Hypercalcaemia and parathyroid hyperplasia associated with renal adenocarcinoma

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Summary

A patient with recurrent renal adenocarcinoma had progressive hypercalcaemia associated with hypophosphataemia and inappropriately high circulating levels of immuno-reactive parathyroid hormone. At post-mortem, there was no evidence of bone metastases but hyperplasia of all four glands was found. It is suggested that the malignant tissue was producing a parathyroid-stimulating substance.

Introduction

Hypercalcaemia in patients with malignant disease is usually due to bone metastases but is sometimes associated with inappropriately high levels of immuno-reactive parathyroid hormone in the serum (Tashjian, Levine and Munson, 1964; Sherwood *et al.*, 1967; Roof *et al.*, 1971). In most such cases, this immuno-reactive parathyroid hormone seems to be produced by the malignant tissue but occasionally there is an associated parathyroid adenoma (Dent and Watson, 1964; Katz *et al.*, 1970; Kaplan *et al.*, 1971) or, rarely, parathyroid hyperplasia (Case Records of the Massachusetts General Hospital, 1957, 1964; Stone, Waterhouse and Terry, 1961). Previously reported associations of malignant disease with parathyroid hyperplasia have all been in patients with squamous cell carcinoma of the bronchus. This report is of a patient with parathyroid hyperplasia and renal adenocarcinoma.

Case report

A 29-year-old man was admitted to hospital because of haematuria due to a tumour of the right kidney. Nephrectomy was performed and the histological diagnosis was adenocarcinoma (Fig. 1). Total plasma calcium (corrected for plasma protein concentration) and inorganic phosphate were normal

at 9.6 and 3.5 mg/100 ml respectively. Eighteen months later he was re-admitted with a painful mass in the right hypochondrium. Plasma calcium had risen to 10.4 mg/100 ml and plasma phosphate was now 3.1 mg/100 ml. A second operation was decided against and he was treated with antimitotic drugs. Three weeks later, he was hypercalcaemic, plasma calcium being 14.6 mg/100 ml and the plasma phosphate 2.1 mg/100 ml. Skeletal X-rays were normal. But 3 months later, despite treatment with corticosteroids, plasma calcium had risen further to 18.6 mg/100 ml. Plasma phosphate was now 1.8 mg/100 ml, creatinine 1.7 mg/100 ml, urea 46 mg/100 ml and alkaline phosphatase 53 iu/l. Serum immuno-reactive parathyroid hormone (assayed according to the method of Arnaud, Tsao and Littledike, 1971) was 0.5 ng/ml, the upper limit of normal being 0.4 ng/ml when plasma calcium is within the normal range. Despite rehydration and infusions of sodium phosphate, the patient died one month later (22 months after admission).

At post-mortem, a large retroperitoneal tumour was found, the microscopic appearance being the same as that of the original renal lesion. No bone metastases were found either on macroscopic or microscopic examination, but there was increased osteoclastic activity and trabecular remodelling. All four parathyroids were enlarged (total mass 410 mg) with generalized chief cell hyperplasia (Fig. 2).

Discussion

There are several reasons for believing that this patient's rapidly progressive hypercalcaemia was due to hyperparathyroidism and not to bone metastases. Firstly, there was no evidence of bone metastases during life or *post mortem*. Secondly, hypercalcaemia due to bone metastases is often accompanied by hyperphosphataemia because increased bone resorption leads to an increased rate of removal of both calcium and phosphate from bone, and also

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FIG. 1. Operative specimen of renal adenocarcinoma, $\times 144$.

FIG. 2. Post-mortem specimen of parathyroid hyperplasia, $\times 144$.

because the hypercalcaemia leads to parathyroid suppression with a consequent increase in renal tubular resorption of phosphate. Thirdly, there was clear evidence of parathyroid overactivity: the serum concentration of immuno-reactive parathyroid hormone was increased and parathyroid hyperplasia was found at post-mortem.

The association of renal adenocarcinoma and parathyroid hyperplasia in this patient could obviously be fortuitous, but the similarity in time course between the growth of the tumour and the development of the features of hyperparathyroidism suggests that the malignant tissue was producing a parathyroid-stimulating substance. A speculative

possibility is that this substance was a metabolite of vitamin D, since it is known that the normal kidney produces a number of such metabolites and it is conceivable that one or more of them might be capable of stimulating parathyroid activity.

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