Departments of Oncology, and Medicine, Royal Postgraduate Medical School, London W12 0HS
M Harrison, MRCP, registrar
N James, MRCP, registrar
K Broadley, MB BS, senior house officer
S R Bloom, DSC, professor
S Wimalawansa, MRCP, senior lecturer
J Waxman, MD, senior lecturer

Department of Surgery, Lister Hospital, Stevenage
R Armour, FRCS, consultant surgeon

Department of Medicine, Queen Elizabeth Hospital, Birmingham
D Heath, FRCP, reader

calcaemia. A Meta-iodo-benzylguanidine scan showed no tumour uptake and a technetium bone scan no bone metastases. Urinary concentration of vanillylmandelic acid and serum concentrations of calcitonin, 1,25 hydroxy vitamin D, parathyroid hormone, somatostatin, and gut peptides were normal. He was treated with cisplatin and doxorubicin chemotherapy¹ given monthly for three months, but this produced no response. Chemotherapy was changed to fluorouracil, methotrexate, and lomustine. He received three treatment cycles again without response and remained consistently hypercalcaemic. By January 1989 his condition had deteriorated further, and chemotherapy was discontinued. In February 1989 his hypercalcaemia (corrected calcium of 3.36 mmol/l) caused appreciable symptoms. The urinary concentration of vanillylmandelic acid was raised (mean 61.5 mmol/24 h) without change in any other measured hormone. His hypercalcaemia was treated by hydration and with diuretics and disodium etidronate. His serum calcium remained raised. At this stage octreotide treatment was started. The dosage was increased over two days from 50 mg to 100 mg twice a day. There was an immediate decrease in serum corrected calcium concentration from 3.31 to 2.21 mmol/l, and for the first time in 18 months the patient became normocalcaemic. This was associated with a dramatic improvement in his symptoms. As a result of treatment parathyroid hormone related peptide values, which were grossly raised, fell from a pretreatment level of 3.10 pg/l to 0.9 pg/l measured using the PB35 antibody (intra-assay variation <8%, interassay variation <12%, assay sensitivity 0.1 pg/l, no cross reactivity with parathyroid hormone fragments 1-34 or 1-84 or with other related or unrelated peptides; levels undetectable in normal controls)⁴ without significant change in any other hormone or in urinary vanillylmandelic acid concentrations. In situ hybridisation was performed on paraffin embedded material obtained from the original operation. Using an antisense probe parathyroid hormone related peptide mRNA was clearly shown in

the tumour, while control studies with a sense probe were negative (D A Heath *et al*, unpublished data). The response was transient, and six weeks after starting somatostatin his serum calcium was 3.23 mmol/l, but the patient remained without hypercalcaemic symptoms for a further four months.

Comment

Hypercalcaemia in malignancy may relate to humoral mechanisms or to local osteolysis. The cause for humoral hypercalcaemia has been recently described and relates to secretion of parathyroid hormone related peptide.² Hypercalcaemia has been previously reported in pheochromocytoma³ but may result from coexistent hyperparathyroidism. In our patient serum parathyroid hormone values were normal and there were no bone metastases. We showed increased serum concentrations of parathyroid hormone related peptide and its expression within the tumour itself. Our patient became normocalcaemic with treatment, and normocalcaemia was associated with a decrease in concentrations of parathyroid hormone related peptide. Somatostatin analogues may have a role in treating the humoral hypercalcaemia of malignancy, particularly in diphosphonate resistance, and this is currently under investigation.

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Treatment of a malignant pancreatic endocrine tumour secreting parathyroid hormone related protein

D Wynick, W A Ratcliffe, D A Heath, S Ball, M Barnard, S R Bloom

Department of Medicine, Royal Postgraduate Medical School, London W12 0NN
D Wynick, MRCP, Wellcome Trust training fellow
S Ball, MB, medical senior house officer
M Barnard, MRCP, MRC training fellow
S R Bloom, FRCP, professor of endocrinology

Queen Elizabeth Medical Centre, Birmingham B15 2TH
W A Ratcliffe, PHD, principal biochemist, department of clinical chemistry
D A Heath, FRCP, consultant physician, department of medicine

Correspondence to: Professor Bloom.

Hypercalcaemia associated with pancreatic endocrine tumours (islet cell tumours) is most commonly due to primary hyperparathyroidism as part of the syndrome of multiple endocrine neoplasia type I. The concentration of serum parathyroid hormone should be raised in such cases. Hypercalcaemia may also occur in association with tumours secreting vasoactive intestinal polypeptide, with low or undetectable parathyroid hormone concentrations.¹ If the tumour has not disseminated resecting the primary lesion cures the hypercalcaemia, thus indicating a humoral mechanism for the raised serum calcium concentration. We report on a patient with hypercalcaemia and a malignant pancreatic endocrine tumour with metastases to the liver whose tumour appeared to secrete only parathyroid hormone related protein. The long acting somatostatin analogue octreotide was used to try to suppress the hypercalcaemia.

Case report

A 37 year old woman presented in 1985 with a one month history of right upper quadrant pain, polyuria, and lethargy. Investigations showed a corrected serum calcium concentration of 3.46 mmol/l (normal 2.2-2.6 mmol/l) and a serum phosphate concentration of 0.48 mmol/l (normal 0.8-1.4 mmol/l). The results of other haematological and biochemical tests were normal. Angiography and computed tomography showed a tumour of 5×4 cm in the tail of the pancreas and metastases in both lobes of the liver; biopsy confirmed a malignant islet cell tumour. Over the next four years the number and size of the liver metastases slowly grew with a concurrent rise in the calcium concentration to over 3 mmol/l despite introducing oral steroids (15 mg/day), oral phosphates (1.9 g three times daily), and a low calcium diet (<250 mg/day). The biochemical findings of hypercalcaemia, hypophosphataemia with an undetectable serum parathyroid hormone (by both amino terminal and mid-molecule radioimmunoassay), and a normal ^{99m}Tc methylene diphosphonate bone scan suggested that the tumour was secreting parathyroid hormone related protein. A liver biopsy guided by ultrasound was performed and the specimen stained for vasoactive intestinal polypeptide, gastrin, glucagon, insulin, neurotensin, somatostatin, and pancreatic polypeptide. All were negative, which concurred with the normal plasma gut hormone estimations.² Intense staining was present, however, for neurone specific

enolase, a recognised islet cell tumour marker. In situ hybridisation of the biopsy specimen was strongly positive for parathyroid hormone related protein,⁴ and the mean serum parathyroid hormone related protein⁴ was also raised at 17.5 pmol/l (normal <5 pmol/l), suggesting that the tumour was synthesising and secreting parathyroid hormone related protein. To suppress this the long acting somatostatin analogue octreotide (SMS 201-995) was given at a dose of 250 µg subcutaneously twice a day and the concentration of serum calcium fell to and was maintained at 2.3 mmol/l (A in the figure). This decrease was accompanied by

Corrected serum calcium (●) and plasma parathyroid hormone related protein (○) concentrations by time in days. Treatment with octreotide 250 µg twice a day was started at A, the low calcium diet relaxed at B, and oral phosphates discontinued at C

a fall in the concentration of plasma parathyroid hormone related protein, and both remained suppressed for the entire month of octreotide treatment. After two weeks of treatment the low calcium diet was relaxed (B in figure), and a week later oral phosphate supplements were also discontinued (C). These

changes in treatment did not alter the mean concentrations of calcium or parathyroid hormone related protein nor was a further increase in the dose of octreotide necessary. Octreotide treatment was discontinued after six weeks; the serum calcium concentration rose to 3.35 mmol/l within 36 hours, and when octreotide was reintroduced it fell again to 2.47 mmol/l within 24 hours. The patient was well and normocalcaemic after six months of treatment with octreotide 250 µg twice a day.

Comment

As far as we know this is the first reported case of a patient with a malignant pancreatic endocrine tumour that synthesised and secreted parathyroid hormone related protein and associated hypercalcaemia. Since other endocrine tumours such as small cell lung cancer and non-endocrine tumours such as breast carcinoma and meningiomas have high densities of cell surface somatostatin receptors⁵ the use of octreotide may be beneficial in the long term in treating associated hypercalcaemia.

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ONE HUNDRED YEARS AGO

There is equal reason to regret and to complain of an article on this subject fulminated against Mr. Chaplin by the *Standard* of January 4th. The article in question was characteristic of the anti-muzzling agitation, but, in spite of inventiveness and false colouring, nothing will hide from reasoning people the real facts upon which the present muzzling regulations have been framed by the President of the Board of Agriculture. These facts, collected and published *in extenso*, as they were nearly three years ago by the Select Committee of the House of Lords on Rabies in Dogs, etc., are known to every scientist.

The article in question purports to be a review of the circumstances under which muzzling has become necessary, but it consists really of two incompatible parts, one being an abusive attack on Mr. Chaplin, the other being a summary of most of what is not true about the muzzle. The former of these is put forward for obvious reasons both as exordium and peroration, and is positively nothing more than an attempt to inflame political rancour on this, the most innocently scientific subject that can be conceived. The praiseworthy and eminently humane efforts of the Government to stamp out a fell disease, affecting not only man, but the lower animals as well, the writer tries to hamper and block by raising party feelings.

But if any points in the article really bear on the subject of the extermination of hydrophobia, they are to be found in the other division of the subject, that to which the article should obviously have been confined—namely, How can rabies be prevented, and, looking at the matter from a common sense point of view, what is likely to result from the working of the regulations? The writer of the article, by ingenious innuendo and by forgetfulness or ignorance—perhaps both—contrives to convey the following amazing statements: First, that the muzzle causes and “propagates” rabies, that “mad dogs do not travel far,” that “the symptoms of approaching rabies are well known to all who are really familiar with dogs,” that the muzzle is “torture” and “wanton cruelty.”

All these are old, well-worn fabrications which have done service for the last few years. To those who are unfamiliar with the proceedings of popular agitators it must seem extraordinary that such repeatedly exploded fictions should find credulous listeners. But the fifteen years which are said to elapse before any truth is finally recognised by the public at large have not half expired. Six years ago the bare existence of rabies was doubted by many, and only three years ago denied utterly by the originators of the agitation, which our able and usually well-advised contemporary has so unaccountably fathered.

Nothing but the steady refutation of false statements and the publication of the splendid results already effected by muzzling regulations in this country will bring about the desired freedom, not only from hydrophobia, but also from the muddy stream of misrepresentation with which some are ready to besmear this, which, thanks to M. Pasteur, is one of the clearest pages in the annals of disease.

A solitary outcry of the kind we have felt obliged to refer to in the above terms does, in the end, real good to the progress of sanitary science and preventive medicine, for it shows to what desperate straits and to what unsavoury depths a writer is reduced when he is championing the cause of a few selfish and unfeeling individuals against the health of the nation and the welfare of the canine race.

The measures adopted by the President of the Board of Agriculture are calculated to secure the local eradication of the disease from the Home and the Northern Counties, which are the most important centres of its propagation. It does, indeed, appear strange that those who profess to guide public opinion should fail to remark that Mr. Chaplin's action is not, as the *Standard* mischievously asserts, “stupid” or “a pure fad,” but is guided by the general principles which have been so successful in stamping out other contagions of animals, and which are endorsed by the whole civilised and veterinary world.

(*British Medical Journal* 1890;i:85)