Severe Nausea and Hyperemesis Secondary to Immune-Checkpoint Inhibitor Induced Adrenal Insufficiency and Hypothyroidism

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INTRODUCTION

Cancer remains a major public health problem worldwide and is the second leading cause of death in the United States. It has plagued loved ones and friends and continues to impact individuals significantly.

Understanding the complexity of cancer has made great progress over the years, with cancer therapy and treatment continuing to make great strides.

In recent years, it has been discovered that the body's innate immune system could be utilized to fight neoplastic cells. This therapy, known as immune checkpoint inhibitors (ICI), are increasingly utilized in the treatment of various types of advanced cancers, such as renal cell carcinoma (RCC), lung cancer and melanoma.

While the mechanism of action in using the body's own immune system to stop cancer have been positive, there has been documented cases of autoimmune side effects called immune-related adverse events (irAE).

We present a case of adrenal insufficiency and hypothyroidism in a patient on ICI with persistent nausea and vomiting.

CASE PRESENTATION

HPI: 61-year-old male with metastatic clear cell RCC status post right nephrectomy currently on Nivolumab and Ipilimumab presented to the emergency department with a 2-month history of generalized weakness and persistent nausea and vomiting.

Vitals, Physical Exam: BP=88/66 mmHg, HR=102, PE unremarkable.

Lab Studies: CBC, CMP WNL. (-) Thyroid and adrenal antibodies, **TSH=21.3mcIU/mL, AM cortisol <0.5mcg/mL.** No serologic evidence of pituitary dysfunction.

Imaging: CT abdomen showed no clear etiology to explain symptoms.

Procedures: Esophagogastroduodenoscopy (EGD) to evaluate for gastric outlet obstruction, metastasis, or GI irAE were negative.

Assessment: Hypothyroidism and adrenal insufficiency.

Treatment: Hydrocortisone 20mg qAM + 10mg after lunch and levothyroxine 125 mgm.

Follow-up: Patient gradually improved, discharged with complete resolution of symptoms, and no readmissions.

Conclusions: Patient developed hypothyroidism and adrenal insufficiency caused by ICI with Nivolumab and Ipilimumab.

Figure 1: irAEs with ICI therapy [6]

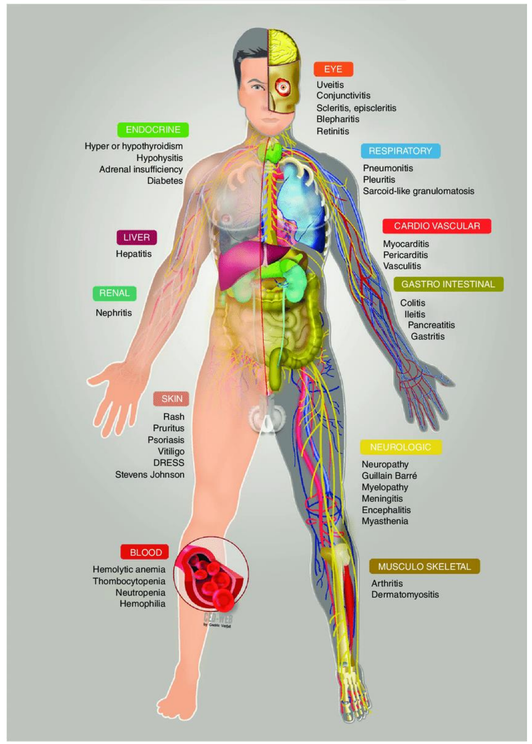

Figure 2: How CTLA-4 and PD-1 inhibitors target neoplastic cells [2]

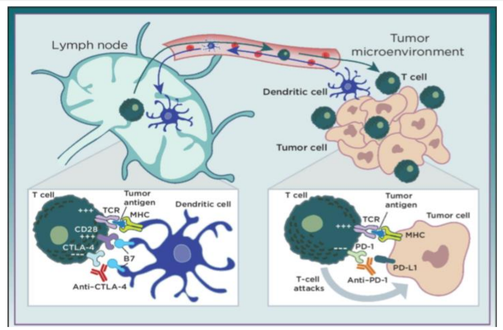

Figure 3: Frequency of endocrine irAEs associated with ICI [3]

Monoclonal antibodies	Endocrinopathies				
	Hypophysitis (%)	Hypothyroidism (%)	Hyperthyroidism (%)	Primary adrenal insufficiency (%)	Type 1 DM (%)
Anti-CTLA-4					
Ipilimumab[a]	1.5–17	1.5–6.8	4	0.8–1.6	NR
Tremelimumab[b]	0.4–2	2.3	0–3	1	NR
Anti-PD-1					
Nivolumab[c]	0.6–1.5	9–10.8	2.7	1	0.9
Pembrolizumab[d]	0.6–1	7–9.1	3.4–7.8	NR	0.2
Anti-PD-L1					
Avelumab[e]	NR	5	0.4	0.5	0.1
Atezolizumab[f]	0.2	2.5–4.2	0.6–1.1	0.4	0.2–0.3
Durvalumab[g]	<0.1	5.5–9.6	4.9–5.7	0.5–0.9	0.1
Combined therapy					
Nivolumab + ipilimumab[h]	4–12.8	4–27	4.3–14	4–8*	NR
Pembrolizumab + ipilimumab[i]	9.1	6–13.6	4.5–6	6*	NR
Durvalumab + tremelimumab[j]	NR	5.9	NR	NR	NR

Discussion

- Programmed cell death-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) are essential proteins that are primarily involved in suppressing the immune reaction to self-antigens, resulting into immunologic tolerance.
- Neoplastic cells can use the same protein activity to evade the body's immune response.
- Nivolumab and Ipilimumab selectively inhibit (PD-1) and (CTLA-4) respectively and lead to an increase in baseline T-cell specific immune response against tumor cells.
- This process can also result in autoimmune responses to various systems in the body. irAE are graded based on their severity from 1 to 4 (1 as mild, 2 as moderate and 3-4 as severe). Having severe irAE necessitate stopping ICI therapy.
- Examples of irAE include dermatologic, gastrointestinal, endocrine, hepatic, pulmonary and renal systems involvement. Of these, the most serious ones can include adrenal crisis, hypophysitis, colitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, among others.
- Consider obtaining baseline values of TSH, fT4, baseline bowel habits, full initial dermatologic exam, 8AM cortisol and ACTH for patients newly started on ICI therapy.
- With the increased utility of ICI for treatment of various malignancies, it is of the upmost importance to recognize irAEs to avoid unnecessary delay and avoid unnecessary procedures.
- Late recognition of irAEs, such as in our case, can result in recurrent admissions and prolong agony in a patient who is already suffering from advanced malignancy.

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