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Case Report of a Rapidly Progressing Thyroiditis Following Immune Checkpoint Inhibitor Therapy with Pembrolizumab and Accidential Exposure to Iodine in a 30-Year-Old Male Patient With Metastatic Melanoma

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Abstract

Immune checkpoint Inhibitor Therapy (ICI) represents a novel approach of modern oncology and has improved survival in metastatic melanoma, lung cancer and renal cancer. The main endocrine complications of ICI, usually irreversible, include thyroid dysfunctions and hypophysitis. The exact mechanisms by which ICI may induce a stimulated immune response leading eventually to Immune Related Adverse Events (irAEs) are still not fully understood. This case report illustrates irAEs of ICI during therapy with the humanized monoclonal anti-PD-1 antibody Pembrolizumab (Keytruda) causing destructive thyroiditis in a 30-year-old male patient with metastatic melanoma. After initiation of therapy with Pembrolizumab 05/2021 and exposure to iodine containing contrast media during a CT-scanning 06/2021 the patient showed clinical and biochemical manifestation of acute hyperthyroidism (TSH <0,01 mU/l (0.27-4.20), FT4 >100 pmol/l (9.1-23.0)) and destructive thyroiditis. The thyroglobulin concentration was three fold elevated, Thyroid Peroxisome Antibody (TPOAb) were moderately elevated but no Thyroid Receptor Antibody (TRAb) were detected. Because of grade 3 endocrine complication, hospitalization was necessary, therapy with sodium perchlorate, propranolol and glucocorticoids were initiated. Rapid manifestation of hypothyroidism 08/2021 (TSH 66 mU/l, FT4 3.0 pmol/l, FT3 <1.50 pmol/l) required immediate substitution with levothyroxine. Shrinkage of thyroid volume to less than one third of initial size occurred within 7 months. Neither adrenal insufficiency, hypophysitis nor autoimmune diabetes mellitus were seen in this patient. Pembrolizumab therapy was not discontinued at any time. Staging did not reveal tumor progress. Interdisciplinary management and follow up of patients with ICI and endocrine complications are crucial to detect relevant irAEs at an early stage and initiate appropriate therapy in order to maintain ICI.

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Introduction

Immune checkpoints are crucial for immunologic self-tolerance, regulate our immune system and prevent immune cells from attacking cells. Programmed Death Receptor-1 (PD-1) is a Cell Surface Receptor (CD279) and responsible for down regulating the immune system, thus suppressing T-cell inflammatory activity to promote self-tolerance. One strategy of tumor cells to dodge the immune response is to enhance immune checkpoint inhibitory activity [1,2]. Immune Checkpoint Inhibitors (ICI) can block inhibitory checkpoint molecules. Antibody therapy is directed against Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4), PD1, or one of its ligands, PD-L1. The therapy is administered as monotherapy or in combination regimens [2].

ICI-therapy revolutionized therapy in oncology and improved survival in metastatic melanoma, lung cancer, renal cell carcinoma and many other tumor entities [1,3].

Autoimmune and inflammatory effects of this therapy can affect the skin, gastrointestinal tract, liver and endocrine system. Immune Related Adverse Events (irAEs) of the endocrine system occur approximately in 0-29% of patients. IrAEs are irreversible in at least 50% of the cases, and may include hypophysitis, thyroid dysfunctions, adrenal insufficiency and type-1 diabetes mellitus. The precise mechanisms by which ICI lead to raised immune reactions and specific endocrinopathies are still not understood [1-6].

This article is focused on endocrine complications due to PD-1-inhibition. Intensity of symptoms are defined as grade 1 (no symptoms) to 5 (fatal). The frequency of endocrine adverse events of PD1-/PD-L1-inhibition as monotherapy is 0.2-2.6% (≥grade 3: 0.1-0.6%) for hypophysitis, 0.6-8.6% (≥grade 3: 0-0.5%) for hyperthyroidism, 2.5-9.8% (≥grade 3: 0-0.8%) for hypothyroidism, 0.3-4.3% (≥grade 3: 0-0.8%) for adrenal insufficiency and 0.2-5.8% (≥grade 3: 0-0.5%) for autoimmune diabetes mellitus type1 [7,8].

Thyroid dysfunction appears to occur more often in PD1-/PD-L1-inhibition compared to CTLA4-inhibition and most frequently occur irAEs with anti-PD-1 antibody treatment. Indications for Pembrolizumab (anti-PD1 antibody) are e.g. metastatic melanoma, non-small and small cell lung cancer, Hodgkin lymphoma, urothelial cancer, solid cancers, renal cell cancer, head and neck cancer, respectively. The best evidence for the use of ICI-therapy results from trials in advanced melanoma. Better survival compared to cytotoxic chemotherapy was seen in both, pre-treated and treatment-naïve patients with Pembrolizumab, ipilimumab and nivolumab [1,3,4,6,8].

In this report, we present a case of a 30-year-old male patient with metastatic melanoma on adjuvant therapy with Pembrolizumab causing acute destructive thyroiditis with initial hyperthyroidisms and subsequent rapid hypothyroidism.

Medical history and tumor diagnosis / therapy of the patient

A 29-year-old male patient was diagnosed with a primary dermal malignant melanoma localized at the dorsum of the left foot with a vertical infiltration of 6.7mm after Breslow and Clark-level V. At the first time of consultation (12/2020) in our department of dermatology the lesion was not completely excised (R1). Neither the first staging with lymph node ultrasound revealed no pathologies nor the presurgical staging with 18FDG Positron Emission Tomography (PET/CT) and brain MRI. A second excision to achieve 2cm of safety margins as well as a diagnostic Sentinel Lymph Node Biopsy (SLNB) were done. The SLNB revealed a micro lymph node metastasis in 1 of 1 detected lymph node (BRAF wild type). The statement of the following interdisciplinary tumor conference was an open inguinal lymph node dissection on the left-hand side followed by adjuvant therapy by an ICI. The open inguinal lymph node dissection in 01/2021 showed no further metastasis (0 of 5 nodes affected) allowing plastic reconstruction of the primary melanoma by skin graft in 02/2021. Afterwards the adjuvant treatment with Pembrolizumab 400mg every 6 weeks was initiated on 14thmay 2021. Until the end of May 2021 no laboratory abnormalities were present including TSH, FT4, FT3, respectively. Prior to the second application of Pembrolizumab another staging with a whole body CT and brain MRI was scheduled for 06/2021 and a blood sample was taken with the incidental finding of a severe hyperthyreosis on 16thjune with TSH <0,01mU/l (0.27-4.20), FT4 >100pmol/l (9.1-23.0), each value provided by the laboratory of university hospital Jena. Unfortunately, the external radiologist, unaware of the recent hyperthyreosis, performed the CT with contrast media containing iodine on 17thjune (80ml of Ultravist 300). On the very same day, the dermatologist contacted the department of endocrinology aware of suppressed TSH and the application of iodine containing contrast media without premedication by sodium perchlorate.

In absence of the patient our recommendation by phone was to immediately start sodium perchlorate (20gtt. t.i.d.), 20mg of methimazole once a day as well as 75mg of propranolol once a day. We succeeded to get in contact with the patient being on a weekend trip far from Jena. We recommended to seek urgent medical examination and therapy at the next emergency unit. At hospital in Munich the patient presented with palpitations, nausea, diarrhea and feeling “hot” (RR 140/90mmHg, 110/min, temperature 36.9°C). External laboratory was: TSH <0.01mU/l; FT4 46.7pmol/l (9-19); FT3 25.5pmol/l (2.6-5.7), CRP 5.9mg/l (<5.0). The patient stayed overnight from 17th-18thjune and dismissed himself the other day on medication with sodium perchlorate (20gtt. t.i.d.), methimazole (40mg) and propranolol (10mg).

Clinical presentation with irAE

The first personal contact with the patient was on 22nd June 2021 in our outpatient clinic for endocrinology. He complained of dizziness, palpitations, hyperhidrosis, sleep disorders and mild diarrhea. WHO Well being 5 survey revealed 6 points (<10 points: indicative of depressive mood). Family history (mother: Hashimoto thyroiditis). Smoking history of 10 pack years.

Physical examination: Height 191cm, weight 145kg, BMI 39.7kg/m², RR 170/105mmHg, heart rate 115/min, no dyspnea, no cyanosis, no edema, no palpable lymph nodules, at complete consciousness, increased thyroid gland palpable freely moving after swallowing, neck circumference 46cm, cor: Regular heartbeat, tachykardia, no murmur; general hyperreflexia. No further clinical abnormalities were diagnosed.

Sonography of the thyroid (GE logic S7 Expert, 8-12MHz linear head): Total volume 31ml, right lobe 14.7ml, left lobe 16.4ml. Parenchyma hypoechogenic, vascularization normal. No thyroid nodules. No cervical lymph nodules: Struma diffusa, morphological signs in line with thyroiditis (**Figure 1**).

ECG: sinus tachycardia, 109/min, PQ 146ms, QRS 88ms, QTc 426ms.

Laboratory results: TSH: 0.01mU/l (0.27-4.20), FT4: 92.9pmol/l (9.1-23.0), FT3: 30.7pmol(l (2.5-5-8), thyroglobulin: 221.6ng/ml (2.0-70.0), Thyreoglobulin Antibody (TgAb): 36.6U/ml (0.0-60.0), Thyroid Peroxisome Antibody (TPOAb): 82U/ml (0-60), Thyroid Receptor Antibody (TRAb) <0.8U/l (<1.8), CRP: 15.2mg/l (0.0-5.0), HbA1c 5.28% (5.0-6.2).

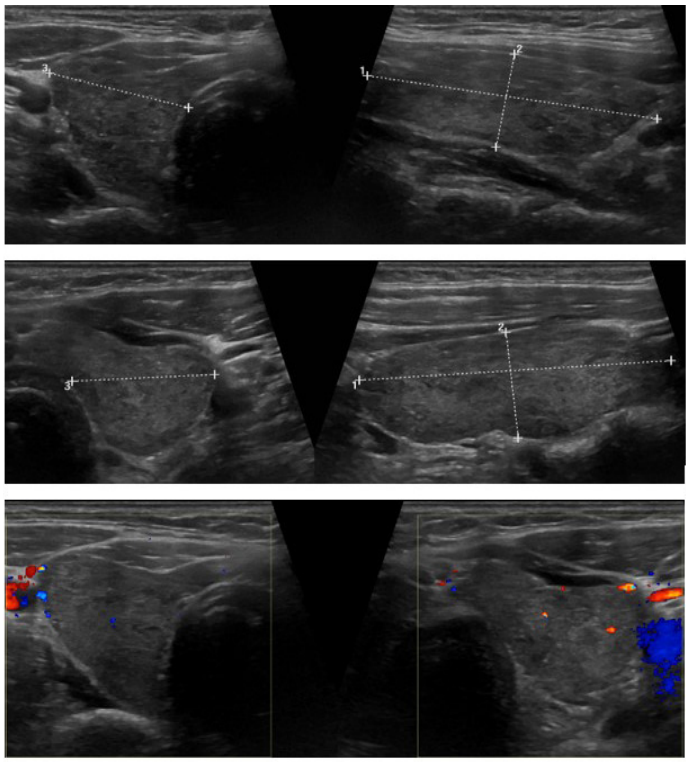

Figure 1: First sonography of the thyroid (total volume 31.1ml) at manifestation of thyroiditis 06/2021 (right lobe 14.7ml; left lobe 16.4ml; duplex sonography).

Diagnosis

We diagnosed acute destructive thyroiditis with overt hyperthyroidism induced by ICI with pembrolizumab boosted by Accidential exposure to iodine.

Diagnostic procedures and interdisciplinary treatment

While being hospitalized for 4 days on our endocrinological ward, the patient suffered from tachycardia, hyperhidrosis at day and night, mild diarrhea and psychomotor agitation.

We continued therapy with sodium perchlorate (1ml=300mg: 3x20gtt./day) and propranolol (25mg 3x/day) but stopped therapy with methimazole (40mg/day) since relevant autoimmunity had been ruled out before (see thyroid autoantibody levels above). We applied methylprednisolone intravenously over 3 consecutive days with 250mg per day. Blood glucose levels were mildly elevated during steroid therapy.

At admission medication was: Sodium perchlorate (1ml=300mg) 3 x 20gtt., propranolol 4 x 25mg, colecalciferol 1 x 1000IU, ibuprofen 3 x 600mg (and on demand) and pantoprazole 1x40mg (for 4 weeks).

We explicitly recommended protection of the thyroid with sodium perchlorate at any time of next elective iodine exposure in terms of Ct-scanning for staging reasons.

ICI with Pembrolizumab was continued per protocol by our dermatologists every 6 weeks. Regular CT-scans and brain MRI were done without any signs of further metastases until 01/2022.

Only 6 weeks after initial diagnosis, in 08/2021 rapid developing hypothyroidism presented with clinical signs of increased BMI (+2.3kg/m², fatigue, weakness and relevant decrease in WHO5 with 3 points and typical laboratory results (TSH 66mU/l, FT4 3.0pmol/l, FT3 <1.50pmol/l). Hormone replacement with levothyroxine 50µg per day was initiated and the patient instructed on correct intake. Ultrasound controls showed a successively reduced thyroid volume (08/21: 21ml; 12/21: 7.2ml).

By now, the patient underwent 7 regular follow up visits in our endocrinological outpatient clinic. Dosage of levothyroxine had to be increased stepwise. The current dose is 175µg levothyroxine per day. Symptoms of hypothyroidism diminished with decline of TSH (17.3mU/l) and elevation of levothyroxine-dose. Normalization of TSH was not reached by now. Local pain was not reported at any time. With the start of levothyroxine therapy, the patient´s mood improved and he lost 10.6kg within 3 months. Blood pressure and Heart Rate normalized (RR 134/88mmHg, 71/min).

The slightly increased TPOAb titer normalized while TRAb were not elevated at any time. Thyroglobulin equally completely normalized (<0.8ng/ml: 2.0-70.0).

Regular thyroid scans showed a decrease of total thyroid volume to one third of original size (11/2021: 7ml). Hypervascularization was neither seen at first nor in other control visits (Figure 1 and 2).

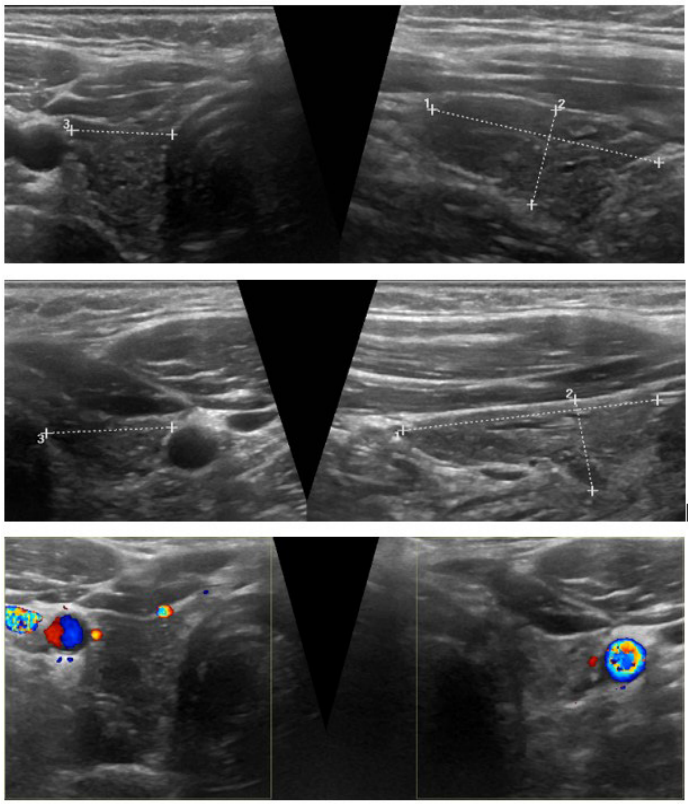

Figure 2: Recent sonography of the thyroid (total volume 7.2ml), at 175µg levothyroxine 11/2021 (right lobe 2.8ml; left lobe 4.4ml; duplex sonography).

12/2021 ACTH (cosyntropin) stimulation test and metyrapone test ruled out not only primary adrenal insufficiency (adrenal autoantibodies negative) but also secondary adrenal insufficiency due to hypophysitis (Table 1). Moreover prolactine, hGH, IGF-1, and IGFBP3 remained normal.

Gonadal pituitary axis was not impaired (LH and FSH low-normal, total testosterone mildly reduced, free testosterone in

normal range, SHBG reduced). Clinical signs of erectile dysfunction or lack of testosterone were negated.

Up to now glucose metabolism is normal and no sign of autoimmune diabetes mellitus is present (HbA1c 5.31%, fasting glucose (4.6mmol/l) was normal and no ketonuria or acidosis present, specific autoimmune antibodies were negative (Table 2).

Follow up visits in our endocrinological outpatient department every 4 months and regular interdisciplinary exchange with dermatologists are planned.

Table 1: Presentation of TSH and FT4.

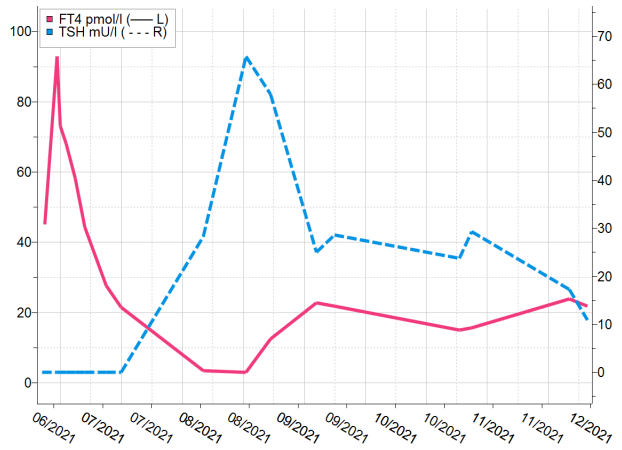

Table 2: Additional endocrine laboratory and specific endocrine test results.

Insulin Ab	4.4 %	(<10)
ICA	negative	(negative)
GADA	<0.7 U/ml	(<0.9)
ZnT8	<10 E/ml	(<15)
adrenal antibodies	negative	(negative)
ACTH-test: Cortisol 0min after. ACTH: 444,0nmol/l; cortisol 60min after ACTH: 753,0nmol/l; cortisol 120min after. ACTH: 895,0nmol/l (normal stimulation: cortisol 60min after ACTH: >550nmol/l)		
Metyrapone test: ACTH after metyrapone 8am: 197,0pg/ml; 11-desoxycortisol 8am: 95,20µg/l; cortisol after. metyrapone 8am: 195,0nmol/l; (normal stimulation (ACTH >150pg/ml, 11-DOC>70µg/l)		

Discussion

ICI-therapy recently became a powerful new tool in a variety of tumours. Endocrine autoimmune diseases occur frequently as side effect, most often thyroid dysfunctions. Close interdisciplinary surveillance of affected patients is necessary, since irAEs may occur late or even after cessation of therapy [9].

The close monitoring of thyroid function is crucial to detect potential side effects at an early stage. This has also recently been highlighted in the guidelines of the German Society for Endocrinology (DGE) [8]. The frequency of hyperthyroidism in monotherapy with a PD1- odder PD-L1-antibody was found in up to 10% of the treated patients. Combination with a CTLA4-antibody further increases the rate to 15-20%, while with monotherapy with the latter the rate is around 5%. The time of onset varies and may occur within a few days after therapy-initiation up to 15 months after the last application. Specific biochemical marker predicting the autoimmune-courses are not found yet. [10].

Incidence of treatment-related endocrine irAEs in major melanoma trials of Pembrolizumab at any grade was 8.7% for hypothyroidism, 3.2% for hyperthyroidism, 0.7% for hypophysitis and least 0.4% for diabetes mellitus. Incidence for high-grade endocrinopathies ≥grade 3-5 (hospitalization required) was 0.4% for hypophysitis and 0.4% for autoimmune diabetes mellitus [3,5,6,9]. Other data confirm these findings with about 5-10% of thyroid disorders in patients receiving anti-PD-1/PD-L1 alone [2,4].

A meta-analysis from 2017 confirmed a significant risk of hyperthyroidism (relative risk of 3.44) and hypothyroidism (relative risk of 6.79), but no significant risk of diabetes mellitus (relative risk of 0.7) and hypopituitarism (relative risk 0.53) in patients treated with PD-1-inhibitors (nivolumab and Pembrolizumab) [11]. Grade 3-5 adverse events are seen in about 7-19% of patients receiving PD1-/PD-L1 antibodies [2,6].

Explicit mechanisms by which ICI cause thyroid dysfunction have not been fully revealed yet, but the expression of PD-L1 und PD-L2 in the thyroid tissue might play a crucial role [1,4].

Regarding our patient, we conclude thyroiditis initially at grade 1/2 with rather non-specific symptoms and more acute symptoms of hyperthyroidism at grade 3 with need for hospitalization after the accidental iodine application as mentioned above.

For the treatment of acute hyperthyroidism under ICI-therapy, it is primarily recommended to control the symptoms. In addition to unspecific beta-blockers (e.g. propranolol), sodium perchlorate has to be administered after iodine-exposition. In case of severe symptoms or when conversion to Grave´s disease is diagnosed, methimazole is indicated. Systemic high-dose glucocorticoids are reserved for severe symptoms, because evidence of a benefit in regard to the endocrine disorder is still lacking, but signs for poorer prognosis regarding the malignant disease exist. Nevertheless, In Grave´s disease with eye-involvement (endocrine orbitopathy) corticosteroids are the keystone of the treatment.

Thyroperoxidase inhibitors (methimazole, carbiamazole) are not recommended for destructive thyroiditis. To control symptoms beta-blocker (e.g. propranolol 40-120mg/day) and steroids (1mg/kg/day methylprednisolone for 1-2 weeks) are used [1-5,8]. Initially, our patient received methimazole but was discontinued quickly after laboratory results indicated no TRab in favour of propranolol and methylprednisolone.

The destructive thyroiditis seen in our patient occurs in the majority of thyroid disorders caused by ICI [8]. Rapid development of hyperthyroidism, as seen in our patient, results of the acute release of thyroid hormones when thyroid cells are destroyed in the state of acute destructive thyroiditis. The absence of endocrine orbitopathy, no Hypervascularization in duplex sonography and elevated thyroglobulin levels corroborated the diagnosis of destructive thyroiditis [4,8]. Experts recommend to start with 50µg levothyroxine when FT4 levels drop below normal limits [1-3,5], as we did in this patient. Thyroglobulin levels normalized with transition to hypothyroidism in our patient as described in Okura et al. [4].

Treatment guidelines recommend to continue ICI therapy if hormone replacement is possible and the patient is well [3]. Also in our patient Pembrolizumab therapy was given as scheduled. A systematic review of case reports with Pembrolizumab reported about irAEs in 10 patients (1 patient with hypothyroidism and 1 patient with diabetes mellitus; 5 patients with cutaneous irAEs) [12]. In Pembrolizumab melanoma studies the median time to

onset of hyperthyroidism was 1.4 months and 3.3 months for hypothyroidism. Further studies report transition to hypothyroidism within 3-6 weeks after ICI treatment initiation [4,5]. This is in line with the development of symptoms in our patient.

As mentioned above, Grave´s disease induced by ICI-treatment is described and therefore screening for thyroid-specific antibodies is recommended. Endocrine orbitopathy is known to occur in association to ICI-treatment as an adverse effect of autoimmunopathy and should be kept in mind. Preexisting latent autoimmune disease of the thyroid predisposes to exacerbation when ICI-therapy is used but does not represent a contraindication [10]. The sonographic imaging of the thyroid is fundamental in every functional abnormality. Sonographic features of thyroiditis are the same as in sporadic disease and increased perfusion is suggestive for Grave´s disease.

We cannot rule out that the Accidential exposure to iodine has aggravated the initially asymptomatic hyperthyroidism to the rapidly destructive thyroiditis. Oncologists and radiologists must carefully monitor TSH, particularly prior to the application of iodine in CT-scanning for staging. If TSH is suppressed, Sodium perchlorate must be given before the administration of iodine.

In our case report the patient received Pembrolizumab as monotherapy. A meta-analysis showed highest incidence of both hypothyroidism and hyperthyroidism in patients receiving combination therapy of PD-1 plus CTLA-4 inhibitors (13). The latter combination is associated with a 30% chance of irAEs in general [1,2]. So far no hints of hypophysitis occurred in our patient. Due to the often unobtrusive clinical symptoms hypophysitis is under-diagnosed [3].

International and national endocrine experts recommend following diagnostic paths. First, patients must be informed thoroughly considering possible adverse events of ICI. Before the first application of ICI a complete check-up comprising blood pressure, drinking volume, fasting blood glucose, sodium, potassium, creatinine, TSH, FT4, morning cortisol (9am, in some cases ACTH), testosterone in males, estradiol in females, FSH, LH and repeated regularly. Before any other application of ICI: symptoms, blood pressure, drinking amount, fasting blood glucose, sodium, potassium, creatinine, TSH, FT4, cortisol (9am). Before starting levothyroxine therapy, hypocortisolism must be ruled out [1-5,8,13,14].

Patients with pre-existing autoimmune or inflammatory disorders (e.g. psoriasis, thyroiditis, rheumatoid arthritis) should be monitored even closer because the risk for irAEs is significantly increased [1,2,12,15].

Interdisciplinary treatment between oncologists, dermatologists, immunologists and endocrinologists is crucial for ICI regimes to handle endocrine irAEs. International guidelines are already set up for the management of ICI toxicities, e.g. ASCO, SITC, NCCN [1]. With expanding indications for ICI, the number of irAEs will increase. It is recommended to involve endocrinological expertise early and not only in severe adverse events of patients with ICI [4,5,12].

Conflicts of interest

S.S. received speaker fees from Novartis only (2015, 2016) and congress and travel grants from MSD (2013), Novartis (2015, 2016), HRA Pharma (2016-2019), Dr. Schär (2019), Swedish Orphan Biovitrum GmbH (Sobi) (2020-2021), metaX Institut für Diätetik GmbH (metaX) (2020-2021), Vitaflo Comidamed GmbH (2021), AMRYT-Pharma (2021) and BioMarin GmbH Deutschland und Biomarin International Ltd. (2019-2021). C.W. received travel grant from Novartis Oncology in 2018. S.G., C.K. and G.W. had no conflicts of interest.

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