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Adrenal insufficiency due to immunotherapy: A case report and review

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Abstract

Immunotherapy is an exciting and revolutionary targeted therapy for many different types of cancers. It was first used successfully in treating melanoma patients, but now its therapy has improved the survivals of other cancers including lung and colon cancers. The therapy involved using immune checkpoint inhibitors which are molecules that increase the endogenous immune response against tumors. Unfortunately, these inhibitor molecules have also been associated with emergence of a new subset of autoimmune-like toxicities, known as immune- related adverse events. Although the skin and colon are commonly involved, any organ can be affected. Most of these toxicities are diagnosed by excluding other secondary infectious or inflammatory causes. In this case report, we are presenting a patient who underwent immunotherapy treatment for colon cancer for 10 months prior to hospitalization. Two weeks after completion of his 10th monthly cycle of immunotherapy, he was hospitalized for possible septic shock which was mildly responsive to fluid resuscitation. His condition remained critical and unstable for 5 days after initiation of broad- spectrum IV antibiotics and pressor management, with GI symptoms and hypotension and leukocytosis and fevers and generalized weakness. Morning cortisol and ACTH stimulation testing finally confirmed adrenal insufficiency one week into the hospitalization. Infectious work up returned negative. Patient was started on stress doses of steroids which immediately corrected his blood pressures and GI symptoms and fevers within 48 hours. At time of discharge after almost 2 weeks of hospitalization, his infectious evaluation was essentially negative. This case highlights the rare adverse autoimmune adrenalitis associated with immunotherapy.

Keywords

Immunotherapy; immune-related adverse events; adrenal insufficiency; cortisol; adrenocorticotrophic hormone; shock; pembrolizumab.

Abbreviations

ACTH: Adrenocorticotrophic hormone; GI: Gastrointestinal; IV: Intravenous; COPD: Chronic obstructive pulmonary disease; PCR: Polymerase chain reaction; COVID-19: SARS-Coronavirus.

Introduction

Adrenal insufficiency is a rare side effect of immunotherapy in cancer patients. It is rarely reported due to its low incidence. Physicians need to be aware of this uncommon immune-related adverse event due to increasing use of this modality for treating cancers. Patients with this adverse event can present with nonspecific symptoms of fatigue and weight loss and anorexia, symptoms often attributed to cancer itself. However, it can also present in shock, and catastrophic consequences can occur if the diagnosis was not made in a timely manner. Our case described a 70 year- old man with stage III colon cancer who developed adrenal insufficiency as result of pembrolizumab treatment. We review the current medical literature regarding this uncommon side effect to alert the physicians of this unique adverse event.

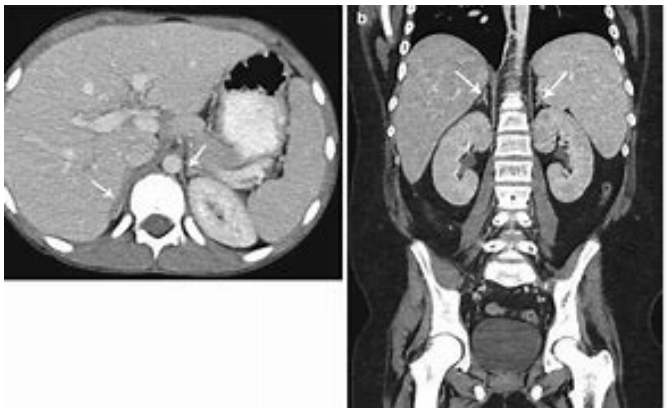
Case Presentation

The patient is a 70 year- old man with COPD and hypertension and recent diagnosis of colon cancer. He was started on pembrolizumab chemotherapy for colon cancer in December 2019 for stage III colon cancer. He tolerated at least 10 cycles of this chemotherapy with generalized fatigue. His cancer was responding to the treatment. His last dose prior to hospitalization was early October 2020. Two weeks prior to his hospitalization, patient started having generalized weakness and body aches and nausea and diarrhea. He was eventually seen at our hospital ER with low BP 75/60 and tachycardia. He had temperatures of 102 with leukocytosis of 14K. He had elevated lactate levels. He was admitted to intensive care unit for possible bacterial septic shock. Blood and urine and respiratory cultures were obtained. He was aggressively fluid resuscitated and broad -spectrum IV antibiotics with Vancomycin and Cefepime were given. Respiratory nasal PCR testing was done. Despite 3 to 4 liters of fluids in the initial 12 hours, his blood pressures remained tenuous and he was started on IV pressor management. His cardiac echo done during second hospital day showed moderate amount of pericardial effusion but could not exclude cardiac tamponade. Urgent pericardiocentesis was done with drainage of serosanguinous 30 cc of pericardial fluid. He was evaluated by cardiothoracic surgery who deemed that pericardial window was not needed.

After 48 hours of IV pressor management, patient was weaned off IV therapy and started on oral midodrine low dose of 5 mg TID which was able to sustain his systolic pressure around 85-90. All his blood pressure medications had been held since admission. Fluid resuscitation continued for a total of at least 12 liters over 3 days. His nasal swab was negative for COVID-19, but positive for enterovirus. The patient developed right pleural effusion likely due to expansion fluid therapy. Diagnostic thoracentesis revealed transudative effusion with eventual negative pleural fluid culture. Screening morning cortisol returned on day 3 with low level of 2.4 mcg/dL. ACTH stimulation test was then performed on the same day. By hospital day 6, patient continued to have anorexia and poor appetite and tenuous systolic pressures of 85-90 despite oral midodrine therapy and IV fluids. Results from ACTH stimulation returned on the same day

with low cortisol response of 3.7 mcg/dL and elevated ACTH serum level of 78 pg/mL. Patient was immediately started on IV hydrocortisone 100 mg with 50 mg IV every 6 hours. Since all blood cultures and urine cultures and stool cultures were negative, IV antibiotics were stopped. Interestingly, patient's blood pressures responded very quickly to 130/80 after 24 hours of stress steroid therapy. Midodrine and fluids were discontinued. Patient's blood pressures continue to rise to above 140/90. His GI symptoms and fevers and diarrhea and fatigue all spontaneously improved within 48 hours of initiation of steroid therapy. Abdomen CT scanning done during first week of hospitalization showed no adrenal enlargement or adrenal metastasis or hemorrhage. His adrenal antibodies, 21-hydroxylase antibodies, returned positive 1 week after discharge from the hospital. His serum aldosterone level was also low. By hospital day 9, patient was weaned off stress doses of IV steroid therapy and started on maintenance dose of 5 mg prednisone and 0.1 mg of fludrocortisone. He was monitored on this maintenance dose of steroids with stable BP of 120/70 for 48 hours. He was successfully discharged from the hospital after 10 days of hospitalization.

Abd CT images: normal adrenal glands appearance:



Laboratory findings:

Nasopharynx specimen PCR testing:

COVID	not detected	(Ref: not detected)
Influenza A	not detected	(Ref: not detected)
Influenza B	not detected	(Ref: not detected)
Parainfluenza 1-4	not detected	(Ref: not detected)
Adenovirus DNA	not detected	(Ref: not detected)
RSV	not detected	(Ref: not detected)
Rhinovirus/Enterovirus	detected	(Ref: not detected)

Chemistry Labs

Admission labs drawn		
Sodium	126 mmol/L	(Ref: 136-144)
Potassium	5.1 mmol/L	(Ref: 3.5-5.0)
BUN	17 mg/dl	(Ref: 8-20)
Creatinine	1.95 mg/dl	(Ref: 0.6-1.27)

Hospital Day 2 lab drawn		
Screening AM Cortisol	2.4 mcg/dl	(Ref: 4 – 22)
Hospital Day 3 ACTH stimulation test performed		
ACTH stimulation test:		
Pre-ACTH cortisol	3.2 mcg/dl	(Ref: 4 – 22)
Post-ACTH cortisol	4.3 mcg/dl	(Ref: response > 18)
ACTH	78 pg/ml	(Ref: 6 – 50)
Hospital Day 5 labs drawn		
Aldosterone	2 ng/dl	(Ref: 3 -16 supine)
Plasma Renin	7.6 ng/ml	(Ref: 0.25 – 5.82)
Hospital Day 8 labs drawn		
21 – Hydroxylase Antibody	Positive	(Ref: negative)
(antibody results returned after discharge)		
Laboratory results at discharge		
Sodium	138 mmol/L	(Ref: 136-144)
Potassium	4.2 mmol/L	(Ref: 3.5- 5.0)
BUN	16 mg/dl	(Ref: 8- 20)
Creatinine	1.3 mg/dl	(Ref: 0.6- 1.27)

Discussion

Over the past several years, immunotherapy using immune checkpoint inhibitors have emerged as a powerful tool in the fight against cancer. These monoclonal antibodies block immune check points and strengthen the immune system by unleashing T-cells to fight cancer. As they increase the endogenous immune response toward tumors, they can also trigger autoimmune adverse effects, known as immune-related adverse events [3]. These adverse side effects can affect numerous organs in the body involving the skin, colon, liver, lungs, and endocrine organs. Less commonly, the kidneys and the heart and the nervous system may also be affected [1]. While dermatologic side effects are most common with prevalence ranging from 40-60%, endocrinopathies are uncommon with prevalence ranging from 1-6% based on review of literature [3]. These endocrine side effects include hypophysitis, thyroid dysfunction, insulin-deficient diabetes mellitus, and primary adrenal insufficiency. Because of the increasing use of immunotherapy in oncology and the potentially life-threatening nature of the endocrinopathies if not promptly recognized and treated, it is vital and important for physicians to be aware of the clinical manifestations, diagnosis, and management of these endocrine side effects [2].

The most serious endocrine immune- related adverse event is primary adrenal insufficiency with prevalence less than 1%. It can present as acute adrenal crisis and become catastrophic if missed. The adrenal insufficiency seen could be central due to hypophysitis with low to normal ACTH. These patients can also develop pan-hypopituitarism. Less commonly, the adrenal insufficiency seen could be primary due to autoimmune inflammation and destruction of adrenal glands [2]. Our patient here clearly has primary

adrenal insufficiency with elevated ACTH and suboptimal response to ACTH stimulation test. The primary adrenal insufficiency was also confirmed by his low serum aldosterone level and high renin levels from impairment of zona glomerulosa of the adrenal cortex. Abdomen CT scan was done to assess for radiologic signs of adrenalitis or inflammation and enlargement. Even though the adrenal glands were normal on CT imaging, the radiologic imaging did exclude secondary causes of adrenal insufficiency in cancer patients like adrenal metastasis or adrenal hemorrhage.

The patient's primary adrenal insufficiency explained why his blood pressure was still borderline low around systolic 80-90 despite 12-13 L of normal saline infusion over 3 to 4 days. When the laboratory values finally confirmed adrenal insufficiency a week later, the patient's immediate response within 24-48 hours to stress does of IV hydrocortisone 50 mg q6 also strengthened the diagnosis. His hypotension and fatigue and GI symptoms of anorexia and diarrhea and nausea all improved dramatically as the result of the therapy.

Primary adrenal insufficiency is a rare complication of immunotherapy. Only a few case reports have been published. In one review by Byun et al, two cases of primary adrenal insufficiency were reported among 256 patients (0.8%) treated with immunotherapy agent ipilimumab [2]. The incidence of primary adrenal insufficiency is difficult to estimate in part because many clinical trials involving immunotherapy report adrenal insufficiency as an adverse event but do not specify whether the insufficiency is primary or central in etiology. Thus, the pathogenesis is not well understood. Elevated levels of 21-hydroxylase antibodies were seen in several of these patients, but their roles in pathogenesis remains unclear. Certain reports mention adrenalitis on CT with enlargement of adrenal glands with smooth borders. Transient increased FDG uptake in the adrenal glands consistent with adrenalitis on PET scan has been reported [4]. The definitive nature of the adrenal insufficiency in these clinical cases is compatible with adrenal destruction by an autoimmune mechanism induced by immunotherapy.

Diagnosis requires high clinical suspicion as there are no clinical signs specific for immunotherapy related adrenal insufficiency. Both acute and progressive subacute presentation have been reported. Many of the subacute symptoms are similar to side effects of the toxic anticancer treatment. Median time to onset is highly variable, ranging from 2 to 5 months from the initiation of therapy. A few cases have also been reported after termination of pembrolizumab [4]. In acute presentations, clinical signs may appear within days and often triggered by a concurrent infection. Signs and symptoms of immunotherapy- related primary adrenal insufficiency are similar to those of non-iatrogenic central adrenal insufficiency. Patients may show asthenia, fatigability, anorexia, nausea or vomiting, diarrhea, abdominal pains, orthostatic hypotension, tachycardia, and confusion. Frank shock can ensue in acute cases. Hyponatremia and hyperkalemia have been described due to the presence of both glucocorticoid and mineralocorticoid deficiency [6].

In patients with these symptoms suggestive of adrenal insufficiency, morning cortisol and ACTH should be obtained prior to administration of corticosteroids for diagnostic purposes. However, in acutely ill patients with typical clinical symptoms and signs, empiric treatment with steroids should not be delayed. ACTH stimulation test should also be done for confirmation of adrenal insufficiency. Measurement of

plasma renin and aldosterone can be helpful to determine if mineralocorticoid deficiency is also present. These tests may need to be interpreted appropriately in the setting of IV fluids, which can influence the levels of renin and aldosterone. Anti-21-hydroxylase antibodies should be assayed. A non-emergency adrenal CT scan should be taken to exclude other etiologies like cancer metastasis, infection, hemorrhagic necrosis, or granulomatosis. [4]. In cases of acute adrenal insufficiency, 100mg intravenous hydrocortisone should be given followed by continuous infusion of 50mg q6. This dose can be tapered once patient clinically and hemodynamically improved. As immunotherapy related primary adrenal insufficiency is often permanent, these patients will require long term treatment similar to therapy for Addison's disease. Replacement hormones will include daily hydrocortisone of 20-30 mg in divided doses and fludrocortisone of at least 0.1 mg daily. Immunotherapy may be postponed but should never be definitively contraindicated [5]. As this condition is rare, data are insufficient to recommend systemic routine cortisol level before or during immunotherapy. Blood tests for anti-21-hydroxylase antibodies before immunotherapy are not indicated due to the rarity of this condition. There is no need for screening for adrenal insufficiency before or during immunotherapy [3].

Conclusion

The acute presentation of patient's primary adrenal insufficiency was triggered by his concurrent enterovirus viral infection (not COVID). Within one week, he developed symptoms of fatigue and anorexia and diarrhea and hypotension due to volume depletion. These symptoms were non-specific and were initially attributed to his viral syndrome. In retrospect, they were all symptoms of adrenal crisis. Despite aggressive fluid resuscitation, his symptoms did not improve until stress dose of steroids were initiated. His BP normalized up to 130/90 within 48 hours. He was eventually discharged with maintenance steroid therapy. Interestingly, he was re-admitted one month later for hypotension and fatigue and nausea and vomiting again because he forgot to take his maintenance dose of steroids since going home as he was living by himself. He was discharged to assisted living facility after the second hospitalization to make sure that he will be compliant with his maintenance dose steroid therapy. Endocrinology consult during the second hospitalization also confirmed that he will need to be on long term maintenance steroid therapy for his primary adrenal insufficiency caused by immunotherapy.

Furthermore, this case is also interesting in that adrenal insufficiency symptoms occurred about 10 months after initiation of pembrolizumab, much longer than the median onset time of 2-6 months for these side effects [1].

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