# A case of fatigue and confusion in an elderly man with metastatic melanoma

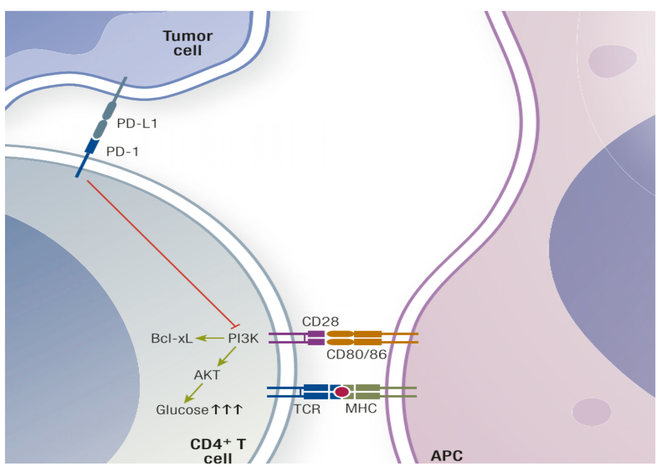
Aleksandra Abrahamowicz, MD
Department of Internal Medicine , University of Washington, Seattle, WA.

## Learning Objectives

1) Recognize checkpoint inhibitor therapy as an important tool in current cancer treatment modalities.
2) Understand the toxicities associated with anti-programmed death-1 (PD1) therapy
3) Emphasize the importance of diagnostic diligence when the initial workup is unrevealing and initial therapies do not provide symptomatic relief

## Background

- Checkpoint inhibitors are powerful therapeutic agents in cancer treatment and work primarily by strengthening the body's T-cell response.[1] One such category of checkpoint inhibitors, such as pembrolizumab and nivolumab, target the glycoprotein PD1 on T cells and thereby prevents binding with programmed death ligand on tumor cells, an interaction that typically results in T cell apoptosis. [1]
- These therapies can be associated with immune-related adverse events including adrenal insufficiency, hypothyroidism, and hypophysitis.[2]




Chang L-S, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. *Endocr Rev*. 2019;40(1):17-65. doi:10.1210/er.2018-00006

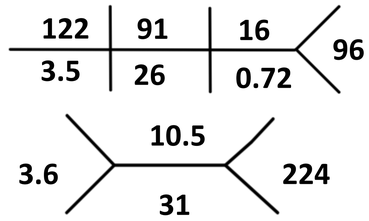
## Clinical Case

### Presentation

**An 89-year-old man with past medical history of metastatic melanoma and aortic stenosis who presented to the Emergency Department (ED) with progressive confusion and fatigue.**

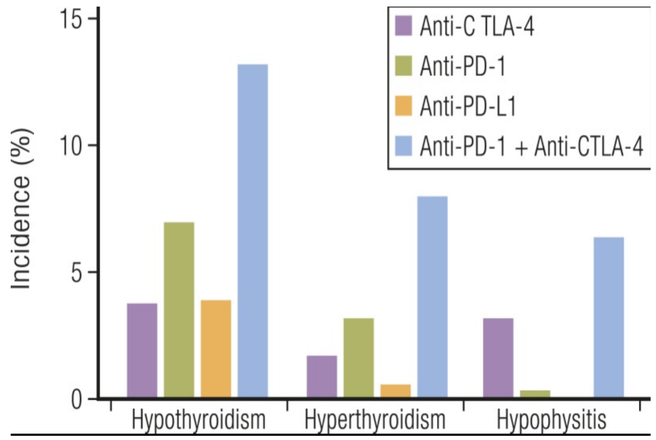
- His medical history was notable for metastatic melanoma, diagnosed five years prior to presentation, with metastases to the liver, lung, and bones as well as aortic stenosis and hypertension
- The melanoma was most recently treated with pembrolizumab followed by nivolumab but both of these medications were discontinued due to severe pruritus. His last dose of nivolumab was four months prior to presentation.
- On presentation, he had mild encephalopathy but the remainder of his exam was unremarkable. He was hemodynamically stable, and initial laboratory data was unremarkable except for a sodium of 122 mEq/L.
- Computed tomography of the chest, head, and cervical spine, did not reveal any acute abnormality.
- Initial daily laboratory data showed sodium values between 122-126 mEq/L despite volume resuscitation with lactated ringers.
- The patient's home medication doxepin was discontinued due to concern for syndrome of inappropriate antidiuretic hormone secretion, and he was started on sodium chloride tablets.
- Extensive laboratory and diagnostic workup was pursued.
- The patient's morning cortisol level was 1.0 mcg/dL. A cosyntropin stimulation test was ordered which showed inadequate response of the patient's cortisol at both 30 and 60 minutes. ACTH was low at 6.1.
- He was diagnosed with secondary adrenal insufficiency and started on hydrocortisone. By the next day, the patient noticed a dramatic improvement in his cognitive function and energy, and he was discharged to home shortly thereafter.

### Admission Labs




**Lactate 1.6**
**Ca: 8.5**

## Checkpoint inhibitor therapy-associated toxicities

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## Discussion

- In this clinical case, the patient presented with confusion and hyponatremia to 122, and was diagnosed with secondary adrenal insufficiency. This diagnosis should be considered in patients who present with hypotension, electrolyte abnormalities and dehydration.[1]
- Immune -elated adverse events are a known side effect of checkpoint inhibitor therapy and are usually irreversible.[3]
- The incidence of immune-related adverse events typically occurs on the order of months, with some studies reporting a median time to onset of about 20 weeks. [2,4]
- This case highlights the challenges of the diagnostic workup in a medically complex patient presenting with non-specific complaints and underscores the necessity for diagnostic diligence when the initial workup is unrevealing.

## References

1. Chang L-S, Barroso-Sousa R, Tolaney SM, Hodi FS, Kaiser UB, Min L. Endocrine Toxicity of Cancer Immunotherapy Targeting Immune Checkpoints. *Endocr Rev*. 2019;40(1):17-65. doi:10.1210/er.2018-00006
2. Ariyasu R, Horiike A, Yoshizawa T, et al. Adrenal Insufficiency Related to Anti-Programmed Death-1 Therapy. *Anticancer Res*. 2017;37(8):4229-4232.
3. Ferrari SM, Fallahi P, Elia G, et al. Autoimmune Endocrine Dysfunctions Associated with Cancer Immunotherapies. *Int J Mol Sci*. 2019;20(10):2560. doi:10.3390/ijms20102560
4. Kassi E, Angelousi A, Asonitis N, et al. Endocrine-related adverse events associated with immune-checkpoint inhibitors in patients with melanoma. *Cancer Med*. 2019;8(15):6585-6594. doi:10.1002/cam4.2533