CASE REPORTS

Hypocalcaemic response to streptomycin in malignant hypercalcaemia

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Summary

We report a case of malignant hypercalcaemia associated with primary hepato-cellular carcinoma in whom streptomycin produced a notable and reproducible fall in serum calcium. A hypocalcaemic response to streptomycin has been reported from experimental animals but not previously from man.

Introduction

Malignant hypercalcaemia (pseudohyperparathyroidism) is occasionally associated with primary hepatocellular carcinoma (PHC) or cholangio carcinoma which has not metastasized to bone (Becker, Sternberg and Kalser, 1963; Keller, Goldschneider and Lafferty, 1965; Knill-Jones *et al.*, 1970). Normocalcaemia is restored if the tumour is resected or a liver transplant undertaken (Knill-Jones *et al.*, 1970). Generally, treatment of PHC with radiotherapy or chemotherapy has met with little success and the prognosis remains poor (El-Domeiri *et al.*, 1971; Falkson, 1973). In the case reported here, the primary liver cancer was irresectable. The hypercalcaemia proved refractory to treatment with oral phosphates, glucagon and saline infusions, but responded transiently to intra-arterial mitomycin-C and markedly to parenteral streptomycin. The hypocalcaemic effect of streptomycin has been reported from experimental animals (Galante *et al.*, 1970), but not previously from patients with hypercalcaemia.

Case report

A 45-year-old male patient presented in January 1973 with dyspepsia, polyuria, polydipsia and marked weight loss, all of which had been present for 6 months. He was moderately emaciated with slight epigastric tenderness and a one finger smooth hepato-

megaly. A bruit was heard over the right lobe of the liver. The remainder of the examination was unremarkable.

Investigations in January 1973 were: haemoglobin 15.2 g/100 ml; ESR (Westergren) 30 mm in the first hour; bilirubin (total) 0.8 mg/100 ml; alkaline phosphatase 36.6 and 30.1 K.A. units; 5-nucleotidase 21.6 units (normal 2-17); serum calcium 7.2 mEq/l and 7.0 mEq/l; serum phosphorus 2.2 mg/100 ml and 1.5 mg/100 ml; ionized serum calcium 3.2 mEq/l; serum albumin 2.96 g/100 ml; γ -globulin 2.51 g/100 ml; serum electrolytes: urea 38 mg/100 ml, potassium 4.1 mEq/l, sodium 142 mEq/l, chlorides 101 mEq/l and carbon dioxide content of 28 mEq/l; blood gas status (Astrup): pH 7.50, pCO₂ 36.5 mmHg, base excess + 4.5 mEq/l and standard bicarbonate 28.5 mEq/l.

The immunodiffusion test for α -fetoprotein was positive and the complement fixation test for hepatitis-B (Australia) antigen was positive in a titre of 1/16.

The phosphate excretion index when the patient was on a routine ward diet was + 0.31 (normal + 0.09 to - 0.09); creatinine clearance (24-hr) was 100 ml/min; urinary electrolyte excretion per day (mean of fourteen estimations over 28 days); calcium 225 mEq/l (167-374 mEq/l); phosphorus 617 mg/100 ml (290-1530 mg/100 ml); sodium 31 mEq/l (12-76 mEq/l); potassium 22 mEq/l (8-43 mEq/l); urinary pH was never below 5.8 and in the short urinary acidification test of Wrong and Davies (1959) the urine pH fell to 5.40 at 4 hr and 5.55 at 10 hr. A 50 g oral glucose tolerance test and D-xylose absorption test was normal.

Liver scan with ^{99m}Tc sulphur-colloid revealed two filling defects in the right lobe of the liver in a postero-superior position. Percutaneous biopsy of these areas

showed features of a hepatocellular carcinoma with loss of normal architecture. Radiographic skeletal surveys were repeated at monthly intervals (January, February, March) and these did not indicate features of bony metastases or signs of primary hyperparathyroidism. A bone scan was not performed. Two coin lesions, each 1 cm in diameter, were noted in the left lower lobe of the lung. Excision biopsy of these was performed on 15 January 1973 through a left thoracotomy incision. Histology was consistent with metastases from a PHC.

Treatment

As the tumour was not amenable to resection, control of the hypercalcaemia was attempted. Neutral phosphates, 3 g/day, produced no significant decrease in serum calcium levels. Saline infusion (300 mEq/day) produced a marked calcium diuresis with a return to normal of the metabolic alkalosis. However, it failed to lower the high serum calcium levels. Glucagon (1.0 mg three times per day, given as parenteral injection) did not affect serum calcium levels. Steroids were withheld until resectability of the tumour was assessed by means of biopsies, but were then not given as a hypocalcaemic response to streptomycin was observed. Following two short courses of penicillin and streptomycin for respiratory

infection, a marked fall in serum calcium was noted (14 January 1973–18 January 1973 calcium fell from 6.6 mEq/l to 5.6 mEq/l, and 24 January 1973–27 January 1973 from 6.0 mEq/l to 4.9 mEq/l) with a marked rise 48 hr after the streptomycin was stopped. Treatment with streptomycin was repeated during February and March (Fig. 1). Treatment with saline infusions was also used. Each course of streptomycin produced a prompt reduction of serum calcium and a slow, significant decrease in serum alkaline phosphatase. Isoenzyme estimation by starch-gel electrophoresis (Taswell and Jeffers, 1963) showed a predominant decrease in the bone isoenzyme during streptomycin treatment. No alteration in creatinine clearance or urinary electrolyte excretion was noted on this regime, nor was the metabolic alkalosis corrected unless saline infusion was added to the treatment.

In view of this response to streptomycin, coeliac artery perfusion with mitomycin-C, a *Streptomyces*-derived cytotoxin, was performed according to the method of Yamada *et al.* (1970). A total dose of 120 mg was given. Addition of this chemotherapeutic agent to the treatment led to a transient fall in serum calcium and alkaline phosphatase levels which returned to normal within 4 days. No radiological shrinkage of the tumour was observed with mitomycin-C. At this point the patient requested to be

FIG. 1. The effect of streptomycin, daily saline infusions and mitomycin-C on hypercalcaemia. Serum calcium and alkaline phosphatase fell during streptomycin and mitomycin therapy. Saline infusions corrected the metabolic alkalosis.

allowed to return to his rural home and was lost to follow-up.

Discussion

The mechanism of hypercalcaemia in PHC is unknown. One reported case of cholangiocarcinoma with hypercalcaemia had elevated immuno-reactive parathyroid hormone levels (Knill-Jones *et al.*, 1970). Such ectopic parathormone production is known in many other tumours which produce the syndrome of pseudohyperparathyroidism. That this case is one of pseudohyperparathyroidism is indirectly adducible from the following features: the high initial serum calcium levels (Lafferty, 1966), a marked metabolic alkalosis (Heineman, 1965) which is not attributable to vomiting, diarrhoea or gross electrolyte loss, rapid weight loss, absence of renal calculus disease and failure to demonstrate radiographic signs of primary hyperparathyroidism. Bony metastases are extremely rare in PHC (Moseley, 1967) and were not observed in this patient. The presence of microscopic bone deposits could not be verified.

The hypocalcaemic action of the *Streptomyces*-derived antibiotics has recently been reported by Galante *et al.* (1970) who showed that streptomycin and other amino-glycosides produce a dose-related fall of serum calcium in rats. Clinically a similar response is noted in the present case of pseudohyperparathyroidism. The hypocalcaemic effect in animals is abolished in euparathyroid-thyroidectomized animals and was related to a rise in plasma calcitonin levels. Calcitonin levels were not measured in this patient and production of hypocalcaemia by action of this hormone was not established.

Glucagon, a hypocalcaemic agent in man (Birge and Avioli, 1969) and a calcitonin-releasing agent in medullary carcinoma of the thyroid (Melvin, Voelkel and Tashjian, 1970), did not produce any fall in serum calcium in the present case. It is now known that glucagon does not stimulate calcitonin-release in normal subjects, i.e. those without medullary carcinoma (Tashjian *et al.*, 1970), an observation which is reflected in the present patient as he did not show a calcitonin-like response to glucagon.

The *Streptomyces*-derived cytotoxic, mithramycin (*S. plicatus*), produces short lived hypocalcaemia with single dose injections in malignant hypercalcaemia (Slayton *et al.*, 1971). The present case shows that another *Streptomyces*-derived cytotoxin, mitomycin-C (*S. caespitosus*), produces a temporary fall in serum calcium not unlike the response noted with mithramycin. Mithramycin and mitomycin are structurally unrelated; however, Galante *et al.* (1970) point out that the hypocalcaemic effect of the amino-glycosides is unrelated to their structure and from the present case this seems to apply to the cytotoxic derivatives of this group.

Further investigation of the relationship between streptomycin and serum calcium is needed in order to establish the role of this aminoglycoside in human calcium turnover.

Acknowledgments

The authors would like to thank the Superintendent, Johannesburg General Hospital, for permission to publish this case and Dr Ipp for undertaking the alkaline phosphatase isoenzyme estimations.

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