FORUM

Incomplete recovery from COVID-19-associated acute kidney injury in kidney transplant recipients: prior graft injury matters the most

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This Forum discusses the paper by Bajpai et al: Recovery of kidney function after AKI because of COVID-19 in kidney transplant recipients.Transpl Int. 2021:34; xxx.

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Acute kidney injury (AKI) occurs frequently in the course of COVID-19 in the general population, its incidence ranging from 7% in hospitalized patients [1] to above 20% in patients admitted to ICU [2]. The definitive pathogenesis is still unclear. However, because in most cases the pattern of injury is acute tubular necrosis and endothelial injury [3,4], it is likely that most cases of AKI are the result of hemodynamic instability, cytokine-related injury, and dysfunction of the coagulation cascade. In a minority of cases, patients may additionally develop severe proteinuria because of new-onset focal segmental glomerular sclerosis (often collapsing variant) or acute endothelial injury that may eventually lead to poor prognosis [5]. Unlike hospitalized patients who developed AKI in the course of disease other than COVID-19, patients with COVID-19 seem to have persistent kidney functiondecline after discharge (−14 ml/min/1.73 m^2 per year) [6]. Moreover, the proportion of COVID-19 patients that remain dialysis-dependent long after discharge from the hospital, is higher compared with patients developing AKI in the course of other diseases of similar severity. In fact, the proportion of patients requiring RRT for COVID-19 who remained dialysis-dependent two months after discharge was 18% [2], about twofold to threefold higher than the percentage of patients admitted to ICU and requiring renal replacement therapy (RRT) for conditions other than COVID-19 [7]. The reason for the apparent poor prognosis of AKI in patients with COVID-19 compared with AKI in other conditions of similar severity is currently unknown.

It is also unclear whether the AKI risk is increased in kidney transplant recipients compared with the general population. In a recent predominantly African American Cohort, the incidence of AKI was approximately 70% [8] and that requiring RR was 16% [8], suggesting a striking increased risk in kidney transplant recipients. Indeed, there are several factors that might aggravate the incidence and the severity of AKI in the kidney

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transplant recipients compared with the general population, such as the higher prevalence of prior kidney dysfunction, the higher prevalence of comorbidities, the nephrotoxic effect of anti-rejection drugs. Calcineurin inhibitors may aggravate kidney hypoperfusion, mTOR inhibitors might impair recovery from AKI, and both of them are also implied in increasing the risk of thrombotic mycroangiopathy [9]. The additional concern is related to the risk of graft rejection that may result from the widespread practice of reducing anti-rejection therapy in the course of severe COVID-19 infection [9]. To date, only a handful of cases of rejection in the course of COVID-19 have been reported in the literature. That may result from the logistical difficulties of performing graft biopsy in COVID-19 patients or to a dampened allo-reactive response in the course of COVID-19, different from what occurs during other viral infections [10]. However, the evidence on the specific determinants of AKI in kidney transplant recipients with COVID is currently scarce. In addition, the incidence of acute a chronic rejection in these patients is largely unknown, as well as the rate of full recovery of graft dysfunction after discharge from the hospital.

In this issue of the journal, Bajpai *et al.* [11] report on largest series published so far of kidney transplant recipients developing AKI during COVID-19. Out of 452 recipients followed up at five centers, 50 (11%) had AKI secondary to COVID-19. The study focus on the 42 recipients who had at least 3-month follow-up. Most of them had severe COVID-19. Fifty percent had pneumonia with respiratory compromise (defined as oxygen saturation $\leq$94% at room air or partial pressure of oxygen/fraction of inspired oxygen <300), and 29% developed KDIGO stage-3 AKI (i.e., serum creatinine increase by three times or above 4 mg/dl, and/or urinary output of zero in 12 h or <0.2 ml/kg/h in 24 h). Graft function recovery was in general poor. Complete recovery of graft function at 3 months occurred in only 40% of them. Worsening of proteinuria was seen in 36% of patients, while 10% of patients had new-onset proteinuria. Dialysis dependence after discharge was present in 14%. Compared with patients with complete recovery, those with incomplete recovery had prior graft dysfunction (average CKD-EPI eGFR 55 vs. 69 ml/min/.173 m^2; average daily proteinuria 400 vs. 100 mg), more extended organ involvement and admission (as suggested by the SOFA score at admission), reduced organ perfusion (as suggested by orthostatic hypotension), and more severe forms of AKI (AKI Stage 3, in 40% vs. 10%). At the last follow-up after discharge, which occurred after a median of 5 months, the loss of graft function appeared persistent. Overall, those findings suggest that prior graft dysfunction in the setting of a most severe form of COVID-19 was a major determinant of failed recovery of graft function after discharge from the hospital.

This study shed some light on the causes of graft dysfunction that have mediated the relationship between prior graft dysfunction and lack of graft function recovery. In fact, eleven biopsies were performed. Not surprisingly, the pattern of lesion did not differ greatly from those reported in the nontransplant populations [3,4], as above 80% of the biopsies revealed acute tubular injury. Thrombotic microangiopathy was described in two cases (18%), in one of them in the contest of chronic active rejection. One additional patient developed focal segmental glomerular sclerosis. The newest findings concern the prevalence of rejection. Borderline lesions of T cell-mediated rejection and chronic active antibody-mediated rejection were relatively uncommon, being found in 18% and 25% of the case, respectively. Unfortunately, the study did not provide data on previous monitoring of circulating anti-HLA antibodies; therefore, we cannot identify which patients were at highest risk of developing full-blown rejection. One patient developed de novo donor-specific anti-HLA antibodies. This patient was likely at increased immunologic risk prior to COVID-19, since one year earlier the patient had received anti-rejection treatment for borderline cell-mediated rejection. The most striking finding is the relative absence of tubule-interstitial inflammation in the vast majority of the eleven biopsies, despite the fact the most of the patients underwent immunosuppression reduction. However, steroid doses were increased in half of the patients. Finally, it is intriguing to speculate that in the 33% (3/9) of the cases showing mesangial deposition of IgA/C3, such deposition originated from mucosal sites (upper respiratory and gastrointestinal tract) infected with SARS-CoV-2.

Taken together, the above findings are consistent with the notion that impaired recovery in kidney transplant recipient who had developed COVID-19-associated AKI, share similar underlying mechanisms with the general population, and that prior graft dysfunction is one of the major determinant of impaired recovery. In patients with subclinical (possibly unrecognized) chronic rejection, COVID-19 infection, along with the associated immunosuppression reduction, may represent the trigger causing the development of full-blown chronic/active antibody-mediated rejection, which account for the lack of graft function recovery in a minority of the cases.

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