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Letter to the Editor

Immune checkpoint inhibitor–associated hypophysitis—World Health Organisation VigiBase report analysis

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Dear Editor,

Immune checkpoint inhibitors (ICIs) are revolutionary cancer treatments for many malignancies. Their use has dramatically increased and for growing indications. ICIs are monoclonal antibodies that release the brakes of the immune system, enhancing T-lymphocyte responses against neoplasms [1]. They act by blocking checkpoints whose normal function is to inhibit dendritic cell–mediated T-cell activation via cytotoxic T-lymphocyte antigen 4 (CTLA4) or induce T-cell exhaustion via programmed cell death protein 1 (PD1) and programmed cell death ligand 1 (PDL1) [1]. Similarly, there has been increasing recognition in immune-related adverse events (irAEs) related to the drug's mechanism of action by targeting host tissues. Among the endocrine irAEs, hypophysitis has been described; its incidence ranges between <1% and 18.3% and depends on the ICI regimen, cancer indication, diagnostic criteria and severity grading. So far, the largest series have been less than 100 cases [2–4].

To further characterise ICI-associated hypophysitis, we used the World Health Organisation pharmacovigilance database of individual case safety reports (ICSRs), VigiBase (http://www.vigiaccess.org) [5] We searched the Medical Dictionary for Regulatory Activities (MedDRA) preferred term 'hypophysitis' associated with the following drugs: anti-CTLA4 (ipilimumab and tremelimumab), anti-PD1 (nivolumab and pembrolizumab) and anti-PDL1 (atezolizumab, durvalumab and avelumab). This database has already successfully been used to describe the spectrum of cardiovascular diseases and other irAEs on ICI therapy [6–11].

A total of 689 ICSRs of hypophysitis were declared up to November 4, 2018. We observed a dramatic rise in reporting, going from 0.1 cases per month in 2010 to 19.2 cases per month in 2018. This may be explained by the increased use of ICIs and awareness of ICI-associated hypophysitis. Patient characteristics are

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summarised in Table 1. Of the 689 total cases, 409 of 633 (64.6%) occurred in male patients, and the median age was 63 years, ranging from 20 to 88 years. Most cases were reported in European countries (317/689, 46.0%), followed by the Americas (277/689, 40.2%). The most common indications for ICI use were melanoma, lung cancer and renal cancer; 441 of 544 (81.1%), 61 of 544 (11.2%) and 16 of 544 (2.9%), respectively, reflecting the overall use of these medications. Regarding the therapy regimen, ipilimumab monotherapy accounted for more

Table 1
VigiBase analysis—ICI-related hypophysitis.

Characteristics		N (%)	Data availability N (%)
Region			689 (100)
	Africa	1 (0.1)	
	Americas	277 (40.2)	
	Asia	45 (6.5)	
	Europe	317 (46.0)	
	Oceania	49 (7.1)	
Reporting year			689 (100)
	2010–2014	107 (15.5)	
	2015	109 (15.8)	
	2016	101 (14.7)	
	2017	180 (26.1)	
	2018	192 (27.9)	
Gender			633 (91.9)
	Male	409 (64.6)	
Age at onset (years)			478 (69.4)
	Median; range; IQR	63; 20–88; 54–69	
Indications			544 (79.0)
	Melanoma	441 (81.1)	
	Lung cancer	61 (11.2)	
	Renal cancer	16 (2.9)	
	Others[a]	26 (4.8)	
Regimen			689 (100)
Anti-PD1 monotherapy		158 (22.9)	
	Nivolumab	101 (14.7)	
	Pembrolizumab	54 (7.8)	
	Nivolumab–pembrolizumab sequential	3 (0.4)	
Anti-PDL1 monotherapy		10 (1.5)	
	Durvalumab	2 (0.3)	
	Atezolizumab	7 (1.0)	
	Avelumab	1 (0.1)	
Anti-CTLA4 monotherapy	Ipilimumab	396 (57.5)	
Combination therapy	Nivolumab + ipilimumab	125 (18.1)	
Time to onset (days)			173 (25.1)
	Median; range; IQR	76; 2–690; 46–116	
Number of doses before onset			
	Median; range	3; 1–69	
Associated irAEs	Any irAE	321 (46.6)	689 (100)
	Thyroiditis	99/321 (30.8)	
	Enterocolitis	61/321 (19.0)	
	Dermatologic	44/321 (13.7)	
	Pneumonitis	24/321 (7.5)	
	Hepatitis	24/321 (7.5)	
	Diabetes	15/321 (4.7)	
	Arthritis	14/321 (4.4)	
	Ophthalmologic	14/321 (4.4)	
	Nephritis	11/321 (3.4)	
	Pancreatitis	5/321 (1.6)	
	Adrenalitis	3/321 (0.9)	
	Meningitis	3/321 (0.9)	
	Myositis	2/321 (0.6)	
	Myocarditis	2/321 (0.6)	
Seriousness			560 (81.3)
	Fatalities	19 (3.3)	

CTLA4, cytotoxic T-lymphocyte antigen 4; IQR, inter quartile range; PD1, programmed cell death protein 1; PDL1, programmed cell death ligand 1.
[a] Other cancers: bladder (n = 3), digestive tract (n = 5), prostate (n = 4), thyroid (n = 2), haematologic (n = 4), ovarian (n = 4), head and neck (n = 1), neuroendocrine carcinoma of the skin (n = 1), mesothelioma (n = 1) and urothelial (n = 1).

than half of the cases (396/689, 57.5%), followed by nivolumab plus ipilimumab combination therapy (125/689, 18.1%) and nivolumab monotherapy (101/689, 14.7%). These data are in line with previous observations highlighting that hypophysitis is more likely to occur on anti-CTLA4 therapy as compared with anti-PD1 or anti-PDL1 therapy [2,4].

The median time from initial exposure to ICI to hypophysitis diagnosis was 76 days (IQR: 46–116); hypophysitis was most commonly reported after three drug doses (median, 3; range, 1–69). Associated irAEs were observed in 321 of 689 patients (46.6%). By far, the most frequently concomitantly reported irAE (among these 321 ICI hypophysitis cases with concurrent irAE) was thyroiditis which occurred in 30.8% of cases, followed by enterocolitis (19%), dermatologic manifestations (13.7%), pneumonitis (7.5%) and hepatitis (7.5%) (see Table 1). Less frequently (<5%), other concurrent irAEs involved multiple systems, representing the wide spectrum of immune-mediated events associated with ICI use. Of the 560 ICI hypophysitis cases with available data concerning their outcomes, nine (3.3%) were fatal.

In a systematic review and meta-analysis of endocrine dysfunction among patients on ICIs, Barroso-Sousa *et al.* described a cohort of 85 hypophysitis cases reported among 6472 patients exposed. Among the 76 patients with advanced melanoma, 34 (45%) presented grade 3 or higher hypophysitis according to the Common Terminology Criteria for Adverse Events grading system. The incidence of hypophysitis was higher with combination therapy (6.4%) as compared with any monotherapy (3.2%, 0.4% and <0.2%; for anti-CTLA4, anti-PD1 and anti-PDL1, respectively) [4]. Occurrence of hypophysitis appeared to be favoured in anti-CTLA4 compared with anti-PD1/anti-PDL1 and to be a favourable marker in terms of survival [4,12,13]. Iwama *et al.* suggested that the anti-CTLA4 association with hypophysitis was possibly a surrogate of an on-target effect of these drugs because of pituitary expression of CTLA4 [14]. Thus, the association of hypophysitis with anti-PD1/anti-PDL1 monotherapy in ~25% of our case series suggests that mechanisms might be more complex.

In the general population, hypophysitis is an extremely rare disease with an annual incidence of one in nine million [15]. Very few medications other than ICIs have been associated with drug-induced hypophysitis; examples include interferon alfa which was only a concomitant treatment in one patient of our series [16]. Considering that ICI indications have substantially expanded, clinicians across disciplines should be aware of this new aetiology of hypophysitis. Although this entity was largely restricted to patients with melanoma (given that ipilimumab was approved only in this disease), the recent approvals for ipilimumab and nivolumab in combination for both melanoma and renal cell carcinoma suggest that hypophysitis will be more frequently encountered in clinical practice. Our observations highlight the importance of a high index of suspicion, especially given that hypophysitis is an early irAE occurring, with ipilimumab being the most commonly associated ICI, which is in agreement with previous observations [17].

The inflammation of the pituitary gland results in local compressive effects and systemic hormonal deficiency. Patients present with headaches and less often visual field deficits due to pituitary inflammation or with isolated fatigue or hyponatremia due to low adrenal and thyroid hormone production. Diagnosis includes biochemical panel (8 h cortisol and adrenocorticotropic hormone in the absence of glucocorticoid drug treatment, oestradiol in women, total testosterone in men, luteinising hormone, follicle-stimulating hormone, free thyroxine, thyroid-stimulating hormone, electrolytes and plasma/urine osmolality); as well as radiologic studies preferably by magnetic resonance imaging focussing on the pituitary (assessing for pituitary enhancement or occasionally an empty sella). When diagnosed, treatment depends on clinical severity and hormonal deficit type and does not require ICI cessation [18]. High-dose steroids may be considered for patients with compressive symptoms, although hormone replacement is acceptable. Associated irAEs are relevant concomitant conditions that must be addressed.

Limitations of our work include the nature of the study (pharmacovigilance reports), the fact that these reports do not allow the possibility of being categorical about causality and the incompleteness of all clinical variables. With available information, it may be challenging to attribute outcomes like fatalities to hypophysitis or to disease progression.

Conflict of interest statement

J.J.M. has served on advisory boards at Bristol-Myers, Pfizer, Novartis, Regeneron, Takeda, Decipher and Myokardia and has received research funding from Pfizer and Bristol-Myers Squibb. D.B.J. serves on advisory boards for Array BioPharma, BMS, Genoptix, Incyte and Merck and receives research funding from BMS and Incyte. The other authors have no conflict of interest to disclose.

Disclosures

The supplied data from VigiBase come 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 World Health Organisation (WHO).

References

[1] Johnson DB, Chandra S, Sosman JA. Immune checkpoint inhibitor toxicity in 2018. J Am Med Assoc 2018;320:1702. https://doi.org/10.1001/jama.2018.13995.

[2] Abdel-Rahman O, ElHalawani H, Fouad M. Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis. Future Oncol 2016;12:413–25. https://doi.org/10.2217/fon.15.222.

[3] Iglesias P. Cancer immunotherapy-induced endocrinopathies: clinical behavior and therapeutic approach. Eur J Intern Med 2018;47:6–13. https://doi.org/10.1016/j.ejim.2017.08.019.

[4] Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, 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. https://doi.org/10.1001/jamaoncol.2017.3064.

[5] Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. Drug Inf J 2016;42:409–10. https://doi.org/10.1177/009286150804200501.

[6] Moslehi JJ, Salem J-E, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet 2018;391:933. https://doi.org/10.1016/S0140-6736(18)30533-6.

[7] Wright JJ, Salem J-E, Johnson DB, Lebrun-Vignes B, Stamatouli A, Thomas JW, et al. Increased reporting of immune checkpoint inhibitor–associated diabetes. Diabetes Care 2018;41: e150–1. https://doi.org/10.2337/dc18-1465.

[8] Wang DY, Salem J-E, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis JAMA oncol. 2018. https://doi.org/10.1001/jamaoncol.2018.3923.

[9] Arnaud L, Lebrun-Vignes B, Salem J-E. Checkpoint inhibitor-associated immune arthritis. Ann Rheum Dis 2018 May 3. https://doi.org/10.1136/annrheumdis-2018-213470. annrheumdis-2018-213470 [Epub ahead of print] No abstract available. PMID: 29724725.

[10] Anquetil C, Salem J-E, Lebrun-Vignes B, Johnson DB, Mammen A, Stenzel W, et al. Immune checkpoint inhibitor–associated myositis. Circ 2018;138:743–5. https://doi.org/10.1161/CIRCULATIONAHA.118.035898.

[11] Salem J-E, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018;19: 1579–89. https://doi.org/10.1016/S1470-2045(18)30608-9.

[12] Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, et al. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab 2014;99:4078–85. https://doi.org/10.1210/jc.2014-2306.

[13] Scott ES, Long GV, Guminski A, Clifton-Bligh RJ, Menzies AM, Tsang VH. The spectrum, incidence, kinetics and management of endocrinopathies with immune checkpoint inhibitors for metastatic melanoma. Eur J Endocrinol 2018;178:173–80. https://doi.org/10.1530/EJE-17-0810.

[14] Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med 2014;6. 230ra45-230ra45, https://doi.org/10.1126/scitranslmed.3008002.

[15] Faje A. Hypophysitis: evaluation and management. Clin Diabetes Endocrinol 2016;2:15. https://doi.org/10.1186/s40842-016-0034-8.

[16] Pekic S, Popovic V. Diagnosis of endocrine disease: expanding the cause of hypopituitarism. Eur J Endocrinol 2017;176:R269–82. https://doi.org/10.1530/EJE-16-1065.

[17] Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol 2017;28:2377–85. https://doi.org/10.1093/annonc/mdx286.

[18] Joshi MN, Whitelaw BC, Carroll PV. Mechanisms in endocrinology: hypophysitis: diagnosis and treatment. Eur J Endocrinol 2018;179:R151–63. https://doi.org/10.1530/EJ3E-17-0009.