Capillary Leak Syndrome Following Immune Checkpoint Inhibition: A Unique Cause of Acute Kidney Injury

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Introduction

Immune checkpoint inhibition (ICI) is associated with acute kidney injury (AKI) via direct cytotoxicity including allergic interstitial nephritis (AIN), acute tubular necrosis (ATN), and glomerulopathy.[1]

ICI uncommonly causes capillary leak syndrome (CLS) — increased capillary protein permeability leading to hypotension, anasarca, and intravascular volume depletion. The mechanism proposed for CLS is T-cell stimulation of cytokines that induce vascular endothelial leak.

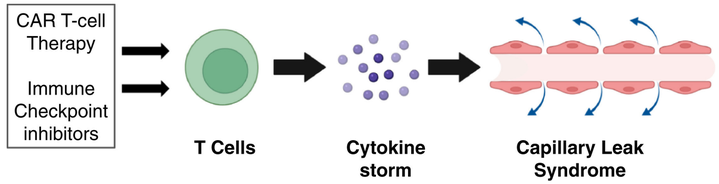

Figure 1. Izzedine H, Mathian A, Amoura Z, Ng JH, Jhaveri KD. Anticancer drug-induced capillary leak syndrome. Kidney International Reports. 2022;7(5):945-953. doi:10.1016/j.ekir.2022.02.014

We report a case of CLS following pembrolizumab (Keytruda) therapy resulting in severe prerenal AKI that was reversed with IV immunoglobulin (IVIG) treatment and albumin infusion.

Case

A 71-year-old male with a history of metastatic Hurthle cell tumor on pembrolizumab immunotherapy presented with recurrent falls due to hypotension. Last immunotherapy session was 8 weeks prior to admission. 2 weeks prior to admission, the patient presented to an outside facility for anasarca and hypotension resulting in antihypertensive discontinuation. Patient returned home with worsened anasarca associated with a 35 lb. weight gain over 6 weeks.

At our hospital, he was administered IV fluids due to persistent hypotension (total 6 L crystalloid fluids) with albumin 25 g/day BID for 3 days. His baseline creatinine was 1.16 mg/dL, but increased to 2.9 mg/dL on admission, peaking to 4.72 mg/dL on hospital day 10 with ongoing hypotension. ICI can induce hypophysitis[2], but ACTH stimulation testing was normal.

Urinalysis showed no hematuria and low-grade proteinuria. Urine studies (two separate collections) showed urine sodium < 5 mmol/L, urine Cl <10 mmol/L, and elevated urine creatinine, suggesting renal underperfusion.

Worsened anasarca prompted diuresis attempts, yet urine output (UO) remained low. Uremia developed requiring 4 hemodialysis sessions without fluid removal.

Right heart catheterization to assess volume status showed low biventricular filling pressures and cardiac output (Table 1). CLS was suspected and albumin 25 grams was started for 3 days. IVIG was administered after receiving preauthorization (Gammagard 0.05 mg/kg/day for 5 days). Two days after receiving IVIG, creatinine improved to 2.43 mg/dL and UO increased. 14 days after administering IVIG, creatinine was 0.9 mg/dL and UO on torsemide was 1.7 – 2.0 L / day.

Results

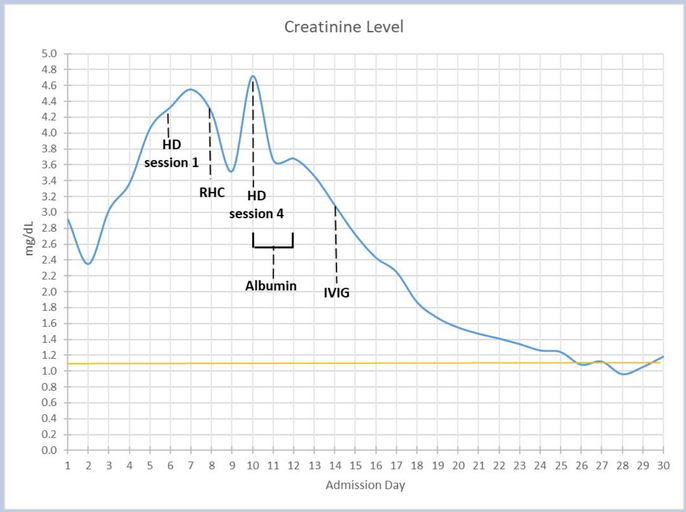

Figure 2. Creatinine (Cr) throughout admission. Baseline Cr (—) 1.16 mg/dL. Cr increased on day 6 to 4.25 mg/dL and uremia required hemodialysis (HD) for three consecutive days. After right heart catheterization (RHC) he was dialyzed again and then albumin infusions started (25 grams for 5 doses.) By day 14 (IVIG administration) Cr was 3.09 mg/dL. Delay of IVIG was due to preauthorization by insurance.

RA (mmHg)	PCWP (mmHg)	CO (L/min)
4	6	5.79

Table 1. Right heart catheterization (RHC) data: low biventricular filling pressures and low cardiac output. Echocardiogram this admission showed LVEF 55-65% and the low cardiac output on RHC was interpreted due to low filling volumes.

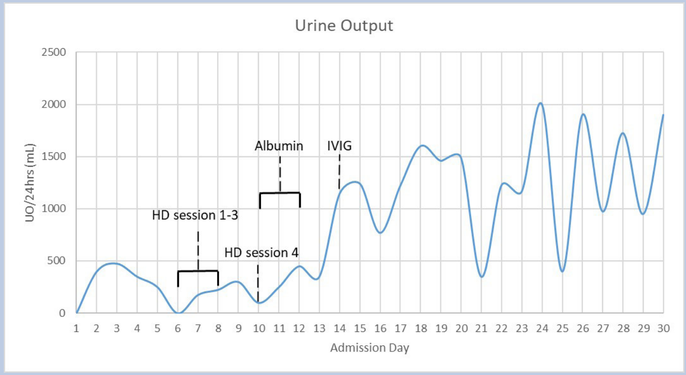

Figure 3. Urine output throughout admission. Improved upon administration of IVIG and albumin.

Discussion

ICI are known to uncommonly cause CLS.

- CLS results in end-organ injury, generally through endothelial disruption and hypoperfusion.

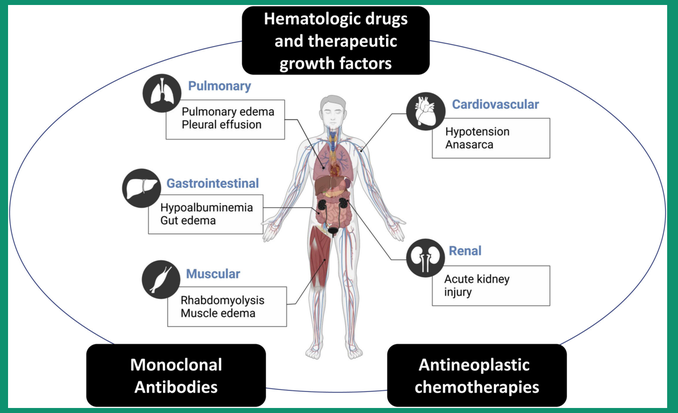

Figure 4. Izzedine H, Mathian A, Amoura Z, Ng JH, Jhaveri KD. Anticancer drug-induced capillary leak syndrome. Kidney International Reports. 2022;7(5):945-953. doi:10.1016/j.ekir.2022.02.014

ICI mediated CLS can cause a prerenal AKI that differs from most reports of ICI associated AKI (AIN, ATN, glomerulopathy)[1].

- Our case is a rare and under-recognized form of AKI in checkpoint inhibitor use.
- Prerenal azotemia arose from intravascular volume depletion leading to decreased renal perfusion.

CLS and AKI reversed with IVIG and albumin therapy.

- Reported cases of CLS have not shown improvement with steroid use.[3] Steroids were not administered in our patient.
- Albumin infusions (25 grams IV for 5 doses) were provided when the diagnosis of CLS was suspected, following the right heart catheterization.
- IV crystalloid fluid resuscitation did not restore intravascular depletion.
- IVIG may be considered as treatment in immunotherapy induced CLS as a way to minimize T cell activation.[3]
- The patient made renal recovery back to baseline and did not need long term dialysis.

References

1. Tian R, Liang J, Li R, Zhou X. Acute Kidney Injury Induced by Immune Checkpoint Inhibitors. Kidney Dis (Basel). 2022;8(3):190-201. Published 2022 Apr 4. doi:10.1159/000520798
2. Jessel S, Weiss SA, Austin M, et al. Immune Checkpoint Inhibitor-Induced Hypophysitis and Patterns of Loss of Pituitary Function. Front Oncol. 2022;12:836859. Published 2022 Mar 8. doi:10.3389/fonc.2022.836859
3. Qin H, Vlaminck B, Owoyemi I, Herrmann SM, Leung N, Markovic SN. Successful Treatment of Pembrolizumab-Induced Severe Capillary Leak Syndrome and Lymphatic Capillary Dysfunction. Mayo Clin Proc Innov Qual Outcomes. 2021;5(3):670-674. Published 2021 Jun 7. doi:10.1016/j.mayocpiqo.2021.01.004