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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 lymphocyte responses. IL-2 exerts its functional effects by interaction with the trimeric IL-2 receptor complex, comprising CD25 (IL-2 receptor α), CD122 (IL-2 receptor β), and CD132 (IL-2 receptor γ).[1] In addition to its immune-activating effects, IL-2 has a dual role in regulating and suppressing T cell responses by regulatory T (T_{Reg}) cells, which constitutively express high levels of CD25 and are critical for the maintenance of peripheral tolerance and inflammatory control.[2] Thus, T_{Reg} cells are beneficial in preventing the development of autoimmune disease, but they also limit the extent of cell-mediated immunity, including antitumor 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 therapy composed of human anti-CD25 conjugated to a pyrrolobenzodiazepine dimer currently under phase 2 investigation in the treatment of refractory or relapsed Hodgkin lymphoma (NCT04052997).[3] Camidanlumab tesirine is directed to CD25 on the tumor cells and is internalized and cleaved releasing pyrrolobenzodiazepine dimers, which enter the nucleus and cross-link the DNA, thereby preventing cell division. Camidanlumab tesirine also depletes T_{Reg} cells given their high expression of CD25, and this is proposed to enhance effector T cell activity within the tumor microenvironment.[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–AIN is the most common etiology.[5] The pathogenic mechanism underlying drug-induced–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.[6]

We present a case of AIN owing 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 PRESENTATION

A 43-year-old man presented to the emergency department with complaints of fever and new-onset rash. Past medical history was significant for refractory Hodgkin lymphoma diagnosed 3 years before. The patient's Hodgkin lymphoma was initially treated with 6 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine and achieved a disease remission. Unfortunately, months after, he developed a relapse treated with 2 cycles of rituximab, ifosfamide, carboplatin, and etoposide in preparation of a possible autologous stem cell transplant. The patient's disease continued to progress, and treatment was transitioned to brentuximab, and ultimately bendamustine was added. Further advancement of the disease prompted 4 cycles of nivolumab, which was also unsuccessful. Autologous stem cell transplant was not possible owing 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 (thyroid-stimulating hormone 0.06 μIU/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. After 4 weeks, the thyroid studied was found to have evolution to a hypothyroid state post-thyroiditis (thyroid-stimulating hormone 145.357 μIU/ml, free T4 0.84 ng/dl). Methimazole had been discontinued at that point, and levothyroxine was initiated. Through this, camidanlumab tesirine was continued, and the patient had received 5 cycles before this presentation to the hospital.

The medications of the patient included the following: camidanlumab tesirine 30 μg/kg i.v. every 3 weeks for the past 4 months, dexamethasone 4 mg orally twice a day premedication with trial infusions, levothyroxine 50 μg orally once a day, and clobetasol cream topically as needed for rash. There was no history of use of nonsteroidal anti-inflammatory drug or proton pump inhibitor or any other new medications. Further history revealed that the patient had developed fever the week before, 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 and 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 examination results were unremarkable except for skin findings. Dermatologic examination results 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 1a-c).

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, estimated glomerular filtration rate 116 ml/min per 1.73 m^2). Complete blood cell count results 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/h, and C-reactive protein level at 107.15 mg/l. Urinalysis results revealed hematuria with 3 to 5 red blood cells per high power field reported, pyuria with 6 to 9 white blood cells per high power field, and myoglobinuria, although creatinine kinase level was normal at 73 U/l (reference range 30–220 U/l). Urine microscopy findings revealed granular casts and white blood cell casts. Urine protein-to-creatinine ratio was 1.1. Result of infectious workup was negative. Renal ultrasound results revealed normal-sized kidneys bilaterally with preserved cortical thickness and no evidence of hydronephrosis or renal calculi.

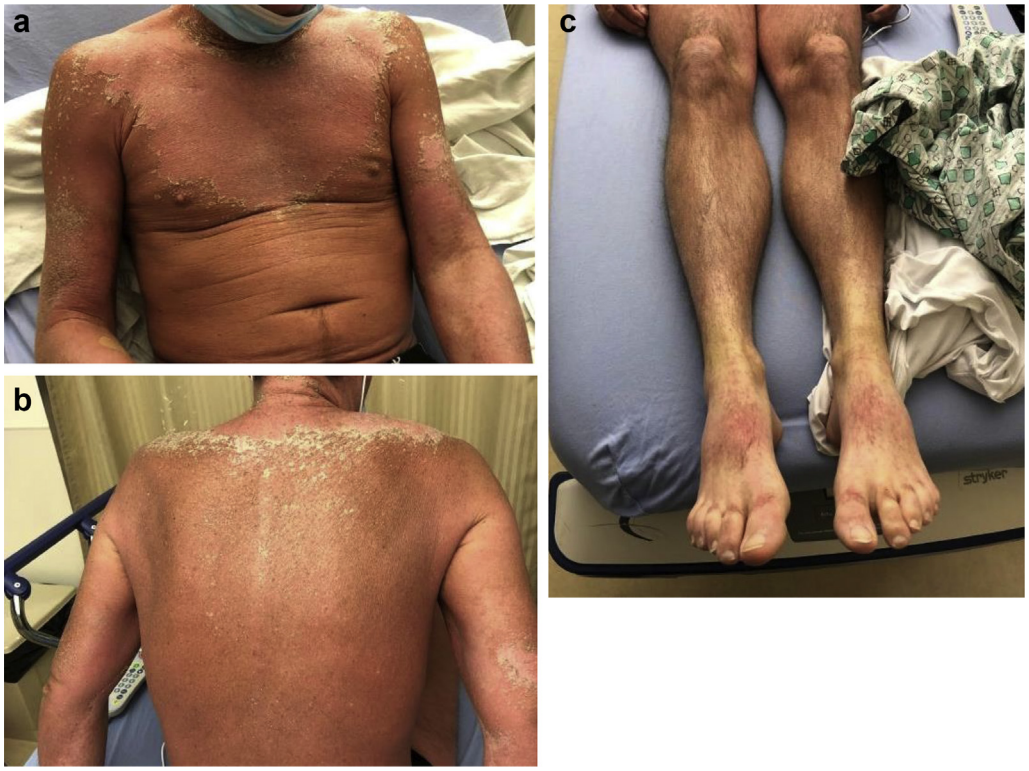

Figure 1. Photographs of the patient's rash to the (a) chest, (b) back, and (c) legs at presentation.

Table 1. Summary of laboratory results

Laboratory tests	May 7, 2020 Post fifth cycle of camidanlumab tesirine	June 29, 2020 Presentation to ED	July 2, 2020 Renal biopsy performed	July 3, 2020 Solumedrol initiated	July 5, 2020	July 30, 2020	May 11, 2021 New baseline kidney function	Reference range
Hemoglobin (g/dl)	12.2	10.4	9.6	10.1	9.1	11.3		13.4–16.8
White blood cells (K/μl)	9.64	16.34	15.59	11.76	18.18	11.13		3.73–10.10
Platelets (K/μl)	301	355	426	457	521	387		146–337
Eosinophils (K/μl)	<0.04	0.67	1.01		<0.04	0.07		0.0–0.48
Creatinine (mg/dl)	0.84	6.31	7.77	8.53	6.80	1.67	1.5	0.70–1.30
Estimated glomerular filtration rate (ml/min per 1.73 m^2)	>60	10	8	7	9	45	56	>60
Blood urea nitrogen (mg/dl)	18	50	63	75	89	30		7–22
Albumin (g/dl)	3.9	3.4				4.2		3.5–5.0
Erythrocyte sedimentation rate (mm/h)		50				31		<15
C-reactive protein (mg/l)		107.15						<10.00
Thyroid-stimulating hormone (μIU/ml)	0.029	137.418				44.876		0.550–4.780

ED, emergency department.

The patient underwent a kidney biopsy given the severe AKI. Renal pathology results revealed diffusely active interstitial inflammatory cell infiltration with focal increased eosinophils involving the entire renal cortex (Figure 2a and b). Concurrent acute tubular necrosis was present. Interstitial fibrosis and tubular atrophy were mild. Evaluation of the glomeruli revealed 8 of 9 unremarkable, with 1 globally sclerosed glomerulus. Hyaline arterial changes were mild. Immunofluorescence analysis did not reveal positive staining in the glomeruli. Electron microscopy did not reveal electron-dense immune-type deposits, and there was mild to segmentally moderate podocyte foot process effacement. Immunohistochemical staining results revealed numerous $CD3^+$ T cells and positive programmed death-ligand 1 (PD-L1) staining in tubular epithelial cells (Figure 2c). Overall, the renal biopsy result was consistent with a severe AIN. This result was in keeping with the presenting clinical manifestations of fever, diffuse rash, and peripheral eosinophilia of the patient.

The creatinine level of the patient 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

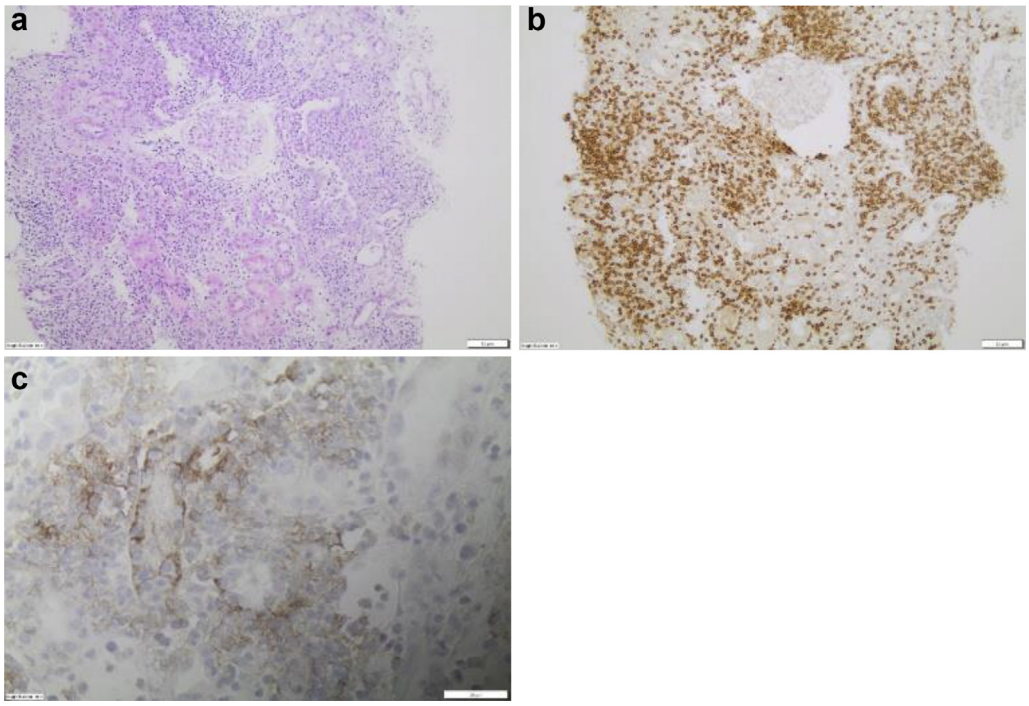

Figure 2. Morphologic findings in a kidney biopsy. (a) Diffuse interstitial inflammation in the renal cortex (glomerulus appears unremarkable). Hematoxylin and eosin stain, original magnification ×100. (b) Inflammation contains numerous $CD3^+$ T cells, immunohistochemistry, original magnification ×100. (c) PD-L1 staining in tubular epithelial cells, immunohistochemistry, original magnification ×40. PD-L1, programmed death-ligand 1.

potential culprits for AIN on clinical history and medication review, including the temporal association with camidanlumab tesirine, it was felt that the anti-CD25 antibody-drug conjugate 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 i.v. daily for 3 days and then transitioned to oral prednisone at 1 mg/kg/d with a slow taper. He was discharged with improvement in creatinine at 6.8 mg/dl, and 4 weeks after, 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 rechallenge 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 best of 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.[5] drug-induced–AIN classically presents with the triad of fever, rash, and eosinophilia in the setting of a recently initiated culprit medication. Although our patient presented with all 3 features, <10% of patients will exhibit this triad of findings.[7] Renal injury in drug-induced–AIN may not develop immediately after drug initiation, and in some cases, it can take months to appear, complicating identification of the medication culprit. Urinary finding such as white blood cell casts also lacks 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 that he presented 4 weeks after his last dose of camidanlumab tesirine and still developed AKI. Therefore, steroid therapy was initiated given the renal biopsy results revealed significant activity without chronicity, and the evidence that early therapy is associated with improved outcomes in AIN.[8] Our patient received premedication with 4 mg dexamethasone twice a day with each infusion of camidanlumab tesirine. Although the renal injury was steroid responsive, it is likely the frequency and dose of dexamethasone given, equivalent to approximately 26.7 mg of prednisone, were not sufficient to prevent the development of AIN. He was successfully treated with high-dose steroids slowly tapered in 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).[9]

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 T_{Reg} 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 through the targeted elimination of $CD25^{+}$ cells, including the T_{Reg} cells. This depletion of T_{Reg} cells results in an imbalance of immune activation versus suppression in the kidney, and in our patient, it 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.[S1] In clinical trials evaluating camidanlumab tesirine, the development of autoimmune disease, including thyroiditis and Guillain-Barré syndrome, has been reported as a major adverse event.[3] Rises in creatinine levels and AKI were also reported (9 of 133 patients, 6.7%), but the etiology of renal injury was not identified, and it is possible that a proportion may have been episodes of AIN. The development of skin rash was also a common adverse event (38 of 133 patients, 28.6%).[S2]

Our patient had previously been treated with anti–programmed cell death protein-1 (PD-1) therapy (nivolumab). Previous 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, including AIN.[S3] Longer latency periods leading to the development of AIN have been implicated with ICIs compared with non–ICI-related AIN.[S4] In addition, 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.[S5] A review of the literature of nivolumab-

Table 2. Teaching points

	Teaching points
1.	Immunotherapies incite kidney injury through disruption of renal immune homeostasis.
2.	Immune dysregulation with immunotherapy may manifest systemically with multiorgan effects.
3.	Identification and withdrawal of the offending drug should be the first-line treatment of immunotherapy-associated AIN.
4.	Anti-CD25 antibody-drug conjugate camidanlumab tesirine can induce AIN.
5.	AIN secondary to camidanlumab tesirine may be steroid responsive after drug withdrawal.

AIN, acute interstitial nephritis.

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 >6 months before. The median time interval from the 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.[S6]

It has been reported that renal tubular epithelial staining for the ligand of PD-1, PD-L1, is associated with anti–PD-1 immunotherapy-related AIN.[S7] 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 evaluate the potential contribution of nivolumab to the presentation of our patient, 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, anti–neutrophil cytoplasmic autoantibody-associated glomerulonephritis, focal segmental glomerular sclerosis, and IgA vasculitis, and is not specific to ICI-related AIN.[S8] 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 up-regulation 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 previous exposure to nivolumab may have reduced the threshold for immune-related adverse events with camidanlumab tesirine by priming T cells toward activation. Whether such legacy effects on T cell reactivity develop after ICI therapy is unknown. The sum effect of the sequential use of immunotherapies may have also contributed to the robust presentation in this case.

CONCLUSION

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. Nevertheless, as more immune pathways are targeted by novel drugs, subsequent alterations in immune homeostasis are inevitable, with autoimmune injury as a potential consequence (Table 2).

DISCLOSURE

All the authors declared no competing interests.

PATIENT CONSENT

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

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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