

HYPERCALCEMIA ASSOCIATED WITH GIANT CONDYLOMA ACCUMINATUM

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Abstract. A 48-year-old Negro male is presented with a recurrent giant condyloma accuminatum. With each recurrence, the patient developed elevation of serum calcium which reverted to normal after removal of the tumor. It is proposed that such a sequence of events, along with other clinical and laboratory data, supports the concept that this tumor was functioning as a para-endocrine tissue by releasing a parathyroid-like hormone.

Hypercalcemia, without bone metastasis, may occur in association with several types of tumor, most commonly carcinomas of the lung or kidney (9). The only skin neoplasms which have been reported in association with this metabolic abnormality are malignant melanoma (11), and squamous cell carcinoma of the penis (2) or vulva (16). Current research (3, 8, 13) has shown that several of these highly proliferative tissues contain a protein with parathyroid hormone immunogenicity and it is presumed that this substance is responsible for the hypercalcemia.

One tumor not often considered when discussing neoplasms is verruca vulgaris. Fortunately, this growth is mainly confined to the surface membranes and rarely undergoes enormous cellular proliferation

with frank invasion of underlying tissue. However, giant condyloma accuminatum of the perineal-rectal area represents an exception. Not only may this enormous, highly-proliferative, verrucous growth undergo carcinomatous degeneration with metastases but serious blood loss may occur. This is the first reported case of this tumor being associated with hypercalcemia.

CASE REPORT

A 48-year-old Negro male was admitted to the Philadelphia General Hospital in May 1972 with a bleeding giant condyloma accuminatum in the rectal area. This was the third documented recurrence of this patient's tumor which had previously been excised in 1966, 1967 and 1969. The patient complained of generalized weakness, rectal pruritus and pain, frequent headaches, abdominal pains, anorexia, and aching in both shoulders and elbows, all of 2 months' duration. The past medical history revealed that the patient had had active pulmonary tuberculosis, treated in 1967, and late latent syphilis. At the time of physical examination the patient was noted to have poor dentation, exophthalmos (present since birth) and a large fungating mass protruding from the rectum (Fig. 1). The neck did not contain a palpable thyroid gland or masses. There were no other pertinent physical findings. Laboratory values included the following: Hb 10.7 g%, Hct 33.7%, sodium 135 mEq/l, potassium 4.1 mEq/l, chloride 101 mEq/l, CO₂ 32 mEq/l, BUN 5 mg%, creatinine 0.8 mg%, glucose 94 mg%, calcium 12.4 mg%, phosphorous 2.4 mg%, alkaline phosphatases 121 IU/l, T-3 27% (normal 25 to 35.5%), T-4 10.2 µg% (normal 4.5 to 13), uric acid 6.4 mg%, RPR card test—reactive 1:8 dilutions, FTA-ABS positive. Three sputums for AFB were negative. ECG, IVP, barium enema and protein electrophoresis were within normal limits, as were X-rays of the skull, hands and lateral neck films. A chest X-ray showed fibrous stranding in the right upper lobe.

The patient's tumor mass was removed surgically. At the time of operation, sigmoidoscopy failed to reveal extension of the mass into the rectal canal. Pathological examination of the excised tissue showed a typical condyloma accumi-

Abbreviations:

AFB	= acid fast bacillus
BUN	= blood urine nitrogen
ECG	= electrocardiogram
FTA-ABS	= fluorescent treponemal antibody absorbed
Hct	= hematocrit
Hgb	= hemoglobin
IU/l	= international units per liter
IVP	= intravenous pyelogram
mEq/l	= milliequivalents per liter
RPR	= rapid plasma reagin
T-3	= triiodothyronine resin uptake test
T ₄	= thyroxine
TRP	= tubular reabsorption of phosphorous

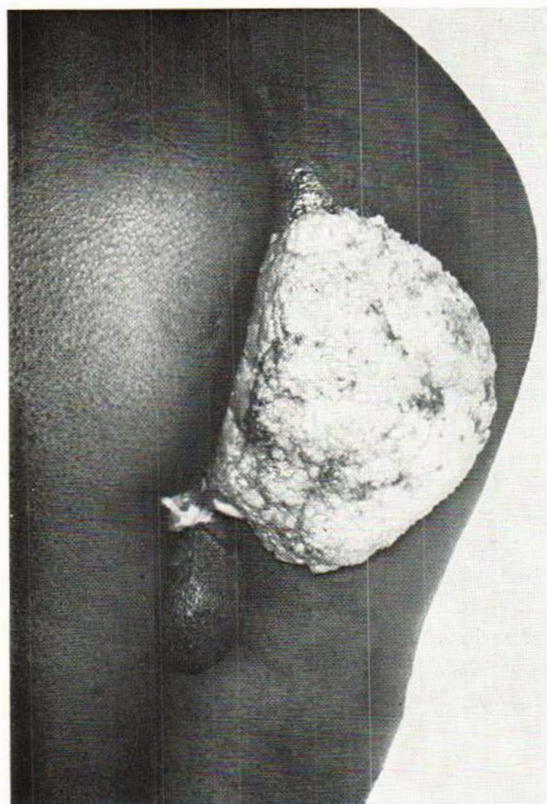


Fig. 1. The enormous, fungating condyloma accuminatum involving the gluteal cleft and right medial buttock.

tum with a highly inflammatory fibrous stroma (Fig. 2). Although dysplastic squamous cells were noted to extend as far as the basal cell layer, no invasion of the dermis was seen (Fig. 3). The patient made an uneventful recovery and there



Fig. 2. Arborization and acanthosis with vacuolization of nuclei typical of condyloma accuminatum. Also note the inflammatory fibrous stroma as well as the vasodilatation ($\times 100$).

has been no recurrence of the lesion, 3 months postoperatively.

Preoperatively, it was noted that the patient's serum calcium was elevated and a tentative diagnosis of primary hyperparathyroidism was considered. Several preoperative calcium determinations substantiated an elevated serum calcium. Postoperatively, the patient's serum calcium and phosphorous returned to normal (Fig. 4). The % TRP was also normal. The urinary calcium which was determined before surgery, on May 31, 1972, was 288 mg/24 hours and postoperatively on June 23, 1973, was 72 mg/24 hours.

When reviewing the patient's previous medical records, it was noted that in 1969, he had had a serum calcium of 13.5 mg%, a phosphorous of 4.0 mg%, and an alkaline phosphatase of 80 IU/l. Subsequent to excision of the condylomata at that time, the serum calcium also became normal. Unfortunately, serial calcium determinations and close follow-up of the patient were not carried out.

DISCUSSION

Hypercalcemia in association with neoplasms, when bony metastases are not apparent, has been known for a number of years. In 1941, Fuller Albright (1) first suggested that a hypernephroma of the kidney may have been responsible for the production of a parathyroid-like hormone with subsequent hypercalcemia. In this case, irradiation of the tumor corrected the metabolic abnormality.

The incidence of hypercalcemia associated with tumors has been reported to be as high as 9.1% (18); however, this figure includes cases with metastases to the bone. Although several different types of neoplasms without skeletal involvement have been associated with an elevated serum calcium, most of the reported cases are tumors of the kidney or lung

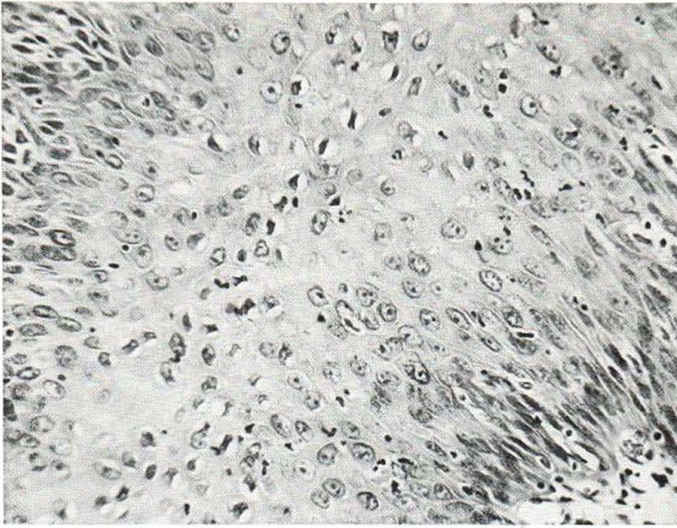


Fig. 3. Cellular dysplasia is noted extending to and included in the basal cell layer ($\times 450$).

(9). Cutaneous neoplasms are only rarely seen with this metabolic abnormality, although malignant melanoma (11) and squamous cell carcinoma of the penis (2) or vulva (16) have been reported.

What is the cause of hypercalcemia associated with neoplasms? When presented with a patient such as ours, the following causes of hypercalcemia should be considered: primary osteoporosis, prolonged immobilization, multiple myeloma, sarcoidosis, excessive milk intake (alkali or vitamin D), skeletal metastases, hyperthyroidism, myxedema, and Addison's disease. These were eliminated on the basis of history, physical examination, and laboratory data. One is then left with three further possibilities (1) primary hyperparathyroidism, (2) secondary hyperparathyroidism due to a parathyroid trophic hormone, or (3) an ectopically produced substance capable of elevating the serum calcium.

In the present case, primary hyperparathyroidism will be excluded from further consideration as the patient's elevated serum calcium would not have returned to normal after excision of the neoplasm if this were the cause. However, preoperatively this was the most tenable explanation. The second possibility, a parathyroid trophic substance, was certainly possible in our case. Although no such substance has thus far been isolated from any neoplasm, in cases of hypercalcemia associated with tumors in which the parathyroid glands (12, 10) were removed, a few of these glands were found to be hyperplastic. Parathyroidectomy was not performed on our patient as we did not feel this was indicated.

Among the ectopically (outside the parathyroid gland) produced substances suggested in the literature for the production of hypercalcemia by a tumor

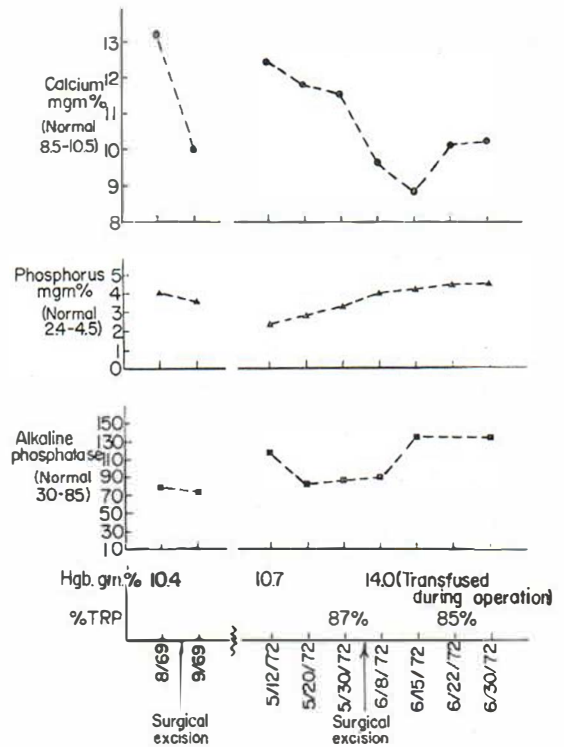


Fig. 4. The correction of hypercalcemia occurred on two occasions subsequent to removal of the condyloma accuminatum. Also note the degree of concomitant anemia.

are: a parathyroid-like hormone (12), osteolytic substances (10), and a vitamin D substance (12). Osteolytic substances have been mentioned in association with breast carcinomas. Vitamin D substances would presumably directly stimulate intestinal calcium transport as well as mobilization of calcium from bone. There is no substantial evidence that these are elevated in association with neoplasms.

By far the most thoroughly investigated of the above possibilities is the parathyroid-like hormone. When the symptoms and signs of an endocrine disorder are due to an endocrine-like substance being secreted by a nonendocrine tissue, the term para-endocrine syndrome is applied (7). The para-endocrine syndromes which have been described include the following: hypoglycemia, polycythemia, hyponatremia, hypercalcemia, Cushing-like and carcinoid syndrome (15). We feel our patient represents such a para-endocrine syndrome.

By utilizing radioimmunoassay techniques, several investigators have identified, in various types of tumors, a substance which is immunologically identical with parathyroid hormone. These include renal adenocarcinomas (3), hepatoma (8), squamous cell carcinomas (13), and reticulum cell sarcomas of the spleen (8). Because radioimmunoassay for parathyroid hormone was not available to us, we did not demonstrate parathyroid-like hormone in the condyloma. However, these techniques have many problems which have in the past left doubt as to the true significance of the results.

Parathyroid hormone is a protein composed of 84 amino acids, of which only 20 are necessary for biological activity (17, 5). Therefore unless the biological potency of the isolated substance is clearly demonstrated, one cannot be absolutely certain one is dealing with biologically active parathyroid hormone. It is possible to have immunological identity without necessarily having biological identity. To date, no tumor of man has been shown to contain a biologically active parathyroid hormone. This is probably due to the fact that the quantity of hormone necessary to produce the desired effect (hypercalcemia) in animals is greater than that found in any tumor of man. However, an animal model, the VX2 carcinoma of rabbit (6), does exist, from which a successful biological assay has been performed. This would tend to substantiate the presumption that a neoplasm may produce a biologically active hormone-like parathyroid hormone.

We feel, therefore, that a patient's clinical and

laboratory response to surgery or irradiation of a neoplasm are of greater importance in verifying the production of a parathyroid-like hormone by the tumor, than is radioimmunoassay. A few investigators have set up clinical criteria to aid in establishing such production. Sherwood (17) considered the following circumstantial evidence, (a) absence of skeletal metastases, (b) hypophosphatemia, (c) lack of hyperplastic parathyroid glands, (d) absence of hypercalcemic response to steroids, (e) correction of hypercalcemia by removal of the tumor, and (f) return of hypercalcemia with recurrence of tumor growth. Our patient fulfilled four of these six criteria. Lack of hyperplastic parathyroid glands could only have been established by needless surgery; however, we do not discount the possibility that the condyloma could have produced a parathyroid trophic substance which could have resulted in the same sequence of events. A trial of steroids did not seem justifiable in this patient.

In addition to the above criteria, Lafferty (9), who has extensively reviewed pseudohyperparathyroidism, would add the following points in differentiating hypercalcemia due to ectopic production from that produced by a parathyroid adenoma: (a) the duration of symptoms (anorexia, bone pains, headaches, abdominal pains) is usually present for only 2 to 6 months; (b) the serum calcium often is greater than 14 mg%; (c) a serum chloride below 102 mEq/l in the absence of vomiting or respiratory alkalosis definitely speaks against the presence of a parathyroid adenoma, and (d) the hematocrit is usually less than 38%. Our patient illustrates three of these four points. However, his anemia undoubtedly was partially related to direct blood loss from a highly vascular tumor. The highest serum calcium determination was 13.2 mg% in 1969 but, as mentioned previously, follow-up clinic attendance by the patient was poor. On admission, his serum chloride was 101 mEq/l. Unfortunately, no further electrolyte studies were done.

The histological picture of our patient's tumor did not suggest an invasive anaplastic growth. However, dysplastic cells were noted throughout the acanthotic epidermis and within the basal cell layer. In reviewing the biopsies of giant condylomata acuminata, some of which became malignant, Dawson et al. (4) concluded that the histological appearance did not always correlate well with the clinically observed biological behavior. In view of the fact that our patient experienced severe rectal pain, and

that the tumor itself had a serosanguineous discharge, ulceration and bleeding should be regarded with suspicion of malignant degeneration. Equally suggestive of this is the repeated recurrence of the condyloma (14).

In summary, we feel our patient demonstrates a para-endocrine syndrome (pseudohyperparathyroidism) resulting from the production of a parathyroid hormone-like substance by a recurrent condyloma accuminatum. This was strongly suggested clinically by the recurrence of the hypercalcemia with regrowth of the tumor, and the subsequent return of the serum calcium to normal upon surgical excision. We would emphasize that although condylomata accuminata are generally benign, they may lead to other problems in addition to malignant degeneration with metastases. Our patient developed an anemia secondary to blood loss as well as symptoms of hyperparathyroidism. This case is undoubtedly a rare occurrence. Nevertheless, clinicians should be aware that any highly proliferative tissue has the potential for the production of unusual proteins, some of which may have endocrine activity.

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REFERENCES

1. Albright, F.: Case records of the Massachusetts General Hospital. *N Engl J Med* 255: 789, 1941.
2. Anderson, E., Everett, G. & James, F.: Penile malignancy and hypercalcemia. *JAMA* 192: 328, 1965.
3. Buckle, R. M., McMillan, M. & Mallinson, Chr.: Ectopic secretion of parathyroid hormone by a renal adenocarcinoma in a patient with hypercalcemia. *Brit Med J* 4: 724, 1970.
4. Dawson, D. F., Duckworth, J. K., Bernhardt, H. & Young, J. M.: Giant condyloma and verrucous carcinoma of genital area. *Arch Path* 79: 225, 1965.
5. Editorial: Hormones and histones. *Lancet* *i*: 86, 1967.
6. Gertner, H. R., Wilson, J. R. & Woodward, E. R.:

Parahormone biopsy of plasma in hypercalcemic tumor rabbits. *Proc Soc Exp Biol Med* 116: 177, 1964.

7. Goodall, C. M.: On paraendocrine cancer syndromes. *Int J Cancer* 4: 1, 1969.
8. Knill-Jones, R. P., Buckle, R. M., Parsons, V., Calne, R. Y. & Williams, R.: Hypercalcemia and increased parathyroid-hormone activity in primary hepatoma. *N Engl J Med* 282: 704, 1970.
9. Lafferty, F. D.: Pseudohyperparathyroidism. *Medicine* 45 (3): 247, 1966.
10. Maulig, G. M., Cohen, J. L. & Sherwood, L. M.: Ectopic production of parathyroid hormone by carcinoma of the breast. *N Engl J Med* 285: 154, 1971.
11. Menguy, R.: Pseudohyperparathyroidism due to malignant melanoma. *Surg Clin North Am* 49 (1): 49, 1966.
12. O'Grady, A. S., Morse, L. J. & Lee, J. B.: Parathyroid hormone-secreting renal carcinoma associated with hypercalcemia and metabolic alkalosis. *Ann Intern Med* 63: 858, 1965.
13. Riggs, B. L., Arnaud, C. D., Reynolds, J. C. & Smith, L. H.: Immunologic differentiation of primary hyperparathyroidism from hyperparathyroidism due to nonparathyroid cancer. *J Clin Invest* 50: 2079, 1971.
14. Rook, A. & Wilkinson, D. S. (Editor): *Textbook of Dermatology*, p. 759, F. A. Davis Co., Philadelphia, Pa., 1968.
15. Ross, L. & Shelley, E.: Mesonephric carcinoma of the ovary producing hypercalcemia. *Am J Obstet Gynecol* 100: 418, 1968.
16. Schatter, W. E., Ship, A. G., Preper, W. J. & Batter, F. C.: Syndrome resembling hyperparathyroidism associated with squamous cell carcinoma. *Ann Surg* 148: 890, 1958.
17. Sherwood, L. M., O'Riordan, J. L. H., Aurbach, G. D. & Potts, J. T. J.: Production of parathyroid hormone by nonparathyroid tumors. *J Clin Endocrinol Metab* 27: 140, 1967.
18. Warwick, O. H., Vendt, E. R. & Olin, J. S.: The clinical features of hypercalcemia associated with malignant disease. *Can Med Assoc J* 85: 719, 1961.

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