

Tumour induced hypophosphataemia associated with small cell carcinoma of the bronchus

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We report a paraneoplastic syndrome complicating small cell bronchogenic carcinoma, characterised by a proximal renal tubular defect, renal phosphate wasting, hypophosphataemia, aminoaciduria, glycosuria, and diffuse bone pain.

Case report

A 37 year old man gave a two month history of mild dysphagia, weight loss, haemoptyses, and pain affecting the lumbar spine, buttocks, and thighs. He had been previously well with no relevant past medical history. There were no abnormal physical findings. A barium meal showed nothing abnormal but the chest radiograph showed a left hilar mass and bronchoscopy revealed neoplastic occlusion of the left upper lobe bronchus. Bronchial biopsy specimens confirmed small cell carcinoma.

Investigations showed that the serum phosphate concentration was 0.5 (normal 0.8-1.5) mmol/l (1.5 (2.5-4.6) mg/100 ml), serum calcium 2.6 mmol/l (10.4 mg/100 ml) (corrected for the low serum albumin), and alkaline phosphatase 170 U/l (figure). His full blood count and urea, creatinine, and electrolyte concentrations were normal. He had persistent 2% glycosuria despite normal blood sugar concentrations. Aspartate transaminase activity was 90 (normal 0-35) U/l and γ glutamyl transaminase activity 217 (normal 0-50) U/l. Alkaline phosphatase isoenzymes showed an increase in the bone fraction. Radiographs of the spine and pelvis were normal.

He was initially treated with vincristine, adriamycin, cyclophosphamide, and etoposide and the same drug regimen was repeated three weeks later (figure). There was no radiographic improvement and he developed increasingly severe back pain, which now prevented him from standing. Examination showed considerable paraspinal muscle spasm and generalised skin and palmar crease hyperpigmentation. Serum cortisol concentrations at 09.00 and 24.00 hours were 583 (normal 138-690) nmol/l (21 (5-25) μ g/100 ml) and 607 (normal 96-330) nmol/l (22 (3.5-12) μ g/100 ml) respectively, urinary free cortisol 1330 (normal 96-330) nmol 24 h (48 (3.5-12) μ g/24 h); but the serum adrenocorticotrophic hormone (ACTH) concentration was 58 (normal < 10-80)

ng/l and the serum potassium concentration remained within the normal range. Serum sodium concentration fell to 113 (normal 136-148) mmol (mEq)/l, serum osmolality was 246 (normal 275-295) mmol (mosm)/kg, and urine osmolality 742 mmol/kg. The plasma arginine vasopressin concentration was 73.3 pg/ml (with hypo-osmolality the physiological range should be less than the detection limit of 0.25 pg/ml). Parathormone concentrations were normal, and a bone scan was normal.

It was thought that his pain might be due to extradural metastatic disease but irradiation of the spine and chest failed to alleviate his symptoms and did not alter the chest radiograph. Despite severe and persistent hypophosphataemia, renal tubular reabsorption of phosphate (TmP/GFR) was very low (figure), and urinary chromatography showed excessive excretion of the amino acids threonine, serine, glycine, cystine, tyrosine, and lysine. Serum osmolality remained low (217 mmol/kg), with a grossly raised serum arginine vasopressin concentration (112 pg/ml), which failed to respond to fluid restriction (750 ml/day). Demeclocycline was given in the terminal stages but failed to correct the hyponatraemia. He deteriorated and died three months after presentation.

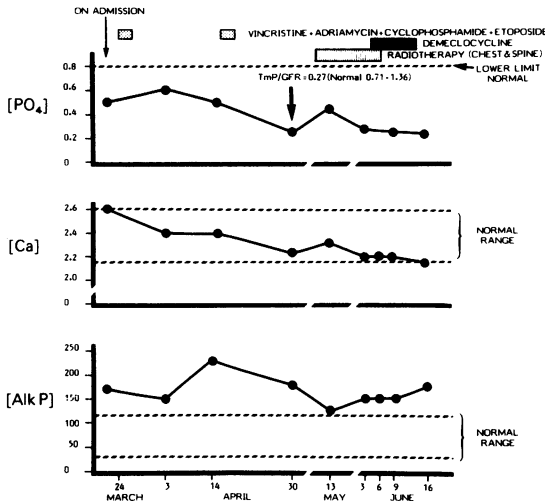
Discussion

Small cell carcinoma in this patient was complicated by the development of two definite paraneoplastic syndromes—tumour induced hypophosphataemia, which was the probable cause of his pain, and inappropriate antidiuretic hormone secretion. In addition, his skin hyperpigmentation and high cortisol concentrations raised the possibility of the ectopic ACTH syndrome, but this was not unequivocally established since he never developed hypokalaemia and the only measurement made of the serum ACTH concentration was normal. Alternatively, the raised cortisol concentrations could have been stress induced.

Tumour induced hypophosphataemia is a rare condition most frequently described with benign mesenchymal neoplasms of bone¹ and more recently with prostatic carcinoma.² Characteristically, as in this case, the mechanism leading to hypophosphataemia is impairment of proximal renal tubular reabsorption of phosphate, characterised by a low TmP/GFR.^{1,3,4} Aminoaciduria and glycosuria occur but not invariably.^{1,3} Serum calcium concentrations are normal but serum alkaline phosphatase activity is raised and reduced concentrations of 1α -dihydroxycholecalciferol

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Changes in serum phosphate, calcium, and alkaline phosphatase and treatment received during a three month period. [PO₄]-serum phosphate (mmol/l); [Ca]-serum calcium (corrected for albumin; mmol/l); [Alk P]-serum alkaline phosphatase (IU/l); TmP/GFR-renal tubular reabsorption of phosphate.

(1,25(OH)₂D₃) have been reported in some cases.^{3,4} In the fully established syndrome radiographic changes of osteomalacia appear.¹⁻⁴

Diffuse bone pain and muscle weakness are the usual presenting symptoms¹⁻⁴ and some patients have been misdiagnosed as having ankylosing spondylitis.⁵ When tumour resection has been possible there has been rapid resolution of symptoms and biochemical abnormalities, suggesting that a tumour derived substance is concerned in the pathogenesis.^{1,3-6} Certain tumours propagated in animals cause reduced serum concentrations of 1,25-(OH)₂D₃ and 25-hydroxycholecalciferol-1-hydroxylase activity in the kidney,⁶ while a saline extractable substance derived from a giant cell tumour rapidly depressed tubular reabsorption of phosphate in mice.⁷ Theoretically, impairment of renal tubular function by a tumour derived factor could simultaneously prevent conversion of 25-hydroxycholecalciferol to 1,25-(OH)₂D₃ since hydroxylation occurs within the mitochondria of the renal tubules.³

There are only two previous reports of hypophosphataemia complicating small cell carcinoma of the bronchus.^{8,9} In both cases hypophosphataemia developed

after administration of demeclocycline to treat inappropriate antidiuretic hormone secretion. It was argued that the tubular defect in these cases was probably due to demeclocycline induced renal toxicity rather than a paraneoplastic syndrome.⁹ Demeclocycline toxicity could not be implicated in our patient since the drug was only given during the terminal stages.

While there is no direct evidence for a tumour derived phosphaturic factor in our patient the close temporal relationship between onset of symptoms, hypophosphataemia, and tumour diagnosis supports a causal relationship. Furthermore, progressive hypophosphataemia paralleled worsening of symptoms over a short period and the relatively brief interval from diagnosis to death would account for the absence of radiographic changes of osteomalacia seen in cases associated with more slowly growing mesenchymal tumours. Recognition of this paraneoplastic syndrome as a cause of skeletal pain might have allowed more effective symptomatic treatment. Administration of high doses of vitamin D and phosphate supplements have been used successfully to treat other patients when tumour resection has been impossible.¹

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