Title: Acute interstitial nephritis triggered by a novel anti-CD25 antibody-drug conjugate, camidanlumab tesirine

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Introduction

Interleukin-2 (IL-2) is an essential cytokine in cellular immunity responsible for stimulating T cell proliferation and the development of effector and memory T lymphocytes responses. IL-2 exerts its functional effects via interaction with the trimeric IL-2 receptor (IL-2R) complex, comprised of CD25 (IL-2Rα), CD122 (IL2-Rβ), and CD132 (IL-2Rγ).\textsuperscript{1} In addition to its immune activating effects, IL-2 has a dual role in regulating and suppressing T cell responses via regulatory T cells (T\textsubscript{Reg}), which constitutively express high levels of CD25 and are critical for the maintenance of peripheral tolerance and inflammatory control.\textsuperscript{2} Thus, T\textsubscript{Reg} cells are beneficial in preventing the development of autoimmune disease, but also limit the extent of cell-mediated immunity, including anti-tumor responses.

CD25 is aberrantly expressed in various hematological malignancies and has been exploited as a therapeutic target. Camidanlumab tesirine, also known as ADCT-301, is a novel antibody-drug conjugate (ADC) therapy composed of human anti-CD25 conjugated to a pyrrolobenzodiazepine (PBD) dimer currently under phase 2 investigation in the treatment of refractory or relapsed Hodgkin lymphoma (NCT04052997).\textsuperscript{3} Camidanlumab tesirine is directed to CD25 on tumor cells and is internalized and cleaved releasing PBD dimers, which enter the nucleus and cross-link DNA thereby preventing cell division. Camidanlumab tesirine also depletes T\textsubscript{Reg} cells given their high expression of CD25, and this is proposed to enhance effector T cell activity within the tumor microenvironment.\textsuperscript{4}

Acute interstitial nephritis (AIN) is a frequent cause of acute kidney injury (AKI), present in up to 27% of renal biopsies performed for AKI, and drug-induced (DI) AIN is the most common etiology.\textsuperscript{5} The pathogenic mechanism underlying DI-AIN is thought to be the result of immune activation against medications deposited in the kidney interstitium. An immune origin to AIN is supported by symptoms of hypersensitivity, dose-independent reactions, and recurrence after rechallenge.\textsuperscript{6}

We present a case of acute interstitial nephritis due to camidanlumab tesirine therapy in a patient with refractory Hodgkin lymphoma, presenting with the triad of systemic features including fever, generalized rash, and eosinophilia.
Case Report

A 43-year-old male presented to the emergency department with complaints of fevers and new onset rash. Past medical history was significant for refractory Hodgkin lymphoma (HL) diagnosed 3 years prior. The patient’s HL was initially treated with 6 cycles of Adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) and achieved a disease remission. Unfortunately, months later he developed a relapse treated with two cycles of rituximab, ifosfamide, carboplatin, etoposide (R-ICE) in preparation of a possible autologous stem cell transplant (ASCT). The patient’s disease continued to progress and treatment was transitioned to brentuximab and ultimately bendamustine was added. Further advancement of disease prompted four cycles of nivolumab which was also unsuccessful. ASCT was not possible due to disease progression. Experimental therapy was then pursued through a clinical trial with camidanlumab tesirine. After 3 cycles of treatment, the patient developed symptoms of tachycardia, weight loss, periorbital edema, and fatigue, and workup was consistent with thyroiditis (TSH 0.06 uIU/mL, Thyrotropin receptor antibody <1.0 IU/L). He received treatment with a short course of prednisone 60 mg orally for 5 days, methimazole, and propranolol with resolution of symptoms. Four weeks later, thyroid studied revealed evolution to a hypothyroid state post thyroiditis (TSH 145.357uIU/mL, Free T4 0.84 ng/dL). Methimazole had been discontinued at that point and levothyroxine initiated. Through this, camidanlumab tesirine was continued and the patient had received 5 cycles prior to this presentation to hospital.

The patient’s medications included: camidanlumab tesirine 30 µg/kg IV every 3 weeks for the past 4 months, dexamethasone 4 mg PO BID premedication with trial infusions, levothyroxine 50 µg PO OD, and clobetasol cream topically prn for rash. There was no history of NSAID or PPI use or any other new medications. Further history revealed that patient had developed fevers the week prior, ranging from 101.2°F to 103.5°F, which he managed with acetaminophen. During that time, the patient’s rash appeared, initially as raised erythematous papules limited to his back that then progressed to a diffuse desquamating rash involving the face, ears, trunk, back, and extremities. The patient also complained of chills, poor appetite, and dry mouth.

Physical exam was unremarkable except for skin findings. Dermatological exam revealed large areas of desquamation over the face, ears, neck, chest, back, arms, and legs, with collarettes of scale to the upper arms, neck, and abdomen with mucous membranes spared (Figure 1).

Investigations are summarized in Table 1 and were significant for AKI with an initial creatinine of 6.31 mg/dL (baseline creatinine 0.7 mg/dl, eGFR 116 mL/min/1.73m²). Complete blood count revealed anemia (hemoglobin 10.4 g/dL), leukocytosis with peripheral eosinophilia (white blood cells 16.34 K/µL, absolute eosinophils 0.67 K/µL), and thrombocytosis (platelet 355 K/µL). Inflammatory markers were elevated, including sedimentation rate at 50 mm/hr, and C-reactive protein at 107.15 mg/L. Urinalysis demonstrated hematuria with 3-5 red blood cells/hpf reported, pyuria with 6-9 WBC/hpf and myoglobinuria, although creatinine kinase was normal at 73 U/L (reference range 30-220 U/L). Urine microscopy revealed granular casts and WBC casts. Urine protein/creatinine ratio was 1.1. Infectious work up was negative. Renal ultrasound demonstrated normal sized kidneys bilaterally with preserved cortical thickness and no evidence of hydronephrosis or renal calculi.
The patient underwent a kidney biopsy given the severe AKI. Renal pathology revealed diffusely active interstitial inflammatory cell infiltration with focal increased eosinophils involving the entire renal cortex (Figure 2). Concurrent acute tubular necrosis was present. Interstitial fibrosis and tubular atrophy were mild. Evaluation of the glomeruli revealed 8/9 unremarkable, with 1 globally sclerosed glomerulus. Hyaline arterial changes were mild. Immunofluorescence analysis did not show positive staining in the glomeruli. Electron microscopy did not show electron dense immune type deposits, and there was mild to segmentally moderate podocyte foot process effacement. Immunohistochemical staining revealed numerous CD3+ T cells as well as positive PD-L1 staining in tubular epithelial cells (Figure 2). Overall the renal biopsy was consistent with a severe AIN. This result was in keeping with the patient’s presenting clinical manifestations of fever, diffuse rash, and peripheral eosinophilia.

The patient’s creatinine continued to rise and eventually peaked at 8.53 mg/dL. Despite severe AKI, the patient did not develop an indication for renal replacement therapy. Given the absence of other potential culprits for AIN on clinical history and medication review, as well as the temporal association with camidanlumab tesirine, it was felt that the anti-CD25 ADC therapy was the trigger for AIN. It had been 4 weeks since the last dose of camidanlumab tesirine was administered and further doses were suspended. Given progressive renal dysfunction despite stopping the offending agent, the patient was started on pulse steroids with methylprednisolone 500 mg IV daily for three days and then transitioned to oral prednisone at 1 mg/kg/day with a slow taper. He was discharged with improvement in creatinine at 6.8 mg/dL and 4 weeks later there was further improvement in creatinine to 1.67 mg/dL, though kidney function ultimately did not return to baseline (Table 1). The patient was removed from the clinical trial as it was felt that re-challenge with camidanlumab tesirine would likely result in another episode of AIN.
Discussion

We report a case of AIN with systemic manifestations secondary to a novel immunotherapy camidanlumab tesirine, an anti-CD25 antibody-drug conjugate. To our knowledge this is the first reported case of AIN with this therapy. Drugs are the most common etiology of interstitial nephritis, accounting for approximately 75% of cases. DI-AIN classically presents with the triad of fever, rash, and eosinophilia in the setting of a recently initiated culprit medication. While our patient presented with all three features, <10% of patients will exhibit this triad of findings. Renal injury in DI-AIN may not develop immediately following drug initiation, and in some cases can take months to appear, complicating identification of the medication culprit. Urinary finding such as WBC casts, also lack sensitivity and specificity. Given these challenges, when AIN is clinically suspected, prompt kidney biopsy should be considered to establish a diagnosis.

The initial approach to management of AIN should be to discontinue the inciting medication, if identifiable. The half-life of camidanlumab tesirine is reported to be approximately 2.7 days with systemic clearance of the drug in <7 days (manufacturer data). This patient failed initial conservative management given he presented four weeks after his last dose of camidanlumab tesirine and still developed AKI. Therefore, steroid therapy was initiated given the renal biopsy demonstrated significant activity without chronicity, and the evidence that early therapy is associated with improved outcomes in AIN. Our patient received premedication with 4 mg BID dexamethasone with each infusion of camidanlumab tesirine. While the renal injury was steroid responsive, it is likely the frequency and dose of dexamethasone given, equivalent to approximately 26.7 mg of prednisone, was not sufficient to prevent the development of AIN. He was successfully treated with high dose steroids slowly tapered over 4 months. The optimal management of AIN has not been defined, and current treatment strategies with glucocorticoids are based on retrospective analyses and the ideal dose and duration of therapy remain controversial. A randomized controlled trial of prednisolone versus supportive management in the treatment of AIN is currently ongoing (NCT04376216).

The immunologic mechanism of injury in AIN is through the activation of T cells in response to the expression, or deposition of nephritogenic antigens in the kidney tubulointerstitium. T cell activation is inherently counterbalanced by the action of TReg cells in the healthy kidney to maintain immune tolerance, and likely explains why not all individuals exposed to the same drug develop AIN. Camidanlumab tesirine acts via the targeted elimination of CD25+ cells, including TReg cells. This depletion of TReg cells results in an imbalance of immune activation versus suppression in the kidney, and in our patient likely precipitated the development AIN. Immune dysregulation triggered by camidanlumab tesirine may have also contributed to our patient’s thyroiditis and skin rash. Activated T cells in this setting were also a likely driver of the profound eosinophilia, through the production of eosinophilopoietic cytokines and growth factors. In clinical trials evaluating camidanlumab tesirine, the development of autoimmune disease, including thyroiditis and Guillain-Barre syndrome, has been reported as a major adverse event. Rises in creatinine and AKI were also reported (9/133 patients, 6.7%), but the etiology of renal injury was not identified and it is possible a proportion may have been episodes of AIN. The development of skin rash was also a common adverse event (38/133 patients, 28.6%).
Our patient had previously been treated with anti-programmed cell death protein-1 (PD-1) therapy (nivolumab). Prior exposure to an immune checkpoint inhibitor (ICI) somewhat confounds the interpretation of camidanlumab tesirine as the trigger for AIN, as ICIs are associated with immune-related adverse events (irAEs), including AIN.\textsuperscript{\text{53}} Longer latency periods leading to the development of AIN have been implicated with ICIs compared to non-ICI related AIN.\textsuperscript{\text{54}} Additionally, a single dose of nivolumab has been reported to be capable of occupying PD-1 on T cells beyond 6 months, although this begins to decline at 87 days.\textsuperscript{\text{55}} A review of the literature of nivolumab associated AIN revealed that in reported cases, AKI developed while patients were actively receiving anti-PD-1 therapy, and none were reported after drug discontinuation. The timing of onset of AKI in our patient argues in favor of camidanlumab tesirine as the etiology, as nivolumab had been discontinued for more than 6 months prior. The median time interval from last ICI dose to AKI has been reported to be 21 days (range 7-63 days) and a clinical presentation with rash and eosinophilia is rare with ICI-related AIN.\textsuperscript{\text{56}}

It has been reported that renal tubular epithelial staining for the ligand of PD-1, programmed cell death protein ligand-1 (PD-L1), is associated with anti-PD-1 immunotherapy related AIN.\textsuperscript{\text{57}} In this study, tubular epithelial PD-L1 staining was absent in patients who developed ATN while on nivolumab, and in non-PD-1 related cases of AIN. To assess the potential contribution of nivolumab to our patient’s presentation, we tested for PD-L1 in the kidney and interestingly identified positive tubular epithelial staining. A recent study has reported that renal tubular PD-L1 staining is frequently present in various forms of kidney pathology, including diabetic nephropathy, lupus nephritis, ANCA-associated glomerulonephritis, FSGS, and IgA vasculitis, and is not specific to ICI-related AIN.\textsuperscript{\text{58}} We speculate that immune injury triggered by camidanlumab tesirine may have induced the expression of PD-L1 in kidney tubular epithelial cells. From an immune homeostasis perspective, it is conceivable that the upregulation of intrarenal PD-L1 expression in response to an ongoing T cell-mediated tubulointerstitial injury could provide a renal protection mechanism against further immune injury. We cannot rule out the possibility that prior exposure to nivolumab may have reduced the threshold for irAEs with camidanlumab tesirine by priming T cells towards activation. Whether such legacy effects on T cell reactivity develop following ICI therapy is unknown. The sum effect of the sequential use of immunotherapies may have also contributed to the robust presentation in this case.

Given the important role the immune system plays in cancer surveillance, it is not surprising that novel therapies redirecting the immune response toward tumor elimination have been effective. The development of immunotherapies for cancer continues to be a rapidly expanding field. However, as more immune pathways are targeted by novel drugs, subsequent alterations in immune homeostasis are inevitable, with autoimmune injury as a potential consequence.
Table 1: Summary of laboratory results

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<tbody>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.2</td>
<td>10.4</td>
<td>9.6</td>
<td>10.1</td>
<td>9.1</td>
<td>11.3</td>
<td>13.4-16.8</td>
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<td>White Blood Cells (K/µL)</td>
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<td>16.34</td>
<td>15.59</td>
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<td>Platelets (K/µL)</td>
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<td>63</td>
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<td>Albumin (g/dL)</td>
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<td>Erythrocyte Sedimentation Rate (mm/hr)</td>
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<td>C-Reactive Protein (mg/L)</td>
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Table 2: Teaching Points

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<table>
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<tbody>
<tr>
<td>1</td>
<td>Immunotherapies incite kidney injury through disruption of renal immune homeostasis</td>
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<tr>
<td>2</td>
<td>Immune dysregulation with immunotherapy may manifest systemically with multi-organ effects</td>
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<tr>
<td>3</td>
<td>Identification and withdrawal of the offending drug should be the first line treatment of immunotherapy-associated AIN</td>
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<tr>
<td>4</td>
<td>Anti-CD25 antibody-drug conjugate camidanlumab tesirine can induce AIN</td>
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<tr>
<td>5</td>
<td>AIN secondary to camidanlumab tesirine may be steroid responsive following drug withdrawal</td>
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Figure 1: Photographs of patient’s rash to (A) chest, (B) back, and (C) legs at presentation
Figure 2: Morphologic findings in a kidney biopsy. (A) Diffuse interstitial inflammation in the renal cortex (glomerulus appears unremarkable). Hematoxylin and Eosin stain, magnification 100x. (B) Inflammation contains numerous CD3+ T cells, immunohistochemistry, magnification 100x. (C) PD-L1 staining in tubular epithelial cells, immunohistochemistry, magnification 40x.
Disclosures

The authors declare they have no disclosures to report.

Patient Consent

The authors declare that they have obtained consent from the patients discussed in the report.

Supplementary Material

Supplementary references (PDF)
Supplementary information is available at KI Report’s website
References


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