Diabetes insipidus: A rare endocrine complication of immune check point inhibitors: A case report and literature review

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Abstract. Immune checkpoint inhibitors (ICIs), including anti-programmed cell death protein 1 (PD-1), anti-programmed cell death protein ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibodies, are novel therapeutic agents widely used in numerous malignancies. They are known to cause multiple immune-related endocrine adverse events (irAEs); however, anterior pituitary hypophysitis with secondary hypopituitarism is the most frequently reported irAE, especially in patients receiving anti-CTLA-4 treatment. By contrast, posterior pituitary involvement, such as central diabetes insipidus (CDI), is relatively rare and only few case reports have been published. The present report describes the case of a 53-year-old woman with metastatic melanoma treated with nivolumab an anti-PD-L1 monoclonal antibody. At 6 months after the initiation of nivolumab treatment, the patient was diagnosed with deficiency of the corticotrope and thyreotrope axes and in the following 2 months the patient was diagnosed with progressive development of polyuria-polydipsia syndrome. The diagnosis of partial CDI was retained based on plasma and urinary osmolalities, the water deprivation test and baseline copeptin levels as well as on the absence of the bright spot in the posterior pituitary in magnetic resonance imaging. Systematic research of the literature revealed a total of 13 cases reports (including 14 patients) presenting with CDI treated with monotherapy with CTLA-4 (n=5) or PD-1/PD-L1 Abs (n=6) or combined treatments (n=3). The improved understanding of the mechanisms of ICI action along with their extensive use should contribute to the early recognition of irAE symptoms. We hypothesized that clinicians should be aware of this clinical entity and its symptoms and treat it appropriately.

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Introduction

Immune check point inhibitors (ICI) are associated with immune related adverse events (irAEs) involving multiple endocrinological organs (1). Hypophysitis and thyroid abnormalities are the most common endocrine irAEs reported to date (2). Overall, the incidence of hypophysitis is up to 17% in patients treated with ICI with male predominance. The mean age at onset is approximately 60 years old and the mean time to onset of the diagnosis at aproximately 10.5 weeks. The prevalence of hypophysitis depends on the type and the dose of ICI; 70% of cases were due to cytotoxic T-lymphocyte protein 4 (CTLA-4) blockade, 23% to programmed cell death protein 1 (PD-1) blockade, or in 2% of the cases to its ligand (PD-L1) blockade, and in 3.9% to combination therapy (CTLA-4 and PD-1) (2-4). At present, the CTLA-4 antibodies (Abs), ipilimumab, PD-1 Abs nivolumab, pembrolizumab, cemiplimab and PD-L1 Abs atezolizumab, avelumab, and durvalumab are Food and Drug Administration (FDA)- and European Medicines Agencies (EMA)-approved (5,6).

In a systematic review and meta-analysis including data from 38 randomized clinical trials comprising 7,551 patients investigating the use of ICIs in the treatment of various cancer types, hypophysitis incidence ranged from 1.5 to 13.3% in patients treated with CTLA-4 Abs and 0.3-3% in those with PD-1Abs. Recently, isolated cases reports have described the diagnosis of central diabetes insipidus (CDI) due to dysfunction of posterior pituitary/hypothalamus in patients treated with ICI (1,7-16).

According to data from the WHO global database of individual case safety reports (17) between January 2011 and March 2019, a total of 6,089 ICI-related endocrine AEs were reported, of which 1,144 (18.8%) were pituitary events, including hypophysitis (n=835), hypopituitarism (n=268), pituitary enlargement (n=28), and other (n=13), while CDI was reported in 7 out of 1,072 (0.7%) of the registered hypophysitis/hypopituitarism cases.

Herein, we report the case of a patient diagnosed with simultaneous anterior and posterior hypophysitis (panhypophysitis) induced by nivolumab and discuss the emerging difference in the incidence of hypophysitis/CDI among subclasses of ICIs and the related pathogenic mechanisms.

Case report

A 53-year-old female patient was followed at Laikon General Hospital for metastatic melanoma of the left tibial treated with multiples surgeries due to local recurrences. A treatment with nivolumab-a PD-L1 Ab-was introduced at January 2021. The patient received 240 mg flat dose by intravenous infusion every 2 weeks and achieved a partial response (RECIST 1.1) within 6 months, based on computerised tomography (CT) scanning. Her other routine medication included venlafaxine. A thorough baseline work-up revealed normal electrolyte, hepatic, and renal function at the initiation of immunotherapy and before every session.

However, 6 months after the initiation of nivolumab she presented with extreme fatigue necessitating a precipitating hormonal work-up which revealed deficiency of the corticotrope and thyreotrope axis. The detailed biochemical work-up is shown in Table I. A replacement treatment with hydrocortisone (25 mg/24 h) and thyroxine (50 μg/24 h) was initiated with prompt clinical improvement. Two months after the diagnosis of the anterior pituitary deficiency the patient was complaining for frequent nocturia (three to four times with increased volume each night), fatigue, polydipsia, and polyuria. Biochemical analyses showed normal 24-h urinary collection and blood levels of sodium, potassium and calcium as well as glucose levels. A 24-h urinary collection showed an important water diuresis of 5.3 lt/day with low urinary osmolality 184 mOsm/kg (500-800) and urine specific gravity of 1,002. Plasma osmolality was also found increased at 309 mOsm/Kg (280-295) indicating a possible diagnosis of DI. Of note, the patient denied any use of non-steroid anti-inflammatory drugs or other over-the counter medications. Moreover, a recent cerebral CT performed in the context of the staging for the melanoma was normal without suspicion of secondary metastases. The patient refused initially the hospitalisation for further functional test. Thus, we decided to perform the measurement of baseline copeptin levels which was found low at 2,4 pmol/l being in favour of CDI (Table II).

Following these results, the patient eventually accepted to be hospitalised and a water deprivation test followed by desmopressin (DDAVP) administration test was performed (Table III) (18). The weight, blood pressure, urinary and plasma osmolality were measured at baseline at the initiation of the test (at 8.00 am) as well as during the phase of dehydration (every 2 h). The water deprivation test was interrupted after 6 h due to hypernatremia at 146 mmol/l and patient's intolerance with symptoms of dizziness (orthostatic symptoms with systolic blood pressure at 105 mmHg in decubitus and 90 mmHg in the upright position). Urinary osmolality as well as plasma osmolality remained unchanged during the 6 h water deprivation excluding a primary polydipsia syndrome. We then administrated 2 μg of desmopressin (DDAVP) intravenously with immediate amelioration of clinical symptoms of polyuria-polydipsia and an increase of the urinary osmolality from 327 to 716 mOsm/kg (39%) in favor of partial CDI (19), (Table II). The results of the water deprivation test are shown in Table IV.

Table I. Baseline biochemical parameters of the patient at diagnosis and post-treatment of DI.

Biochemical parameter	Onset of DI diagnosis	After the treatment of DI	Normal range
Blood			
Sodium, mmol/l	143	139	136-143
Potassium, mmol/l	4.9	4.4	3.7-4.9
Calcium, mmol/l	9.4	9.6	8-10
Creatinine, mg/dl	1.11	1.03	0.7-1.2
Osmolality, mOsmol/kg H_2O	309.92	294	280-295
Urine			
Urine specific gravity	1.004	1.020	1.010-1.030
Osmolality, mOsmol/kg H_2O	184	757	500-800
Sodium, mEq/24 h	175	nd	40-200
Potassium, mEq/24 h	87	nd	25-120
Calcium, mEq/24 h	138	nd	100-300
Serum			
TSH, μIU/ml	0.98	0.99	0.27-4.7
FT4, ng/dl	0.80	1.13	0.7-2
ACTH, pg/ml	<3.0	<2.9	7.0-64
Prolactin, ng/ml	31.0	32	4.8-23.3
Cortisol, μg/dl	1.04	0.7	6.2-19.4
LH, IU/l	49.7	51	7.7-58.5
FSH, IU/l	87.9	89	25.8-134.8

DI, diabetes insipidus; TSH, thyrotropin hormone; FT4, free T4; ACTH, adrenocorticotropic hormone; LH, luteinizing hormone; FSH, follicle stimulating hormone; nd, no data.

Pituitary magnetic resonance imaging (MRI) did not show signs of hypophysitis (Fig. 1), however, the posterior pituitary bright spot was absent in the non-contrast T1 sagittal sequalae (Fig. 1A).

The patient was started a replacement treatment with oral desmopressin (DDAVP) at 60 mg once daily with titration of the dose increasing to twice daily with evident improvement of her polyuria, nycturia, and polydipsia and re-initiation of nivolumab. Panhypopituitarism including CDI persisted after 6 months of follow up.

Literature review

Systematic review of the literature. To identify studies and determine their eligibility, a systematic research was conducted in the PubMed Database on June 10, 2022. Research included the following keywords: 'diabetes insipidus', 'immunotherapy', 'immune check-point inhibitors', 'posterior hypophysitis', 'pituitary'. The above keywords were also combined with the

Table II. Differential diagnosis of the polyuria syndrome based on the water deprivation test and copeptin levels.

Biochemical parameters	Normal	Central DI	NDI	Primary polydipsia	Partial CDI
Baseline urinary osmolality, (mOsm/kg)	>300	<300	<300	300-800	300-800
Urinary osmolality after water derivation[a], mOsm/kg	800-1,200	<300	<300	300-800	300-800
Urine osmolality after administration of desmopressin, mOsm/kg		Increase >50%	No response	Normal	Increase <50%
Baseline copeptin levels[b], pmol/l	Normal	<4.9	>21.4	Normal	Normal/low

[a]Sensitivity, 86%; specificity, 70%. [b]Sensitivity, 100%; specificity, 100%. DI, diabetes insipidus; NDI, nephrogenic diabetes insipidus; CDI, central diabetes insipidus.

Table III. Description of the water deprivation test.

Steps to follow	Parameters or criteria to evaluate
Before any measurement: Correction of any electrolyte abnormalities, including serum potassium and calcium and discontinuation of any medications that can affect urine output for at least 24 h	Diuretics, SGLT-2 inshibitors, DDAVP, carbamazepine, chlorpropamide, glucocorticoids and non-steroidal anti-inflammatory drugs; smoking and caffeine
Baseline measurements (every 2 h)	Weight, blood pressure, heart rate prior to initiation of dehydration, plasma osmolality, serum sodium, urine osmolality; urine output and urine osmolality, serum sodium and plasma osmolality
Criteria of discontinuation	i) Loss of >3% of body weight; ii) elevation of serum sodium to above normal limits (≥146-150 mmol/l); and iii) orthostatic hypotension or orthostatic symptoms or intractable thirst
Administration of DDVAP (2 μg intravenous or intramuscular)	When DDVAP is administrated: i) Dehydration phase is completed for 8 h; or ii) two consecutive urine osmolality measurements do not differ by >10% and there is loss of 2% body weight; or iii) premature termination of dehydration phase due to loss of >3% of body weight, elevation of serum sodium to above normal limits, or intractable
Measurement post-DDAVP administration	Urine and serum/plasma measurements are obtained hourly for 1-2 h after the injection. In patients with complete forms of DI, the test can be performed in <8 h while in those with partial DI the test could last longer (even 18 h)

DDAVP, desmopressin; DI, diabetes insipidus; SGLT-2, sodium-glucose cotransporter-2.

Boolean operators AND and OR. PICOT (population, intervention, comparison, outcomes, time) criteria were used in order the irrelevant articles to be excluded. Articles that do not align with the PICOT format were dismissed. More specifically, studies including population without malignancy (irrelevant population) or population presenting CDI induced by other causes than immunotherapy (irrelevant intervention) as well as studies including ICI-treated patients with hypophysitis without data on CDI (irrelevant outcome) were also excluded. Additionally, we excluded not original studies (Reviews or systematic reviews/meta-analysis) or *in vitro*/*in vivo* studies. Finally eligible for inclusion in our analysis were studies on humans with malignancy treated with immunotherapy and presenting ICI-induced DI. Four of the investigators (PP, DM, MM and AK) independently examined all potentially eligible titles and abstracts. Full manuscripts were obtained as necessary to finalise eligibility (studies which were available only as abstracts were excluded). Reference lists of eligible studies

Table IV. Water deprivation test/DDAVP administration in the present case.

Sampling time (t)	Weight, kg	Serum osmolality, mOsmol/kg H_2O	Urine osmolality, mOsmol/kg H_2O
08:00	84.5	304.73	351
09:00			356
10:00	83.5	306.59	291
11:00			294
12:00	84.5	306.76	334
13:00			332
14:00	83.5	304.07	327
After 2 μcg DDAVP IV administration			
15:00 (t=0)		305	457
15:30 (t=+30 min)	84.5	303	na
16:00 (t=+60 min)		300	683
16:30 (t=+90 min)	84.4	303	na
17:00 (t=+120 min)		299	716

DDAVP, desmopressin; IV, intravenous; na, not applicable.

were also searched through to identify additional studies. Only English language papers published were selected. Research strategy is illustrated in the flow diagram (Fig. 2).

Results. PubMed research revealed 583 English written reports; n=13 of them concerned *in vitro* or animal studies. From the remaining 570 studies, we further excluded n=283 not original papers (reviews, systematic reviews or meta-analyses) providing no data on clinical cases with ICI-induced DI. Based on full text of the rest 287 original studies and cases reports, n=139 were excluded as they included either not relevant population or not relevant treatment (n=121 articles studied adults and n=12 children without malignancy presenting DI induced by other causes besides immunotherapy and n=6 articles studied patients presenting DI post-COVID vaccination), further n=135 articles were excluded because although they included patients with malignancy treated with ICI, they provided data for other pituitary deficiencies but not DI (not relevant outcome). Finally, we ended-up to only 13 cases reports reporting data on DI among ICI treated patients (Flow diagram). A total of 14 patients presenting with DI post-immunotherapy with predominance of the male sex (11 males vs. 1 female, in 2 patients sex was not specified) were described (Table V), (1,7-16,20,21). All patients had been treated with ICIs for solid malignancies except two cases treated for Hodgkin lymphoma and acute myeloid leukaemia. Five patients had been treated with CTLA-4 Abs monotherapy, 6 with PDL-1 Abs monotherapy and the rest 3 with combined therapies (CTLA-4Abs and PDL-1Abs). The median time from the initiation of immunotherapy to DI onset varied from immediate after the first cycle of PD-1 Ab (sintilimab) to 270 days post-initiation of PD-L1 Ab (atezolizumab). Five patients presented isolated injury of the posterior pituitary with maintenance of the secretion of the anterior pituitary. In 7 patients, CDI was associated with deficiency of the anterior pituitary (panhypopituitarism) from which, in one case treated with atezolizumab, there was a strong suspicion for hypothalamitis based on imaging findings (hypothalamic mass). In 5 cases, CDI was either transient or prolonged (varying from 5 days to 5 months) whether in 3 cases was chronic (more than 6 months of duration). In the majority of cases in which MRI's data were available, pituitary image was normal (n=5) or showed an adenomatous lesions with or without stalk thickening (n=2). Interestingly, none of the patients with available imaging data presented absence of the bright spot on the MRI.

Discussion

This is the case of a 53 year old woman treated with nivolumab for metastatic melanoma, presenting with a syndrome of polyuria-polydipsia, 6 months post-initiation of immunotherapy and 2 months after the diagnosis of the anterior pituitary deficiency (insufficiency of the corticotrope and thyreotrope axes). The diagnosis of partial CDI was retained based on biochemical findings that included inappropriately low urine osmolality for serum osmolality increased less than 50% after desmopressin administration in combination with low baseline copeptin levels. CDI induced by nivolumab treatment was confirmed through the medical history of the patient, the pituitary MRI and the water deprivation tests which allowed to exclude nephrogenic DI (NDI) and primary polydipsia.

DI is a rare condition that affects one in 25,000 persons (14,22). CDI is the most common form of DI and is generally the result of hypothalamic-neurohypophysial dysfunction leading to inadequate arginine vasopressin (AVP) secretion from the posterior pituitary or inadequate production from the hypothalamus (19). The majority of the causes of CDI are acquired (idiopathic and iatrogenic) whereas inherited/familial CDI causes account for approximately 1% of cases (19). CDI develops when more than 80% of the AVP-secreting neurons are damaged. The less common NDI is caused by a partial or complete resistance of AVP receptors to vasopressin. Some of the commonest NDI etiologies are electrolytic disturbances including hypokalemia and hypercalcemia. In our patient, both the potassium and calcium levels were within the normal limits.

In our patient the exclusion of metastatic disease was also challenging. Indeed, the posterior pituitary is most frequently affected by metastases, due to its vascularisation by the inferior hypophyseal artery (23). Besides, its small size compared to the anterior pituitary explain why the same volume of metastatic tissue can produce earlier symptoms compared to the adenohypophysis damage (24). In our case pituitary MRI did not show any evidence of metastatic disease, stalk thickening or posterior pituitary mass.

Secondary hypophysitis related to ICI has a reported incidence ranging from 8 to 13% in patients treated with CTLA-4 Abs therapy (25) and from 8.5 to 9.0% in patients treated with PD-1 Abs therapy (26). Unlike other forms of hypophysitis

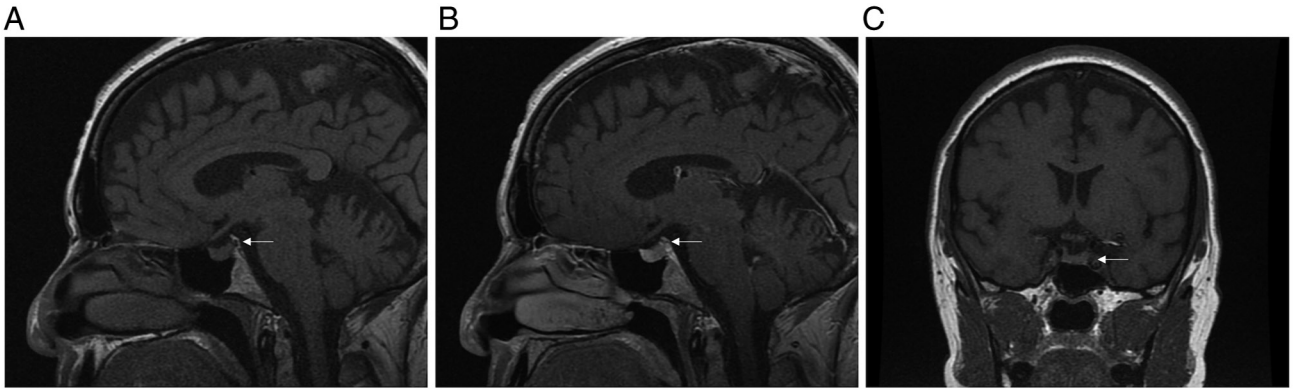

Figure 1. MRI of our patient's pituitary gland. (A) Non-contrast T1 sagittal sequence showing the absence of the bright spot of the posterior pituitary gland (white arrow). (B) Post-contrast T1 sagittal sequence showing a normal posterior pituitary gland (white arrow). (C) Pre-contrast T1 coronal sequence showing a normal posterior pituitary gland (white arrow).

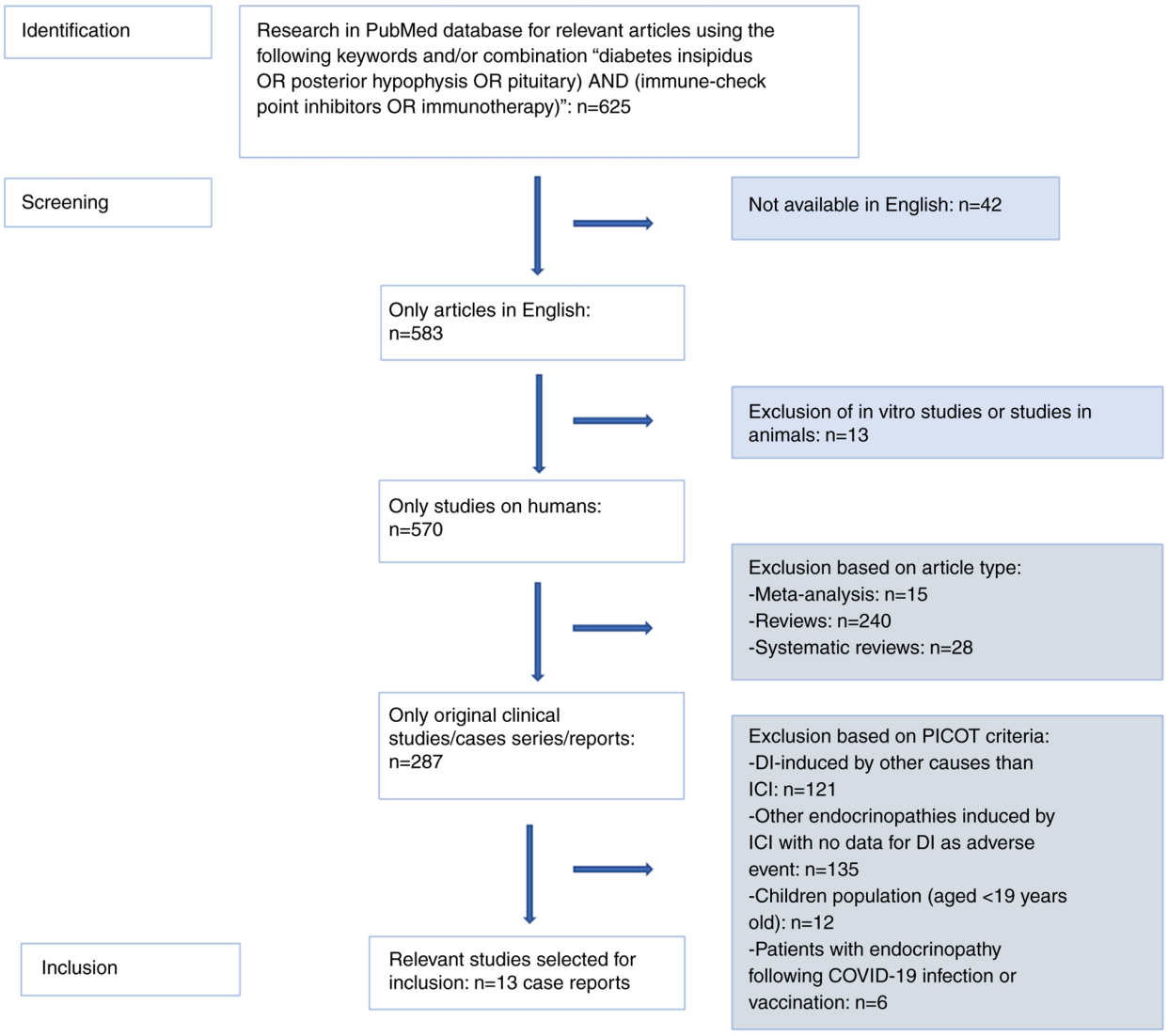

Figure 2. Flow diagram of the research strategy for the identification of cases reporting immunotherapy-induced DI. COVID-19, coronavirus disease 2019; DI, diabetes insipidus; ICI, immune checkpoint inhibitor; PICOT, population, intervention, comparison, outcomes, time.

(lymphocytic, granulomatous, xanthomatous, and plasmacytic), the ICIs-associated hypophysitis is more common in males (27) and typically occurs after a period of 2 to 3 months post-immunotherapy as in our case. Older age and male sex are potential risk factors (27). Moreover, ACTH and thyrotropin deficiency are the most common abnormalities an observation

Table V. Cases in the literature presenting with ICI-induced central DI.

First author/s, year	Age, years	Sex	Malignancy	Drug	ICI category	Dysfunction of pituitary	Dysfunction of hypothalamus	Median time to onset of DI, days	Duration of DI	MRI findings	Grade of AE	Follow-up, days	(Refs.)
Dillard *et al*, 2010	50	M	Adenocarcinoma of prostate	Ipilimumab	CTLA-4 Ab	Panhypopituitarism	No	84	3 weeks	Normal	III	ND	(7)
Nallapanemi *et al*, 2014	62	M	Melanoma	Ipilimumab	CTLA-4 Ab	Panhypopituitarism	No	121	5 months	ND	II	180	(8)
Gunawan *et al*, 2018	52	M	Melanoma	Ipilimumab + nivolumab	CTLA-4 Ab (+) PD-1 Ab	Isolated posterior pituitary	No	28	ND	ND	I	ND	(9)
Zhao *et al*, 2018	73	M	Merkel cell carcinoma	Avelumab	PD-L1 Ab	Isolated posterior pituitary	No	112	6 weeks	Normal	I	240	(1)
Tshuma *et al*, 2018	74	F	Bladder cancer	Atezolizumab	PD-L1 Ab	Panhypopituitarism	Yes	270	ND	Hypothalamic mass	I	365	(10)
Deligiorgi *et al*, 2020	71	M	Adenocarcinoma of the lung	Nivolumab	PD-L1 Ab	Isolated posterior pituitary	No	90	ND	Normal	IV	[a]	(11)
Barnabei *et al*, 2020	64	M	Melanoma	Ipilimumab	CTLA-4 Ab	Panhypopituitarism	No	60	5 days	Normal	I	1,230	(12)
Grami *et al*, 2020	30	M	Acute myeloid leukemia	Ipilimumab + nivolumab	CTLA-4 Ab (+) PD-1 Ab	Panhypopituitarism	No	ND	ND	ND	III	ND	(13)
Brilli *et al*, 2020	68	M	Mesothelioma	Tremelimumab and durvalumab	CTLA-4 Ab (+) PD-L1 Ab	Isolated posterior pituitary	No	60	Persisted	Normal	ND	570	(16)
Yu *et al*, 2021	60	M	Hodgkin lymphoma	Sintilimab	PD-1Ab	Isolated posterior pituitary	No	Immediate	3 months	Nodular signal	II	90	(14)
Fosci *et al*, 2021	62	M	Hypopharynx cancer	Nivolumab	PD-1 Ab	Panhypopituitarism	No	35	50 days[b]	Stalk enlarged	I	24	(15)
Terán *et al*, 2022	46	M	Adenocarcinoma of the lung	Nivolumab	PD-1 Ab	Panhypopituitarism	No	62	ND	ND	I	ND	(20)
Amereller *et al*, 2022	2 cases	1F/1M	ND	Ipilimumab	CTLA-4 Ab	ND	ND	ND	ND	ND	ND	ND	(21)

[a]The patient died before initiation of treatment with desmopressin. [b]The patient died 50 days after desmopressin initiation. Ab, antibody; AE, adverse events; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DI, diabetes insipidus; F, female; ICI, immune-check point inhibitor; M, male; ND, no data; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1.

confirmed in our case; however it can also affect sex hormones, growth hormone, and prolactin.

Patients treated with ICIs rarely develop CDI secondary to an autoimmune process involving the hypothalamo-posterior pituitary region. Dysregulation of the posterior pituitary-hypothalamic axis induced by ICI has been reported in 13 case reports that are available in the current literature (summarized in Table II), (1,7-16,20,21). Almost all patients developed CDI with a substantial delay from treatment administration, ranging from 28 to 270 days, except in one case where CDI developed immediately after sintilimab, a PD-1 inhibitor (14). From the 14 patients presenting with CDI with available data on their treatment, 5 had been treated with monotherapy with CTLA-4 Abs, 6 with monotherapy with PD1-Abs whereas 3 cases had been treated with combination treatment (CTLA-4 Abs and PD-1 Abs). Regarding our case, this is the fourth case of nivolumab-induced CDI published in the literature (11,15,20) and the first female patient presenting with nivolumab-induced CDI. In two other cases CDI was induced by a combination treatment with nivolumab and ipilimumab (9,13).

The pathophysiological mechanism for ICI-induced CDI remains unclear and may be linked to multiple pathways (28). Prior works suggested that type II and type IV hypersensitivity reactions as well as ectopic pituitary CTLA-4 expression may be associated with anti-CTLA-4 treatment-related hypophysitis (29,30). PD-1 may also be expressed in pituitary cells or lymphocytes and PD-L1 was expressed in pituitary adenomas (31).

In many cases of patients with suspected DI, the diagnosis may be obvious based on serum and urinary osmolalities. If the serum osmolality is greatly increased, with concomitant low urinary osmolality, no further testing may be necessary. The diagnostic challenge arises when there are symptoms of polyuria and polydipsia with inappropriate normal or 'almost normal' serum osmolality or sodium levels or when NDI or primary polydipsia should be excluded. In such cases, dynamic test such as water deprivation test is required since direct measurement of plasma AVP is seldomly performed because of its rapid clearance. However, yet even under optimal conditions water deprivation test often require long periods of observation, and still is of low sensitivity (86%) and specificity (70%) (19,32).

Recently, copeptin-C-terminal peptide of pro-vasopressin-levels, either baseline or after stimulation (with hypertonic saline infusion or with L-arginine stimulation), has proven to be the most convenient and accurate way for the diagnosis of DI. Copeptin is co-secreted with AVP and is a surrogate of its secretion as it is a more stable compound (33,34). Baseline copeptin levels <4.6 pmol/l are diagnostic of CDI, whereas levels >21.4 pmol/l are diagnostic of NDI with 100% sensitivity and specificity (19,33,35). If baseline levels are intermediate the diagnosis could be either CDI or PP; in that case stimulated copeptin levels are required (36-38). A randomized multicenter prospective study is currently being carried out (clinical trials. gov NCT03572166) in order to confirm the arginine-stimulated copeptin cut-off levels. Unfortunately, copeptin measurement has not been routinely used in most laboratories.

In the MRI, CDI generally manifests as a pituitary 'bright spot' absence with or without enlargement (2-3 mm) of the pituitary stalk, although this finding alone is not necessarily sufficient to support CDI diagnosis. The posterior pituitary bright spot is a manifestation of stored vasopressin and although it is missing in 20% of the general population (39), its absence on MRI is consistent with CDI. In our patient no bright spot was apparent arguing in favour of the CDI. On the contrast, no other abnormality was observed on the MRI on the rest of the pituitary gland in favour of hypophysitis which may presents a mild-to-moderate diffuse enlargement of the pituitary gland (40).

In conclusion, the recent widespread use of ICIs in oncology could explain why clinicians should be aware of the potential risk for developing CDI. For normoglycemic patients presenting with persistent polyuria/polydipsia syndrome during ICI therapy and in particular anti-PD-1/PD-L1, testing for DI via serum and urine specific osmolalities, urine specific gravity, and, if needed, a water deprivation test are required. Patients' symptoms of CDI can be easily controlled with DDAVP. As ICI are relatively new agents, rare side effects such as DI should be reported to the Food and Drug Administration adverse event reporting system (FAERS) to better understand their side effects and effective management of drug related adverse events.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

HG and AA conceived and designed the study. MM, DM, AA, PP, AK and DZ collected and interpreted all relevant clinical and laboratory data. AA, PP and HG prepared the manuscript. HG and AA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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