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Case report

Combination checkpoint inhibitor therapy induces multiple immune major related adverse events in the treatment of vaginal melanoma: A cautionary case report

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ABSTRACT

Background: Immune checkpoint inhibitors (ICI) eliminate cancer cells through release of inhibition of cytotoxic CD8+ lymphocytes. Potent systemic activation of immune cells provides unprecedented efficacy in some types of advanced cancer therapy, but also often induces serious immune related adverse events (irAEs) that can be devastating if not promptly identified and properly managed. Herein, we describe the case of multiple major irAEs manifesting after administration of combination ICI therapy in a patient with vaginal melanoma.

Case:

A 54-year-old, G2P0 woman with recurrent metastatic vaginal melanoma, following three doses of combination nivolumab-ipilimumab immunotherapy, presented for admission at our tertiary care center for the work-up of sudden-onset of colitis of unknown etiology. Prior to admission at our facility, the patient was diagnosed with a severe maculopapular rash, headaches and hyponatremia in the weeks immediately following initiation of therapy. During work up of the colitis, infectious etiologies were ruled out, and the patient was discharged on a steroid taper for treatment of presumed immune-related colitis. Consideration of salt-supplement resistant hyponatremia with new onset frontal headache in the setting of immune-related colitis indicated possible hypophysitis. With high suspicion for multiple high grade irAEs, ICI was discontinued, and the patient was given high dose intravenous steroids prior to discharge with a prednisone dose taper for outpatient management. After control of irAEs was achieved, ipilimumab therapy was subsequently discontinued to minimize the chance of recurrent irAEs, yet nivolumab monotherapy was resumed in an attempt to control disease progression that could occur in with iatrogenic immunosuppression.

Conclusion: ICIs have demonstrated the ability to induce improved long-term survival in metastatic cutaneous or mucosal melanomas, including those of gynecologic origin. As ICI therapy becomes more widespread, healthcare providers across all fields of medicine need be vigilant to recognize the symptoms of irAEs that can often masquerade as common illnesses to prevent potentially dangerous irreversible immune toxicities.

1. Introduction

The development of immunotherapeutic agents that utilize immune cells to recognize and destroy malignant cells has markedly expanded the frontiers of cancer therapy in the past decade (Rusch et al., 2018). One class of these agents, Immune Checkpoint Inhibitors (ICIs), target tumor antigens via monoclonal antibody-mediated activation of T cells. ICIs have demonstrated durable responses and increased long-term survival in advanced malignancies such as metastatic melanoma (Rusch et al., 2018; Simsek et al., 2018) However, ICIs are also associated with immune-related adverse events (irAEs) caused by the systemic activation of cytotoxic lymphocytes aberrantly targeting healthy tissues (Harris et al., 2016).

We report the case of a patient with metastatic vaginal melanoma with three consecutive high-grade irAEs and discuss the importance of prompt identification and management to prevent serious immunotherapy-related sequelae. The patient gave written informed consent to publish the following case.

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Table 1
Timeline of irAEs for six months after initiation of combination ICI therapy for vaginal melanoma after initiation demonstrating severe and varied diagnoses.

Date	Event	Trigger	Toxicity Grade*	Initial Diagnosis	Associated irAE	Work-Up/ Treatment	Response to Treatment
December 5, 2018	ipi/nivo #1** - ipi: 450 mg;250 mL NS - nivo:140 mg;50 mL NS	Rash	Grade III	ir Rash	ir Rash	Topical Cream/PO Hydroxyzine	Complete
December 26, 2018	ipi/nivo #2 - ipi: 450 mg;250 mL NS - nivo:140 mg;50 mL NS	Headache	Grade II	Complicated Migraine	ir Hypophysitis	Fioricet	Moderate
January 16, 2019	ipi/nivo #3 - ipi: 450 mg;250 mL NS - nivo:140 mg;50 mL NS	Hyponatremia	Grade II	Isolated Hyponatremia 2/ 2 Dehydration	ir Hypophysitis	1 L NS; Salt Tabs	Minimal
January 16, 2019	ipi/nivo #3 - ipi: 450 mg;250 mL NS - nivo:140 mg;50 mL NS	Persistent Hyponatremia/Possible Hypophysitis	Grade II	ir Abnormality	ir Hypophysitis	Laboratory Values; Steroid Taper	Moderate
February 6, 2019	Hospital Admission	Colitis #1	Grade II	ir Colitis	ir Colitis	Steroid Taper	Minimal
February 15, 2019	Hospital Re-Admission	Colitis #2	Grade II	Community-Acquired vs. Nosocomial Gastroenteritis	ir Colitis	*C. Diff* panel, Steroid Taper	Complete; Hyperglycemia 2/2 Steroid Treatments

Common Terminology Criteria for Adverse Events (CTCAE): *(Accessed on September 26, 2019)*.
SERVICES., U.S.D.O.H.A.H., Common Terminology Criteria for Adverse Events (CTCAE) Version 5. 2010. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

* Toxicity Grade: The toxicities were graded utilizing the National Institute of Health's Common Terminology Criteria for Adverse Events (CTCAE) system for grading AE. These were graded retrospectively as only the toxicity grade of the rash was documented in the electronic medical record charts for the patient. Grade II headache is for headaches with moderate pain that limit instrumental ADLs. Grade II hyponatremia (if graded as isolated hyponatremia alone) for Na between 125 and 129 with no symptoms. Grade II Hypophysitis for local or noninvasive intervention indicating limits only to age-appropriate instrumental ADLs. Grade II colitis for colitis associated with abdominal pain and/or blood or mucus in the stool.

** Ipilimumab was dosed with weight-based dosing at 3 mg/kg and Nivolumab was dosed at 1 mg/kg

2. Case

A 54-year-old, G2P0 female with locoregional metastatic melanoma of the vagina who had received three doses of combination ICI immunotherapy presented for admission at our tertiary care center in February of 2019 for severe colitis. Past medical history was significant for morbid obesity, hypertension, type 2 diabetes mellitus, hyperlipidemia, a remote history of smoking with no history of abnormal pap smears. Family oncological history was significant for ovarian cancer in her maternal grandmother. No further risk factors nor environmental exposures were noted.

The patient was diagnosed in 2016 with vaginal melanoma via an in-office biopsy by her primary gynecologist (Table 1). She was then referred to our institution for evaluation by gynecologic oncology. Pathology from a 2-centimeter vaginal wall mass resected by our team confirmed metastatic melanoma with tumor-free margins. The patient was referred to a melanoma specialty clinic for further evaluation, after which we decided to co-manage care and monitor with regular clinic visits and serial imaging.

Over the next two years, the patient denied new symptoms and imaging had no evidence of new disease. However, in September of 2018, three days of vaginal bleeding prompted further investigation. Though serial CT scans had not demonstrated evidence of new disease, pelvic exam revealed a new right vaginal sidewall mass. A biopsy from the succeeding exam under anesthesia confirmed melanoma recurrence.

Combination ICI therapy with programmed cell death 1 (PD-1) inhibitor, nivolumab (nivo), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4) inhibitor, ipilimumab (ipi), was initiated for systemic control. Throughout the treatment course, the patient received two doses of ipi/nivo in December 2018 and one dose in January 2019.

2.1. Rash

The day after first dose of ipi/nivo, the patient developed a tender erythematous maculopapular rash on the lower extremities that spread to the upper extremities and face. This rash mildly improved with topical triamcinolone 0.1% and oral hydroxyzine but persisted; upon re-evaluation prior to immunotherapy dose 3, it was retrospectively diagnosed as a grade III dermatitis likely secondary to ICI therapy. She was initiated on an 80 mg prednisone taper with a 20 mg/week reduction in dosage for 4 weeks and referred to dermatology for further evaluation.

2.2. Headache

Following her second dose of ipi/nivo, the patient experience new-onset frontal headaches and fatigue. Initially, headaches were an 8/10 on a subjective pain scale; after initiating Fioricet (Acetaminophen-Butalbital-Caffeine) every four hours as needed for severe headaches, her pain decreased to a 3–4/10. She simultaneously endorsed intermittent fatigue, but denied any visual changes, nausea or vomiting.

2.3. Hyponatremia

Prior to receiving the third dose of ipi/nivo, reconsideration of the dermatitis as an irAE prompted further work up, including a basic metabolic panel revealing a sodium level of 129 mEq/L. Conservative management with daily supplementation of 2 g of oral sodium tablets was initiated with plan for repeating serum sodium levels one week later in clinic. The patient was, however, subsequently admitted to the hospital.

2.4. Colitis

Following the third dose of ipi/nivo, the patient experienced two-weeks of profuse diarrhea refractory to over-the-counter antidiarrheals and was admitted for further work up and management. The patient described 5–10 daily episodes of watery, non-bloody diarrhea with mild abdominal cramping. She denied fever, chills, nausea, exposure to sick contacts or recent antibiotic use. At the time of admission, the patient was completing the last week of her dermatitis-related steroid taper; she was re-initiated on a prednisone dosage of 80 mg (planned taper by 20 mg/week) to treat presumed immunotherapy-related colitis (irC). Following treatment initiation, the patient had three loose stools before resolution of diarrhea.

2.5. Hypophysitis

During the first hospital admission, the patient's refractory hyponatremia was further investigated. Laboratory work-up demonstrated persistent hyponatremia (sodium, 128mEQ/L) despite sodium supplementation, hypothyroidism with a low thyroid stimulating hormone level of 0.087 mU/l and low thyroxine of 0.82 mU/l, and hypogonadism with both follicle-stimulating hormone (8.3 IU/L) and luteinizing hormone (2.4 IU/L) at significantly low levels for a post-menopausal woman. These laboratory findings paired with clinical symptoms of headache and fatigue strongly suggested immune-related hypophysitis (irH). As irC and irH are managed with similar steroid courses, we made no adjustments to her planned steroid taper (Nagai and Muto, 2018).

2.6. Recurrence of colitis

Nine days following discharge from her initial admission, the patient presented to an outside hospital reporting one week of copious diarrhea. The patient was transferred to our institution, where she continued to have diarrhea with severe crampy abdominal pain and intermittent frank bright red blood per rectum as well as nausea, dizziness, decreased appetite and intake. After admission, diarrhea decreased to 4–5 episodes daily, but fatigue and discomfort persisted. A stool sample was negative for *Clostridium difficile*. Initiation of IV methylprednisolone (2 mg/kg) lead to resolution of symptoms, and on hospital day four, patient was deemed stable for discharge home with a prednisone taper (initial dose 120 mg with 20 mg/week reduction in dosage). Follow-up was scheduled with her primary care physician to review a blood glucose log as the patient developed hyperglycemia.

2.7. Therapy adjustment

At her most recent follow-up appointment, the patient reported persistent mild vaginal bleeding and discharge, but noted resolution of symptoms suggesting irAEs. Imaging and physical exams since hospital discharge has demonstrated stable disease with no evidence of new metastases. The amended treatment plan at time of publication was to discontinue ipilimumab and continue with biweekly nivolumab monotherapy.

3. Discussion

This patient initially presented to our institution for inpatient admission for the work-up and treatment of colitis. Hospital admission allowed for ample opportunity to consider the full cohort of clinical symptoms since the initiation of ipi/nivo therapy. Synthesizing the symptoms of headache, fatigue, and salt supplementation-refractory hyponatremia (previously documented and treated as isolated non-immune events) with new confirmatory laboratory findings, we diagnosed and treated our patient for irC and irH. This case demonstrates the importance of educating providers about distinct toxicity profiles of immunotherapy treatments; despite unassuming initial clinical presentations, irAEs can have potentially serious irreversible downstream sequelae (Harris et al., 2016; Nagai and Muto, 2018).

Despite increased efficacy with combination nivolumab and ipilimumab compared to monotherapy, studies have consistently correlated ICIs with high rates of irAEs in patients receiving anti-PD1 (10–20%), anti- CTLA4 monotherapy (30%), and combination therapy (55–60%) (Harris et al., 2016; Zhou et al., 2019). Such adverse events can manifest as dermatitis, colitis, hypophysitis, hepatitis, pneumonitis, nephritis and myocarditis (Harris et al., 2016; Zhou et al., 2019; Solinas et al., 2018). Of the many possible immune-related adverse events, often the most insidious are endocrine irAEs as they can be a sign of irreversible immune toxicity that may require long-term hormone supplementation (Solinas et al., 2018; Weber et al., 2012). IrH and other endocrine irAEs are often asymptomatic or present with non-specific, mild-grade symptoms (Solinas et al., 2018). The most commonly reported clinical symptoms associated with irH are headache, fatigue, confusion, weakness and hyponatremia (Solinas et al., 2018). These symptoms can result from non-immune etiologies such as disease burden, prior chemotherapy treatments, benign tension headaches, or simple dehydration.

Although irAE therapy recommendations have not been strictly established, ICI therapy is typically held and patients are admitted for high-dose intravenous steroid treatment with a subsequent oral steroid taper (Harris et al., 2016; Weber et al., 2012; Puzanov et al., 2017). Providers can consider treatment with biologic monoclonal antibody (infliximab) for steroid non-responsive adverse events (Puzanov et al., 2017). Further management and resumption of ICI therapy should be determined by the nature of the irAE (i.e pituitary hormone replacement for hypophysitis) and response to treatment. Patients should also be monitored for irAE symptom relapses with regular outpatient follow-up (Weber et al., 2012).

As symptoms of irAEs often masquerade as common illnesses and patients receiving ICI therapy may not always present directly to their specialists for evaluation, irAEs may be unknowingly written off and treated symptomatically with minimal work-up. The recognition and management of irAEs in patients receiving ICI therapy hinges on the ability of healthcare providers to identify at-risk patients (Harris et al., 2016; Weber et al., 2012). Historically, gynecologists and gynecologic oncologists have had limited exposure to ICIs as primary mucosal melanomas of gynecologic origin are rare (Shiavone et al., 2016). However, multiple current clinical trials are elucidating the role of ICI as they continue to be approved as valid options for treating a multitude of malignancies (Castellano et al., 2018). Increasing education about clinical triggers for the work-up of irAEs is thus critically important for all providers who could be the first clinical touchpoint for patients (Weber et al., 2012).

4. Conclusion

For patients for whom ICI therapy may be indicated, we recommend that both patients and healthcare providers be educated prior to initiation on the breadth of presentation of immune-toxicities and common treatment recommendations of irAEs.

Author contributions

T. Graham Norwood contributed to the clinical management of the patient, the gathering of data, the review of existing literature and the writing and editing of the manuscript.

Michelle J. Wang contributed to the clinical management of the patient, the gathering of data, the review of existing literature and the writing and editing of the manuscript.

Warner K. Huh contributed to the clinical management of the patient, the gathering of data, the review of existing literature and the writing and editing of the manuscript.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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