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Sacituzumab-govitecan-induced severe acute tubulointerstitial nephritis requiring hemodialysis

Geneva Guarin[1*], Audrey Netzel[2], Karen Marie Flores[2], Arun Cumpelik[3] and Ron Bose[3]

Abstract

Background Sacituzumab govitecan is an antibody-drug conjugate that is FDA approved for refractory metastatic triple-negative breast cancer. It targets the human trophoblastic cell-surface antigen 2 (Trop-2) with SN-38, a topoisomerase I inhibitor, attached to the antibody [1]. SN-38 breaks DNA strands and induces tumor apoptosis [2]. Acute kidney injury (AKI) is one of its adverse effects mainly prerenal due to gastrointestinal toxicity, but it has not been reported to cause acute tubulointerstitial nephritis (ATIN).

Case Presentation This report describes a rare adverse effect of sacituzumab govitecan, the approach to diagnosing the etiology of the patient's AKI, and the mechanism by which sacituzumab govitecan causes ATIN. A woman with metastatic ER positive, PR positive, HER2 negative breast cancer who was initiated on sacituzumab govitecan presents with vomiting and diarrhea, and findings of nephrotic-range proteinuria, negative anti-PLA2R antibody, and severe AKI requiring hemodialysis. She underwent kidney biopsy and pathology showed ATIN characterized by patchy interstitial inflammation alongside tubular injury without glomerular and vascular involvement. With intermittent renal replacement therapy, furosemide challenge, and a course of prednisone, the patient's kidney function recovered.

Conclusions Sacituzumab has a high affinity for Trop-2 protein which is also expressed within the collecting ducts, and to a lesser extent, the proximal tubule. Individuals, such as this patient, who express a homozygous genotype for UGT1A1*28 allele are at increased risk for AKI from sacituzumab govitecan due to decreased glucuronidation of SN-38.

Keywords Sacituzumab, Govitecan, ATIN, AKI, Trop-2

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Background

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate (ADC) approved for unresectable locally advanced, or metastatic hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, or metastatic triple-negative breast cancer. One of its common adverse effects is diarrhea which may cause acute kidney injury (AKI), but it has not been reported to cause severe acute tubulointerstitial nephritis (ATIN).

Case presentation

A 51-year-old woman with metastatic ER positive, PR positive, HER2 negative breast cancer who previously received multiple lines of therapy, most recently sacituzumab govitecan, hypertension, diabetes mellitus, pulmonary embolism, and asthma, initially presented outpatient with three days of anorexia, non-bloody vomiting, large-volume watery diarrhea, and poor oral intake. No fever or chills. Home medications include amlodipine, apixaban, metformin, rosuvastatin, and levothyroxine. No proton pump inhibitor or non-steroidal anti-inflammatory drugs. She received IV fluids and was sent to the emergency department. Five days before the onset of symptoms, she received the second dose of first cycle of sacituzumab govitecan. In the outside hospital, she was found to have tachycardia, fever, normal blood pressure, respiratory rate, and oxygen saturation. Work-up revealed absolute neutrophil count 100, hemoglobin 10.2, platelet 112, sodium 125, potassium 4.2, serum creatinine 3.43, serum bicarbonate 17, anion gap of 19, normal lactate. Urine culture on admission was negative. She received cefepime and vancomycin, later deescalated to cefepime after blood cultures grew *Proteus mirabilis.* Vancomycin level was supratherapeutic at 30.4mcg/mL before it was discontinued. She received symptomatic treatment for nausea and diarrhea and was maintained on IV fluids. Non-contrast CT ruled out obstructive uropathy. However, her creatinine rose to 6.5 g/dL.

She was transferred to our hospital for further management. On presentation, she was confused, febrile, normotensive, and had atrial fibrillation in rapid ventricular response, requiring ICU admission. CT head showed no acute abnormality. She did not require pressors and blood pressure remained stable with IV fluids. Atrial fibrillation initially reverted to sinus rhythm with metoprolol. Cefepime was continued for neutropenic sepsis. IV sodium bicarbonate was started for severe metabolic acidosis. Despite supportive treatment, oliguric AKI continued to worsen; creatinine 7.32, and BUN 77, therefore continuous renal replacement therapy (CRRT) was started on hospital day 2. During CRRT, atrial fibrillation recurred, prompting amiodarone loading. Metabolic acidosis improved. CRRT was discontinued on hospital day 7. However, urine output remained minimal. IV furosemide and intermittent hemodialysis were started (Supplementary).

Work-up included elevated protein/creatinine ratio 4,584.2 mg/g, 24-hour urine protein 453 mg, negative anti-PLA2R antibody, negative dsDNA, ANA 1:80 titer, serum protein electrophoresis immunotyping without paraprotein, negative hepatitis panel, and negative ADAMTS13 activity. Kidney biopsy was performed on hospital day 11 (Supplementary) with result of ATIN. Prednisone 60 mg was given for two weeks with subsequent taper with famotidine as ulcer prophylaxis. Eventually, she no longer required hemodialysis. IV furosemide 80 mg daily was continued, further improving urine output. One week after discharge, serum creatinine was 1.58 and BUN 37 and three weeks later her kidney function was back to baseline normal levels. Further doses of sacituzumab-govitecan were withheld.

Discussion and conclusions

Pathology results confirmed ATIN, characterized by patchy interstitial inflammation alongside tubular injury without glomerular and vascular involvement (Figs. 1 and 2). The patient's nephrotic-range proteinuria, not fully explained by the renal pathology, was likely secondary to the timing of renal biopsy occurring after improvement of proteinuria to 453 mg/day. It may also reflect that the primary source of protein leakage originated from the renal tubules and not the glomerulus. Moreover, the degree of proteinuria, reaching 80.7 g/g, is more commonly associated with both glomerular and tubular damage that would only recover after total resolution of proteinuria and a return to baseline renal function [3]. The lack of glomerular involvement and presence of intact foot processes (Supplementary) suggest that the large degree of proteinuria may reflect the inherent inaccuracy of this equation when used in a non-steady state of renal function [4].

Regardless of this factor, the biopsy results consistently demonstrate tubular inflammation with nuclear reactive changes, tubular dilatation, and loss of the tubular epithelial cell brush border (Supplementary). Plasma cells are also found in the infiltrates indicating inflammation. Tubular damage, although not previously associated with sacituzumab govitecan use, is not an unexpected physiologic outcome. AKI was observed in up to 24% of patients with resulting loss of renal function severe enough to cause dose interruption in 6% of patients [5]. The mechanism behind renal injury and specific location of renal damage has not been previously described. It is known, however, that the Trop-2 protein, as encoded by the tumor-associated calcium signal transducer 2 (TACSTD2) gene, is expressed within the kidney. The Human Protein Atlas identified that the Trop-2 protein

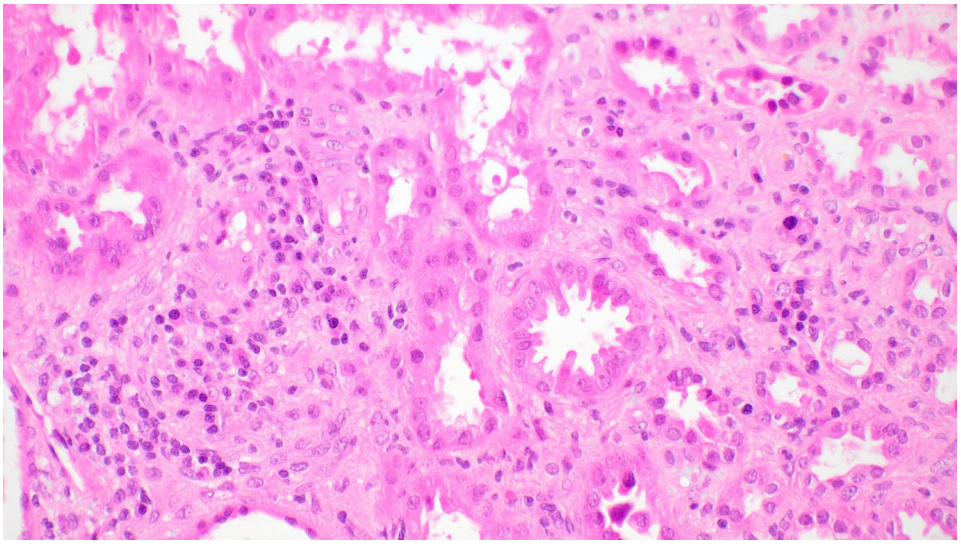

Fig. 1 H&E stain of renal parenchyma demonstrating edematous interstitial space with patchy interstitial inflammation

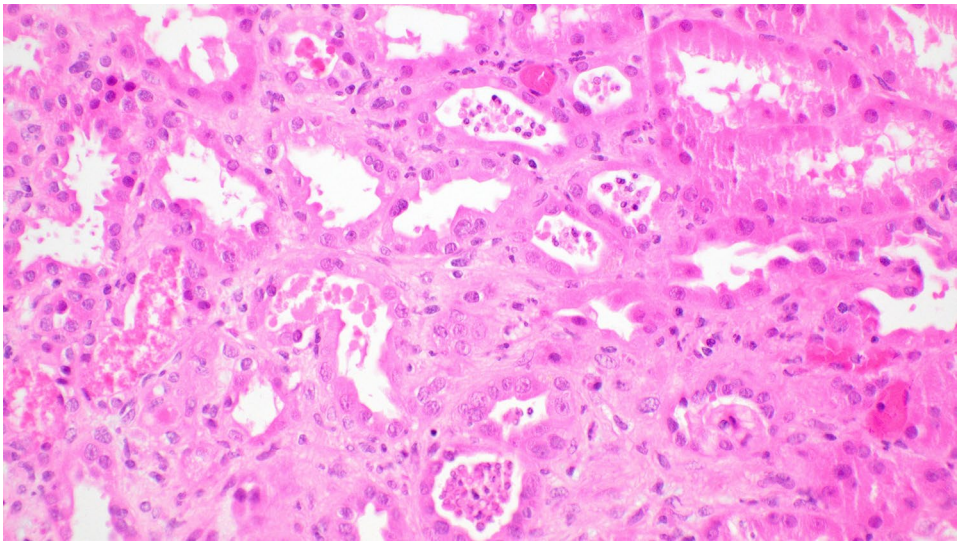

Fig. 2 H&E stain of renal parenchyma demonstrating diffuse tubular injury as evidenced by tubular dilatation, tubular epithelial cell nuclear reactive changes, and loss of the tubular epithelial cell brush border

is expressed primarily within the collecting ducts and, to a lesser extent, the proximal tubule cells within the renal parenchyma [6]. This consistency between results obtained from this patient's biopsy and those found in the Human Protein Atlas support an association between sacituzumab govitecan and ATIN.

Govitecan is an active metabolite of irinotecan, a topoisomerase 1 inhibitor. Although the metabolism and excretion of sacituzumab govitecan has not been exclusively studied, it is presumed to follow similar clearance pathways as its precursor irinotecan. Effective clearance of this topoisomerase 1 inhibitor requires UGT1A1-dependent glucuronidation followed by renal and biliary elimination of the SN-38 glucuronide [7]. The patient expresses a homozygous genotype for the UGT1A1*28 allele and thus is at increased risk of experiencing greater toxicity such as neutropenia and gastrointestinal toxicity, because of decreased glucuronidation of SN-38. Post marketing and case reports list AKI as occurring in <1% of patients who received irinotecan without a UGT1A1 mutation. In most of these patients, AKI was pre-renal secondary to diarrhea [8]. In individuals with UGT1A1*28 alleles receiving govitecan, the risk for adverse events such as AKI is increased [9].

ATIN, which differs from acute interstitial nephritis (AIN) by the former's additional involvement of renal tubules, is primarily caused by pharmacologic agents. Alternative causes include infection and autoimmune or systemic diseases. When this renal damage is drug-induced, renal function typically falls within 7 to 10

days after exposure and is typically associated with non-nephrotic range proteinuria, less than 1 g/day [7].

In evaluating this patient's ATIN, a thorough work-up ruled out autoimmune conditions. Review of medications received before and during hospitalization identified three possible pharmacologic causes of ATIN: pantoprazole, vancomycin, and sacituzumab govitecan. Pantoprazole is well-documented to cause ATIN and AIN, particularly in patients receiving multiple nephrotoxic agents [10]. Because pantoprazole is not a home medication of this patient and none was given until hospitalization at outside hospital, it is unlikely that it contributed to AKI, proteinuria, nor the tubular injury. Vancomycin, at a supratherapeutic level, is rarely associated with AIN, and is more commonly associated with acute tubular necrosis [11]. In this patient, vancomycin did reach a supratherapeutic level after the second dose. However, she experienced worsening renal function prior to administering vancomycin with documentation of worsening proteinuria before achieving supratherapeutic levels of this medication. Both pantoprazole and vancomycin were eliminated as causes of ATIN due to the timing of administration of medications as compared to the worsening renal symptoms. Sacituzumab govitecan was administered twice before hospitalization, with the second dose being given nine days prior to the development of non-nephrotic range proteinuria associated with worsening renal failure. This places her AKI within the expected 7–10 days after drug exposure, consistent with drug-induced ATIN.

Abbreviations

AKI	Acute kidney injury
AIN	Acute interstitial nephritis
ANA	Anti-nuclear antibody
ATIN	Acute tubulointerstitial nephritis
BUN	Blood urea nitrogen
CT	Computed tomography
CRRT	Continuous renal replacement therapy
DSDNA	Double-stranded deoxyribonucleic acid
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
PLA-2R	Phospholipase A2 receptor
PR	Progesterone receptor
TACSTD2	Tumor-associated calcium signal transducer 2
Trop-2	Human trophoblastic cell-surface antigen 2
UGT	UDP-glucuronosyltransferase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03828-z.

Supplementary Material 1

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Author contributions

G.G. wrote the abstract, case presentation, proofread the whole manuscript, and prepared the abbreviations list, references, figures and supplementary figures. A.N. and K.F. contributed to discussion and conclusions. A.C. contributed to case presentation. R.B. contributed to conclusions.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval

Not applicable for this case report as confirmed by our institutional IRB.

Consent for publication

The patient provided her written informed consent for their personal or clinical details to be published in this study.

Clinical trial number

Not applicable.

Competing interests

Dr. Ron Bose discloses a potential conflict of interest given he is consulting for Genentech and Puma Biotechnology, Inc. and he receives an institutional grant from Puma Biotechnology, Inc. All other authors of this article do not have financial and non-financial competing interests to disclose.

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