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Clinical Research Article

Combined Hypophysitis and Type 1 Diabetes Mellitus Related to Immune Checkpoint Inhibitors

Yasunori Fujita,[1,*] Fumika Kamitani,[2,*] Masaaki Yamamoto,[1] Hidenori Fukuoka,[3] Yushi Hirota,[1] Nobuharu Nishiyama,[3] Naho Goda,[3] Yuko Okada,[3] Yuiko Inaba,[3] Hiroki Nakajima,[2] Yukako Kurematsu,[2] Keitaro Kanie,[1] Hiroki Shichi,[1] Shin Urai,[1] Masaki Suzuki,[1] Naoki Yamamoto,[1] Hironori Bando,[3,4] Genzo Iguchi,[1,5,6] Hirotaka Suto,[7,8] Yohei Funakoshi,[7,8] Naomi Kiyota,[7,8] Yutaka Takahashi,[2] and Wataru Ogawa[1]

[1]Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, Kobe, Japan
[2]Department of Diabetes and Endocrinology, Nara Medical University, Nara, Japan
[3]Division of Diabetes and Endocrinology, Kobe University Hospital, Kobe, Japan
[4]Division of Development of Advanced Therapy for Metabolic Diseases, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan
[5]Medical Center for Student Health, Kobe University, Kobe, Japan
[6]Division of Biosignal Pathophysiology, Kobe University Graduate School of Medicine, Kobe, Japan
[7]Division of Medical Oncology and Hematology, Kobe University Graduate School of Medicine, Kobe, Japan
[8]Department of Medical Oncology and Hematology, Cancer Center, Kobe University Hospital, Kobe, Japan

Correspondence: Hidenori Fukuoka MD, PhD, Division of Diabetes and Endocrinology, Kobe University Hospital, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe 650-0017 Japan. Email: fukuokah@med.kobe-u.ac.jp.
*__Authorship note__: Fujita Y. and Kamitani F. contributed equally to this work.

Abstract

Context: The occurrence of multiple endocrinopathies due to immune checkpoint inhibitors (ICIs) is a relatively common adverse event. However, the occurrence of a combination of hypophysitis and type 1 diabetes mellitus (T1DM) is extremely rare, and its clinical features are unclear.

Objective: We comparatively analyzed the clinical features of this combination and each individual ICI-induced endocrinopathy.

Methods: We reported 3 cases that we encountered and reviewed previously reported cases of patients with combined hypophysitis and T1DM due to ICIs.

Results: Anti-programmed cell death-1 (anti-PD-1) antibodies were prescribed to all 3 cases. The duration from ICI initiation to the onset of endocrine disease was 12 to 48 weeks. Several human leukocyte antigen (HLA) haplotypes that have disease susceptibility to hypophysitis were detected in all 3 patients. With the 17 previously reported cases, combined endocrinopathies were more common in men (85%). The onset age was in the 60s for both combined and single endocrinopathies. Anti-PD-1 antibodies were used in most of the cases (90%). The time from ICI initiation to the onset of endocrinopathies was 24 (8-76) weeks for hypophysitis and 32 (8-76) weeks for T1DM in patients with combined endocrinopathies, which was not significantly different from that for each single endocrinopathy.

Conclusion: We presented 3 cases of patients with combined endocrinopathies of hypophysitis and T1DM that may have been caused by anti-PD-1 antibodies. There was no difference in the time from ICI initiation to the onset of endocrinopathies between combined and single endocrinopathies. Further case accumulation and pathogenic investigations are required.

Key Words: immune checkpoint inhibitors, hypophysitis, diabetes mellitus, combined endocrinopathies, HLA haplotype

Abbreviations: ACTH, adrenocorticotropic hormone; CPR, C-peptide reactivity; CTLA-4, cytotoxic T-lymphocyte antigen 4; DM, diabetes mellitus; fT4, free thyroxine; GAD, glutamic acid decarboxylase; HbA1c, glycosylated hemoglobin; HLA, human leukocyte antigen; IAD, isolated ACTH deficiency; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TPO, thyroid peroxidase; TSH, thyrotropin (thyroid-stimulating hormone).

Immune checkpoint inhibitors (ICIs) have recently emerged as promising drugs for several metastatic cancers, and their demand is growing rapidly. They increase the T cell antitumor activity by blocking intrinsic downregulators of the immune system, including programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) [1, 2]. Several monoclonal antibodies that target PD-1 (eg, nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) have been approved and are widely used for advanced cancers. Moreover, the combination of anti-programmed cell death-1 (anti-PD-1) and CTLA-4 antibodies is more effective than their individual

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use for several metastatic cancers, such as melanoma, non-small cell lung cancer, and renal cell carcinoma [3, 4].

ICIs can cause autoimmune toxicity, termed as immune-related adverse events (irAEs), due to the activated immune system. These irAEs can occur in various organs, such as the skin, digestive tract, liver, muscles, nerves, and endocrine organs [5]. Among them, endocrinopathies are common, which include thyroid dysfunction, hypophysitis, type 1 diabetes mellitus (T1DM), and primary adrenal insufficiency. Since serious conditions, such as thyrotoxic storm, adrenal crisis, and diabetic ketoacidosis, can be life threatening, these irAEs require early detection [6]. The profiles of ICI-related endocrinopathies are known to vary according to the type of ICIs. For example, thyroid dysfunction appears to be more common with anti-PD-1 antibodies and the combination of ipilimumab plus nivolumab than with anti-CTLA-4 antibody monotherapy [7]. Hypophysitis is observed in 8% to 13% of the patients on anti-CTLA-4 antibody treatment, while it is relatively rare (0.1% to 0.4%) in those on anti-PD-1 antibodies [8]. Besides, hypophysitis caused by anti-PD-1 antibodies mainly results in the deficiency of adrenocorticotropic hormone (ACTH), while anti-CTLA-4 inhibitors impair the production of multiple pituitary hormones, including thyroid-stimulating hormone (TSH) [9]. ICI-related diabetes mellitus (DM) is rare. Accordingly, the combination of hypophysitis and T1DM related to ICIs is considered one of the rarest combinations. Recently, several cases of multiple endocrine disorders associated with ICIs have been reported [10, 11]. However, their etiology and clinical features remain unclear. We hereby report 3 cases of combined endocrine disorders of hypophysitis and T1DM related to ICIs, along with their human leukocyte antigen (HLA) profiles. Additionally, we reviewed the previously reported cases of this combination and summarized their clinical features.

Case Presentations

Case 1

A 64-year-old female patient with a history of hypertension and type 2 DM (T2DM) had multiple primary lung tumors, which were diagnosed during her health checkup. Her lung tumors were diagnosed as well-differentiated mucus-producing adenocarcinoma, as per the results of histopathological studies; thus, lung adenocarcinoma was highly suspected. Chemotherapy with cisplatin and pemetrexed was performed and the tumor responded to cisplatin/pemetrexed; however, the tumor progressed during maintenance pemetrexed. As a next treatment, anti-PD-1 antibody with nivolumab, 200 mg (3 mg/kg), every 2 weeks, was initiated, and the tumor was found to shrink. Six months into nivolumab therapy, she began to feel general fatigue and loss of appetite. Because of low adrenocorticotropic hormone (ACTH) and cortisol levels, she was referred to our department, as adrenal insufficiency was suspected. Her early-morning serum cortisol levels were low (1.6 μg/dL), with low plasma ACTH levels (13.2 pg/mL), suggesting ACTH deficiency. And also, serum insulin-like growth factor 1 (IGF-1) levels were low (−3.6 SD), suggesting growth hormone deficiency. The other endocrinological findings, including TSH levels, were within the normal limit (Table 1). ACTH and cortisol showed no response to the insulin tolerance test, while normal response was seen in growth hormone and other pituitary hormones, leading to the diagnosis of isolated ACTH deficiency (IAD). Magnetic resonance imaging (MRI) of the pituitary gland showed heterogeneous enhancement without gland enlargement or atrophy, which is consistent with the diagnosis of hypophysitis [8]. After initiating oral hydrocortisone (15 mg/day), her symptoms, including general fatigue and appetite loss, improved immediately.

Although she was diagnosed with T2DM at 50 years of age, she maintained good glycemic control without drug treatment until nivolumab initiation. Her glycosylated hemoglobin (HbA1c) levels started to elevate from 6.8% at initiation and reached 8.1% at 6 months later, although her insulin secretion was not at the insulin-dependent diabetes mellitus level (serum C-peptide immunoreactivity ×100/plasma glucose: C-peptide reactivity [CPR]-index 1.39) [12, 13]. Sitagliptin was started and this effectively reduced her HbA1c levels to 7.3%. However, at 9 months into nivolumab therapy, a marked increase in plasma glucose levels (328 mg/dL) and HbA1c levels (8.7%) were observed on one of the routine follow-up examinations by her oncologist. At admission, she had general fatigue and loss of appetite, and she lost 5 kg of weight in 2 months. Her laboratory examinations revealed urinary ketones and impaired insulin secretion (CPR-index 0.31, urinary CPR 18.8 μg/day) (Table 1). Anti-glutamic acid decarboxylase (GAD) antibody, anti-insulinoma-associated antigen (IA2) antibody, and anti-insulin autoimmune antibody (IAA) were not detected, with no elevation of pancreatic enzyme, indicating the diagnosis of acute-onset T1DM due to nivolumab. After 3 years, her insulin secretion was further impaired (CPR-index, 0.10), consistent with the time course of T1DM. Two-and-a-half years after the initiation of ICI, the tumor progressed.

According to the HLA typing results, she was detected with HLA-C14:02 and HLA-DPB1*05:01, which is commonly reported in Japanese patients with IAD (Table 2) [14]. However, she presented with no HLA haplotypes that have been reported to be associated with thyroiditis or T1DM.

Case 2

A 65-year-old male patient with no underlying illness was diagnosed with esophageal cancer at the health check gastrointestinal endoscopy. He participated in a clinical trial of combination nivolumab and ipilimumab therapy. Seventeen days after the drug initiation, he began to feel general fatigue and hyperhidrosis. His endocrinological findings revealed low serum TSH levels (0.004 μIU/mL) with high free thyroxine (fT4) levels (>5 ng/dL). Anti-TSH receptor antibody was not detected, while thyroid-stimulating immunoglobulin was not checked. In the meantime, both anti-thyroid peroxidase (TPO) antibody (>600 IU/mL) and anti-thyroglobulin (Tg) antibody (477 IU/mL) were detected. Ultrasonography of his thyroid gland showed a heterogenous, diffuse swelling with moderate or decreased Doppler flow. We considered destructive thyroiditis rather than Graves disease and followed up with b-blocker alone. Thyrotoxicosis spontaneously improved and 1 month later, hypothyroidism progressed, and he started taking levothyroxine.

Three months after the initiation of nivolumab and ipilimumab, he began to have a headache. Low levels of ACTH and cortisol were reported, and he was re-sent to us to evaluate adrenal insufficiency. MRI showed an enlarged pituitary gland with mild enhancement. Early-morning endocrinological findings showed low ACTH and cortisol levels (<1 pg/mL and

Table 1. Laboratory findings of 3 present cases

		Lower range	Upper range	Case 1	Case 2	Case 3
Laboratory findings at admission for hypophysitis						
WBC	/μL	3300	8600	6000	10600	3200
Neutrophil	%	38.5	80.5	69.7	67.9	45.5
Lymphocyte	%	16.5	49.5	19.9	20.1	34.6
Eosinophil	%	0	8.5	4.3	3.5	8.7
Hemoglobin	g/dL	11.6	14.8	12.7	14.8	9.6
Platelet	/μL	15.8	34.8	23.8×10^4	34.5×10^4	18.0×10^4
Total protein	g/dL	6.6	8.1	6.8	7.6	5.5
Albumin	g/dL	4.1	5.1	4.1	4	3.5
AST	IU/L	13	30	18	26	34
ALT	IU/L	7	23	9	35	21
LDH	IU/L	124	222	171	163	177
CK	IU/L	M 59/F 41	M 248/F 153	43	52	121
BUN	mg/dL	8	20	9	15.1	12
Creatinine	mg/dL	0.46	0.79	0.52	0.8	0.71
UA	mg/dL	M 4.0/F 3.0	M 7.0/F 5.5	3.5	—	2.1
Na	mEq/L	138	145	137	139	118
K	mEq/L	3.6	4.8	3.9	4.2	4.1
Cl	mEq/L	101	108	10.3	10.5	84
Endocrinological findings at admission for hypophysitis						
ACTH	pg/mL	7.2	63.3	13.2	< 1	2.5
Cortisol	μg/dL	3.7	19.4	1.6	0.2	0.6
TSH	μIU/mL	0.50	5.00	4.30	0.67	2.96
free T4	ng/dL	0.90	1.70	0.93	1.42	1.41
GH	ng/mL	0	2.47	0.23	0.39	0.49
IGF-I	ng/mL	depend on age		40	78	27
IGF-I SDS		−2.0 S.D.	2.0 S.D.	−3.6 S.D.	−1.8 S.D.	− 3.9 S.D.
PRL	ng/mL	4.3	13.7	17.1	13.3	22.6
LH	mIU/mL	M 2.2/PF 11	M 8.4/PF 50	10.6	3.9	16.2
FSH	mIU/mL	M 1.8/PF 26	M 12/PF 120	24.1	14.7	24.9
E2	pg/mL	M 14.6/PF -	M 49/PF 47	<10	—	—
Testosterone	ng/mL	M 2.4	M 10.4	—	6.6	—
Hematological and urinary findings at admission for type 1 diabetes						
Plasma glucose	mg/dL	73	109	328	533	1119
HbA1c	%	4.6	6.2	8.7	8.4	9.8
Serum CPR	ng/mL	0.80	2.50	1.03	0.41	0.55
Total ketone bodies	μmol/L	26	122	500	5168	19370
ΔCPR (glucagon 1 mg)	ng/mL	insulin dependence <1.0 insulin independence ≧ 1.0		0.3	0.03	—
Urinary CPR	μg/day	insulin dependence <10 insulin independence ≧ 20		18.8	—	1.8

Abbreviations: ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CPR; C-peptide reactivity; FSH; follicle-stimulating hormone; GH, growth hormone; IGF-1, insulin-like growth factor 1; LDH, lactate dehydrogenase; LH; luteinizing hormone; M, male; PF, postmenopausal female; PRL, prolactin; SDS, standard deviation score; TSH, thyroid-stimulating hormone; UA, uric acid; WBC, white blood cell.

0.2 mg/dL, respectively; Table 1). No responses of ACTH and cortisol were elicited during the corticotropin-releasing hormone (CRH) test (data were not shown). Other pituitary hormonal function, excluding TSH, was found to be not disrupted, while insufficient TSH response to TRH was shown, probably due to central hypothyroidism induced by ICIs (Table 1), but levothyroxine overdose could not be ruled out. He was diagnosed with hypophysitis related to ICIs. Hydrocortisone replacement therapy (20 mg) was initiated, resulting in improvement of his headache. Two months later, a follow-up MRI showed that the pituitary swelling had subsided, supporting the diagnosis of hypophysitis, but no improvement of ACTH function was seen at that time.

One year after nivolumab and ipilimumab initiation, he began to feel frequent thirst and polydipsia. Laboratory findings

Table 2. HLA haplotypes reported to be associated with the development of the disease

		A	C	B	DR	DQ	DP
T1DM	Non-ICI [15]				B1*04:05 B1*08:02 B1*09:01	B1*04:01 B1*03:02 B1*03:03	
	ICI [6]				B1*04:05	B1*04:01	
IAD	Non-ICI [14]		C*14:02				B1*05:01
	ICI [14]				B1*04:05 B1*09:01	B1*04:01 B1*04:01 B1*06:01	B1*05:01 B1*05:01 B1*09:01
					B5*01:02		
ICI-related secondary adrenal insufficiency (including IAD) [16]			Cw12		B52 DR15		
Thyroiditis	Non-ICI [17]				DR3 The presence of Arg 74 in the DR3 amino acid-binding pocket		
	ICI [18]						A1*01:03 B1*02:01 allele

Abbreviations: IAD, Isolated ACTH deficiency; ICI-related, immune checkpoint inhibitor-related; T1DM, type 1 diabetes mellitus.

(Table 1) showed marked hyperglycemia (533 mg/dL), ketosis (total ketone bodies = 5168 μmol/L), and elevated HbA1c levels (8.4%), while his HbA1c levels were 5.9% a month earlier. This episode marked the rapid progression from euglycemia to diabetic ketoacidosis. At admission, his endogenous insulin secretion was found to be depleted (CPR-index 0.08), with an elevation of pancreatic enzymes elastase (330 IU/L) and lipase (77 IU/L). High levels of serum insulin autoantibody (IAA) (222 ng/mL), without his previous history of insulin injections, rapid increase in plasma glucose level, and ketoacidosis indicated a diagnosis of fulminant T1DM. At the same time, other autoantibodies associated with T1DM, including anti-GAD, anti-insulinoma-associated antigen (anti-IA2), anti-islet cell antibodies (anti-ICA), and anti-zinc transporter 8 (anti-ZnT8) antibodies, were not elevated. He started insulin treatment and his symptoms improved. A year after the initiation of ICI, the tumor maintained stable disease and ICI was continued.

According to the HLA typing result, he had HLA-B52, HLA-Cw12, HLA-DR15, HLA-DQB1*06:01, HLA-DPB1 *09:01, and -DRB5*01:02, commonly reported in Japanese patients with IAD (Table 2) [14, 16]. However, he had no HLA haplotypes that have been reported to be associated with thyroiditis or T1DM.

Case 3

A 74-year-old female patient undergoing arrhythmia treatment was diagnosed with ureteral cancer by gross hematuria. She received chemotherapy (gemcitabine, cisplatin), which was immediately discontinued due to the development of a skin rash, and underwent left nephroureterectomy. One-and-a-half years later, metastasis to the psoas major lymph nodes was noticed on computed tomography, so she received chemotherapy (gemcitabine, carboplatin) again. However, pembrolizumab was initiated due to the progression of metastasis to iliopsoas lymph nodes 2.5 years after the first diagnosis.

Before the initiation of pembrolizumab, she had positive anti-TPO antibody (57.8 IU/mL) with euthyroid status. Two months after initiation, she developed primary hyperthyroidism (TSH <0.03 μIU/mL, free triiodothyronine 4.5 pg/mL, and fT4 2.23 ng/dL), without anti-TSH receptor antibody detection and with no symptoms, while thyroid-stimulating immunoglobulin was not checked. She was diagnosed with destructive thyroiditis and she had been followed without any treatment. One month later, her fT4 levels spontaneously declined to 0.12 ng/dL, and she required thyroid hormone replacement.

A month later, she began to complain of general fatigue and vomiting. Her laboratory examination results (Table 1) revealed hyperglycemia (1119 mg/dL) with ketosis (total ketone bodies 19 370 μmol/L) and high HbA1c levels (9.8%). Her plasma glucose level was 100 mg/dL until 3 weeks prior. This episode marked the rapid progression from euglycemia to diabetic ketoacidosis. The CPR-index at hospitalization was 0.05, with high amylase (416 U/L) and high anti-GAD antibody levels (538.5 U/mL). Insulin therapy was prescribed with the diagnosis of T1DM related to pembrolizumab. On day 14 of her admission, her urinary CPR levels were quite low (1.8 μg/day) (Table 1), indicating the depletion of endogenously secreted insulin. Since the lymph node metastasis lesion shrank, pembrolizumab could be discontinued.

At 6 months into pembrolizumab therapy, she began to experience nausea and general fatigue again, with hyponatremia (118 mEq/L) and low cortisol (0.6 μg/dL) and ACTH levels (2.5 pg/mL) (Table 1). MRI showed a normal pituitary gland without enlargement or atrophy. The early-morning ACTH and cortisol levels were low (4.2 pg/mL and 0.2 mg/dL, respectively; Table 1). No responses in ACTH and cortisol were elicited during the corticotropin-releasing hormone (CRH) test, while the growth hormone (GH) normally responded to GH-releasing peptide-2 (data not shown). Taken together with the presence of normal pituitary hormone levels, she was diagnosed with IAD and started on hydrocortisone replacement therapy (20 mg/day), which improved her nausea

and fatigue. Three years after the initiation of ICI, the tumor continues to show complete response.

According to the HLA typing results, she had HLA-DPB1*05:01, which is commonly reported in Japanese patients with IAD (Table 2) [14]. However, she presented with no HLA haplotypes that have been reported to be associated with thyroiditis or T1DM.

Although this variant is found in 36% of Japanese patients, HLA*A24:02, which has not been reported to be associated with T1DM, IAD, and thyroiditis, was found in all the 3 cases. Further investigation is needed to state these associations.

Review of Literature

We performed an extensive search of PubMed, Web of Science, SCOPUS, Japan Medical Abstracts Society, and Google using the following terms: *hypophysitis*, *isolated ACTH deficiency*, *type 1 diabetes mellitus*, *cancer*, *therapy*, and *immune checkpoint inhibitor*. In total, we found 17 cases, including congress proceedings in Japan. Among them, we included patients who had combined endocrinopathies of hypophysitis and T1DM related to ICIs. These cases are summarized in Table 3. These patients were predominantly male (94.1%), and their mean age was 64 (45–73) years. Most patients were treated with anti-PD-1 antibodies (nivolumab or pembrolizumab), except for 2: one was treated with ipilimumab alone and another, with anti-PD-L1/CTLA-4 bispecific antibody. None of the17 reported cases had a clear family history of autoimmune disease, and only 1 patient had a history of autoimmune disease.

Regarding the sequential order of hypophysitis and T1DM onset, it has been reported that hypophysitis was followed by T1DM in 10 patients, T1DM was followed by hypophysitis in 5 patients, and both concurrently developed in 2 cases. Three patients (Case 5, 16, 17) developed thyroiditis in addition to hypophysitis and T1DM. In Case 3, the patient demonstrated combined pituitary hormone deficiency, including ACTH, TSH, and gonadotropin. Although some cases were included that were not described as to whether the ACTH deficiency was permanent, to the best of our knowledge, none of the cases had ACTH recovery. We summarized the time to the onset of these irAEs in Table 4 and described the median and minimum to maximum. Hypophysitis developed with a median of 23.5 (8-76) weeks after anti-PD-1 antibody initiation, 13 weeks after anti-CTLA-4 antibodies initiation, 14 weeks and 37 weeks after combination of anti-PD-1 and anti-CTLA-4 antibodies initiation, 44 weeks after anti-PD-L1/CTLA-4 bispecific antibody initiation and 8 weeks after switching from anti-CTLA-4 antibodies to anti-PD-1 antibodies (Case 1). On the other hand, T1DM developed with a median of 32 (8–76) weeks after anti-PD-1 antibody initiation, 9 weeks after anti-CTLA-4 antibody initiation, 14 weeks and 103 weeks after combined anti-PD-1 and anti-CTLA-4 antibody initiation, and 100 weeks after anti-PD-L1/CTLA-4 bispecific antibody initiation. Regarding the onset time of T1DM in Case 1, it occurred after 9 cycles of anti-PD-1 antibodies. Since we could not clarify the exact period of 1 cycle of this regimen, the onset time was calculated excluding Case 1.

The symptoms at the onset of T1DM included polydipsia (47%), thirst (35%), and polyuria (35%), while fatigue/asthenia/weakness (41%), hypoglycemia (18%), accidental detection of hypotension (18%), and disturbance of consciousness (6%) were the symptoms of hypophysitis. No patient had a history of DM. Anti-islet-specific autoantibodies were identified only in 2 cases (Case 7 and 16). Although HLA haplotypes have not been analyzed in many cases, HLA class II typing was performed for Case 7, and HLA haplotype susceptible to acute-onset and fulminant T1DM in the Japanese population was found (DRB1*04:05-DQB1*04:01). In Case 16, HLA haplotype susceptible to T1DM in the Japanese population was found (DRB1*08:02-DQB1*03:02). Moreover, for Case 4, *CTLA4* gene analysis was conducted, and the *CTLA4* polymorphism susceptible to fulminant T1DM was found, while no other disease-associated HLA haplotype was detected in Cases 3, 4, 7, and 14.

Multiple endocrine disorders other than the combination of hypophysitis and T1DM were reported in 5 cases of hypophysitis and thyroiditis [26], 1 case of primary adrenocortical insufficiency and thyroiditis [27], and 2 cases of hypophysitis and primary adrenocortical insufficiency [28, 29]. In our review of 17 cases, many cases were complete response (n = 2), partial response (n = 3), or stable disease (n = 2) to the cancers, with the exception of 1 case with progressive disease, while posttreatment information was not available in 8 patients.

Discussion

To our knowledge, this paper presents the highest number of case reports of a combination of hypophysitis and T1DM as ICI-related multi-endocrinopathies. Among the 3 patients, 2 had additional thyroiditis. The patients underwent HLA genotyping, and some haplotypes with susceptibility to IAD were reported in all the cases. HLA*A24:02, a frequent variant in Japanese patients, was found in all the cases as the common factor. We also reviewed, for the first time, the literature presenting this extremely rare combination in 17 patients and found that the clinical features of this combination and of each single ICI-related endocrinopathy showed no marked differences.

Regarding hypophysitis, all the present cases were diagnosed with hypophysitis according to the diagnostic criteria [30]. ICI-related hypophysitis has been shown to impair TSH and/or gonadotropin secretion in addition to ACTH secretion [8], but our cases, except for Case 2, presented here had IAD. In Case 2, TSH and ACTH deficiency due to hypophysitis were suspected. Combined pituitary deficiency related to ICIs is generally associated with ipilimumab monotherapy or combination with ipilimumab and anti-PD-1/PD-L1 therapy rather than anti-PD-1/PD-L1 monotherapy [8].

ICI-related DM is quite rare, and the onset of this complication is rapidly induced. In our Case 1, rapid worsening of her glucose levels with ketosis and weight loss strongly suggesting the rapid decline in endogenous insulin secretion. This condition was thought to be acute-onset rather than fulminant T1DM. Conversely, in our Case 2, the patient was diagnosed with fulminant T1DM due to the rapid onset of ketosis, reduced insulin secretion, and increased secretion of pancreatic enzymes [31]. However, positive result for anti-pancreatic b-cell-associated antibody (IAA) is not a typical feature of this condition. Furthermore, in our Case 3, the patient showed sudden onset of hyperglycemia, ketoacidosis, almost depleted insulin secretion, and elevated levels of pancreatic enzymes, strongly suggesting the presence of fulminant T1DM. In the meantime, her high HbA1c levels (>8.7%) and positive anti-pancreatic b-cell-associated antibody status (anti-GAD

Table 3. Clinical characteristics of ICI-related hypophysitis and T1DM; literature review

Case	Age/ sex	Target cancer	ICI	Time to onset of ICI-related hypophysitis or T1DM from ICI initiation	Deficient hormone	Symptoms at onset	Thyroid antibody	Family history of autoimmune disease	History of autoimmune disease
1	55/M	Malignant melanoma	Ipi → Pem	Hypophysitis; 8 weeks T1DM; 9 cycles after Pem initiation[a]	TSH, Gn, Cortisol Insulin	Hypophysitis; fatigue, blurring of vision, feeling generally unwell T1DM; tiredness, polyuria, polydipsia	N.A.	—	—
2	55/M	Pulmonary pleomorphic carcinoma	Nivo	FT1DM; 19 weeks Hypophysitis; 23 weeks	ACTH, Insulin	FT1DM; worsing of Performance Status, thirst, polydipsia Hypophysitis; weakness, nausea, and hypotension	N.A.	N.A.	N.A.
3	64/M	Malignant melanoma	Ipi	FT1DM; 9 weeks Pan-hypopituitarism; 13 weeks	ACTH, TSH, Gn	FT1DM; vomiting, polydipsia, transient fever, progressive confusion Pan-hypopituitarism; N.A.	N.A.	N.A.	N.A.
4	52/F	Breast cancer	Nivo	Hypophysitis; 28 weeks FT1DM; 32 weeks	ACTH, Insulin	Hypophysitis; fatigue, hypoglycemia, hypotension FT1DM; polydipsia, thirst	—	N.A.	N.A.
5	70/M	Gastric cancer	Nivo	T1DM; 32 weeks Hypophysitis; 36 weeks Thyroiditis; 36 weeks	ACTH, Insulin, T4	T1DM; N.A. Hypophysitis; hypoglycemia, disturbance of consciousness Hypothyroidism; N.A.	TPO Ab 24 IU/ mL	N.A.	—
6	70/M	Non-small cell lung cancer	Pem and Ipi	FT1DM, Hypophysitis; 14 weeks	ACTH, Insulin	FT1DM; fatigue, nausea, vomiting Hypophysitis; nausea, hyponatremia	N.A.	N.A.	—
7	72/M	Large cell neuroendocrine carcinoma	Pem	Hypophysitis, T1DM; 76 weeks	ACTH, Insulin	diarrhea, appetite loss	—	—	—
8	69/M	Non-small cell lung cancer	Nivo	Hypophysitis; 16 weeks FT1DM; 32 weeks	ACTH, Insulin	Hypophysitis; fatigue FT1DM; thirst, polyuria, polydipsia	N.A.	N.A.	N.A.
9	73/M	Lung adenocarcinoma	Nivo	Hypophysitis; 8 weeks FT1DM; 28 weeks	ACTH, Insulin	Hypophysitis; N.A. FT1DM; fatigue, thirst, polyuria, polydipsia	N.A.	N.A.	N.A.
10	70/M	Lung adenocarcinoma	Nivo	Hypophysitis; 8 weeks T1DM; 32 weeks	ACTH, Insulin	Hypophysitis; N.A., FT1DM; thirst, fatigue	N.A.	N.A.	N.A.
11	47/M	Malignant melanoma	Nivo	T1DM; 24 weeks Hypophysitis; 32 weeks	ACTH, Insulin	T1DM; N.A. Hypophysitis; fatigue, hypoglycemia	N.A.	N.A.	N.A.
12	59/M	Malignant melanoma	Nivo	Hypophysitis; 20 weeks T1DM; 44 weeks	ACTH, Insulin	N.A.	N.A.	N.A.	N.A.

(*continued*)

Table 3. Continued

Case	Age/sex	Target cancer	ICI	Time to onset of ICI-related hypophysitis or T1DM from ICI initiation	Deficient hormone	Symptoms at onset	Thyroid antibody	Family history of autoimmune disease	History of autoimmune disease
13	66/M	Renal cell carcinoma	Nivo	Hypophysitis; 24 weeks T1DM; 64 weeks	ACTH, Insulin	N.A.	N.A.	N.A.	N.A.
14	51/M	Malignant melanoma	Nivo and Ipi	Hypophysitis; 37 weeks FT1DM; 103 weeks (8 weeks after discontinuation)	ACTH, Insulin	Hypophysitis; orthostatic hypotension and weakness FT1DM; polyuria, polydipsia and weight loss	TPO Ab <28 IU/mL	N.A.	N.A.
15	45/M	Non-small cell lung cancer	anti-PD-L1/CTLA-4 bispecific antibody (KN046)	Hypophysitis; 44 weeks T1DM; 100 weeks	ACTH, Insulin	Hypophysitis; fatigue T1DM; nausea, vomiting, and poor appetite	TPOAb 163.10 U/mL TgAb >500 U/mL	N.A.	N.A.
16	67/M	Malignant melanoma	Nivo	FT1DM; 8 weeks Thyroiditis; 8 weeks Hypophysitis; 33 weeks	ACTH, Insulin, T4	Hypophysitis; malaise and loss of appetite FT1DM, thyroiditis; thirst, polyuria, and weight loss	Tg Ab (+) TPO Ab (+)	N.A.	Chronic thyroiditis
17	59/M	Malignant melanoma	Nivo	Thyroiditis; 10 weeks Hypophysitis; 14 weeks T1DM; 36 weeks	ACTH, Insulin, T4	Hypophysitis; nausea T1DM; malaise, weight loss, polydipsia, and polyuria Thyroiditis; dullness	Tg Ab 52.8 IU/mL	N.A.	N.A.
Our Case 1	64/F	Tumors of unknown primary	Nivo	Hypophysitis; 28 weeks T1DM; 36 weeks	ACTH, Insulin	Hypophysitis; fatigue T1DM; fatigue and loss of appetite	TPO Ab 9.25 IU/mL Tg Ab <10 IU/mL TRAb(III) < 0.8 IU/L	—	—
Our Case 2	65/M	Esophageal cancer	Nivo and Ipi	Thyroiditis; 2 weeks Hypophysitis; 12 weeks FT1DM; 48 weeks	ACTH, Insulin, (T4)	Drug-induced thyroiditis or painless thyroiditis; fatigue, hyperhidrosis Hypophysitis; headache FT1DM; thirst and polydipsia,	TPO Ab >600 IU/mL Tg Ab 477 IU/mL TRAb(III) < 0.8 IU/L	—	—
Our Case 3	74/F	Ureteral cancer	Pem	Destructive thyroiditis; 8 weeks T1DM; 16 weeks Hypophysitis; 24 weeks	ACTH, Insulin, T4	Destructive thyroiditis; no symptoms T1DM; fatigue and vomiting Hypophysitis; nausea and fatigue	TPO Ab 57.8 IU/mL	—	—

Abbreviations: Ab, antibody; CR, complete response; FT1DM, fulminant type 1 diabetes mellitus; GAD, glutamic acid decarboxylase; IA-2, insulinoma-associated antigen-2; ICI, immune checkpoint inhibitor; Ipi, ipilibumab; N.A., not available; Nivo, nivolumab; PD, progressive disease; Pem, pembrolizumab; PR, partial response; SD, stable disease; T1DM, type 1 diabetes mellitus; Tg, thyroglobulin; TPO, thyroid peroxidase antibody; TR, TSH receptor; ZnT8, zinc transporter 8.

[a]The time to onset based on the administration interval used in clinical studies of nivolumab [19] and pembrolizumab [20].

Table 4. Comparison of clinical features between the combined endocrinopathies and each single endocrinopathy

	Combined endocrinopathies			Single endocrinopathy	
	a) Hypophysitis + T1DM	b) Our cases	a) + b)	Hypophysitis	T1DM
Age of onset [years]	median 64 (45–73)	median 65 (64–74)	median 64.5 (45–74)	over 60 [21] median age 54 [22], 70 [23]	median 63 (31–84) [6]
Sex % (number)	Men 94.1% (16), Women 5.9% (1)	Men 33.3% (1), Women 66.7% (2)	Men 85.0% (17), Women 15.0% (3)	Men dominant [21] (2–5 times greater risk than in women)	Men 57% [6]
Time to onset	PD-1: Hypophysitis; 23.5 weeks (8–76 weeks), T1DM; 32 weeks (8–76 weeks) CTLA-4; Hypophysitis 13 weeks T1DM; 9 weeks PD-1 + CTLA-4; Hypophysitis; 14 weeks and 37 weeks, T1DM; 14 weeks and 103 weeks CTLA-4 → PD-1; Hypophysitis 8 weeks after anti-CTLA-4 antibodies initiation, T1DM; 9 cycles after Pem initiation PD-L1/CTLA-4 bispecific; Hypophysitis; 44 weeks, T1DM; 100 weeks	PD-1; Hypophysitis 24 weeks and 28 weeks, T1DM 16 weeks and 36 weeks PD-1+CTLA-4; Hypophysitis 12 weeks, T1DM 48 weeks	PD-1; Hypophysitis; 24 weeks (8–76 weeks), T1DM; 32 weeks (8–76 weeks) CTLA-4; Hypophysitis; 13 weeks, T1DM; 9 weeks PD-1 + CTLA-4; Hypophysitis; 14 weeks (12–37 weeks), T1DM; 48 weeks (14–103 weeks) CTLA-4 → PD-1; Hypophysitis 8 weeks, T1DM; 9 cycles after Pem initiation PD-L1/CTLA-4 bispecific; Hypophysitis; 44 weeks, T1DM; 100 weeks	PD-1; 12–24 weeks [21] CTLA-4; 8–16 weeks [21] PD-L1; up to 48 weeks [8], 52 weeks, 56 weeks [24] Combination therapy; earlier for those on combination treatment (4 weeks on average) [21]	PD-1; 1–48 weeks [6] CTLA-4; 13.6 weeks [25] PD-L1; 9–15 weeks [6]
Used ICIs	PD-1: 70.6% (12/17) CTLA-4: 5.9% (1/17) PD-1 + CTLA-4: 11.8% (2/17) CTLA-4→PD-1: 5.9% (1/17) PD-L1/CTLA-4 bispecific: 5.9%(1/17)	PD-1:66.7% (2) PD-1+ CTLA-4:33.3% (1)	PD-1; 70.0% (14/20) CTLA-4; 5.0% (1/20) PD-1 + CTLA-4; 15.0% (3/20) CTLA-4→PD-1; 5.0% (1/20) PD-L1/CTLA-4 bispecific: 5.0%(1/20)	CTLA4; 3.2% [6] PD-1; 0.4% [6] CTLA-4→PD-1; 6.4% [6]	rare, almost PD-1 or PD-L1 [6]

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Pem, pembrolizumab; T1DM, type 1 diabetes mellitus.

antibody) were not typical features of fulminant T1DM. These findings were consistent with previous results; it has a pathology similar to that of fulminant T1DM [31] but has some differences, such as b-cell-associated antibody positivity (50% of the case reports reviewed indicated positive status [6]). Furthermore, in fulminant T1DM, 98% of patients have elevated pancreatic enzymes [6], while in ICI-induced DM, the reported rate is 32%, although this is only for reference since it is conspicuous in cases where the enzymes are not routinely measured [32]. In our cases, pancreatic enzyme elevation was not observed in Case 1 but was elevated in Cases 2 and 3.

In the literature review, we found 17 cases of hypophysitis combined with T1DM as an ICI-related endocrinopathy (Table 3). There were few discussions about the differences in the clinical features of this combination and of each single ICI-related endocrinopathy. Regarding the age at onset, both hypophysitis + T1DM and each single endocrinopathy occurred in the patients' 60s. However, it cannot be ruled out that the age at onset of combined endocrinopathies may be higher. Although the patients in our review were predominantly female, previous reports have shown that both single and combined endocrinopathies are common in males. It has been suggested that the prevalence of ICI-related hypophysitis in men may reflect the fact that melanoma and lung cancer, the most common cancers treated with ICIs, are more common in men. However, in a study of melanoma patients, it has been reported that hypophysitis was more common in men even after adjusting for gender, suggesting that the fact that cancer itself is more common in men may not affect the prevalence of ICI-related hypophysitis [33]. There are also reports of male predominance in ICI-related DM in patients with melanoma. The higher frequency of combined endocrinopathies in men may reflect the higher frequency of malignancies themselves that are treated with ICI in men [32, 34, 35]. However, it cannot be ruled out that these endocrine disorders may be more common in males due to their greater exposure to ICIs. The development of hypophysitis as a single endocrinopathy has been associated with the use of anti-CTLA-4 antibodies or a combination of anti-CTLA-4 and PD-1 antibodies, while that of T1DM is predominantly associated with the use of anti-PD-1 or PD-L1 antibodies. In contrast, the development of combination endocrinopathies was associated with the use of anti-PD-1 antibodies or combination therapy, including anti-PD-1 antibodies than CTLA-4 or PD-L1 monotherapy. ACTH deficiency due to ICI is generally irreversible [8, 21], and after the diagnosis of ACTH deficiency, hydrocortisone replacement has been continued in all our cases. In all 17 cases in our review, hydrocortisone replacement was also continued, except for 7 cases that we could not specify.

The time from ICI initiation to onset of ICI-related hypophysitis or T1DM endocrinopathy is dependent on the type of ICI used. Those with anti-PD-1 or PD-L1 antibody initiation are longer than those with anti-CTLA-4 antibody for single endocrinopathies. Since combined endocrinopathies were mostly associated with anti-PD-1 antibodies, we compared the time from anti-PD-1 antibody initiation to onset of single and combined endocrinopathies; no apparent differences were found between the two. In cases of combined endocrinopathies, the time to onset was not accurately described in 2 cases (Case 1 and 2 of the literature review). Therefore, we calculated the time to onset based on the administration interval used in clinical studies of nivolumab [19] and pembrolizumab [20]. Since the number of cases with ICIs other than anti-PD-1 antibodies is too small, further case accumulation is needed.

In addition to hypophysitis and T1DM, thyrotoxicosis was observed in 2 of 3 cases (in Case 2, after 2 weeks of nivolumab and ipilimumab therapy, and in Case 3, after 8 weeks of nivolumab therapy). Both cases were negative for TSH receptor antibody, and their hyperthyroidism was recovered spontaneously, supporting the diagnosis of destructive thyroiditis. Previous reports of thyrotoxicosis showed a median onset time of 3 weeks (1–9 weeks) with a combination of nivolumab and ipilimumab and of 6 weeks (0–63 weeks) with nivolumab alone, suggesting that the onset may be relatively early as seen in our review. Furthermore, ICI-related hypophysitis [36, 37] and thyroiditis [38, 39] are thought to be associated with longer overall survival. Except for 2 cases of progressive disease in our study, many cases who developed combined endocrinopathies were partial or complete response or stable disease for their original cancers. This suggests that these ICI-related combined endocrinopathies may be associated with effective response to the cancers as shown in single one. However, as far as we know, there have been no reports on the association between the development of ICI-related T1DM and overall survival. In addition, some reports of the present literature review have not mentioned their prognosis. Therefore, we believe that further observational studies are needed of the longitudinal clinical course regarding the association between combined endocrinopathies and the prognosis, and further accumulation of ICI-related multi-endocrinopathies data is needed to clarify their clinical features.

Although the precise pathogenesis of ICI-related endocrinopathies remains unclear, it has been shown that several HLA haplotypes are associated with the disease development [6]. Several disease-sensitive haplotypes are reported not only for various autoimmune endocrinopathies, including T1DM (DRB1*04:05-DQB1*04:01, DRB1*08:02-DQB1*03:02, DRB1*09:01-DQB1*03:03) [15], IAD (C*14:02, DPB1*05:01, DRB1*04:05-DQB1*04:01-DPB1*05:01, DRB1*09:01-DQB1*03:03-DPB1*05:01) [14], and thyroiditis (HLA-DR3 and an association with the presence of Arg 74 in the DR3 amino acid-binding pocket) [17], but also for ICI-related endocrinopathies, such as thyroiditis (HLA-DPA1*01:03 and HLA-DPB1*02:01 allele, and their haplotype frequencies) [18], IAD (DQB1*06:01, DPB1*09:01 and DRB5*01:02) [14], T1DM (DRB1*04:05-DQB1*04:01), and secondary adrenal insufficiency (B52, Cw12, DR15) [16] (Table 2). In our cases, HLA haplotypes with susceptibility to IAD were identified in Case 1 (C*14:02, DPB1*05:01), Case 2 (B52, Cw12, DR15, and DQB1*06:01, DPB1*09:01 and DRB5*01:02), and Case 3 (DPB1*05:01) [14-16]. Additionally, HLA*A 24:02 was identified as a common haplotype in all 3 cases, suggesting the susceptible haplotype for this combination of endocrinopathies related to ICIs. Since this haplotype is frequently found in 37.9% of Japanese [40], its presence in the 3 patients may also be a coincidence. Further studies on combined endocrinopathies especially in non-Japanese patients are needed.

In addition to HLA, *CTLA-4* or *PD-L1* gene polymorphisms have been reported as a factor associated with autoimmune endocrinopathies, including T1DM, autoimmune thyroid disease, and primary adrenal insufficiency [6]. Further, *CTLA-4* $+6_{230}$ *G/A* is reported to be a significant variant associated with the co-existence of T1DM and

autoimmune thyroid disease [41]. In this case series, we could not perform *CTLA-4* gene analysis. Further studies are required, including this polymorphism, to clarify the pathology of ICI-induced combined endocrinopathies.

In conclusion, we presented 3 cases of complicated combined endocrinopathies comprising hypophysitis and T1DM due to ICIs. The use of anti-PD-1 antibodies may be associated with the occurrence of combined endocrinopathies. HLA genotyping was performed in all 3 cases, and the hypophysitis- or T1DM-associated haplotype was frequently found (HLA*A 24:02). Further case accumulation and pathogenic investigations are needed to identify the significant features of this extremely rare occurrence of combined endocrinopathies as irAEs.

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Disclosures/Conflict of Interest

None to be declared.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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