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CASE REPORT

Cisplatin-induced hyperglycaemic hyperosmolar coma

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ABSTRACT

We present a case of severe hyperglycaemic hyperosmolar derangement after treatment with cisplatin in a patient without previous diabetes mellitus. Limited data are available on this adverse reaction, explaining why impaired glucose handling due to cisplatin is not generally recognised.

KEYWORDS

Cisplatin, diabetes mellitus, hyperosmolar coma

CASE REPORT

A 43-year-old man with a T2bN1M0 squamous cell carcinoma of the oropharynx was treated with cisplatin (*cis*-diamminedichloroplatinum (II), CDDP) 100 mg/m^2 intravenously once every four weeks with concurrent radiotherapy (35 fractions of 2 Gy). The patient was prehydrated to reduce cisplatin nephrotoxicity. Dexamethasone 10 mg was administered intravenously on the cisplatin infusion days and 8 mg orally on the three subsequent days as antiemetic therapy.

Six days after the third cycle of cisplatin the patient was admitted in a lethargic state. His temperature was 38.0 °C; blood pressure was 110/60 mmHg with a pulse rate of 110 beats/min. The skin and mucosal layers were desiccated. Laboratory analysis of the serum revealed hyperglycaemia, hypernatraemia, increased osmolality and impaired renal function (*table 1*). Arterial blood gas analysis showed no abnormalities (*table 1*). Ketonuria was absent. All in all, the patient had developed a severe hyperglycaemic hyperosmolar state, even though he had no history of glucose intolerance, had a body mass index of 21 and his prior renal function tests had been normal. Furthermore, family history revealed no diabetes mellitus. Autoantibodies to pancreatic islands, insulin and glutamic acid decarboxylase, which is linked to (preclinical) type I diabetes mellitus, were not detectable. Treatment was initiated with intravenous insulin and fluid administration. However, shortly after arrival, the patient became comatose, resulting in respiratory failure and a subsequent need for intubation and mechanical ventilation. After normalisation of the internal homeostasis and weaning from the ventilator, the patient persistently required insulin treatment during the next months of follow-up.

DISCUSSION

In this patient without a pre-existing glucose intolerance and no risk factors for diabetes type 1 or 2, we searched for treatment-related causes of the hyperglycaemic derangement. Because cisplatin is highly emetogenic, glucocorticoids are often prescribed as adjuncts; these drugs are well known for their diabetogenic action. However, glucocorticoid-induced diabetes generally occurs in persons with an impaired glucose metabolism, which is hallmarked by reversibility after discontinuing the drug. Moreover, the low levels of insulin and C-peptide relative to the glucose concentration as in the described case (*table 1*) point toward an insulin deficit rather than the insulin resistance observed with glucocorticoid use.[1,2] Taken together, these findings preclude a glucocorticoid-induced event.

Cisplatin is an inorganic platinum compound that is widely used for the treatment of a variety of tumours, including head and neck carcinoma. Cisplatin is believed to exert its anticancer activity by forming cross-links with DNA, thereby impairing DNA replication, transcription and repair, ultimately leading to cell death.[3] Nephrotoxicity and neurotoxicity are the most common adverse reactions.

Table 1. *Laboratory analysis of serum obtained at presentation*

	Measured value	Reference value
Glucose	67.9 mmol/l	4.0 - 7.8 mmol/l
Sodium	162 mmol/l	135 - 145 mmol/l
Potassium	3.9 mmol/l	3.5 - 5.0 mmol/l
Urea nitrogen	27.4 mmol/l	2.5 - 6.7 mmol/l
Creatinine	151 mmol/l	70 - 110 mmol/l
Osmolality	423 mosmol/kg	275 - 300 mosmol/kg
pH	7.39	7.36 - 7.44
pCO_2	5.6 kPa	4.5 - 6.0 kPa
pO_2	11.0 kPa	10.0 - 13.3 kPa
Bicarbonate	25 mmol/l	21 - 27 mmol/l
Oxygen saturation	0.95 mol/mol	0.95 - 0.98 mol/mol
Insulin	< 20.0 mU/l	
C-peptide	0.81 mmol/l	0.2 - 1.2 mmol

Hyperglycaemia due to cisplatin in humans remains under-recognised; however, in a retrospective study, 11 of 202 (5%) cancer patients developed diabetes after receiving cisplatin.[4] These patients had received 100 mg/m² cisplatin and hyperglycaemia was documented after a median period of 19 days after treatment, ranging from 7 to 30 days. In this study, two patients presented with hyperosmolar coma; both required insulin treatment from then on.

The mechanism of diabetes mellitus due to cisplatin in humans is obscure. Animal studies demonstrate that cisplatin impairs insulin secretion, possibly by induction of somatostatin and nitric oxide.[5,6] As insulin requirement persists in cases of hyperglycaemic hyperosmolar coma, permanent alterations in glucose metabolism due to cisplatin appear to have occurred. Of interest, pancreatic β-cell function is protected against toxic insults by thioredoxin, an ubiquitous protein involved in balancing the cellular reductive-oxidative state. Thioredoxin prevents rats from developing diabetes after exposure to streptozotocin, a cytotoxic drug used in a classical animal model to elicit diabetes mellitus, but also attenuates cisplatin toxicity.[7] When this protective mechanism fails, it appears conceivable that permanent damage can arise, leading to lasting β-cell dysfunction.

CONCLUSION

When assessing the probability scale as proposed by Naranjo *et al.*, we designate the presented case of a severe hyperglycaemic hyperosmolar coma as a 'probable' adverse reaction of cisplatin.[8] The low levels of insulin and C-peptide, and the ongoing insulin requirement are indicative of a contributory role for cisplatin. Still, limited data exist on the development of diabetes mellitus in humans after cisplatin treatment and hyperglycaemic hyperosmolar derangement currently remains an unlisted adverse reaction. Given the frequent concomitant use of glucocorticoids, cases of cisplatin-related diabetes mellitus may have been wrongly attributed to these drugs. Therefore, the presented case has been reported to the Netherlands Pharmacovigilance Centre (Lareb). We advise regular (self-) monitoring of serum glucose levels to prevent patients receiving cisplatin to develop such a detrimental condition.

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