Immune checkpoint inhibitors and adrenal insufficiency: a large-sample case series study

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Background: Adrenal insufficiency (AI) represents a rare, yet potentially life-threatening immune checkpoint inhibitor (ICI)-related adverse event. The clinical characteristics of ICI-induced AI are still poorly defined due to its low incidence but need to be comprehensively understood.

Methods: We systematically retrieved and screened the PubMed/Medline, Embase, Web of Science, and Cochrane Library databases for all articles published on AI related to anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4), anti-programmed cell death protein-1 (PD-1) receptor or its ligand (PD-L1), or combination ICI therapy. The retrieved articles were reviewed and selected in accordance with the exclusion criteria. The detailed data of individual cases were then collected and analyzed.

Results: We identified 206 ICI-induced AI patients, comprising 11 (5.3%) primary AI patients, 191 (92.7%) secondary AI patients, and 4 (1.9%) mixed-type AI patients. The subclassification of the secondary AI patients, comprising 108 isolated adrenocorticotropic hormone (ACTH) insufficiency (IAD) and 83 multiple pituitary hormone deficiency (MPHD) patients, revealed that 56.5% of secondary AIs were related to IAD. Fatigue, anorexia/loss of appetite, headache, and nausea/vomiting were the most prevalent symptoms, and MPHD patients had a significantly higher rate of headache than primary AI patients and IAD patients (67.2% *vs.* 9.1% *vs.* 10.2%; P=0.000). Further, anti-PD-1-induced AI patients showed more complex and poorer clinical manifestations than anti-CTLA-4-induced patients, including a higher rate of emergency admission (28.7% *vs.* 4.9%; P=0.003), tachycardia (30.4% *vs.* 0; P=0.014), hypotension (50.0% *vs.* 8.6%; P=0.000), hypoglycemia (19.5% *vs.* 2.6%; P=0.014), hyponatremia (64.2% *vs.* 33.3%; P=0.002), and a prolonged median duration from ICI initiation to symptom onset (26 *vs.* 9 weeks; P=0.000).

Discussion: The ICI-induced AI events could be primary, secondary, or mixed-type, and IAD was the most common reason for such events. The symptoms were usually unspecific and could be complex. AI should be excluded in a timely manner, and the patients should be followed-up with and receive extra attention for AI events even after the discontinuation of ICI treatment. Additionally, the discrepancy in relation to clinical characteristics between anti-PD-1- and anti-CTLA4-induced AI events warrants further exploration.

Keywords: Immune checkpoint inhibitors (ICIs); immune-related adverse events (irAEs); adrenal insufficiency (AI)

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Introduction

Immune checkpoint inhibitors (ICIs), including anti-cytotoxic T-lymphocyte antigen 4 (CTLA4), anti-programmed cell death protein-1 (PD-1), and anti-programmed death-ligand-1 (PD-L1), are monoclonal antibodies that aim to unleash the power of the human immune system against malignancies, and represent the most important anti-cancer treatments in recent years (1,2). However, these therapies have corresponding side effects. Due to the ubiquitous existence and high complexity of immune system regulation, the implementation of ICIs may disturb homeostasis and potentially result in a range of autoimmune-related toxicities, known as immune-related adverse events (irAEs), which are widely associated with immune cells attacking healthy organs or tissues in systems including the respiratory, digestive, urinary, nervous, and endocrine systems (3).

Adrenal insufficiency (AI) is an endocrine adverse event associated with ICI treatment. It has been reported that the incidence of AI in monotherapy ICI treatment was 0.7%, with an incidence of grade 3 or above of 0.2%. In contrast, the incidence of AI increased with combination ICI treatment compared to single agent (4.2%) (4,5). Despite its low incidence, it can be life-threatening if not diagnosed in a timely manner and properly treated, which has raised new concerns about ICIs (6). However, the symptoms of AI are usually unspecific and heterogeneous, and its clinical course and characteristics are far from being well defined. Although there have been previous case reports and meta-analyses (7), these studies have focused more on the incidence of various adverse events and have not provided detailed descriptions and comparisons of the clinical features of the different subtypes of AI, such as primary AI, secondary AI [including multiple pituitary hormone deficiency (MPHD) and isolated adrenocorticotropic hormone (ACTH) insufficiency (IAD)] and mixed AI. However, complex concomitant symptoms may require long-term or lifelong replacement hormone therapy and timely attention to the differential clinical presentation can provide an important basis for identifying the different subtypes of AI and for timely adjustment of treatment regimens. Given the increasing use of these agents in clinical practice and the availability of a wealth of new data, we focused on ICI-induced AI by including the most recent publications and clinical trial reports comparing the incidence of different types of AI and the clinical characteristics of their subtypes in different ICI treatment regimens. We believe this will extend the understanding of irAEs and may provide meaningful guidance for identifying AI and providing timely and appropriate treatment.

We present the following article in accordance with the PRISMA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-7006/rc).

Methods

Literature search strategy

We conducted a thorough search of databases, including the PubMed/Medline, Embase, Web of Science, and Cochrane Library databases, without any restrictions as to language or publication date, to retrieve any relevant articles. We also searched the reference lists of the retrieved articles. All the approved ICIs were taken into consideration. The detailed search strategy for each database is provided in Appendices 1-4. All the articles were reviewed independently by two reviewers (i.e., Wang ZQ and Cui K), and any disagreement was resolved through discussion. Primary AI, secondary AI, and IAD were defined as per the established biochemical diagnostic criteria (8,9).

Study selection

This article is a large-sample case series study based on literature designed to assess the risk of ICI-related AI events. Our inclusion criteria therefore included all clinical trials (and/or cohorts) in which (I) participants had received at least one previous ICI treatment; (II) ICI-related AI events were clearly reported in the safety data of the participants included, with or without clinical severity grading; and (III) were published in English. Articles were excluded from the analysis if they met any of the following exclusion criteria: (I) were off-topic; (II) were duplicated across different databases; (III) did not describe any clinical cases; (IV) lacked individualized descriptions of cases; (V) were conferences abstracts; (VI) included patients who had used glucocorticoids 6 months before the diagnosis of AI; and/or (VII) included patients who had metastasis in the adrenal or pituitary glands. The flowchart for the literature search and review is shown in *Figure 1*.

Statistical analysis

The quantitative data are expressed as the mean ± standard deviation (SD) for normally distributed data, or the median

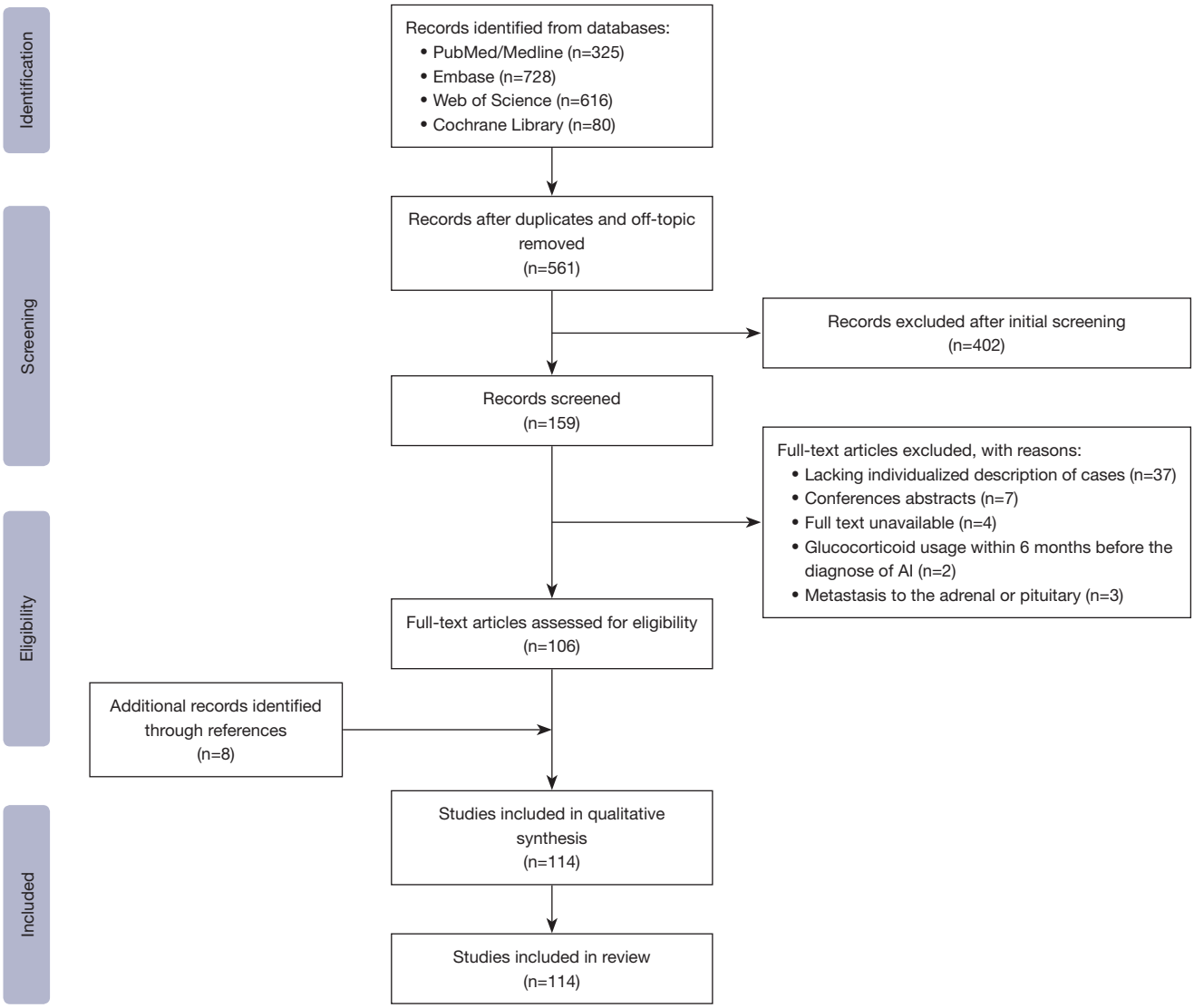

Figure 1 Flowchart of literature screening and selection. AI, adrenal insufficiency.

(interquartile range) for non-parametric data. The categorical data are expressed as the number and ratio. The Kolmogorov-Smirnov test was used to check the normal distribution of the quantitative variables. The Student's *t*-test was used for mean comparisons of normally distributed data, and the Mann-Whitney test was used for mean comparisons of non-parametric data. The Chi-square test or Fisher's test was used to for ratio comparisons. A P value <0.05 was considered statistically significant. All the statistical processing was conducted in IBM SPSS Statistics version 26.0.

Results

The selection of articles

Three hundred and twenty-five, 728, 616, and 80 articles were retrieved from the PubMed/Medline, Embase, Web of Science and Cochrane Library databases, respectively, and 8 additional articles were identified from the reference lists of the retrieved articles (7-14). Ultimately, a total of 114 articles (comprising 206 patients with ICI-induced AI) were included in the study (see *Figure 1*).

Table 1 Classification of all ICI-induced AI events

The classification of AI	No. of cases (%)
Primary	11/206 (5.3)
Secondary AI (hypopituitarism)	191/206 (92.3)
IAD	108/191 (56.5)
MPHD	83/191 (43.5)
TSH	72/83 (86.7)
Gonadotrophins	42/83 (50.6)
Prolactin	10/83 (12.0)
Growth hormone	1/83 (1.2)
Mixed type	4/206 (2.4)

ICI, immune checkpoint inhibitor; AI, adrenal insufficiency; IAD, isolated ACTH insufficiency; MPHD, multiple pituitary hormone deficiency; TSH, thyroid stimulation hormone.

Clinical characteristics of patients with ICI-induced AI

Of the 206 patients with individualized information about ICI-induced AI (see *Table 1* and Table S1), 11 (5.3%) had primary AI, 191 (92.3%) had secondary AI, and 4 (1.9%) had mixed-type AI that showed evidence of both primary and secondary AI. IAD consisted mostly of secondary AI cases (56.5%), and thyroid stimulation hormone (TSH) (86.7%) was the most frequently affected hormone (other than ACTH) in the rest of the cases.

The clinical characteristics are summarized in *Table 2*. The results have been displayed separately, as they may indicate different underlying mechanisms. Briefly, the 3 types of AI occurred predominantly in males, and the patients had mean ages at symptom onset of 59.7, 62.9, and 57.5 years for primary AI, secondary AI, and mixed-type AI, respectively. In relation to the 3 types of AI cases, melanoma accounted for the most cases (43.8%, 51.3%, and 50.0%, respectively), followed by non-small cell lung cancer (NSCLC) (37.5%, 15.7%, and 50.0%). The most widely used agents, including nivolumab (37.5%, 36.1%, and 25.0%), and ipilimumab (25.0%, 27.7%, 50.0%) for the 3 types of AI cases, respectively, and pembrolizumab (18.8%, and 15.5%) for the primary and secondary AI cases, respectively, represent the main causes of ICI-induced AIs. The median time from ICI initiation to symptom onset were 17 weeks for primary AIs and 15 weeks for secondary AIs, and the median time from the last administration to symptom onset were 30 days for primary AIs and 14 days for secondary AIs. 26.7% of patients with primary AIs and 22.6% of patients with secondary AIs were admitted to the emergency department due to severity or exaggeration of the symptoms; the mixed-type AI patients were excluded from this analysis due to data unavailability (as indicated by the slash in *Table 2*).

Tachycardiac (42.9%, 22.2%), hyponatremia (75.0%, 53.6%), and hypotension (72.7%, 34.7%), hypoglycemia (18.2%, 11.7%) were all observed in primary and secondary AIs at different rates, while eosinophilia was only reported in secondary AIs (30.0%). The subclassification revealed that 56.5% of secondary AIs were related to IAD. Abnormalities on adrenal computed tomography (CT)/magnetic resonance imaging (MRI) scans were observed in 20.0% (1/5) of primary AI cases and 33.3% (1/3) of mixed-type AI cases, and enlargements of the adrenal gland and abnormalities in brain MRI scans were observed in 39.5% of secondary AI cases, including the enlargement of the pituitary gland and/or infundibulum (59/191, 30.9%), the loss of the pituitary bright spot (2.6%, 5/191), and empty sella (1.0%, 2/191). 1 case of enlargement of the pituitary gland (33.3%, 1/3) was observed in the mixed-type of AI cases, and none (0/5) were observed in the primary AI cases. Thyroiditis/hypothyroidism and type 1 diabetes mellitus (T1DM) were the most common concomitant irAEs in both primary and secondary AI cases. 0% and 26.2% of primary and secondary AI patients, respectively, discontinued the use of ICIs due to AI.

The symptoms of different types of AIs

The mixed-type AI cases were excluded from this part of the analysis, as too few cases were reported. The main symptoms of primary AI were fatigue (90.9%, 10/11), nausea/vomiting (54.5%, 6/11), and joint pain (45.5%, 5/11). The main symptoms of IAD were fatigue (67.6%, 73/108), anorexia/loss of appetite (54.6%, 59/108), nausea/vomiting (27.8%, 30/108), and weakness (13.0%, 14/108). The most prevalent symptoms of MPHD were headache (62.7%, 52/83), followed by fatigue (57.8%, 48/83), nausea/vomiting (21.7%, 18/83), anorexia/loss of appetite (21.7%, 18/83), and drowsiness/lethargy (10.8%, 9/83).

The comparison analysis revealed a significantly higher rate of anorexia/loss of appetite ($P<0.001$) and weakness ($P=0.032$) in IAD patients compared to those with other types of AIs, headache ($P<0.001$), and decreased libido ($P=0.05$) in MPHD patients, and joint pain ($P<0.001$), confused/disorientation ($P<0.001$), and a cold sensation ($P=0.017$) in primary AI cases (see Appendix 1). Several rare

Table 2 Clinical characteristics of different types of ICI-induced AI

Characteristics	Classification		
	Primary AI (n=11)	Secondary AI (n=191)	Mixed type (n=4)
Age (year), mean ± SD [range]	59.7±9.9 [42–76]	62.9±11.7 [31–87]	57.5±1.7 [56–60]
Gender (male), n (%)	7/11 (63.6)	135/191 (70.7)	3/4 (75.0)
Ethnicity (Asian), n (%)[#]	5/11 (45.5)	79/191 (41.4)	2/4 (50.0)
Tumor type, n (%)			
Melanoma	5/11 (45.5)	98/191 (51.3)	2/4 (50.0)
NSCLC	3/11 (27.3)	30/191 (15.7)	2/4 (50.0)
Renal cell cancer	0/11 (0.0)	23/191 (12.0)	0/4 (0.0)
HNSC	0/11 (0.0)	9/191 (4.7)	0/4 (0.0)
Gastric cancer	0/16 (0.0)	7/191 (3.7)	0/4 (0.0)
Urothelial cancer	0/16 (0.0)	7/191 (3.7)	0/4 (0.0)
Other types	3/11 (27.3)	17/191 (8.9)	0/4 (0.0)
Medical record of immune-mediated diseases, n (%)	0/11 (0.0)	4/191 (2.1)	0/4 (0.0)
Anti-CTLA-4, n (%)			
Ipilimumab	4/16 (25.0)	53/191 (27.7)	2/4 (50.0)
Anti-PD-1, n (%)			
Nivolumab	6/16 (37.5)	69/191 (36.1)	1/4 (25.0)
Pembrolizumab	3/16 (18.8)	22/191 (11.5)	0/4 (0.0)
Tislelizumab	0/16 (0.0)	2/191 (1.0)	0/4 (0.0)
Camrelizumab	0/16 (0.0)	1/191 (0.5)	0/4 (0.0)
Anti-PD-L1, n (%)			
Atezolizumab	2/16 (12.5)	2/191 (1.0)	1/4 (25.0)
Avelumab	0/16 (0.0)	1/191 (0.5)	0/4 (0.0)
Combined agents, n (%)	1/16 (6.3)	32/191 (16.8)	0/4 (0.0)
Sequential, n (%)	0/16 (0.0)	8/191 (4.2)	0/4 (0.0)
Time from ICI initiation to symptom onset (weeks), median [interquartile range]	17 [15–18]	15 [9–30]	–
Time from the last administration to symptom onset (days), median [interquartile range]	30 [12.75–30]	14 [7–30]	–
Over 1 month from the last administration to symptom onset, n (%)	4/7 (57.1)	24/81 (29.6)	–
Emergency admission, n (%)	4/11 (36.4)	36/159 (22.6)	–
Tachycardiac, n (%)	3/7 (42.9)	16/72 (22.2)	–
Hyponaemia, n (%)	8/11(72.7)	82/153 (53.6)	–
Hypotension, n (%)	8/11 (72.7)	50/144 (34.7)	–

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Classification		
	Primary AI (n=11)	Secondary AI (n=191)	Mixed type (n=4)
Hypoglycemia, n (%)	2/11 (18.2)	18/154 (11.7)	–
Eosinophilia, n (%)	0/2 (0.0)	33/110 (30.0)	–
Abnormality on brain MRI, n (%)	–	65/172 (39.5)	1/3 (33.3)
Abnormality on adrenal CT/MRI, n (%)	1/5 (20.0)	–	1/3 (33.3)
Symptoms improvement after glucocorticoid treatment, n (%)	11/11 (100.0)	191/191 (100.0)	4/4 (100.0)
Discontinuation of ICIs due to AI, n (%)	0/2 (0.0)	17/65 (26.2)	–
Other irAEs, n			
Thyroiditis/hypothyroidism	3	32	0
T1DM	2	10	1
Colitis	0	10	0
Skin toxicity	0	7	0
Hepatitis	0	4	0
Pneumonitis	0	3	0
Pancreatitis	0	2	0
Others	2	4	1

[#], the address information of the institution by which the cases were reported were used alternatively when ethnicity information was not specified. ICI, immune checkpoint inhibitor; AI, adrenal insufficiency; SD, standard deviation; NSCLC, non-small cell lung cancer; HNSC, head and neck squamous cancer; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand-1; MRI, magnetic resonance imaging; CT, computed tomography; irAEs, immune-related adverse events; T1DM, type 1 diabetes mellitus.

symptoms were also reported; all the AI-related symptoms are summarized in *Figure 2*.

Subgroup analysis of ICI-induced secondary AI

Next, we performed a subgroup analysis of the secondary AI cases in relation to the type of regimen (i.e., monotherapy *vs.* combined/sequential therapy), the subtype of secondary AI (i.e., IAD *vs.* MPHD), and the type of ICI (i.e., PD-1 *vs.* CTLA-4) (see *Table 3*). The results revealed no significant differences in the clinical characteristics of secondary AI induced by monotherapy compared to that of combined/sequential therapy, except for a relatively prolonged latency period from ICI initiation to symptom onset (P=0.082).

In relation to the two different secondary AI subtypes, there was no difference in terms of age and gender between the IAD and MPHD patients; however, the IAD patients had a significantly prolonged latency period from ICI initiation to symptom onset (P=0.000) and from last administration to symptom onset (P=0.030), and compared to IAD, the MPHD patients had a significantly higher rate of emergency admission (P=0.034), hyponatremia (P=0.000), abnormalities in the brain MRI scans (P=0.000), and a slightly higher rate of discontinuation of ICIs due to AI (P=0.092).

No difference was found in relation to age and gender between the PD-1- and CTLA-4-induced secondary AI patients. Additionally, the PD-1-induced patients experienced a significantly prolonged latency period before symptom onset (P=0.000), and a higher rate of emergency admission (P=0.003), tachycardia (P=0.014), hypotension (P=0.000), hyponatremia (P =0.002), and hypoglycemia (P = 0.014) compared to CTLA-4-induced secondary AI patients. Further, PD-1 induced more IAD (45.2%) than CTLA-4 (17.0%) (P=0.000), and abnormalities in the brain MRI scans were more common in CTLA-4-induced

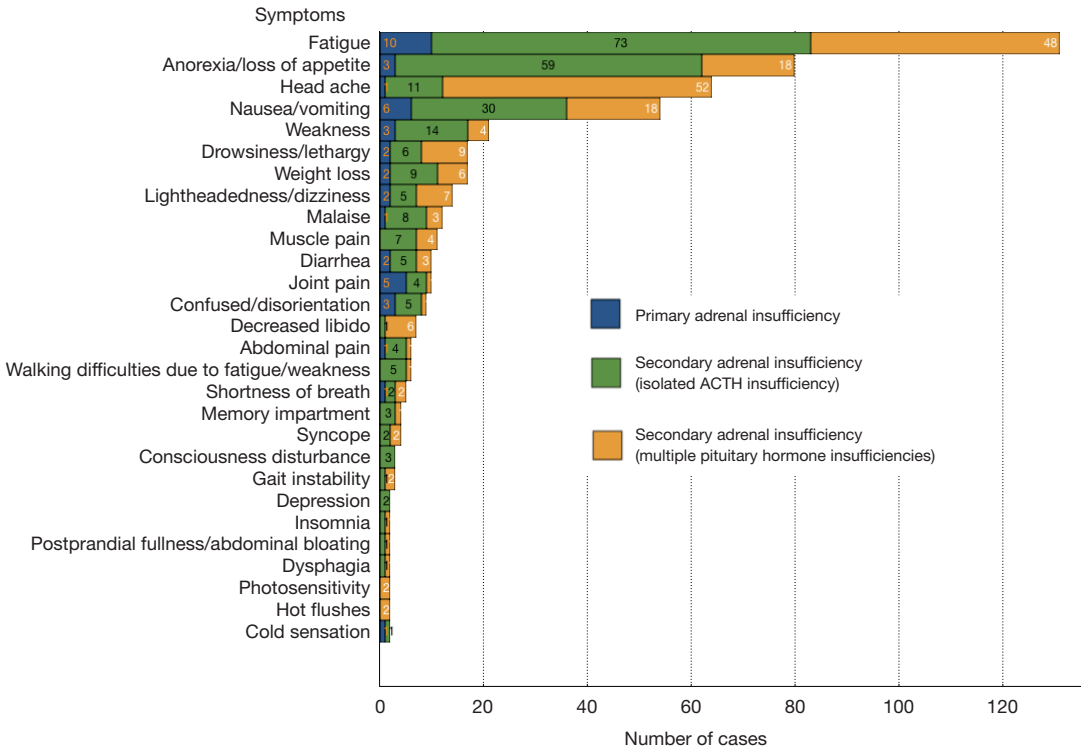

Figure 2 Summary of the onset symptoms of AI across different types of AI cases. ACTH, adrenocorticotropic hormone; AI, adrenal insufficiency.

patients than PD-1-induced patients (P=0.000).

Discussion

It is widely reported that AI is a rare irAE secondary to ICI treatment, with a prevalence rate that varies from <1% to about 5% (4,5); however, due to its low incidence, the clinical course and characteristics are far from well defined. Due to its non-specific and complicated clinical manifestations, and the potential serious consequences if the diagnosis is incorrect or delayed, a comprehensive understanding of the clinical characteristics of ICI-induced AI events is needed. Immune-related AI is associated with dyssecretion of the hypothalamic-pituitary-adrenal axis, a complex collection of direct actions and feedback interactions. It is affected by feedback and negative feedback between hormones such as corticotropin-releasing hormone (CRH) from the hypothalamus, ACTH from the anterior pituitary and cortisol from the adrenal cortex, which are involved in the regulation of many vital activities of the body (10). Primary AI is a low-incidence condition caused by dysfunction of the adrenal cortex, which does not produce enough cortisol, aldosterone or androgens to satisfy the requirements of the organs, resulting in a range of clinical symptoms (11). In contrast, secondary AI is most often caused by inflammation of the pituitary gland or hypopituitarism, resulting in a decrease in ACTH release, which in turn leads to a decrease in the production of cortisol. adrenal cortisol secretion. In brain MRI, this often appears as an enlargement and enhancement of the pituitary stalk or funnel. In addition to this, other hormones that may be affected include an increase in thyrotropin, luteinizing hormone and/or follicle stimulating hormone, growth hormone or prolactin (12). Hypopituitarism, manifested as MPHD, has been reported in >20% of patients treated with epilimumab (13).

We focused on ICI-induced AI by including the most recent publications and clinical trial reports, and identified 206 patients, of whom the largest proportion had IAD (108/206, 52.4%). A recent public systematic review (14) of only the PubMed/Medline databases focused on ICI-related IAD, and identified a total of 60 IAD cases. In the present study, we advanced this number to 108 IAD cases, which further confirmed that IAD is becoming the dominant

Table 3 Clinical characteristics of different subgroup of ICI-induced secondary AI

Characteristics	Regimen			Subtypes			Type of ICI		
	Monotherapy	Combined/ sequential therapy	P value	IAD	MPHD	P value	Anti-PD-1	Anti-CTLA-4	P value
Age (≥60 y), %	64.2 (97/151)	60.0 (24/40)	0.621	67.6 (73/108)	58.3 (49/84)	0.186	68.4 (65/95)	54.7 (29/53)	0.097
Gender (male), %	73.5 (111/151)	65.0 (26/40)	0.288	74.1 (80/108)	70.2 (59/84)	0.555	74.7 (71/95)	69.8 (37/53)	0.518
Time from ICI initiation to symptom onset (weeks), median [interquartile range]	17 [9–30]	12 [8–15.5]	0.082	24 [14–34]	10 [8–19]	0.000	26 [15–36]	9 [4–11]	0.000
Time from the last administration to symptom onset (days), median [interquartile range]	14 [7–35.5]	14 [7–20]	0.355	20 [10–44.5]	10 [7–30]	0.030	14 [7–37]	14 [8.5–35.5]	0.890
Over 1 month from the last administration to symptom onset, %	30.9 (21/68)	23.1 (3/13)	0.745	41.2 (14/34)	29.5 (13/44)	0.284	33.3 (17/51)	26.7 (4/15)	0.758
Emergency admission, %	22.8 (27/131)	17.2 (5/29)	0.681	13.5 (12/89)	26.7 (20/75)	0.034	28.7 (25/87)	4.9 (2/41)	0.003
Tachycardiac, %	21.0 (13/62)	20.0 (2/10)	1.000	19.4 (6/31)	24.4 (10/41)	0.611	30.4 (14/46)	0.0 (0/15)	0.014
Hypotension, %	36.4 (40/110)	29.4 (10/34)	0.457	29.5 (23/78)	41.8 (28/67)	0.122	50.0 (36/72)	8.6 (3/35)	0.000
Hyponaemia, %	54.2 (65/120)	51.5 (17/33)	0.787	38.8 (31/80)	69.9 (51/73)	0.000	64.2 (52/81)	33.3 (12/36)	0.002
Eosinophilia, %	30.5 (25/82)	28.6 (8/28)	0.848	20 (15/75)	22.6 (14/62)	1.000	29.6 (21/71)	20.0 (2/10)	0.717
Hypoglycemia, %	14.4 (19/132)	6.3 (2/32)	0.252	11.0 (6/79)	16.2 (12/74)	0.098	19.5 (16/82)	2.6 (1/38)	0.014
IAD, %	58.9 (89/151)	47.5 (19/40)	0.194	–	–	–	45.2 (47/104)	17.0 (9/53)	0.000
Abnormality on brain MRI, %	35.1 (46/131)	50.0 (19/38)	0.097	17.2 (16/93)	68.4 (52/76)	0.000	14.1 (11/78)	66.7 (34/51)	0.000
Discontinuation of ICIs due to AI, %	26.3 (15/57)	25.0 (2/8)	1.000	18.4 (7/38)	37.0 (10/27)	0.092	21.6 (8/37)	10.0 (2/20)	0.467

ICI, immune checkpoint inhibitor; AI, adrenal insufficiency; IAD, isolated ACTH insufficiency; ACTH, adrenocorticotropic hormone; MPHD, multiple pituitary hormone deficiency; PD-1, programmed cell death protein-1; CTLA-4, cytotoxic T-lymphocyte antigen 4.

cause of ICI-induced AIs, which were rare before ICIs were introduced into clinical settings (5). We found that primary AI was much rarer than secondary AI, but it still made up 5.3% of all the ICI-induced AI cases, while 2.4% of cases were mixed-type AI (i.e., both primary and secondary AI). This ratio may be underestimated, as not all of the patients received a corticotropin-stimulation test. This is concerning because patients with mixed-type and primary AI may need mineralocorticoid replacement in addition to glucocorticoid replacement (15).

Consistent with previous reports (16), fatigue, anorexia/loss of appetite, headache, nausea/vomiting, weakness, and drowsiness/lethargy were the most prevalent symptoms, while less common symptoms included abdominal pain, syncope, and insomnia. These symptoms may overlap with those of the tumor itself. The timely exclusion of AI is necessary when patients, who are receiving ICIs, present with these symptoms. In addition, we noted that a significantly higher portion of MPHD patients presented with headaches cases compared to those with other types of AI. This knowledge may assist physicians to identify the hormones affected other than ACTH. The high prevalence of headache in MPHD cases may be due to the high frequency of pituitary enlargement. The subgroup analysis showed that the abnormalities in the brain MRI scans of MPHD patients were about 4 times more than those of the IAD cases. Additionally, over 20% of all cases were complicated by at least 1 endocrine system irAE other than AI and hypophysitis. Such complications mainly included thyroiditis, primary hypothyroidism, and T1DM. Such complications may further complicate the clinical manifestations, and require more accurate diagnosis.

Combined ICI therapy is usually considered more toxic than monotherapy (5), but we did not find significant differences in relation to the clinical characteristics of ICI-induced AI events between the different regimen groups, except for a slightly prolonged latency period from ICI initiation to symptom onset in the combined therapy cases. Notably, the difference was not statistically significant, but this may be due to the small sample number of patients who received combined therapy. The characteristics of anti-PD-1- and anti-CTLA-4-induced secondary AIs cases were compared, and the results unexpectedly revealed the emergency admission rate of the anti-PD-1-induced group was about 6 times higher than that of the anti-CTLA-4-induced group. Further, the anti-PD-1 group had more complex and poorer clinical manifestations than the anti-CTLA-4-induced group, including a significantly higher rate of tachycardiac, hypotension, hypoglycemia, and hyponaemia. Further, the anti-PD-1-induced group had more IAD patients (45.2% *vs.* 17%) and a significantly longer median duration of ICI usage (26 *vs.* 9 weeks) than the anti-CTLA-4-induced group, which may account for the huge differences between the two groups.

The IAD and MPHD cases were also analyzed, and we found that the IAD patients had a significantly lower rate of emergency admission (13.5% *vs.* 26.7%; P=0.034) and hyponatremia (38.8% *vs.* 69.9%; P=0.000) than their MPHD counterparts, which is consistent with the findings of previous research that IAD patients have less obvious clinical and radiological signs (14). These findings may help to exclude the contribution of higher IAD rates in the anti-PD-1 group to the differences in clinical characteristics between cases of anti-PD-1- and anti-CTLA-4-induced secondary AIs. We speculate that there are three potential reasons for this phenomenon: (I) the significantly longer exposure time of PD-1 group to ICI therapy may lead to toxic accumulation; (II) the significantly prolonged latency period before symptom onset may indicate a less aggressive course of disease, which may lead to an ignorance of symptoms at first onset for patients and physicians; and (III) there may be different mechanisms between the anti-PD-1 and anti-CTLA-4 drugs affecting the endocrine organs, which warrants further exploration. Regardless of the reason for this discrepancy, these results remind us of the diverse safety profile of different ICI drugs and the need to pay attention to AI events during ICI treatment, especially given the long period from ICI initiation to symptom onset (median: 17 weeks for primary AI, and 15 weeks for secondary AI), and especially in patients receiving anti-PD-1 treatment (median: 24 weeks).

In addition, we found that over 30% of cases in both the anti-PD-1- and anti-CTLA-4-induced groups developed AI over 1 month after the last dose of ICI treatment, and 6 cases experienced AI events for as long as 6–15 months (17-22) after the last administration. Such findings warrant the long-term follow-up of patients who received ICI treatment even after the discontinuation of ICI treatment with an emphasis on AI events.

All the patients were treated with glucocorticoids for AI and their symptoms quickly improved; however, about 25% of all patients discontinued the use of ICIs due to a consistent deficiency in ACTH or the potential risk of the recurrence or exaggeration of symptoms, and this rate was consistent across the different subgroups.

Distinguishing the different types of AI, in addition to the differences in clinical symptoms described above, a combination of laboratory tests and imaging features also provide the basis for diagnosis. The release of cortisol is pulsatile and has a distinct circadian rhythm, with a peak around 8 a.m. and a trough at 23–24 p.m. (12). The ACTH stimulation test, paired with morning cortisol levels, can therefore be used to differentiate the diagnosis of primary AI and hypophysitis; in patients with confirmed cortisol deficiency, elevated ACTH levels suggest primary AI, while low ACTH levels suggest secondary AI (9). Furthermore, in primary AI, there may be significant hyponatremia and hyperkalemia; In secondary AI, low or inappropriately normal TSH levels and low free thyroxine (FT4) levels may also be observed, and enlargement or enhancement of the pituitary region on MRI of the brain may also provide important information for the diagnosis of secondary AI (23). In conclusion, follow-up monitoring of possible clinical signs, laboratory tests and imaging assessments in immunotherapy is essential for the prevention and early recognition of AI, and timely discontinuation of immunotherapy or steroid replacement therapy can reduce the serious consequences of AI.

In this study, we conducted an exhaustive literature review and undertook comprehensive data collection and analysis; however, this study also has its limitations, including that it is retrospective nature, and that not all parameters of interest were available for every patient. An additional limitation to be considered by the reader is the potential risk of selection bias in the study sample, as not all cases were reported in academic journals.

In conclusion, we focused on AI by searching the most recent publications and clinical trial reports and conducted a large sample case series analysis of ICI-induced AI cases, with a sample size that allowed us to conduct a detailed analysis. The results effectively revealed the heterogeneity of ICI-induced AI cases. Attention should be paid to potential AI events in patients receiving ICI treatment.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-7006/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-7006/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

Search strategy for PubMed

#1

("nivolumab"[MeSH] OR nivolumab*[tw] OR "opdivo"[tiab] OR "ono-4538"[tiab] OR "ono 4538"[tiab] OR "ono4538" [tiab] OR "mdx-1106"[tiab] OR "mdx 1106"[tiab] OR "mdx1106"[tiab] OR "bms-936558"[tiab] OR "bms 936558"[tiab] OR "bms936558"[tiab] OR "pembrolizumab" [Supplementary Concept] OR pembrolizumab*[tw] OR "sch-900475"[tiab] OR "keytruda" [tiab] OR "mk-3475" OR lambrolizumab*[tiab] OR "atezolizumab"[Supplementary Concept] OR atezolizumab*[tw] OR "mpdl3280a"[tiab] OR "mpdl-3280a"[tiab] OR "tecentriq"[tiab] OR "rg7446"[tiab] OR "rg-7446"[tiab] OR "durvalumab" [Supplementary Concept] OR durvalumab*[tw] OR "medi4736"[tiab] OR "medi-4736"[tiab] OR "imfinzi"[tiab] OR "ipilimumab"[MeSH] OR ipilimumab*[tw] OR "yervoy"[tiab] OR "mdx 010"[tiab] OR "mdx010"[tiab] OR "mdx-010"[tiab] OR "mdx-ctla-4"[tiab] OR "mdx ctla 4"[tiab] OR "tremelimumab"[Supplementary Concept] OR tremelimumab*[tw] OR "ticilimumab"[tiab] OR "cp 675"[tiab] OR "cp675 cpd"[tiab] OR "cp-675"[tiab] OR "cp-675,206"[tiab] OR "cp-675206"[tiab] OR "cp675206"[tiab] OR "cp 675206"[tiab] OR "avelumab"[Supplementary Concept] OR avelumab*[tw] OR "bavencio"[tiab] OR "msb-0010682"[tiab] OR "msb0010682"[tiab] OR "msb0010718c"[tiab] OR "msb-0010718c"[tiab] OR "cemiplimab"[Supplementary Concept] OR cemiplimab*[tw] OR "cemiplimab-rwlc"[tiab] OR "regn2810"[tiab] OR "libtayo"[tw] OR "toripalimab"[Supplementary Concept] OR toripalimab*[tw] OR "js001"[tiab] OR "camrelizumab"[Supplementary Concept] OR camrelizumab*[tw] OR "shr-1210"[tiab] OR "shr 1210"[tiab] OR "sintilimab"[Supplementary Concept] OR sintilimab*[tw] OR "ibi 308"[tiab] OR "ibi308"[tiab] OR "ibi-308"[tiab] OR "tislelizumab"[Supplementary Concept] OR tislelizumab*[tw] OR "bgb-a317"[tiab] OR immune checkpoint inhibitor*[tiab] OR immune check-point inhibitor*[tiab])

#2

("adrenal insufficiency"[MeSH] OR "adrenal insufficiencies"[tiab] OR "hypoadrenalism"[tiab] OR "adrenal gland hypofunction"[tiab] OR "hypofunction, adrenal gland"[tiab] OR "hypopituitarism"[tiab] OR "panhypopituitarism"[tiab] OR "hypophysitis"[tiab] OR "hypophysitides"[tiab] OR "adrenalitis"[tiab] OR "autoimmunity"[tiab] OR isolated ACTH syndrome*[tiab] OR isolated adrenocorticotropic hormone (ACTH) syndrome*[tiab] OR (("adrenal"[tiab] OR "adrenocortical"[tiab] OR "pituitary"[tiab] OR "pituitary gland"[tiab]) AND (insufficienc*[tiab] OR disturbanc*[tiab] OR disorder*[tiab] OR abnormal*[tiab] OR dysfunction*[tiab] OR hypofunction*[tiab] OR toxicit*[tiab] OR complication*[tiab] OR deficienc*[tiab] OR failure*[tiab] OR side-effect*[tiab] OR sideeffect*[tiab] OR side effect*[tiab] OR adverse event*[tiab] OR adverse effect*[tiab])))

#3

#1 AND #2

Appendix 2

Search strategy for Embase

#1

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https://dx.doi.org/10.21037/atm-21-7006

#2

('adrenal insufficiency' OR 'adrenal insufficiencies':ti,ab OR 'hypoadrenalism':ti,ab OR 'adrenal gland hypofunction':ti,ab OR 'hypofunction, adrenal gland':ti,ab OR 'hypopituitarism':ti,ab OR 'panhypopituitarism':ti,ab OR 'hypophysitis':ti,ab OR 'hypophysitides':ti,ab OR 'adrenalitis':ti,ab OR 'autoimmunity':ti,ab OR isolated ACTH syndrome*:ti,ab OR isolated adrenocorticotropic hormone (ACTH) syndrome*:ti,ab OR (('adrenal':ti,ab OR 'adrenocortical':ti,ab OR 'pituitary':ti,ab OR 'pituitary gland':ti,ab) AND ('insufficienc*':ti,ab OR 'disturbanc*':ti,ab OR 'disorder*':ti,ab OR 'abnormal*':ti,ab OR 'dysfunction*':ti,ab OR 'hypofunction*':ti,ab OR 'toxicit*':ti,ab OR 'complication*':ti,ab OR 'deficienc*':ti,ab OR 'failure*':ti,ab OR 'side-effect*':ti,ab OR 'sideeffect*':ti,ab OR 'side effect*':ti,ab OR 'adverse event*':ti,ab OR 'adverse effect*':ti,ab)))

#3

#1 AND #2

Appendix 3

Search strategy for Web of Science

#1

(TS=('nivolumab*' OR 'opdivo' OR 'ono-4538' OR 'ono 4538' OR 'ono4538' OR 'mdx-1106' OR 'mdx 1106' OR 'mdx1106' OR 'bms-936558' OR 'bms 936558' OR 'bms936558' OR 'pembrolizumab*' OR 'sch-900475' OR 'sch 900475' OR 'sch900475' OR 'keytruda' OR 'mk-3475' OR 'mk3475' OR 'mk 3475' OR 'lambrolizumab*' OR 'atezolizumab*' OR 'mpdl3280a' OR 'mpdl-3280a' OR 'tecentriq' OR 'rg7446' OR 'rg-7446' OR 'durvalumab' OR durvalumab* OR 'medi4736' OR 'medi-4736' OR 'imfinzi' OR 'ipilimumab*' OR 'yervoy' OR 'mdx 010' OR 'mdx010' OR 'mdx-010' OR 'mdx-ctla-4' OR 'mdx ctla 4' OR 'tremelimumab*' OR 'ticilimumab*' OR 'cp 675' OR 'cp675 cpd' OR 'cp-675' OR 'cp-675,206' OR 'cp-675206' OR 'cp675206' OR 'cp 675206' OR 'avelumab*' OR 'bavencio' OR 'msb-0010682' OR 'msb0010682' OR 'msb0010718c' OR 'msb-0010718c' OR 'cemiplimab*' OR 'cemiplimab-rwlc' OR 'regn2810' OR 'libtayo' OR 'toripalimab*' OR 'js001' OR 'camrelizumab*' OR 'shr-1210' OR 'shr 1210' OR 'sintilimab*' OR 'ibi 308' OR 'ibi308' OR 'ibi-308' OR 'tislelizumab*' OR 'bgb-a317' OR 'immune checkpoint inhibitor*' OR 'immune checkpoint inhibitor*'))

#2

(TS=('adrenal insufficiency' OR 'adrenal insufficiencies' OR 'hypoadrenalism' OR 'adrenal gland hypofunction' OR 'hypofunction, adrenal gland' OR 'hypopituitarism' OR 'panhypopituitarism' OR 'hypophysitis' OR 'hypophysitides' OR 'adrenalitis' OR 'autoimmunity' OR isolated ACTH syndrome* OR isolated adrenocorticotropic hormone (ACTH) syndrome* OR (('adrenal' OR 'adrenocortical' OR 'pituitary' OR 'pituitary gland') AND ('insufficienc*' OR 'disturbanc*' OR 'disorder*' OR 'abnormal*' OR 'dysfunction*' OR 'hypofunction*' OR 'toxicit*' OR 'complication*' OR 'deficienc*' OR 'failure*' OR 'side-effect*' OR 'sideeffect*' OR 'side effect*' OR 'adverse event*' OR 'adverse effect*'))))

#3

#1 AND #2

Appendix 4

Search stradegy for Cochrane

#1

(nivolumab* OR opdivo OR ono NEXT 4538 OR ono4538 OR mdx NEXT 1106 OR mdx1106 OR bms NEXT 936558 OR bms936558 OR pembrolizumab* OR sch NEXT 900475 OR sch900475 OR keytruda OR mk NEXT 3475 OR mk3475 OR lambrolizumab* OR atezolizumab* OR mpdl3280a OR mpdl NEXT 3280a OR tecentriq OR rg7446 OR rg NEXT 7446 OR durvalumab* OR medi4736 OR medi NEXT 4736 OR imfinzi OR ipilimumab* OR yervoy OR mdx NEXT 010 OR mdx010 OR mdx NEXT 010 OR mdx NEXT ctla NEXT 4 OR tremelimumab* OR ticilimumab OR cp NEXT 675 OR cp675 OR cp NEXT 675 OR cp NEXT 675 NEXT 206 OR cp NEXT 675206 OR cp675206 OR avelumab* OR bavencio OR msb NEXT 0010682 OR msb0010682 OR msb0010718c OR msb NEXT 0010718c OR cemiplimab* OR cemiplimab NEXT rwlc OR regn2810 OR libtayo OR toripalimab* OR js001 OR camrelizumab* OR shr NEXT 1210 OR sintilimab* OR ibi NEXT 308 OR ibi308 OR tisleli-

https://dx.doi.org/10.21037/atm-21-7006

zumab* OR bgb NEXT a317 OR immune NEXT checkpoint NEXT inhibitor*):ti,ab

#2

(adrenal NEXT insufficiency OR adrenal NEXT insufficiencies OR hypoadrenalism OR adrenal NEXT gland NEXT hypofunction OR hypopituitarism OR panhypopituitarism OR hypophysitis OR hypophysitides OR adrenalitis OR autoimmunity OR isolated NEXT ACTH NEXT syndrome* OR isolated NEXT adrenocorticotropic NEXT hormone NEXT (ACTH) NEXT syndrome* OR ACTH OR ((adrenal OR adrenocortical OR pituitary OR pituitary gland) AND (insufficienc* OR disturbanc* OR disorder* OR abnormal* OR dysfunction* OR hypofunction* OR toxicit* OR complication* OR deficienc* OR failure* OR side-effect* OR sideeffect* OR side effect* OR adverse event* OR adverse effect*))):ti,ab

#3

#1 AND #2

https://dx.doi.org/10.21037/atm-21-7006

Table S1 Details of symptoms across different groups

Symptoms	Primary AI cases (n=11)	IAD (n=108)	MPHD (n=83)	Total	P value
Fatigue	10	73	48	131	0.066
Anorexia/loss of appetite	3	59	18	80	0
Headache	1	11	52	64	0
Nausea/vomiting	6	30	18	54	0.064
Weakness	3	14	4	21	0.032
Drowsiness/lethargy	2	6	9	17	0.208
Weight loss	2	9	6	17	0.469
Lightheadedness/dizziness	2	5	7	14	0.189
Malaise	1	8	3	12	0.493
Muscle pain	0	7	4	11	0.631
Diarrhea	2	5	3	10	0.109
Joint pain	5	4	1	10	0
Confused/disorientation	3	5	1	9	0
Decreased libido	0	1	6	7	0.05
Abdominal pain	1	4	1	6	0.283
Walking difficulties due to fatigue/ weakness/malaise	0	5	1	6	0.322
Shortness of breath	1	2	2	5	0.338
Memory impartment	0	3	1	4	0.659
Syncope	0	2	2	4	0.856
Consciousness disturbance	0	3	0	3	0.266
Gait instability	0	1	2	3	0.644
Depression	0	2	0	2	0.415
Insomnia	0	1	1	2	0.926
Postprandial fullness/abdominal bloating	0	1	1	2	0.926
Dysphagia	0	1	1	2	0.926
Photosensitivity	0	0	2	2	0.238
Hot flushes	0	0	2	2	0.238
Cold sensation	1	1	0	2	0.017

AI, adrenal insufficiency; IAD, isolated ACTH insufficiency; ACTH, adrenocorticotropic hormone; MPHD, multiple pituitary hormone deficiency.

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