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ORIGINAL ARTICLE

Autoimmune polyendocrine syndrome induced by immune checkpoint inhibitors: a systematic review

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Abstract

Objective To summarize the clinical characteristics and immunological and genetic features of patients who developed autoimmune polyendocrine syndrome type II (APS-2) after treatment with immune checkpoint inhibitors (ICIs).

Design and methods Several databases (MEDLINE/EMBASE/Cochrane) were searched for studies published between January 2000 and February 2020 involving patients with two or more endocrine disorders after ICI therapy.

Results Our final review included 22 articles comprising 23 patients (median age 56 years; 65.2% male patients). Of these patients, 60.9% received anti-programmed cell death 1 (PD-1) therapy, 17.4% received anti-programmed cell death ligand 1 (PD-L1) therapy, and 4.3% received anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monotherapy. Patients underwent a median of four treatment cycles before the onset of the primary adverse event; the median time of onset was 8.5 weeks. Endocrine organs affected by ICI administration included the thyroid gland (18/23, 78.3%), pancreatic islets (17/23, 73.9%), pituitary gland (11/23, 47.8%), and adrenal gland (2/23, 8.7%). Related autoantibodies were detected in 65.2% of patients. In patients with diabetes, glutamic acid decarboxylase antibody was closely related to the development of diabetes ketoacidosis. The human leukocyte antigen genotype was reported in 34.8% (8/23) of patients, 5 (62.5%) of which had risk genotypes.

Conclusions As a serious adverse event of ICI treatment, APS-2 is presented with abrupt initiation time and rapid development. Physicians should be aware of potential endocrine disorders and continue monitoring hormone status when treating cancer patients with ICIs.

Keywords Autoimmune polyendocrine syndrome · Immune checkpoint inhibitors · Endocrinopathy · Immune-related adverse effect

Abbreviations

ACA	Adrenal cortex antibody
APS-2	Autoimmune polyendocrine syndrome type II
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DKA	Diabetes ketoacidosis; FSH, follicle-stimulating hormone
FT4	Free thyroxine
GAD	Glutamic Acid Decarboxylase
HLA	Human leukocyte antigen
ICI	Immune checkpoint inhibitor
irAE	Immune-related adverse event
LH	Luteinizing hormone
NSCLC	Non-small cell lung cancer
21-OH Ab	21-Hydroxylase antibody
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
T1DM	Type 1 Diabetes Mellitus
TPO	Thyroid peroxidase antibody
TSH	Thyroid stimulating hormone

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Introduction

Immune checkpoints are negative modulators of the immune system to prevent an overactivated immune response. Monoclonal antibodies called immune checkpoint inhibitors (ICIs) have been developed to blockade these regulators, including cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1), as well as its ligand, programmed cell death ligand 1 (PD-L1). These agents have shown remarkable antitumor effects on diverse cancer types by overcoming immune tolerance and enhancing immunity of the tumor microenvironment. The anti-CTLA-4 antibody, ipilimumab, has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of melanoma. In addition, PD-1 inhibitors (pembrolizumab and nivolumab) and PD-L1 antibodies (atezolizumab, durvalumab, and avelumab) have been shown to improve overall survival in various cancers and have also been approved by the FDA [1].

While activating the immune system, ICIs are also expected to induce autoimmune diseases, often named immune-related adverse events (irAEs) [2]. These side effects could involve many organs including the gastrointestinal tract, skin, and endocrine glands. Among the endocrinopathies caused by PD-1 or PD-L1 inhibitors, hypothyroidism (6.1%) and hyperthyroidism (2.8%) are most commonly observed [3]. By contrast, Type 1 Diabetes Mellitus (T1DM, 0.2%) and primary adrenal insufficiency (0.7%) is rare in patients treated with ICIs [4]. Hypophysitis is a rare adverse event in patients on PD-1 inhibitors (0.4%) and PD-L1 antibodies (< 0.1%) while its incidence is relatively high in those treated with CTLA-4 inhibitors (3.2%) [4].

Sometimes, patients treated with ICIs develop autoimmune polyendocrine syndrome type II (APS-2), defined as having two or three of the following endocrinopathies: autoimmune thyroid disease, type 1 diabetes, and Addison's disease (adrenal insufficiency) [5]. In 1926, the occurrence of adrenal insufficiency and hypothyroidism in a single patient was firstly described by Schmidt [6]. APS-2, a polygenetic disease, is characterized by increased autoantibodies in the blood and infiltrating lymphocytes in the impaired glands, leading to failure of multiple endocrine glands. It is known that patients at risk of APS-2 have mutations in CTLA-4 or human leukocyte antigen (HLA) DR3-DQ2 and DR4-DQ8 [5]. Several cases have reported two or more endocrine irAEs in an individual patient after the administration of ICIs [7]. However, whether APS-2 is associated with immune checkpoint inhibition has yet to be elucidated. Herein, we provide an overview of case studies on APS-2 related to PD-1/PD-L1 or CTLA-4 inhibitors to provide some evidence of the association.

Methods

Literature search

We conducted a search of several databases (MEDLINE/EMBASE/Cochrane) for studies on patients with two or more endocrine disorders after immune checkpoint inhibition from January 2000 to February 2020. Different terms of "autoimmune polyendocrine syndrome" and various current available ICIs were combined by Boolean operators AND/OR to form the search approach, which is provided in Supplementary Table 1. In addition, we enrolled five more case reports from two published reviews [7, 8].

Study selection

We intended to select cancer patients who developed two or three autoimmune endocrinopathies, including autoimmune thyroid disease, T1DM, and adrenal insufficiency, during the treatment of ICIs with adequate clinical data. After removing the duplicates, two independent investigators reviewed the title and abstract to initially exclude the articles that did not fit our inclusion criteria. Language was restricted to English, and only case reports were included. We excluded conference abstracts, reviews, systematic review or meta-analysis articles, corresponding letters, and off-topic articles. Then, further selection was conducted by reviewing full texts. Patients with only one endocrine disorder after the checkpoint inhibition or with any history of autoimmune or endocrine disease were excluded.

Data extraction

The following data were extracted from each report: year and author of publication, age, gender, country, primary cancer situation, checkpoint inhibitor treatment, number of therapy cycles, endocrine adverse event (hypophysitis, thyroiditis, hypothyroidism, hyperthyroidism, primary adrenal insufficiency, and diabetes mellitus), time intervals between the onset of disorders, corresponding laboratory test results, autoimmune antibodies, and HLA genotypes.

Statistical analysis

We conducted the statistical analysis using SPSS version 20.0 software. Descriptive statistics were utilized to evaluate data. For continuous data, median and range were used and for categorical variables, frequencies and percentages were used. For two-group comparison, the Mann–Whitney

U test was utilized. *P* values under 0.05 were considered statistically significant.

Results

Our search yielded a total of 843 articles after the removal of duplicates. Of these articles, 811 articles were excluded by reviewing title and abstract. The remaining 32 publications were further assessed based on the full text. Seven reports were excluded because only one endocrine disorder was present in each patient. In addition, three other articles were excluded because they were diagnosed with type 2 diabetes before receiving immune checkpoint therapy. Finally, 22 articles with 23 patients were enrolled in our review [7–28]. The flow chart of publication selection is shown in Fig. 1.

Case characteristics

The median age of patients selected was 56 years (range 43–83 years), with a male predominance (15/23, 65.2%). Most patients were from United States (7/23, 30.4%), followed by Italy (3/23, 13.0%) and Japan (3/23, 13.0%). Other cases were reported in diverse countries including Australia, France, United Kingdom, Ireland et al. The major cancer types of the identified cases were melanoma (11/23, 47.8%) and lung cancer (7/23, 30.4%). The rest of the cases were other cancer types, including breast cancer, bladder cancer, gastric cancer et al.

More than half of the patients (14/23, 60.9%) received anti-PD-1 therapies (nivolumab or pembrolizumab), and four patients (17.4%) received anti-PD-L1 therapies (avelumab, atezolizumab, or durvalumab). Among these patients, one 55-year-old man received a combination therapy of durvalumab and bacillus Calmette-Guérin [28]. Additionally, only one patient was treated with the anti-CTLA-4 therapy ipilimumab alone, and two patients (8.7%) received a combination therapy of ipilimumab with nivolumab. Furthermore, two patients received ICI treatments in a sequence: one was treated with ipilimumab followed by pembrolizumab, and the other received nivolumab followed by a combination of ipilimumab and nivolumab. These case characteristics are summarized in Table 1.

Clinical features

Detailed patient characteristics and critical laboratory test results are presented in Table 2. The median immune checkpoint therapy course received before onset of the

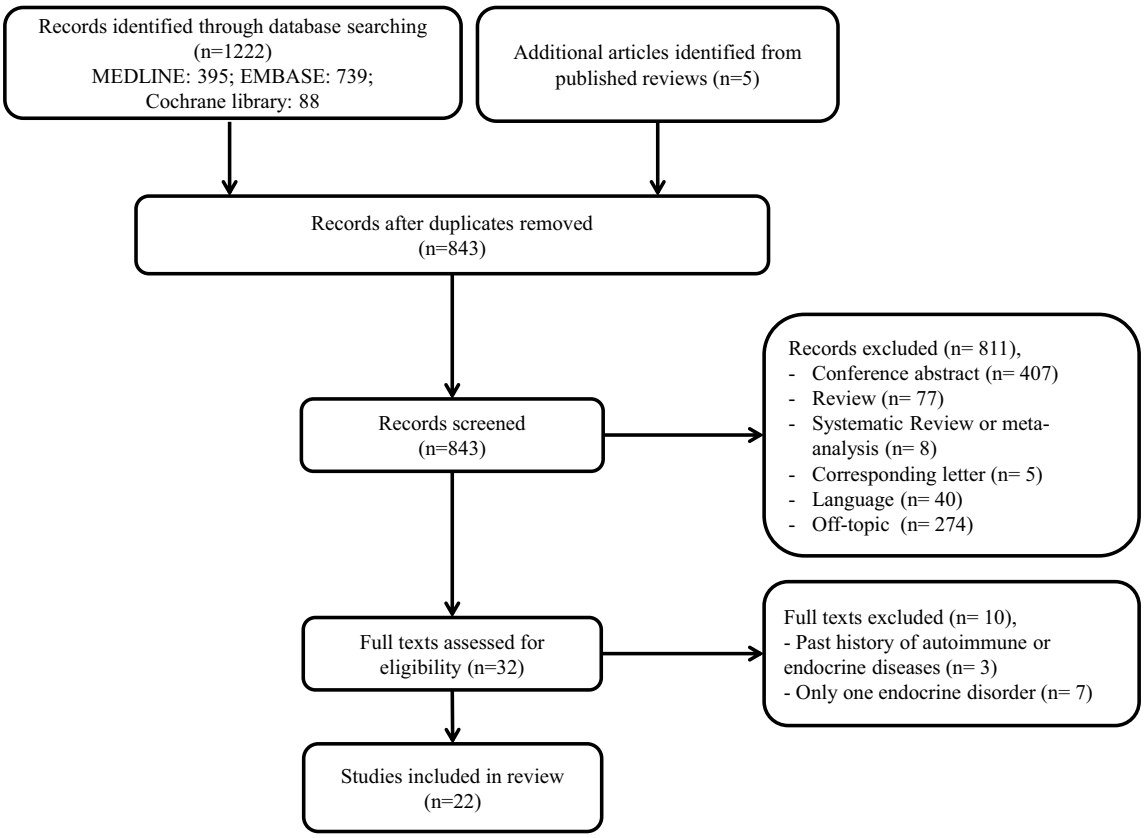


Fig. 1 Flow chart of article selection

Table 1 Summary of patients characteristics

Characteristics	Value	Percentage (%)
Age (years)		
Median (range)	56 (43–83)	
Gender		
Male	15	65.2
Female	8	34.8
Country		
US	7	30.4
Italy	3	13.0
Japan	3	13.0
Australia	2	8.7
France	2	8.7
UK	2	8.7
Irland	1	4.3
Korea	1	4.3
Portugal	1	4.3
Spain	1	4.3
Cancer type		
Melanoma	11	47.8
Lung cancer	7	30.4
Bladder cancer	1	4.3
Breast cancer	1	4.3
Gastric cancer	1	4.3
Renal cell carcinoma	1	4.3
Parotid gland adenocarcinoma	1	4.3
Type of checkpoint inhibitor		
PD-1	14	60.9
PD-L1	4	17.4
CTLA-4	1	4.3
CTLA-4 + PD-1	2	8.7
Others[a]	2	8.7

CTLA-4 cytotoxic T-lymphocyte antigen 4, *PD-1* programmed cell death 1, *PD-L1* programmed cell death ligand 1, *UK* United Kingdom, *US* United States

[a]One was treated with ipilimumab followed by pembrolizumab, and the other received nivolumab followed by a combination of ipilimumab and nivolumab

first adverse event was 4 cycles (range 1–13 cycles), and the median time from therapy initiation to irAE onset was 8.5 weeks (range 2–30 weeks; Fig. 2a). Early-onset autoimmune disorders (within 2 cycles) were witnessed in 30.4% patients (8/23) who received nivolumab, pembrolizumab, atezolizumab, durvalumab, or a combination of ipilimumab and nivolumab.

Endocrine organs affected by ICI administration included the thyroid gland (18/23, 78.3%), pancreatic islets (17/23, 73.9%), pituitary gland (11/23, 47.8%), and adrenal gland (2/23, 8.7%). In most patients (21/23, 91.3%), two sites were involved in immune checkpoint therapy. Nearly half of them presented with thyroiditis and T1DM, followed by five patients who developed T1DM with hypophysitis. In addition, two other patients showed disorders of three endocrine glands, displaying thyroiditis, T1DM and hypophysitis.

Among the 18 patients who presented with a thyroid disorder, 5 (27.8%) transitioned from hyperthyroidism to hypothyroidism, 11 (61.1%) had a single hypothyroidism phase, and 2 (11.1%) had hyperthyroidism. Patients with hypothyroidism exhibited increased thyroid stimulating hormone (TSH) levels with low free thyroxine (FT4) or free triiodothyronine levels, whereas those with hyperthyroidism presented with the opposite laboratory values. Another most frequently affected organ was the pancreatic islet, precipitating the onset of T1DM. Most patients with T1DM (12/17, 70.6%) presented with diabetes ketoacidosis (DKA), with a median plasma glucose of 35.8 mmol/L (range 21.9–48.1 mmol/L). T1DM patients without DKA (5/17) had a lower median plasma glucose of 22.7 mmol/L (range 21.1–37.7 mmol/L) ($P < 0.05$, Fig. 2b). Specific laboratory tests results are shown in Table 2. Eleven patients with the pituitary gland affected developed hypophysitis. In nine of these patients (81.8%), only the adrenal axis was affected, with decreased cortisol and adrenocorticotropic hormone. The other two patients with hypophysitis had more axes involved. Besides adrenal insufficiency, one patient presented with lower luteinizing hormone (LH) and follicle-stimulating hormone (FSH) or testosterone, suggesting the diagnosis of hypogonadotropic hypogonadism induced by autoimmune hypophysitis. In another patient, the thyroid axis was also involved, with decreased TSH and FT4 [13]. In addition, two patients had adrenal gland impairment with decreased cortisol [12, 25]. Thorough endocrine function evaluations and imaging results suggested these two patients were diagnosed as having adrenalitis.

Of the 20 patients with reported outcomes, only three of them (15.0%) exhibited progressive disease. Three patients showed complete response, nine showed partial response, and five presented with stable disease (Fig. 2c).

Immunological and HLA features

At least one of the relative autoantibodies was detected in 65.2% (15/23) patients. It is notable that one patient presented with two positive islet-related antibodies (glutamic acid decarboxylase [GAD] autoantibody; islet cell autoantibody) and three elevated thyroid antibodies (thyroglobulin antibody; thyroid peroxidase [TPO] antibody; thyrotropin receptor antibody). In the remaining 14 patients, only one or two positive autoantibodies were detected. The median onset of first irAE was 2 cycles (range 1–15 cycles) of ICI treatments for autoantibody-positive patients and 7 cycles (range 4–13 cycles) for autoantibody-negative patients ($P < 0.05$, Fig. 2d).

Table 2 Summary of case reports of APS-2 related to ICI therapies

Author (year)	Age	Gender	Country	Cancer type	Therapy	Onset duration (week/cycle)[a]	Condition	Autoantibody	HLA genotype	Response
Hansen (2016)	58	Male	US	Melanoma	Pembrolizumab	NR	Hypothyroidism	GAD (+)	NR	PR
						52/17	T1DM			
Kong (2016)	68	Male	Korea	Lung cancer	Pembrolizumab	21/7	T1DM (DKA)	(−)	DRB1*0901-DQB1*0303	PR
						0	Hyperthyroidism			
Lowe (2016)	54	Male	US	Melanoma	Ipilimumab and nivolumab	2/1	Hyperthyroidism	TSHRAb (+), GAD (+)	A2, DQB1*0602	CR
						6/1	Hypothyroidism			
						11/1	T1DM (DKA)			
						0	Hypophysitis (adrenal insufficiency)			
Humayun (2016)	55	Male	UK	Melanoma	Ipilimumab	8/4	Hypophysitis (hypopituitarism)	(−)	NR	SD
					Pembrolizumab	NR/9	T1DM (DKA)			
Kuru (2017)	83	Female	US	Melanoma	Nivolumab	30/15	Thyroiditis (hypothyroidism)	TPO (+)	NR	PR
						3/0	Hypophysitis (adrenal insufficiency)			
Marchand (2017)	55	Male	France	Lung cancer	Nivolumab	19/9	T1DM (DKA)	(−)	NR	PR
						4/0	Hypophysitis (adrenal insufficiency)			
Paepegaey (2017)	55	Female	France	Melanoma	Pembrolizumab	17/6	Thyroiditis (hyperthyroidism)	21-OH Ab (+), ACA (+)	NR	PD
						2/0	Hypothyroidism			
						12/4	Adrenalitis (Acute adrenal crisis)			
Li (2017)	63	Male	US	Lung cancer	Nivolumab	4/1	T1DM (DKA)	GAD (+), TPO (+)	NR	PD
						9/NR	Hypothyroidism			
Aziz (2018)	69	Male	US	Gastric cancer	Avelumab	13/7	Thyroiditis (hyperthyroidism)	NR	NR	NR
						17/8	Hypothyroidism			
						0	Adrenalitis (adrenal insufficiency)			
Sakurai (2018)	68	Female	Japan	Renal cell carcinoma	Nivolumab	2/1	Thyroiditis (hyperthyroidism)	TgAb (+), TPO (+)	DRB1*09:01-DQB1*03:03	NR
						4/2	Hypothyroidism			
						8/4	T1DM			

Table 2 (continued)

Author (year)	Age	Gender	Country	Cancer type	Therapy	Onset duration (week/cycle)[a]	Condition	Autoantibody	HLA genotype	Response
Sum (2018)	75	Male	US	Melanoma	Nivolumab and ipilimumab	5/3	T1DM	GAD (+)	NR	CR
						2/0	Hypophysitis (adrenal insufficiency)			
Tzoulis (2018)	56	Female	UK	Lung cancer	Nivolumab	6.5/3	T1DM (DKA)	GAD (+)	NR	PR
						30/14	Hypothyroidism			
Okahata (2019)	52	Female	Japan	Breast cancer	Nivolumab	30/13	Hypophysitis (adrenal insufficiency)	(−)	DRB1*14:05, 14:06	NR
						4/0	T1DM		DQB1*03:01, 03:03	
Erra (2019)	63	Male	US	Melanoma	Ipilimumab	9/4	Hypophysitis (adrenal insufficiency)	(−)	NR	PR
						43/0	Hypothyroidism			
Gunjur (2019)	77	Female	Australia	Melanoma	Pembrolizumab	3/1	T1DM (DKA)	GAD (+), IA2 (+)	DRB1*04.16; DQB1*02.05	CR
						6/3	Thyroiditis (hypothyroidism)		DQA1*01.03	
Hakami (2019)	52	Male	Irland	Melanoma	pembrolizumab	12/5	Thyroiditis (hypothyroidism)	(−)	NR	PR
						8/2	T1DM (DKA)			
Lanzolla (2019)	60	Male	Italy	Lung cancer	Atezolizumab	6/2	T1DM (DKA)	21-OH Ab (+), APA (+)	DRB1*04; DQB1*03	PD
						5/2	Hypophysitis (adrenal insufficiency, hypogonadotropic hypogonadism)			
Lupi (2019)	80	Male	Italy	Melanoma	Pembrolizumab	4/2	Thyroiditis (hypothyroidism)	TgAb (+), TPO (+)	NR	SD
						26/7	Hypophysitis (adrenal insufficiency)			
Lupi (2019)	43	Female	Italy	Melanoma	Nivolumab	3/2	Thyroiditis (hypothyroidism)	TPO (+), APA (+)	DQB1*02; DQB1*0602	SD
						8/4	T1DM (DKA)		DQA1*0102	
					Ipilimumab and nivolumab	17/1	Hypophysitis (adrenal insufficiency)			

Table 2 (continued)

Author (year)	Age	Gender	Country	Cancer type	Therapy	Onset duration (week/cycle)[a]	Condition	Autoantibody	HLA genotype	Response
Machado (2019)	55	Male	Portugal	Lung cancer	Nivolumab	12/7	Thyroiditis (hyperthyroidism)	(−)	NR	PR
						4/0	Hypothyroidism			
						53/33	Hypophysitis (adrenal insufficiency)			
Mengíbar (2019)	55	Male	Spain	Bladder cancer	Durvalumab[b]	3/1	T1DM (DKA)	GAD (+), IA2 (+), TPO (+), TSHRAb (+), TgAb (+)	NR	SD
						2/0	Thyroiditis (hypothyroidism)			
Patel (2019)	49	Female	Australia	Lung cancer	Durvalumab	13/6	T1DM (DKA)	GAD (+)	NR	PR
						4/0	Hypothyroidism			
Kurihara (2020)	48	Male	Japan	Parotid gland adenocarcinoma	Nivolumab	18/5	T1DM	TSHRAb(+)	DRB1*04:05	SD
						0	Thyroiditis (hyperthyroidism)			

21-OH Ab 21-hydroxylase antibody, *ACA* adrenal cortex antibody, *APA* anti-pituitary antibody, *CR* complete response, *DKA* diabetes ketoacidosis, *GAD* Glutamic Acid Decarboxylase, *HLA* human leukocyte antigen, *IA2* islet cell autoantibody, *NR* not reported, *PD* progressive disease, *PR* partial response, *SD* stable disease, *T1DM* Type 1 Diabetes Mellitus, *TgAb* thyroglobulin antibody, *TPO* thyroid peroxidase antibody, *TSHRAb* thyrotropin receptor antibody, *UK* United Kingdom, *US* United States

[a]For the primary onset disorder, it is time from initiation of therapy; for the secondary disorder, it is time from the last disorder

[b]Combined with BCG (Bacillus Calmette–Guérin)

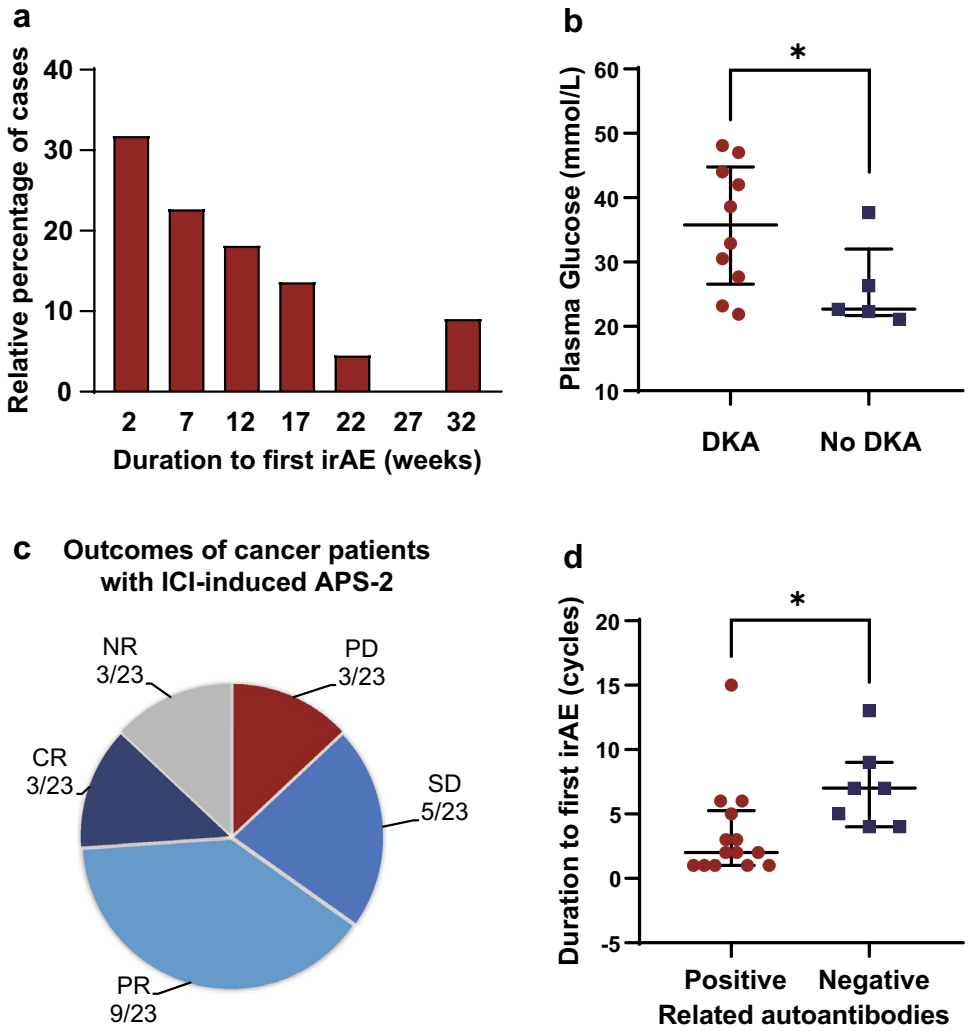


Fig. 2 Clinical features of APS-2 cases induced by ICI treatments. **a** Histogram of duration to the first adverse event (weeks). $n=22$ reporting time to first onset. **b** Plasma glucose levels between T1DM patients with or without DKA. $n=10$ T1DM cases with DKA, $n=5$ T1DM cases with no DKA. **c** Outcomes of cancer in APS-2 patients triggered by ICIs. **d** Duration to the onset of first adverse event (cycles) by autoantibody positivity. In this figure, the duration to the onset of first adverse event is presented as the number of cycles that patients received. $n=14$ patients reporting time to first onset with positive autoantibodies, $n=7$ patients reporting time to first onset with negative autoantibodies. Values are presented as the median ± interquartile range; $*P<0.05$. *APS-2* autoimmune polyendocrine syndrome type II, *CR* complete response, *DKA* diabetes ketoacidosis, *ICI* immune checkpoint inhibitor, *irAE* immune-related adverse event, *NR* not reported, *PD* progressive disease, *PR* partial response, *SD* stable disease

Meanwhile, autoantibody-positive patients showed earlier onset time than negative patients (positive, 4.5 weeks; negative, 12 weeks; $P<0.05$).

The GAD antibody is the most frequently detected positive autoantibody. Of 17 patients with T1DM, 8 (47.1%) exhibited positive GAD antibody and 75.0% of these GAD-positive patients (6/8) developed T1DM with DKA. Thyroid-related autoantibodies were detected as positive in 38.9% patients (7/18) who later developed immune-related thyroid disorders. Moreover, test results for other autoantibodies, including 21-hydroxylase antibody (21-OH Ab), adrenal cortex antibody (ACA), and anti-pituitary antibody, were also positive in patients with relative endocrine events.

The HLA genotype was analyzed and reported in 34.8% (8/23) of patients. Among these reported results, five patients (62.5%) presented with risk genotypes. A well-known susceptible allele, HLA-DR4, was detected in three patients, whereas the protective haplotype HLA-DQ6 was present in two patients.

Discussion

Immune checkpoint inhibition therapies have shown strong effects against various types of malignant cancer, and the number of patients receiving these treatments has been increasing rapidly. Meanwhile, more and more immune-related or inflammatory side effects have been reported. Although rare, APS-2 is an endocrine irAE that can cause severe outcomes. To summarize the clinical characteristics and immunological and genetic features of patients with APS-2 after immune checkpoint inhibition, we conducted the current systematic review of cases reports on this rare adverse event induced by ICI treatments.

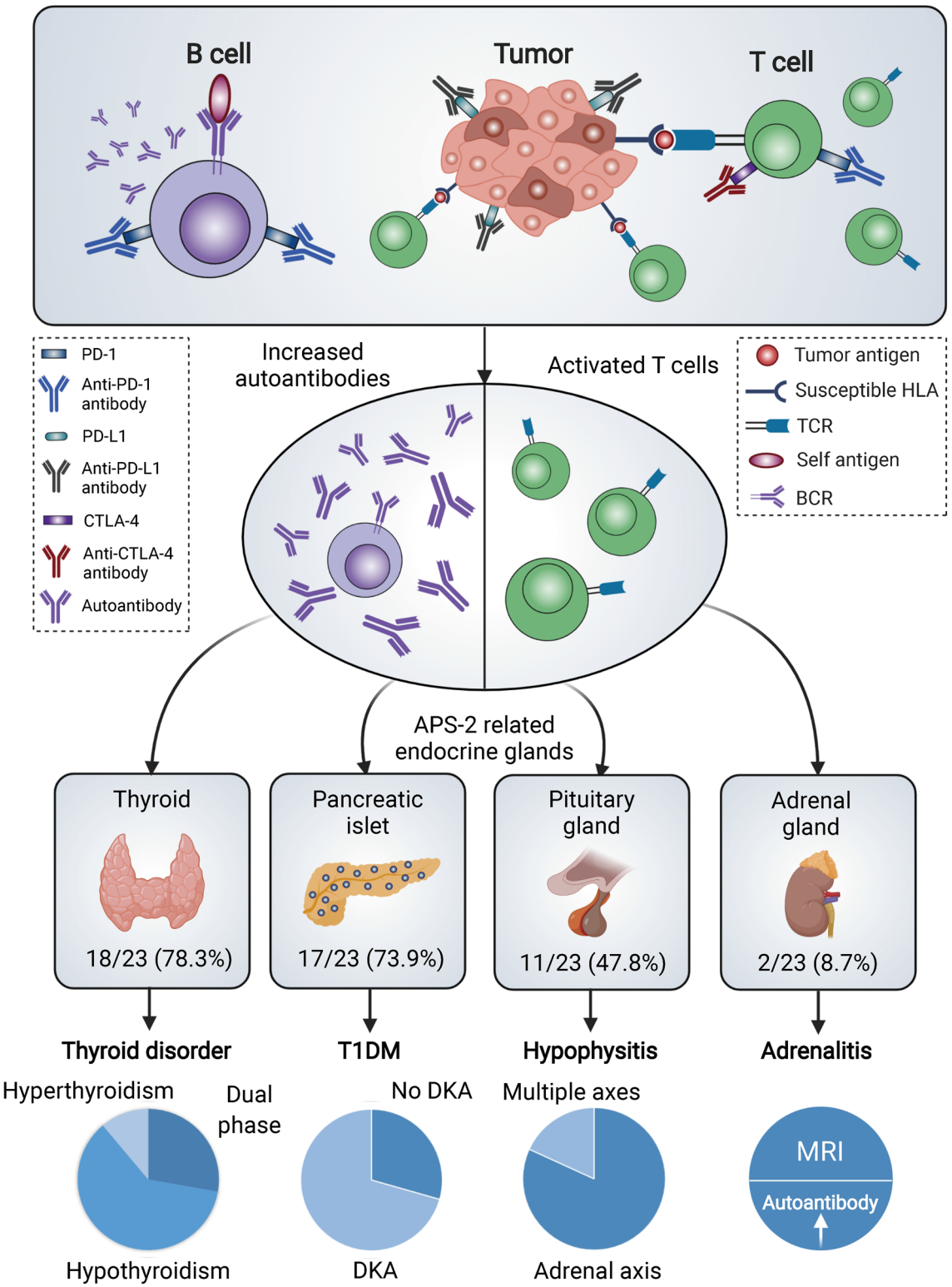
Immune checkpoint blockade therapy has significantly changed strategies for treating cancer as a supplement to comprehensive treatment including surgery, radiotherapy, chemotherapy, and target therapy. Under physiological conditions, CTLA-4 and PD-1/PD-L1 pathways are critical in self-tolerance and restricting autoimmune response. However, in tumor tissues, these immune checkpoint pathways

are triggered to help cancer cells escape from immunity [29]. Therefore, ICIs which can block the overactivation of these pathways are used to enhance the antitumor immune response, providing impressive survival improvement for cancer patients. Meanwhile, the immune checkpoint blockade can promote the generation of autoantibodies by stimulating humoral immune response [30] as well as activate autoimmune T-cell reaction, thus causing immune-related adverse events [31] (Fig. 3). Increasing evidence from meta-analyses, systematic reviews, clinical trials, and case reports support that a wide range of organs are involved in inflammatory or immune-related side effects after ICI treatments [2, 32–39]. The severity of these side effects varies from mild to life threatening. Nevertheless, the co-occurrence of two or more endocrine disorders (e.g., APS) during immunotherapy has been far from well summarized due to its low incidence.

To better examine APS-2 during immune checkpoint blockade, we searched three databases of medical publications. We identified five additional case reports which were not included in the searching results from two published literature reviews [7, 8]. After careful review, only 23 cancer patients who presented with two or more endocrine glands affected by ICIs and had not been diagnosed with any autoimmune or endocrine diseases before treatment were included in our research. A review of case reports can provide detailed manifestations of rare but significant side effects that are seldom described in clinical trials. However, it cannot display the general profile of a disorder. It is well known that women are at a higher risk of autoimmune diseases because of sex-related differences in both innate and adaptive immune responses to self-antigens. Existing studies have suggested that these differences are caused by genes and hormones [40]. We hypothesized that as a special autoimmune adverse event, APS-2 also affects a greater proportion of women. Interestingly, approximately twice the number of male patients with ICI-induced APS-2 than the number of female patients were enrolled in our study. We speculate that the main reason why a higher proportion of male patients was observed in our systematic review is that more men receive ICI treatments than women, a common feature of many immunotherapy clinical trials [41–43]. For example, in a meta-analysis of 20 eligible randomized controlled trials of patients with advanced cancer, 67% of 11,351 patients were male, which was very similar to the male percentage of our results [41]. However, it has not yet been determined whether men are more susceptible to APS-2 induced by ICIs than women; hence, this requires further investigation. Meanwhile, because metastatic melanoma and lung cancer are earlier approved indications for immune checkpoint antibodies, they were more frequently treated with ICIs and were the predominant cancer types among all the included patients. Additionally, all the available antibodies targeting CTLA-4, PD-1, or PD-L1, as well as combination therapies could trigger multiple endocrine side effects. Notably, more APS-2 patients induced by PD-1/PD-L1 blockade than CTLA-4 inhibition may be due to the wider usage of PD-1/PD-L1 antibodies. To date, five PD-1/PD-L1 blockade drugs have been approved for a wide range of indications whereas only ipilimumab has been approved for melanoma treatment as an anti-CTLA-4 therapy [31]. Thus, it is not surprising that more patients with cancer receive PD-1/PD-L1 therapies than CTLA-4 blockade. Moreover, other studies suggested that patients receiving PD-1/PD-L1 inhibitor treatment had a higher risk of immune-related thyroid disorder than those receiving anti-CTLA-4 treatment [44, 45]. Consistent with this, a systematic review concluded that some other irAEs including pneumonitis, hypothyroidism, arthralgia, and vitiligo were more common with the use of PD-1 antibodies [46]. Therefore, we inferred that APS-2 induced by ICIs may also be associated with the PD-1 pathway. However, this requires validation in further studies.

Induced by various types of immunotherapies, most patients developed two disorders, with the co-occurrence of autoimmune thyroiditis and type 1 diabetes most common. Given that both hypothyroidism and hyperthyroidism are observed with high incidence in patients undergoing anti-PD-1/PD-L1 treatments [3], it is not surprising that the thyroid gland was most frequently affected gland in this study. However, the relatively rare autoimmune disease, T1DM, also occurred in most of the included cases, indicating APS-2 and autoimmune diabetes share some similarities of pathogenesis. Most T1DM patients included experience rapidly developing DKA in our research, suggesting that APS-2 triggered by immunotherapy has life-threatening outcomes. Therefore, T1DM patients induced by ICI treatment with other endocrine organs affected should receive immediate insulin therapy to prevent the occurrence of DKA.

Another important manifestation of APS-2, adrenal insufficiency, is related to an autoimmune reaction in the pituitary or adrenal glands. Most patients with hypophysitis only showed an impaired adrenal axis, whereas two patients exhibited reduced production of FSH, LH (gonadal axis), and TSH (thyroid axis) in addition to adrenal insufficiency. Three enrolled patients who received therapies containing ipilimumab all developed hypophysitis, which is consistent with the association between ipilimumab and high hypophysitis incidence [4]. Besides autoimmune hypophysitis, two patients were diagnosed with autoimmune adrenalitis. Paepegaey et al. [25] reported a patient who presented with acute adrenal crisis. Further laboratory tests confirmed the diagnosis of autoimmune adrenalitis by positive autoantibodies (21-OH Ab, ACA). Aziz et al. [12] diagnosed adrenal cortical atrophy using abdomen Magnetic Resonance Imaging (MRI). Abrupt onset of adrenal insufficiency can cause life-threatening acute adrenal crisis, which requires



immediate medical attention. The key clinical features of APS-2 cases enrolled in our study are illustrated in Fig. 3.

The occurrence of irAEs, including APS-2 in our research, always suggests effective activation of the immune system via immune checkpoint inhibition. In a retrospective study of patients with advanced non-small cell lung cancer (NSCLC) treated with PD-1 blockade, thyroid dysfunction was found to be associated with longer progression-free and overall survival [47]. Moreover, a recent prospective study of NSCLC revealed improved

◂**Fig. 3** Schematic diagram of immune-related APS-2 induced by ICIs. Immune checkpoint blockade activates humoral immune response as well as cytotoxic T cells. Both increased level of autoantibodies and activated T cells contribute to the destruction of targeted endocrine glands. The glands involved in immune-related APS-2 include thyroid, pancreatic islets, pituitary gland, and adrenal gland. Dual phase means that patients with thyroid disorder experienced a transition from hyperthyroidism to hypothyroidism. More than 70% patients with T1DM had DKA. Most cases with hypophysitis presented with adrenal axis affected while two had multiple axes affected. Two patients manifested with adrenalitis were diagnosed by elevated autoantibodies or MRI results. *APS-2* autoimmune polyendocrine syndrome type II, *BCR* B cell receptor, *CTLA-4* cytotoxic T-lymphocyte antigen 4, *DKA* diabetes ketoacidosis, *HLA* human leukocyte antigen, *MRI* Magnetic Resonance Imaging, *PD-1* programmed cell death 1, *PD-L1* programmed cell death ligand 1, *T1DM* Type 1 Diabetes Mellitus, *TCR* T-cell receptor

survival in patients with skin-related adverse events induced by PD-1 treatment [48]. Other reports also suggested that the development of autoimmune adverse events was associated with a higher response rate to ICI treatments [49–51], although not all investigations have supported the conclusion [52, 53]. In our study, as one of the rarest irAEs, APS-2 triggered by ICIs indicated better efficacy of the immune checkpoint blockade. Notably, only 15.0% of the cancer patients with reported outcomes presented with progressive disease. Most patients with cancer showed at least stable disease in response to ICI therapies, suggesting that the presentation of APS-2 may be related to a good response to ICI therapies. Therefore, more efforts should be made to overcome the severe adverse event, APS-2, to ensure better survival.

APS-2 is a relatively more common variety of autoimmune polyendocrine syndrome (prevalence, 1:1,000) than APS type 1 [5]. Although the pathogenesis of this disease is still not clear, it is thought to be a polygenetic disease associated with HLA genotypes and other immune-related genes. Among these genes of interest, *CTLA-4* with heterozygous mutations that reduce its expression and with missense mutations that disturb ligand binding were reported to interfere with T and B cell homeostasis, leading to a complex autoimmune disease [54]. Based on this study, we suggested that CTLA-4 blockade promotes both T-cell activation and humoral immunity to induce APS-2 in cancer patients, similar to the mechanisms to induce other irAEs. In addition, the study that analyzed skin toxicity adverse events in patients with NSCLC receiving PD-1 therapy identified several T-cell antigens shared between lung tumors and skin tissues. The T cells responding to these antigens present in blood biopsy samples were found to infiltrate skin lesions and tumor tissues, providing evidence that inhibition of the PD-1 pathway may trigger APS-2 by enhancing T-cell activation [48]. Although several relevant studies have indicated the possible mechanisms of APS-2 induced by ICIs, more specific and direct studies are still required.

Clinical laboratory tests related to mechanisms, including HLA risk allele analysis and autoantibody test, were carried out in our enrolled cases. One patient in our review had genotype HLA-DR4-DQ3, which shows genetic susceptibility to T1DM and adrenal insufficiency [7, 16]. Two more patients had the DR4 genotype, which confers the risk of T1DM and thyroiditis [8, 27, 55]. Furthermore, HLA DR9-DQ3 was detected in two Asian patients [10, 24], and this haplotype is closely related to T1DM in Asia [56, 57]. However, a protective haplotype, DQ6 [58], was identified in two patients [16, 19]. These HLA results support that APS-2 is closely associated with HLA subtypes and suggest that all autoimmune endocrinopathies, including APS-2, T1DM, thyroiditis, and adrenal insufficiency, may share some similar pathogenesis and mechanisms. In addition, autoantibody results have suggested a significant role of autoantibodies in the development of immune-related APS-2. In one article, a close association between ICI-induced thyroid disorders and anti-thyroid antibodies was reported [30]. Consistent with this, patients with APS-2 or related autoimmune endocrinopathies have been found to generate positive autoantibodies, such as GAD, TPO, and 21-OH Ab [5, 59–61]. Notably, nearly two-thirds of the patients enrolled in our study were positive for related autoantibodies. Moreover, the onset of the primary adverse event varies from weeks to nearly 1 year, and autoantibody-negative patients showed a significantly later onset of APS-2 than autoantibody-positive patients. Collectively, these results suggest that immune checkpoint blockade also enhances humoral immunity, consequently generating higher levels of autoantibodies during the pathogenesis of APS-2 triggered by ICIs. Similar results of HLA genotypes and autoantibodies reported in both spontaneous and ICI-induced endocrinopathies indicate that immune checkpoint inhibition would be a potential approach to studying the mechanisms of these complex autoimmune disorders.

To the best of our knowledge, this is the largest and most comprehensive systematic review of case reports on APS-2 after ICI therapies. Lanzolla et al. [7] summarized 16 cases of immune-related APS after anti-PD-1 or anti-CTLA-4 therapy with limited clinical features concluded. Additionally, Gunjur et al. [8] conducted a review of cases of anti-PD-1/PD-L1–induced APS-2. However, both studies only included partial reports of ICIs. Moreover, some patients had previous history of autoimmune or endocrine diseases while some didn't have adequate clinical data. However, our study has some limitations. Case reports tend to describe side effects with rare, unique, and severe features, whereas unremarkable cases remain unreported. Therefore, the included cases may not represent all APS-2 cases induced by ICIs. These cases were published by different authors, with some incomplete clinical information and laboratory test results. Moreover, we could not know which population

these patients were selected from, so we could not estimate an incidence of this disorder and identify risk factors.

We conducted this comprehensive review primarily to provide a larger scale view of APS-2 induced by ICI therapy, including clinical characteristics, immunological features, and genetic findings. We also aimed to increase the awareness of this severe adverse event during the increasing administration of these novel immune therapies. Our results show that APS-2 triggered by ICIs can suddenly cause lethal events including adrenal crisis and DKA. Thus, we suggest detecting autoantibodies and monitoring the related hormone levels during treatments for early discovery of endocrine disorders. Moreover, our study provides some evidence for elucidating the mechanisms of irAEs and APS-2. However, because the data of these reports are far from enough to research the underlying mechanisms and discover novel predictive markers, we suggest oncologists collect related genetic and clinical information of more APS-2 patients induced by ICIs.

In conclusion, this systematic review examined APS-2, a special endocrine adverse event, after ICI therapy. The time from therapy initiation to APS-2 is abrupt, and this disorder develops rapidly. Life-threatening events, including adrenal crisis and severe DKA, may occur. Therefore, physicians should be aware of potential endocrine disorders during ICI treatments.

Author contributions We declare that all authors made fundamental contributions to the manuscript. All authors contributed to the study conception and design. Database search and data analysis was conducted by WX. Study selection and data extraction were performed by NJ and SM. The manuscript was written by ZZ. BX and ZD reviewed the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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