CASE REPORT

Cisplatin-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) with life-threatening hyponatraemia

Aaron C. Tan,¹ Gavin M. Marx²

¹Department of Medical Oncology, Royal North Shore Hospital, St Leonards, New South Wales, Australia

²SAN Integrated Cancer Centre, Sydney Adventist Hospital, Wahroonga, New South Wales, Australia

Correspondence to
Dr Aaron C. Tan,
tan.aaron.c@gmail.com

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SUMMARY

We present a case of cisplatin-induced syndrome of inappropriate antidiuretic hormone (SIADH) in a patient with metastatic recurrent urothelial carcinoma. Cisplatin-induced SIADH is an uncommon but potentially life-threatening toxicity. Pharmacogenetic characteristics may result in different toxicity profiles in different populations. With such widespread use of cisplatin in a diverse range of cancers, prompt recognition is crucial to detect and prevent severe neurological sequelae.

BACKGROUND

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) results in impaired water excretion and consequent water intoxication and hyponatraemia. In patients with cancer, SIADH is most commonly driven by ectopic ADH production, a paraneoplastic syndrome frequently seen in small cell lung cancer.¹ Chemotherapy agents, however, represent an important cause of SIADH, with vinca alkaloids (eg, vincristine and vinblastine) and alkylating agents (eg, cyclophosphamide) most commonly implicated.² Vincristine may result in direct neurological toxicity to the neurohypophysis altering the normal osmoreceptors that control ADH secretion.³ Cyclophosphamide may potentiate the effect of ADH and can be exacerbated by recommendations to have high fluid intake to prevent chemical cystitis.⁴ Cisplatin-induced SIADH is uncommon, and the mechanism of action remains unknown.

CASE PRESENTATION

A male patient, age in 40s, was initially diagnosed with a high-grade papillary urothelial carcinoma. He had no other significant medical history and was an ex-smoker of 30 pack-year history having ceased 2 years prior. He initially presented with left-sided abdominal pain, with a CT scan showing a 26 cm dilated left kidney caused by a large ureteric tumour. This was decompressed via nephrostomy before he underwent an open left nephroureterectomy. Histopathology revealed an 18 cm high-grade papillary urothelial carcinoma, with 0.5 mm of invasion into the wall of the ureter, and none of four lymph nodes was involved (pT2N0). There was no metastatic disease on CT, and he received six cycles of adjuvant chemotherapy with

carboplatin and gemcitabine, which was tolerated well with dose reductions for myelosuppression. A follow-up cystoscopy 5 months post his initial surgery showed evidence of non-muscle invasive low-grade papillary carcinoma. Subsequently, he also received six doses of intravesical BCG. Further cystoscopy showed ongoing carcinoma in situ, and a further six doses of intravesical mitomycin C were administered. He remained under surveillance thereafter with regular cystoscopies that were normal.

Four years following his initial diagnosis, he developed a cough and left-sided chest pain and a CT showed a large left lung mass. A positron emission tomography scan revealed extensive mediastinal and supraclavicular lymphadenopathy and bony metastases. Right supraclavicular lymph node biopsy was consistent with recurrent urothelial carcinoma. Consequently, he commenced chemotherapy with cisplatin and gemcitabine. Two days following his first dose of chemotherapy, he presented with severe nausea, dyspnoea and general fatigue. The nausea had persisted despite regular metoclopramide and ondansetron, and he was administered dexamethasone and cyclizine.

INVESTIGATIONS

His blood results revealed a serum sodium of 109 mmol/L which had dropped from 133 mmol/L prior to his chemotherapy, with normal renal function. He was clinically assessed as euvoletic through physical examination. Serum osmolality was low at 240 mOsm/kg, urine osmolality high at 574 mOsm/kg and urine sodium high at 121 mmol/L, biochemically consistent with SIADH, and he was admitted to the intensive care unit for ongoing management. He was noted to be drowsy but had no other neurological sequelae. Other investigations are shown in [table 1](#). MRI of the brain showed a small cortical focus of enhancement in the right frontal lobe consistent with small metastasis, and atypical small foci of restricted diffusion in the right frontal lobe and left precentral gyrus.

DIFFERENTIAL DIAGNOSIS

His SIADH was considered cisplatin induced, however, may have been influenced by numerous other factors. This includes medication related (as he had 5 days of ibuprofen prior to admission),

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Table 1 Investigation results

Investigation	Value	Normal range
Admission day 1		
Serum sodium (mmol/L)	109	135–145
Serum potassium (mmol/L)	4.2	3.5–5.5
Serum magnesium (mmol/L)	0.79	0.65–1.0
Serum corrected calcium (mmol/L)	2.3	2.15–2.55
Creatinine (μ mol/L)	80	60–110
Serum osmolality (mOsm/kg)	240	275–295
Urine osmolality (mOsm/kg)	574	50–1500
Urine sodium (mmol/L)	121	
Serum glucose (mmol/L)	7.4	3.6–7.8
Total cholesterol (mmol/L)	3.9	3.9–5.5
Triglycerides (mmol/L)	1.4	0.5–1.7
Admission day 3		
Vasopressin level (pmol/L)	6.0	≤ 7.0
Morning cortisol (nmol/L)	407	70–650
TSH (mIU/L)	1.01	0.4–3.5
Aldosterone (pmol/L)	33	48–631
Admission day 5		
DHEAS (μ mol/L)	2.4	3–16
ACTH (pmol/L)	4.9	<12.1

ACTH, adrenocorticotrophic hormone; DHEAS, dehydroepiandrosterone sulfate; TSH, thyroid-stimulating hormone.

malignancy related (with pulmonary and cerebral disease) and renal related (prior nephroureterectomy).

TREATMENT

He was placed on a fluid restriction (600 mL over 24 hours) and started on intravenous hypertonic 3% normal saline. As he was polyuric with a urine output of 300–500 mL/hour and his serum sodium increased to 118 mmol/L after 4 hours, he was given a dose of desmopressin (DDAVP). His sodium gradually increased to 125 mmol/L, however, dropped again to 120 mmol/L once his hypertonic saline was ceased. He was maintained on fluid restriction and started on oral salt tablets and urea, with his serum sodium increasing to 130 mmol/L 10 days after admission and remaining stable thereafter.

OUTCOME AND FOLLOW-UP

Unfortunately he developed complications of pulmonary emboli, and was found to have rapidly progressive disease. He received palliative radiotherapy to a large mediastinal mass, bilateral supraclavicular masses and a sacral mass causing cauda equina syndrome. He received three doses of weekly paclitaxel, however continued to deteriorate and died 6 weeks after admission.

DISCUSSION

Cisplatin has been previously documented to cause SIADH, with the first case reported by Levin *et al*⁵ in a patient with malignant thymoma. Subsequent reports have included patients with ovarian cancer,⁶ non-small cell lung cancer,^{7–10} oesophageal cancer,¹¹ cervical neuroendocrine tumour¹² and squamous cell carcinoma,¹³ paediatric osteosarcoma,¹⁴ teratoma,¹⁵ another with malignant thymoma¹⁶ and our patient with urothelial carcinoma. The hyponatraemia can be life threatening, resulting in seizures, coma and even death. Our case represents the lowest serum sodium level from cisplatin-induced SIADH reported to date. Fortunately, our patient did not suffer significant adverse

neurological consequences, although his MRI did show abnormal and atypical findings. The mechanism resulting in SIADH remains to be elucidated but has been proposed to occur via renal tubular necrosis and impaired sodium reabsorption.¹⁷ Neurotoxicity due to cisplatin may also contribute to the development of SIADH.¹² Although cases of carboplatin-induced SIADH have also been reported,¹⁸ the mechanism does not appear to be a class effect related to platinum compounds, as many of the reported cases were subsequently administered carboplatin without adverse effect on sodium levels. Furthermore, our patient had previously safely received multiple doses of carboplatin. Tumour subtype also does not appear significant given the diversity of reported cases. Interestingly, more than half of the cases of cisplatin-induced SIADH have been reported from Japan or Korea. Pharmacogenetic differences may potentially explain different toxicity profiles in the East Asian population,¹⁹ as has been well demonstrated for other chemotherapy agents, notably S-1.²⁰ Certain genetic polymorphisms have been found which correlate with different cisplatin toxicities, including ototoxicity and myelosuppression.^{21 22}

Hyponatraemia in general is extremely common following administration of cisplatin.^{23 24} A diagnostic approach to determine the aetiology of hyponatraemia importantly involves assessment of the plasma and urine osmolality, extracellular fluid volume status and urinary sodium level.²⁵ Cerebral or renal salt wasting syndrome (RSWS) is an important cause to differentiate from SIADH, as biochemical findings are often similar, however management differs significantly. Cisplatin has been well documented to cause RSWS.²⁶ Volume status is critical in differentiating between the two conditions with euvoemia in SIADH and hypovolaemia in RSWS. However, clinical volume assessment is notoriously difficult and unreliable.²⁷ Fractional excretion of sodium and urate have been suggested as additional investigations to aid in the diagnostic approach.²⁸ Although these values were not calculated in our patient, the low aldosterone level would argue against a hypovolaemic state and support the diagnosis of SIADH.

Cisplatin-induced SIADH is an uncommon but potentially severe and life-threatening toxicity. With widespread use of cisplatin in a diverse range of cancers, prompt recognition is important to detect and prevent severe neurological sequelae.

Learning points

- ▶ Cisplatin-induced syndrome of inappropriate antidiuretic hormone (SIADH) is an uncommon but potentially life-threatening toxicity and prompt recognition is crucial to detect and prevent severe neurological sequelae.
- ▶ Pharmacogenetic characteristics may elucidate the underlying mechanism of action of cisplatin-induced SIADH.
- ▶ Cisplatin-induced SIADH can occur despite previous uncomplicated carboplatin exposure.

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