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Case Report

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Pembrolizumab related central diabetes insipidus

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Summary

This case report describes a case of anti-programmed cell death protein 1 (PD-1) antibody-related central diabetes insipidus without features of infiltrative process on neuroimaging. It involved a 63-year old man who was initially admitted for immunotherapy-related pneumonitis and was subsequently diagnosed with new central diabetes insipidus on the background of advanced non-small cell lung cancer treated with pembrolizumab. This clinical phenomenon is exceedingly rare and has been reported with anti-cytotoxic T lymphocytes-4 (CTLA-4) agent [1]. Central diabetes insipidus associated with anti-PD-1 monotherapy has only been described in three case reports [2-4]. Neuroimaging plays an important role to identify other process including metastatic infiltration. Multi-disciplinary patient care remains the key in managing patients with immunotherapy-related endocrinopathies.

Keywords: Immunotherapy, Lung Cancer, Endocrinopathy, Diabetes Insipidus

Background

Immunotherapy-related endocrinopathy is a well-recognized entity ranging from thyroid dysfunction to hypophysitis, which is usually associated with anterior pituitary hormonal dysfunction. Posterior pituitary deficiency such as diabetes insipidus is rare and has been reported with anti-CTLA-4 agent. In this case report, we describe a patient who developed anti-PD-1 antibody related central diabetes insipidus following pembrolizumab administration.

Case Presentation

A 63-year-old man presented to hospital with acute dyspnoea preceded by two-week- history of malaise. Two months earlier the patient had been diagnosed with stage IV lung adenocarcinoma (EGFR, ALK wild-type with PD L1 expression >50%) with bilateral frontal cerebral lobe and adrenal metastasis. He had completed whole brain radiation therapy along with tapering dexamethasone 4mg daily and received first cycle of pembrolizumab ten days prior to presentation. Other significant history included osteoarthritis and reformed smoking of twenty pack-years.

On presentation, he was febrile and hypotensive. Physical examination revealed bilateral course crepitations without other infective signs. His presentation was further complicated by type 1 respiratory failure and refractory hypotension despite fluid resuscitation, intravenous corticosteroids. He was subsequently admitted to the intensive care unit for inotropic support.

Investigations

Initial investigations revealed normal inflammatory markers and serum glucose levels (8.8 mmol/L) with mild hyponatremia (134 mmol/L). Chest radiography demonstrated non- specific bilateral peri-bronchial markings. He was treated with empirical intravenous piperacillin/tazobactam, azithromycin and stress dosing corticosteroids for presumed pneumosepsis. CT pulmonary angiography performed two days later showed new bilateral pulmonary opacities suspicious for immunotherapy-related pneumonitis. He was commenced on intravenous methylprednisolone 1mg/kg (three day course) with ongoing piperacillin/tazobactam for infective coverage.

Incidentally, on his third day of admission he was noted to be polyuric (4L/day). Blood results revealed new hypernatremia (153 mmol/L) with a simultaneous serum osmolality of 321 (275-300 mosmol/kg) and urine osmolality of 154 mosmol/kg. In the absence of hyperglycemia (7.6 mmol/L), desmopressin challenge (4mg subcutaneous) was performed, with improvement in urine output, serum sodium (147 mmol/L), serum osmolality (310 mosmol/kg) and urine osmolality (509 mosmol/kg), raising the suspicion of central diabetes insipidus.

Visual field was preserved on examination. Subsequent water deprivation test confirmed the diagnosis (serum sodium 152 mmol/L; serum osmolality 305 mosmol/kg; urine osmolality 89 mosmol/kg) with a positive desmopressin response (serum sodium 139 mmol/L and improvement in urine output from

130ml/hr to 40ml/hr). MRI head/pituitary showed a cystic space within anterior pituitary raising possibility of necrosis with partial treatment response to cerebral metastasis. Importantly, the posterior pituitary bright spot on T1-weighted images was not visible, raising the suspicion of hypophysitis. Anterior pituitary biochemical screen revealed thyroid-stimulating-hormone of 0.29 (0.5-4.5) mIU/L, free T4 of 13 (10-20) pmol/L and free T3 of 2.4 (3.1-5.4) pmol/L, suggesting potential early thyroid dysfunction. Assessment for cortisol deficiency was unreliable due to concurrent glucocorticoids replacement but warrants investigation following recovery from acute illness considering initial presentation withhypotension. Evaluation for other hormonal profile such as prolactin, gonadotropins and insulin-like growth factor 1 were not performed.

Outcome and Follow-Up

Regular desmopressin 200 microg oral twice daily was commenced with resolution in hypernatremia. Unfortunately, his prolonged admission was further complicated by secondary pneumonia and progressive type 1 respiratory failure. Given his poor quality of life and clinical deterioration despite maximal treatment, a shared joint decision was made for best supportive care. He died in the palliative care ward, four weeks into his admission.

Discussion

The emergence of immunotherapy has changed the landscape of medical oncology therapeutics over the last decade and is currently being used widely in cancer treatment. Immune checkpoint blockade increases activity of the immune system, which also leads to inflammatory side effects termed immune-related adverse events [5]. Immunotherapy- related endocrinopathy is a well-recognized entity and has a wide spectrum ranging from thyroid dysfunction, which is more commonly associated with anti-PD-1 monoclonal antibodies, to hypophysitis, which is usually more common with anti-CTLA-4 monoclonal antibodies [5,6].

While anti-CTLA-4 agents such as ipilimumab and combination anti-CTLA-4/ PD-1 therapy were reported to have similar incidence of hypophysitis (9.1% and 8%), combination treatment is associated with a higher incidence of grade 3-4 hypophysitis (12% vs 7%) [6]. It is usually associated with anterior pituitary hormone deficiencies, with adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone deficiency being described as the most common abnormalities [6].

Posterior pituitary deficiency such as diabetes insipidus is uncommon. Current available literature has shown that immunotherapy related central diabetes insipidus is more commonly associated with anti-CTLA-4 agents, either as monotherapy or in combination with anti-PD-1 monoclonal antibody [1]. This clinical phenomenon has also been described with anti-PD-1 or anti PD-L1 monotherapy [1]. Onset of symptoms including polyuria and polydipsia occurred as early as four weeks after commencement of immunotherapy. Interestingly, Yu et al. reported a case of immediate central diabetes insipidus following treatment with sintilimab, an anti-PD-1 agent [4].

Concurrent anterior pituitary dysfunction requiring hormonal replacement is more common with combination anti-CTLA-4 and anti PD-1 therapy [1]. Although isolated central diabetes insipidus is more commonly seen with anti PD-1/PD-L1 monotherapy, simultaneous anterior hormonal dysfunction has been reported. Tshuma et al reported a case of hypothalamitis with severe hypothalamic dysfunction following 12 cycles of atezolizumab, anti-programmed death-ligand 1 (PD-L1) agent [7]. Our patient may have early hypothyroidism but it is otherwise difficult to establish if he had co-existing adrenal insufficiency due to exogenous corticosteroid administration.

MRI of pituitary, in addition to hormonal profile evaluation, is useful to establish diagnosis considering immunotherapy-related posterior pituitary dysfunction is a rare phenomenon [8]. Hypopituitarism in the context of malignancy can occur as a result of metastatic infiltrates of pituitary gland, direct mass effect from adjacent compressive lesion or radiotherapy-induced hypopituitarism [9]. Hypophysitis may appear as an enlargement of pituitary gland with MRI, which may even precede clinical diagnosis of hormonal deficiency [6]. In our case, neuroimaging demonstrated loss of posterior pituitary bright spot on T1-weighted images without infiltrative lesion, raising the suspicion of hypophysitis. Otherwise, majority of the case reports available on literature review reported normal brain MRI with preserved posterior bright spot.

Similar to managing other immunotherapy-related endocrinopathies, multi-disciplinary care including endocrinology consultation is recommended. Hormonal supplementation remains the key component whilst immunotherapy should be held off especially in grade 3-4 toxicities until patient is stabilized on replacement hormones [10]. Interestingly, Zhao et al. described remission of symptoms and biochemical abnormalities of diabetes insipidus despite discontinuation of desmopressin, suggesting potential reversibility of posterior pituitary dysfunction in immunotherapy [9].

Learning Points

1. Immunotherapy-related diabetes insipidus is exceedingly rare but requires high clinical vigilance.
2. Neuroimaging may be used to rule out other pathological process including metastatic infiltration.
3. Multi-disciplinary patient care remains the key in managing patients with immunotherapy-related endocrinopathy.

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