The Proportion of Memory CD8⁺ T Cell Predicts Infection Event in Patients with Peritoneal Dialysis

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Abstract
Introduction: The immune senescence marked by the inflammation of memory T cell is established in end-stage renal disease (ESRD) patients with peritoneal dialysis (PD). These patients suffer high incidence of infectious disease, which has been relevant to immune dysfunction. However, the association of immune senescence with infection in PD patients is not clear. This prospective study aimed to investigate the relationship between proportion of T cell subsets and infection event in patients on PD. Methods: We enrolled patients on PD >6 months from January 1, 2016 to December 30, 2016 and followed them until April 30, 2020. Baseline T cell subsets from blood were collected at the time of recruitment. The primary end point was infection event including peritonitis, exit site infection, pneumonia, urinary tract infection, and other infection. Results: There were 94 patients (46 male) with a mean age of 56.1 ± 14.9 years old enrolled during the follow-up period, and 26 patients suffered infection events. A higher proportion of effector memory (EM) CD8⁺ T cells was found in patients with infection than in those without infection. There was no difference in the distribution of EM CD8⁺ T cells between PD-related and non-dialysis infection. Increased level of EM CD8⁺ T cells was risk factor for first infection event in PD patients. Conclusion: High level of EM CD8⁺ T cells could be a significant predictor of infection event in patients on PD.

Introduction
Infection is a common complication in patients with end-stage renal disease (ESRD), leading to high hospitalization and mortality [1]. Higher rate of infection was observed in patients with peritoneal dialysis (PD) when compared to hemodialysis patients, partly due to a higher incidence rate of dialysis technique-related infections in PD patients [2–4]. However, overall risk for dialysis and non-dialysis technique-related infections remains stable in PD patients after 6 months of treatment [2]. The risk factors for infection events among PD patients were the elderly, diabetes, and hypoalbuminemia, which was associated with an increased level of systemic inflammation.

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Meanwhile, systemic inflammation rather than local inflammation predicted PD patients’ survival [7].

T-cell dysfunction, including aging of T cells, decline of CD4/CD8 ratio, and accumulation of circulating memory and effector T cells, was found in ESRD patients [8]. Memory T cell pool is composed of heterogeneous subsets that differ in phenotype and function, subdivided into central memory (CM) T cell (CD45RO⁺, CCR7⁺) and effector memory (EM) T cell (CD45RO⁺, CCR7⁻) in peripheral blood. Marked by proliferative capacity and preferential localization to lymphoid, CM CD8⁺ T cells maintain antigen-experienced memory cells and convert to effector cells responding to pathogen recount [9, 10]. By contrast, EM CD8⁺ T cells rapidly migrate to the inflamed tissue and kill the infected cells by producing cytokines [10, 11].

Alteration of CD8⁺ T cell subsets, induced by dialysis modality as well as aging and CMV infection [12, 13], could be associated with adverse clinical outcomes. It has been reported that senescence of CD8⁺ T cells contributes to high risk for cardiovascular disease in CKD patients [14, 15], and increased proportion of terminally differentiated memory CD8⁺ T cells in kidney transplantation patients is associated with a higher risk for skin carcinoma and a lower risk for rejection [16, 17]. Also, EM CD8⁺ T cells could provide robust resistance against certain acute infections by production of proinflammatory cytokines and immediate response to re-counter to antigen [18].

Despite the strong association between inflammation level and memory CD8⁺ T cell, few study demonstrated impact of CD8⁺ T cell distribution on infectious disease in PD patients. In this study, we conduct a prospective study to evaluate the relationship between the degree of CD8⁺ T cell subsets and infection event in PD patients.

**Materials and Methods**

**Patients**

We enrolled patients who had been on standard continuous ambulatory peritoneal dialysis at least for 6 months in the Blood Purification Center, Zhongshan Hospital, Fudan University. Patients were registered from January 1, 2016 to December 30, 2016, and individuals with malignant tumors, autoimmune disease, infection, medication of immunosuppressants within 3 months, or those <18 years were excluded. Every enrolled patient with the written informed consent was followed until they died, switched to hemodialysis, received renal transplantation, withdrew from PD, or until the end of the study on April 30, 2020. The study (Approval No: B2017-108R) was approved by the Ethical Committee, at Zhongshan Hospital, Fudan University. Every enrolled patient gave their written informed consent.

**T Cell Differentiation Analysis**

Peripheral blood cells were obtained at the time of recruitment. PBMCs were isolated by gradient centrifugation and resuspend by staining buffer. T cells stained by CD3-PE (BioLegend) were separated into CD4⁺ and CD8⁺ T cells as determined by CD4-APC and CD8a-PerCP/Cy5.5 (BD Bioscience). CD45RO-FITC (Miltenyi Biotec) and CCR7-APC/Cy7 (BioLegend) was further used to analyze T cell differentiation: NAIVE subset (CCR7⁺ CD45RA⁺), CM subset (CCR7⁺ CD45RA⁻), EM subset (CCR7⁻CD45RA⁻), and EMRA subset (CCR7⁻CD45RA⁺).

**End Point Evaluation**

The end point was infection complications after registration. Infections were categorized as dialysis related (peritonitis, exit site infection) and non-dialysis related infections (pneumonia, urinary tract infection, and other infection). An infection event was diagnosed by a nephrologist who was blinded to the data, according to clinical manifestation, laboratory data, and radiographic findings, which was confirmed by positive culture or effective antimicrobial treatment. All patients were evaluated every month.

**Data Analysis and Statistics**

The data were expressed as the means ± standard deviation or medians and interquartile range (IQR). Independent sample t test or Mann-Whitney U test was used for normally distributed variables or skewed variables. Cox proportional hazards models and the Kaplan-Meier method were used to determine the association of proportion of T cells and the first infection event. All statistical analyses were performed using SPSS version 23.0. The statistical significance level was considered at p < 0.05 in 2-tailed testing.

**Results**

Ninety-four patients (46 males) were enrolled in this study, with a mean age of 56.1 ± 14.9 years old. The median follow-up time was 37.0 (25.5–41) months. During the follow-up period, 26 patients suffered 33 episodes of infectious events, including 17 peritonitis (51.5%), 7 pneumonia (21.3%), 6 urinary tract infection (18.2%), and 3 other site infections (9.0%). The incidence of infectious events was 12.4% per patient-year. The median duration from the time of blood sampling collecting to the first episode of infection was 14 (7, 24.5) months.

Decreased percentage of and increased percentage of EM CD8⁺ T cells were found in patients with infection compared to those without infection (online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000526207). However, other subsets of CD8⁺ or CD4⁺ T cells were not different between patients with or without infection. Levels of EM CD8⁺ T cells in patients suffered PD-related infection showed no difference as compared to those with non-dialysis infection (online suppl. Table S2).
The median percentage of naïve or EM CD8+ T cells was further analyzed for the correlation between infection events. The high level of naïve CD8+ T cells could not predict first infection event (Fig. 1). However, the increased incidence of infection events was found in the high EM CD8+ T cell group compared to that in the low group (Fig. 2), considering the different distribution of age between the high and low EM CD8+ T cell groups (Table 1). The patients were further divided into four groups according to age and level of EM CD8+ T cells. The older patients with high level of EM CD8+ T cells had greater cumulative hazard rate for infection event than younger patients with
low level of EM CD8+ T cells ($p = 0.03$, Fig. 3). Meanwhile, increased infection rate was found in patients with high level of EM CD8+ T cells as compared to the same aged-patients (<65 years) with low level of EM CD8+ T cells ($p = 0.025$, Fig. 3). However, in older patients (≥65 years), there was no difference of infection rate between high and low level of EM CD8+ T cells ($p = 0.668$, Fig. 1).

Cox proportional hazard models were used to evaluate these conventional and unconventional risk factors related to infection in PD patients. In univariate Cox regression analysis, EM CD8+ T cells were significantly associated with infection event (EM CD8+ T cells as dichotomous variable: hazard ratio [HR], 3.75; 95% confidence interval [95% CI], 1.15–9.34; $p = 0.004$). Other significant variables included age, history of diabetes, and prealbumin (Table 2). Then, a series of models were constructed to analyze confounding risk factors (models 1–3). In model 3, the covariates with $p < 0.05$ for predicting infection event included age, history of diabetes, and prealbumin [6]. The results showed that CD8+ EM T cells still remained significant after adjustment for the above confounding risk factors (Table 3).

**Discussion**

In this study, we found baseline proportion of CD8 T cell subsets was associated with incidence of infection event in ESRD patients. Patients on peritoneal dialysis with increased percentage of EM CD8+ T cells were prone to infectious disease, including peritonitis.
ESRD patients exhibited the enhanced immunosenescence of CD8+ T cells, which was similar to that seen in healthy elderly people [12, 19]. Apart from age, other factors like chronic CMV infection or persistent inflammation could also prompt exhaustion of the CD8+ T cell system and expansion of memory T cell in ESRD patients [12, 19–21]. Dialysis could also increase proportion of memory CD8+ T cells in comparison with that of ESRD patients without dialysis, independent of dialysis vintage, and underlying kidney disease [22]. In our former study, dialysis modality could alter the distribution of CD8+ T cell subset [12], which was consistent with other studies [23, 24]. Impaired response of age-associated CD8+ T cell defects contribute to increased susceptibility to pathogen and diminished vaccine response [12, 13, 25]. In health individuals, memory CD8+ T cells develop in response to diverse pathogen, and elevated level of EM CD8+ T cells could provide specific protection against certain pathogen [25, 26]. With normal aging, decreased proliferative capacity, differentiation, and function of EM CD8+ T cells contribute to enhanced proportion of infectious disease in elderly [12, 13, 25], which was also found in ESRD patients [27]. The ineffective immune response to new antigen in ESRD patients was due to contracted naïve CD8+ T cells and loss of T cell receptor repertoire particularly within the CD8+ memory T cell subset [22, 28]. Some studies found response of EM CD8+ T cells to new pathogens was acquired by depleting preexisting memory population [29]. So, the increased proportion of circulating memory CD8+ T cells in ESRD patients may hamper proper response to new infection. Other studies have reported the accumulation of memory CD8+ cells induced by uremia is associated with increased risk of infection in ESRD patients [13, 14]. In our study, PD patients with an increased baseline level of EM CD8+ T cells were susceptible to peritonitis, pneumonia, and other infection diseases. We also found age and diabetes were independent risk for infection in PD patients, in accordance with former studies [30, 31]. However, we did not link the level of serum albumin or serum creatinine (Scr) to risk of infection in PD patients. Mehrotra R et al. [6] demonstrated PD patients with baseline serum albumin <3.0 g/dL have increased risk for in-

![Fig. 3. Kaplan-Meier curves of first infection event during follow-up in patients on peritoneal dialysis stratified by age and level of EM CD8+ T cell group.](image-url)
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Infection-related mortality when compared with patients with serum albumin 4.00–4.19 g/dL. Whereas the levels of serum albumin within the infected group and the non-infected group in our study were all above 3.0 g/dL. Further, the dynamic change rather than baseline of serum albumin predict risk for mortality of PD patients [6]. Study has found lower risk of death in PD patients with Scr >8.0 mg/dL than in those with Scr <4.0 mg/day [32]. However, Scr in our PD patients was all above 8.0 mg/dL, so the association of Scr and infection event was uncertain. Furthermore, we did not find association between level of inflammatory markers and infection event in PD patients. Elevated proinflammatory cytokines such as IL-6, TNF-α, and hsCRP, which were found in patients with uremia, could predict all-cause mortality in dialysis patients [33]. Like serum albumin, study has demonstrated the progressive rather than the persistent high level of hsCRP could predict infection risk in PD patients [34]. Other study also found plasma TNF-α instead of IL-6 could be risk factor for organ infection in patients with PD [35]. However, there was not association between TNF-α and PD-related infection. In our study, the predominant infection was peritonitis, meanwhile the median level of TNF-α in our study was much higher than the cut-off (7.5 pg/mL). So the dynamic changes of inflammatory cytokines could be more effective indicator of infection event.

We did not find significant difference of EM CD8+ T cells between patients with PD-related infection and other infection. After pathogen-recount in localized tissue, specific memory CD8+ T cells could relocate to inflamed tissue [36, 37]. Apart from circulation T cells, the peritoneal T cells were established to affect peritoneal dialysis outcomes [38]. Roberts et al. [39] reported peritoneal EM T cells of PD patients construct first line against pathogen. However, discrepancy of response to antigen between circulating memory T cells and resident memory T cells needs to be further demonstrated. Gerlach et al. [40] found another memory CD8+ T cells with predominant migratory and high capability of proliferation in peripheral tissue, according to the expression of CX3CR1. We hypothesized that inappropriate migration of circulating EM CD8+ T cells to infected tissue or impaired response of resident memory T cell to antigen contribute to high risk for infection in ESRD patients.

Contracted pool of naïve CD8+ T cells increased risk for infection and all-cause mortality in ESRD patients, which could not been reversed by renal transplantation [41, 42]. Despite decline of naïve CD8+ T cells of infected

| Table 2. Univariate Cox proportional hazard model of infection event |
|-----------------|-----------------|-----------------|
| Variable        | Hazard ratio    | p value         |
| Age             | 1.04 (1.01, 1.06)| 0.012           |
| Gender          | 0.59 (0.27, 1.30)| 0.19            |
| BMI             | 0.95 (0.84, 1.07)| 0.43            |
| Primary hypertension | 0.84 (0.39, 1.82) | 0.66            |
| Diabetes        | 2.95 (1.34, 6.28)| 0.005           |
| CVD             | 1.01 (0.38, 2.69)| 0.97            |
| Dialysis vintage, months | 1.01 (0.99, 1.02) | 0.29            |
| WBC (x10⁹/L)    | 1.10 (0.95, 1.28)|                |
| Neutrophil (x10⁹/L) | 1.02 (0.83, 1.24) | 0.88            |
| Lymphocyte (x10⁹/L) | 1.23 (0.70, 2.17) | 0.48            |
| T cell (x10⁹/L) | 1.00 (0.99, 1.00) | 0.76            |
| CD4 T cell (x10⁹/L) | 1.00 (0.99, 1.00) | 0.64            |
| CD8 T cell (x10⁹/L) | 1.00 (0.99, 1.00) | 0.15            |
| CD4/CD8         | 1.05 (0.68, 1.62)| 0.82            |
| Albumin (g/L)   | 0.96 (0.87, 1.05)| 0.37            |
| Prealbumin (g/L) | 0.004 (0.00, 0.31)| 0.013          |
| Scr (µmol/L)    | 0.99 (0.92, 1.06)| 0.66            |
| BUN (mmol/L)    | 1.00 (0.99, 1.00) | 0.62            |
| Calcium (mmol/L)| 0.57 (0.09, 3.31)| 0.53            |
| Phosphorus (mmol/L) | 1.15 (0.54, 2.45)| 0.71            |
| iPTH (pg/mL)    | 0.99 (0.99–1.00) | 0.50            |
| β2-MG (mg/L)    | 1.01 (0.97, 1.05) | 0.53            |
| Iron (µmol/L)   | 0.93 (0.86, 1.02) | 0.12            |
| Ferritin (µg/mL)| 1.00 (0.99, 1.00) | 0.96            |
| IL-6 (pg/mL)    | 1.01 (0.98, 1.05) | 0.52            |
| TNF-α (pg/mL)   | 0.99 (0.98, 1.02) | 0.70            |
| hsCRP (mg/L)    | 1.00 (0.98, 1.03) | 0.72            |
| nPCR (g/kg/day) | 0.63 (0.09, 4.32) | 0.64            |
| Renal Kt/V      | 0.57 (0.24, 1.37) | 0.204           |
| EM CD8, %       | 3.75 (1.51, 9.34) | 0.004           |
| Naïve CD8, %    | 0.98 (0.96, 0.99) | 0.02            |
| CM CD8, %       | 0.98 (0.93, 1.03) | 0.42            |
| EMRA CD8, %     | 1.01 (0.98, 1.05) | 0.47            |

| Table 3. Multivariate Cox proportional hazard model of infection event |
|-----------------|-----------------|-----------------|
| Model           | Hazard ratio    | (95% confidence interval) | p   |
| Unadjusted      | 3.75            | 1.51–9.34        | 0.004 |
| Model 1         | 3.12            | 1.31–7.47        | 0.01  |
| Model 2         | 3.81            | 1.47–9.88        | 0.006 |
| Model 3         | 3.05            | 1.21–7.71        | 0.018 |

Model 1: adjust for age, gender, BMI, cardiovascular disease, diabetes, hypertension, albumin, prealbumin, BUN, Scr; Model 2: adjust for white blood cell, neutrophil, monocyte, lymphocyte, b2-microglobulin, ferritin, hsCRP, TNF-α, IL-6; Model 3: age, diabetes, prealbumin.
group in our study, the level of naïve CD8+ T cells did not predict incidence of infection event in PD patients. Instead of latency CMV infection, senescence markedly reduced thymic output of naïve CD8+ T cells, increased apoptosis of naïve CD8+ T cells and turnover to memory cells [43].

We have some limitations. First, the small sample size from one center in our study needs further larger study to support the finding. Second, the proportion of CD8+ T cells and association with inflammation marker was not evaluated in patients with infectious episode. Third, considering dynamic CD8+ T cells subsets, the proportion of CD8+ T cells varied within short period should be reevaluated.

Conclusions

We showed that the elevated proportion of EM CD8+ T cells, rather than naïve cells, predicts the risk for infection event in PD patients. However, the impact of memory CD8+ T cells on inflammation milieu is necessary to be investigated.

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