MEDICAL PRACTICE

Clinical Problems

Hypercalcaemia in Patients with Advanced Mammary Cancer

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British Medical Journal, 1971, 3, 573-577**Summary**

Hypercalcaemia and hypercalciuria are common complications of advanced mammary cancer. Of 127 patients with the disease 63 (49.5%) had some abnormality of calcium balance. Eighteen (14%) of these patients developed severe progressive hypercalcaemia and became acutely ill.

Most patients had skeletal metastases, and the usual cause of hypercalcaemia was rapid destruction of bone by the cancer. One patient with severe uncontrollable hypercalcaemia and minimal skeletal involvement probably developed the complication due to inappropriate secretion of a parathyroid-hormone-like substance by massive hepatic deposits.

Severe hypercalcaemia was controlled successfully in 13 of the 18 patients, the serum calcium levels returning to normal and the acute symptoms disappearing. Unfortunately, successful correction of the hypercalcaemia rarely was followed by prolonged survival from the underlying malignant disease. The incidence of subsequent objective response to pituitary ablation was less than usual, and only three patients survived for more than one year after the episode of hypercalcaemia.

Introduction

In 1855 Virchow described diffuse ectopic calcification in a patient with extensive skeletal metastases from a mammary

carcinoma.¹ He suggested that these findings might be related to a raised level of calcium in the blood. In recent years the association of hypercalcaemia and breast cancer has attracted much attention, and it is now known to be a not infrequent complication, which if untreated may prove fatal. Unfortunately the symptoms caused by hypercalcaemia are varied and may be attributed wrongly to progression of the malignant disease.

This paper records the incidence of calcium abnormalities in 127 women with advanced mammary cancers treated in the Hammersmith Hospital breast unit during the three years 1966-8. All patients were admitted to hospital before starting treatment for their cancers. Each patient was placed on a diet containing less than 25 mEq of calcium a day for five days. At least two serum calcium measurements were made during this period. The urinary calcium levels were measured on days 4 and 5 in most but not all patients. Both serum and urinary calciums were measured by the method of MacIntyre.² The finding of any abnormality in the levels of calcium led to a more prolonged period of biochemical investigation. A radiological skeletal survey also was done in each patient, consisting of a lateral x-ray examination of the skull, lateral and anteroposterior views of the cervical, dorsal, and lumbar spines, a posterior-anterior film of the chest, and an anteroposterior film of the pelvis.

All surviving patients were seen regularly in the follow-up clinic. The serum calcium measurements and skeletal surveys were repeated every three months, or more frequently if indicated clinically. Further urinary calcium measurements were made whenever a patient was readmitted to hospital for any reason.

Incidence of Calcium Abnormality

Altogether 63 (49.5%) out of the 127 patients had some abnormality of calcium balance. Twenty-one patients (16.5%) showed evidence of transient or more prolonged hypercalciuria but remained normocalcaemic. A further 24 (19%) developed

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"incidental" hypercalcaemia which was symptomless, with the levels returning to normal without treatment. In only one of these patients was the serum calcium more than 6.0 mN (laboratory normal 4.7 to 5.5 mN). In one patient the hypercalcaemia persisted for three months, and in another for one month. In the remainder the hypercalcaemia was present for less than four days. Fifteen of these patients with hypercalcaemia also had hypercalciuria, which often preceded the raised serum levels.

Eighteen patients (14%) developed pronounced hypercalcaemia which resulted in acute symptoms of varying degrees of severity and which often required strenuous therapy. In all these patients the serum calcium levels were above 6.0 mN. Six of these patients had developed hypercalciuria previously from 1 to 24 months before the severe hypercalcaemic episode.

Clinical Features of Severe Acute Hypercalcaemia

The most common complaint in the 18 patients with acute hypercalcaemia was of a recent and often severe increase in skeletal pain. Gastrointestinal symptoms were prevalent, particularly anorexia, nausea, and vomiting. In eight patients severe vomiting led to pronounced dehydration. Many patients complained of progressive weakness, lethargy, and somnolence, and five became noticeably disorientated. One patient developed coma.

In eight of the 18 patients the hypercalcaemia occurred at varying times after starting hormonal therapy for their advanced disease. Six of these patients were receiving fluoxymesterone (an androgen) and the other two stilboestrol. In three other patients the hypercalcaemia developed after they had undergone pituitary ablation. The remaining seven patients became acutely hypercalcaemic before receiving any hormonal therapy.

Skeletal Metastases

Eighty-six of the 127 patients in the series (68%) had radiologically apparent skeletal metastases. For the individual patient there was no correlation between the serum calcium and the extent of skeletal involvement. Some patients with extensive skeletal metastases never became hypercalcaemic, while others with apparently minimal skeletal involvement showed pronounced hypercalcaemia; however, only one of the 18 patients who developed acute symptomatic hypercalcaemia did not have evidence of skeletal disease.

Case Reports

Details of the 18 patients with acute hypercalcaemia are given in Tables I and II.

Case 1.—A woman aged 45 was started on fluoxymesterone therapy for skeletal metastases in June 1967. She was admitted to hospital on 7 January 1968 with a recent history of severe increase in bone pain, vomiting, and general prostration. She was stuporous on admission and the serum calcium was found to be 8.0 mN. The fluoxymesterone was stopped and she was treated by intravenous infusions of saline. There was no response, the serum calcium rising to 10.0 mN. Thyrocalcitonin was added to the regimen and there was slight but temporary improvement (Fig. 1). With the addition of intravenous and oral inorganic phosphate and cortisone her general condition improved considerably and the serum calcium gradually fell, though never to normal. Pituitary ablation with yttrium-90 was carried out on 30 January, when her serum calcium was 6.2 mN. After pituitary ablation the serum calcium remained slightly raised, the level ranging between 5.7 and 6.8 mN. She required continuous phosphate therapy to maintain these levels, the serum calcium showing signs of rising whenever the phosphate was stopped. She had considerable relief of bone pain after pituitary ablation, but her condition deteriorated and she died in March 1968. At necropsy widespread skeletal metastases were confirmed and there was also evidence of nephrocalcinosis.

TABLE I—Acute Hypercalcaemia Occurring after Hormonal Therapy or Pituitary Ablation

Case No.	Highest Recorded Serum Calcium	Preceding Hormonal Therapy	Treatment of Hypercalcaemia	Response of Hypercalcaemia to Treatment	Subsequent Response of Mammary Cancer	Survival after Hypercalcaemic Episode
1	10.0 mN	Fluoxymesterone 7 months	Stop fluoxy., saline, thyrocalcitonin, phosphate, cortisone, pituitary ablation	Yes	Relief of pain	2 months. Died of carcinoma
2	8.3 mN	Fluoxymesterone 4 months	Stop fluoxy., cortisone, pituitary ablation	Yes	None	2 months. Recurrence of hypercalcaemia terminally
3	7.6 mN	Fluoxymesterone 3 months	Stop fluoxy., pituitary ablation	Yes	Relief of pain	18 months. Died of carcinoma
4	8.9 mN	Fluoxymesterone 1 month	Stop fluoxy., saline phosphate, pituitary ablation	Yes	None	1 month. Recurrence of hypercalcaemia terminally
5	8.8 mN	Fluoxymesterone 2 weeks	Stop fluoxy., pituitary ablation	Yes	None	5 months. Died of carcinoma
6	9.5 mN	Fluoxymesterone 2 weeks	Stop fluoxy., saline, phosphate, pituitary ablation	No	—	Did not survive episode
7	6.3 mN	Stilboestrol 1 month	Stop stilb., pituitary ablation	Yes	Partial regression	4 months. Died of pneumonia
8	10.8 mN	Stilboestrol 3 weeks	Stop stilb., saline, phosphate	Yes	Relief of pain from subsequent pituitary ablation	22 months. Died of carcinoma
9	8.3 mN	Pituitary ablation 2 months previously	Saline, phosphate	Yes	None	1 month. Died of carcinoma
10	9.0 mN	Pituitary ablation 2 weeks previously	Cortisone	Yes	None	2 months. Died of carcinoma
11	8.5 mN	Pituitary ablation 6 months previously	Nil	No	—	Terminal event. Did not survive episode

TABLE II—Acute Hypercalcaemia Occurring before Hormonal Therapy

Case No.	Highest Recorded Serum Calcium	Treatment of Hypercalcaemia	Response of Hypercalcaemia to Treatment	Subsequent Response of Mammary Cancer	Survival after Hypercalcaemic Episode
12	6.3 mN	Saline	Yes	No specific therapy	1 month. Died of carcinoma
13	6.6 mN	Saline	Yes	No specific therapy	3 months. Died of carcinoma
14	6.6 mN	Pituitary ablation	Yes	Complete regression	33 months. Alive and well
15	7.7 mN	Saline, phosphate, pituitary ablation	Yes	None	4 months. Died of carcinoma
16	9.6 mN	Saline, phosphate, oophorectomy	No	None	1 week. Did not survive episode
17	6.2 mN	Saline, stilboestrol	No	None	Did not survive episode
18	9.3 mN	Nil	—	—	Died within few hours of admission

FIG. 1—Case 1. Effect of thyrocalcitonin on hypercalcaemia. There was a slight but temporary fall in the level of the serum calcium.

Case 3.—This patient, aged 49, developed an acute hypercalcaemic crisis in October 1966, three months after starting fluoxymesterone therapy for skeletal metastases. Her serum calcium reached 7.6 mN (Fig. 2). She was treated with a low calcium diet and immediate pituitary ablation by the implantation of yttrium-90. The serum calcium rapidly returned to normal, and though the skeletal metastases continued to increase she remained free from hypercalcaemia until her death in April 1968.

FIG. 2—Case 3. In this patient the hypercalcaemia was precipitated by treatment with fluoxymesterone. The hypercalcaemia responded to a low calcium diet and pituitary ablation. The latter was incomplete, however, and a second implantation of rods of yttrium-90 was carried out 7 months later. Though the skeletal metastases subsequently increased in size the patient remained normocalcaemic.

Case 8.—A 53-year-old spinster was started on stilboestrol therapy for painful metastases of the spine on 16 July 1967. On 8 August she was admitted to hospital as an emergency in a semicomatose state. Her admission had been preceded by severe back pain, anorexia, and intense vomiting. Repeated serum calcium levels on admission ranged from 10.2 and 10.8 mN. Stilboestrol was stopped and she was treated with an intravenous saline infusion and inorganic phosphate. Her clinical condition improved rapidly and the serum calcium returned to normal. Pituitary ablation was carried out on 19 September. She was kept in a low calcium diet thereafter and died in June 1969 without any recurrence of hypercalcaemia (Fig. 3).

Case 16.—A 31-year-old woman was transferred to Hammersmith Hospital in November 1968. Two weeks previously she had undergone local excision of a small carcinoma of the left breast. She complained of fatigue, abdominal pain, and breathlessness. On examination she was drowsy and dyspnoeic on effort. There was massive nodular hepatomegaly but she was not jaundiced. There was no radiological evidence of skeletal metastases. She was hypercalcaemic, the serum calcium being 9.6 mN. She was treated for 48 hours with intravenous saline infusions, but the hypercalcaemia

FIG. 3—Case 8. Hypercalcaemic crisis precipitated by stilboestrol therapy. The hypercalcaemia responded to a low calcium diet, intravenous saline, and inorganic phosphate. When the patient was normocalcaemic pituitary ablation was carried out. Though her mammary cancer did not respond and her skeletal metastases increased in size she remained normocalcaemic and free from pain. In May 1969 she required an Austin Moore prosthesis for a transcervical fracture of the left femur.

failed to respond. Intravenous inorganic phosphate was given but with little response. After a further 48 hours bilateral oophorectomy was carried out. After operation the serum calcium fell to 7.4 mN, but her condition deteriorated rapidly and she died. At necropsy the liver weighed 2,100 g and was almost totally replaced by metastatic tumour. There were no macroscopic skeletal metastases

FIG. 4—Case 16. Photomicrographs of a rib (a) and of a dorsal vertebra (b) from a patient who died from acute hypercalcaemia and massive malignant hepatomegaly. There is pronounced osteoclastic destruction of bone similar to that occurring in hyperparathyroidism (H. and E. $\times 290$.)

but a solitary focus was found in her lumbar spine on histological examination. There was evidence of excessive osteoclastic activity in the bones (Fig. 4) similar to that occurring in hyperparathyroidism. In this patient the hypercalcaemia probably resulted from inappropriate secretion of a parathyroid-hormone-like substance by the tumour and was not due to destruction of bone by metastases.

Discussion

AETIOLOGY

Several mechanisms may be responsible for the development of hypercalcaemia in patients with mammary cancers. Usually the condition is associated with osteolytic skeletal metastases, when large amounts of calcium may be liberated into the circulation.³⁻⁵ There does not appear to be any correlation between the extent of skeletal involvement and the risk of hypercalcaemia. If the excess circulating calcium is successfully excreted in the urine symptoms of hypercalcaemia may not occur. Many patients show transient hypercalcaemia, therefore, without ill effect.

Hypercalciuria may precede symptomatic hypercalcaemia, however, and if detected should not be regarded lightly. Six of our patients who developed acute symptomatic hypercalcaemia had shown hypercalciuria previously. Acute hypercalcaemia may appear to be induced by hormonal therapy.^{5,6} Eight of our patients were receiving either fluoxymesterone or stilboestrol when the condition developed, the treatment often having started only a few weeks previously. In three other instances acute hypercalcaemia occurred in patients who had undergone a recent pituitary ablation. It is noteworthy that only one of these 11 patients had shown any objective regression of metastases, and presumably the hypercalcaemia was due to progressive destruction of bone.

Seventeen of the 18 patients in our series who developed acute hypercalcaemia had obvious skeletal metastases, emphasizing their importance in the development of this complication. Other mechanisms occasionally apply, however, and in particular the inappropriate secretion by the tumour of parathyroid-hormone-like substances, parathyrotropic hormone, or osteolytic steroids.^{4,7-9} One of these mechanisms presumably applied in the patient (Case 16) who died from uncontrollable hypercalcaemia with massive hepatic metastases and evidence of osteoclastic activity similar to that occurring in hyperparathyroidism. Hypercalcaemia may also occur in the presence of adrenal insufficiency, but there was no evidence of this in any of our patients, including the three who had undergone pituitary ablation.

The findings in the present study confirm that hypercalciuria and hypercalcaemia are common complications of advanced mammary cancer. Thomas and his colleagues¹⁰ detected hypercalcaemia in 42% of their patients at some stage of the disease, and other workers have reported similar findings.^{11,12}

TREATMENT

In our series two distinct patterns of hypercalcaemia emerged. The first type was represented by a symptomless transitory rise of the serum calcium, usually never above 6.0 mN and returning to normal without specific treatment. The second type was acute, progressive, and potentially fatal. Specific therapy, often strenuous, was required to control the hypercalcaemia, and was not always successful. The symptoms produced by the hypercalcaemia were various and often bizarre, but most patients experienced a severe increase in skeletal pain at the onset and dehydration was common.

Because the symptomatology is varied and often similar to that occurring solely due to progression of the underlying disease, it is important to consider hypercalcaemia whenever sudden deterioration occurs in a patient with advanced

mammary cancer. In particular, the possibility of hypercalcaemia should be considered whenever acute deterioration occurs soon after starting hormonal therapy.

Any patient with *symptomless* hypercalcaemia should be advised to take a low calcium diet and to maintain a liberal fluid intake. Such a patient should be kept under close observation in the outpatient clinic until the serum calcium returns to normal. Patients with persistent hypercalciuria should also be advised to take a low calcium diet and watched carefully for the development of hypercalcaemia.

Patients with acute *symptomatic* hypercalcaemia must be admitted to hospital and placed on low calcium intake by excluding milk and all milk products. Rehydration is necessary, and as intravenous isotonic saline encourages a calcium diuresis³ this should be used when vomiting precludes oral fluids. A fluid intake of at least 3 litres a day is usually required.

These simple measures were insufficient in most of our patients, many of whom were critically ill on admission to hospital. Inorganic phosphate therapy was therefore used in several patients who were resistant to the initial hydration regimen. Phosphates were given according to the recommendations of Thalassinou and Joplin,¹³ who described in great detail the rationale of this treatment.

Whenever possible the phosphate was given by mouth. A neutral phosphate mixture was used containing 1 g of elemental phosphorus in 60 ml of the mixture, the usual dosage regimen being 60 ml eight-hourly. A liberal fluid intake was maintained during the phosphate therapy, which was discontinued when the serum calcium fell to normal. Occasionally prolonged therapy with phosphate was required to maintain a normal serum calcium (Case 1). In some patients it was necessary to give the phosphate intravenously. The intravenous preparation used contained 1 g of elemental phosphorus in 330 ml of solution, this dose being given each day as a single infusion over a period of six hours. The intravenous preparation was replaced by the oral mixture as soon as the patient was able to take this. Satisfactory lowering of the serum calcium was achieved in five of the seven patients in whom phosphate therapy was used, with accompanying clinical improvement.

The reported complications of phosphate therapy are undue hypocalcaemia and ectopic calcification, especially nephrocalcinosis.^{4,14,15} No patient became unduly hypocalcaemic but nephrocalcinosis was found at necropsy in one patient who died two months after prolonged phosphate therapy (Case 1).

Corticosteroids have often been used in the treatment of hypercalcaemia of malignant disease^{16,17} but results generally have been disappointing, and corticosteroids clearly are not so effective as phosphates.¹⁸ Cortisone was used in the treatment of three of our patients, with possibly some benefit in two. One (Case 1) also received calcitonin therapy with slight but only temporary improvement. Calcitonin inhibits bone resorption and plays a part in maintaining calcium balance,¹⁹ but in the treatment of hypercalcaemia the results have been disappointing.²⁰

When severe hypercalcaemia occurs soon after starting hormonal therapy for advanced mammary cancer the hormone must be discontinued. Subsequent major endocrine ablation is not necessarily followed by a recurrence of hypercalcaemia, and paradoxically may be required to control the hypercalcaemia completely. Six of our patients who had been on hormonal therapy before becoming acutely hypercalcaemic underwent pituitary ablation before the calcium levels returned to normal. In another woman (Case 6) severe hypercalcaemia persisted despite pituitary ablation, and she died. In one patient (Case 8) the serum calcium returned to normal without resort to immediate ablation, which was done subsequently without any recurrence of hypercalcaemia. Severe hypercalcaemia occurring *after* pituitary ablation, though responding temporarily to treatment, was followed by early death from the malignant disease in our series.

Endocrine treatment may also be required to control completely acute hypercalcaemia occurring in patients with advanced

mammary cancer who have not received previous hormonal therapy. One such patient in our study (Case 14) was treated exclusively by rehydration and immediate pituitary ablation. She remains in complete remission almost three years after the episode of hypercalcaemia.

Severe hypercalcaemia was treated successfully in 13 of the 18 patients in our series, the serum calcium levels returning to normal and the acute symptoms disappearing. Unfortunately successful correction of the hypercalcaemia was rarely followed by prolonged survival from the underlying malignant disease. Only three patients lived for more than one year after the episode and all but six were dead within three months.

In the experience of Hall and his colleagues⁶ the development of hypercalcaemia in patients with advanced mammary cancers does not necessarily imply failure of the disease to respond to treatment. Their patients who developed hypercalcaemia fared slightly better than those who remained normocalcaemic. Our experience, however, suggests the opposite: only one patient (Case 14) subsequently obtaining genuine prolonged regression of metastatic disease. Three others obtained worthwhile symptomatic relief of bone pain for varying periods of time despite the lack of objective evidence of response. This is in contradistinction to the usual incidence of total response to pituitary ablation of between 25 and 30%.

The development of acute hypercalcaemia must be regarded as a sinister event in patients with advanced mammary cancer. Nevertheless, an occasional patient who survives the episode will subsequently obtain a good remission from major endocrine ablation. For this reason it is imperative that the complication should be recognized and appropriate treatment given before it becomes irreversible. Calcium imbalance occurs much more frequently in patients with advanced mammary cancers than is

generally appreciated, and constant vigilance is necessary to detect it.

We are grateful to Professor I. D. P. Wootton and the staff of the department of chemical pathology at Hammersmith Hospital and the Royal Postgraduate Medical School for doing the calcium estimations on the patients in this study.

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Any Questions?

We publish below a selection of questions and answers of general interest

Storage of Semen

What is the best available technique for the storage and later use of human semen under home conditions?

The storage of human semen for later use "under home conditions" is not a practical possibility.

Sense of Smell

Is there any evidence that women have a more acute sense of smell than men?

This question is often asked because there is circumstantial evidence of a specific biological role for olfaction in the female. The best known example is the reaction of women towards food during early pregnancy when the psychological and physiological effects of flavours seem to be greatly magnified and altered. The rôle of smell in sexual stimulation throughout the animal kingdom and its likely effect on the hormonal balance is well recognized, and in some species the pregnant female may even abort if she smells an unknown male. These effects can be abolished by destroying the olfactory bulbs.

This type of evidence however suggests a sexual function for smell which may not yet have been as dramatically demonstrated in the male. It does not imply an increased acuity of smell. Most attempts at measuring the sense of smell qualitatively and quantitatively¹—and tests are still rather crude—have not shown any measurable difference between men and women.

Smokers and non-smokers differ in their sensitivity to smells, and as women are still more numerous among the latter this could explain the apparent difference between the sexes.

¹ Douek, E. E., *Journal of Laryngology and Otology*, 1967, 81, 431.

Notes and Comments

Magnesium Sulphate for Ischaemic Heart Disease.—DR. S. E. BROWNE (Dartford, Kent) writes: In your expert's reply ("Any Questions?" 15 May, p. 396) it was stated that intramuscular treatment was preferable to intravenous therapy. In using the latter method with several series of patients (92 in all) with angina pectoris, the improvement rate has never been less than 90% as opposed to a rate of 50-60% in intramuscular treatment. A report¹ on intravenous magnesium sulphate therapy with 29 patients suffering from angina has been published.

OUR EXPERT replies: Dr. Browne draws attention to a further report of his experience with the use of magnesium sulphate in patients with ischaemic heart disease. He now appears to favour the intravenous route though the reactions that may occur when magnesium sulphate is injected intravenously may be quite alarming. Similar results to those which he obtains have not, so far as I am aware, been reported by others, and a series of 29 patients suffering from angina without any control observations does not represent a critical evaluation of this form of treatment.

¹ Browne, S. E., *Practitioner*, 1969, 202, 562.