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Immunotherapy-induced endocrinopathies: assessment, management and monitoring

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***Abstract*:** Immunotherapy with checkpoint inhibitors has transformed the treatment of cancer, but frequently results in immune-mediated adverse events affecting multiple organs, amongst which endocrine adverse events are frequent. The patterns of endocrine adverse events differ between inhibitors of the CTLA-4 and PD-1/PD-L1 pathways, but most frequently involve the thyroid and pituitary with insulin deficient diabetes also emerging as an important adverse event. These frequently result in long-lasting hormone deficiency requiring replacement. This review explores the mechanism of action of checkpoint inhibitors and details the expected endocrine adverse events and typical presentations. The effect of high-dose glucocorticoids therapy to treat nonendocrine adverse events is also discussed.

Keywords: cancer, diabetes, endocrinopathy, glucocorticoids, hypophysitis, immunotherapy, thyroiditis

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Introduction

Immunotherapy with immune checkpoint inhibitors (ICIs) has transformed the treatment of cancer by harnessing the power of the immune system. ICIs inhibit the immunological pathways that control T-cell activation or anergy.[1] There are two classes of ICIs currently licensed: those that inhibit cytotoxic T-cell lymphocyte antigen-4 (CTLA-4) pathway, for example ipilimumab, and those that inhibit the program death-1 receptor or ligand (PD-1 or PD-L1) pathways, for example atezolizumab, durvalumab, nivolumab and pembrolizumab.

CTLA-4 is expressed on T cells and competes against CD28 to bind the co-stimulatory molecule B7 on antigen presenting cells. CTLA-4 does not produce a stimulatory signal, thereby counteracting the activating CD28/B7 and T-cell receptor/major histocompatibility complex pathways, inhibiting T-cell function. CTLA-4 blockade supports activation and proliferation of effector T cells and reduces immunosuppressive regulatory T cells.[2]

PD-1, also a member of the CD28/B7 family, is expressed on T cells. Binding of its ligands inhibits T-cell proliferation, immunostimulatory cytokine production and T-cell survival. Blockade of PD-1 or PD-L1 influences the effector phase of the immune response to restore the function of T cells in the periphery.[2]

The potential of ICIs was first demonstrated in malignant melanoma where ipilimumab, and then the combination of nivolumab and ipilimumab, were found to dramatically improve survival as a first-line treatment for metastatic disease.[3] Meanwhile, single-agent immunotherapy or a combination of chemotherapy and immunotherapy is now the standard of care for patients with advanced stage non-small cell lung cancer and adjuvant immunotherapy improves survival for patients undergoing radical chemoradiotherapy for locally advanced disease.[4] As our understanding of how best to use ICIs increases, their role has expanded to include the treatment of a range of malignancies including bladder, breast and renal cancer, as well as lymphomas. It is not an overstatement to say that in the future, immunotherapy will be an integral part of the treatment of most cancers.

Initiation of checkpoint therapy is often associated with immune-related adverse events (irAEs).

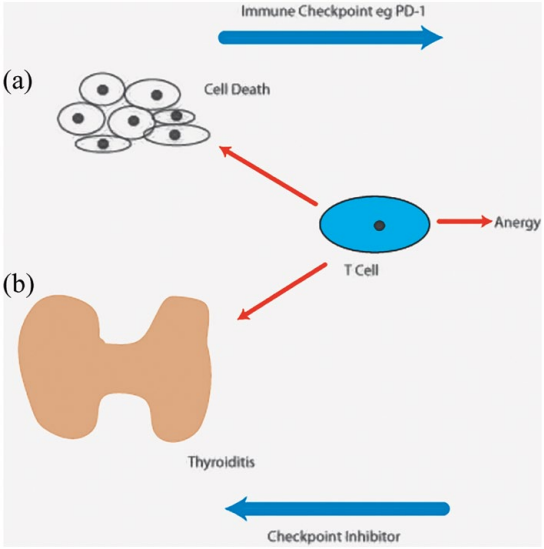

Figure 1. The immune checkpoints, such as the PD-1/PD-L1 or CTLA-4 pathways serve to drive autoreactive T cells towards anergy, preventing autoimmunity. Immune checkpoint inhibitors (ICIs) prevent this, enabling an immune-mediated response against a cancer (a). However, they also promote immune responses against self, in this case the thyroid (b) resulting in thyroiditis.

Multiple organs can be affected in immune-mediated reactions including colitis, hepatitis, dermatitis and pneumonitis amongst others, whilst occurrence of classic autoimmune syndromes such as sarcoidosis are also described.[5,6] The majority of irAEs are manageable and reversible, although corticosteroid or other immunosuppressive therapy may be required. However severe life-threatening irAEs may also occur.[7,8] Toxicities are graded according to the Common Terminology Criteria for Adverse Events system, and higher-grade toxicities may necessitate withholding ICIs and administering high-dose corticosteroids until improvement followed by slow tapering of corticosteroids.[8,9] However, these criteria were mainly developed to grade the toxicity of cytotoxic chemotherapy and may not always be relevant to long-term endocrine sequalae, for example the criteria for different grades of hyperglycaemia do not match the diagnostic criteria for diabetes.

The pathways targeted by current ICIs, CTLA-4 and PD-1/PD-L1 are known to be involved in innate autoimmunity in both thyroid disease[10] and diabetes.[11] It is therefore perhaps not surprising that blockade of these pathways promotes the development of endocrinopathy that resembles natural autoimmune endocrine disease (Figure 1). Furthermore, earlier attempts to modulate the immune system in cancer, through interferon and interleukin-2 have also resulted in endocrine dysfunction.[12,13] However, there are also important differences from the common endocrine presentations that will be highlighted in this review.

Endocrine toxicities of ICIs are amongst the more common irAEs described, predominantly thyroid and pituitary dysfunction, but diabetes resembling type 1 diabetes has also been well described.[14,15] Unlike other irAEs, disruption of the endocrine system tends to be irreversible and lead to a need for lifelong hormone supplementation. The protean symptoms of endocrine dysfunction can lead to hospitalization and death if not recognised early. Thus, clinicians need to be alert to the signs and symptoms of the likely endocrine consequences of ICIs, whilst endocrinologists need to be aware of the likely patterns of endocrine dysfunction.

Given that many nonendocrine irAEs are managed with high-dose corticosteroids,[8,9] consideration also needs to be given to the management of side effects of high-dose glucocorticoid treatment, including hyperglycaemia, osteoporosis and the risk of adrenal suppression.

Thyroid

The thyroid gland is the endocrine organ most commonly affected by ICI therapy. Determining the frequency of thyroid abnormalities from trials can be challenging due to a variety of definitions used.[16] Several large retrospective reviews, however, have shown around 30% of patients with a variety of primary malignancies develop thyroid dysfunction following ICIs.[17–19] Thyroid dysfunction is most common following combination therapy with PD-1 and CTLA inhibitors, followed by PD-1/PDL-1 alone and least common with ipilimumab monotherapy.[15,20]

Both hyperthyroidism and hypothyroidism are described, presumed due to an immune-mediated destructive thyroiditis. Hyperthyroidism occurs earlier in therapy, and is usually transient with a high incidence of subsequent hypothyroidism, although this is not universal.[17,18] Hypothyroidism can develop either after hyperthyroidism, or *de novo*, and usually occurs later.[21,22] Most patients with frank hypothyroidism require

thyroid hormone replacement and recovery seems a relatively rare occurrence once clinically overt hypothyroidism has developed,[18] although it is described in those with subclinical hypothyroidism only.[17]

Notably, despite the presumed immune mediated process, the proportion of patients with positive thyroid peroxidase antibodies is far lower than observed in Hashimoto's thyroiditis, ranging from 18% to 45% in more recent studies.[18,23] Several studies, however, have reported an association between thyroid autoimmunity at baseline, as manifested by positive thyroid autoantibodies, and subsequent risk of ICI induced thyroid dysfunction[24,25] although results differ as to whether thyroid peroxidase or thyroglobulin antibodies show this association. Some studies report that a higher level of thyroid-stimulating hormone (TSH) at baseline also predicts subsequent thyroid dysfunction.[17,25]

There are also cases of Graves' disease and thyroid eye disease occurring in combination or alone, mostly in patients treated with the CTLA-4 inhibitor ipilimumab.[26–31] Amongst those cases reporting iodine or technetium uptake it was increased, although reports of TSH-receptor antibodies were inconsistent.

Management

The product specifications for ICIs recommend regular monitoring of thyroid dysfunction, so many patients are diagnosed on the basis of abnormal thyroid function tests rather than in response to symptoms. Indeed, many patients are asymptomatic, although typical symptoms of both hyperthyroidism and hypothyroidism are described, and clinical correlation of abnormal results is required; for example, a low TSH result in the presence of normal FT4 and FT3 must be carefully interpreted to differentiate between asymptomatic primary hyperthyroidism or secondary hypothyroidism (see below).

In hyperthyroidism antithyroid drugs are rarely required, although guidelines suggest the use of beta blockers in symptomatic patients,[32] but there is a role for antithyroid drugs where Graves' disease is possible, for example in the presence of orbitopathy or persistent thyrotoxicosis. Glucocorticoids may be required in the rare situation of a painful thyroiditis. Interestingly, although hyperthyroidism frequently progresses to hypothyroidism, there are reports that those treated with glucocorticoids for other immune related events may not progress.[17,25] High-dose glucocorticoid treatment may also be required in those individuals that develop severe orbitopathy owing to Graves' disease. Whilst thyroiditis can usually be readily distinguished from Graves' disease based on clinical presentation and time course, TSH receptor antibodies, technetium uptake or doppler ultrasonography may have a role in selected cases.

Hypothyroidism is managed with levothyroxine replacement with standard approaches, and most guidelines recommend a similar approach to sporadic thyroid disease, with treatment in the case of a low T4 or persistently raised TSH more than twice the upper limit of normal.[9]

In general, ICI therapy should not be stopped in cases of thyroid irAEs, although interruption of treatment may be required in cases of severe thyrotoxicosis, and cases of severe thyroid eye disease.

Once hypothyroidism has developed, follow-up should be on the same basis as other causes of hypothyroidism and specialist endocrine input may not be required for uncomplicated hypothyroidism.

Pituitary

Pituitary irAEs have also emerged as an important and potentially life-threatening toxicity. With increasing experience, it seems there are two distinct patterns of pituitary involvement. The CTLA-4 inhibitor ipilimumab alone or in combination with a PD-1 inhibitor causes a condition closely resembling lymphocytic hypophysitis, with frequent enlargement of the pituitary and often multiple pituitary hormone deficiencies.[33–40] The PD-1 and PD-L1 inhibitors less commonly affect the pituitary, and when they do, it most frequently results in isolated adrenocorticotropic hormone (ACTH) deficiency.[41,42] Both conditions, however, are referred to in the literature and in clinical trials as hypophysitis. In this article, we refer to 'ipilimumab induced hypophysitis' and 'isolated ACTH deficiency' to separate these presentations. Hypophysitis is being reported with increasing frequency, likely due to the increasing use of ICIs, but probably also reflecting increased recognition.[43]

Ipilimumab-induced hypophysitis has been described following treatment of patients with melanoma and renal cancer, although most reports and series are based on use in melanoma. Although the reported incidence has varied between trials, a recent meta-analysis showed an incidence of 5.6% in patients treated with ipilimumab monotherapy, and 8.8–10.5% treated with a combination of ipilimumab and nivolumab;[20] although a previous analysis suggested slightly lower figures, the incidence was still highest after combination therapy.[15] Some case series have shown an increased risk in men and with older age.[35,44]

Hypophysitis is a relatively late side effect of ipilimumab, generally occurring after the third or fourth cycle of treatment,[34] with a median time of onset of 83 days, with no difference in those receiving combination therapy.[21]

Whilst many patients present with signs or symptoms of endocrine dysfunction, headache is frequently described,[35,36,45] and some patients have pituitary enlargement on magnetic resonance imaging (MRI).[36,44,46] Visual field defects, however, seem to be rare. Pituitary imaging, usually with MRI, is recommended, especially in patients presenting with headache or visual disturbance, not only to assess pituitary enlargement, but also to rule out pituitary metastases as an alternative cause of hypopituitarism.

ACTH deficiency is the most common endocrine abnormality, with TSH and gonadotrophin deficiency also common.[35,36,44,45] Prolactin levels are variable. Diabetes insipidus seems to be a rare occurrence.[47] Two studies have shown that a fall in TSH predicts the development of hypophysitis,[44,48] but this has not been validated prospectively.

An autopsy series supports an immune basis for hypophysitis, with T-cell infiltrates and IgG immunofixation in affected pituitaries,[33] whilst direct pituitary expression of CTLA-4 was also found, a finding confirmed in a mouse model where hypophysitis could be induced by ipilimumab even without the presence of a cancer.[49]

In contrast, patients receiving a PD-1 or PD-L1 inhibitor alone have a much lower risk of pituitary involvement[15] at between 0.5% and 1%,[20] and reports to date have shown isolated ACTH deficiency without other pituitary hormone deficiencies or MRI changes.

Management

Monitoring of symptoms is crucial to detect signs of pituitary insufficiency. Fatigue, hypoglycaemia, hypotension and hyponatraemia are suggestive of cortisol deficiency and urgent assessment and treatment is required. A falling TSH level or other biochemical evidence of secondary hypothyroidism (such as a fall in free T4 levels without a rise in TSH) should prompt fuller assessment of pituitary function, as should the onset of headache in a patient treated with ipilimumab (although the prospective value of this is not known). Nor is it known whether screening with cortisol measurements is helpful, but prompt assessment in those with compatible symptoms is required, preferably with a morning cortisol level. Morning cortisol levels below 350 nmol/l may represent hypoadrenalism, and cortisol levels less than 100 nmol/l highly indicate cortisol deficiency and urgent assessment must take place to start on glucocorticoid treatment. A detailed drug history with regards to recent glucocorticoid use is essential to enable interpretation of results, especially given the prevalent use of corticosteroids in around a third of patients for nonendocrine adverse events.[50] Dynamic testing of cortisol secretion with a cosyntropin (short synacthen) test might fail to demonstrate cortisol deficiency if the adrenal glands are intact in the acute phase of hypopituitarism. An insulin tolerance test is the gold standard to assess ACTH deficiency, but its use is limited owing to the risks associated with inducing hypoglycaemia. Thus, a high clinical index of suspicion is required and all unstable patients receiving ICIs should be assumed to have cortisol deficiency until proven otherwise.

Unwell patients should be treated with high dose hydrocortisone intravenously initially and, when stable, they should be established on oral glucocorticoid (hydrocortisone or prednisolone) replacement under endocrinologist advice, as in any other presentation of hypoadrenalism. ACTH and renin levels may be required to rule out primary adrenal insufficiency.[32] High-dose corticosteroids do not improve endocrine outcomes,[45] and have been associated with worse oncological outcomes,[51] although may have a role in rare patients with significant pituitary enlargement to prevent chiasmal compression. Thus, clinically

stable patients identified with cortisol deficiency may be safely treated with replacement doses of oral glucocorticoids, such as hydrocortisone or low-dose prednisolone.[52]

When hypophysitis is suspected, a diagnosis of secondary hypothyroidism is made when low TSH level is found in the presence of low and even normal free T4 and free T3. It is important to highlight that treatment with levothyroxine must take place only after hypocortisolism has been excluded. It can be difficult to distinguish sick euthyroid syndrome from secondary hypothyroidism, especially in unwell patients owing to the malignancy or other irAEs, so clinical correlation is critical.

Other hormone replacement including oestrogen or testosterone could be considered when safe and clinically indicated. Growth hormone replacement will usually be contraindicated owing to the malignancy, so detailed assessment of this axis is not helpful. There are reports of normalization of thyroid axis and gonadotrophins after treatment withdrawal,[44] but secondary adrenal insufficiency usually persists.

Patient education is vital, especially around sick day rules and treatment of adrenal crisis, particularly given the risk of other irAEs, for example colitis causing diarrhoea.

Diabetes

ICI treatment may lead to pancreatitis affecting endocrine and exocrine pancreatic function. A presumed autoimmune-mediated pancreatitis is also described[53] and can result in hyperglycaemia.[54] However, there are now multiple case reports in the literature of new onset insulin-requiring hyperglycaemia and worsening of hyperglycaemia in patients with pre-existing type 2 diabetes following treatment with PD-1/PD-L1 inhibitors.[55,56] Although this was reported to be a rare side effect, meta-analysis now reports rates of between 0.4% and 2%,[20] and can occur up to a year into therapy.[57]

Many patients present with diabetic ketoacidosis (DKA), and rapid onset of insulin deficiency, termed fulminant diabetes, is often described.[54,57–59] GAD and islet antigen 2 antibody positivity is described but is not universal, whilst some reports show the presence of high-risk HLA alleles for autoimmune diabetes.[55] Notably there is no evidence that corticosteroid treatment reverses the insulin deficiency.[60]

Management

Given the rapid onset of insulin deficiency described, all acutely unwell patients receiving ICI should have their plasma glucose checked, with urgent assessment of ketosis and acidosis if hyperglycaemia is detected. DKA should be managed with standard approaches, whilst those with new onset hyperglycaemia without DKA should be commenced on subcutaneous insulin.

As with any new diagnosis of diabetes requiring insulin treatment, prior to discharge, patients must have a system in place to ensure safe and regular administration of insulin. Patients should be referred to the diabetes team, and a diabetes specialist nurse review is crucial to provide initial education. This is particularly important as patients might also receive glucocorticoids that will likely exacerbate hyperglycaemia. Most guidelines recommend continuing the ICI once glucose levels are controlled,[8] although this approach has been challenged given the report of residual beta cell function in a patient presenting with fulminant diabetes after withdrawal of the ICI.[61]

Adrenals

Primary adrenal insufficiency post ICI therapy has been seldomly reported, with only a few cases being described in the literature since 2011. It is, however, extremely important to be aware of its occurrence in view of the potentially catastrophic consequences of an unrecognised adrenal crisis. The cases described in the literature were related to treatment with ipilimumab,[62] nivolumab,[63–65] pembrolizumab[66] and avelumab.[67] On imaging, one patient had adrenalitis with bilateral enlargement of the adrenal glands on a computed tomography (CT) scan, a second case had increased uptake on a positron emission tomography-CT scan, and a third case showed atrophic adrenals on follow-up scan post-diagnosis of adrenal insufficiency with positive CYP21 antibodies.[14] Out of those, three cases presented as adrenal crisis, two were found to have low morning cortisol, and one presented with hyponatraemia.[14]

Table 1. Frequency of different endocrinopathies.

		CTLA-4 inhibitor	*PD-1/PD-L1 inhibitor*
Pituitary	Hypophysitis/hypopituitarism	+++	–
	Isolated ACTH deficiency	+	++
Thyroid	Thyroiditis/transient hyperthyroidism	++	+++
	Hypothyroidism	++	+++
	Graves' disease/thyroid eye disease	+	?
Pancreas	Insulin-deficient diabetes	–	++
Adrenal	Primary adrenal insufficiency	+	+

ACTH: adrenocorticotropic hormone; CTLA-4: cytotoxic T-cell lymphocyte antigen-4; PD-1/PD-L1: program death-1 receptor or ligand.
+++>5%.
++0.5–5%.
+<0.5%.
?Unknown.
-Not described.

Management

Distinguishing between primary and secondary adrenal insufficiency is important to determine treatment, since mineralocorticoid (fludrocortisone) replacement may be required in primary adrenal insufficiency, and to guide radiological investigation looking for potential adrenal or pituitary metastasis. Otherwise management of the unwell patient with primary adrenal insufficiency is as per standard approaches.

Parathyroids

Hypoparathyroidism is a rare event and only a few case reports have described its occurrence as an adverse effect of ICI therapy.[68–70]

Management

Acute hypocalcaemia can be a medical emergency presenting with neuromuscular irritability and seizures. It should be treated as per general guidelines with intravenous calcium infusion in cases of severe symptomatic hypocalcaemia, and oral calcium replacement in mild to moderate cases. In patients with hypoparathyroidism, active vitamin D (calcitriol) or vitamin D analogue (1-alfacalcidol) is required to maintain calcium homeostasis and skeletal health.

Endocrine consequences of high-dose glucocorticoid use

About one third of patients receiving an ICI will require high-dose glucocorticoid treatment for the management of nonendocrine irAEs[50] and these patients are at risk of glucocorticoid-induced hyperglycaemia and osteoporosis (as well as nonendocrine toxicity of glucocorticoids such as gastritis and infection) that should be managed as per existing guidelines.[71,72] These patients will also be at risk of adrenal suppression. As multiple irAEs can occur in the same patient, it is possible that some of these patients will also have ACTH deficiency and distinguishing ongoing adrenal suppression from ACTH deficiency as a separate irAE may be challenging.

Conclusion

The advent of ICIs has resulted in many new presentations of endocrine disease (summarized in Table 1). Physicians in many medical specialties, especially those in acute medical care and emergency medicine, should be alert to signs and symptoms of ICIs and how to diagnose and treat them. Endocrinologists need awareness of these manifestations to ensure prompt recognition and management of such potentially life-threatening but manageable toxicities of cancer treatment. Many patients do not recover endocrine function

but some achieve long-term survival even after treatment of metastatic cancers, therefore resulting in a rapidly increasing number of patients requiring lifelong hormone replacement therapy under specialist endocrine supervision.

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References

1. Buchbinder E and Hodi FS. Cytotoxic T lymphocyte antigen-4 and immune checkpoint blockade. *J Clin Invest* 2015; 125: 3377–3383.
2. Buchbinder EI and Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. *Am J Clin Oncol* 2016; 39: 98–106.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, *et al.* Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; 373: 23–34.
4. Doroshow DB, Sanmamed MF, Hastings K, *et al.* Immunotherapy in non-small cell lung cancer: facts and hopes. *Clin Cancer Res* 2019; 25: 4592–4602.
5. Abdel-Wahab N, Shah M and Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: a systematic review of case reports. *PLoS One* 2016; 11: e0160221.
6. De Velasco G, Je Y, Bosse D, *et al.* Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol Res* 2017; 5: 312–318.
7. Spain L, Diem S and Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev* 2016; 44: 51–60.
8. Brahmer JR, Lacchetti C, Schneider BJ, *et al.* Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. *J Clin Oncol* 2018; 36: 1714–1768.
9. Haanen J, Carbonnel F, Robert C, *et al.* Management of toxicities from immunotherapy: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: iv119–iv142.
10. Fathima N, Narne P and Ishaq M. Association and gene–gene interaction analyses for polymorphic variants in CTLA-4 and FOXP3 genes: role in susceptibility to autoimmune thyroid disease. *Endocrine* 2019; 64: 591–604.
11. Martinov T, Spanier JA, Pauken KE, *et al.* PD-1 pathway-mediated regulation of islet-specific $CD4^+$ T cell subsets in autoimmune diabetes. *Immunoendocrinology (Houst)* 2016; 3: e1164.
12. Atkins MB, Mier JW, Parkinson DR, *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; 318: 1557–1563.
13. Weijl NI, Van der Harst D, Brand A, *et al.* Hypothyroidism during immunotherapy with interleukin-2 is associated with antithyroid antibodies and response to treatment. *J Clin Oncol* 1993; 11: 1376–1383.
14. Tan MH, Iyengar R, Mizokami-Stout K, *et al.* Spectrum of immune checkpoint inhibitors-induced endocrinopathies in cancer patients: a scoping review of case reports. *Clin Diabetes Endocrinol* 2019; 5: 1.
15. Barroso-Sousa R, Barry WT, Garrido-Castro AC, *et al.* Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. *JAMA Oncol*. Epub ahead of print 4 October 2017. DOI: 10.1001/jamaoncol.2017.3064.
16. Ferris R and Gillison ML. Nivolumab for squamous-cell cancer of head and neck. *N Engl J Med* 2017; 376: 595–596.
17. Morganstein DL, Lai Z, Spain L, *et al.* Thyroid abnormalities following the use of cytotoxic T-lymphocyte antigen-4 and programmed death receptor protein-1 inhibitors in the treatment of melanoma. *Clin Endocrinol (Oxf)* 2017; 86: 614–620.

18. Iyer PC, Cabanillas ME, Waguespack SG, *et al*. Immune-related thyroiditis with immune checkpoint inhibitors. *Thyroid* 2018; 28: 1243–1251.

19. Gay S, Rossi G, Corica G, *et al*. Can baseline endocrinological examination and thyroid ultrasound predict the development of thyroid disease in immunotherapy-treated patients? Results from a prospective, single-center, open-label study. *Endocrine*. Epub ahead of print 7 March 2019. DOI: 10.1007/s12020-019-01854-8.

20. de Filette J, Andreescu CE, Cools F, *et al*. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. *Horm Metab Res* 2019; 51: 145–156.

21. Scott ES, Long GV, Guminski A, *et al*. The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. *Eur J Endocrinol* 2018; 178: 173–180.

22. Campredon P, Mouly C, Lusque A, *et al*. Incidence of thyroid dysfunctions during treatment with nivolumab for non-small cell lung cancer: retrospective study of 105 patients. *Presse Med* 2019; 48: e199–e207.

23. Mazarico I, Capel I, Gimenez-Palop O, *et al*. Low frequency of positive antithyroid antibodies is observed in patients with thyroid dysfunction related to immune check point inhibitors. *J Endocrinol Invest*. Epub ahead of print 17 May 2019. DOI: 10.1007/s40618-019-01058-x.

24. Kobayashi T, Iwama S, Yasuda Y, *et al*. Patients with antithyroid antibodies are prone to develop destructive thyroiditis by nivolumab: a prospective study. *J Endocr Soc* 2018; 2: 241–251.

25. Kimbara S, Fujiwara Y, Iwama S, *et al*. Association of antithyroglobulin antibodies with the development of thyroid dysfunction induced by nivolumab. *Cancer Sci* 2018; 109: 3583–3590.

26. Borodic G, Hinkle DM and Cia Y. Drug-induced Graves' disease from CTLA-4 receptor suppression. *Ophthalmic Plast Reconstr Surg* 2011; 27: e87–e88.

27. Borodic GE and Hinkle D. Ipilimumab-induced orbital inflammation resembling Graves' disease with subsequent development of systemic hyperthyroidism from CTLA-4 receptor suppression. *Ophthalmic Plast Reconstr Surg* 2014; 30: 83.

28. McElnea E, Ni Mhealoid A, Moran S, *et al*. Thyroid-like ophthalmopathy in a euthyroid patient receiving ipilimumab. *Orbit* 2014; 33: 424–427.

29. Azmat U, Liebner D, Joehlin-Price A, *et al*. Treatment of Ipilimumab induced Graves' disease in a patient with metastatic melanoma. *Case Rep Endocrinol* 2016; 2016: 1–4.

30. Rhea L, Yoon JW and Jang S. Rapid development of Graves' ophthalmopathy after treatment with ipilimumab and recurrence with pembrolizumab in a patient with previously treated Graves' disease. *J Oncol Pract* 2018; 14: 747–749.

31. Sagiv O, Kandl TJ, Thakar SD, *et al*. Extraocular muscle enlargement and thyroid eye disease-like orbital inflammation associated with immune checkpoint inhibitor therapy in cancer patients. *Ophthalmic Plast Reconstr Surg* 2019; 35: 50–52.

32. Higham CE, Olsson-Brown A, Carroll P, *et al*. Society for endocrinology endocrine emergency guidance: acute management of the endocrine complications of checkpoint inhibitor therapy. *Endocrine Connections* 2018; 7: G1–G7.

33. Caturegli P, Di Dalmazi G, Lombardi M, *et al*. Hypophysitis secondary to cytotoxic T-lymphocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. *Am J Pathol* 2016; 186: 3225–3235.

34. Lam T, Chan MM, Sweeting AN, *et al*. Ipilimumab-induced hypophysitis in melanoma patients: an Australian case series. *Intern Med J* 2015; 45: 1066–1073.

35. Albarel F, Gaudy C, Castinetti F, *et al*. Long-term follow-up of ipilimumab-induced hypophysitis, a common adverse event of the anti-CTLA-4 antibody in melanoma. *Eur J Endocrinol* 2015; 172: 195–204.

36. Faje AT, Sullivan R, Lawrence D, *et al*. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. *J Clin Endocrinol Metab* 2014; 99: 4078–4085.

37. De Sousa SM, Long GV and Tonks KT. Ipilimumab-induced hypophysitis: early Australian experience. *Med J Aust* 2014; 201: 198–199.

38. Chodakiewitz Y, Brown S, Boxerman JL, *et al*. Ipilimumab treatment associated pituitary hypophysitis: clinical presentation and imaging diagnosis. *Clin Neurol Neurosurg* 2014; 125c: 125–130.

39. Torino F, Barnabei A, De Vecchis L, *et al*. Hypophysitis induced by monoclonal antibodies to cytotoxic T lymphocyte antigen 4: challenges

from a new cause of a rare disease. *Oncologist* 2012; 17: 525–535.

40. Dillard T, Yedinak CG, Alumkal J, *et al*. Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary* 2010; 13: 29–38.

41. Kanie K, Iguchi G, Bando H, *et al*. Two cases of atezolizumab-induced hypophysitis. *J Endocr Soc* 2018; 2: 91–95.

42. Okano Y, Satoh T, Horiguchi K, *et al*. Nivolumab-induced hypophysitis in a patient with advanced malignant melanoma. *Endocr J* 2016; 63: 905–912.

43. Guerrero E, Johnson DB, Bachelot A, *et al*. Immune checkpoint inhibitor-associated hypophysitis-World Health Organisation VigiBase report analysis. *Eur J Cancer* 2019; 113: 10–13.

44. Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. *Pituitary* 2016; 19: 82–92.

45. Min L, Hodi FS, Giobbie-Hurder A, *et al*. Systemic high-dose corticosteroid treatment does not improve the outcome of ipilimumab-related hypophysitis: a retrospective cohort study. *Clin Cancer Res* 2015; 21: 749–755.

46. Rodrigues BT, Otty Z, Sangla K, *et al*. Ipilimumab-induced autoimmune hypophysitis: a differential for sellar mass lesions. *Endocrinol Diabetes Metab Case Rep* 2014; 2014: 140098.

47. Zhao C, Tella SH, Del Rivero J, *et al*. Anti-PD-L1 treatment induced central diabetes insipidus. *J Clin Endocrinol Metab* 2018; 103: 365–369.

48. De Sousa SMC, Sheriff N, Tran CH, *et al*. Fall in thyroid stimulating hormone (TSH) may be an early marker of ipilimumab-induced hypophysitis. *Pituitary*. Epub ahead of print 31 January 2018. DOI: 10.1007/s11102-018-0866-6.

49. Iwama S, De Remigis A, Callahan MK, *et al*. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. *Sci Transl Med* 2014; 6: 230ra245.

50. Horvat TZ, Adel NG, Dang TO, *et al*. Immune-related adverse events, need for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering cancer center. *J Clin Oncol* 2015; 33: 3193–3198.

51. Faje AT, Lawrence D, Flaherty K, *et al*. High-dose glucocorticoids for the treatment of ipilimumab-induced hypophysitis is associated with reduced survival in patients with melanoma. *Cancer* 2018; 124: 3706–3714.

52. Choudhury S, Lightman S and Meeran K. Improving glucocorticoid replacement profiles in adrenal insufficiency. *Clin Endocrinol (Oxf)* 2019; 91: 367–371.

53. Cramer P and Bresalier RS. Gastrointestinal and hepatic complications of immune checkpoint inhibitors. *Curr Gastroenterol Rep* 2017; 19: 3.

54. Marchand L, Thivolet A, Dalle S, *et al*. Diabetes mellitus induced by PD-1 and PD-L1 inhibitors: description of pancreatic endocrine and exocrine phenotype. *Acta Diabetologica*. Epub ahead of print 5 October 2018. DOI: 10.1007/s00592-018-1234-8.

55. Galligan A, Xu W, Fourlanos S, *et al*. Diabetes associated with immune checkpoint inhibition: presentation and management challenges. *Diabet Med*. Epub ahead of print 17 June 2018. DOI: 10.1111/dme.13762.

56. Clotman K, Janssens K, Specenier P, *et al*. Programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus: mini-review. *J Clin Endocrinol Metab*. Epub ahead of print 30 June 2018. DOI: 10.1210/jc.2018-00728.

57. Okamoto M, Okamoto M, Gotoh K, *et al*. Fulminant type 1 diabetes mellitus with anti-programmed cell death-1 therapy. *J Diabetes Investig* 2016; 7: 915–918.

58. Mizab Mellah C, Sanchez Perez M, Santos Rey MD, *et al*. Fulminant type 1 diabetes mellitus associated with pembrolizumab. *Endocrinol Diabetes Nutr* 2017; 64: 272–273.

59. Munakata W, Ohashi K, Yamauchi N, *et al*. Fulminant type I diabetes mellitus associated with nivolumab in a patient with relapsed classical Hodgkin lymphoma. *Int J Hematol* 2017; 105: 383–386.

60. Aleksova J, Lau PK, Soldatos G, *et al*. Glucocorticoids did not reverse type 1 diabetes mellitus secondary to pembrolizumab in a patient with metastatic melanoma. *BMJ Case Rep*. Epub ahead of print 25 November 2016. DOI: 10.1136/bcr-2016-217454.

61. Sakai G, Saito D, Nakajima R, *et al*. Intrinsic insulin secretion capacity might be preserved by discontinuing anti-programmed cell death protein 1 antibody treatment in 'anti-programmed cell death protein 1 antibody-induced' fulminant type 1 diabetes. *J Diabetes Investig* 2018; 9: 448–449.

62. Min L and Ibrahim N. Ipilimumab-induced autoimmune adrenalitis. *Lancet Diabetes Endocrinol* 2013; 1: e15.

63. Coskun NSS, Simsir IY and Göksel T. A case with a primary adrenal insufficiency secondary to nivolumab. *Eur Respir J* 2016; 48: PA4853.

64. Trainer H, Hulse P, Higham CE, *et al*. Hyponatraemia secondary to nivolumab-induced primary adrenal failure. *Endocrinol Diabetes Metab Case Rep*. Epub ahead of print 20 November 2016. DOI: 10.1530/edm-16-0108.

65. Akarca FK, Can O, Yalcinli S, *et al*. Nivolumab, a new immunomodulatory drug, a new adverse effect; adrenal crisis. *Turk J Emerg Med* 2017; 17: 157–159.

66. Hanna RM, Selamet U, Bui P, *et al*. Acute kidney injury after pembrolizumab-induced adrenalitis and adrenal insufficiency. *Case Rep Nephrol Dial* 2018; 8: 171–177.

67. Aziz K, Shahbaz A, Umair M, *et al*. Avelumab inducing hypothyroidism and hypoadrenalism: a case report and review of literature. *EXCLI J* 2018; 17: 526–530.

68. Piranavan P, Li Y, Brown E, *et al*. Immune checkpoint inhibitor-induced hypoparathyroidism associated with calcium-sensing receptor-activating autoantibodies. *J Clin Endocrinol Metab* 2019; 104: 550–556.

69. Manohar S, Kompotiatis P, Thongprayoon C, *et al*. Programmed cell death protein 1 inhibitor treatment is associated with acute kidney injury and hypocalcemia: meta-analysis. *Nephrol Dial Transplant* 2019; 34: 108–117.

70. Win MA, Thein KZ, Qdaisat A, *et al*. Acute symptomatic hypocalcemia from immune checkpoint therapy-induced hypoparathyroidism. *Am J Emerg Med* 2017; 35: 1039 e1035–1039

71. Joint British Diabetes Societies. Management of hyperglycaemia and steroid (glucocorticoid) therapy, https://www.diabetes.org.uk/resources-s3/2017-09/JBDS%20management%20of%20hyperglycaemia%20and%20steriod%20therapy_0.pdf (2014, accessed 18 March 2018).

72. Compston J, Cooper A, Cooper C, *et al*. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2017; 12: 43.