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The Endocrinological Side Effects of Immunotherapies

Anush Patel, Haisam Abid and Amrat Kumar

Abstract

The use of immunotherapies is gaining importance in the treatment of advanced malignancies. There are many checkpoints in the immune system which prevents T-cells from attacking one's own body cells. The cancer cells can camouflage from the T-cells and the immune system is unable to mount an effective anti-tumor response. The immunotherapies, mainly monoclonal antibodies anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein-1 (PD-1) and anti-PD-1 ligand molecules (PD-L1 and L2) reactivate the immune system to act against cancerous cells but they can also cause T-cells to attack healthy cells causing various autoimmune diseases, which are known as immune related adverse events (irAEs). Current clinical data shows increased incidence of pituitary disorders with CTLA4 inhibitors and thyroid dysfunction in patients with PD-1/PD L-1 blockade. There have also been association of type 1 diabetes mellitus and primary adrenal insufficiency in patients with immune check point inhibitors. In this chapter we will discuss the incidence, characteristic findings, diagnosis and management of various endocrinological side effects due to targeted immunotherapies used in various malignancies.

Keywords: cancer immunotherapy, immune check point inhibitors, endocrine side effects, thyroid dysfunction, hypophysitis, primary adrenal insufficiency, Type 1 diabetes mellitus

1. Introduction

Immune system detects and destroys abnormal cells through immune surveillance and as a part of this prevents growth of many impending cancers. Immunotherapies work by either activating or suppressing the immune system and have emerged as important part of how we treat different types of cancers in last few decades [1].

Immune inhibitor pathway plays an important role in maintenance of self-tolerance, and cancer cells evade immune mediated destruction by upregulation of immune inhibitory pathways. Immunotherapy can be used to suppress these immune checkpoints resulting in antitumor activity. Immune check point inhibitors have significantly improved prognosis for patients with various advanced malignancies like melanoma, non-small cell lung carcinoma, Hodgkin lymphoma, urothelial carcinoma, renal cell carcinoma and head and neck cancer. As medical oncology treatments are changing from anatomical sites to molecular sites – immunotherapies have established role in certain molecular patterns as well (i.e. MSI high, TMB high metastatic tumors).

Immunotherapies include wide array of drugs with different mechanisms including monoclonal antibodies, immunomodulators, cytokines, checkpoint

inhibitors, chimeric antigen receptor T cell therapy, cancer vaccines and oncolytic viruses while many other new approaches are being investigated.

Targeting the immune inhibitory pathways for cancer treatment can lead to immunologic self-tolerance imbalance, resulting in immune-related adverse events (irAEs) which can virtually affect all the organ systems; including eye and brain which are usually unaffected by immune system [2–4]. Different immunotherapies usually affect different organs, as Anti-CTLA-4 mAbs are likely to affect colon and pituitary gland, while anti-PD-1 (L1) mAbs affect thyroid gland.

Among Anti-CTLA-4 mAbs, Ipilimumab has been approved for melanoma, kidney cancer and now NSCLC, and has significantly changed the natural history of advanced tumor. Another immunotherapeutic drug tremelimumab is under development. Common side effects associated with anti-CTLA-4 mAbs include pruritis, diarrhea, rash and fatigue with severe to life-threatening adverse events occurring in less than 5% cases. Anti PD-1 and PD-L1 mAbs have similar toxicity profile [5]. Nivolumab, pembrolizumab, and cemiplimab are anti PD-1 mAbs, while atezolizumab, avelumab, and durvalumab target PD-L1. In general, anti-PD-1 mAbs are associated with far fewer irAEs than Anti-CTLA-4 mAbs. Common side effects associated with Anti PD-1 (L1) mAbs fatigue, rash, pruritus and itchy with severe to life-threatening adverse events occurring in 2–3% of cases. The combination of Anti-CTLA-4 and Anti PD-1 (L-1) antibodies have shown better antitumor results but however they have been associated with higher incidence of immune therapy related adverse event than monotherapy [6, 7].

Usually these irAEs arise within 3–6 months of starting the immunotherapy but it may take few years and thus needs close monitoring for years after completion of therapy. These side effects can be graded from mild to moderate as Grade 1–2 and severe to life threatening as Grade 3–4 [2, 8].

In general, mild Grade 1 side effects usually requires symptom management and does not require immunotherapy discontinuation. Grade 2 or moderate side effects usually managed with temporary discontinuation of checkpoint inhibitor. For severe to life-threatening Grade 3 and 4 side effects immunotherapy is permanently discontinued and these patient usually require high dose of corticosteroids.

Some studies have shown association of irAEs with better antitumor efficacy, the data remains conflicting and needs further research confirm whether occurrence of irAEs predicts better outcome [9–13].

2. Endocrinological adverse effects of immunotherapy

Immunotherapy can cause wide array of endocrine side effects. More common irAEs are hypophysitis leading to hypopituitarism, primary or secondary thyroid dysfunction, primary or secondary adrenal insufficiency, autoimmune diabetes mellitus leading to diabetic ketoacidosis.

3. Pituitary dysfunction

3.1 Incidence

3.1.1 Anti-CTLA-4 mAbs

Hypophysitis is one of the more common immunotherapies induced endocrinopathies and is more common after anti CTLA–4 therapy, reaching around 13% after treatment with ipilimumab [14, 15]. Ipilimumab induced hypophysitis (IH) occurs more frequently in males and in older age when compared to lymphocytic autoimmune hypophysitis even when adjusted for melanoma incidence for age and sex [15–17].

IH is a type II hypersensitivity reaction in which CTLA-4 antibodies bind to antigen expressed on pituitary cells resulting in complement activation and gland destruction [18, 19]. Some studies have suggested that IH development may be associated with better antitumor outcomes in terms of morbidity and mortality [14]. The data on whether other agents and radiotherapy can alter the risks of hypophysitis is limited.

In the reported studies the average time to IH diagnosis is about 9 weeks; though time to endocrine abnormalities development has not been routinely reported in trials.

The radiographic changes seen on MRI including heterogenous pituitary enlargement with thickening of stalk are the sensitive and specific indicator of hypophysitis and may be the first signs of pituitary dysfunction occurring before hormonal disturbances or development of symptoms [1, 20]. The degree of pituitary enlargement can be mild in the patient's with IH and resolves quickly after glucocorticoids treatment [14].

Most common laboratory abnormalities observed at the time of diagnosis includes central hypothyroidism with reduction of TSH and secondary adrenal insufficiency. Hyponatremia secondary to adrenal insufficiency and hypothyroidism is frequently noted but central diabetes insipidus is rare with IH. Also growth hormone or prolactin axis disturbances occur less compared to other hormonal deficiencies. Usually, other hormonal deficiencies improved with treatment except for adrenal insufficiency which requires lifelong with steroid treatment [14, 21, 22].

3.1.2 Anti-PD-1 and anti PD-L1 mAbs

Multiple studies have shown that incidence of Anti-PD-1 and anti PD-L1 mAbs associated hypophysitis is less compared to Anti-CTLA-4 antibodies. Average incidence of hypophysitis was 0.6% in patients treated with pembrolizumab and nivolumab, <0.1% in durvalumab and 0.2% with atezolizumab [23–26].

3.2 Diagnosis and treatment

3.2.1 Monitoring

Patients receiving immunotherapy treatments should have baseline pituitary function test done. Routine thyroid function test monitoring with monthly TSH and free T4 level checks is recommended during the treatment and when patient develops symptoms suggestive of hypophysitis. Those patients who receives anti-CTLA-4 agents routine monitoring of ACTH and cortisol level should be done.

3.2.2 Diagnosis

A clinician must have high index of suspicion for the hypophysitis diagnosis as patient may present with vague symptoms or use of exogenous glucocorticoids may mask their presentation so regular monitoring is critical. When suspected, MRI should be performed to assess pituitary and rule out other causes of pituitary dysfunction along with hormone profile evaluation including TSH and free T4, ACTH, cortisol, LH, FSH, prolactin, estradiol and females and distress return in males. It is recommended to investigate for diabetes insipidus only if patient is presenting with symptoms such as polyuria or polydipsia.

3.2.3 Treatment

High dose glucocorticoids course is given when hypophysitis is suspected which may reverse inflammatory process and prevent the need for longer term hormone

replacement in some cases. However, in most patient's long-term hormonal supplementation for affected hormones is required with thyroid hormone replacement for central hypothyroidism or steroid replacement for secondary adrenal insufficiency. In premenopausal female estradiol replacement and in men testosterone placement should be considered.

4. Thyroid dysfunction

Immunotherapy related thyroid dysfunction can range from painless thyroiditis with transient thyrotoxicosis, transient or long-standing hypothyroidism, thyroid associated orbitopathy, and occasionally thyroid storm [27–29].

4.1 Incidence

Thyroid disorder can present with nonspecific symptoms such as fatigue and weakness. It is important to distinguish between primary versus secondary hypothyroidism, as former is more likely with anti-PD-1 and anti-PD-L1 mAbs with incidence ranging from 4–19.5%; and later is more suggestive from hypophysitis induced by anti-CTLA-4 mAbs [30].

For patients treated with nivolumab and pembrolizumab, the incidence rates of hypothyroidism were similar at 6.5% and 7.9% respectively. Incidence rate for hypothyroidism with ipilimumab, nivolumab or pembrolizumab, atezolizumab, and the combination of ipilimumab plus nivolumab were 3.8, 7.0, 3.9, and 13.2 percent, respectively [31].

Primary hyperthyroidism is seen less frequently with immunotherapy with incidence rates for hyperthyroidism with ipilimumab, nivolumab or pembrolizumab, atezolizumab, and the combination of ipilimumab plus nivolumab were 1.7, 3.2, 0.6, and 8 percent, respectively [31].

4.2 Monitoring

Baseline thyroid function test should be obtained before initiation of immunotherapy and after that regular monitoring of thyroid hormone levels including TSH and free T4 is recommended before each treatment and also when symptoms arise.

4.3 Diagnosis

High TSH with low free T4 indicates primary hypothyroidism and a low TSH and low free T4 indicates hypophysitis. In thyroiditis with transient thyrotoxicosis low TSH and high free T4 may be followed by more long-standing hypothyroidism high TSH and low free T4.

4.4 Treatment

While asymptomatic patients with mildly elevated TSH level < 10 can be observed, thyroid hormone replacement remains the mainstay of treatment in hypothyroidism. Dosage adjustment should be done every 4–6 weeks based on TSH level. Patients with thyroiditis and transient thyrotoxicosis can be managed symptomatically with beta blockers. Immunotherapy can be continued except and case of severe thyrotoxicosis when drug might need to be paused until symptoms resolve. Many patients may have subclinical hypothyroidism (TSH >20 mIU/L and normal T4) with symptoms, and in our experience, this should be treated with close monitoring for clinical improvement.

5. Primary adrenal insufficiency

5.1 Incidence

The adrenal insufficiency with immunotherapy is rare [32], there have been case reports which showed the association of immunotherapies and adrenal insufficiency. Data shows that there is a risk of 0.8–1.6% of adrenal insufficiency with ipilimumab either as a monotherapy or combination with anti-PDL 1 therapy. There is a 1% risk of primary adrenal insufficiency with nivolumab and median time of onset is around 4.5 months. Data suggests that there is 0.5% risk of primary adrenal insufficiency with avelumab and 0.4% risk of adrenal insufficiency in patients with atezolizumab.

There have been reports of subclinical form of adrenalitis with immune check point inhibitors, with normal endocrine function but radiographic evidence of inflammation of adrenal glands known as adrenalitis-symmetrically enlarged and smooth adrenal glands [33].

5.2 Characteristic findings

It is very rare to have primary adrenal insufficiency associated with adrenal crisis. Characteristic findings may include weight loss, fatigue, anorexia, nausea, vomiting, abdominal pain, orthostatic hypotension, hypoglycemia, eosinophilia, hyperpigmentation, hyponatremia, hyperkalemia or hypercalcemia.

5.3 Diagnosis

Low or suppressed morning serum cortisol with high ACTH levels will be seen in patients with adrenal insufficiency.

5.4 Treatment

Adrenal crisis is one of the most serious and life-threatening endocrinological side effect of immunotherapy, which requires prompt diagnosis and treatment. If there is high clinical suspicion of adrenal crisis, after obtaining serum cortisol and ACTH levels, treatment should be started without waiting for the results to come back. Patients should be given stress doses of steroids, IV hydrocortisone 100 mg every six to eight hours and aggressive fluid resuscitation should be made as there is high risk of hypovolemic shock. Endocrinologist consult is highly recommended as well.

6. Type 1 diabetes mellitus

6.1 Incidence

Type 1 diabetes mellitus is also a rare side effect in patients treated with immunotherapy. Type 1 DM has been observed in around 1% of patients treated with nivolumab and in 0.2% of patients treated with pembrolizumab. The median time of onset from starting immunotherapy is around 4.5 months.

6.2 Diagnosis

Type 1 DM is rare but when present, ketoacidosis must be investigated and treated [34]. Anti-GAD65 can be performed to look for autoimmunity.

6.3 Mechanism

The most likely mechanism of developing insulin dependent diabetes mellitus is inappropriate activation of T cells which cause destruction of pancreatic islet cells [35].

6.4 Treatment

Patients with immune mediated type 1 diabetes mellitus should be referred to endocrinology and treated with basal-bolus insulin regimen.

7. Conclusion

With the widespread use of immunotherapies in cancer, the incidence of side effects of immune check point inhibitors is also increasing. Physicians should be aware of different immune related adverse events (irAE).

Hypophysitis and thyroid dysfunction are the most common endocrinological side effects of immune check point inhibitors. Patients who receive anti-CTLA-4 therapy, the pituitary hormones should be regularly monitored and if there is concern for central adrenal or thyroid dysfunction, treatment should be instituted as soon as possible, and immunotherapy should be held.

Primary thyroid dysfunction is more common in patients who receive anti-PD1 and anti-PD-L1 antibodies. Patients may develop hyper or hypothyroidism. Hyperthyroidism is mainly transient, which can lead to hypothyroidism requiring life-long thyroid hormone treatment.

Most of the endocrine side effects of immune check point inhibitors can be adequately treated, clinicians should regularly monitor hormone levels so that it can be promptly diagnosed and treated. In patients with mild to moderate endocrinopathies, immunotherapy can be continued with careful monitoring.

Physicians should be aware that irAEs can occur during and after the treatment with immunotherapies and a multidisciplinary approach should be used in managing it. Patient's education is also very important, and physicians should guide them about the symptoms and signs to look for and notify the physicians.

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