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Nephrogenic Diabetes Insipidus Following High Dose Epirubicin Chemotherapy for Metastatic Soft Tissue Sarcoma

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A 52 YEAR old woman presented with an extensive pelvic recurrence of a low grade neural sarcoma which had been completely excised 2 years previously. There were also multiple pulmonary metastases and, apart from mild dyspnoea on exertion, there were no other specific symptoms. Her ECOG performance status was 1. Routine haematological and biochemical investigations were normal, and chemotherapy was started with high dose epirubicin 150mg/m^2 intravenously (i.v.) three times a week (with ondansetron 8 mg i.v. and dexamethasone 8 mg i.v. as an antiemetic prophylaxis) as part of a clinical trial. Following this, she experienced vomiting and diarrhoea, but also increasing thirst and polyuria. She developed myelosuppression (neutrophil nadir 0.51×10^9/l), but serum biochemical analysis revealed no significant abnormalities (potassium 4.1 mmol/l, urea 3.3 mmol/l, serum creatinine 60 μmol and corrected calcium 2.22 nmol/l). A 24 h urine creatine clearance was 60 ml/min. Urinalysis revealed pus cells, but no organism was grown from any of the cultures. She subsequently received two further cycles, and continued to complain of polydipsia and polyuria. Abdominal ultrasound demonstrated mild hydronephrosis on the right plus slight dilatation of the left calyceal system. Creatinine clearance had risen to 92 ml/min, urea 9.3 mmol/l, sodium 142 mmol/l, potassium 4.2 mmol/l, creatinine 149 μmol/l and calcium 2.5 mmol/l. The rest of her routine biochemistry parameters were normal. Plasma osmolality was 296 mmol/kg (normal range 275–295), urine osmolality 191 mmol/kg, thyroxine 106 nmol/l and thyroid-stimulating hormone (TSH) 3.92 mU/l indicated a euthyroid state. Serum cortisol at 9 a.m. was 564 nmol/l and parathyroid hormone (PTH) was 3.3 pmol/l (both within normal ranges). A standard water deprivation test was carried out which suggested the diagnosis of nephrogenic diabetes insipidus (Figure 1). A brain C.T. scan showed no evidence of intracerebral metastatic disease, or ventricular enlargement. Ultrasound now revealed moderate bilateral hydronephrosis secondary to pelvic disease, measuring 12 cm × 13 cm × 12 cm. Despite this, renal function remained adequate, with urea 7.7 mmol/l creatinine 125 μmol/l, and creatinine clearance 56 ml/min. The patient had subjective improvement after intranasal deamino-D-arginine vasopressin (DDAVP), and this was administered at 20 μg, three times daily. Unfortunately, her disease continued to progress and despite further care, she died 6 weeks later.

Nephrogenic diabetes insipidus (NDI) occurs when there is insensitivity of the renal collecting tubules to the phsyiological effects of antidiuretic hormone (ADH). Drug-induced NDI has been increasingly recognised over the years (for review see Singer and Forrest [1]) although there is little evidence implicating cytotoxic drugs in the aetiology of this syndrome [2–5]. There has been no reported correlation with electrolyte disturbance or endocrine abnormality either at standard or high doses of epirubicin, and non-haematological toxicities such as nausea, vomiting, diarrhoea and stomatitis have generally showed a lack of correlation with dose [6–10]. There is a clear temporal relationship between the administration of epirubicin and the onset of polyuria and polydipsia in this particular patient, and the lack of significant renal impairment at the onset of symptoms and the mild degree of the hydronephrosis make obstructive nephropathy an unlikely cause (although it may have contributed to it in the later stages). Although we feel that an idiosyncratic response to epirubicin is the likely cause, there is the possibility that the combination of mild hydronephrosis and high dose epirubicin has had additive or synergistic effects on the ADH/water clearance mechanisms to such an extent that clinical nephrogenic DI occurred.

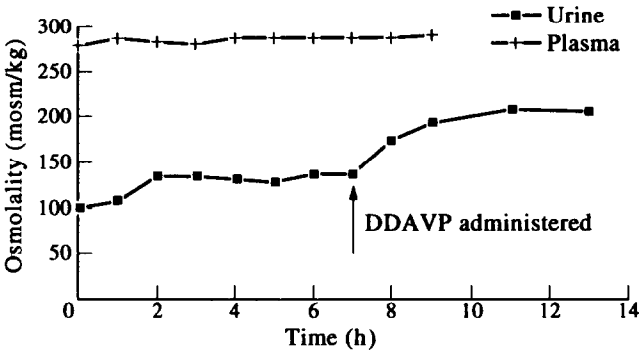

Figure 1. Results of water deprivation test showing failure to concentrate the urine in response to DDAVP. The patient achieved a 4 h post DDAVP urine osmolarity of 27% greater than the baseline value, and as such fulfils the diagnostic criteria for nephrogenic DI.

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