Medical Memoranda

Dilutional Hyponatraemia and Myasthenic Syndrome in a Patient with Bronchial Carcinoma

Although the occurrence of dilutional hyponatraemia and a myasthenic syndrome in association with malignant bronchial neoplasms has been recognized for some time (Anderson, Churchill-Davidson, and Richardson, 1953; Schwartz, Bennett, Curelop, and Barter, 1957), the finding of both these disorders in the same patient is of unusual interest. The characteristic clinical and electromyographic findings in patients with oat-cell carcinomas and myasthenia were given recently (Lambert, Eaton, and Roeke, 1966; Lambert and Roeke, 1965), and the abnormality appears to be a defect of neuromuscular transmission in the rested muscle. There is good evidence that the syndrome of renal sodium loss and hyponatraemia is due to inappropriate production of an antidiuretic substance by the tumour itself (Amatruda, Mulrow, Gallagher, and Sawyer, 1963; Bower, Mason, and Forsham, 1964). We report here the occurrence of dilutional hyponatraemia in a patient whose bronchial carcinoma presented with myasthenic symptoms and in whom the Lambert–Eaton phenomenon was demonstrable both clinically and electromyographically.

CASE REPORT

A fitter’s mate aged 55 was first admitted to the Brook General Hospital in December 1963, under the care of Dr. Raymond Hierons, with a year’s history of variable muscle-weakeness of the arms and legs, loss of weight, and several episodes of diplopia. He had suffered from a productive winter cough for many years and habitually smoked 10 to 15 cigarettes daily. A barium-meal examination in June 1963 had revealed a small gastric ulcer, which subsequently healed. On the basis of abnormal chest x-ray appearances and the finding of malignant cells in the sputum a diagnosis of bronchial carcinoma was made in January 1964 and he was transferred to the National Hospital (N.H. A.15796), under the care of Professor R. W. Gilliatt, for electromyographic studies. Examination at that time showed him to be thin. There were bilateral ptosis, slight weakness of the sternomastoid muscles, and proximal-muscle weakness in the limbs which was striking at rest but which diminished with continued effort. Supinator and biceps reflexes were obtainable but other tendon reflexes were absent. The plantar responses were flexor. He showed no cerebellar or sensory deficit. Atrial fibrillation, paresis of the left vocal cord, and signs of collapse of the left upper lobe were present.

Investigations.—The urine was normal, haemoglobin 13.9 g./100 ml., white-cell count normal, E.S.R. 7 mm. in one hour, plasma sodium 136 and potassium 4.8 mEq/l. Blood urea 24 mg./100 ml.; serum calcium 10.4 mg./100 ml.; alkaline phosphatase 87 I.U./l. Serum proteins, electrophoresis, and empirical tests of liver function were normal. Resting urinary excretion of 17-ketogenic steroids was 13.9 mg./24 hours. The E.C.G. showed atrial fibrillation but no other abnormalities.

Electromyographic Findings (Dr. R. G. William).—Muscle action potentials were recorded with surface electrodes over left extensor digitorum brevis in response to supramaximal stimulation of the anterior tibial nerve at the ankle and measured 2 mV in the resting state. After a 10-second period of sustained voluntary contraction the amplitude of the muscle action potential was increased fourfold. Motor-conduction velocity in the right median nerve was 49 m/sec. in the forearm (normal range 49–68 m/sec.) and 48 m/sec. between axilla and elbow (normal range 48–70 m/sec.). In the right lateral popliteal nerve motor-conduction velocity was 31 m/sec. (normal range 39–52 m/sec.). The sensory action potential recorded through surface electrodes over the right median nerve at the wrist in response to stimulation of the right index finger measured 15 μV (normal range 9–45 μV) with a latency of 3.9 msec. (normal range 2.5–4 msec.).

Edrophonium chloride and neostigmine had no effect on the patient or weakness. The bronchial neoplasm was inoperable, and he was treated with intravenous and oral cyclophosphamide, together with digoxin. Subsequently his condition deteriorated, with continuing loss of weight, and on readmission in September 1964 he was emaciated and ill, with hepatomegaly, generalized lymphadenopathy, and multiple subcutaneous metastases. Atrial fibrillation was still present; blood-pressure 140/90 and no finger-clubbing. In the nervous system the findings were unchanged except that the weakness at rest of proximal muscle groups in upper and lower limbs was more pronounced, although the increase in power after effort persisted. Electromyographic studies were repeated; they confirmed continued post-effort potentiation of the muscle action potentials.

Further investigations at this time showed no albumin, sugar, or casts in the urine. Haemoglobin was 12.8 g./100 ml., with a P.C.V. of 42%, a normal white count, and E.S.R. of 15 mm. in one hour. The plasma electrolytes were as follows: sodium 120, potassium 4.3, chloride 85, and bicarbonate 24 mEq/l. Serum magnesium 1.4 mg./100 ml. Blood urea 20 mg./100 ml. Serum calcium 10 mg./100 ml. Serum proteins 6.8 g./100 ml. with normal electrophoresis. Alkaline phosphatase 200 I.U./l. Protein-bound iodine 5.8 μg./100 ml. The C.S.F. at this time had a sodium content of 140 mEq/l, potassium 2.6 mEq/l., chloride 101 mEq/l., and magnesium 1.04 mg./100 ml. Urinary electrolyte excretions: sodium 150 and potassium 40 mEq/24 hours. Urine osmolalities varied between 256 and 464 mosm/kg. Urinary keto- genic steroid excretion was 13.2 mg./24 hours, plasma cortisol levels were 33.6 μg./100 ml at 9 a.m. and 24.4 μg./100 ml at midnight in a single 24-hour period, and the urinary aldosterone excretion was 29 μg./24 hours. The response to a standard oral metyrapone test was an increase in urinary ketogenic steroid excretion from 8 and 11 mg./24 hours in two control collections to 37 and 24 mg./24 hours on the first and second days of the test respectively. Bioassays for vasopressin in both blood and urine were carried out while the patient was on an unrestricted fluid intake (Dr. Julius Lee, Charing Cross Hospital Medical School), and these results are set out in the Table.

Antidiuretic Activity in Urine, Blood, and Necropsy Material (Arginine, Vasopressin)

<table>
<thead>
<tr>
<th>Date</th>
<th>Specimen</th>
<th>Result</th>
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<tbody>
<tr>
<td>8/10/64</td>
<td>Urine</td>
<td>530 millionis/24 hours* (osmolality of bulked specimen 570 mosm/kg)</td>
</tr>
<tr>
<td>10/10/64</td>
<td>Blood</td>
<td>500 millionis/ml†</td>
</tr>
<tr>
<td>21/11/64</td>
<td>Samples of secondary carcass</td>
<td>35, 14, and 10 million/ mg. of acetone-dried tissue‡</td>
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<tr>
<td>8/10/64</td>
<td></td>
<td>∗ Normally &lt; 40 millionis/24 hours.</td>
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<td></td>
<td></td>
<td>† Normally &lt; 1 millionis/ml.</td>
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<td></td>
<td>‡ Normal tissue (brachios, liver, kidney, lymph node) contains &lt; 1 millionis/mg</td>
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The effects of treatment with 9α-fluorohydrocortisone, prednisone, and increasing sodium and potassium supplements on the plasma electrolytes, urinary excretion of sodium and potassium, and total body weight are shown in the Chart. With 4 mg. of 9α-fluoro- hydrocortisone and 4 g. sodium chloride daily some increase in plasma sodium concentration did occur, but there was no significant diuresis. The sodium chloride supplement was raised to 6 g. daily, and the continued losses of both sodium and potassium were maintained in successive 24-hour urines. The plasma potassium concentration fell to a low level, and eventually an oral supplement of 12 g. of potassium daily was required to maintain an adequate plasma potassium concentration. The introduction of prednisone 30 mg. daily produced an improvement in the patient’s well-being, but...
although the proximal muscle weakness became much less marked the Lambert-Eaton phenomenon persisted electromyographically.

On this regimen of 9α-fluorohydrocortisone 4 mg/day, prednisone 30 mg/day, and the large sodium and potassium supplements, it was possible to maintain the plasma sodium and potassium concentrations in the low normal range, although a high level of blood antidiuretic activity persisted—that is, 8 µunits/ml on 3 November (see Table). Temporary reduction in the dose of 9α-fluorohydrocortisone produced a fall in the plasma sodium concentration with an increase in body weight (see Chart).

Results of treatment with 9α-fluorohydrocortisone, prednisone, and electrolyte supplements.

From 12 November he developed increasing mediastinal obstruction and died in coma nine days later. At necropsy 50 hours after death (Dr. W. G. P. Mair) carcinoma tumour was present in the lower end of the trachea, and extended into the main bronchi of both sides. There was obliteration of the left upper-lobe bronchus. Numerous metastases to mediastinal and cervical lymph nodes were present and a mass of carcinoma lay in front of the pericardium. Both the liver and adrenals contained large masses of tumour. The pituitary contained tumour in both anterior and posterior lobes, occupying up to half the area of the sections examined. Sections through the hypophalamic region showed no metastases. The histological appearances of the primary tumour and the metastases were those of anaplastic round-cell carcinoma. One metastasis, from the anterior abdominal wall, was assayed for antidiuretic activity (see Table).

DISCUSSION

Since Schwartz et al. (1957) described the cases of two patients with bronchogenic carcinoma and severe hyponatraemia, heavy renal sodium loss, and normal renal and adrenal function, and suggested that this was a dilutional hyponatraemia caused by an inappropriate secretion of antidiuretic hormone, further case reports have appeared, and this unusual metabolic complication of bronchial neoplasm is now well established (Ross, 1963). Demonstration of large amounts of antidiuretic material in the urine of such a patient was provided by Thorn and Transbol (1963), and the more recent finding of high concentrations of vasopressin in both blood and tumour in two further cases (Bower et al., 1964; Lee et al., 1964) strongly suggests elaboration by the tumour of a substance with vasopressin activity.

Hyponatraemia in our patient developed between his first admission in January 1964 and his second admission in September 1964, coinciding with the appearance of widespread metastases consisting of anaplastic carcinoma. The plasma electrolyte findings, high urinary wastage of sodium, and the absence of haemocencentration or evidence of renal or adrenal disease are typical of a predominantly dilutional hyponatraemia. Although the electrolyte composition of the cerebrospinal fluid was normal as regards sodium and potassium, at a time when plasma sodium concentration was considerably reduced, chloride and magnesium concentrations were low in both fluid and plasma. Resting excretion of 17-ketogenic steroids was within the normal range and a roughly threefold rise in their excretion occurred in the course of a metrapone test. The high resting plasma cortisols, with loss of the normal diurnal rhythm, was an unexpected finding and perhaps best explained by the action of vasopressin as a corticotrophin-release factor (Landon, James, and Stoker, 1965), although corticotrophin-like material has been isolated from tumour tissue in these patients (Meador, Liddle, Island, Nicholson, Lucas, Nuckton, and Luetscher, 1962). The aldosterone excretion was towards the upper limit of normal and the results of injection of aldosterone suggested continued sensitivity of the renal tubules to administered aldosterone (see Chart). Lowering the dose of 9α-fluorohydrocortisone from 4 to 2 mg/day was associated with a slight fall in plasma sodium, but more striking was the diuresis which occurred on reinstituting the higher dosage after a few days. In spite of the suggestion here of an inhibitory effect on endogenous vasopressin production or action a high level of antidiuretic activity in the blood persisted.

In the case of myasthenia showing post-effort potentiation of muscular activity studied by Lambert and Rooke (1965), nearly all associated with bronchial neoplasms, no abnormalities in plasma electrolytes were reported. Treatment in our case was effective in restoring the electrolyte pattern towards normal but in no way influenced the Lambert-Eaton phenomenon, as recorded electromyographically, and it seems that the dilutional hyponatraemia and myasthenia were coincidental observations in this patient.

We are grateful to Professor R. W. Gilliatt and Dr. Raymond Hierons for allowing us to publish this case; to Professor J. N. Cumings for his advice; and Dr. E. J. Ross for arranging the plasma cortisol and aldosterone estimations at University College Hospital. The Chart was kindly prepared by the National Hospital Photographic Department.

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REFERENCES