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Higher serum Granzyme-B level and Intragraft Granzyme-B, phosphoSMAD-3+ cells are associated with inflammatory interstitial fibrosis and tubular atrophy

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Objectives:

Inflammatory **I**nterstitial fibrosis and tubular atrophy (i-IF/TA) is a prominent histological lesion reported in late biopsy and poorly associated with graft survival. Cytotoxic T cell secrets Granzyme-B, which cleaves cytoskeleton protein, and activates pro-IL-1β, and TGF-β into their active form, leading to inflammation, fibrosis, and the apoptosis in target cell. The association of Granzyme-B+ cytotoxic T cell and phospho-SMAD-3 expression has been not explored in i-IF/TA in depth.

Methods: The circulating frequency of CD3+CD8+Granzyme-B+ cytotoxic T (CTLc) was measured by the flowcytometry; serum and PBMCs culture supernatants Granzyme-B and proinflammatory cytokines TGF-β, IL-1β level by the ELISA, Intragraft Granzyme-B mRNA transcript expression by the RT-PCR and Granzyme-B^+, pSMAD-3^+ Cell was analyzed by the immunohistochemistry techniques. Independent T-test for continuous variables and Pearson correlation was applied for the different variables.

Results:

The circulating frequency of cytotoxic-T cell ($CD3^+CD8^+$Granzyme-B^+) in SGF vs i-IF/TA was (27.96±4.86 vs 23.19±3.85%, p=0.011), $CD3^+$T cell was (66.08±6.8 vs 65.18±9.35%; p=0.68), $CD3^+CD8^+$T cell was (37.29±4.11 vs 34.68±5.43%; p=0.28). Serum Granzyme-B level was in SGF vs IF/TA was (100.82±22.41 vs 130.32±46.60, p=0.038 pg/ml), serum TGF-β level was (367.50±31.50 vs 318.81±48.39, p=0.005), IL-1β level was (49.14±17.03 vs 63.69±23.13, p=0.076). Intragraft Granzyme-B mRNA transcript expression in SGF vs i-IF/TA was (1.01±0.048 vs 2.10±1.02-fold, p<0.001). Granzyme-B^+ cell/mm^2 count was (0.40±0.69 vs 2.20±1.27; p=0.001). The intragraft phosphorylated SMAD-3^+ cell was (3.70±1.82 vs 6.73±3.21; p=0.008). The intragraft Granzyme-B+ cell count was positively correlated with pSMAD-3+ cell (r=0.315, p=0.047). The frequency of circulating CTLc was negatively correlated with urine proteinuria (r= -0.51, p<0.001), serum creatinine (r= -0.28, P=0.007) and eGFR (r= -0.28, p=0.037). While urine proteinuria was positively correlated with serum Granzyme-B level (r= 0.343, p=0.001), intragraft Granzyme-B mRNA transcript expression (r= 0.38, p<0.001).

Conclusions: