The Era of Immunotherapy: Nivolumab-Induced Adrenalitis And Encephalitis Presenting As Psychosis

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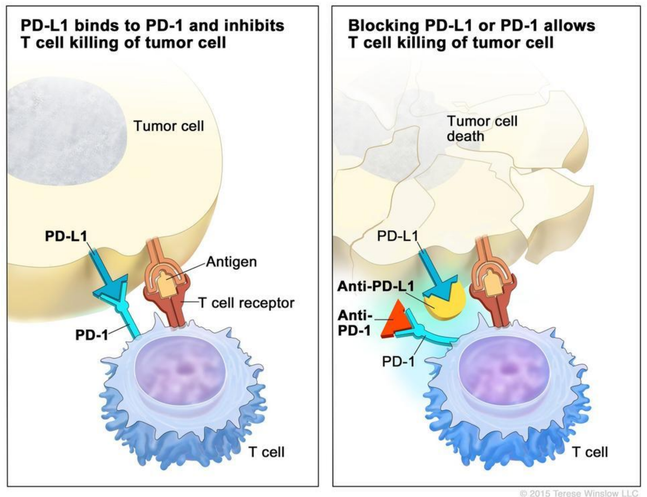
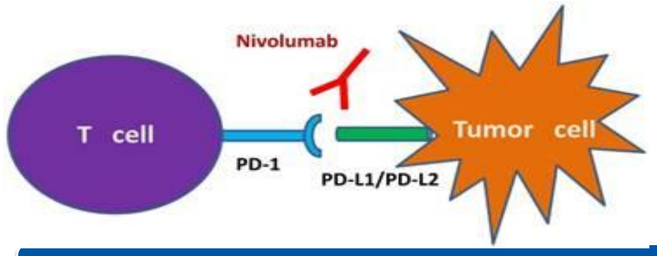
Introduction

Great progress has been made in the treatment of metastatic renal cell carcinoma with the addition of immune checkpoint inhibitor (ICI), Nivolumab. Nivolumab is a monoclonal antibody that specifically targets the programmed cell death-1 (PD-1) receptors on immune cells. It prevents the PD-1 mediated transmission of inhibitory signals that would normally weaken T cell activity, thereby restoring antitumor activity. Use of ICIs, whose mechanisms and manifestations are quite different from other oncological agents, elicit new and unexpected side effects called immune-related Adverse Events (irAEs). As the use of novel immunotherapy for the management of cancer accelerates, it is critical for clinicians to be aware of the toxicities associated with these agents. This case is unique in that it highlights two serious, sequential adverse events from checkpoint inhibition in a single patient.





Case Report

A 66-year-old man with stage 4 renal cell carcinoma status post left sided nephrectomy on nivolumab for the past 3 weeks, deep vein thrombosis, and hypothyroidism presented to the emergency department with a 5 week history of nausea, anorexia, confusion, and personality changes. He had no prior psychiatric history. Physical examination was significant for moderate dehydration, disorientation to time and place, and paranoid ideations. Upon workup in the emergency department, the patient was found to have undetectable morning cortisol. He was admitted to the Family Medicine Inpatient Service for treatment of adrenal insufficiency and was started on physiological replacement doses of corticosteroids. MRI of the brain was unremarkable. The patient's psychosis continued to worsen with paranoid delusions, hallucinations, and delirium. High dose olanzapine and haloperidol mitigated his symptoms but did not resolve them. Psychiatry was consulted after ruling out other causes, and a presumptive diagnosis of ICI autoimmune encephalitis was made. The patient's mentation gradually improved with steroids, and by discharge his only remaining psychiatric symptom was pleasant confabulation. At discharge, he continued a physiologic dose of hydrocortisone 20 mg in the morning and 10 mg in the evening. He has not developed any further irAEs or recurrence of the psychosis.

Discussion

This is the first report of monotherapy with Nivolumab inducing sequential acute adrenal insufficiency and autoimmune encephalitis. With an irAE incidence of 15%, checkpoint inhibitor-induced cortisol deficiency may go undiagnosed in patients presenting acutely to an emergency department. This case highlights the importance of considering urgent cortisol measurement on any acutely ill patient on a checkpoint inhibitor with new onset non-specific symptoms on presentation. Random serum cortisol should be drawn preferably with a paired plasma ACTH followed by immediate glucocorticoid replacement therapy without waiting for results as this is a medical emergency. Confirmation of cortisol deficiency and detailed investigation of the etiology can be completed electively once the patient is stabilized.

Direct causality of the encephalitis being due to ICI is a clinical diagnosis. The rapid progression of neurological symptoms with recent Nivolumab therapy, neurological improvement after immunosuppressive therapy, and comorbid adrenal insufficiency is not expected in other types of autoimmune encephalitis. This case report raises several important clinical issues. There is considerable variation in the presentation of ICI induced autoimmune encephalitis that can obscure its diagnosis. If a patient is suspected of having autoimmune encephalitis after receiving an immune checkpoint inhibitor, steroid therapy should be initiated immediately to prevent significant mortality. Treatment can be escalated with IVIG and plasmapheresis if no clinical improvement from steroids.

Patients on ICIs can be provided with educational materials that they can share with primary care providers who may not be familiar with these new agents. IrAEs exhibit variable patterns, and precipitating factors have not been identified. Clinical vigilance is paramount for diagnosis. With the increasing prevalence of ICI usage, it is vital for primary care providers to be aware of the features and diagnostic criteria for irAEs. As demonstrated in this case, early recognition and treatment is essential to optimize clinical outcomes and minimize the effect of irAEs.

Conclusion

Much remains to be understood about the mechanism and risk factors predisposing to irAEs. As the use of checkpoint inhibitors expands, it is inevitable that the number of patients with irAEs will increase. Primary care providers need to be aware of irAEs associated with checkpoint inhibitors. Due to potential for life threatening adverse events, the effectiveness of early recognition and treatment of irAEs is vital, while preserving the ability to continue oncologic treatment.

Adverse event	Any grade, *n* (%)	Grades I–II, *n* (%)	Grades III–IV, *n* (%)
Any adverse event	60 (71.4)	53 (63.1)	35 (41.7)
Any immune-related event	47 (56.0)	39 (46.4)	25 (29.8)
Immune-related adverse event			
Dermatologic/skin			
Pruritus	8 (9.5)	8 (9.5)	0 (0)
Rash	20 (23.8)	13 (15.5)	7 (8.3)
Gastrointestinal			
Diarrhoea	24 (28.5)	20 (23.8)	4 (4.8)
Colitis	6 (7.2)	1 (1.2)	5 (6.0)
Endocrine			
Hypothyroidism	2 (2.4)	2 (2.4)	0 (0)
Hypopituitarism	6 (7.1)	1 (1.2)	5 (6.0)
Hypophysitis	1 (1.2)	0 (0)	1 (1.2)
Adrenal insufficiency	1 (1.2)	0 (0)	1 (1.2)
Abnormal hepatic function	1 (1.2)	0 (0)	1 (1.2)
Musculoskeletal			
Arthritis	8 (9.6)	5 (6.0)	3 (3.6)
Other[a]	20 (23.8)	11 (13.0)	9 (10.7)

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