Endocrine-related adverse events associated with targeted treatment and immune checkpoint blockage in hematological malignancies

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Hematology in Clinical Practice
2023, vol. 14, 11–17
DOI: 10.5603/HCP.2023.0003

ISSN: 2720–1015
e-ISSN: 2720–2690

Received: February 23, 2023
Accepted: March 15, 2023

ABSTRACT

The introduction of tyrosine kinase inhibitors and immune checkpoint inhibitors considerably improved the treatment of many hematological malignancies. However, these new classes of drugs are associated with novel hitherto not observed endocrine-related adverse effects. Therefore, this review aims to get insight into the pathogenesis of endocrine-related AEs and summarize their management according to the current European recommendations.

Key words: endocrine complications, tyrosine kinase inhibitors, immunotherapy, immune checkpoints, thyroiditis, hypophysitis

INTRODUCTION

The registration of targeted treatment with the use of small-molecule specific tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have unquestionably improved the prognosis in diverse hematological malignancies [1, 2]. However, the introduction of these two groups of therapeutics into clinical practice has been associated with novel hitherto not observed endocrine-related adverse effects (AEs) that have initially puzzled the medical community [3]. Nowadays, the mechanisms underlying endocrine and metabolic complications of the use of these therapies are well described (reviewed in [4–7]) and awareness of the problem is raising among physicians. This review aims to summarize the current understanding of endocrine-related AEs and the recommendations of the European Society of Medical Oncology (ESMO) [8] and the European Society of Endocrinology (ESE) [9] for their management.

ICIS AND TKIS IN HEMATO-ONCOLOGY

The introduction of ICI that unleashes the suppressed immune response has revolutionized the modern treatment of solid tumours and is being intensively developed in the treatment of hematological malignancies. Currently, two ICI are registered in hemato-oncology, i.e. humanized IgG4 anti-programmed death receptor 1 (PD-1) monoclonal antibodies (mAbs) pembrolizumab and nivolumab used mainly in the treatment of relapsed/refractory (r/r) classical Hodgkin lymphoma (HL) and optionally in the treatment of r/r primary mediastinal B-cell lymphoma (PMBL) and extranodal NK/T-cell lymphoma. Nevertheless, agents targeting both PD-1 as well as programmed death ligand 1 (PD-L1) have been intensively tested in combinations in clinical trials in diffuse large B-cell lymphoma (DLBCL) [10], therefore new registrations are possible. As the AEs induced by ICI are radically different from those traditionally associated with anti-cancer therapy it is crucial to be aware of their characteristics and management modes. Fortunately, most ICI-induced endocrine-related AEs are mild, most commonly grade 1 or 2 according to Common Terminology Criteria for Adverse Events (CTCAE) and are

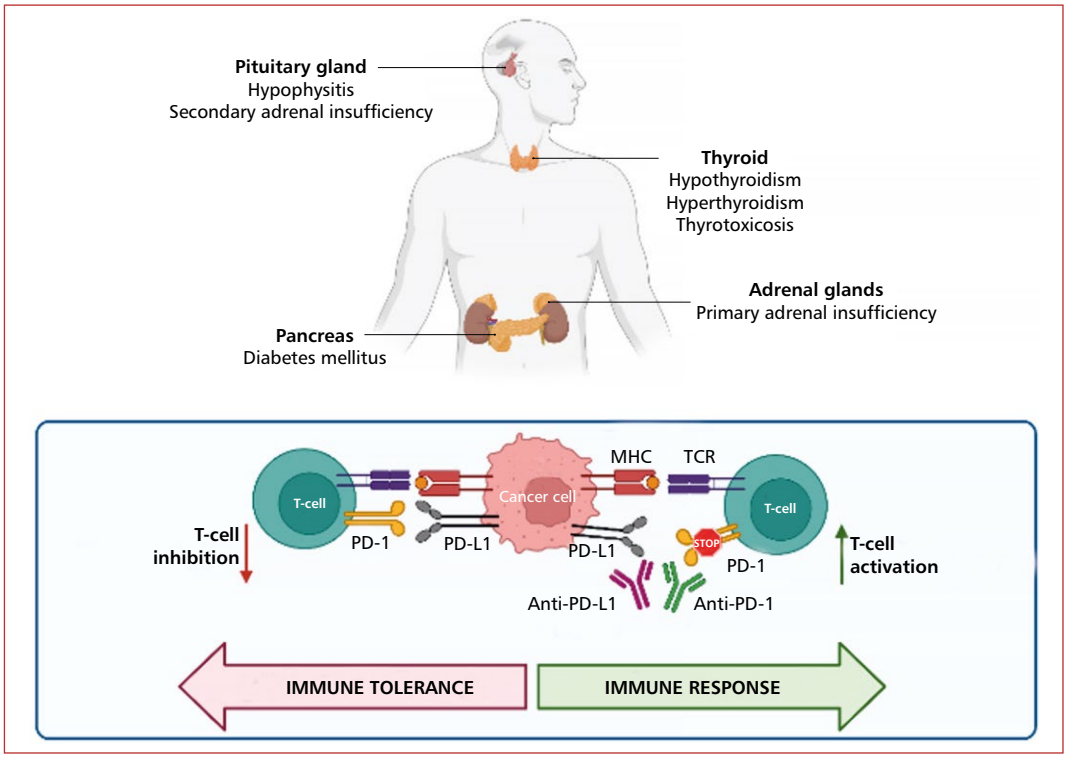

Figure 1. Mechanism of induction of endocrine-related adverse effects (AEs) by immune checkpoint inhibitors (ICIs). The use of anti-programmed death receptor 1/programmed death ligand 1 (anti-PD-1/anti-PD-L1) abrogates immune tolerance by inducing T-cell activation. Endocrine organs affected by ICI-induced toxicity are presented; MHC — major histocompatibility complex; TCR — T-cell receptor

not considered indications to stop the therapy. Typically they develop in the first few weeks or months after the first dose, but they can develop at any time during ICI therapy, even after its discontinuation [6].

The development of endocrine-related AEs in ICI-treated patients is a consequence of disinhibition of the immune system and is thought to represent a bystander effect from activated T-cells (Figure 1). This is due to the role that checkpoint molecules play in the prevention of autoimmunity. The PD1-PD-L1 axis has been demonstrated to play a crucial role in inducing self-tolerance both at the central level by controlling thymocyte positive and negative selection as well as at the peripheral level by promoting regulatory T-cells (Treg) development and function and directly inhibiting self-reactive T-cells [11]. Observations from solid tumours suggest that the presence of immune-related AEs correlates with improved progression-free and overall survival [12, 13], however extensive studies are needed to conclude if this can be extrapolated to hematological malignancies.

Tyrosine kinases (TK) are enzymes that catalyse the transfer of phosphate groups from adenosine triphosphate (ATP) to tyrosine residues. As more than 70% of onco- and protooncogenes are TK, TK inhibitors (TKIs) are an attractive class of anti-cancer therapeutics blocking signal transduction and cell proliferation that are extensively used in the targeted therapy of both solid and hematological malignancies. The currently used TKIs in hemato-oncology include imatinib, dasatinib, nilotinib, bosutinib, ibrutinib and the newly registered asciminib.

THYROIDITIS

Thyroid dysfunction is the most common side effect of both TKIs and anti-PD-1 mAbs, therefore its development needs to be considered and monitored in TKI- and ICI-treated patients. Both these classes of agents induce biphasic destructive thyroiditis with the evolution (Figure 2) similar to de Quervain's granulomatous subacute thyroiditis from which it can be differentiated by the absence of pain. However, a molecular mechanism leading to thyroid dysfunction is different in these two classes of drugs (Figure 2). Both TKI- and ICI-induced thyroid dysfunction can manifest with a transient thyrotoxic phase with mild symptoms (i.e., palpitations, fatigue, weight loss, anxiety, diarrhoea) caused by increased release of thyroid hormone from inflamed thyroid tissue followed by euthyroidism or hypothyroidism phase. Also, the hypothyroid phase is most often characterized by mild symptoms (bradycardia, cold intolerance, constipation and the most common ones i.e. fatigue and weight gain) [4, 14], however, it is often persistent, especially when overt [9]. Sometimes only a hypothyroidic phase is reported, more commonly in the case of TKIs, probably due to mild symptoms of and transient character of thyrotoxicosis that may be sometimes overlooked. Moreover, in patients with hypothyroidism at

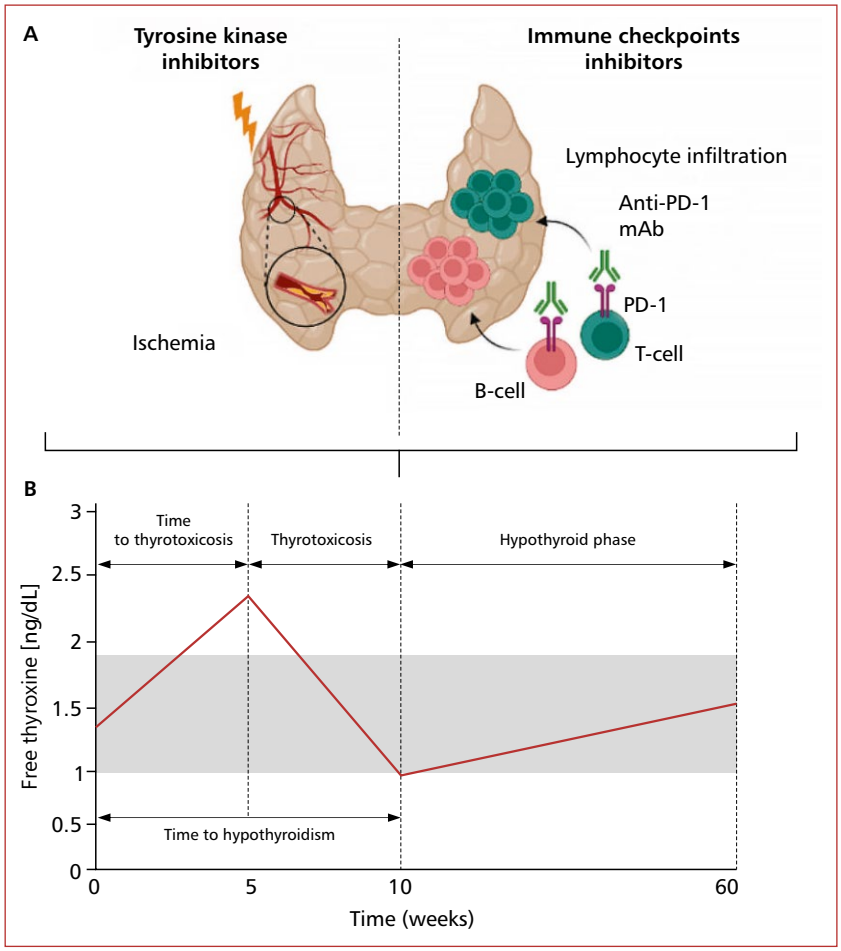

Figure 2A, B. Mechanisms of induction of thyroiditis by tyrosine kinase inhibitors (TKIs) and by immune checkpoint inhibitors (ICIs) and its biochemical evolution; anti-PD-1 — anti-programmed death receptor 1; mAb — monoclonal antibody

the beginning of treatment with TKIs and ICIs, higher doses of levothyroxine may be needed after treatment initiation [9]. The management of TKI- and ICI-induced thyroiditis is summarized in Table 1.

Importantly, the interpretation of thyroid-stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) levels in cancer patients may be complicated by 1) the performed CT examination with the use of iodinated contrast media (transient hyperthyroidism that should be managed as described in [15]), 2) other drugs used (e.g., glucocorticosteroids that decrease TSH, inhibit T4 conversion to T3, so fT4 is increased with diminished fT3 levels, lithium and amiodarone leading to transient hyperthyroidism), 3) sick euthyroid syndrome (low fT3 or low fT3 and fT4 levels in euthyroid patients with serious diseases due to inhibition of 5-deiodinase activity). Therefore, laboratory measurements need to be analysed carefully alongside clinical symptoms.

TKI-induced thyroid dysfunction

Numerous clinical observations have reported an undeniable TKI-mediated thyroid dysfunction in cancer patients (reviewed in [4, 16, 17]). It has been demonstrated that the risk depends on the agent used with a high probability for sunitinib, sorafenib imatinib, and moderate risk for dasatinib and nilotinib [17]. It is widely accepted that TKIs induce progressive destruction of the thyroid by decreasing the gland's vascularity and leading to ischemia due to inhibition of the vascular endothelial growth factor receptor (VEGFR) activation [17]. Examples of ultrasound images of TKI-induced thyroiditis are shown in Figure 3. As hypothyroidism is more commonly reported for this group of drugs, additional mechanisms leading to decreased levels of free thyroid hormones have been proposed including a decrease in enteric thyroid hormone absorption, increased hepatic metabolism of T4 and T3, inhibition of T4 deiodination, inhibition of the monocarboxylate transporter 8 (MCT8) thyroid hormone transporter across the plasma membrane, reducing the supply of T3 to peripheral tissues but also centrally, in the thyrotropic cells at the pituitary gland level (reviewed in [4, 18]).

ICI-induced thyroid dysfunction

Thyroid dysfunction is the most common endocrinopathy following ICI and is much more common in patients

Table 1. Evaluation and management of possible endocrinopathies in tyrosine kinase inhibitor (TKI)- and immune checkpoint inhibitor (ICI)--treated patients (adopted on the basis of [9])

EVALUATION OF POSSIBLE ENDOCRINOPATHIES IN TKI- AND ICI-TREATED PATIENTS
Baseline • Clinical evaluation for the following symptoms: extreme weakness, weight loss or gain, unusual headache patterns, changes in visual acuity and visual field, nausea, vomiting, arrhythmias, hypotonia, hypertension, nausea, vomiting, abdominal pain, diarrhoea, and constipation • Laboratory measurement of morning TSH, fT4, cortisol, glucose, electrolytes (sodium, potassium, calcium) levels
Every 4–6 weeks and 4–6 weeks after the last treatment cycle • Clinical evaluation for the above-listed symptoms • Laboratory measurement of morning TSH, fT4, cortisol, glucose, electrolytes (sodium, potassium, calcium) levels
Additional evaluation for suspected endocrinopathies • Hypothyroidism: anti-TPO, anti-TG antibodies • Hyperthyroidism: anti-TSHR antibodies, fT3, thyroid ultrasound • Hypophysitis: ACTH, LH, FSH, testosterone (men), oestrogen (women), pituitary MRI can be considered • Diabetes: blood pH, urine ketones, C peptide, autoantibodies (GADA, IA2, IAA, anti-ZnT8)
MANAGEMENT OF POSSIBLE ENDOCRINOPATHIES IN TKI- AND ICI-TREATED PATIENTS
Adrenal insufficiency In each case of suspicion of AE (i.e., hypotonia, weakness, nausea, low sodium, elevated potassium, hypoglycemia) always consider glucocorticoid supplementation e.g., 10–20 mg hydrocortisone orally in the morning, 5–10 mg at noon. In every case of suspected adrenal crisis (the above-listed symptoms manifested with high intensity) in acutely unwell ICI-treated patient 100 mg hydrocortisone intravenously or intramuscularly followed by 50 mg every 6 h and fluid resuscitation should be administered, preferably after securing a blood sample for cortisol and ACTH testing. **Do not delay treatment while waiting for these results as this can be fatal!**
Thyroid disorders • **Overt** (low TSH, high fT4 and fT3) **and subclinical hyperthyroidism** (decreased TSH, normal fT4 and fT3) — endocrine consultation is recommended • Other possible causes need to be ruled out i.e. Graves' disease, toxic nodular goitre and autonomous thyroid nodule by performing additional tests: anti-TSHR antibodies, thyroid ultrasonography and/or thyroid scintigraphy. In such cases of overt hyperthyroidism, anti-thyroid drugs should be initiated. Treatment of subclinical hyperthyroidism should be conducted according to the national guidelines (Polish guidelines summarized in [22]) • Iodinated contrast media-induced hyperthyroidism should be also considered • In ICI- and TKI-induced thyroiditis anti-thyroid drugs are contraindicated. In severe thyrotoxicosis symptomatic treatment with the use of a beta-blocker (for example propranolol) and 1–2 mg/kg prednisone may be considered. TSH, fT3, and fT4 levels should be evaluated every 2–3 weeks • **Overt** (high TSH, low fT3 and fT4) **and subclinical** (elevated TSH, normal fT4 and fT3) **hypothyroidism** endocrine consultation may be considered to rule out Hashimoto's thyroiditis (elevated anti-TPO, typical ultrasound image), this diagnosis does not change further treatment • Start treatment with levothyroxine in patients with overt hypothyroidism. Treatment of subclinical hypothyroidism should be conducted according to the national guidelines (Polish guidelines summarized in [23]) • TSH, fT3, and fT4 levels should be evaluated every 4–8 weeks, and discontinuation of levothyroxine supplementation should be tried after cessation of ICI/TKI. Thyroid disorders do not contraindicate further use of ICI, in the case of overt disorders transient ICI discontinuation might be considered

ACTH — adrenocorticotropic hormone; anti-TG — anti-thyroglobulin; anti-TPO — anti-thyroid peroxidase; anti-TSHR — anti-thyroid-stimulating hormone receptor; FSH — follicle-stimulating hormone; fT3 — free triiodothyronine; fT4 — free thyroxine; LH — luteinizing hormone; MRI — magnetic resonance imaging; TSH — thyroid-stimulating hormone

treated with PD-1 targeting agents than in those treated with anti-cytotoxic T-cell antigen 4 (CTLA-4) mAbs [9]. Hypothyroidism is reported in approximately 7% and hyperthyroidism in 3.2% of patients treated with anti-PD-1 therapy [13]. Thyroid dysfunction typically occurs after a few weeks after ICI initiation and can happen even after a single therapeutic dose [8]. Healthy thyroid tissue does not express PD-L1. However, while CTLA-4 blockage induces only T-cell proliferation, PD-1 is expressed not only on the surface of cytotoxic T-cells but also on B- and NK-cells and the use of anti-PD-1 mAbs can induce the proliferation of all these immune cells. Histologic evaluation of ICI-induced thyroiditis revealed lymphocytic infiltration by both B-cells and cytotoxic T-cells [19]. Thyroid dysfunction following ICI is more common in women, individuals with high anti-thyroid peroxidase (anti-TPO) antibody titre [20] and those with a history of hypothyroidism and seem to be independent of the patient's age, cancer subtype and the dose of ICI [9, 21].

HYPOPHYSITIS

Other common endocrine dysfunctions during TKIs and ICI treatment is acute hypophysitis resulting in hypopituitarism leading to central adrenal insufficiency (AI), central hypothyroidism and hypogonadotropic hypogonadism. Hypophysitis appears most often in men over 60 years of age and is 2–5 times more frequent than in women. The incidence reported is up to 20% with ipilimumab, 8% with the combination of ipilimumab and nivolumab, 0.6% with nivolumab, and 0.7% with pembrolizumab [21, 22].

While the mechanism is still not clear, it is without doubt caused by the activation of the immune system as patients treated simultaneously with anti-CTLA-4 and chemotherapy do not develop this complication probably because of lymphocyte depletion [23]. By now several mechanisms have been suggested. Firstly, ICI can act directly as some populations of pituitary cells, mainly thyrotophic and lactotroph cells express CTLA-4 antigen [24]. Secondly, ICI can trigger hypersensitivity reactions due to unleashing of the immune system. Finally, ipilimumab being an IgG1 antibody is a potent inductor of both activation of classical complement pathway as well as antibody-dependent cell-mediated cytotoxicity (ADCC), while nivolumab and pembrolizumab belong to far less active IgG4 subclass. Therefore, ICI-induced hypophysitis is rarely found in hematological patients treated with ICI. ICI-mediated hypophysitis typically affects the anterior lobe. Typically, this complication occurs after 2–3 months of the treatment initiation and is characterized by unspecific symptoms, like

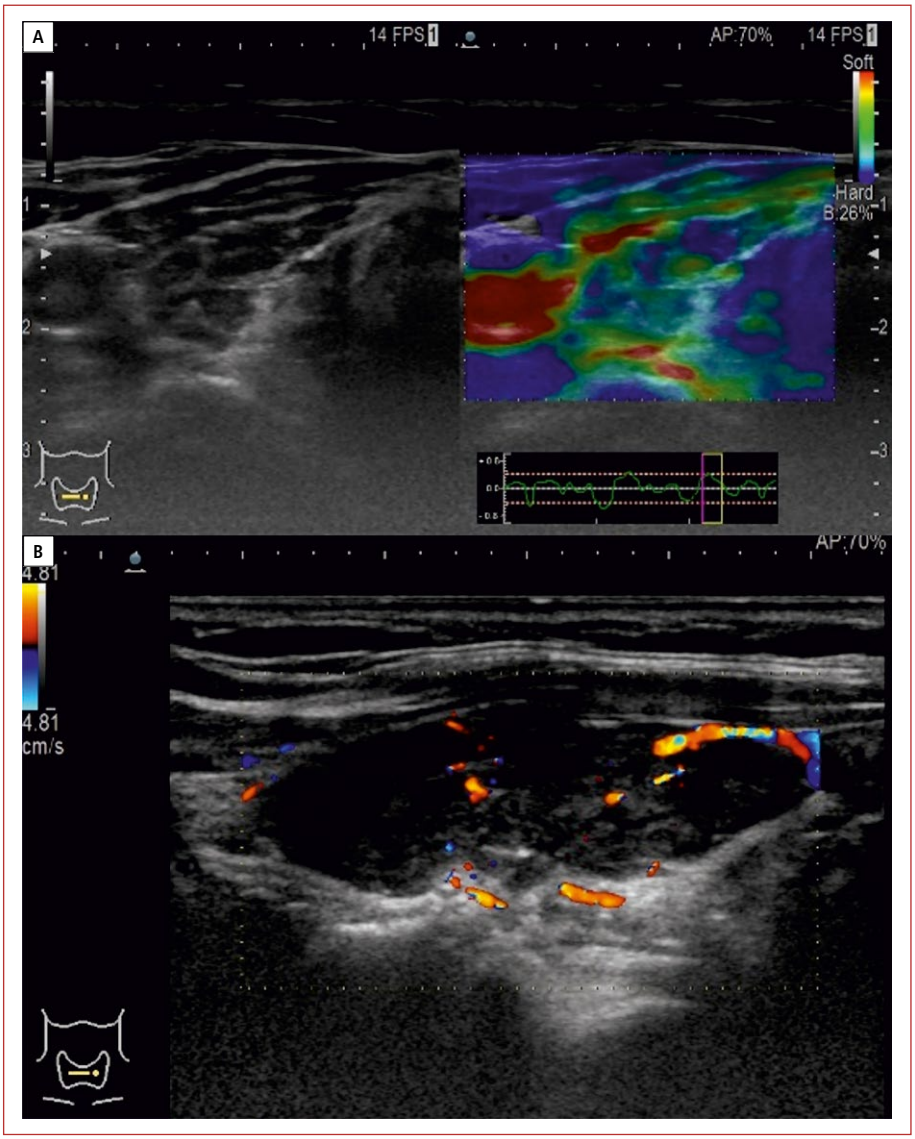

Figure 3. Ultrasound images: **A.** Transverse view of right lobe shows ultrasound changes due to thyroiditis by tyrosine kinase inhibitor (TKI) (left image). Thyroid gland with a heterogeneous, hypoechogenic pattern of structure with multiple hyperechogenic bands observed in both lobes, which probably corresponds to the areas of parenchymal fibrosis with a pseudo-nodular appearance. The strain elastography shows sample areas of hard strain (blue), which corresponds with the part of thyroiditis (right side); **B.** Sagittal view of the right lobe thyroid gland in patients after 3 weeks of initiation TKI therapy. The ultrasound shows hypoechogenic, irregular echogenicity of parenchyma with decreased vascularity

headaches, fatigue, visual impairment, hyponatremia (likely due to AI) with or without pituitary enlargement and rarely causing symptoms related to mass effect. Less commonly, patients present with neuropsychiatric symptoms such as confusion, memory loss and hallucinations [8, 21].

We recommend consultation with an endocrinologist in all cases of suspected hypophysitis. Current guidelines require the replacement of deficient hormones (physiologic doses of glucocorticoids and levothyroxine) to manage confirmed hypophysitis [21]. Central AI can be life-threatening. In the presence of both AI and hypothyroidism, corticosteroid replacement should be started before initiating levothyroxine replacement, because levothyroxine may increase the clearance of cortisol. In the case of gonadotropin deficiency causing hypogonadotropic hypogonadism, initiation of treatment is less urgent. ACTH deficiency persists in 86–100% of cases and long-term hormonal replacement is indicated, whereas 13–36% of patients continue to have TSH deficiency and 13–53% have gonadotropin deficiency. Recovery from TSH and gonadotropin deficiencies may occur after 10–15 weeks [21]. So far only two cases of diabetes insipidus caused by hypophysitis have been reported [26, 27]. In both cases, spontaneous remission was achieved with one requiring no treatment and the other demonstrating reversibility after 6 weeks of desmopressin. Interestingly, magnetic resonance imaging (MRI) imaging does not reveal specific changes with up to 25% of patients having a normal MRI pituitary scan [8].

DIABETES MELLITUS

Disinhibition of the immune response can lead to the destruction of pancreatic islets resulting in the development of diabetes mellitus (DM) type 1. It is a rare ICI-induced complication affecting up to 2% of treated patients, most of them are treated with anti-PD1 [9]. Importantly, as hyperglycemia develops rapidly with up to 70% of cases manifested as diabetic ketoacidosis with nausea, vomiting, abdominal pain, lethargy or even coma, ICI-induced DM is a potentially life-threatening complication of treatment [28]. Therefore, it is important to bear in mind the possibility of this complication and suspect it in patients with polyuria, polydipsia, and weight loss. Importantly, as the destruction of pancreatic islets develops rapidly glycated hemoglobin (HbA_{1c}) is not a good laboratory marker of this complication. These patients need to be treated with insulin and consulted by a diabetologist.

OTHER RARE ENDOCRINOPATHIES

As the mechanism of ICI-induced endocrine-related AEs is an inflammatory process due to increased activation of effector cells and disinhibited presentation of autoantigens it can lead to dysfunction of other endocrine glands. By now reports on parathyroid inflammation leading to late-onset (4–11 months following treatment initiation) hypoparathyroidism have been rare with only six cases described (reviewed in [9, 28]). However, if severe, hypocalcemia can lead to potentially life-threatening arrhythmias due to the prolongation of QT interval. Therefore, it is important to bear in mind the unspecific symptoms of low calcium concentration such as nausea, vomiting, paresthesia, abdominal pain, confusion and fatigue and consider measuring calcium level corrected to albumin. When hypocalcemia is detected, magnesium, phosphate, 25-OH-vitamin D and parathyroid hormone (PTH) should be assessed [9]. The treatment is exactly as in hypoparathyroidism caused by other alethiological factors: calcium and vitamin D supplementation. Due to the rarity of reports on ICI-induced hypoparathyroidism, it is difficult to define its mechanism however, two of the published reports identified calcium-sensing receptor (CaSR) activating antibodies as responsible for suppressed PTH secretion [8, 9]. Importantly, the identified antibodies were IgG1 and IgG3 Abs that induce complement-dependent and antibody-dependent cytotoxicity of immune cells that may be responsible for the destruction of the gland which may explain why in both these cases hypoparathyroidism persisted. Moreover, despite no evidence of a direct or indirect effect of ICI therapy on bone metabolism, ESE suggests the use of calcium and vitamin D supplements in all patients treated with ICI [9].

Primary adrenal insufficiency (PAI) is another rarely reported AEs following the use of ICI with only 46 confirmed cases out of 50,000 ICI-associated AEs reported since 2008 in World Health Organization (WHO) VigiBase [9] and 15 literature reports on patients treated with PD-1 and PD-L1 mAbs [29]. The induction of anti-21-hydroxylase antibodies has been reported in some of the patients. In imaging, both adrenal enlargement with hypermetabolism due to inflammation and adrenal hypoplasia and atrophy have been observed [29]. The symptoms of adrenal insufficiency have been presented in the paragraph concerning central AI. Of note, due to increased ACTH secretion hyperpigmentation, which is not present in central AI, can be observed. It has to be noted that PAI leads to a lack of aldosterone, therefore apart from glucocorticoid supplementation, the replacement therapy with fludrocortisone (0,05–0,15 mg/ /day) and a diet without salt restriction is recommended [9]. Alike in central AI also here there is no evidence of the cessation of the disease after ICI withdrawal.

DISCUSSION

Nowadays, TKI and ICI play an important part in the management schemes of certain malignancies of hematological origin. Although at the beginning of the implementation of these groups of drugs, the endocrine-related AEs caused perplexity in the medical community, their widespread use led to the elaboration of explicit guidelines. Currently, the most promising novel agents in the targeted therapy of hematological malignancies are chimeric antigen receptor (CAR) T-cells, including armoured CAR constructs engineered to combat the negative impact of the tumour microenvironment and to provide additional stimuli to the immune cells [31] and bispecific antibodies targeting both malignant cells and the immune effectors [31]. Considering their mechanism of action the endocrine-related AEs of these new agents are carefully monitored in clinical trials. By now there is only one report suggesting the development of transient Hashimoto's thyroiditis with high levels of anti-TPO and anti-thyroglobulin (TG) antibodies, signs of inflammation in ultrasound but no thyroid hormone deficiency, following the therapy with CD19-targeting CAR-T cells in two DLBCL patients [32]. Therefore, it seems that the administration of these new agents does not induce endocrine-related AEs, however, longer observations are needed to confirm that.

Article information

Conflict of interest: The authors declare no conflict of interest.

Funding: None.

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