

# Immune Checkpoint Inhibitor-Associated Primary Adrenal Insufficiency: WHO VigiBase Report Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

**Key Words.** Endocrine toxicity • Immune checkpoint inhibitors • Immune-related adverse events • Immunotherapy • Primary adrenal insufficiency

## ABSTRACT

**Background.** Immune checkpoint inhibitors (ICIs) have transformed cancer therapy but may also trigger autoimmune adverse drug reactions (ADRs) referred to as immune-related adverse events (irAEs). Although endocrinopathies are among the most common form of irAEs, primary adrenal insufficiency (PAI) is infrequent and has only been published in case reports. The aim of this study was to identify and characterize the main features of PAI-irAE.

**Materials and Methods.** Suspected PAI-irAE cases were identified using VigiBase, the World Health Organization's pharmacovigilance database of individual case safety reports.

**Results.** From September 2, 2008, through October 5, 2018, a total of 50,108 ICI-associated ADRs were reported. Since 2008, there were 451 cases of PAI-irAE identified of which 45 were "definite PAI" and 406 "possible PAI." Patients were mainly male (58.1%) with a median age of 66 years (range, 30–95). Indications of ICI were predominantly for melanoma (41.2%)

and lung cancer (28.6%). The majority of patients were treated with ICI monotherapy (nivolumab: 44.3%, pembrolizumab: 11.7%, ipilimumab: 23.6%), and 17.9% were treated with ICI combination therapy. These events occurred with a median time to onset of 120 days (range, 6–576). ICI-associated PAI was associated with significant morbidity ( $\geq 90\%$  severe) and mortality (7.3%). Fatality rates were similar in the subgroups of combination therapy versus monotherapy. There were no relevant differences in clinical or demographical characteristics and outcomes between "definite" versus "possible" PAI group.

**Conclusion.** Our study represents the largest clinical description and characterization of PAI-irAE. Although ICI-associated PAI is a rare adverse event, early recognition is important to implement corticosteroid treatment. Further studies are required to elucidate risk factors and reversibility of this rare but severe irAE. *Clinical trial identification number.* NCT03492242 *The Oncologist* 2020;25:696–701

**Implications for Practice:** Immune checkpoint inhibitor (ICI)-associated primary adrenal insufficiency (PAI) is a rare adverse event that is important to recognize because it may be severe and life-threatening, requiring emergent and often lifelong hormonal replacement therapy. Awareness regarding this ICI-related endocrinopathy is strongly encouraged among clinicians in addition to patient education about common PAI symptoms that should prompt urgent medical evaluation. In clinical practice, close monitoring and investigation for PAI is crucial to allow for early management and to further define the pathophysiology and prognosis of ICI-PAI. Corticotrophin (adrenocorticotrophic hormone) circulating level evaluation may be often lacking but should be considered as part of the diagnostic workup to differentiate PAI from secondary (central) adrenal insufficiency.

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## INTRODUCTION

Over the last decade, immune checkpoint inhibitors (ICIs) have demonstrated durable antitumor activity in subgroups of patients with cancer, significantly improving patient survival. ICIs are antibodies that prevent the interaction of immune checkpoints, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1), allowing for T-cell activation and antitumor activity [1, 2].

ICIs include PD-1 inhibitors (anti-PD-1 antibodies: nivolumab, pembrolizumab, cemiplimab), programmed cell death-ligand 1 (PD-L1) inhibitors (anti-PD-L1 antibodies: atezolizumab, avelumab, durvalumab), and CTLA-4 inhibitors (anti-CTLA-4 antibodies: ipilimumab, tremelimumab) [3]. ICI combination therapy such as ipilimumab and nivolumab has demonstrated efficacy in a growing number of cancers [4]. However, ICIs have been shown to trigger autoimmune-like manifestations in cutaneous, gastrointestinal, endocrine, hepatic, cardiovascular, neurologic, and renal organ systems, which are termed immune-related adverse events (irAEs). The increase use of ICI has led to an increase of reported irAEs, highlighting the need for close monitoring of patients during therapy and accurate recognition of toxicities.

Endocrine immune-related adverse events are among the most common irAEs that have been reported in clinical trials and postmarketing settings with ICI, which include hypothyroidism, hyperthyroidism, hypophysitis, primary adrenal insufficiency (PAI), and insulin-deficient diabetes mellitus [1, 5, 6]. PAI is a rare but potentially serious event that can be life-threatening if diagnosis is delayed. Unlike thyroid or pituitary dysfunction, PAI is less well-known in the immunotherapy context [7]. A few oncologic series have reported adrenal insufficiency (AI) rates of less than 1% in monotherapy and 4%–8% in combination therapy, but often without any specific description regarding the primary cause of AI. Indeed, AI can be related to central AI caused by hypophysitis or alternatively by abrupt withdrawal of glucocorticoid therapy [8]. Currently there are only six cases to date that have identified and adequately described the primary cause of AI [9–14]. Because of the significant lack of supporting studies and the rarity of case reports, only limited data are available describing the incidence and characterization of PAI-irAE, timing between onset of ICI therapy and irAEs occurrence, or types and doses of ICI involved. As such, the objective of our study was to further characterize PAI-irAE using VigiBase, the World Health Organization's (WHO) global database of individual case safety reports (ICSRs) [15].

## MATERIALS AND METHODS

### Pharmacovigilance Study Design and Data Sources

The study is a descriptive analysis based on adverse drug reactions reported within VigiBase, the WHO global deduplicated ICSR database, originating from more than 130 countries [15]. VigiBase is managed by Uppsala Monitoring Center and contains more than 16 million ICSR submitted by national pharmacovigilance centers since 1967. These reports originate from different sources such as health care professionals, patients, and pharmaceutical companies and are generally provided postmarketing. The use of confidential electronically

processed patient data was approved by the French National Commission for Data Protection and Liberties (Commission Nationale de l'Informatique et des Libertés; reference: 1922081). This work is part of NCT03492242 [16–19].

### Procedures

We performed a search for severe adverse events associated with anti-CTLA-4 (ipilimumab, tremelimumab), anti-PD-1 (nivolumab, pembrolizumab), and anti-PD-L1 (atezolizumab, durvalumab, avelumab) and their combinations. We searched all adrenal insufficiency-irAE (AI-irAE) according to the Medical Dictionary for Drug Regulatory Activities (MedDRA): “adrenal cortical hypofunction,” between November 14, 1967, and October 5, 2018. Cases were first identified by the following MedDRA terms: “secondary adrenocortical insufficiency,” “adrenocorticotrophic hormone deficiency,” “hypophysitis,” “blood corticotrophin decreased,” “hypopituitarism,” and “hypothalamo-pituitary disorder,” and their combinations were excluded from our study. Then, only PAIs that were defined by the MedDRA terms “adrenal insufficiency,” “adrenal suppression,” “Addison's disease,” “adrenocortical insufficiency acute,” “adrenal disorder,” “adrenal crisis,” and “adrenitis” were included in the study. Finally, cases were excluded from analysis if there was uncertainty regarding the origin of AI. PAI-irAEs specifically considered in the analysis were those suspected to be induced by ICI.

As this was a descriptive pharmacovigilance database study, clinical and biological evidences for PAI diagnosis were not similar among all ICSR. Therefore, we defined two groups of PAI according to the medical data available: (A) definite PAI and (B) possible PAI. The specific MedDRA terms used for discrimination of these two latter groups are detailed in supplemental online Table 1.

We collected demographic and clinical data including sex, age, cancer type, reporting region, immunotherapy agents administered, time to onset of PAI, concurrent irAEs, fatal outcomes, and year of toxicity reporting. A severe adverse event was defined as an outcome of death, being life-threatening, requiring hospitalization (initial or prolonged), leading to persistent or significant disability or incapacitation, or leading to any other medically important conditions. Of note, the first reports of ICSR associated with ICI started in 2008.

### Statistical Analysis

Characteristics of cases were described in terms of means ( $\pm$  SD) or medians (with range max) for quantitative variables, and in terms of effective and proportion for qualitative ones. To compare proportions, chi-square and Fischer's exact tests were calculated according to the sample size. We used GraphPad Prism 6 software for statistical analysis.

## RESULTS

### Selection of Population

From September 2, 2008, through October 5, 2018, there were 50,108 adverse events reported with immunotherapy in VigiBase. Of these, 54.4% occurred in men. We identified

**Table 1.** Clinical characteristics of patients with ICI-associated primary adrenal insufficiency (*n* = 451) collected from VigiBase (last accessed October 2018)

Characteristics	<i>n</i> (%)
Reporting region	
Americas	211 (46.8)
Europe	116 (25.7)
Australia	8 (1.8)
Asia	116 (25.7)
Reporters	
Health care professional	364 (80.7)
Non-health care professional	59 (13.1)
Unspecified	28 (6.2)
Reporting year	
2018	169 (37.5)
2017	147 (32.6)
2016	53 (11.7)
2015	51 (11.3)
2014	13 (2.9)
≤2013	18 (4.0)
Sex	
Female	162 (35.9)
Male	262 (58.1)
Unspecified	27 (6.0)
Age at onset ( <i>n</i> = 369), median (range max), years	66 (30–95)
Indication of ICI	
Skin cancer	186 (41.2)
Lung cancer	129 (28.6)
Renal cancer	31 (6.9)
Gastrointestinal cancer	6 (1.3)
Ovarian cancer	2 (0.4)
Bladder cancer	3 (0.7)
Pancreatic carcinoma	2 (0.4)
Breast cancer	3 (0.7)
Endometrial cancer	3 (0.7)
Myeloma	3 (0.7)
Glioblastoma	2 (0.4)
Hepatocellular cancer	1 (0.2)
Pleural cancer	3 (0.7)
Vulvar cancer	2 (0.4)
Prostate cancer	1 (0.2)
Testis cancer	1 (0.2)
Hodgkin's disease	1 (0.2)
Neoplasm of unknown sites	19 (4.2)
Data unspecified	53 (11.7)

Abbreviation: ICI, immune checkpoint inhibitor.

671 ICSRs of AI by using the high-level MedRA term “adrenal cortical hypofunctions.” We refined our search, which resulted in the exclusion of 84 ICSRs of corticotrophin deficiency and 136 ICSRs with a possible involvement of a central origin for

**Table 2.** Drugs involved in and outcomes of ICI therapies inducing primary adrenal insufficiency

Drug characteristics and outcomes	<i>n</i> (%)
Suspected drugs	
Only ICI	398 (88.2)
ICI plus one other drug	44 (9.8)
ICI plus two or more other drugs	9 (2.0)
Drugs	
Monotherapy anti-PD-1 or anti-PD-L1	264 (58.5)
Nivolumab	200 (44.3)
Pembrolizumab	53 (11.7)
Atezolizumab	7 (1.6)
Durvalumab	3 (0.7)
Avelumab	1 (0.2)
Monotherapy anti-CTLA-4 (ipilimumab)	106 (23.6)
Combination therapy	81 (17.9)
Nivolumab + ipilimumab	75 (16.6)
Pembrolizumab + ipilimumab	5 (1.1)
Tremelimumab + durvalumab	1 (0.2)
Time to irAE onset ( <i>n</i> = 120), median (range max), days	120 (6–576)
Drug dosing	
Nivolumab	
1–2 mg/kg	54/197 (27.4)
≥3 mg/kg	143/197 (72.6)
Pembrolizumab	
≤2 mg/kg	12/31 (38.7)
>2 mg/kg	19/31 (61.3)
Ipilimumab	
<5 mg/kg	92/121 (76.0)
>5 mg/kg	29/121 (24.0)
Severe adverse event	411 (91.1)
Death	33 (7.3)
Malignant neoplasm progression	21 (4.7)
Number of patients without concurrent irAE	216 (47.9)
Characterization of concurrent irAE	
Endocrine disorders	32 (13.4)
Diabetes	8 (3.4)
Thyroid disorder (hypo, 11; hyper, 7; unknown, 1)	19 (8.0)
Hypercalcemia	1 (0.4)
Lung toxicity	22 (9.2)
Neurotoxicity	17 (7.1)
Nephrotoxicity	18 (7.6)
Cardiotoxicity	17 (7.1)
Liver toxicity	12 (5.0)
Cutaneous toxicity	10 (4.2)
Gastrotoxicity	6 (2.5)
Osteo-muscular toxicity	6 (2.5)
Hematotoxicity	6 (2.5)
Ocular toxicity	5 (2.1)
Other	57 (23.9)

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1.

the AI. A total of 451 PAI-irAEs were identified with a notable marked increase in reporting of PAI-irAEs over this time period. Over 50% of cases were reported since 2017 (Table 1) with 12.25 cases per month in 2017 and 14.1 cases per month in 2018 versus less than 5 cases per month before 2016. Among these 451 ICSRs of PAI, 45 were identified as “definite PAI” and 406 as “possible PAI.”

### Description of Population

Clinical characteristics of patients are presented in Table 1. Approximately half of the ICSRs originated from the Americas, 26% from Europe, and 26% from Asia. Patients with ICI-associated PAI had a median age of 66 years (range, 30–95; data available in 369/451 reports) and were men in 58% of cases. Patients received ICI mainly for melanoma (41.2%, 186/451 ICSRs) or lung cancer (28.6%, 129/451 ICSRs). A majority of patients were treated with ICI monotherapy: 58.5% of the reported ICSRs were on anti-PD-1 or anti-PD-L1 and 23.6% on anti-CTLA-4 (Table 2). Only 18% of ICSRs with ICI-associated PAI had received combination ICI therapy. ICIs were the only suspected drug of PAI-irAEs in 88.2% of the cases (Table 2). Time to onset was available in 120 ICSRs. In these ICSRs, the median time of PAI onset was 120 days (range, 6–576; Table 2). Concurrent irAEs occurred in 235 affected ICSRs and included 32 endocrinologic toxicity reports (Table 2). PAI-irAEs were associated with at least one other concomitant irAE in 52.1% of ICSRs. Endocrine irAEs other than PAI represented 14.9% of reported irAEs.

In our analysis, severe complications, defined by life threatening, prolonged hospitalization, or physical disability, were observed in more than 90% of the ICSRs (Table 2). ICI-associated PAI resulted in significant morbidity and mortality with death in 7.3% of ICSRs. The mortality rate was not significantly different between combination therapy and monotherapy (3.6% vs. 8.2%,  $p = .24$ ). Moreover, no significant difference of mortality rate was shown between PD-1/PD-L1 and CTLA-4 monotherapies (6.7% vs. 11.8%,  $p = .09$ ). There was no difference between ICSRs identified as “definite” versus “possible” PAI in terms of clinical and demographical characteristics and outcomes, except for the reporting region (supplemental online Tables 2 and 3). Although the percentage of severe adverse events was higher in “definite” PAI group, the mortality rate was similar between the two groups.

### DISCUSSION

Our study represents the largest description and characterization of PAI-irAE to date. ICI-associated PAI is a rare adverse event but is essential to recognize because of the severity necessitating emergent treatment. We noted a dramatic increase of ICI-associated PAI reports during the last years in parallel with the development of new ICIs and increased use of existing ICI therapeutics [20]. The frequency and the mechanism of PAI in this context, however, are still unknown.

In our study, we found that PAI-irAE affected a distinct gender and age distribution compared with autoimmune

AI [21]. Indeed, 58% of our patients were men, and the diagnosis was reported during the seventh decade. Only six cases of ICI-associated PAI were reported in literature: three men and two women (one unspecified sex) who were younger than our population (age 52 years; range, 43–56) [9–14]. In Europe, the prevalence of peripheral AI is estimated from 82 to 144 per million, and the most frequent etiology in adults is autoimmune AI (formerly called Addison’s disease), which is estimated at 4.4 to 6.0 per million per year [22]. Autoimmune AI typically occurs more in women than men (between 54% and 83% according to the studies) with a peak incidence between 30 to 50 years of age. The larger proportion of men in this context of ICI-associated PAI could be explained by the indication of ICI use, in particular lung and kidney cancer, which affect men more than women [23, 24]. Similarly, the proportion of men diagnosed with melanoma has been steadily increasing.

Another interesting outcome of this study was the large range (6 to 576 days) with a median time of 4 months to onset of PAI. This result is consistent with the six reported cases of PAI-irAE with an important variation of PAI occurrence between 10 and 252 days after first dose administration of ICI. This highlights the importance of remaining vigilant throughout the entire treatment period, especially because clinical symptoms of PAI may be nonspecific. AI should be suspected in the setting of asthenia, nausea, vomiting, and low blood pressure; only more advanced cases present with hyponatremia or hyperkalemia. Moreover, the development of guidelines for monitoring is of primary importance, as PAI is an emergency with high morbidity and mortality rates (7.3% in our study). In the common autoimmune AI, an increased rate of mortality was also observed, likely caused by adrenal crisis, infection, or cardiovascular disease [22].

The pathophysiology of this PAI-irAE is not well defined but is likely mediated by autoimmune activation caused by ICI. In the six published case reports, antiadrenal antibodies were detected in only two patients [11, 12]. On imaging, adrenal atrophy was described in one patient [12] and “adrenitis” in two other reports [9, 10]. In the context of common autoimmune AI, autoantibodies against the adrenal cortex, more specifically anti-21-hydroxylase (21-OH) antibodies, are detected in 83%–88% of cases [20], with increasing prevalence of 90% in the 2 years after diagnosis [25]. However, the absence of antibodies does not exclude an autoimmune origin in PAI-irAE. The adrenocortical failure may not manifest itself until 90% of the cells are destroyed. The rapid time to occurrence of PAI (a few days in some cases) may reflect an enhanced destruction of the adrenal cortex in comparison with autoimmune AI, perhaps via a cytotoxic T-cell-mediated process. In recent years, studies have established that 21-OH was a major T-cell autoantigen in autoimmune AI [26]. Furthermore, single nucleotide polymorphisms associated with increased risk for PAI have been reported in immune-related genes. These genes have been shown to encode proteins that regulate T- and B-cell activation and differentiation [27]. In particular, CTLA-4 polymorphisms as well as PD-L1 polymorphisms are linked to autoimmune endocrinopathies such as PAI [1].



**Table 3.** Differences between primary and secondary adrenal insufficiency: clinical, biological, and radiological evaluation and management

	Primary adrenal insufficiency	Secondary adrenal insufficiency
Clinical symptoms	<p>Hypotension Asthenia, weakness Anorexia, weight loss, Hypoglycemia</p> <p>+ Dehydration Melanoderma Digestive symptoms (nausea, vomiting, pain) Autoimmune context</p>	<p>Pale skin Pituitary tumoral syndrome (headache, visual field loss) Recent corticosteroid use</p>
Biological evaluation	<p>Low cortisol (&lt;5 µg/dL) OR Cosyntropin test (cortisol&lt;18µg/dL; these thresholds should be taken with caution according to the assay kits used)</p> <p>+ Depletion hyponatremia Hyperkalemia High ACTH Presence of anti-21 hydroxylase Ab</p>	<p>+ Dilution hyponatremia Normal kalemia Normal/low ACTH Other pituitary disorders</p>
Radiological evaluation	Adrenal CT scan	Pituitary MRI
Management	<p>Start treatment without waiting for the plasma cortisol results: Glucocorticoid replacement: Hydrocortisone treatment</p> <p>+ After oral hydrocortisone relay mineralocorticoid replacement may be initiated and secondarily adapted by the endocrinologist</p>	
		<p>+ Other pituitary hormonal replacement if necessary</p>

Abbreviations: Ab, antibody; ACTH, adrenocorticotrophic hormone; CT, computed tomography; MRI, magnetic resonance imaging.

However, the destruction of the adrenal cortex and therefore irreversible PAI is not the sole explanation underlying the pathophysiology of PAI-irAEs. An alternative mechanism may involve a phenomenon of “cellular sideration” of the adrenal cortex, and thus it may be a reversible condition. Improved diagnosis of ICI-associated PAI and long-term follow-up of patients are essential for a better understanding of its long-term evolution.

To the best of our knowledge, this study is the largest description of ICI-associated PAI. There are, however, limitations to our study. First, the absolute frequency of adrenal toxicities cannot be assessed because VigiBase does not capture the number of individuals exposed to a given drug. Second, incomplete data in some cases precludes precise characterization of demographic and clinical features. For example, the systematic determination of antiadrenal antibodies status cannot be evaluated. In

addition, VigiBase reporting is voluntary, and thus not all data fields are systematically included, leading to incomplete data points and potential reporting bias. In fact, adrenocorticotrophic hormone (ACTH) level is essential for confirmation of the peripheral origin of PAI, but this data was not available in many reports. Accordingly, we excluded ICSRs with reported conditions such as central AI, hypophysitis, and decreased blood corticotrophin to ensure a better ascertainment of PAI. We also performed a detailed and supplemental analysis of “definite PAI” versus “possible PAI” ICSRs based on the information available, which, in fact, demonstrated no differences between both entities in terms of demographical characteristics and outcomes, except for the reporting region. Of note, definite PAI was much less frequently reported than possible PAI.

Because of the significant impact of PAI on morbidity and mortality, an understanding of the pathophysiology and early recognition is crucial for effective management of this adverse event. As such, the purpose of our study was, first and foremost, to raise clinician awareness of the importance of ICI-associated PAI and, secondly, to characterize this illness in order to enhance our understanding of the disease for more effective treatment of these patients. Thus, in order to help physicians to properly diagnosis and treat this adrenal complication, we believe it essential to underline the key elements for the diagnosis of PAI and its differences from secondary (central) AI (Table 3) [28].

## CONCLUSION

ICI-associated PAI is a rare adverse event that is important to recognize because it may be severe and life-threatening, requiring emergent and often lifelong hormonal replacement therapy. Clinicians are strongly encouraged to be aware of this ICI-related endocrinopathy; however, patient education of common PAI symptoms that should prompt urgent medical evaluation is also emphasized. In clinical practice, it is important to carefully study and monitor for PAI to allow for early management and to further define the pathophysiology and prognosis of ICI-associated PAI. Corticotrophin (ACTH) circulating level evaluation may be often lacking but should be considered as part of the diagnostic workup to differentiate PAI from secondary (central) AI.

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The supplied data from VigiBase was obtained from a variety of sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the Uppsala Monitoring Center or the World Health Organization.

## AUTHOR CONTRIBUTIONS

**Conception/design:** Virginie Grouthier, Bénédicte Lebrun-Vignes, Joe-Elie Salem, Anne Bachelot

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## DISCLOSURES

**Javid J. Moslehi:** Pfizer, Novartis, Bristol-Myers Squibb, Audentes, Nektar, Regeneron, AstraZeneca (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

## REFERENCES

1. Chang LS, Barroso-Sousa R, Tolaney SM et al. Endocrine toxicity of cancer immunotherapy targeting immune checkpoints. *Endocr Rev* 2019; 40:17–65.
2. Castinetti F, Albarel F, Archambeaud F et al. French Endocrine Society Guidance on endocrine side-effects of immunotherapy. *Endocr Relat Cancer* 2019;26:G1–G18
3. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 2018;359: 1350–1355.
4. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol* 2015;33:1974–1982.
5. Wright JJ, Salem JE, Johnson DB et al. Increased reporting of immune checkpoint inhibitor-associated diabetes. *Diabetes Care* 2018;41:e150–e151.
6. Guerrero E, Johnson DB, Bachelot A et al. Immune checkpoint inhibitor-associated hypophysitis -World Health Organisation VigiBase report analysis. *Eur J Cancer* 2019;113:10–13.
7. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: A systematic review and meta-analysis. *JAMA Oncol* 2018;4: 173–182.
8. Haissaguerre M, Hescot S, Bertherat J et al. Expert opinions on adrenal complications in immunotherapy. *Ann Endocrinol* 2018;79: 539–544.
9. Bacanovic S, Burger IA, Stolzmann P et al. Ipilimumab-induced adrenalitis: A Possible pitfall in 18F-FDG-PET/CT. *Clin Nucl Med* 2015;40: e518–e519.
10. Min L, Ibrahim N. Ipilimumab-induced autoimmune adrenalitis. *Lancet Diabetes Endocrinol* 2013;1:e15.
11. Paepegay AC, Lheure C, Ratour C et al. Polyendocrinopathy resulting from pembrolizumab in a patient with a malignant melanoma. *J Endocr Soc* 2017;1:646–649.
12. Hescot S, Haissaguerre M, Pautier P et al. Immunotherapy-induced Addison's disease: A rare, persistent and potentially lethal side-effect. *Eur J Cancer* 2018;97:57–58.
13. Trainer H, Hulse P, Higham CE et al. Hypo-natraemia secondary to nivolumab-induced primary adrenal failure. *Endocrinol Diabetes Metab Case Rep* 2016;2016:16-0108.
14. Akarca FK, Can O, Yalcinli S et al. Nivolumab, a new immunomodulatory drug, a new adverse effect; adrenal crisis. *Turk J Emerg Med* 2017;17: 157–159.
15. Lindquist M. VigiBase, the WHO global ICSR database system: Basic facts. *Drug Inf J* 2008;42: 409–419.
16. Davis EJ, Salem JE, Young A et al. Hematologic complications of immune checkpoint inhibitors. *The Oncologist* 2019;24:584–588.
17. Salem JE, Manouchehri A, Moey M et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: An observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018;19:1579–1589.
18. Anquetil C, Salem JE, Lebrun-Vignes B et al. Immune checkpoint inhibitor-associated myositis. *Circulation* 2018;138:743–745.
19. Wang DY, Salem JE, Cohen JV et al. Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncol* 2018;4:1721–1728.
20. Giblin AV, Thomas JM. Incidence, mortality and survival in cutaneous melanoma. *J Plast Reconstr Aesthetic Surg JPRAS* 2007;60:32–40.
21. Dalin F, Nordling Eriksson G, Dahlqvist P et al. Clinical and immunological characteristics of autoimmune Addison disease: A nationwide Swedish multicenter study. *J Clin Endocrinol Metab* 2017;102:379–389.
22. Chabre O, Goichot B, Zenaty D et al. Group 1. Epidemiology of primary and secondary adrenal insufficiency: Prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. *Ann Endocrinol* 2017;78:490–494.
23. Levi F, Ferlay J, Galeone C et al. The changing pattern of kidney cancer incidence and mortality in Europe. *BJU Int* 2008;101:949–958.
24. Ljungberg B, Campbell SC, Cho HY et al. The epidemiology of renal cell carcinoma. *Eur Urol* 2011;60:615–621.
25. Coco G, Dal Pra C, Presotto F et al. Estimated risk for developing autoimmune Addison's disease in patients with adrenal cortex autoantibodies. *J Clin Endocrinol Metab* 2006;91: 1637–1645.
26. Hellesen A, Bratland E, Husebye ES. Autoimmune Addison's disease - An update on pathogenesis. *Ann Endocrinol* 2018;79:157–163.
27. Mitchell AL, Pearce SHS. Autoimmune Addison disease: pathophysiology and genetic complexity. *Nat Rev Endocrinol* 2012;8:306–316.
28. Reznik Y, Barat P, Bertherat J et al. SFE/SFEDP adrenal insufficiency French consensus: Introduction and handbook. *Ann Endocrinol (Paris)* 2018 Feb;79:1–22.



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