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Differentiating Acute Interstitial Nephritis From Immune Checkpoint Inhibitors From Other Causes

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have significantly improved outcomes for patients with neoplasms in advanced stages.[1] On the other hand, ICIs have immune-related adverse events. These adverse events affect mostly other organs than the kidney, such as skin or gastrointestinal tract.[2] The incidence of nephrotoxicity with monotherapy with any ICI is about 2%, which increases to 5% in combination therapy.[S1] Acute tubulointerstitial nephritis (AIN) is the most common pattern of kidney damage related to ICIs.[3] Globally, without considering ICI nephrotoxicity, AIN is estimated to account for 15% to 20% of cases of acute kidney injury (AKI).[4,S1–S6] This is crucial because patients who are treated with ICIs, may also be taking other drugs that potentially cause AIN, and therefore, knowing the particularities about ICI-related AIN could be helpful in clinical practice to better understand the phenotypic differences between the 2 types of AIN. In addition, several studies have now shown that being on proton pump inhibitors is a risk factor for AIN from ICI therapy.[S1–S4,S6]

We aimed to determine whether the kidney histopathologic findings with special staining help differentiate ICI-related AIN from non-ICI related AIN. We also review the management and results of AKI in this context, focusing on the characteristics of corticosteroid therapy used.

RESULTS

Clinical Features

The main clinical data at presentation of patients with ICI-related and non-ICI-related AIN are summarized in Table 1. The clinical presentation consisted of AKI in all 23 patients. AKI occurred on previous chronic renal disease in 2 patients of the ICI group and presented with severe proteinuria (8.8 g per 24 hours) in 1 non-ICI related case.

The median time between the start of ICI treatment and the presentation with AKI was 14.6 months (interquartile range: 3.1–54.2). The interval between non-ICI related AIN diagnosis by kidney biopsy and the start of the culprit drug was 87 days (interquartile range: 23–694 days). Among the 12 patients with non-ICI related AIN, 3 had previously been exposed to penicillins, 4 to sulfonamides, 3 to allopurinol, 1 to nonsteroidal anti-inflammatory drugs, and 1 to omeprazole. No patient in the ICI group referred prior exposure to proton pump inhibitors.

Histologic Findings

The histologic diagnosis was AIN in 8 and 10 of the ICI-related and non-ICI related AKI cases, respectively,

Table 1. Main clinical and biological characteristics according to the etiology of the AIN

Clinical findings	ICI-related (n = 11)	Non-ICI related (n = 12)	P-value
Age	70 (60–74)	56 (53–60)	0.25
Drugs involved (no. of cases) [a]More than 1 drug per patient is possible Sex, female/male	NIV (4), PEM (2), DOS (1), CEM (1), NIR (2), IPI (2), DUR (1), ATE (2), TRE (1) 6 (55%)/5 (45%)	NSAIDs (2), PPI (3), ALL (1), CIP (2), LEV (1), CEF (4), AMP-B (1) 6 (50%)/6 (50%)	
Comorbidities			
Diabetes mellitus	9 (81%)	9 (81%)	1.0
Hypertension	6 (55%)	2 (18%)	0.07
Serum creatinine	3.2 (2.3–4.2)	3.6 (3.2–4.2)	0.22
Hyperkalemia	3 (27%)	None	0.06
Hypokalemia	1 (9%)	None	0.3
Acidosis	6 (54%)	2 (18%)	0.07
Proteinuria, mg/24 h	333 (240–498)	267 (203–797)	0.87
Normal range	2	5	
Proteinuria range (200–1000 mg/24 h)	6	15	
Proteinuria range (>1000 mg/24 h)	2	3	
Microhematuria	3 (27%)	5 (45%)	0.37
Pyuria	9 (82%)	6 (55%)	0.17

AIN, acute tubulointerstitial nephritis; ALL, allopurinol; AMP-B, amphotericin-B; ATE, atezolizumab (anti-PD-L1); CEF, ceftriaxone; CEM, cemiplimab (anti-PD1); CIP, ciprofloxacin; DOS, dostarlimab (anti-PD1); DUR, durvalumab (anti-PD-L1); ICI, ICI, immune checkpoint inhibitors; IPI, ipilimumab (anti-CTLA4); LEV, levofloxacin; NIR, niraparib (PARP inhibitor); NIV, nivolumab (anti-PD1); NSAIDs, nonsteroidal anti-inflammatory drugs; PEM, pembrolizumab (anti-PD1); PPI, proton pump inhibitor; TRE, tremelimumab (anti-CTLA-4).

with chronic-active tubulointerstitial nephritis in the remaining cases. The main histopathological findings in both groups are summarized in Table 2. The percentage of cortical tissue affected was significatively larger in the ICI-related cases. Positive staining for the PD1 molecule and its ligand, PD-L1, was observed in 10 of the 11 ICI-related cases but only in 1 of the non-ICI related ($P < 0.001$). PD1 was expressed on interstitial inflammatory cells, whereas PD-L1 was presented mainly in isolated tubular cells. The characteristic findings described in tubulointerstitial nephritis associated with ICI are shown in Supplementary Figure S1.

Treatment, Evolution, and Outcome

All 23 patients discontinued the drug associated with AIN and started on corticosteroids at diagnosis, with an initial intravenous bolus in the 11 ICI-related cases and 10 of the non-ICI related. Only 1 patient in the ICI group received additional immunosuppressive therapy with MMF. Dialysis was necessary for 1 patient in each group. Corticosteroids were started within the first week after the histologic diagnosis in 10 of the 11 patients with ICI-related AIN, and 9 of the 12 patients with non-ICI related AIN who were started on this therapy. Treatment duration was 74 (55−102) days in the whole cohort; there were no differences among ICI-related and non-ICI related groups.

The serum creatinine levels at fixed landmarks during follow-up are shown in Supplementary Figure S2. Despite variability, there was a decreased trend to normal levels after the first month of follow-up. There was no statistically significant difference between both groups at any follow-up landmark. Nine patients with non-ICI related AKI and all 11 with ICI-related recovered renal function after a median time of 3 months (Supplementary Figure S3), without any significant difference between both groups.

Table 2. Histologic findings in ICI-related and non-ICI related AIN

Finding	ICI-related n = 11	Non-ICI related n = 12	P-value
Cortical tissue affected (%)	50 (50–60)	25 (20–25)	< 0.001
Interstitial inflammatory cells other than lymphocytes			
Eosinophils	7 (64%)	6 (50%)	0.41
Plasma cells	5 (45%)	3 (25%)	0.40
Histiocytes	5 (45%)	3 (25)	0.40
Tubulitis moderate and severe	7 (64%)	3 (25)	0.09
IFTA <25%	8 (72%)	10 (83%)	0.64
IHC			
PD1	10 (91%)	1 (9%)	< 0.001
PDL1PD-L1	10 (91%)	1 (9%)	< 0.001

AIN, acute tubulointerstitial nephritis; ICI, immune checkpoint inhibitors; IFTA, interstitial fibrosis and tubular atrophy; IHC, immunohistochemistry

DISCUSSION

There are various major findings in this study. First, ICI-related AIN has some differential morphologic and phenotypical aspects compared with non-ICI related AIN. The percentage of cortical tissue affected was larger in the ICI-related cases. Positive staining for the PD1 molecule and its ligand, PD-L1, was also observed in 10 of the 11 ICI-related cases; howevere, only in one of the non-ICI related. These findings agree with the previous publication by Cassol *et al.*[5] that described that immunohistochemistry with anti PD-L1 antibodies

might help in the differential diagnosis in this clinical setting. They contrast with the experience published by Hakroush *et al.*,[6] who described a distinct PD-L1 expression in renal compartments in multiple murine models of kidney injury and in some human cases with various underlying kidney diseases. PD-L1 was frequently expressed in various renal pathologies independent of ICI therapy and the authors argued that it could potentially be a prerequisite for susceptibility to develop AKI and deleterious immune-related AIN. Unfortunately, the study lacks the clinical and histologic description of the patients included.

Being able to confirm histologically that an AIN is or is not related to ICI treatment is relevant for several reasons. First, because the use of multiple drugs in cancer patients is very common and these 2 types of AIN have a different mechanism of injury and therefore the therapeutic approach should not be necessarily the same. In classic drug-induced AIN, there is an antigen that activates the immune response through a delayed hypersensitivity immune reaction.[3] Therefore, given the relevance of the antigen in the process, the importance of permanently withdrawing medication when AIN occurs is understandable. Secondly, in ICI-related AIN, it is not clear why some patients have serious immune-related adverse events and others do not; but considering the multifactorial mechanism of injury, it could be feasible and safe to treat a patient with ICI again after presenting this type of adverse event, if the oncological disease requires it, and the complication has been detected and treated on time.[2]

The short time interval between clinical suspicion and biopsy and the low rate of chronicity found in the specimens confirm that the diagnosis of AIN related to ICI and AIN not related to ICI was made early in this cohort. This fact allowed early initiation of steroid treatment and as we will explain later, it had a positive impact on renal prognosis. It has been suggested that delayed onset of corticosteroid treatment might be a reason to explain the lack of efficacy of corticosteroids in some patients with drug-induced AIN. A previous study[7] suggested that early administration of corticosteroids was associated with a greater recovery of baseline kidney function, whereas a delay in treatment longer than 3 weeks significantly decreased the likelihood of complete kidney function recovery. Our study corroborates these findings.

Furthermore, because most cases of ICI-related AIN in this cohort were resolved within weeks or months of starting steroid therapy, in our experience it would be feasible and safe to resume immune checkpoint blockade after the adverse event has been resolved. However, data on long-term kidney prognosis, including patients with more severe form are lacking.

In conclusion, our results suggest that there is a specific histologic profile that segregates AIN related to ICI and AIN not related to ICI in real world practice. Immunohistochemistry with anti-PD-L1 antibodies is necessary to make this differential diagnosis. We also suggest the importance of early kidney biopsy to establish the time of evolution and the potential response to steroid treatment in this clinical setting. These results contribute to the stratification of patients into more consistent disease groups for therapeutic, epidemiologic, and basic research. Prospective studies are warranted to confirm these findings.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Results.

Supplementary Conclusions.

Supplementary References.

Figure S1. Tubulointerstitial nephritis associated with ICICPI was characterized by focal to diffuse interstitial lymphocytic infiltrate associated with tubulitis and edema

(A, Periodic acid–Schiff stain, 200×). Immunohistochemistry demonstrated PDL-1 expression on tubular epithelial cells (B, 400×) and few PD1+ lymphoid cells (C, 400×). PDL-1 was also expressed on interstitial inflammatory cells (D, 400×).

Figure S2. Levels of serum creatinine after AKI in patients with ICI-related and nonrelated AIN. Boxes represent the median and interquartile range.

Figure S3. Time to full recovery of renal function according to the etiology of the AIN.

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