CLINICAL VIGNETTE

Ipilimumab Induced Hypopituitarism

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Introduction

Ipilimumab is a monoclonal antibody directed against the extracellular domain of cytotoxic T-lymphocyte-associated antigen (CTLA-4). It been used as an effective therapy in treating various cancers including metastatic melanoma.[1] However, it may cause pituitary dysfunction, reported as hypopituitarism or hypophysitis. This most often develops within the first year of treatment.[1] We report a case of Ipilimumab-induced hypopituitarism in a 58-year-old man with metastatic melanoma after four dosages of Ipilimumab treatment.

Case Presentation

This is a 58-year-old man with metastatic melanoma of left calf. After surgical resection of the melanoma, he received four dosages of Ipilimumab over two months. His melanoma went into remission. His TSH before the fourth dosage of Ipilimumab was 0.77 mcIU/ml (0.3 -4.7 mcIU/ml) and free T4 was 1.4 ng/dl (0.8-1.6 ng/dl). The 8am cortisol was 9.1 mcg/dl (4.0-22.0 mcg/dl) and 8 am ACTH was 29 pg/ml (6 - 50 pg/ml).

Two weeks after receiving the fourth dosage of Ipilimumab, he noticed a mild headache, decreased energy, hot flushes, diarrhea, mild difficulty with word findings, and lack of coordination. His repeat biochemical testing showed a low 8 am cortisol (0.7 mcg/dl), low normal 8am ACTH (9 pg/ml), low TSH (0.04 mcIU/ml), low Free T4 (0.7 ng/dl) and low testosterone with a value of less than 6 ng/dl (200-1000 ng/dl). MRI of the brain was normal.

Patient was diagnosed with Ipilimumab-induced hypopituitarism. He was prescribed hydrocortisone 15 mg in the morning and 5 mg at night, levothyroxine 88 mcg daily, and testosterone gel one packet applied on each shoulder in the morning. After a few weeks of treatment, he experienced a dramatic improvement in energy along with resolution of hot flushes, diarrhea, and headaches. His Free T4, CMP, ACTH, and testosterone will be monitored.

Discussion

Although Ipilimumab has been shown to increase the overall survival in metastatic melanoma,[2] it can cause autoimmune and inflammatory effects especially on the endocrine system.[3] The endocrinopathies affected by Ipilimumab are often irreversible.[4] The pituitary, thyroid, and adrenal glands are the endocrine organs that are typically affected.[5] A phase III trial designed to evaluate Ipilimumab as an adjuvant therapy following resected stage III melanoma showed 5.1% of treated patients developed hypophysitis.[6]

The precise mechanism by which Ipilimumab leads to hypopituitarism remains unknown. Hypophysitis induced by CTLA-4 blockade may be due to T cell mediated pituitary destruction,[7,8] or possibly due to ectopic expression of CTLA-4 in the pituitary gland, resulting in the complement activation and subsequent inflammation after Ipilimumab treatment.[9]

A retrospective review of 155 adults with metastatic melanoma from 2008 to 2013 showed male gender and older age are risk factors for Ipilimumab-induced hypophysitis.[10] In hypophysitis following CTLA-4 blockade, both ACTH and TSH secretion have been reported to be affected in 60-100% patients, while hypogonadotropic hypogonadism has been reported in 83-87% of male patients.[7]

There is a clear relationship between Ipilimumab dose and overall toxicities. In a dose escalation study of Ipilimumab in patients with metastatic melanoma, 8 of 46 patients (17%) experienced autoimmune hypophysitis requiring hospitalization and life threatening consequences: 1/8 patient (13%) at the 5mg/kg dose, but 7/33 patients (21%) at 9mg/kg dose.[11]

The median time to onset of Ipilimumab-induced endocrinopathies varies but tends to occur within the first year of treatment. One retrospective review of hypophysitis induced by Ipilimumab showed median time to onset of hypophysitis symptoms was 4 months.[12] Another retrospective study showed median time to develop Ipilimumab induced hypophysitis was 8.4 weeks (rage 6.9-10.3 weeks).[10]

Symptoms of Ipilimumab induced hypophysitis can be relatively nonspecific and very subtle, making diagnosis challenging. However, there should be a low threshold to consider hypophysitis in patient receiving Ipilimumab.[13] The most common symptoms from secondary adrenal insufficiency due to hypophysitis include nausea, vomiting, weakness, fatigue, mild cognitive dysfunction, hypotension, fever, and headache. Symptoms of secondary hypothyroidism may not be present. Symptoms of testosterone deficiency should be identified as patients may not readily volunteer this

information.[14] Patients may also have isolated hypothyroid or adrenal insufficiency symptoms based on where the inflammation occurred within the pituitary gland. The degree of pituitary enlargement in patient with Ipilimumab-induced hypophysitis was mild. It is recommended to measure thyroid function before each Ipilimumab treatment. The presence of symptoms should prompt physician to check 8 am ACTH, Cortisol, TSH, Free T4, FSH. LH, testosterone, SHBG, CBC, CMP, and pituitary MRI.[10]

Current recommended treatment is high dose (1-2 mg/kg/day of prednisone or equivalent) steroids for moderate to severe symptoms like headache or visual field defect.[15] It is not clear if initial high dose steroids are beneficial in treating hypophysitis.[13] Physiological replacement of glucocorticoid can be used for mild symptoms. Thyroid hormone replacement can began if Free T4 drops below normal range after initiation of glucocorticoid therapy. Testosterone replacement therapy can be used if hypogonadism is present.[14] Patients with adrenal insufficiency will likely need indefinite replacement dose steroids. All patients should be advised to wear a medical alert bracelet or necklace identifying adrenal insufficiency.[14] Most of the endocrinopathies are nonreversible although a few small studies reported the recovery of thyroidal and gonadal functions. Two retrospective reviewed showed two patients recovered from adrenal functions.[10]

Conclusion

Hypophysitis is a recognized side effect of Ipilimumab therapy. A high clinical suspicion for hypophysitis in patients receiving this drug is important due to the potentially life threatening consequences. Hormone replacement especially glucocorticoids should be initiated promptly. It is important to counsel patients that they may need to stay on hormone replacement indefinitely.

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Submitted September 15, 2017