

LETTER

Immune checkpoint inhibitors as
potential triggers for ANCA vasculitisFaten Aqeel , Jose Monroy-Trujillo, Duvuru Geetha

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Immune checkpoint inhibitors (ICIs) have made a tremendous impact on the survival of patients with certain cancers. ICIs work by interrupting co-inhibitory signalling pathways resulting in the elimination of cancer cells using the body's immune system. However, these therapies do not come without side effects. Immune-related adverse events have been implicated due to the over-activation of the immune system. Experimental and genetic studies have investigated the role of programmed cell death protein 1 (PD-1), programmed cell death protein-ligand 1 and cytotoxic T lymphocyte-associated antigen 4 in the pathogenesis of medium and large vessel vasculitis. A systemic review by Daxini *et al* summarised 20 cases of confirmed vasculitis associated with ICIs. The majority of the cases were of medium and large vessel vasculitis except for two cases of small vasculitis with skin and digit involvement.¹ Little is known about the relationship between ICIs and renal-limited pauci-immune glomerulonephritis secondary to anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV). A systemic review summarised 12 cases, with only 2 cases having positive ANCA serologies (1 with anti-myeloperoxidase (anti-MPO) and the other 1 with unknown ANCA type). Median time to glomerular disease was 73 days (IQR: 53–102 days). The reported ICIs were nivolumab (n=5), pembrolizumab (n=3), ipilimumab plus nivolumab (n=2), tremelimumab (n=1) and ipilimumab (n=1).² A case of de novo granulomatosis with polyangiitis (GPA) with lung and renal involvement and rapid rise in anti-proteinase-3 (anti-PR3) titres has also been reported.³ In addition, two case reports of systemic AAV without renal involvement have been described, with one case presenting as de novo anti-PR3 AAV and the other case presenting as relapsed GPA of unknown ANCA type.^{4,5} In GPA, it has been shown that PD-1 expression on T helper cells is increased using flow cytometry, CD3 and PD-1 staining. In addition, the

expression of PD-1 on CD4(+) and CD25(+) T cells has been shown to correlate negatively with relapse rates.⁶ We report a case of de novo MPO ANCA positive AAV and a case of relapsing PR3 ANCA positive AAV following treatment with IC

The demographics and clinical data were retrieved after a review of the electronic health record. The type of cancer, ICI treatment, onset of vasculitis, ANCA type and treatment are summarised in [table 1](#). Patient 1 was diagnosed with squamous cell carcinoma of the left palatine tonsil. After receiving 7 doses of intravenous 200 mg pembrolizumab every 3 weeks over 5 months, he developed acute kidney injury (AKI) with serum creatinine (sCr) of 7.20 mg/dL, haematuria, proteinuria and foot drop. MPO ANCA was positive at a titre of 98.5 units (normal value: <20.0 units). A kidney biopsy showed pauci-immune necrotising and crescentic glomerulonephritis. He received 1000 mg rituximab every 2 weeks for a total of 2 doses and reduced dose of glucocorticosteroid regimen per the Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis (PEXIVAS) trial.⁷ Remission was achieved with improvement in sCr to 1.8 mg/dL in 6 months after treatment initiation. ICI was permanently stopped. Given no other curable options, his underlying malignancy rapidly progressed and resulted in his demise. Our patient 2 is a female with a history of relapsing PR3 ANCA positive AAV with renal and pulmonary involvement in remission, who experienced a relapse of AAV after 1 dose of 200 mg pembrolizumab to treat squamous cell cancer of the lung. Her relapse was diagnosed clinically based on new onset of AKI with a peak sCr of 2.5 mg/dL compared with her baseline of 1.8 mg/dL, haematuria, proteinuria and a 4-fold increase in PR3 ANCA titre. Remission was achieved with weekly rituximab for a total of four doses and glucocorticoids. By 4 months, she was off glucocorticosteroids. Rituximab was continued every 6 months



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Table 1 Patient characteristics, type of cancer, ICI treatment, onset of vasculitis, ANCA type and treatment

ID	Age (year)	Sex	Race	Type of cancer	ICI	Existing AAV before ICI	ANCA type	Timing of AAV after initiation of ICI (months)	Presenting findings	Treatment	Nadir sCr (mg/dL)	AAV status at last follow-up
1	65	M	C	Squamous cell carcinoma of left palatine tonsil	Pembrolizumab	N	MPO	5	AKI (sCr: 7.20 mg/dL) haematuria, proteinuria and foot drop	RTX+GC	1.5	Remission
2	67	F	C	Squamous cell cancer of the lung	Pembrolizumab	Y	PR3	1	AKI (sCr: 2.5 mg/dL), haematuria and proteinuria	RTX+GC	1.8 (baseline sCr)	Remission

AAV, ANCA associated vasculitis; AKI, acute kidney injury; ANCA, anti-neutrophil cytoplasmic antibody; C, Caucasian; GC, glucocorticosteroids; ICI, Immune checkpoint inhibitor; MPO, myeloperoxidase; N, no; PR3, proteinase-3; RTX, rituximab; sCr, serum creatinine; Y, yes.

for maintenance. ICI was stopped. At the time of last follow-up, 4 months after her AKI, her sCr was 1.8 mg/dL. AAV was in remission, but her cancer had progressed warranting use of chemotherapy. Patient 1 received *Pneumocystis jirovecii* pneumonia prophylaxis and gastrointestinal prophylaxis with pantoprazole. Patient 2 did not receive any prophylaxis.

Our data suggest that ICIs, specifically PD-1 inhibitors, could cause de novo AAV or trigger a relapse of AAV. Close monitoring of disease relapse is critical in patients with AAV undergoing ICI therapy. Further studies are needed to truly evaluate the interplay between PD-1 inhibition and AAV, which will improve our understanding of the pathogenesis of this condition.

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