METASTATIC CARCINOMA SIMULATING HYPERPARATHYROIDISM *

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Upon the basis of experimental and clinical data developed after the discovery of parathormone by Collip,[1] there has been evolved the conception of a clinical syndrome of parathyroid hyperfunction, or hyperparathyroidism. The diagnosis has come to be based upon the following criteria: (1) increased blood calcium, (2) lowered serum phosphorus, (3) increased calcium excretion, (4) widespread rarefaction of bones, and (5) presence of a parathyroid tumor.

Important symptoms are muscular weakness, nausea and vomiting, polyuria and polydipsia, and renal colic.

All of the criteria mentioned have not been present in every reported case; hypercalcemia has been the only constant finding. Thus, in the case reported by Richardson, Aub and Bauer [2] a parathyroid tumor was not found. In Pemberton and Geddie's case [3] there were no demonstrable bony changes. In Wilder's case [4] the calcium excretion was not increased although this may have been influenced by diet and ultraviolet radiation. Barr and Bulger [5] and Hunter [6] present extensive bibliographies which need not be repeated here. Accompanying both articles are abstracts of cases reported up to the past few months.

In the case we wish to report, the interest lies in the decision as to whether we were dealing with a true case of hyperparathyroidism or a simulated condition.

CASE REPORT

Clinical History: The patient, a woman 47 years of age, consulted the Clinic on October 28, 1929, complaining of generalized pains, weakness and vomiting of ten months' duration. The family history was not significant. She had had no infectious diseases. There was nothing to suggest luetic infection. Five years before, a tumor of the left breast had been removed. She had been told at that time that "it might have caused trouble had it not been removed." †

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† A report from the hospital where the operation was performed gave the diagnosis as carcinoma. No microscopic report was obtained.

In general she considered herself to be in good health up to the present illness which had been gradual in onset, starting ten months before. She had been confined to bed for the preceding six weeks. At the onset she was troubled with small areas of soreness and twinges of pain in the anterior thoracic wall.

The ribs were sensitive to pressure and any muscular effort, such as deep breathing or using the pectoral muscles, caused sharp pain. After a time, similar aches and pains appeared in the arms, legs and back. These occasioned much suffering, especially with motion. After a time the muscles became "weak all over" and she was unable to walk or to use her arms except with great effort. Four months before entry, following X-rays of the teeth, three were removed. This was followed by an "osteomyelitis" of the jaw, which had continued to drain. A few weeks before she had developed marked polydipsia and urinary frequency, night and day.

There was marked anorexia. During the preceding month she had vomited several times daily without any definite relation to meals. She had lost 20 pounds in weight since the onset of illness ten months before. A "goiter" had been present for several years.

Physical examination showed a thin, sallow, extremely apathetic woman looking a great deal older than her stated age of 47 years. There was evidence of considerable loss of weight. There was a partial left-sided facial paralysis and left-sided atrophy of the tongue. The musculature everywhere was extremely flabby and all movements were made with considerable effort. In the right mandible, anteriorly, at the site of extraction of two teeth, there was a sinus tract containing a packet of gauze. On removal of the gauze there was an escape of a small quantity of thin purulent material. The breath was uremic. The eye grounds were negative. The right lobe of the thyroid was occupied by a firm rounded mass 5 cm. in diameter. Examination of the heart and lungs elicited nothing significant except that there was pain on deep inspiration. There was some tenderness on pressure on the ribs, anteriorly. There was a scar from the breast operation on the left side. This apparently had been a simple mastectomy. There were no nodules in the axilla or supraclavicularly. The liver edge was palpated two fingers' breadth below the costal margin. Pelvic examination revealed what at first was thought to be a mass, but later was thought to be retroverted uterus. In the right wrist was palpated a bony mass 2 cm. in diameter, obviously arising from one of the carpal bones. All reflexes were present but sluggish. Blood pressure 140/80.

The laboratory examinations at entrance revealed the following: Urine, a very slight trace of albumin with 1 to 3 hyaline casts, 1 to 2 granular casts and 15 to 20 white blood cells per high power field. The urine was negative for Bence-Jones protein. There was a moderate secondary anemia. The white blood cells numbered 10,000. The blood non-protein nitrogen determination showed a value of 56 mg. per 100 cc. The phenolphthalein excretion was 24 per cent in two hours. Wassermann test negative. The blood calcium was 17.3 mg. per 100 cc., the blood phosphorus 4.1 mg. Blood bilirubin 0.8 mg. (van den Bergh).

Following is the report of the X-ray findings, interpreted by Dr. L. B. Morrison:

"The skull shows moderate density and shows some radiolucent areas, two that are at least 1 cm. in diameter, and several areas that are smaller. These are definitely metastatic, the adjoining bone

being of normal density. The right mandible shows an area of diminished density just in front of the first molar and down to about the level of the dental foramen.

The ribs show many minute radiolucent areas of the general process compatible with metastases. The third and fourth dorsal bodies are crushing, and they are quite dense. The trachea is crowded slightly to the left, apparently by a small thyroid.

The scapula and upper end of the right humerus show very definite radiolucent areas in which the bone is being destroyed, the adjoining bone being of normal density. The right hand shows radiolucent areas at the base of the fourth metacarpal, and in relation to the os magnum and unciform. The radius and ulna are of normal density, as is the lower end of the humerus.

The fifth lumbar body and both the sacrum and the ilia show radiolucent areas compatible with a general carcinosis. The liver is becoming slightly enlarged. The lungs show no particular changes. The right femur and tibia show no definite changes. The bone is of normal density."

As seen from the above report, Dr. Morrison considered the bone changes compatible with generalized bone metastases. Moreover, he felt that if the condition was due to hyperparathyroidism, there should be no areas of definitely normal bone without calcium deficiency, as there were here.

During the subsequent period of observation the patient's general condition improved somewhat. Vomiting, at first frequent, was finally controlled by intravenous glucose and by careful diet. Under this treatment, also, the blood non-protein nitrogen became lower and the phthalein excretion greater. Anorexia continued, as did the marked weakness and apathy. The high blood calcium determination was checked and persisted at a high level (Table I). The blood phosphorus continued at a normal level. Albright, Bauer, Ropes and Aub,[7] in studying the phosphorus level in the blood, found that parathormone primarily lowers the phosphorus level. If, however, the serum calcium runs above a critical level of about 14 to 15 mg. per 100 cc., the urinary phosphorus excretion falls and the blood phosphorus rises. This may account for the high blood phosphorus levels in this case.

During the following week studies were made of the calcium excretion. A low calcium diet was given (see Table II). After three

days, all urine and feces were saved for a three-day period for calcium determination. The data are shown in Table III. A negative calcium balance of 139 mg. or 45 per cent was revealed. Bauer, Albright and Aub,[8] however, found that when normal individuals were fed on calcium diets (100 mg. ± daily) negative calcium balances were manifested. Some of them were equal to the negative balance in this case.

TABLE I

Serum Calcium and Phosphorus *

Date	Blood calcium	Blood phosphorus
	mg.	mg.
Nov. 4	17.3	4.1
" 5	17.6	..
" 11	16.6	4.0
" 15	15.0	3.0
Operation		
Nov. 16	..	..
" 17	13.8	3.3
" 18	13.7	3.2
" 19	13.4	..
" 20	13.7	2.5
" 21	13.7	2.5
" 24	12.9	2.9
Dec. 2	14.1	3.1

* Determinations by Miss H. M. Hunt, New England Deaconess Hospital.

TABLE II

Phosphorus and Calcium Intake

Date	Calcium	Phosphorus
	mg.	mg.
Nov. 8	99	169
" 9	91	120
" 10	136	532
" 11	110	149
" 12	102	172
" 13	95	125

Although the evidence was not conclusive, exploration for parathyroid tumor seemed warranted. Operation was done November 16. The report follows:

"Ethylene anesthesia. Usual thyroid exposure. The entire right lobe of the thyroid was occupied by a firm mass 5 cm. in diameter. It was exceedingly friable and was adherent to its bed and to the muscles laterally. Lateral to the upper pole on the right was a flat, bean-shaped mass approximately 2 cm. in length, 1 cm. in width and

TABLE III

Calcium Intake and Output

Date	Calcium intake	Calcium output	
		Urine *	Stools †
	mg.	mg.	mg.
Nov. 11	110	153	37.5
" 12	102	64	20.8
" 13	95	140	31.0
Total	307	357	89.3

Total calcium output	446 mg.
Total calcium intake	307 mg.
Negative balance	139 mg.

* Determinations by Miss H. M. Hunt, New England Deaconess Hospital.
† Determinations by Dr. Alexander Marble, Massachusetts General Hospital.

3 mm. in thickness. It was wax-brown in color and, except for its size, resembled a parathyroid. A subtotal hemithyroidectomy was done on the right side, excising the tumor at the lower pole and the mass lateral to the upper pole. At the left lower pole was palpated a nodule apparently arising from the gland itself. This was excised."

During the next few days following the operation, the patient ran a rather stormy course, with persistent vomiting and a rapid pulse. The blood calcium on the day following the operation was 13.8 mg. as compared with 15 mg. on the day before operation. Eight days after operation it was 12.9 mg., the lowest reading. On December 2, fifteen days after operation, it had risen to 14.1 mg. During the postoperative period her condition was not sufficiently stable to carry out studies of calcium balance. By the time her condition had im-

proved to the extent that they could be started, her relatives wished to take her home and accordingly these studies were unfinished. She died at home six weeks later. An autopsy was not permitted.

Microscopic examination (No. 6839) of tissue removed from region of parathyroid showed a mass of epithelial cells occurring in clusters, occasionally showing an alveolar arrangement, and embedded in a relatively dense stroma. The cells were moderate in size, polyhedral, with large hyperchromatic nuceli. The cell membranes were ill-defined, the cytoplasm fairly dense and acidophilic but free from granules. Rare mitoses were present, but no abnormal or multiple mitoses were seen. No tumor giant cells were encountered. Near the periphery of the tissue were lymphatics distended with masses of tumor cells. Blood vessels, however, were not involved, except a few of the larger arteries which showed invasion of tumor cells into their perivascular lymphatics. The alveolar arrangement was discernible even within the lymphatics. No secretion was present, however.

The thyroid itself contained an adenomatous nodule 4 cm. in diameter, which had undergone cystic degeneration. Microscopic examination of the wall of the nodule showed invasion in several places by clusters of epithelial cells similar to those described above. Other portions of thyroid tissue showed marked variation in size of follicles, many of which were distended with a considerable amount of colloid, and scattered foci of isolated follicles of fetal type embedded in a rather myxomatous stroma. At various points near the capsule of the gland invasion by tumor cells similar to those described above was seen.

Microscopic Diagnosis: Adenocarcinoma, metastatic to thyroid and parathyroid, probably originating from the breast.

Discussion

Although we felt that we were dealing with a case of generalized carcinomatosis arising from the carcinoma of the breast removed five years before, we were unable to reconcile the persistent hypercalcemia with this diagnosis. Personal experience and a search of the literature showed no similar finding in bone metastases in carcinoma. In addition there was a tumor in the region of the parathyroid. The flaccid muscles with the attendant weakness, vomiting, polydipsia and polyuria could be explained by the hyper-

calcemia. In view of these considerations, together with the widespread bone changes, a diagnosis of hyperparathyroidism was considered possible and was the basis for operation.

The discovery of the malignant nature of the tumor was discouraging to the hypothesis of hyperparathyroidism. While the possibility of a primary malignant tumor of the parathyroid invading the adjacent thyroid and not yet giving rise to metastases has to be considered, there are several facts which militate very strongly against this. The morphology of the tumor is strikingly suggestive of adenocarcinoma of the breast. So far as we know, there are no malignant tumors of the parathyroid which have produced hypercalcemia. The character of the roentgenograms of the bone lesions is far more suggestive of carcinomatous metastases than it is of decalcification resulting from hyperparathyroidism. Finally, the rarity of malignant tumors possessed of highly specialized specific functional activity must be considered.

Carcinoma of the breast has been reported by Thompson [9] as metastasizing to the parathyroid glands. He also referred to a case reported by Pepere.

This case is presented as a case of marked hypercalcemia. If marked hypercalcemia is always due to hyperfunction of the parathyroids, we were dealing with a case of hyperparathyroidism. If the hypercalcemia was merely an accompaniment of widespread bone metastases, there are no similar cases recorded in the literature. This report should stimulate further estimation of the serum calcium in metastatic bone carcinoma.

Summary

A case with widespread bone changes, hypercalcemia, negative calcium balance and thyroid tumor, is presented. The X-ray appearance of the bones suggested metastatic carcinoma. Examination of parathyroid-like bodies removed at operation showed probable metastatic carcinoma from mammary cancer removed five years before.

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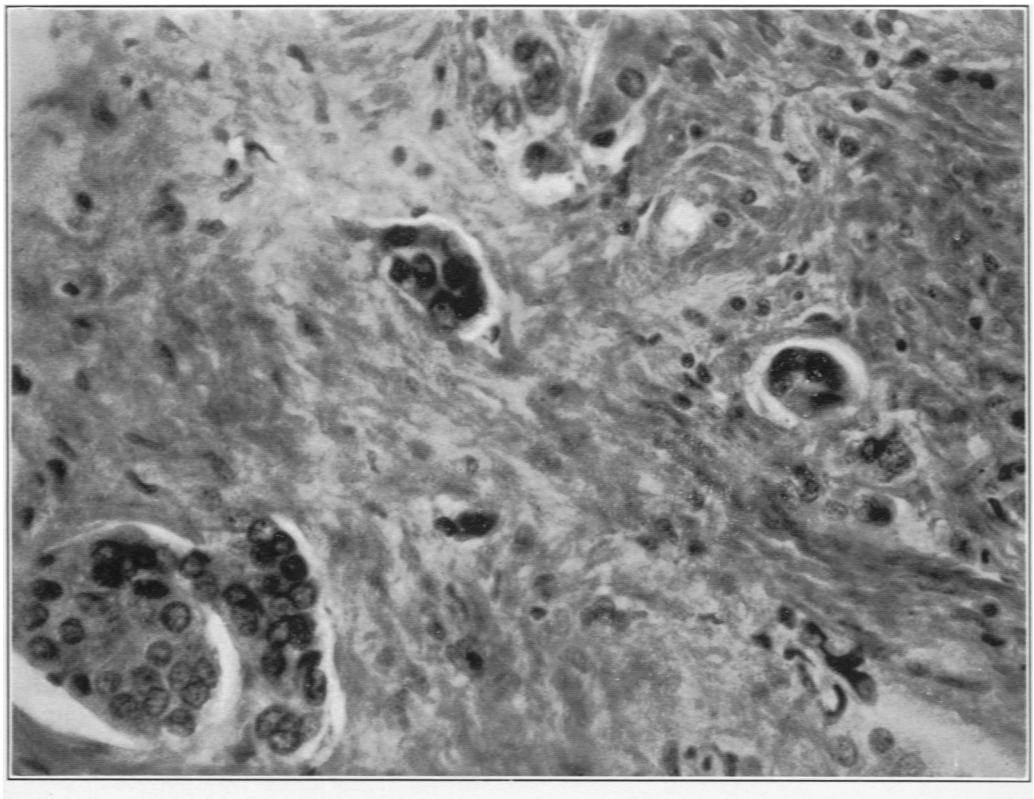
DESCRIPTION OF PLATE

PLATE 81

FIG. 1. Section from mass of tumor tissue from region of parathyroid. Phosphotungstic acid hematoxylin stain. × 400.

FIG. 2. Tumor tissue growing in lymphatic just within capsule of thyroid. Phosphotungstic acid hematoxylin stain. × 400.



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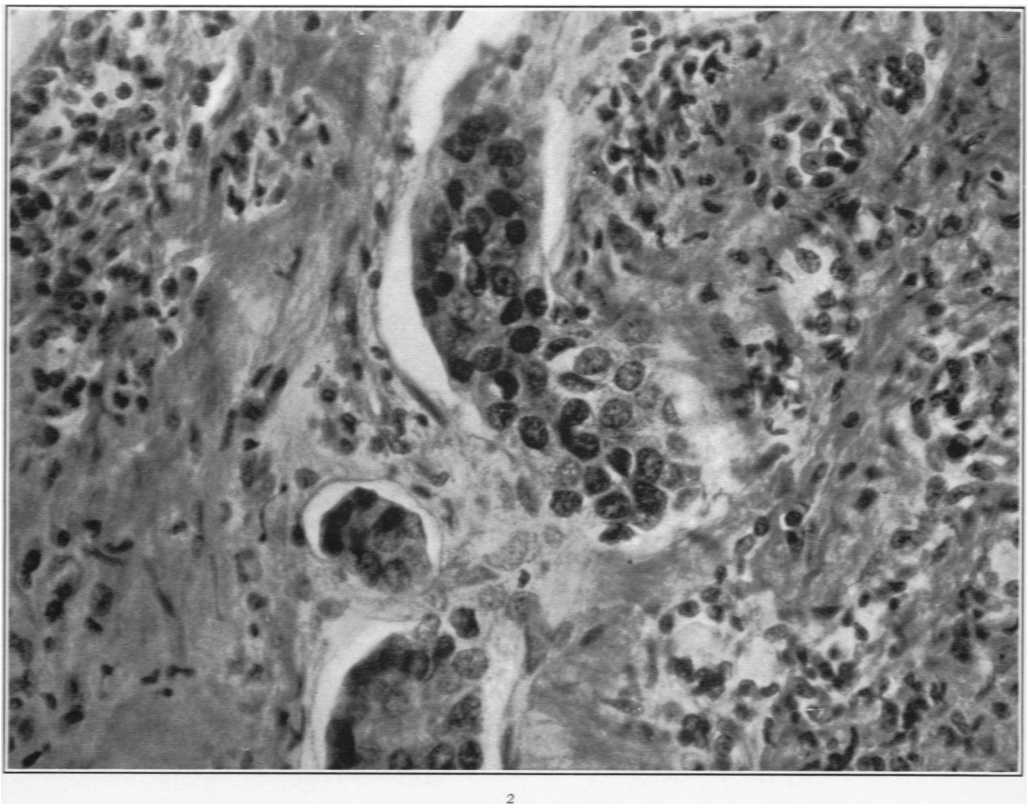

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