Endocrine complications of immunotherapies: a review

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Use of immune checkpoint inhibitors in cancer treatment has increased vastly over the past decade, as both single and combination agent therapies. While having a positive impact on survival rates, adverse effects have been noted, with endocrine effects in around 10% of patients. Thyroid disease and hypophysitis are the most commonly encountered, with diabetes mellitus and primary adrenal insufficiency also reported, as well as more rare endocrinopathies. Patient and clinician education to raise awareness of these effects, as well as regular monitoring to enable early recognition, diagnosis and prompt treatment of the immune side effects, are key. In this review, we discuss the aetiology, presentation and management of the endocrine complications of immunotherapies that are relevant to the general physician, as well as highlighting important areas where further research is still needed.

KEYWORDS: immunotherapy, cancer, endocrine, thyroid, hypophysitis

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Introduction

The advent of immunotherapy has revolutionised cancer treatment across the world. Through harnessing the immune system to target malignant cells, previously untreatable cancers now have radically improved survival rates. The use of immunotherapy has increased over the past decade, becoming commonly used for a number of solid tumours and haematological malignancies. However, a predicted 60–95% of patients experience ill effects, which, if left untreated, may be life-threatening.

Checkpoint inhibitors are a group of monoclonal antibody therapies that can be used in isolation or in combination. They are given via intravenous infusion, typically every 3–6 weeks, for up to 2 years. They exert their effect by upregulating the immune response to malignant cells, blocking the usual inhibitory pathways of T-cell regulation. The receptors cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its associated ligand (PD-L-1) are targeted by the inhibitors. The immune system can be manipulated at two different stages, as CTLA-4 acts in the early stage of triggering an antigen response, while PD-1 and PD-L-1 act in modulating the interaction with peripheral tissue. For this reason, combination therapy has been demonstrated to be effective. The mechanisms of action are summarised in Fig 1.

Ipilimumab, a CTLA-4 inhibitor, became the first approved checkpoint inhibitor in 2011, with 1–2-year survival rates doubling for metastatic melanoma, including for patients with advanced disease. By 2014, the PD-1 inhibitors nivolumab and pembrolizumab were approved, showing superior and sustained increases in melanoma survival. PD-1 inhibitors and newer PD-L-1 inhibitors are now licensed to treat a variety of other cancers, including renal cell carcinoma and non-small cell lung cancer (Table 1). Combination of CTLA-4 and PD-1 inhibitors has been

![Fig 1. Simplified illustration of the mechanism of checkpoint inhibitor modulation of the immune response to cancer cells.](image-url)
### Table 1. List of checkpoint inhibitors and their uses, with notable adverse effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Cancer sites with EMA approval for treatment</th>
<th>Notable adverse effects</th>
<th>Notable endocrine effects(^{10,14,16})</th>
<th>Dose-dependent adverse effects?</th>
<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>Anti-CTLA-4 mAb</td>
<td>Melanoma</td>
<td>&gt;10% fatigue/rash/diarrhoea</td>
<td>Greater risk of hypophysitis than other monotherapy (3%)</td>
<td>Yes</td>
<td>Inferior effects on survival compared with other checkpoint inhibitor monotherapy or combination</td>
</tr>
<tr>
<td>Tremelimumab</td>
<td>Anti-CTLA-4 mAb</td>
<td>Not approved by EMA/FDA currently</td>
<td>Less known, likely similar to ipilimumab</td>
<td>2–5% thyroid dysfunction 1% adrenal insufficiency</td>
<td>Yes</td>
<td>Granted ODD by FDA for treating HCC in combination with durvalumab</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>Anti-PD-1 mAb</td>
<td>Melanoma, NSCLC (PD-1 expressing or non-squamous), Hodgkin’s lymphoma, Urothelial, RCC, Head and neck SCC</td>
<td>&gt;20% fatigue/nausea/diarrhoea 34% skin effects(^3)</td>
<td>5–10% thyroid dysfunction Greater risk of hyperthyroid compared with anti-PD-L-1 Highest incidence diabetes mellitus (1%) 1% adrenal insufficiency</td>
<td>No</td>
<td>Patients with tumours expressing high PD-L-1 levels have a better response and this is used to stratify treatment choice in NSCLC</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>Anti-PD-1 mAb</td>
<td>Melanoma, NSCLC, Hodgkin’s lymphoma, Urothelial, RCC, Head and neck SCC</td>
<td>&gt;10% fatigue/nausea/appetite loss 34% skin effects(^3)</td>
<td>5–10% thyroid dysfunction (greater risk of hyperthyroid compared with anti-PD-L-1) 0.5–1% diabetes mellitus 1% adrenal insufficiency</td>
<td>No</td>
<td>Studies proving benefit after failure of platinum-based chemotherapy</td>
</tr>
</tbody>
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Table 1. List of checkpoint inhibitors and their uses, with notable adverse effects (Continued)

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<tr>
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<th>Notable endocrine effects</th>
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<th>Other comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>Anti-PD-L-1 mAb</td>
<td>NSCLC and SC lung cancer, Breast cancer (triple negative), Urithelial</td>
<td>&gt;10% fatigue/arthralgia/nausea/rash/diarrhoea</td>
<td>Most associated with adrenal insufficiency (1–2%)</td>
<td>No</td>
<td>Generally for advanced or metastatic disease, proven to improve survival particularly in combination with chemotherapy</td>
</tr>
<tr>
<td>Avelumab (Bavencio)</td>
<td>Anti-PD-L-1 mAb</td>
<td>Merkel cell carcinoma, RCC</td>
<td>&gt;10% fatigue/nausea/diarrhoea</td>
<td>1% diabetes mellitus, Fewer adrenal effects than other anti-PD-L-1 mAb</td>
<td>No</td>
<td>Granted conditional marketing authorisation in EU in 2017, awaiting further clinical evidence</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi)</td>
<td>Anti-PD-L-1 mAb</td>
<td>NSCLC</td>
<td>&gt;20% rash/cough/ENT infections &gt;10% drug-related pneumonia</td>
<td>1% diabetes mellitus, 1% adrenal insufficiency, Greater thyroid dysfunction than other PD-L-1 mAb</td>
<td>No</td>
<td>Used when tumours express high PD-L-1 levels</td>
</tr>
<tr>
<td>Ipilimumab and nivolumab</td>
<td>Anti-CTLA-4 mAb and anti-PD-1 mAb</td>
<td>Melanoma, RCC, Head and neck SCC</td>
<td>&gt;50% fever, fatigue, rash Greater incidence of all immune-related adverse effects</td>
<td>20% thyroid dysfunction, 6% hypophysitis, 5–7% adrenal insufficiency</td>
<td>Yes</td>
<td>Used for high-risk RCC as first line, and for melanoma with low PD-L-1 expression. Generally more effective than monotherapy</td>
</tr>
</tbody>
</table>

Unless specified above, information from EMA website. CRC = colorectal cancer; CTLA-4 = cytotoxic T-lymphocyte antigen 4; ENT = ear, nose and throat; EMA = European Medicines Agency; EU = European Union; FDA = US Food and Drug Administration; HCC = hepatocellular carcinoma; mAb = monoclonal antibody; MMR = mismatch repair gene; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; ODD = orphan drug designation; PD-1 = programmed cell death protein 1; PD-L-1 = programmed cell death protein ligand 1; RCC = renal cell cancer; SCC = squamous cell carcinoma.
shown to be effective in metastatic melanoma, colorectal and renal cancer, with a 58% 3-year survival for metastatic melanoma patients (which had previously been 20%). These survival rates demonstrate that these immunotherapy treatments have thus revolutionised the treatment of certain malignancies with a historically poor prognosis.

Despite these encouraging survival data, the drugs are not without adverse effects, ranging from mild biochemical abnormalities to fatal events (incidence reported as 0.64%). The mechanism is due to the exaggerated immune response towards non-cancerous cells, causing significant inflammation and destruction. The most commonly affected systems include the skin, gastrointestinal system, endocrine system and liver. The National Cancer Institute produced the Common Terminology Criteria for Adverse Events (CTCAE) to categorise the spectrum of toxicities from mild (grade 1) to death (grade 5), with severe symptoms requiring hospitalisation defined as grade 3 and above. Incidence of severe events is reported as 26% for monotherapy and increases to 55% with combination therapy. Immune-related endocrinopathies affect around 10% of all patients treated with checkpoint inhibitors. In those receiving PD-1 and CTLA-4 inhibitors, thyroid disease and hypophysitis are the most commonly encountered. Effects on the adrenal glands, pancreas and parathyroid glands have also been reported (Table 2). Most endocrinopathies present with non-specific symptoms, posing a diagnostic challenge as this patient group also can experience vague symptoms from malignant disease and anti-cancer treatment. The most commonly reported side effect of checkpoint inhibitors is fatigue, mostly without endocrine cause. Because of this, symptoms can be dismissed or attributed to other, less treatable causes. Diagnosis is also complicated by extensive use of corticosteroids, anti-emetics (co-administered with checkpoint inhibitors) and episodes of severe illness secondary to immunosuppression, which complicates diagnostic testing of hormonal axes.

While it is not fully understood why endocrine tissue is particularly vulnerable, hypotheses have been proposed. These include the expression of CTLA-4 in pituitary tissue and the role of PD-1/PD-L1 in immune tolerance disruption in the pathogenesis of autoimmune endocrinopathy. Additionally, endocrine tissue is non-regenerative and very low volume, so an immune destruction has large consequences on essential hormone secretion. Given the increasing use of these therapies, many such patients may present on the unselected medical intake. UK guidelines from the Society for Endocrinology provide practical guidance for this setting, but these are only useful if the general physician considers this differential diagnosis. Awareness should be raised as to the risk of such effects in patients on these medications among all physicians in order to avoid preventable morbidity and mortality.

**Endocrinopathies**

**Thyroid**

**Incidence and aetiology**

Primary thyroid disease represents the most common endocrine immune-related adverse effect. Overall incidence is reported as 8% for primary hypothyroidism and 3% for primary hyperthyroidism. Thyroid abnormalities are more commonly associated with PD-1 inhibitors and typically occur 4–10 weeks after initiation of treatment, but can occur up to 3 years later. Typically the disease process is a thyroiditis, which includes a brief, self-limiting thyrotoxic phase that lasts 3–6 weeks, followed by a prolonged hypothyroid phase. This phase is irreversible in two-thirds of patients. The most common mechanism described in the literature is an inflammatory destruction of the thyroid gland by cytotoxic T-cells, causing either excess thyroid hormones due to thyroid tissue breakdown, or inadequate hormone synthesis.

Rarely, isolated hyperthyroidism or hypothyroidism may be seen, and CTLA-4 or PD-1 inhibitors can cause an autoimmune-mediated Graves’ disease.

**Clinical presentation**

Presenting symptoms mirror those outside the use of immunotherapy and include lethargy, weight gain, dry skin and constipation in hypothyroidism, and weight loss, palpitations, anxiety and sweating in hyperthyroidism. Patients may also be identified on routine screening with few or no symptoms. Severe, life-threatening illness, such as myxoedema coma or thyrotoxic storm, is rare, occurring in 0.1% of cases.

**Diagnosis**

Diagnosis is confirmed using routine thyroid function tests (Fig 2). Autoantibodies should be tested if a diagnosis of Graves’ disease is considered (usually in the presence of ophthalmopathy, persistent thyrotoxicosis or a goitre). Incidence of severe events is reported as 26% for monotherapy and increases to 55% with combination therapy. Immune-related endocrinopathies affect around 10% of all patients treated with checkpoint inhibitors. In those receiving PD-1 and CTLA-4 inhibitors, thyroid disease and hypophysitis are the most commonly encountered. Effects on the adrenal glands, pancreas and parathyroid glands have also been reported (Table 2). Most endocrinopathies present with non-specific symptoms, posing a diagnostic challenge as this patient group also can experience vague symptoms from malignant disease and anti-cancer treatment. The most commonly reported side effect of checkpoint inhibitors is fatigue, mostly without endocrine cause. Because of this, symptoms can be dismissed or attributed to other, less treatable causes. Diagnosis is also complicated by extensive use of corticosteroids, anti-emetics (co-administered with checkpoint inhibitors) and episodes of severe illness secondary to immunosuppression, which complicates diagnostic testing of hormonal axes.

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**Pituitary**

**Incidence and aetiology**

Hypophysitis is the most common endocrinopathy caused by CTLA-4 inhibitors. It refers to inflammation of the pituitary gland or stalk, causing disruption of the hypothalamic–pituitary axis. Incidence is reported as 1.3% overall, with incidence on CTLA-4 inhibitors and combination therapy reported as 3% and 6%, respectively. Disruption of the hypothalamic–pituitary axis occurs due to pituitary damage, likely secondary to complement, antibody- and lymphocyte-driven processes, with pituitary necrosis occurring in severe disease. Hypophysitis can typically

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## Table 2. Summary of the adverse endocrine effects of immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Gland</th>
<th>Incidence</th>
<th>Most commonly associated checkpoint inhibitors</th>
<th>Typical time from treatment onset</th>
<th>Symptoms</th>
<th>Screening advised?</th>
<th>Suggested Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid</td>
<td>Hypothyroid: overall 8%, combination up to 13%</td>
<td>Anti-PD-1 mAb or combination</td>
<td>6 weeks (range 4–10 weeks)</td>
<td>Hypothyroid: fatigue, dry skin, constipation, depression, cold sensitivity, weight gain</td>
<td>TSH with every cycle or monthly, and 4–6 weeks after final cycle</td>
<td>TSH, T4, T3</td>
<td>Hold immunotherapy until symptoms controlled, then most can restart Continue if asymptomatic See Fig 2</td>
<td>Typical disease course 3–6 weeks hypothyroid, then prolonged hypothyroid Two-thirds required long-term thyroid replacement Hypothyroidism rarely persists</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroid: overall 2.9%, combination 8%</td>
<td></td>
<td></td>
<td>Hyperthyroid: fatigue, palpitations, diarrhoea, anxiety, insomnia, weight loss</td>
<td></td>
<td>Hypothyroid: Continue immunotherapy Hyperthyroid: continue immunotherapy if asymptomatic, hold if symptomatic and restart when symptoms resolve See Fig 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>Overall 1.3%, combination 6.4%</td>
<td>Anti-CTLA-4 mAb or combination</td>
<td>12 weeks (range 3–72 weeks)</td>
<td>General: fatigue, nausea Hormone deficiency: hypothyroid (see thyroid), low cortisol (see adrenal) and sex hormone deficiency (erectile dysfunction, menstrual disturbance, loss of libido) Mass effect: headache, visual loss</td>
<td>Nil</td>
<td>Low threshold for screening Cortisol (ideally 9am, random if unwell), ACTH, TSH, T4, LH/FSH, oestradiol (if premenopausal), testosterone (men), IGF-1, prolactin MRI pituitary</td>
<td>Hold immunotherapy until symptoms controlled, then most can restart Continue if asymptomatic See Fig 3</td>
<td>Secondary adrenal insufficiency (ACTH deficiency) mainly irreversible Thyroid and sex hormones tend to recover within 3 months</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Overall 0.5%, 1% with anti-PD-1/anti-PD-L-1</td>
<td>Anti-PD-1 or Anti-PD-L-1 mAb</td>
<td>7 weeks (range 1–52 weeks)</td>
<td>Thirst, polyuria, fatigue, weight loss Two-thirds present with DKA</td>
<td>Regular blood glucose monitoring Glucose, ketones, HbA1c, C-peptide, anti-GAD Ab, ICA Ab No imaging advised</td>
<td>Hold while blood glucose uncontrolled, restart once insulin initiated or stable Most need insulin therapy. If mild, trial oral antihyperglycaemic agents</td>
<td>Irreversible</td>
<td></td>
</tr>
<tr>
<td>Adrenal</td>
<td>Monotherapy 1%</td>
<td>Anti-PD-1 or Anti-CTLA-4 mAb or combination</td>
<td>10 weeks (range 1–36 weeks)</td>
<td>Fatigue, dizziness, weakness, nausea, abdominal pain</td>
<td>Nil</td>
<td>Low threshold for 9am cortisol Cortisol, ACTH, TFT CT adrenals</td>
<td>High-dose steroids initially, wean to hydrocortisone 20–30 mg/day Fludrocortisone if postural hypotension persists</td>
<td>Irreversible</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; CTLA-4 = cytotoxic T-lymphocyte antigen 4; FSH = follicular stimulating hormone; GAD = glutamic acid decarboxylase; ICA = islet cell antigen; IGF-1 = insulin-like growth factor 1; LH = luteinising hormone; mAb = monoclonal antibody; PD-1 = programmed cell death protein 1; PD-L-1 = programmed cell death protein ligand 1; T4 = thyroxine; T3 = triiodothyronine; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; TSHR = thyroid-stimulating hormone receptor.
Fig 2. Management of thyroid dysfunction secondary to checkpoint inhibitors: a clinical guide. Information as per Society for Endocrinology guidelines and UK Oncology Nursing Society.\textsuperscript{17,45} Ab = antibody; T4 = thyroxine; TFT = thyroid function test; TSH = thyroid-stimulating hormone; TSHR = thyroid-stimulating hormone receptor.

Clinical presentation
Presentation can be non-specific, including symptoms of nausea, fatigue and headache, many of which are common in cancer patients and often associated with its treatment. At presentation, 60% of patients have a headache.\textsuperscript{25} Other symptoms relate to secondary hormone deficiency, with 72% of patients exhibiting symptoms of secondary cortisol deficiency at presentation (dizziness, fatigue, nausea, vomiting, abdominal pain).\textsuperscript{25} Posterior lobe disorders are rare; in those who do experience this, symptoms mainly relate to secondary hormone deficiencies.\textsuperscript{18} Visual disturbance is rare in comparison to primary pituitary disorders as minimal pituitary enlargement occurs, thus reducing the risk of optic chiasm involvement.\textsuperscript{25}

Diagnosis
Diagnosis includes biochemical assessment of the hypothalamic–pituitary axis and imaging of the pituitary. If hypophysitis is suspected, a full pituitary screen is recommended, as summarised in Fig 3.

Imaging of the pituitary is pertinent in ruling out metastatic disease, with magnetic resonance imaging (MRI) being the gold standard.\textsuperscript{3,17,21} Society for Endocrinology guidelines recommend that this is done on an urgent basis, particularly if headache, diplopia or cranial nerve palsies are present.\textsuperscript{17} The pituitary may show mild to moderate enlargement in the acute phase and possible stalk thickening.\textsuperscript{27} Resolution of changes is often seen on repeat imaging within days to weeks.\textsuperscript{2,27}

Treatment
Management involves hormone replacement and referral to an endocrinologist. Those patients requiring glucocorticoid replacement usually require this for the long term. As previously mentioned, glucocorticoid should be initiated prior to thyroid replacement to avoid precipitating an adrenal crisis. Physiological doses are advised, with no evidence that high-dose steroid improves survival or reversibility.\textsuperscript{17,27} Intravenous methylprednisolone is only recommended for neurological complications of hypophysitis.\textsuperscript{17} Maintenance of 5 mg prednisolone once daily or hydrocortisone 10 mg twice daily is generally sufficient. Patient education is important, particularly regarding sick day rules and parenteral hydrocortisone administration if severely unwell.\textsuperscript{21} Mineralocorticoids do not need to be replaced as they are still produced due to renin–angiotensin regulation.\textsuperscript{3,15}

In patients requiring thyroid and gonadal hormone replacement, this is usually on a temporary basis. Thyroid replacement should start at a low dose and be titrated to T4 levels, with TSH monitoring useful for indication of pituitary thyrotroph recovery.\textsuperscript{1} Sex hormone replacement can be considered with oestradiol for premenopausal women and testosterone for men, with caution paid to contraindications – particularly malignancy related and risk of thrombosis with oestrogen replacement.\textsuperscript{29}
Pancreas

Incidence and aetiology

While less common than thyroid or pituitary disease, the life-threatening consequences of pancreatic tissue destruction caused by checkpoint inhibitors are clinically important. PD-1 and PD-L1 agents are associated with a 1% incidence of diabetes mellitus (DM), either new-onset type 1 DM or worsening type 2 DM. The mechanism appears similar to the permanent autoimmune process of type 1 DM, but with faster, aggressive destruction of beta islet cells, likely mediated by T-cells, requiring rapid insulin replacement. Of those developing type 1 DM secondary to immunotherapy, approximately 70% of patients exhibit a recognised genetic predisposition to DM. The alternative cause of corticosteroid use should also be considered as a more common cause for hyperglycaemia.

Clinical presentation

Presenting symptoms include thirst, polyuria, polydipsia, dehydration, weight loss and lethargy. Approximately two-thirds of patients present in diabetic ketoacidosis, with the remainder with severe hyperglycaemia. The median time from treatment initiation to presentation is 7–17 weeks, with a small number of cases presenting years after treatment initiation.

Diagnosis

Investigations tend to reveal an elevated plasma glucose, a very low or absent serum C-peptide, reflecting the rapid destruction of pancreatic tissue, and only a mildly elevated HbA\textsubscript{1c}, given the acuity of the disease process. Autoantibodies are positive in about half of patients, with cases of both pre-existing and newly developed autoantibodies both reported. Despite this, Society for Endocrinology guidelines state that pancreatic autoantibodies (islet cell and GAD (glutamic acid decarboxylase)) should be taken, with potential use to distinguish between type 1 and 2 DM.

Treatment

Given the aggressive pathophysiology, insulin therapy is usually essential. It is noted that, unlike other immune-related adverse events, the disease process is worsened by glucocorticoids as a consequence of increased insulin resistance with no evidence to support reversal of the beta cell damage. Insulin therapy is usually essential. It is noted that, unlike other immune-related adverse events, the disease process is worsened by glucocorticoids as a consequence of increased insulin resistance with no evidence to support reversal of the beta cell damage. Insulin therapy is usually essential. It is noted that, unlike other immune-related adverse events, the disease process is worsened by glucocorticoids as a consequence of increased insulin resistance with no evidence to support reversal of the beta cell damage.

Adrenal

Incidence and aetiology

Primary adrenal insufficiency (PAI) is reported as 1% with either CTLA-4 or PD-1 monotherapy, and 5–7% on combination

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**Note:** The diagram and table provided are placeholders and do not reflect the actual content of the text. The text contains detailed information on the management and treatment of diabetes mellitus and pancreatic conditions associated with checkpoint inhibitors.
therapy. Its likely cause is irreversible antibody-mediated, and possible T-cell-mediated, immune destruction of the adrenal glands, production of glucocorticoids is predominantly affected, with only one-third of patients symptomatic of mineralocorticoid deficiency.

Clinical presentation
Presenting symptoms are non-specific including fatigue, nausea, dizziness and anorexia, so a high clinical index of suspicion is required. In a review of 451 patients with PAI secondary to checkpoint inhibitors, 90% presented with adrenal crisis, and mortality was recorded as 7%. Time of onset can range from 6 days to 18 months post-treatment initiation. A thorough history of recent steroid use is needed, including inhaled, topical or injected therapy. All can suppress adrenal function and adrenal insufficiency from exogenous steroid use is a more common diagnosis than adrenalitis.

Diagnosis
Electrolyte monitoring may aid diagnostic suspicion and should also be monitored following diagnosis, as hyponatraemia and hyperkalaemia can occur. Diagnosis can be made from a low morning cortisol with a high morning adrenocorticotropic hormone (ACTH), with confirmation provided by a poor response to synthetic ACTH. Computed tomography (CT) of the adrenal glands may demonstrate atrophy or adrenalitis and facilitate exclusion of other causes. Anti-21-hydroxylase antibodies may also be helpful in excluding autoimmune aetiology, but are not commonly done.

Treatment
Management requires prompt replacement of glucocorticoids (hydrocortisone 20–30 mg/day), and mineralocorticoids (fludrocortisone) if required. If the patient is acutely or life-threateningly unwell initially, Society for Endocrinology guidelines advocate higher-dose glucocorticoids, tapering to physiological dose following clinical recovery, with prompt endocrine referral. As with pituitary-related insufficiency, patient education in terms of sick day rules and emergency hydrocortisone is vital. Patients can be supplied with an NHS steroid card to improve management in the emergency setting. It is advised to hold immunotherapy while unwell, with scope for continuing it later when stable on hormone replacement.

Parathyroid
Incidence and aetiology
Parathyroid involvement appears to be exceedingly rare, with only five case reports of hypoparathyroidism reported and no hyperparathyroidism. Unlike other endocrinopathies, most patients have described a reversible inflammatory process. Onset is later, reported between 4 and 11 months following initiation of either PD-1 inhibitor or combination therapy.

Clinical presentation
Hypocalcaemia can present as nausea, vomiting, paraesthesia, cramps, abdominal pain, confusion and fatigue. If severe, life-threatening arrhythmias or seizures can occur.

Diagnosis
Diagnosis is confirmed by a low serum calcium with a low or non-elevated parathyroid hormone level. Serum magnesium, phosphate and vitamin D should be monitored alongside calcium. Ruling out alternative causes for hypoparathyroidism, such as previous surgery, should be included in the work-up. Electrocardiography should be performed to assess the QT interval.

Treatment
Management is of calcium replacement, either intravenously or orally depending on the severity of deficiency. Cardiac monitoring may be needed. Ongoing management is then with the initiation and titration of alfacalcidol according to serum calcium levels. There is insufficient evidence to dictate whether cessation of immunotherapy is necessary, and this should therefore be decided on a case-by-case basis. In addition, when considering calcium disorders, the relevance of other oncology factors must be taken into consideration, such as the presence of skeletal metastases and drugs relevant to their management, such as the use of bisphosphonates or denosumab. Hypocalcaemia is an important side effect of these drugs.

Other rare endocrinopathies
Diabetes insipidus
Diabetes insipidus (DI) is rarely reported in immunotherapy – only two cases to date – in comparison to pituitary metastasis as a cause. It is thought to be a consequence of inadequate antidiuretic hormone (ADH) secretion secondary to hypophysitis affecting the posterior pituitary. Patients presented with polyuria, polydipsia, thirst and fatigue, with diagnosis being confirmed by serum osmolality >295 mmol/l and urine osmolality <600 mmol/l. Spontaneous remission was demonstrated in both cases, with one requiring no treatment and the other demonstrating reversibility after 6 weeks of desmopressin (DDAVP). It is important to note that there is potential for DI to be masked until concomitant ACTH deficiency is treated. Furthermore, only one case of ACTH-dependent Cushing’s syndrome has been reported. Presentation included mild symptoms of cortisol excess (weight gain, depression and fatigue) and there was spontaneous resolution, then development of secondary cortisol insufficiency. By far a more common cause is iatrogenic Cushing’s syndrome, with corticosteroids used frequently for cancer-related symptoms, non-endocrine immune-related adverse events and hypersensitivity reactions.

Polyglandular endocrinopathies have also been described, commonly the thyroid gland and one of the other aforementioned endocrinopathies.

Other considerations
Clinician and patient education
Endocrine complications of checkpoint inhibitors require prompt diagnosis in order to prevent significant morbidity and mortality. Patient education of these adverse effects is important to aid early recognition of the endocrinopathies and prevent delay in diagnosis. Patients should be counselled to inform healthcare professionals if they are currently or previously receiving checkpoint inhibitors. Dissemination of information to physicians in both primary and secondary care is also pertinent in supporting prompt diagnoses.

Screening
Since the presentation of these complications may be indolent and non-specific, screening offers a potentially useful tool. Regular
monitoring of thyroid function and blood glucose is universally recommended, but screening for adrenal and pituitary disease is more challenging. 1,2,19 Although the consequences of glucocorticoid deficiency carry high morbidity and mortality, and thus screening may appear sensible, this is a topic of debate. No national guidance is available regarding UK endocrinopathy screening. In terms of being able to identify individuals at increased risk of developing complications, early work suggests that genetic predispositions may play a role in this. 9 Fluorodeoxyglucose–positron emission tomography (FDG-PET) scans can also incidentally diagnose immunotherapy-mediated endocrinopathies by diffuse uptake. Comparison with baseline scans is required and often only patients with curative intent will receive regular PET scans, which doesn’t typically align with those receiving immunotherapy currently. Patients may not exhibit symptoms at this point, which poses a therapeutic dilemma.

**The role of high-dose steroids**

There is debate as to whether high-dose steroids may be helpful in the management of checkpoint-induced endocrinopathies. Current UK Society for Endocrinology guidelines advise that there is no indication for intravenous methylprednisolone for routine management of endocrinopathies, with hypophysitis with associated neurological features being the only exception. 17 In contrast, European guidelines recommend use in severe hypophysitis and severe thyrotoxicosis or thyroiditis; however, there have not been proven benefits for milder disease or other endocrinopathies. 2 Limited evidence is available to support these guidelines, but benefit likely outweighs risks when pituitary oedema is causing severe headache, cranial nerve palsy or visual disturbance. 29

Immunotherapy itself is not the only endocrine consideration in cancer treatment. While taking checkpoint inhibitors, one-third of patients take corticosteroids, mainly to treat non-endocrine adverse effects or for brain metastases. 46 Awareness of detrimental effects of steroids, such as steroid-induced hyperglycaemia, iatrogenic adrenal insufficiency or immunosuppression, should also be considered. 30

**Adverse effects and cancer prognosis**

Some retrospective data have suggested that patients who develop immunotherapy-induced hypophysitis survive on average 1 year longer than those who do not, and those who develop thyroid dysfunction survive 2 years longer than those who do not. 18 However, the population sizes in these studies are small, and data on long-term outcomes of endocrine effects may be skewed by follow-up bias. Early evidence has suggested that timing of adverse effects may be associated with survival, reporting that developing the effects within the first 3 months of treatment is associated with better outcomes. Further work is needed before firm conclusions can be made. 47

**COVID-19**

The COVID-19 pandemic has brought additional challenges to cancer therapy. Early outcomes suggest that cancer patients are at increased risk of mortality and morbidity, but there is currently no evidence that use of checkpoint inhibitors worsens outcomes. 48,49 Conflicting hypotheses exist suggesting that checkpoint inhibitors could either dampen the viral response by exhaustion of T-cells, or opposingly, amplify the exaggerated immune response to viruses like SARS-CoV-2. 48,50 Experience from previous viruses suggests that the latter rarely occurs. To reduce the risk in vulnerable patients, regular screening for COVID-19 plus prompt recognition and management of any immune-related adverse effects is recommended.

**Conclusion**

Checkpoint inhibitors offer huge benefits for those with advanced cancer and although adverse effects are significant, the increase in survival that these treatments offer justifies this risk. Prompt identification and management of endocrine effects can minimise impact on patient experience and mortality. Further research is needed to improve understanding of predisposing and protective factors, and ways of improving current management.

**Key points**

- Endocrine adverse effects of checkpoint inhibitor immunotherapy occur in around 10% of patients.
- Thyroid disease and hypophysitis are the most common, which can occur from weeks to many months after treatment.
- Primary adrenal insufficiency and diabetes mellitus are also reported, along with other more rare endocrinopathies.
- Early recognition and management are key, with referral to an endocrinologist for ongoing management.
- Non-specific symptoms require a high index of suspicion for investigation.
- Patient and clinician education and awareness of these effects are vital.
- Some debate remains surrounding the use of screening for endocrinopathies and high-dose steroids in their treatment.
- Early data suggest that endocrine adverse effects may be associated with better cancer survival outcomes.

**References**


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