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The management of nivolumab-induced endocrine immune-related adverse events

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ABSTRACT

Immune-mediated endocrine adverse events induced by nivolumab therapy are related to the activation of the immunological system, and often they affect the pituitary, thyroid, and pancreas leading to hypophysitis, thyroiditis, and diabetes mellitus. The exact pathomechanism of nivolumab-induced endocrinopathy usually remains unknown. The endocrine adverse events are unique when compared to other immune-mediated adverse events because the manifestations are often irreversible and require a life-long hormonal replacement and careful monitoring. Endocrinopathies in patients with disseminated neoplastic disease, often present with non-specific symptoms, making them difficult to diagnose. The cooperation of a clinical oncologist and endocrinologist is crucial for making a correct diagnosis and for inducing appropriate hormone replacement therapy. This attitude may improve prognosis in oncological patients with endocrine complications of immunotherapy. In this article, we present the current data regarding the clinical management of immune-mediated endocrinopathies, including hypophysitis, thyroiditis, and diabetes mellitus.

Key words: immunotherapy, nivolumab, hypophysitis, thyroiditis, diabetes mellitus type 1

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Introduction

Hormonal disorders that occur during the immunotherapy of neoplasms with 'immune checkpoint inhibitors', also including nivolumab, are relevant to activation of the immunological system and usually involve such endocrine organs as: hypophysis, thyroid, and pancreas. The two major endocrinopathies observed during the immune checkpoint blockade are hypophysitis (typically induced by anty-CTLA-4 antibodies) and thyroiditis leading to thyrotoxicosis and/or hypothyroidism (induced by anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies). The incidence of other dysfunctions of the endocrine system, such as type I diabetes mellitus or primary adrenocortical gland insufficiency, is much lower. The adverse events concerning the endocrine system are unique compared to other immunological complications of the immunotherapy because they are usually irreversible. Immune-mediated endocrinopathies leading to the insufficiency of a given endocrine gland require a permanent hormonal substitution in affected patients [1]. The anti-PD-1 and anti-CTLA-4 antibodies induce similar immunological side effects, also concerning the endocrine system. However, their incidence and intensity are usually less exacerbated after administration of anti-PD-1 antibodies [2, 3].

Correct functioning of the endocrine system is based on a precise functioning of the feedback loops between hypophysis and each peripheral endocrine gland. As well as the endocrine dysfunction, we also observe symptoms associated with the immunological inflammation of a given gland. A good example may be hypophysitis, which causes not only such symptoms as headaches or, less frequently, vision disturbances related to the compression by the enlarged gland of the optic chiasm, but also many symptoms associated with hypothyroidism, adrenal insufficiency, or sexual gland dysfunction. The symptoms of the endocrinopathies in patients with a disseminated neoplastic disease may be unspecific, which impedes the oncologist in making an

appropriate diagnosis [4, 5]. These symptoms may mimic progression of neoplastic disease. On the other hand, thyroiditis may be asymptomatic and detected during the routine hormonal tests. The symptoms of adrenal gland insufficiency are initially very discrete and mostly manifest as weakness, tiredness, nausea, headaches, and hypotension.

Endocrinopathies associated with nivolumab therapy are usually observed during the initial weeks of immunotherapy. In clinical trials with nivolumab, the median time to the onset of endocrinopathies was: 1.5 months for hyperthyroidism, 2.9 months for hypothyroidism, 4.9 months for hypophysitis, and 4.4 months for diabetes mellitus type 1 [6]. However, we should not forget that the occurrence of these complications may be delayed. The endocrinopathies may also occur after the termination of the nivolumab therapy. That is why patients should be carefully monitored for several months after completion of therapy [4, 5].

This paper refers to the characteristics and management of the most common endocrinopathies associated with nivolumab administration.

Hypophysitis

Incidence

Hypophysitis is a typical endocrinopathy occurring during the administration of the anti-CTLA-4 (ipilimumab) antibodies. Its incidence is variable (0–17%) [7, 8]. The differences in the incidence of hypophysitis may result from different doses of ipilimumab, absence of unified schedules of the hormonal control tests, and with a diverse clinical awareness of the occurrence of symptoms of the impaired function of hypophysis. In a recent report the incidence of hypophysitis equalled 10–15% [9]. Improved awareness of oncologists probably results in more frequent diagnosis of hypophysitis [9]. The impairment of hypophysis during the anti-CTLA-4 antibody therapy is independent of the type of neoplasm. However, male sex and older patient's age are considered risk factors for developing hypophysitis. On the contrary, a primary lymphocytic hypophysitis is more frequent in young females, in reproductive age, and often after child delivery [10, 11]. Hypophysitis in patients treated with nivolumab is significantly less frequent (< 1%) [9].

In clinical trials evaluating nivolumab in monotherapy, hypophysitis occurred in 0.6% of patients, and the median time to appearance of symptoms equalled 4.9 months, whereas in patients treated with a combination of nivolumab and ipilimumab this affliction was observed more frequently — in 9% of patients, on average after 2.7 months of immunotherapy [6].

Pathogenesis

The majority of cases of ipilimumab-induced hypophysitis may result from the ectopic expression of CTLA-4 antigens on the cells of a human hypophysis, which may be targeted by the anti-CTLA-4 antibodies [12, 13]. However, the mechanism of nivolumab-induced hypophysitis remains undiscovered.

Symptoms and diagnosis

The symptoms of hypophysitis are relatively unspecific, wherefore an oncologist may have difficulties in making an appropriate diagnosis. The most common symptoms include: headache, tiredness, nausea, reduced appetite, weight loss, cold intolerance, vertigo, and vision disturbances [9, 11, 14]. These symptoms may be overlooked or attributed to a potential progression of the neoplastic disease. The diagnosis of immune checkpoint inhibitor-induced hypophysitis is mostly based on the presence of clinical symptoms, hypopituitarism in hormonal tests, and of a typical magnetic resonance image (MRI) of the pituitary gland (a symmetric enlargement of the pituitary with usually homogenous enhancement post-intravenous contrast administration) after initiating the immunotherapy. During the acute phase of the inflammation the image of the hypophysis is abnormal in 75% of patients while in the other 25% it may be unchanged [4, 5, 9, 10]. An MRI of the central nervous system (CNS) should also be done in order to exclude the metastases to the brain. However, we must remember that performing a MRI of a CNS should not defer the hormonal diagnostics and the initiation of the hormonal replacement therapy.

Management

Anti-PD-1 and anti-CTLA-4 antibody-induced hypophysitis mostly leads to a combined anterior pituitary hormone deficiency. An insufficiency of the posterior lobe occurs extremely rarely and manifests as diabetes insipidus [4, 5, 9, 10]. Administration of high doses of glucocorticosteroids (GCS) is controversial because it does not lead to the resolution of the hypopituitarism. It is recommended that a physiological substitution be started with hydrocortisone and high doses of glucocorticosteroids (e.g. prednisone 1 mg per kg of body weight per day) should be limited only to situations when a so-called 'mass effect' is observed as a strong headache or vision disturbances (Figure 1) [4, 5].

In a patient with suspicion of hypophysitis, first ACTH deficiency should be excluded, which leads to a secondary insufficiency of the adrenal gland. The initial symptoms may be discrete and unspecific. The most common symptoms include: weakness, tiredness,

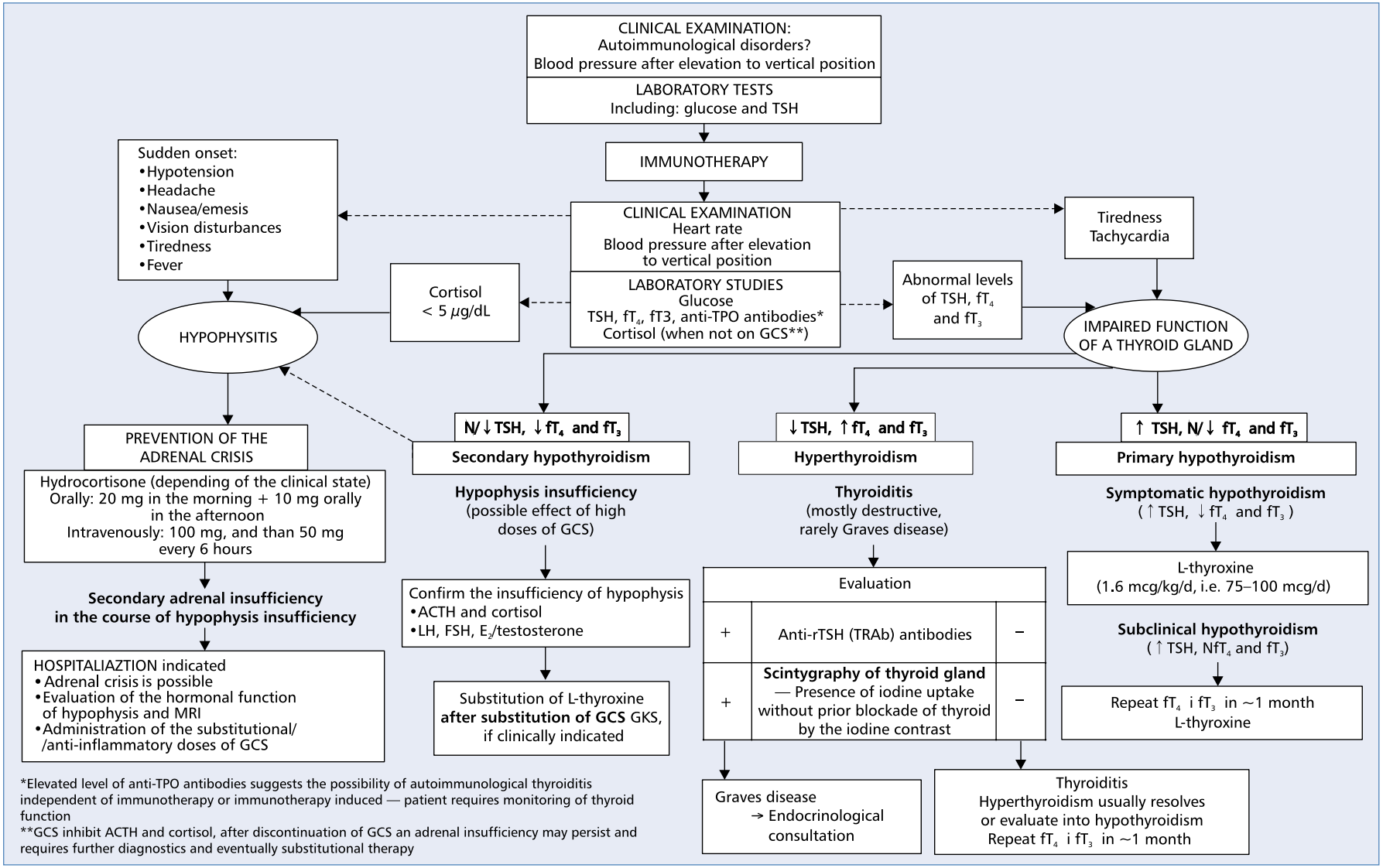

Figure 1. Algorithm of management of nivolumab-induced endocrinopathies

loss of appetite, weight loss, concentration disorders, nausea, vomiting, abdominal pains, low blood pressure with orthostatic hypotension, and headaches. In case of suspicion of adrenal insufficiency we should test the morning concentration of cortisol (at 8 a.m.) and eventually of ACTH. A low concentration of cortisol (< 5 μg/L) associated with low or normal level of ACTH suggests a secondary insufficiency of the adrenal gland induced by hypophysitis. Administration of substitutional doses of hydrocortisone (20–30 mg per day orally) leads to prompt clinical improvement, which also confirms the hypophysitis. We should remember that hypophysitis associated with severe adrenal insufficiency (low blood pressure, dehydration, hyponatraemia, hyperkaliaemia) is equivalent to an adrenal crisis and is a life-threatening condition. Such patients require immediate hospitalisation and urgent intravenous administration of high doses of GCS (hydrocortisone 50–100 mg intravenously every six hours) together with appropriate intravenous hydration and further extended endocrine diagnostics (Figure 1). It is crucial to differentiate an adrenal crisis from a septic crisis, so it is recommended that a.o. blood cultures are taken.

L-thyroxin substitution of a secondary hypothyroidism should be implemented in cases of decreased FT_4 concentration below the minimum reference level and after normalisation of the adrenal function. L-thyroxin is recommended at an initial dose of 25–50 μg administered during fasting, in the morning. The FT_4 level should be controlled in further monitoring and L-thyroxin dose adjustment, unlike the TSH level in primary hypothyroidism.

The serum levels of gonadotropins (FSH and LH), as well as of oestradiol and testosterone in women and men respectively, should be evaluated in patients with diagnosed hypophysitis. Hormonal replacement therapy of hypogonadism should include testosterone administration in men and oestrogens in premenopausal women, and it should be concordant with current recommendations of the endocrine societies.

Nivolumab therapy may be continued once the symptoms subside and a hormonal rebalance of a hypopituitarism is achieved [4, 5].

Thyroiditis

Incidence

During the process of activation of T lymphocytes against neoplastic antigens the immune checkpoint blockade may initiate an attack on the thyroid cells. Thyroid disorders occurring during the nivolumab therapy are the most frequent among endocrinopathies, and its diagnosis rate increases [4, 5]. In the clinical trials the hypothyroidism secondary to the thyroiditis occurred in 9% of patients receiving nivolumab monotherapy (averagely after 2.9 months after the start of the therapy), on the other hand, hyperthyroidism was observed in 2.7% of patients on nivolumab, on average after 1.5 months of therapy, and in a population treated with a combination of nivolumab and ipilimumab hypothyroidism was detected in 22% and hyperthyroidism in 8% of patients [6].

Pathogenesis

The relationship between the induction (by anti-PD-1 antibodies) of the autoimmune processes in the thyroid gland is still unclear. In the study by Orlov et al. [2] classical features of silent, painless thyroiditis, which manifested as a temporary thyrotoxicosis, were observed in 60% of patients whereas in the other 40% a hypothyroid phase was documented. In patients with thyrotoxicosis the antibodies against the TSH receptor (also present in Graves-Basedow disease) were negative whereas 67% of patients had anti-TPO and anti-TG antibodies. These antibodies were positive in all patients in whom hypothyroidism was diagnosed from the beginning of therapy [2].

Symptoms and diagnosis

Painless thyroiditis is typically present and is manifested by temporary thyrotoxicosis (low TSH level, elevated concentrations of FT_4 and FT_3) [2, 15, 16]. Thyrotoxicosis may have an asymptomatic course or induce such symptoms as: palpitations, weight loss, tiredness, and excessive sweating. A hyperthyroid phase of thyrotoxicosis resolves into euthyroidism or more often into hypothyroidism. In some patients immunotherapy-induced thyroid gland disorder is right from the beginning, manifesting with symptoms of hypothyroidism: tiredness, obstructions, cold intolerance, weight gain, hair loss, and hear rate deceleration.

During the acute phase of silent thyroiditis an increased metabolism of 18-fluorodeoxyglucose may be detected by PET-CT imaging within the thyroid gland [16]. In such cases an iodine uptake evaluation test of the thyroid gland will detect an inhibited uptake of 131I. Unfortunately, scintigraphy of the thyroid in oncological patients is rarely authoritative due to frequently performed control CT exams with use of iodine-based contrast [4, 5].

Management

Routine evaluation of thyroid gland functions is recommended before and after administration of the first and each consecutive dose of nivolumab. It is also advisable to test for the presence of anti-thyroid

antibodies, especially in cases of abnormal TSH levels (Figure 1). The acute phase of thyroiditis associated with thyrotoxicosis is usually asymptomatic and does not require any therapy, only monitoring of the TSH, FT_4, and FT_3 levels [17]. In symptomatic cases, especially in the case of tachycardia, it is recommended that a beta-adrenolytic drug is started (e.g. propranolol 3 × 40 mg orally). In the rare cases of severe hyperthyroidism, it is necessary to administer glucocorticosteroids (e.g. prednisone 1 mg/kg of body weight). The literature includes a casuistic report of a thyroid crisis induced by combined therapy with nivolumab and ipilimumab in a patient with a disseminated stage of melanoma. This patient required therapy with a beta-adrenolytic drug, thyreostatics, and systemic administration of GCS, which resulted in clinical improvement and normalisation of the thyroid hormone levels [18].

We should also remember that a decreased level of TSH in a patient receiving immunotherapy may result from the administration of high doses of glucocorticosteroids used to control other immune-related adverse events or neoplastic metastases to the brain. A low TSH level combined with decreased FT_4 level may suggest secondary hypothyroidism in the course of hypophysitis. This suspicion always requires exclusion of insufficiency of the adrenal gland and evaluation of the morning levels of cortisol and eventually of ACTH before starting L-thyroxine substitution.

In the case of primary hypothyroidism, a substitution therapy with an L-thyroxine should be started at a dose of 25–50 μg administered during fasting and in the morning. The dose of L-thyroxine should be adjusted every 4–6 weeks so that the TSH level could reach the normal reference value. A full substitutional dose of L-thyroxine usually equals 1.6 μg/per kg of body weight per day.

In cases of subclinical hypothyroidism and of rightly corrected hypothyroidism immunotherapy with nivolumab may be continued.

Diabetes mellitus type 1

Incidence

Autoimmunological type 1 diabetes mellitus is a rare complication of nivolumab therapy. There are very few case reports accessible in the medical literature [19–22]. In clinical trials with use of nivolumab, diabetes mellitus was diagnosed in 0.9% of patients, on average 4.4 months after beginning immunotherapy. Among patients treated with combination of nivolumab and ipilimumab diabetes mellitus was observed more frequently — in 1.5% of patients, on average 2.5 months after the start of therapy [6].

Pathogenesis

Type 1 diabetes mellitus is caused by destruction of the beta cells of the pancreas by T autoreactive lymphocytes. Nivolumab-induced diabetes mellitus is primarily insulin-dependent and has a fulminant course, as well as having no remission phases, unlike typical autoimmune type 1 diabetes mellitus. In these rapidly progressing cases of hyperglycaemia no autoantibodies to islet cells may be detected; however, in some patients markers of both cellular and humoral activation of the immune system have been identified (e.g. presence of the anti-glutamine acid decarboxylase antibodies) [19]. Moreover, it was stated that same HLA haplotypes predispose to the development of nivolumab-induced diabetes mellitus [23]. However, further studies are necessary in order to confirm the pathogenetic mechanism of this endocrinopathy.

Symptoms and diagnosis

A rapid increase in the glucose level with total deficiency of insulin secretion, confirmed by undetectable serum levels of peptide C at diagnosis, is a characteristic feature of anti-PD-1 antibody-induced diabetes mellitus. Some cases of ketone acidosis were reported as a primary symptom of nivolumab-induced diabetes mellitus [19]. Oncologists must consider that this complication may occur and should routinely monitor serum glucose levels during the immunotherapy (Figure 1). It is important to educated patients about the possible symptoms of development of ketone acidosis e.g.: polyuria, polydipsia, dehydration, nausea, emesis, diarrhoea, and abdominal pain, which may constitute a direct danger to life. Fulminant type I diabetes mellitus is characterised by ketone acidosis and a rapid course, which results in deterioration of the patient's health in a few days or weeks and results from the complete inhibition of insulin secretion. This subtype of diabetes has also been described during nivolumab therapy [21, 23]. The diagnostic criteria of the fulminant diabetes include a rapid onset of hyperglycaemia with ketone acidosis and a normal level of glycated haemoglobin (HbA_{1c}) despite high serum glycaemia and undetectable concentration of peptide C.

It is important to differentiate between the frequent gastrointestinal symptoms associated with nivolumab therapy resulting from e.g. enterocolitis and gastrointestinal symptoms in the course of ketone acidosis in the fulminant form of type 1 diabetes mellitus.

Management

Undiagnosed fulminant diabetes mellitus is a fatal condition. Therapy should be started immediately in each case of type 1 diabetes [22]. Therapy involves typ-

ical management of ketone acidosis with a continuous intravenous insulin-therapy, intravenous hydration, and frequent monitoring of laboratory parameters in order to rebalance the anion gap and electrolytes imbalance. Once the patient's clinical state is improved and acidosis has been resolved a multiple-dose, subcutaneous insulin injection model may be implemented. Cooperation of both the oncologist and endocrinologist is crucial in order to coordinate education of a patient and to plan appropriate ambulatory control. Further management of the diabetes mellitus should by individualised with consideration of the nutritional status of a given patient and of his/her general prognosis for overall survival [19–21].

In the case of a good control of diabetes, therapy with nivolumab may be continued [19–22].

Summary

1. In the case of suspicion of hypophysitis, evaluation of morning concentration of cortisol is crucial. A low cortisol level confirms a diagnosis of a secondary adrenal insufficiency. This condition requires immediate implementation of hydrocortisone supplementation.
2. Hyperthyroidism associated with nivolumab immunotherapy is mostly temporary and does not require use of thyreostatics, only observation or use of beta-adrenolytic drugs.
3. In cases of occurrence of hypothyroidism, it is recommended that substitution with L-thyroxine preparation be implemented.
4. Cooperation between the oncologist and the endocrinologist is crucial in the management of patients with immunotherapy-induced endocrinopathies. Making an appropriate diagnosis of hormonal disorders and adequate hormonal substitution may improve the prognosis of oncological patients in whom immunotherapy-induced endocrinopathies have occurred.

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