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Cancer immunotherapy associated hypophysitis: Pathophysiology and management

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Abstract

Immune checkpoints are small molecules produced by immune cells that play crucial role in maintaining homeostasis of immune system. Targeting the immune checkpoint molecule, specifically, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD1) with inhibitory monoclonal antibodies has been reported to have antitumor activity. The US Food and Drug Administration (FDA) has been recognized several immune checkpoint inhibitors (ICIs) for the treatment of several types of cancer, mainly two types of ICIs that target CTLA-4 and PD1, have been approved as immunotherapeutic agent for cancer treatment. Autoimmune side effects results from immune checkpoint blockade, termed as immune related adverse events (irAEs) are frequent and usually mild, can include multiple endocrinopathies. The unique characteristic of irAEs is their non-reversibility, with incidence and prevalence expected to be increased in the upcoming years. Immune-related hypophysitis (IRH) is one of the most frequently reported irAEs after thyroid dysfunction. Hypophysitis, specifically associated with anti-CTLA-4 therapy, primary adrenal insufficiency (PAI) and diabetes mellitus are rare irAEs but can be fatal if not diagnosed and treated in early stage. Combinatorial therapy using anti- CTLA-4 and anti-PD1 drug is associated with increasing prevalence of IRH. The exact mechanism behind the development of irAEs remain to be elucidated. Most ICI associated endocrinopathies are manifested within 8-12 weeks after the initiation of ICI therapy. Management of ICI associated hypophysitis requires withdrawal of the ICI therapy, initiation of steroids and finally initiation of hormone replacement therapy and usually includes long-term management and care for controlling the irreversible side effects. In this review, we try to summarize the current scenario regarding the epidemiology, mechanism pathophysiology and management procedure for IRH in cancer patients receiving immunotherapy.

Keywords: Cancer immunotherapy; Immune-related adverse events; Hypophysitis; PD1; CTLA-4

1. Introduction

The advent of immunotherapy discloses a novel way to treat a wide verity of malignant disease including several types of cancer such as melanoma, renal cell carcinoma, lung cancer, colorectal, and other cancers [1]. Treatment using immune checkpoint inhibitors (ICIs) to abolish the restriction on the immune cells to initiate antitumor activity, have demonstrated promising results in the field of cancer treatment, especially two ICIs- cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD1) used in cancer treatment exerts effect by blocking the immune checkpoints, unleashing T-cells to fight cancer [2]. ICIs can be used alone or in combination with other checkpoint inhibitors or along with chemotherapeutic drugs. However, immunotherapy using ICIs can trigger onset of immune-related adverse events (irAEs) such as hypophysitis, diabetes mellitus, primary adrenal insufficiency, thyroiditis. Endocrinopathies are not the sole adverse outcome of ICI therapy but can particularly be severe in most of the patients. Therefore, patients must be kept under careful surveillance during ICI treatment [2-4].

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Hypophysis along with associated pituitary dysfunction is observed in patients receiving ICI treatment for cancer. Hypophysitis, a rare clinical condition characterized by a chronic inflammatory infiltration, progressively replaced by fibrotic tissue that alter pituitary gland architecture and causing dysfunction of the gland [5-6]. According to its aetiology, the hypophysitis classified under two broad sub-types- primary hypophysitis and secondary hypophysitis. In primary hypophysitis autoimmune pathogenesis develops without any clear cause and the inflammatory infiltration develops and is restricted to pituitary tissue. Another subtype is secondary hypophysitis, develops when inflammatory disorder is caused to an adjacent or systemic disease with a clearly identified etiological agent or iatrogenic aetiology [5,7]. The development and progression of immune-related hypophysitis (IRH) has been frequently associated with the anti-CTLA-4 and anti- PD1 molecules [8-10]. In clinical practice oncologists frequently use ICIs to treat cancer, as a result, the patients developing IRH become gradually escalated; IRH can also trigger several other endocrine complications, hence requires an early detection, diagnosis and treatment.

1.1. Epidemiology of ICI Associated Hypophysitis

With gradual increase in the use of novel immune targeted therapy for cancer treatment, there has been a rise of immune-mediated systemic adverse events including IRH. Approximately 0-17% of all patients, receiving ICIs, exhibit IRH [3]. IRH is more frequently found in men than women, with a M:F ratio of 4:1 [11]. Since 2011, total 304 cases of IRH have been reported, most of them are outcome of immunotherapy using ipilimumab [12]. In fact, the incidence of IRH varies according to the type of ICIs administered. In patients, receiving anti-CTLA-4 drug, the estimated case of IRH was nearly 5.6% with iplimumab and 1.8% for tremelimumab whereas with the use of anti-PD1 drugs nivolumab and pembrolizumab, the incidence of IRH is significantly reduced, 0.5% and 1.1% respectively. The highest incidence has been observed with combination therapy, ranging from using 8.8%-10.5 % in patients receiving nivolumab plus ipilimumab or pembrolizumab plus ipilimumab. Only in 1.1% cases, patients treated with anti-PD1 therapy are likely to develop hypophysitis[13].

1.2. Pathophysiology of Hypophysitis

The hypophysis is a prime endocrine gland that is divided into anterior and posterior part, adenohypophysis and neurohypophysis, and whose activity is regulated by hypothalamus. Hypothalamic releasing and inhibitory hormones control the activity of adenohypophysis whereas neural signalling networks from the hypothalamus regulates neurohypophyseal secretions [14]. The underlying mechanism of the development of hypophysitis due to ICI treatment is still poorly understood. Studies on murine model and *in vitro* cell line have demonstrated a potential involvement antibody-dependent cell-mediated cytotoxicity along with complement mediated pathway (Fig-1) for IRH development [3]. Recent research demonstrates that ectopic CTLA-4 antigens are expressed in the cells of hypophysis during immunotherapy. Anti-CTLA-4 antibodies bind with the ectopic ligand in the pituitary inducing type II hypersensitivity reaction which ultimately causes constitutive activation of classical complement pathway causing tissue damage and initiation of IRH development [15,16].

CTLA-4, a widely expressed checkpoint molecule in various types of immune cells including helper and cytotoxic T cells. CTLA-4 expression is also found in pituitary adenomas and normal pituitary tissue [4,17]. The anti CTLA-4 antibodies, such as ipilimumab and tremelimumab restrict mononuclear cells activation, so, their use as immunotherapeutic drug results in the aggregation and deposition of complement (C1q) proteins in pituitary cells and antibody dependent cell-mediated cytotoxicity. Moreover, the presence of serum antibodies has been observed against thyrotropic, gonadotropic and corticotropic cells in patients who develop hypophysitis following the use of ipilimumab [15]. The synthesis and secretion of anti-pituitary antibodies suggests that anti-CTLA-4 antibodies administration as a therapeutic agent to cancer patients with high- pituitary expression of CTLA-4 can promote hypophysitis mediated trough T-cell dependent (type IV) and antibody-dependent (type II) anti-CTLA- 4 immune mechanisms [11]. This immune-inflammatory reaction leads to the development of hypophysitis and irAEs to downstream target organs. [18,19]

The occurrence of IRH following the use of anti-PD1/PD-L1 antibodies is significantly lower compared to than that of reported following the use of anti-CTLA-4 antibodies [20]. The explanation regarding this differential outcome may be the fact that there is no ectopic PD1 or PD-L1 expression found in normal hypophysis tissue [4,21]. Moreover, PD1/PD-L1 mainly regulates the inflammatory reactions both in the tumour micro-environment and in peripheral tissues. Therefore, the blockade of this pathway could merely be influencing only the peripheral scenarios [4].
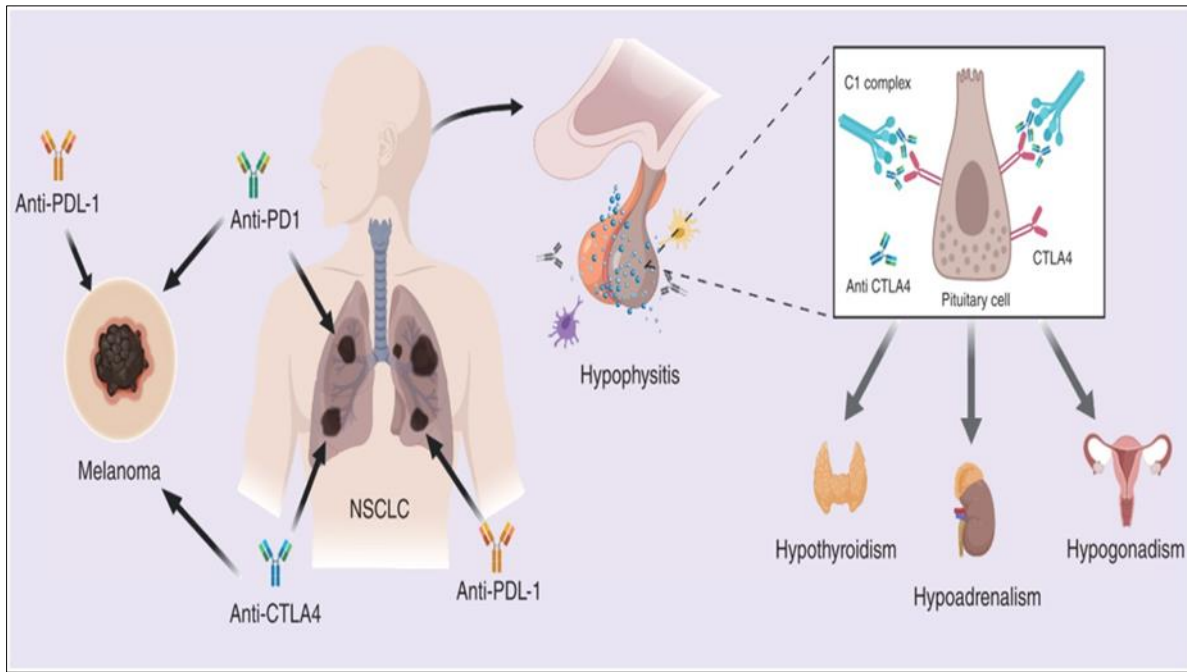
Figure 1 Clinical Pathophysiology of Immune-related hypophysitis [16]

1.3. Clinical Manifestation

Table 1 Toxicity Grading System of ICI Induced Hypophysitis as Defined by The National Cancer Institute, CTCAE [2]

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypophysitis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, minimal, or non-invasive intervention, indicated; limiting age-appropriate, instrumental activities of daily, living	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care	Life threatening consequences; urgent intervention indicated	Death

The manifestation of IRH can be asymptomatic or symptomatic and based on types of ICI used for immunotherapy, however, IRH is rare and only diagnosed when severe [22]. The clinical symptoms raised in between 6 to 12 weeks after the initiation of anti-CTLA-4 therapy. The most common symptoms of IRH are headache and fatigue; additional symptoms may include confusion, memory loss, hallucinations, anorexia, nausea, dizziness, reduced libido, cold intolerance, hot flashes, labile mood and weight loss; visual disturbances due to optic chiasm impingement are rare [9,10]. The presence of these symptoms needs further clinical investigations such as radiographic imaging for exclusion of cerebrovascular disease along with cerebral or leptomeningeal metastases. Patients developing IRH frequently shows myriad of symptoms associated with hormone deficiency which can be detected through clinical manifestation or by blood parameter measurement [14]. Among them central hypothyroidism and primary adrenal insufficiency (PAI) are most common in IRH. The main feature of central hypothyroidism is low or sub-normal free T_4 along with normal or low thyroid stimulating hormone (TSH) [23]. Cancer Patients treated with ICIs develop PAI which may be fatal if treatment with corticosteroids is not initiated promptly after detection. Symptoms of PAI include hypotension, electrolyte imbalance, and dehydration [24,25]. PAI is characterized by reduced or sub-normal level of adreno-corticotrophic hormone (ACTH) and cortisol. Insufficient cortisol hike in response to cosyntropin administration confirms the PAI [24]. These patients require glucocorticoid therapy to keep their symptoms under control. Another common adverse outcome of IRH is hypogonadotropic hypogonadism manifested through reduced or inappropriately normal level of follicle stimulating hormone (FSH) and leutinizing hormone (LH). In men androgen levels are low

whereas in reproductive women reduced level of estradiol is observed; in case of post reproductive aged women subnormal level of FSH and LH indicating development of hypogonadotropic hypogonadism [2,26]. The National Cancer Institute of the United States suggested a classification for IRH, based on its severity; the classification (Table-1) goes from grade 1 for asymptomatic or mild symptoms, to grade 5 which causes death [27].

1.4. Diagnosis & Clinical Approach

The cancer patients on ICIs therapy, if hypophysitis is suspected, appropriate blood parameter analysis along with brain MRI represents the gold standard for the detection. Circulating levels of TSH, FSH, LH, ACTH, prolactin, oxytocin, testosterone and cortisol measurement should also be performed. Concerning imaging studies, observation of pituitary enlargement is a specific gold standard of ICI induced hypophysitis; diffused, mild to moderate level of pituitary enlargement usually reported, sometimes thickening of pituitary stalk results in impingement of the optic chiasm [14,28,29]. Pituitary enlargement may precede the clinical diagnosis of hypophysitis by several weeks. Based on this reporting, brain MRI is recommended for patients receiving ICIs therapy compared with previous studies to monitor the changes in pituitary size and function. In ICI associated hypophysitis pituitary enlargement resolves in 7-30 days nearly in all cases [2,17]. MRI, as a tool for identifying hypophysitis, also allows the possibility of ruling out new metastatic event, cerebrovascular events of leptomeningeal disease [5,9,30]. MRI also used as a powerful diagnostic technique to differentiate central pituitary dysfunction from other irAEs such as autoimmune thyroiditis, PAI, pituitary macroadenomas [11,29].

1.5. Management

Patients suffering from IRH must be counselled regarding the signs and symptoms of hypophysitis, because between two consecutive treatment visits, patient may require prompt management [2]. After the detection of IRH in patients on ICIs therapy, glucocorticoid and thyroid hormone replacement therapy is initiated promptly along with assessment of serum sodium concentration. If hypogonadism is also persisted androgen replacement therapy should be started. A number of patients suffering from IRH partly recover the anterior pituitary function. Thyroidal and gonadal axis recovery has been observed more frequently than adrenal recovery [31-33]. The time duration for recovery is not well understood, mainly due to variation in patient follow up, laboratory diagnosis and attempts to wean hormone therapy.

High doses of steroids have been prescribed for the patient with critical condition, associated with hypophysitis along with symptoms of low serum sodium level, severe headache and visual impairment. In this clinical status, once the hypophysitis is clearly diagnosed, ICI therapy must be aborted and management procedure should be initiated promptly [7,9]. In case of severe effect or hypoadrenalism, the European Society of Medical Oncology recommend the use of methylprednisolone (1–2 mg/kg/per day) for 3–5 days. followed by oral administration of prednisone (1–2 mg/kg), with gradual tapering in 4 weeks [13,17]. Dexamethasone (4 mg in every 6 hour) for 7 days, followed by gradual titration up to 0.5 mg/day and after that switching to hydrocortisone, may be used as an alternative option. Recent guidelines by American Society of Medical Oncologist, recommend use of high-dose steroids such as prednisone or its equivalent, (1–2 mg/kg) for grade 3–4 hypophysitis patients [34-36].

For stable patients, suffering from grade 1-2, European Society of Medical Oncology suggests the administration of low dose oral steroids (1–2 mg/kg) in the case of grade 2 toxicity; whereas for grade 1 toxicity, only the respective hormone replacement therapy is recommended [9, 16].

For certain patients, in whom refractory or recurrent immunotoxicity is observed, nonsteroidal immunosuppressants such as azathioprine, methotrexate and cyclosporin can be successfully used after cessation of immunotherapy. Radiotherapy and radiosurgery to remove the affected region of pituitary has been reported in some patients of primary autoimmune hypophysitis [37,38].

The resumption of ICIs therapy after immunotoxicity represents a challenge to the clinicians, and should be considered after proper assessment   on customized individual basis. Patients must be monitored at strict interval to diagnose the incidence of relapses, complications, and current status of the disease. The decision to restart ICI therapy is not always clear, resumption of immunotherapy often require optimal patient management [14,39,40].

2. Conclusion

Better understanding of immune checkpoint regulation accelerates rapid progression in the treatment of cancer and ongoing research indicates that ICIs will likely to have wide role in treating variety of malignancies. In near future, the number of patients with IRH and other irAEs will increase rapidly. IRH, though rare, is one of the main indications for ICI therapy interruption. The incidence of IRH is currently increasing which may lead to severe clinical consequences

such as irAEs. Therefore, the treatment responses and long-term survival of patients receiving ICIs is a matter of concern and requires prompt recognition and appropriate treatment of IRH. As the aetiology of this complication is still remain beyond complete understanding, the accurate diagnosis requires high index of clinical suspicion, imaging assessment, a multidisciplinary diagnosis approach and a customized individualized hormone replacement therapy. Therefore, oncologists, endocrinologists and primary care providers for these patients should be aware of clinical manifestations, diagnosis, and management. Effective communication and coordination between oncologists and endocrinologists can facilitate optimal management and outcomes for patients -who develop ICI-associated endocrinopathies. Moreover, further research is required to strengthen our understanding in this field for better management of irAEs. Additional studies are required for better clarification of the mechanisms behind the development of irAEs, particularly for IRH. Hence it is greatly important to perform more research in this field to explain the basic mechanism for the betterment of individualized clinical guidelines which will help the clinicians working in this field to make more specific decision and better living the survival of the patients.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest.

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