

CLINICAL REPORTS

The regulation of vasopressin secretion in a patient with oat cell carcinoma of the bronchus

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Summary

We report a patient who had an oat cell bronchogenic carcinoma in association with the syndrome of inappropriate antidiuresis. There was an unusually long interval between the onset of hyponatraemia and clinically evident malignant disease. Dynamic testing of vasopressin secretion showed preservation of baroregulated, but not osmoregulated, vasopressin release. Immunoreactive vasopressin was detected in pleural fluid, which co-eluted with synthetic vasopressin on gel chromatography.

KEY WORDS: bronchus, oat cell carcinoma, vasopressin.

Introduction

Bronchogenic carcinoma with the syndrome of inappropriate antidiuresis (SIAD) has been well documented (Schwartz *et al.*, 1957; Amatruda *et al.*, 1963; Padfield *et al.*, 1976). Evidence has been provided for ectopic arginine vasopressin (AVP) production from tumour tissue (George, Capen and Phillips, 1972), but recently Robertson (1977) has suggested excessive AVP secretion from the neurohypophysis as an alternative mechanism.

The appearance of overt SIAD in patients with bronchogenic carcinoma usually heralds the terminal phase of the illness (Padfield *et al.*, 1976), although SIAD preceding clinical recognition of the tumour (Willis, 1980) has been reported. Our patient demonstrated a number of unusual features; a particularly long period of time between the discovery of hyponatraemia and eventual tumour detection, evidence of both ectopic and neurohypophysial AVP secretion, and the presence of AVP in the pleural fluid.

Case report

Hyponatraemia was first documented in a 58-year-old man in 1977 (4 years before the bronchogenic

carcinoma was evident) when he presented with slight right hemiparesis. Serum sodium was 133 mmol/litre. Chest X-ray was normal. Computerized axial tomography revealed a left-sided occipital haematoma. Persistent hypertension was noted and he was treated with metoprolol and bendrofluazide. In July 1979, he was readmitted to hospital after an episode of loss of consciousness, when serum sodium was 119 mmol/litre. The diuretic was stopped, and following fluid restriction, serum sodium rose. However, 2 months later he had a grand mal seizure (serum sodium 127 mmol/litre).

Initial focal features suggested the occipital haematoma as the cause of the seizure, possibly aggravated by the hyponatraemia. Chest X-ray revealed no abnormality. Adrenal, thyroid and pituitary function were all assessed and found to be normal. He was discharged taking phenytoin. Thereafter, serum sodium remained consistently low (123-132 mmol/litre) with low concomitant plasma osmolality (approx. 260 mOsm/kg). He admitted to drinking large volumes of beer and beer drinker's potomania was considered a possible cause for his hyponatraemia. He had 4 further grand mal seizures between April and October 1980; on each occasion serum sodium was less than 120 mmol/litre. Minimal diffuse shadowing at the left base was noted on the chest X-ray in September 1980, and thought to reflect inflammatory change. Clinical examination of the chest was normal.

In December 1980, his hyponatraemia was fully investigated. His medication which included methyl-dopa, cimetidine, diazepam, sodium valproate, phenytoin, salbutamol and beclomethasone inhalers was stopped. He appeared mildly obtunded, but was not clinically fluid overloaded. Blood pressure was elevated at 190/110 mmHg. There was no evidence of cardiac failure. Examination of the chest was normal. Serum sodium was 128 mmol/litre with a low

chloride of 92 mmol/litre. Electrolytes were otherwise normal. Simultaneous plasma and urine osmolalities were 265 mOsm/kg and 730 mOsm/kg respectively. Urinary sodium excretion was consistently about 100 mmol/24 hr. Glomerular filtration and routine tests of liver function were normal. Fasting lipoprotein levels were within normal limits. Total serum protein was 68 g/litre. A cortisol peak of 1240 nmol/litre following tetracosactrin (Synacthen) excluded adrenal insufficiency and serum thyroxine was normal at 73 nmol/litre. Anterior pituitary function, assessed by administration of releasing hormones for gonadotrophin and thyrotrophin was normal. Serum ethanol was not detected. Chest X-ray still showed slight opacification at the left base.

Random plasma AVP levels, determined by radio-immunoassay (Baylis and Heath, 1977), were markedly elevated. Therefore, inappropriate secretion of antidiuretic hormone was confirmed. Osmoregulation of vasopressin secretion was tested by water loading and hypertonic saline infusion. Following administration of a standard water load of 20 ml/kg, plasma AVP failed to suppress, urine osmolality remained high, free water clearance did not increase and by four hours, only 35% of the load had been excreted (Fig. 1). The infusion of hypertonic (5%) saline at a rate of 0.06 ml/kg/min (Baylis and Robertson, 1980) was associated with fluctuations in vasopressin which bore no relationship to the rise in plasma osmolality from 257 to 271 mOsm/kg (Fig. 2). Baroregulation of AVP secretion was tested by tilting the patient from the horizontal position to 85° tilt (Davies *et al.*, 1976). Following the tilt, there was a 30% fall in mean arterial blood pressure which caused a rise in plasma AVP of 15 fmol/ml (Fig. 3). On the basis of the osmoregulatory studies, a diagnosis of ectopic AVP secretion from an unknown source was made.

Only 2 months later he was readmitted with extreme dyspnoea and signs of a large left-sided pleural effusion. Sputum cytology revealed malignant cells suggestive of an oat cell carcinoma. Similar cells were detected in the pleural aspirate. Immunoreactive AVP was demonstrated in the pleural fluid (17 fmol/ml). The elution profile of this material on Sephadex G-25 co-eluted with synthetic AVP (Fig. 4).

Death occurred one month later. Post-mortem examination confirmed an oat cell carcinoma of the bronchus with metastatic spread to the diaphragm, pancreas and left adrenal gland. There were no cerebral metastases.

Discussion

Mild hyponatraemia was first noted in this patient 4 years before his death. At that stage he had suffered

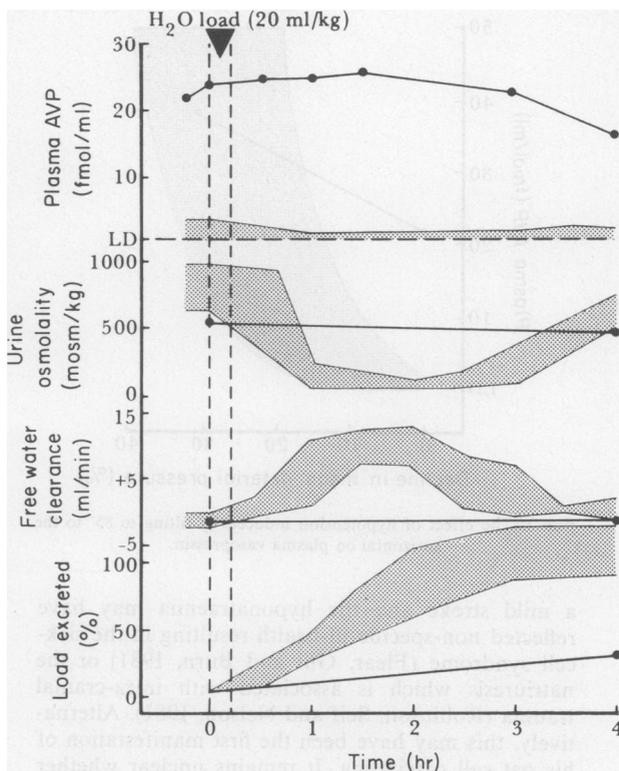


FIG. 1. The effect of an oral water load (20 ml/kg) on plasma vasopressin (AVP) urine osmolality and free water clearance. Shaded areas represent the range of values in healthy normally hydrated adults.

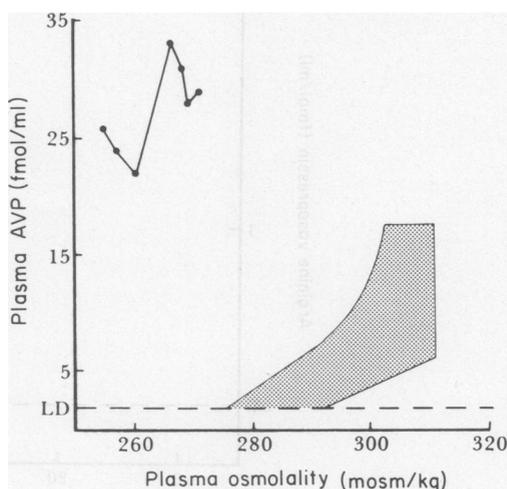


FIG. 2. The relationship of plasma vasopressin to plasma osmolality during infusion of hypertonic (5%) saline (0.06 ml/kg/min).

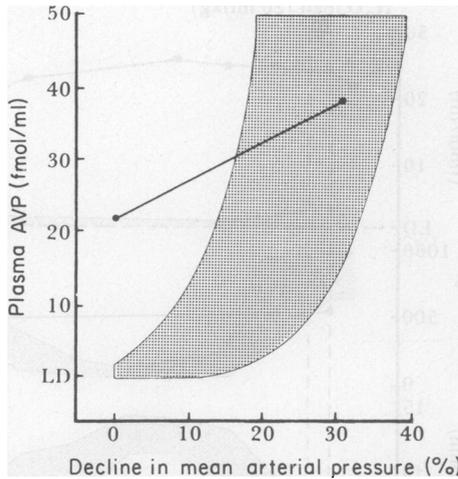


FIG. 3. The effect of hypotension induced by tilting to 85° to the horizontal on plasma vasopressin.

a mild stroke and the hyponatraemia may have reflected non-specific ill-health resulting in the sick-cell syndrome (Flear, Gill and Burn, 1981) or the natriuresis which is associated with intra-cranial trauma (Robinson, Seif and Nelson, 1981). Alternatively, this may have been the first manifestation of his oat cell carcinoma. It remains unclear whether hyponatraemia persisted throughout the following two years, but he was certainly severely hyponatrae-

mic in July 1979 (serum sodium 119 mmol/litre). At that time he was taking a thiazide diuretic for hypertension, known to cause hyponatraemia in a small percentage of patients (Fichman *et al.*, 1971). After withdrawal of the thiazide, hyponatraemia persisted, thus militating against this drug contributing significantly to his hyponatraemia. Although he drank moderate amounts of beer, we feel that beer drinker's hyponatraemia (Demanet *et al.*, 1971) is most unlikely cause for his hyponatraemia since he continued to eat a normal balanced diet, remained well-nourished, and drank no more than 15 pints of beer each week.

From mid-1979 he demonstrated a persistent dilutional hyponatraemia which was well documented. Investigations in 1980 confirmed that he fulfilled the criteria of the syndrome of inappropriate antidiuretic hormone secretion (Barter and Schwartz, 1967). Studies on the osmoregulatory control of AVP secretion showed total loss of osmoregulation, with wide erratic fluctuations in plasma AVP during osmo-stimulatory (hypertonic saline infusion) and osmo-inhibitory (oral water loading) tests. This pattern of response accounts for approximately 35% of all patients with SIAD and may reflect either ectopic hormone production from tumour tissue or erratic production from the posterior pituitary (Zerbe, Stropes and Robertson, 1980). In contrast, baroregulatory control of AVP secretion appeared to be intact. We would suggest that, under basal conditions, AVP was secreted at random from

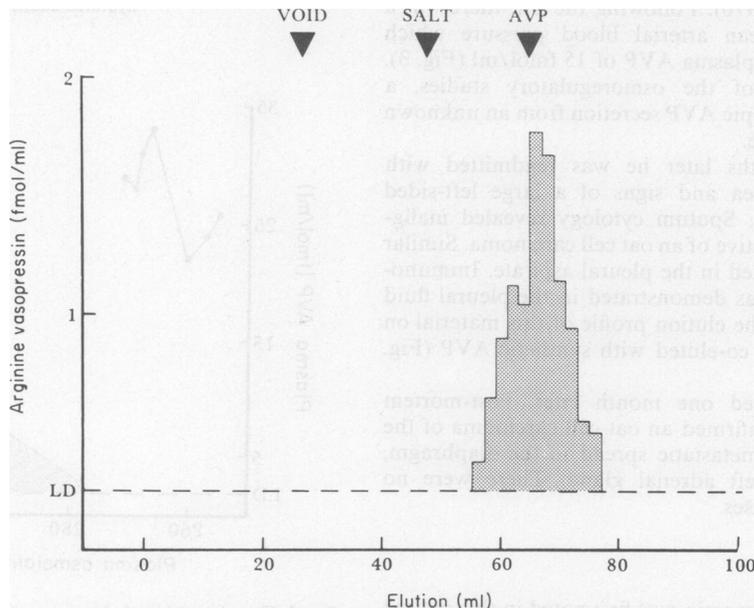


FIG. 4. Elution profile of pleural fluid extracted with florisol on sephadex G-25 (fine).

the tumour, but that following hypotension induced by tilting, AVP was released from the neurohypophysis in the normal physiological manner (Robertson, 1977). The source of the tumour-derived AVP was not apparent until 1981, although in the later part of the previous year the chest X-ray was abnormal.

In 1981, the patient's health deteriorated rapidly, with increasing dyspnoea due to a large pleural effusion. Immunoreactive AVP, not reported previously in pleural fluid, was detected at concentrations similar to plasma values. To check that there was no non-specific interference in the immunoassay, an aliquot of pleural fluid was fractionated on Sephadex G-25, and the material in the fluid co-eluted with synthetic AVP, thus adding considerable evidence that the material in the pleural fluid was AVP. Whether this AVP was a transudate from blood, in which AVP circulates unbound to plasma proteins (Share and Crofton, 1980), or was an exudate from the tumour, remains unclear.

In conclusion, we believe that this patient had SIAD from ectopic production of AVP from an oat cell bronchogenic carcinoma, which was first manifest at least 2 years, and possibly 4 years, before the tumour was evident. This period is considerably longer than the 7 months reported by Willis (1980) and 3 months by Padfield *et al.* (1976). Baroregulation of AVP secretion was retained, but osmotic control was lost. AVP was detected in the pleural fluid.

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