INAPPROPRIATE ANTI-DIURETIC HORMONE SECRETION IN HODGKIN'S DISEASE

MARGARET F. SPITTLE, M.B., B.S., M.R.C.S., L.R.C.P., A.K.C.

Research Registrar, Radiotherapy Department, Westminster Hospital, London, S.W.1

HYPONATRAEMIA due to inappropriate secretion of antidiuretic hormone has been reported in association with some cases of oat cell carcinoma of the bronchus (Schwartz, Bennett, Curelop and Bartter, 1957; Ross, 1963) and a substance with anti-diuretic activity has been extracted from such tumour cells (Armstrong, Mulrow, Gallagher and Sawyer, 1963). One is not aware of any case in the literature in which this syndrome has been associated with the reticulososes. The three cases reported here may, therefore, be of some interest.

Case Histories

Case no. 1

Male, age 27. Telecommunications Engineer. Presented in January 1965 with cervical, axillary and inguinal lymphadenopathy, night sweats, and generalised pruritus, worse on taking alcohol. There was no hepatosplenomegaly. A cervical node biopsy showed pleomorphic cellular proliferation of reticulum cells, lymphocytes, eosinophils and very occasional Reed-Sternberg cells. A diagnosis of Hodgkin's disease was made.

A lymphangiogram gave an excellent demonstration of the lymphatics with large foamy glands characteristic of Hodgkin's disease in the abdomen. Throughout his admission he exhibited a Pel-Ebstein fever.

Investigations: Serum sodium, 141; potassium, 4.2; bicarbonate, 23.5 mEq/l., urea 38 mg/100 ml., specific gravity, 1.0265. Hb. 80% (11.8 g/100 ml.). WBC., 4,400/cu.mm. The bone marrow was very cellular.

The patient was given a course of intravenous nitrogen mustard, totalling 40mg. over two weeks, to which there was good response with regression of node masses. The patient was discharged back to work on chlorambucil. He was fit until May 1965 when, although relatively symptom-free, he again exhibited widespread lymphadenopathy with para-aortic involvement and now had hepatosplenomegaly. X-ray of chest showed enlarged hilar nodes. There were no signs of dehydration. The blood pressure was: 110/70mm. Hg.

Investigations: Serum sodium, 124; potassium, 3.5; bicarbonate, 22mEq./l.; urea, 33 mg/100 ml., sp. gr. 1.0210; urinary aminoacid chromatogram normal. Liver function tests showed evidence of liver damage. Hb 50% (7.4 g/100 ml.). Bone marrow showed a hypocellular marrow, with macronormoblastic erythropoiesis. Total nucleated count, 6,000/cu.mm. Clean specimen of urine showed no abnormality.

The serum sodium was repeatedly low and the serum osmolality ranged between 276 and 278 mOsmol/Kg. (lower limit of normal 280 mOsmol/Kg). The urinary osmolality was 600 mOsmol/Kg. The ratio of urinary to serum osmolality was therefore

2.1 : 1 in the presence of a low serum osmolality.*

These latter figures were thought to be disproportionate, and the patient was deprived of water for 12 hours and a further serum and urinary osmolality were recorded. The serum value had risen to 322 mOsmol/Kg. and that of the urine to 754 mOsmol/Kg. The normal water intake was then increased to 2 litres and the serum osmolality fell to 270 mOsmol/Kg. and the urine to 113 mOsmol/Kg. There was, therefore, not a complete loss of control of secretion of anti-diuretic hormone. The total body water, estimated using tritiated water, was 52 litres (normal 36-48 litres) and the total exchangeable sodium was 2,840 mEq., which was within the normal range for this patient. Therefore, at this time, the patient exhibited dilutional hyponatraemia similar to that shown in cases with carcinoma of the bronchus.

The patient was transfused with 4 pints of blood to correct his anaemia. He was given prednisone, 5mg. tds. and was euthermic on discharge. He returned to normal life.

He was seen in out-patients in July 1965 when he complained of malaise and shortness of breath. He had a temperature of 102.4°F. The haemoglobin had fallen from the post-transfusion figure of 82% (12.1 g/100 ml.); WBC 1,400/cu.mm. Once more there was widespread lymphadenopathy with hepatosplenomegaly. The patient was moderately icteric.

Investigations: Serum sodium, 127; potassium, 4.1; bicarbonate 23 mEq/l.; urea, 42 mg/100 ml, sp. gr., 1.0200; bilirubin, 2.8 mg/100 ml. The osmolality of the serum was 277 mOsmol/Kg. and of the urine 540 mOsmol/Kg., a ratio of 2 : 1. Sternal marrow showed an aplastic picture.

Progress: The patient's condition gradually deteriorated. The prednisone dosage was increased to 50 mg. daily, which maintained the white count at 3,000/cu.mm. and allowed vinblastine sulphate to be given daily in small doses. The serum sodium continued to fall to 119 mEq./l in spite of adequate nutrition until the time of death on July 18th.

Necropsy showed Hodgkin's disease and bronchopneumonia, with generalised lymphadenopathy, and infiltration of the lungs. There were haemorrhages along the mesenteric attachment of the small bowel. The spleen and liver were grossly enlarged and the common bile duct was obstructed by nodes. The adrenals were of normal size and appearance, but showed patchy tumour infiltration of the medulla histologically, with hypoplasia of the cortex. The pituitary and brain were normal in appearance.

*Serum and urine osmolalities estimated with Advanced Osmometer (Advance Instruments, Model 31 LS).

Case no. 2

Female, age 57 on presentation (1954). State Registered Nurse. This patient, with histologically proven Hodgkin's disease, had received radiotherapy to mediastinum and left neck in 1959.

There had been no recurrence of disease but a persistent fall in haemoglobin was noticed six years after diagnosis. The patient was admitted for investigation of her anaemia. She complained of loss of weight, tiredness, blurring of vision and loss of appetite.

On examination there was no abnormality except a palpable spleen. Blood pressure 105/60 mm. Hg.

Investigations: Haemoglobin 66% (9.8 g/100 ml.), PCV 36%, WBC 10,400/cu.mm. with a normal differential count. Sternal marrow showed a slightly hypocellular picture, with mild erythroid hypoplasia and a correspondingly increased myeloid/erythroid ratio. Erythropoiesis was entirely normoblastic though some of the late normoblasts showed slight iron-deficiency. No malignant cells were seen. The chest X-ray showed no significant abnormality.

Serum sodium, 124; potassium, 4.5; bicarbonate, 22 mEq/l; urea, 21 mg./100 ml.; sp. gr., 1.0240. Serum osmolality, 270 mOsmol/Kg. Ratio 1.7 : 1 in the presence of a low serum osmolality. Total exchangeable sodium=1,970 mEq. (normal). Liver function tests normal. Aminoacid chromatogram normal. No occult blood in stools.

Although there were no signs of any active Hodgkin's disease at this time, it was thought that the evidence suggested inappropriate secretion of an anti-diuretic hormone-like substance. She has remained asymptomatic.

Case no. 3

Male, aged 25 on presentation. Manufacturer's Agent. This patient presented with pruritus and cervical lymphadenopathy. Biopsy proved the diagnosis to be Hodgkin's disease. He was treated with irradiation in 1961 to the mediastinum, neck and para-aortic regions, and in 1964 to the axilla. For a period of one year, from 1963-1964, he was treated with steroids.

This patient was admitted many times for thoracentesis of a left pleural effusion. In May 1965 he was admitted with shortness of breath, cough and pruritus. He was dyspnoeic with a temperature of 102°F. Blood pressure 110/70 mm. Hg. There was dullness to percussion at the left lung base and there was hepatosplenomegaly. The chest X-ray showed enlarged hilar nodes and diffuse mottling throughout the lung fields, thought to be due to Hodgkin's infiltration.

Investigations: Serum sodium, 124; potassium, 4.3; bicarbonate, 20.5 mEq/l; urea, 42 mg/100 ml.; sp. gr., 1.0230; alkaline phosphatase, 114 KA units. Urinary aminoacid chromatogram was normal. Serum osmolality, 277. Urine osmolality, 548 mOsmol/kg. Ratio 2.1 : 1.

Steroids were recommenced, but the serum sodium did not rise to within normal limits and the patient pursued a downhill course until his death on 30th June, 1965. He maintained reasonably good nutrition until the time of his death.

Total body water and total exchangeable sodium were not estimated. The adrenal glands were macroscopically normal at necropsy.

Case no. 4

Male, age 19 on presentation. Butcher. This man had histologically proven Hodgkin's disease treated

with radiotherapy to the mediastinum and neck in 1959, to the right neck in 1962 and left neck in 1963. The groins were treated in 1964 and the left iliac and para-aortic regions in 1965.

He had been very well in himself until May 1965, when he presented with hepatosplenomegaly and further para-aortic involvement. He was found to have an ulcerative pharyngitis with deafness, worse on the right. He was acutely ill, anaemic, icteric and unable to swallow. There was a swelling of the posterior pharyngeal wall which was due to glandular enlargement. A nasopharyngiogram supported this diagnosis. Blood pressure 120/70 mm. Hg. He was started on prednisone 5 mg. tds.

Investigations: Serum sodium, 121; potassium, 4 mEq/l; urea 36 mg/100 ml.; serum osmolality, 257; urine osmolality, 535 mOsmol/kg. Ratio 2.1 : 1 (in the presence of a low serum osmolality).

Although this patient was terminally ill, it was thought relevant to include these findings.

Discussion

The normal control of antidiuretic hormone (ADH) secretion from the posterior pituitary depends on the osmolality of the plasma. If this is low—due either to excess of water or deficiency of solute—secretion is suppressed, less water is reabsorbed in the distal renal tubule, and an increased volume of dilute urine enters the bladder. If the hypo-osmolality were due to dilution of solute this would correct the abnormality. If, however, it were due to solute loss in excess of water loss, the large urine volume would result in reduction of the extracellular fluid volume and stimulation of aldosterone secretion by the adrenal cortex. More sodium would be reabsorbed by the kidney, tending to correct the deficit of solute. As the extracellular osmolality rises ADH secretion is stimulated and water is retained. By this means both water and solute losses are corrected.

In either case a low serum osmolality is usually associated with absence of ADH secretion and therefore the passage of a dilute urine. Concentration of the urine to an osmolality above that of the serum must indicate the presence of circulating ADH (though a reduction in GFR alone may bring this about) and in the presence of a low serum osmolality this secretion is "inappropriate" and results in further dilution of the ECF (extracellular fluid). In many clinical states serum osmolality can be equated with serum sodium concentration, and hyponatraemia, with evidence of dilution of the serum and passage of concentrated urine, is very suggestive of inappropriate ADH secretion. However, proof of this syndrome can only be obtained by finding a serum osmolality below normal in the presence of a higher urinary osmolality.

On this evidence dilutional hyponatraemia due to inappropriate ADH secretion has been reported in malignant states, most commonly, oat-cell carcinoma of the bronchus (Schwartz, Bennett, Curelop and Bartter, 1957; Ross, 1963). Evidence that a substance with ADH-like activity comes

from the tumour cells is provided by Amatruda, Mulrow, Gallagher and Sawyer (1963). So far as one is aware this association has not been seen in the reticulososes, although Plimpton & Gellhorn, (1956), have reported hypercalcaemia (also probably endocrine in origin) in one case of Hodgkin's disease.

In all the cases in the present series, Hodgkin's disease was histologically proven. In each case the serum sodium level was at some time 125 mEq/l. or below. This hyponatraemia was associated with a low serum osmolality with a ratio of urine-to-serum osmotic pressure greater than one. There was, therefore, good evidence of inappropriate secretion of ADH. The absence of clinical disturbance associated with the hyponatraemia is also in favour of a dilutional hyponatraemia rather than an Addisonian type, and this was suggested in Case 1 by the fall in serum specific gravity in parallel with sodium. This was confirmed by studies of total body fluids and exchangeable electrolytes. In each case the total exchangeable sodium was in the normal range, but the total body water was increased in volume.

Rees, Rosalki and Maclean (1960) and Ross (1963), also described hyponatraemia in carcinoma of the bronchus associated with increased renal loss of sodium. This was thought to be the result of a proximal renal tubular lesion, since aminoaciduria, glycosuria and phosphaturia were also present. None of our cases had excess aminoacids or glucose in the urine. Moreover, in Rees' case there was evidence of dehydration rather than overhydration. In the patients discussed here there was no evidence of adrenal failure, although one had hypoplasia of the adrenal cortex at post mortem. This was thought to be consistent with long term steroid therapy.

It seems, therefore, that inappropriate secretion of ADH can occur in Hodgkin's disease. It would be of interest to attempt extraction of the anti-diuretic substance from the affected nodes and spleen.

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A CASE OF THROMBOCYTHAEMIA WITH RED CELL APLASIA

A. J. E. BRAFIELD, M.B., M.C. Path.,
Consultant Pathologist

JULIAN VERBOV, M.B., M.R.C.P.,
Medical Registrar

Whipps Cross Hos pital, London, E.11

ESSENTIAL thrombocythaemia and pure red cell anaemia are rare conditions. That they should occur in the same patient is of special interest.

Case Report

Mrs. F. P., aged 76, a known case of neurosyphilis, was admitted on 1st October, 1965, with a history of

weight loss for six months, passing fresh blood per rectum more recently, and loss of appetite for a week or so. She had suffered with classical lightning pains in her lower limbs for five years.

On examination she was pale, thin and blind. A triple rhythm was audible over the lower end of the sternum, and heart rhythm was regular. There were signs of collapse over her left lung base. No