Immune checkpoint inhibitor-mediated hypophysitis: no place like home

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ABSTRACT

Ambulatory emergency care forms a fundamental part of the strategy of trying to ensure safe and sustainable acute care services. Immune checkpoint inhibitor(ICI)-mediated hypophysitis is an important life-threatening complication of therapy. Patients presenting with clinical features and findings consistent with ICI-mediated hypophysitis were considered in the current study. In the absence of severe features (sodium <125 mmol/L, hypotension, reduced consciousness, hypoglycaemia and/or visual field defect), patients were administered a single intravenous dose of hydrocortisone (100 mg), observed for at least 4 h and then discharged on oral hydrocortisone (20 mg, 10 mg and 10 mg). Patients were then seen urgently in the endocrinology outpatient setting for further management. Fourteen patients (median age 64, 10 male) were managed using the pathway. All patients had biochemically confirmed adrenocorticotropic hormone (ACTH) deficiency. Seven of the 14 were treated with combination ICI therapy, with four having pan-anterior hypopituitarism. There were no 30-day readmissions or any associated hypophysitis-related mortality. All patients continued ICI therapy without interruption.

KEYWORDS: Immunotherapy, immune checkpoint inhibitors, hypophysitis, ambulatory care

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Introduction

Ambulatory emergency care forms a fundamental part of the strategy of trying to ensure safe and sustainable acute care services.[1] Its implementation is founded on the evidence that patients presenting with acute illnesses can be stratified as low risk for developing complications and, therefore, do not require traditional inpatient care.[2] There is a range of emergency oncology presentations that can be managed in this setting, reducing pressures on inpatient services and the increasingly recognised risks of emergency department (ED) overcrowding, which is a growing international problem.[3,4]

Immune-mediated toxicities from immune checkpoint inhibitors (ICIs) stem from increased activity within the T cell lineage. They can affect any organ system with a range of severity from mild to life threatening.[5,6] Hypophysitis and, rarely, adrenalitis are potentially life-threatening complications of treatment.[7,8] ICI-mediated hypophysitis has two distinct patterns of presentation: (1) isolated adrenocorticotropic hormone (ACTH) deficiency in those treated with anti-programmed cell death protein 1 (PD-1) agents; and (2) a lymphocytic hypophysitis-like condition with pituitary enlargement and multiple hormone deficiencies in those treated with anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) agents/combination CTLA-4/PD-1 therapy.[9]

ICI-mediated hypophysitis classically presents with features of cortisol deficiency, but the clinical picture is often more nuanced and is occasionally detected with incidental hypocortisolaemia in a clinic setting.[10] Emergency presentations with ICI-mediated hypophysitis are usually admitted for inpatient care and management. We recently reported a pilot study of managing acute presentations with ICI-mediated hypophysitis in an emergency ambulatory setting.[11] In this paper, we describe further results and experience from this pathway and consider the implications for wider ambulatory emergency management of ICI-mediated toxicities.

Methods

Our ambulatory pathway for ICI-mediated hypophysitis was described in our pilot paper.[11] In short, patients were considered who presented acutely with clinical features, such as marked fatigue and headache, with findings consistent with ICI-mediated hypophysitis, at The Christie, a tertiary cancer/endocrinology hospital in the northwest England. The hospital has an acute assessment unit (AAU) and a co-located acute ambulatory care unit (AACU), which receive emergency patients via several access points, including directly from the hospital patient hotline, primary care, paramedic referrals, outpatient clinics and tertiary referrals from other hospitals.

Starting in September 2019, suitable patients were initially investigated and treated in accordance with the UK emergency management guidelines for ICI-mediated hypophysitis.[12] This

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includes initial clinical assessment, paired ACTH and cortisol levels, thyroid function tests and an initial dose of intravenous hydrocortisone (100 mg). Patients with life-threatening features of hypophysitis, described as severe hyponatraemia (Na^+ <125 mmol/L), hypotension (systolic blood pressure (SBP) <90 mmHg), reduced level of consciousness, hypoglycaemia (<4 mmol/L) or visual field defects, were not considered because these presentations require inpatient care. Patients with a history of exogenous glucocorticoid use were also excluded. Patients with incidental asymptomatic hypocortisolaemia from outpatient clinics started treatment oral hydrocortisone, were referred to the endocrinology clinic and also excluded from this study of acute presentations.

After an initial observation period of at least 4 h, patients were discharged with oral hydrocortisone (20 mg in the morning, 10 mg at lunchtime and 10 mg in the evening) and advice with regards to sick-day rules. All patients had access to a 24-h specialist oncology telephone hotline. They were given clear instructions as to the signs and symptoms that should trigger them to seek medical assessment and re-presentation to the hospital.

Urgent outpatient magnetic resonance imaging (MRI) of the pituitary gland (when there was evidence of more than one pituitary deficiency), completion of anterior pituitary function tests and urgent endocrinology follow-up were arranged on discharge. Patients received a telephone follow-up within 48 h from the acute care team to ensure that they were making good clinical progress.

Patients were reviewed in an endocrinology clinic within 2 weeks of acute presentation. Generally, at the first outpatient endocrinology visit, the dose of hydrocortisone was reduced to a lower physiological replacement dose. During the endocrine clinic appointment, patients received an emergency hydrocortisone pack and were given a national emergency hydrocortisone alert card. Initiation of other hormone replacement therapy was started as indicated.

All acute patients treated with ICI presenting to the AAU and AACU were recorded on a prospective database. Basic demographic details, presenting symptoms, site of primary cancer, the type and cycle of ICI, physiological parameters, biochemical results and MRI pituitary results were collected. The primary outcome measure was 30-day readmission related to hypocortisolaemia. Secondary outcome measures included a delay in the next cycle of ICI therapy and complications related to ICI-mediated hypophysitis.

Results

Fourteen patients were managed on the emergency ambulatory ICI-mediated hypophysitis pathway from September 2019 until June 2022. Each patient had classical symptoms of hypocortisolaemia (Table 1). The median age of patients was 64 years (40–77 years) and 10 of the patients were male. All of the patients were keen to be managed in an ambulatory setting.

Seven patients were receiving combination ICI therapy with ipilimumab and nivolumab and seven patients were receiving single-agent PD-1 therapy. Six of the patients were being treated for melanoma, three for renal cancer, two for non-small cell lung cancer and one patient for colorectal cancer and one for gastric cancer (Table 1). None of the patients had received exogenous steroids before presentation. The patient with hypoglycaemia at presentation had known diabetes and was discharged with continuation of blood glucose monitoring and cessation of their gliclazide therapy.

Each patient was seen in an endocrinology clinic within 2 weeks (median 8 (4–13) days). Five of the seven patients treated with combination ICI therapy were subsequently confirmed to have pan-anterior hypopituitarism, with the other two patients having deficiencies in at least two hormones. Each of the patients treated with single-agent PD-1 therapy had isolated ACTH deficiency driving their hypocortisolaemia.

There were no 30-day readmissions related to hypocortisolaemia. Indeed, there were no 30-day readmissions in the cohort for any reason. None of the patients experienced a delay to their next cycle of ICI therapy. None of the patients died from hypocortisolaemia-related complications. Only two patients in the cohort died (one from progressive gastric carcinoma and one from Coronavirus 2019 (COVID-19); 10 and 5 months post-hypophysitis diagnosis, respectively).

Discussion

Fourteen patients who presented acutely were managed on our ambulatory ICI-mediated hypophysitis pathway with no significant complications, no 30-day readmissions and no delay to subsequent ICI therapy. This included a significant proportion of patients who subsequently were proven to have pan-anterior hypopituitarism as well as those with isolated ACTH deficiency.

Therefore, the focus on clinical severity at presentation with an emphasis on prompt treatment and education allows for the prevention of hospital admission as a routine. The key strength to this approach is the nature of collaborative working to develop innovative clinical pathways.

Early recognition and management of ICI-mediated hypophysitis improve patient outcomes and reduce the risk of subsequent complications. There is increasing evidence that patients treated with physiological doses of glucocorticoids for ICI-mediated hypophysitis have superior oncological outcomes.[9,13] Our pathway facilitates rapid specialist endocrine assessment and, therefore, allows for dose adjustment to reduce the risk of both under- and over-replacement with glucocorticoids.

Ensuring that patients with cancer presenting to the ED have access to ambulatory care will require widening of access and careful modelling of services integrating with oncology care and other key specialties.[14] With the increasing indications for ICI therapy, there will inevitably be an increase in emergency presentations with ICI-mediated toxicities.

It is important to try and identify patients with ICI-mediated toxicities traditionally managed in an inpatient setting who are suitable for ambulatory management to reduce not only the impact on acute services, but also the nosocomial risks to patients, as exemplified by the COVID-19 pandemic. This is particularly pertinent in more common toxicities, such as colitis and hepatitis. This will require collaboration between acute medical, oncology and organ specialists. It is likely that hub-and-spoke models supported by national and regional expert groups will be required to deliver this effectively, with regular evaluation during its initial implementation.[15]

This study is limited by both the low number of patients involved and the ability of the pathway to be replicated in several centres because of a lack of specialist acute, endocrinology and oncological care. The aim should be for implementation alongside

Table 1. Clinical features, biochemical results, radiological findings and management of patients within the study cohort

Cancer disease group	ICI	Cycle	Presenting complaint	Blood pressure (mmHg)	Random blood glucose (mmol/L)	Sodium (mmol/L) (133–146)	Cortisol (nmol/L)	ACTH (ng/L) (5–46)	TSH (mU/L) (0.4–5.0)	Free T4 (pmol/L) (10–22)	MRI scan of the pituitary	Time to OPD endo review (days)
Combination ICI therapy												
Melanoma	Ipi/Nivo	1	Headache	150/80	7.9	138	<50	<5	0.13	9.0	NAD	6
			Headache/fatigue/ postural dizziness	110/70	6.9	132	<50	<5	0.05	10.8	Patient did not tolerate MRI	8
			Headache/fatigue	110/70	3.7	131	<50	<5	9.01	14.1	NAD	8
			Fatigue/nausea/headache	110/70	3.7	131	<50	<5	0.03	15.9	Pituitary inflamed	8
Renal	Ipi/Nivo	4	Headache/fatigue	120/70	6.8	134	<50	<5	<0.02	14.4	NAD	7
		3	Headache/fatigue/blurred vision	140/70	5.3	130	<50	<5	<0.02	19.8	Contra-indicated	4
	Nivo; previously Ipi/Nivo	8	Fatigue/nausea/postural dizziness	110/70	5.5	136	<50	10	7.17	12.3	NAD	13
Single-agent PD-1 therapy												
Colorectal	Nivo	6	Headache/fatigue	140/70	5.8	125	<50	<5	5.61	18.1	NAD	7
	Pem	6	Fatigue	110/70	4.7	139	<50	<5	1.53	15.4	Not done	7
Gastric	Nivo	4	Fatigue	140/75	4.7	133	<50	<5	35.79	5.5	NAD	9
Melanoma	Pem	2	Headache/fatigue	110/70	6	139	<50	<5	2.76	10.7	NAD	8
	Nivo	4	Headache/ fatigue/ postural dizziness	140/70	7.0	141	<50	<5	0.27	16.4	Not tolerated	7
NSCLC	Pem	2	Headache/fatigue	100/60	4.9	129	<50	<5	7.72	15.3	NAD	13
		13	Fatigue/postural dizziness	90/50	2.9	135	<50	6	0.25	19.5	NAD	8

ACTH = adrenocorticotrophic hormone; BP = blood pressure; Endo = endocrinology; ICI = immune checkpoint inhibitor; Ipi = ipilimumab; MRI = magnetic resonance imaging; Nivo = nivolumab; NSCLC = non-small cell lung cancer; OPD = outpatient department; TSH = thyroid-stimulating hormone.

other ambulatory emergency oncology pathways as part of the wider strategy for the delivery of acute oncological care.

Our ambulatory care pathway was utilised successfully to treat patients with ICI-mediated hypophysitis. There were no observable adverse outcomes related to its use and the adoption of this pathway for appropriate patients could lead to reductions in hospital admissions, minimising interruptions to cancer care and enhancing the patient experience. ■

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