CLINICAL VIGNETTE

Adrenal Insufficiency Associated with Pembrolizumab and Chemotherapy Treatment for Breast Cancer

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Case Report

A 53-year-old woman was diagnosed with stage II T2N0, 3.3 cm high grade invasive ductal carcinoma, estrogen receptor (ER) negative, progesterone receptor (PR) negative, Human Epidermal Receptor 2 (HER2) negative, triple negative breast cancer (TNBC). She was treated with preoperative carboplatin, docetaxel with pembrolizumab for six cycles followed by bilateral mastectomy and was found to have 1.9 cm node negative residual TNBC at surgery. She resumed pembrolizumab after surgery and was also treated with doxorubicin and cyclophosphamide due to extent of her residual disease. However, this chemotherapy was stopped after two of four planned cycles due to significant fatigue. She was changed to capecitabine while continuing pembrolizumab. Unfortunately, she developed profound fatigue, nausea, and myalgias. She was sleeping 14 hours per day and had difficulty ambulating. She was previously able to walk 10 miles per day. Evaluation revealed that her fasting morning cortisol was 0.3 (reference morning level is 8-25 mcg/dL) and her adrenocorticotropic hormone (ACTH) was 6 (reference 4-46 pg/mL). She was diagnosed with immunotherapy- induced hypophysitis leading to adrenal insufficiency and was urgently referred to endocrinology for same day consultation. She was given one 50 mg dose of hydrocortisone, and noted rapid improvement of her symptoms within one hour. She was started on maintenance hydrocortisone, 20 mg twice a day, with planned indefinite corticosteroid replacement. She did not require interruption of her pembrolizumab therapy, and she was able to complete her adjuvant capecitabine.

Discussion

Since the introduction of immunotherapy as the standard of care in the treatment of multiple cancers, we have encountered several patients who developed immune-related adverse events and endocrinopathies which required treatment and co-management with other specialists. Pembrolizumab is an immune checkpoint inhibitor (ICI) which works by preventing an “off signal” on the immune system by keeping lymphocytes engaged on cancer cells by inhibiting the programmed death-ligand 1 (PD-1) on T cells. ICIs can be used alone or in combination with chemotherapy or other agents. The activation of T lymphocytes can cause off-target autoimmune side effects in any organ system. Immune-related adverse events include but are not limited to colitis, dermatitis, pneumonitis, hepatitis, and endocrinopathies such as thyroiditis, diabetes, and hypophysitis (inflammation of the pituitary gland). Hypophysitis results in reduced levels of hormones such as ACTH, which then leads to reduced cortisol levels. Hypocortisolism can manifest as fatigue, nausea, dizziness, irritability and depression, hypotension, electrolyte abnormalities and joint and muscles aches. Initially, some of these symptoms may be vague or generalized or even misrecognized as symptoms of cytotoxic chemotherapy, cancer progression, or unrelated medical conditions. Patients on physiologic replacement doses of corticosteroids for adrenal insufficiency or patients with undiagnosed adrenal insufficiency undergoing surgery or experiencing severe physiologic stress are at risk for adrenal crisis with life-threatening complications of shock, coma, seizure, or death.

The most common endocrinopathies from ICI are hypothyroidism and hyperthyroidism which occur in approximately 8% and 3.4% of patients on single agent pembrolizumab, respectively.[1] In contrast, hypophysitis or adrenal insufficiency is reported in fewer than 0.8% of patients on pembrolizumab.[1] Hypophysitis is mostly commonly seen with ipilimumab, a different type of ICI which inhibits CTLA-4. While the occurrence of hypophysitis is rare with pembrolizumab alone, in breast cancer patients the drug is often given in combination with chemotherapy. Large trials in TNBC have reported higher rates of endocrinopathies.

Pembrolizumab is approved in combination with chemotherapy for both early-stage high risk and metastatic TNBC. In the phase III randomized control trial, KEYNOTE-522, 1174 patients were randomized to either chemotherapy or chemotherapy plus pembrolizumab prior to surgery for stage II or III TNBC. In this trial, approximately 20% of patients who received pembrolizumab developed either hypo- or hyperthyroidism.[2] This was twice as high as FDA data for single agent pembrolizumab.[1] In the same trial, 2.6% of patients developed adrenal insufficiency, which was greater than three times the FDA published rates for pembrolizumab used alone. In a separate phase III randomized control trial, KEYNOTE-355, 847, patients were randomized to either receive chemotherapy or chemotherapy plus pembrolizumab for inoperable or metastatic TNBC, and 20% of patients experienced hypo/hyperthyroidism.[3] This large landmark trial provides further data that combination therapy led to a doubling of the most common endocrinopathy compared to single-agent therapy. Interestingly, rates of hypophysitis or adrenal insufficiency

were not reported in this trial and may have been under-recognized in this population with advanced disease and likely higher symptom burden. It is not clear why combining chemotherapy would increase the endocrinopathy rates, but it is important to recognize such endocrinopathies so early treatment can be initiated**.**

Even though most immunotherapy related side effects are mild and resolve without therapy or with a short course of steroids, endocrinopathies that develop from immunotherapy require indefinite therapy and may lead to severe symptoms or even life-threatening consequence if left unrecognized. The American Society of Clinical Oncology recommends that patients with adrenal insufficiency who are asymptomatic or have mild symptoms should be referred to endocrinology and initiate replacement hydrocortisone 15-20 mg in divided doses. If the patient simultaneously develops another concurrent endocrinopathy like hypothyroidism, then it is important to initiate other hormonal replacement only after adrenal replacement to avoid precipitating adrenal crisis. Patients need to be educated about stress dosing. Patients with moderate symptoms of adrenal insufficiency should be assessed in clinic and considered for hydration or hospitalization, and considered for pulse dose steroids. For severe symptoms, inpatient management may be needed to provide IV normal saline and steroids.[4] ICI does not have to be permanently discontinued in patients who develop adrenal insufficiency or hypophysitis, and it is safe to resume when their symptoms have stabilized. Daily doses of hydrocortisone of 10-15 mg/m^2 or greater can lead to hypothalamic-pituitary-adrenal axis suppression when administered for a month or longer. These patients are at risk for adrenal crisis during times of severe physiological stress and surgery and require stress doses of glucocorticoids in the perioperative period.

For patients on immunotherapy, our practice is to check morning cortisol and ACTH levels at the completion of preoperative ICI, prior to surgery. If they are diagnosed with adrenal insufficiency, we refer them to endocrinology. Patients with hypophysitis or adrenal insufficiency can still proceed to surgery and adjuvant therapy. These patients require close multidisciplinary care in the perioperative period with their surgeon, anesthesiologist, and endocrinologist.

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