore 30% (74/250

Table 2. Characteristics of 244 surveillance biopsies obtained at 3 and 6 months post-transplant, grouped according to histology results. Six biopsies with isolated vascular compartment inflammation were excluded from the total 250 surveillance biopsies, leaving 244 for the analysis.

	Acute score zero or i only (*n* = 176)	Tubulitis t1+ any i/g/v/ptc (*n* = 54)	Tubulitis t2-3+ any i/g/v/ptc (*n* = 14)	*P*-level
Recipient				
Age, median (IQR)	54 (43–61)	54 (38–62)	45 (33–56)	0.17
Female, *n* (%)	36 (20)	17 (31)	3 (21)	0.24
Primary disease				
ADPKD	30 (17)	7 (13)	3 (22)	0.14
Diabetic	23 (13)	8 (15)	–	
Vascular	15 (9)	5 (9)	2 (14)	
Glomerulopathy	69 (39)	15 (28)	2 (14)	
Other	39 (22)	19 (35)	7 (50)	
Baseline immunosuppression				
Tac-MMF-P, *n* (%)	73 (42)	18 (33)	5 (36)	0.54
Tac-MPS-mTOR, *n* (%)	103 (58)	36 (67)	9 (64)	
Donor				
Age, median (IQR)	53 (44–64)	52 (44–65)	45 (30–61)	0.29
Deceased donor, *n* (%)	91 (52)	30 (56)	11 (79)	0.15
DGF, *n* (%)	47 (27)	12 (22)	5 (36)	0.57
HLA-A-B-DR MM, mean ± SD	3.5 ± 1.5	4.1 ± 1.3	3.8 ± 1.3	0.04
Prior clinical rejection, *n* (%)	8 (5)	5 (9)	1 (7)	0.42
Immunosuppression at the time of biopsy				
Tac-MMF-P, *n* (%)	89 (50)	22 (41)	6 (43)	0.59
Tac-MPS-mTOR, *n* (%)	42 (24)	13 (24)	3 (21)	
Tac-MMF, *n* (%)	35 (20)	14 (26)	5 (36)	
Other, *n* (%)	10 (6)	5 (9)	–	
Allograft histology				
Glomeruli, median (IQR)	17 (12–25)	17 (13–23)	21 (12–29)	0.66
Acute scores, mean ± SD				
i-score	0.2 ± 0.5	1.2 ± 0.6	2.0 ± 0.7	<0.0001
t-score	0	1	2.1 ± 0.4	<0.0001
v-score	0	0.1 ± 0.2	0.1 ± 0.4	0.0002
g-score	0	0.1 ± 0.4	0	<0.0001
ptc-score	0	0.06 ± 0.2	0	0.005
Chronic scores, mean ± SD				
i-score	0.5 ± 0.7	0.5 ± 0.7	0.8 ± 0.8	0.36
t-score	0.5 ± 0.6	0.5 ± 0.7	0.9 ± 0.8	0.13
v-score	0.4 ± 0.6	0.4 ± 0.6	0.5 ± 0.9	0.87
g-score	0.01 ± 0.1	0	0	0.68
C4d positive, *n* (%)	7 (4)	2 (4)	0	0.74
BKV-viraemia, *n* (%)	6 (3)	10 (19)	4 (29)	0.38
Allograft function				
Creatinine [μmol/L], median (IQR)	138 (112–169)	133 (107–170)	138 (103–236)	0.92
eGFR [ml/min], median (IQR)	47 (39–57)	48 (37–58)	49 (28–60)	0.98
Urine protein				
Prot/creat ratio [mg/mmol], median (IQR)	13 (9–23)	18 (10–33)	14 (8–19)	0.11
α1m/creat ratio [mg/mmol], median (IQR)	4.8 (2.8–8.2)	4.4 (3.1–7.6)	5.9 (3.2–10.8)	0.79
sCD30				
ng/ml, median (IQR)	21.6 (14.8–34.5)	26.2 (16.6–41.6)	30.2 (21.2–48.9)	0.06

Tac, tacrolimus; MMF, mycophenolate-mofetil; MPS, mycophenolate-sodium; mTOR, sirolimus or everolimus; P, prednisone; eGFR, estimated glomerular filtration rate calculated by the MDRD formula; sCD30, soluble CD30; DGF, delayed graft function.

surveillance biopsies). BKV-viraemia, as well as serum creatinine, eGFR, total urine protein/creatinine ratio and urinary α1m/creatinine ratio were not different among the two categories ($P \geq 0.15$; data not shown). Median sCD30 concentration was significantly higher in the subclinical inflammation category compared to the no

relevant inflammation category (28.9 ng/ml vs. 21.6 ng/ml; $P = 0.02$; Fig. 2b). However, ROC analysis revealed only an AUC of 0.59 for sCD30 for detection of subclinical allograft inflammation ($P = 0.47$; Fig. 2d), which was similar to the AUC of eGFR, total urine protein/creatinine ratio and urinary α1m/creatinine ratio (AUC ≤ 0.56; $P \geq 0.5$).

Discussion

The key observation in this study was that sCD30 correlates with clinical, but not with subclinical allograft rejection. This is intriguing, and we favour the following explanation for this finding:

Although, clinical and subclinical rejection does not differ histologically regarding the extent of the infiltrate assessed using the Banff scores, the involved cells may vary and may not have the same degree of activation. Indeed, Grimm *et al.* found that during clinical rejection more $CD8^+$ T cells and $CD68^+$ macrophages are involved than in subclinical rejection. Furthermore, they demonstrated that especially the macrophage activation marker allograft inflammatory factor-1, but also the T-cell activation marker perforin are up-regulated during clinical rejection [35]. In analogy, we speculate that sCD30 reflects the degree of T-cell activation, which is likely lower in subclinical than in clinical allograft rejection. Such a limited T-cell activation in the tubulointerstitial compartment might be best detectably in the urine, whereas it is not sufficient to substantially increase systemic blood levels of potential rejection biomarkers [36,37]. So far, there are no studies regarding sCD30 in the urine. sCD30 has a molecular weight of 88 kDa and is unlikely to pass through intact glomeruli [38]. It remains currently unknown, whether sCD30 released by activated T cells in the tubulointerstitial compartment can pass into the urine.

Although sCD30 levels in surveillance biopsies demonstrating 'relevant inflammation' (i.e. tubulitis t1 or higher) were statistically higher than in the 'no relevant inflammation' category (i.e. acute Banff scores zero or only interstitial infiltrates) ($P = 0.02$), ROC analysis revealed a very low AUC of 0.59 ($P = 0.47$). This suggests that sCD30 has no useful diagnostic value to separate these two distinct categories, limiting its clinical application as a noninvasive screening assay for subclinical allograft rejection.

Post-transplant sCD30 concentrations in our cohort were in general lower than in other studies. This might mainly be related to the applied immunosuppression and the time of sampling post-transplant. Indeed, Weimer *et al.* found that patients receiving a tacrolimus-based immunosuppression had significantly lower sCD30 levels at 1-year post-transplant than patients receiving cyclosporine-based immunosuppression [39]. Furthermore, two studies suggest that sCD30 levels decrease post-transplant and reach a nadir at around 20–30 days post-transplant [28,40]. In the later course, sCD30 slightly increase again and reach a plateau in the range of our cohort [28]. Notably, most studies measured sCD30 within the first days post-transplant compared with our study analysing sCD30 mostly beyond 30 days post-transplant.

To the best of our knowledge, this is the first study correlating sCD30 with subclinical rejection. An advantage of this study is the uniform immunosuppression with Tac-MMF/MPS, which is the preferred regimen in many renal transplant centres. Furthermore, patients receiving a T-cell depleting induction therapy were excluded because profound lymphopaenia may confound sCD30 levels. However, this study has also some limitations. As the maintenance immunosuppression was restricted to a Tac-MMF/MPS-based regimen, the results might not be valid for other immunosuppressive therapies. In addition, this is a single centre study with a moderate surveillance biopsy sample size ($n = 250$), which might miss small, – but likely clinically irrelevant – differences because of insufficient statistical power.

In conclusion, sCD30 correlated with clinical, but not subclinical renal allograft rejection limiting its clinical utility as a noninvasive screening biomarker in patients with stable allograft function receiving Tac-MMF/MPS-based immunosuppression.

Authorship

PHM, SS: designed research/study. PHM, MR, GH, PA, HH, SS: performed research/study. PHM, MR, GH, PA, SS: collected data. PHM, SS: analysed data. All: wrote paper.

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