Hypercalcaemic stupor as a presentation of lymphosarcoma

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SYNOPSIS A case is reported of a 32 year old woman with a two year history suggestive of schizophrenia who presented in stupor. This proved to be due to hypercalcaemia with a concomitant high cerebrospinal fluid calcium concentration associated with previously unsuspected lymphosarcoma. Necropsy revealed no significant intracranial abnormality, and mechanisms that may have been involved in the production of the impaired consciousness are discussed.

It is well known that neurological disorders may accompany hypercalcaemia, but in most cases the aetiology of the disturbed calcium state has been evident for some time before. The patient described here presented in stupor without indication of the serious underlying cause; this proved to be due to hypercalcaemia associated with a highly malignant and previously asymptomatic lymphosarcoma.

CASE REPORT

P.L., a 32 year old West Indian woman, was admitted in stupor in August 1974. Two years previously she had developed intermittent shaking of the right side of her body, auditory and visual hallucinations, and features of paranoia and delusions. No abnormal signs were elicited and an electroencephalogram (EEG) was normal. A diagnosis of schizophrenia was made and she was treated with various phenothiazine preparations and hospitalized on five occasions for recurrence of these symptoms.

She was referred to this hospital having had a five day history of chest infection with cough and non-purulent sputum production, but three days before admission she had begun to feel increasingly unwell with mild headache and generalized weakness. On the morning of admission she had been found collapsed on the floor, confused, drowsy, and unresponsive.

On admission she was afebrile, her skin felt unduly hot, and she was slightly dehydrated. Her

pulse was regular at 110/minute, blood pressure 140/70 mmHg. There was enlargement of the posterior cervical, axillary, and left inguinal lymph nodes, and moderate, smooth hepatosplenomegaly. A soft systolic murmur was audible over the left sternal edge and a few coarse râles were heard over the right lung base. Neurological examination revealed a stuporose patient who could be roused with difficulty but was unable to speak coherently. There was no neck stiffness. The cranial nerves were normal, the pupils 4 mm in diameter and responding normally to light. Oculocephalic reflexes were normal. Little spontaneous movement of the limbs was present, although there was slight response to painful stimuli. The tendon reflexes were normal and plantar responses flexor.

An EEG showed diffuse slow wave activity at a frequency of 1-2 Hz over both hemispheres. The cerebrospinal fluid (CSF) was under normal pressure and contained: red blood cells 2 000/mm³, white blood cells 12/mm³ (18% polymorphonuclear cells, 82% lymphocytes); Gram stain revealed no organisms and subsequent cultures and virological studies proved negative. The supernatant fluid was clear. The CSF glucose was 85 mg/dl (simultaneous blood sugar 95 mg/dl), total protein 16 mg/dl, albumin 7 mg/dl, and IgG constituted 1% of the total protein; the Lange colloidal gold curve was normal and CSF Wassermann reaction negative. Haematological investigations revealed: haemoglobin 15.0 g/dl, white cell count 40 000 cells/mm³, about 75% of which were lymphocytes, many being atypical cells with occasional smear cells present; erythrocyte sedimentation rate (Westergren) 25 mm/hr; reticulocyte and platelet counts and tests of bleeding and clotting time were normal. Plasma electrolytes were

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normal but the blood urea was elevated at 168 mg/dl.

A search for other metabolic abnormalities revealed a very markedly elevated serum calcium level of 18.1 (normal 8.5–10.5) mg/dl, with a serum phosphorus level of 4.0 (normal 2.5–4.5) mg/dl and alkaline phosphatase activity of 23 (normal 3–13) KA units/dl. The CSF calcium was 8.2 (normal 4.1–5.9) mg/dl, phosphorus 1.4 (normal 1.4–2.1) mg/dl, and chloride 130 mmol/l. Serum uric acid was elevated at 13.6 mg/dl. The urinary excretion of calcium ranged from 100 to 1 500 mg/day and phosphorus from 450 to 1 020 mg/day. The following were normal: plasma and urinary proteins, albumin and IgG, IgA and IgM levels, serum creatinine, radiological examination of chest and skull, skeletal survey and intravenous urogram, and brain scan; bacteriological cultures of blood, urine, faeces, and sputum were negative. An electrocardiogram demonstrated sinus tachycardia with a QT_c interval of 0.28 seconds, within the normal range. Estimation of parathyroid hormone showed no detectable activity.

A liver scan demonstrated hepatic enlargement with homogeneous dye uptake. Sternal bone marrow biopsy showed infiltration by primitive cells belonging to the lymphocytic series, and these cells together with some mature lymphocytes formed about 15% of all the nucleated cells. An inguinal node biopsy showed appearances of a poorly differentiated, highly malignant lymphosarcoma.

Management was directed towards reduction of the hypercalcaemia (Paterson, 1974). A saline diuresis was instituted and she received steroids, mithramycin, calcitonin, and disodium hydrogen phosphate. Allopurinol and chlorambucil were introduced for treatment of the lymphosarcoma. Her serum calcium levels fell slowly and became normal after nine days; serum phosphorus levels remained normal but the alkaline phosphatase activity was persistently elevated around 20 KA units/dl. The blood urea and uric acid concentrations fell rapidly to normal. The white blood cell count remained between 20 000 and 40 000 cells/mm³, although the abnormal appearances of the cells—which initially became more marked—gradually improved and the frank lymphoblastic changes and smear cells became less evident. A repeat EEG four days after admission when her hypercalcaemia had improved and her serum calcium level was 14.7 mg/dl showed no significant change, as did a third recording 10 days after her admission; the appearances did not correlate with her gradually improving clinical state. She failed to improve significantly for the first week but thereafter gradually became alert, was able to sit out of bed and eat a normal although calcium-free diet. She gave a rational and coherent account of past events, was

fully orientated, and without obvious features suggestive of previous psychiatric illness.

Two weeks after admission, she developed a fulminating septicaemia, became incontinent, confused, and restless, and her serum calcium level rose from a normal value (9.0 mg/dl) to 15 mg/dl within 24 hours. Blood cultures revealed the presence of *Staphylococcus Aureus* and anaerobic streptococci and intravenous antibiotic therapy was instituted, but she suffered a cardiac arrest from which resuscitation was unsuccessful.

Necropsy demonstrated extensive lymphosarcomatous infiltration of enlarged lymph nodes, liver, spleen, upper lobe of the right lung, and left renal parenchyma. Both lungs were congested and purulent material was present in the major bronchi. The cardiovascular and endocrine systems, in particular the parathyroids, were normal, as were the bones. The nervous system was intact with normal meninges and macroscopic brain appearances and the cerebral arteries were patent. The brain was examined in detail at the Department of Neuropathology, Institute of Neurology, Queen Square, and no significant abnormalities were found; in particular there was no evidence of malignant infiltration in either the brain or leptomeninges.

DISCUSSION

The present report describes an unusual, neurological presentation of lymphosarcoma characterized by hypercalcaemic stupor. In disease as widespread as that encountered in this patient, although it is possible that other factors contributed to the overall clinical features, it would seem highly likely that severe hypercalcaemia was the critical one. Thus the clinical improvement after the return towards normal of the high serum calcium level and the impaired clinical state associated with its subsequent rapid increase make the association very probable. The contribution from the elevated blood urea is unlikely to have been significant since its early correction after rehydration was not associated with change in the patient's conscious level. Direct involvement of the central nervous system with malignant disease is also most unlikely to have been present in view of the CSF findings, and such involvement was excluded on examination of the brain at necropsy.

There is thus little doubt that this patient's stupor was caused by severe hypercalcaemia, and an elevated serum calcium concentration is a

well-recognized cause of neurological disease including impaired consciousness (Henson, 1966; Plum and Posner, 1972). The association of disturbances of calcium concentration with psychiatric disorders is also well recognized (Plimpton and Gellhorn, 1956; Lehrer and Levitt, 1960), and it is possible that this patient's earlier history suggesting schizophrenia may have been due to hypercalcaemia, although at that time the EEG was normal. The EEG in the present case was consistent with a metabolic encephalopathy, and a variety of abnormal EEG changes has been recorded in hypercalcaemia, some associated with impaired consciousness (Moure, 1967; Allen *et al.*, 1970). Interestingly, a period of some weeks' normocalcaemia is probably required before the EEG returns to normal (Allen *et al.*, 1970), which is consistent with the observations in the present case where there was striking lack of correlation between the EEG appearances and the clinical state.

Although hypercalcaemia often accompanies malignant disease, it has only rarely been reported in lymphosarcoma. For instance, in a study of over 1 200 cases of lymphosarcoma, Rosenberg *et al.* (1961) mention only four cases in which hypercalcaemia was present, and in two cases this was associated with bone involvement with malignant disease. In this large series stupor was not recorded as a presenting feature. Neurological manifestations including focal symptoms, convulsions, raised intracranial pressure, cranial and peripheral nerve palsies, and herpes zoster have frequently been noted in diseases of the lymphoreticular system, and an extensive literature has accumulated on this subject (for example, Hutchinson *et al.*, 1958; Williams *et al.*, 1959; Rosenberg *et al.*, 1961; Currie *et al.*, 1970; Currie and Henson, 1971). However, at least in lymphosarcoma, hypercalcaemia is often overshadowed by other features which have nearly always previously declared themselves. It is of interest that in patients with lymphomas having cerebral manifestations, a relatively high frequency of normal brain findings at necropsy and spontaneous regression of cerebral symptomatology were noted in an earlier review (Williams *et al.*, 1959): the origin of these cerebral symptoms was unclear, and, since a specific search for hypercalcaemia was not undertaken, it is possible that this dis-

order may have contributed to the cerebral features encountered.

The mechanisms involved in hypercalcaemia cerebral disturbances are not known, although calcium ions have critical effects on excitable membranes including those of cells of the central nervous system (Tschirgi, 1960; Winterstein, 1961); noteworthy is the stupor that may be produced in animals by intraventricular applications of calcium salts (Winterstein, 1961). There is a good correlation between the concentration of the ionized calcium fractions in CSF and plasma (Paupe, 1957), although the concentration of calcium ions in the former is lower, due in part to the difference in protein content between these two fluids (Davson, 1967). The initially very high serum calcium level in the present case was reflected by the high CSF level, and it is reasonable to assume that the cells within the central nervous system were similarly exposed to a markedly elevated calcium concentration.

The origin of hypercalcaemia arising in association with malignant disease including lymphosarcoma is also often not clear. In some instances bone destruction plays a part (Moses and Spencer, 1963), but in others (Myers, 1958; Plimpton and Gellhorn, 1956), as in the present case, there is no evidence of bone involvement and other factors must be considered. Exceptionally, an associated parathyroid tumour has been found, but in the patient described above not only were the parathyroid glands normal at necropsy but plasma parathyroid hormone was undetectable, presumably as a result of suppression of hormone secretion by the hypercalcaemia. Parathyroid-hormone-like polypeptides (perhaps immunologically distinct from 'normal' parathyroid hormone), non-parathyroid humoral substances, an osteolytic sterol, and parathyrotropic substances have all been implicated as causative agents in the hypercalcaemia associated with malignancy (Wills, 1974) but the role of such substances remains uncertain.

The present case supports the view of Plum and Posner (1972) that it is 'sometimes rewarding to obtain a serum calcium determination in patients with unexplained delirium'. Unfortunately, the patient's demise occurred shortly after her admission, and it is salutary to recall that this may have been due to sudden hyper-

calcaemia affecting the heart, despite continuation of therapy for this condition.

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