

Acute kidney injury (AKI) post-mRNA SARS-CoV-2 vaccine in patients with cancer, treated with immune check point inhibitor (ICPi): An immune double whammy!

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Abstract

Background: Immune check point inhibitors (ICPi) have become the first line treatment for most of the cancers and have shown promising results. However, they can provoke reactions, the most feared being immune related adverse events (irAE).

Case presentation: We present a series of three cases, of patients receiving ICPi. All three patients developed AKI after administration of SARS-CoV-2 mRNA vaccine. Two patients had kidney-biopsy-proven acute interstitial nephritis (AIN) which responded to ICPi discontinuation and treatment with steroids. One had presumed AIN based on the high levels of CRP and urine retinol binding protein to creatinine ratio and responded to cessation of ICPi alone.

Conclusion: These three cases demonstrate that a strong immune response from the SARS-CoV-2 mRNA vaccine combined with an uninhibited immune system under influence of ICPi led to an amplification of autoimmunity leading to AKI presenting as AIN.

Keywords

SARS-CoV-2 mRNA vaccine, immune checkpoint inhibitor (ICPi), acute kidney injury (AKI), acute interstitial nephritis (AIN), immune related adverse events (irAE)

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Introduction

Cancer is associated with high morbidity and mortality and is the second leading cause of death in the United States. Identification of the immunobiology of cancer cells escaping the T cell cytotoxic damage has given birth to the modern era of immunotherapy in patients with cancer. In 2018 Nobel Prize in Physiology and Medicine was shared by Drs Tasuku Honjo and James Allison for their seminal discovery of programmed death molecule-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) respectively.¹ Immune check point inhibitors (ICPis) have become the first line therapy for a plethora of cancers such as metastatic melanoma, non-small lung cancer, renal cell carcinoma etc. These monoclonal antibodies block the inhibitory receptors [e.g. Programmed cell death protein 1 (PD-1), Cytotoxic

T-lymphocyte-associated antigen 4 (CTLA-4) etc.] and ligands [Program death ligand-1 (PD-L1)] expressed on the T-lymphocytes and cancer cells and unleash the brakes on the immune system.² Overall survival has improved with the advent of the immunotherapy, but at cost of immune

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related adverse events (irAEs). Virtually any organ system can potentially be affected by ICPI, including the, cardiac, endocrine, gastrointestinal tract, liver, lung, skin, ocular, musculoskeletal, and renal systems.³ The most common kidney adverse effect is acute kidney injury (AKI) with the pathological hallmark being acute interstitial nephritis (AIN).⁴ Various mechanisms for ICPI-AKI have been postulated, most plausible being reactivation of the effector T-lymphocytes previously primed by nephrotoxic drugs, increased expression of PD-L1 by the tubular cells and recruitment of a pro-inflammatory milieu with release of auto antibodies.

SARS-CoV-2 mRNA vaccine has helped mitigate the spread of COVID-19 infection however there are no reported cases in literature of precipitation of AKI in patients with cancer treated with ICPI. There are a few case reports in literature of non-renal irAE post-SARS-CoV-2 mRNA vaccine when administered to patient undergoing treatment with ICPI for example, dermatological and cytokine release syndrome.^{5,6} The plausible explanation is amplification of autoimmunity from SARS-CoV-2 mRNA vaccine under the influence of ICPI. In this case series we discuss three cases who were on treatment with ICPI and developed acute interstitial nephritis after administration of SARS-CoV-2 mRNA vaccine.

Case presentation

Patient 1

A 55 year-old man with a history of metastatic lung adenocarcinoma [(Molecular testing: PDL-1 expression 12%, tumor mutational burden (TMB): high (52 mutations/megabase)] presented with acute kidney injury (AKI). His baseline serum creatinine (SCr) was 1.1–1.3 mg/dL and had been on pembrolizumab, a PD-L1 monoclonal antibody infusion 200 mg every 3 weeks for 10 months duration since October 2020. He had no documented immune related adverse events (irAE). On the day of consult his SCr was noted to be 7.65 mg/dL. Blood work 2 weeks prior showed SCr 1.1 mg/dL. Serum creatinine peaked to 8.08 mg/dL. His SARS-CoV-2 RT-PCR was negative. Other laboratory parameters are in Table 1. Ultrasound of kidney did not show any evidence of obstructive nephropathy. He was not on any proton pump inhibitor (PPI), non-steroidal anti-inflammatory drugs (NSAIDs) and there was no new prescription medication. He had received his first dose of Pfizer SARS-CoV-2 mRNA vaccine a week prior to admission. Post-vaccination, he complained of fatigue and myalgia for 2 days which got resolved after two doses of acetaminophen. He denied any usage of NSAIDs. He was asymptomatic and experienced no change in urinary habits and reported no altered mental status. Clinical examination revealed euvolemia with normal blood pressure and an unremarkable physical exam.

An ultrasound guided kidney biopsy was performed; it, showed 21 glomeruli of which none were globally sclerotic. There was mild tubular atrophy and interstitial fibrosis involving 5%–10% of the cortex sampled. Moderate to severe interstitial infiltrate composed of mononuclear cells admixed with scattered eosinophils were noted. Mild tubulitis and focal tubules exhibiting acute tubular injury were noted. Vasculature was well preserved. Immunofluorescence (IF) was negative. Electron microscopy showed normal endothelial morphology, normal thickness of glomerular basement membrane, absence of electron dense deposits and no effacement of foot processes. The biopsy was consistent with acute interstitial nephritis (Figure 1). Pembrolizumab was discontinued and oral prednisone (1 mg/kg body weight) with a tapering dose was initiated. SCr declined sharply (Figure 2). The most recent assessment of SCr, 6 months after AKI, continued to show a stable SCr of 1.7 mg/dL. His prednisone was tapered over 7 months and then stopped. A second dose of Pfizer SARS-CoV-2 mRNA vaccine was administered approximately 6 months after the index AKI event, with no recurrence of AKI. Rechallenge of pembrolizumab was deferred and patient is now under surveillance, with no documented progression of his cancer.

Patient 2

A 68-year-old female with no significant past medical history was diagnosed to have metastatic melanoma and was initiated on ipilimumab, a CTLA-4 monoclonal antibody 200 mg IV infusion every 3 weeks. She was on the infusion for 6 months with stable baseline SCr 1.3–1.5 mg/dL. First dose of Pfizer SARS-CoV-2 mRNA vaccine was administered she complained of mild fatigue and low-grade fever for a day which subsided with one dose of acetaminophen. The 10 days after the vaccine she presented to the oncology clinic with worsening fatigue. Her SARS-CoV-2 RT-PCR was negative. Blood work revealed SCr of 3.4 mg/dL. She was not on any PPI, NSAIDs and there was no new prescription medication. Nephrology was consulted for new onset AKI. She experienced no change in urinary habits and reported no altered mental status. Clinically she was euvolemic with normal blood pressure and an unremarkable physical exam. Her pertinent laboratory tests on the day of consult are shown in the Table 1.

She underwent an ultrasound guided left kidney biopsy (Figure 1). It showed 17 glomeruli of which three were globally sclerotic. There was no significant interstitial fibrosis or tubular atrophy. Moderate lymphocytic interstitial infiltrate was noted. Acute tubular injury was evident with no significant vascular injury. Immunofluorescence (IF) was negative. Electron microscopy showed preserved endothelial, glomerular basement membrane and podocyte morphology with no electron dense deposits. The biopsy findings were consistent with AIN.

Table 1. Laboratory values on the day of nephrology consult.

	Patient 1	Patient 2	Patient 3	Normal range
Serum				
Sodium	133	138	142	135–145 mEq/L
Potassium	4.5	5.0	4.5	3.5–4.5 mEq/L
Chloride	99	100	106	96–106 mEq/L
CO ₂	21	19	21	23–30 mEq/L
Anion gap	12	13	12	3–11 mEq/L
BUN	63	40	28	6–24 mg/dL
Creatinine	7.65	3.4	2.1	0.6–1.3 mg/dL
Glucose	152	130	94	90–110 mg/dL
Calcium	9.1	9.0	9.7	8.5–10.2 mg/dL
Magnesium	2.0	1.8	1.9	1.3–2.1 mEq/L
Alkaline phosphatase	75	40	122	30–120 IU/L
AST	49	35	24	<40 U/L
ALT	30	40	20	<40 U/L
Albumin	3.9	4.0	4.5	3.5–4.5 g/dL
Protein	7.3	6.8	7.1	6.0–8.3 g/dL
Bilirubin	0.4	0.3	0.3	0.1–1.2 mg/dL
Urinalysis				
Clarity	Clear	Clear	Clear	Clear
Color	Straw	Straw	Straw	
Protein	Negative	1+	Negative	Negative
Blood	Small	None	None	None
Leukocytes	5–10	10–15	None	0–5 cells/hpf
Nitrite	Negative	Negative	Negative	Negative
RBC	2	0	0	0–1 cells/hpf
Eosinophils	Not seen	Not seen	Not seen	0 cells/hpf
Urine protein to creatinine ratio	0.09	0.2	0.1	
Urine culture	Negative	Negative	Negative	
CBC				
WBC	6.9	7.8	6.0	4.5–11 × 10 ³ /mCL
RBC	3.51	4.1	4.3	4.35–5.65 million/mCL
Hemoglobin	11.7	12.2	13.1	12–16.6 g/dL
Platelet count	237	198	123	150–450 × 10 ³ /mCL
Eosinophil count	4%	7%	7.9%	0%–6%

Ipilimumab was discontinued and oral prednisone (1 mg/kg body weight) with a tapering dose was initiated. Trends in SCr are shown in the Figure 2. She was on prednisone 5 mg once daily at 5 months; however, she was hospitalized for septic shock from pneumonia and died due to multiorgan failure. Prior to hospitalization her SCr was 1.6 mg/dL.

Patient 3

A 65 year-old female with history of bladder cancer on pembrolizumab was referred for evaluation for AKI. In December 2020, she was diagnosed with invasive bladder neoplasm. She underwent exploratory surgery with an attempt for cystectomy and potential cure. The surgery was aborted as there was an unresectable pelvic lymph node as surgery would not be curative. She was attempted to be treated with cisplatin

and gemcitabine with no response. Baseline SCr was in 0.8–1.1 mg/dL range. PD-L1 immunohistochemistry showed tumor proportion score (TPS) of 95%. She received her first two doses of Pfizer SARS-CoV-2 mRNA vaccine in February 2021 before starting immunotherapy. She did not experience any major side effects post-vaccination except mild fatigue. Pembrolizumab was started in June 2021. Her SCr remained at her baseline 0.8–1.1 mg/dL for most of her courses since 2020. In February 2022, she received the booster dose of the Pfizer SARS-CoV-2 mRNA vaccine. She denied any fatigue or fever post-booster administration. In March 2022, she was noted to have a SCr of 2.18 mg/dL (was 0.9 mg/dL 3 weeks prior). Despite adequate hydration with fluids, repeat SCr was 2.0 mg/dL. Pembrolizumab was withheld. A kidney sonogram showed mild fullness of the right renal collecting system involving the lower pole and normal left kidney (unchanged from last 2 years). There were no other changes

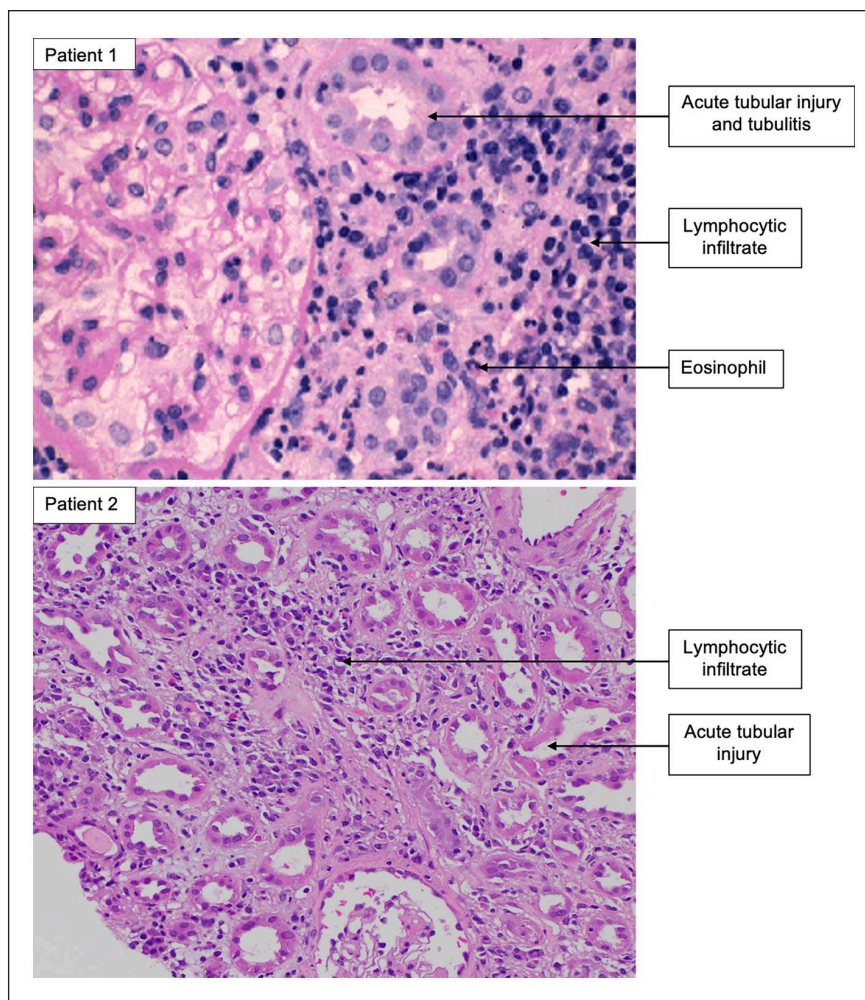


Figure 1. Kidney pathology (H&E) showing acute interstitial nephritis.

in medications or intake of proton pump inhibitors or NSAIDs. Clinically she was euvolemic with normal blood pressure and an unremarkable physical exam. Her pertinent laboratory tests on the day of consult are shown in the Table 1. Additional laboratory tests revealed a C-reactive protein (CRP) of 40mg/dL (was <3 mg/dL prior) and an elevated urine retinol binding protein to creatinine ratio at 3797 mcg/g Cr (normal range: <190). Serological tests were negative for autoimmune diseases and viral causes. A SARS-CoV-2 RT-PCR was negative. AIN was presumed given elevated creatinine and urine retinol binding protein/creatinine ratio. The SARS-CoV-2 vaccine was presumed as the trigger. A repeat PET scan showed good response to immunotherapy and resolution of disease. No steroids were administered. At 6 weeks follow up CRP was <3 and SCr 1.2mg/dl.

Discussion

Immune checkpoint inhibitor (ICPi), is a form of cancer immunotherapy that targets various inhibitors of cell-mediated immunity.² These are the monoclonal antibodies

targeting various check point proteins viz. CTLA-4 (cytotoxic T lymphocyte associated protein-4, PD-1 (programed cell death protein-1), and PD-L1 (programed cell death ligand-1).⁷ These monoclonal antibodies, by blocking the checkpoints upregulate immune activity by unleashing the brakes on the immune system thereby allowing the patient's own immune cells to attack the cancer cells.^{8,9} However, this increases risks for immune-related adverse events (irAE) in various organs for example, kidney (nephritis), GI tract (colitis), endocrine (adrenitis, hypophysitis) etc.³ Acute kidney injury from ICPI is well documented, however such injuries typically occur at a median of 16 weeks following ICPI therapy initiation.⁴ Risk factors include use of NSAIDs, lower baseline eGFR, PPI, and occurrence of extrarenal irAE. AIN is the most common pathological phenotype seen on kidney biopsy (up to 83%) and corticosteroid therapy initiated within 14 days of diagnosis was associated with higher odds of kidney function recovery.⁴ AIN is a histopathological diagnosis, but in certain instances it is not feasible or safe to do a kidney biopsy. A recently published study demonstrated that serum CRP and urinary

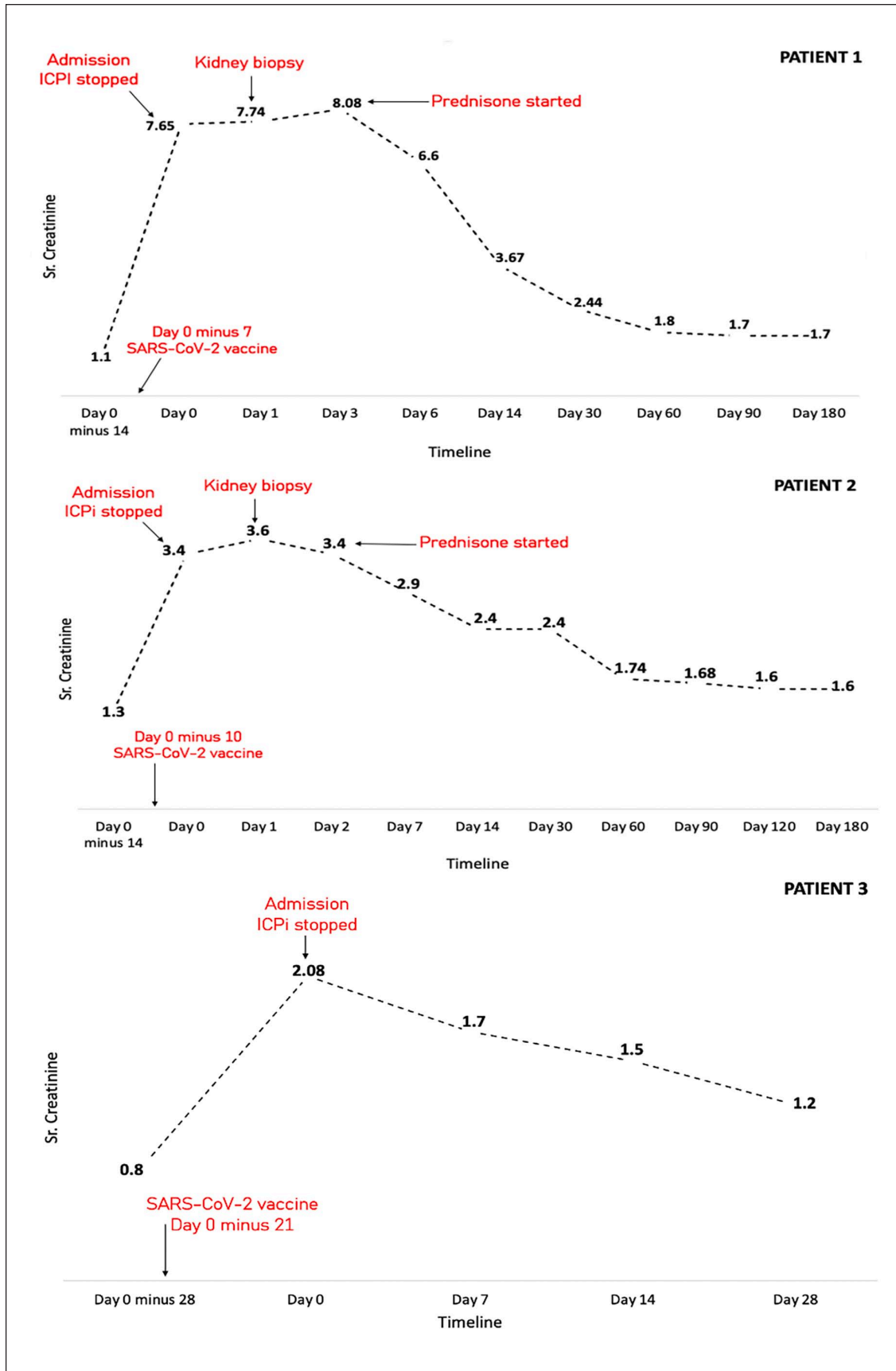


Figure 2. Trends in kidney function (SCr).

retinol binding protein to creatinine ratio (uRBP/Cr) can help differentiate AKI due to ICPI from other causes, with AIN being the predominant lesion.¹⁰ This was demonstrated in our patient no: 3. The mRNA-based vaccines have positively altered the course of the SARS-CoV-2 pandemic. Although both Moderna-mRNA and Pfizer-BioNTech mRNA vaccines have shown great efficacy and safety profile, there is still uncertainty about their side effects. Occurrence of de-novo or relapse of glomerulonephritis (GN) have been reported as complications of SARS-CoV-2 vaccination, with increased risk apparently associated with mRNA vaccines.^{11,12} A case series demonstrated occurrence of AIN in five patients who were administered SARS-CoV-2 vaccine. One of them developed AIN as early as 3 days post-vaccination. This is presumed to be due to ramped-up immune response after the SARS-CoV-2 vaccine. A study involving participants with no prior SARS-CoV-2 infection, demonstrated that first vaccine dose elicited a strong and rapid response to CD-4 T cells. Some of these cells help mount the antibody response while other stimulate the proliferation of the CD-8 T-cells. A meta-analysis demonstrated that incidence of anaphylaxis with Pfizer-BioNTech vaccine was approximately 10 times higher than that associated with all other vaccines.¹³ The development of AIN indicates a T-lymphocyte-mediated injury with an aberrant innate and consequent acquired immune response.¹⁴ A recent study tried to define the kinetics of vaccine induced CD4+ and CD8+ T cells differentiation following SARS-CoV-2-mRNA vaccine. It was noted that all SARS-CoV-2-naïve subjects mounted a robust response to CD4+ T cells following the first vaccine and the second dose further enhanced the activity of both CD4+ and CD8+ T cells.¹⁵ A Danish prospective multicenter non-inferiority trial was conducted in patients with solid organ cancer receiving chemotherapy, immunotherapy and combination. One patient in the immunotherapy arm who received SARS-CoV-2 mRNA vaccine developed Stevens-Johnson syndrome. The authors conclude that treatments which boost immune system, such as vaccination, might contribute to immune related adverse events in patients receiving immunotherapy.⁶ Another study looked at short term safety of SARS-CoV-2 mRNA vaccine in patients receiving ICPI. The investigators noted similar side effect profile as healthy controls and no irAE was observed in patients receiving immunotherapy. Importantly even in patients with previous irAE, vaccine related local side effects were mild and no irAE were observed.¹⁶ Immune related adverse event in the form of cytokine release syndrome (CRS) was reported in a patient with colorectal cancer treated with ICPI, 5 days after he received SARS-CoV-2 mRNA vaccine. The authors conclude that the temporal association of vaccination and occurrence of CRS suggests that CRS was vaccine mediated in the setting of ongoing ICPI treatment.⁵ Components in the SARS-CoV-2 vaccines, such as polyethylene glycol, are also

known to be immunogenic and can trigger hypersensitivity like reaction.¹⁷ Consequently, in our three patients given the proximity of the SARS-CoV-2 vaccination to the onset of AKI, it is plausible that the immune mediated AKI was precipitated due to ramping up of the immune system in presence of ICPI and recent vaccination.

Conclusion

To our knowledge, there is no documentation of vaccine-mediated irAE leading to AKI/AIN in patients receiving ICPI therapy. A strong immune response from the SARS-CoV-2 vaccine combined with an uninhibited immune system under influence of ICPI led to an amplification of autoimmunity. Our as well as the other cases with non-renal irAE mentioned in the discussion, express a strong message of caution and signalize a need to gain comprehensive knowledge of reciprocal interaction of immunotherapy and SARS-CoV-2 mRNA vaccine by investigating large cohorts of patients. We suggest, extra surveillance and more specific immunology-based investigations to uncover the enigma of immunological hyperresponsiveness in patients on ICPI receiving SARS-CoV-2 mRNA vaccine. This is being addressed in a prospective multicentric trial—Vaccination Against COVID in Cancer (VOICE) Trial which is enrolling patients with cancer receiving immunotherapy, chemotherapy and combinations.¹⁸ In January 2021, European Society of Medical Oncology (ESMO) launched a strategy to vaccinate all eligible cancer patients especially those on active treatment with SARS-CoV-2 mRNA vaccine with specific focus on tracking the immune responses and irAE.¹⁹ The tagline for this strategy is—Vaccinate, Monitor, and Educate. The overall rate of AIN from SARS-CoV-2 mRNA vaccine in the context of ICPI is extremely low and systematic multicenter cohort studies will be needed to understand the true incidence of this irAE.

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Author contribution

RB, KG, KDJ and PG: conceptualized the study, RB and KG drafted the manuscript, KDJ and PG reviewed and edited the manuscript.

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