Metastatic Parathyroid Carcinoma and Hormonal Chemotherapy

Case Report and Response to Hexestrol

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APPROXIMATELY 50 cases of carcinoma of the parathyroid gland have been reported in the literature during the past 30 years. All cases satisfied the diagnostic criteria of "a parathyroid tumor which is locally invasive, and/or metastasizes and causes hyperparathyroidism."[15] This rare entity is responsible for 0.5 to 3 per cent of the hyperparathyroidism in reported series. Although nonfunctioning carcinoma may exist, it cannot be diagnosed definitively since microscopic differentiation between this tumor and metastases from malignant tumors arising in the thyroid, thymus, kidney or bronchus (adenoma) is very difficult.

The 5-year cure rate reported for primary adenocarcinoma of the parathyroid is only 30 per cent. Recurrences have ensued after intervals of from 3 months to 9 years following the surgical removal. Survival from the onset of symptoms ranges from 3 months to 25 years with a median of 4 to 5 years.[2, 3, 11, 15]

One problem in the treatment of adenocarcinoma of the parathyroid has been severe renal damage from renal calcinosis secondary to parathyroid hormone secretion by the metastases. Hypercalcemic crisis has caused death of some patients with this disease.[18] Excision of metastatic lesions or of the primary tumor causes serum calcium and phosphate levels to revert to normal so that further damage to the bones and kidneys can be prevented. Nephrocalcinosis of short duration can also be reversed.[10, 12]

Management of hypercalcemic crisis and metastatic disease by other than surgical excision has been disappointing. Radiation therapy has been reported but no objective regression has been observed. Radiation therapy was recommended as an adjuvant to surgical removal of the primary tumor by Castleman.[4] The possible effect of pituitary secretion on the parathyroids has led other investigators to attempt yttrium hypophysectomy[13] for metastatic carcinoma of the parathyroid, but no regression has been observed.

A patient with demonstrated functional pulmonary metastases and hypercalcemia, successfully treated with systemic administration of a synthetic estrogen compound, is here reported.

Case Report

A 48-year-old man was operated upon in April 1961, and an adenocarcinoma of the parathyroid, a 4.5-cm. diameter mass, was removed from the left side of the neck. The lesion invaded the thyroid gland, the muscularis of the esophagus, and surrounding muscles and areolar tissues (Fig. 1). Metastatic carcinoma was found in one lymph node which was resected. Laboratory tests made preoperatively showed: serum calcium 14.8 mg.% and phosphorus, 2.9 mg.%. Serum calcium pro-

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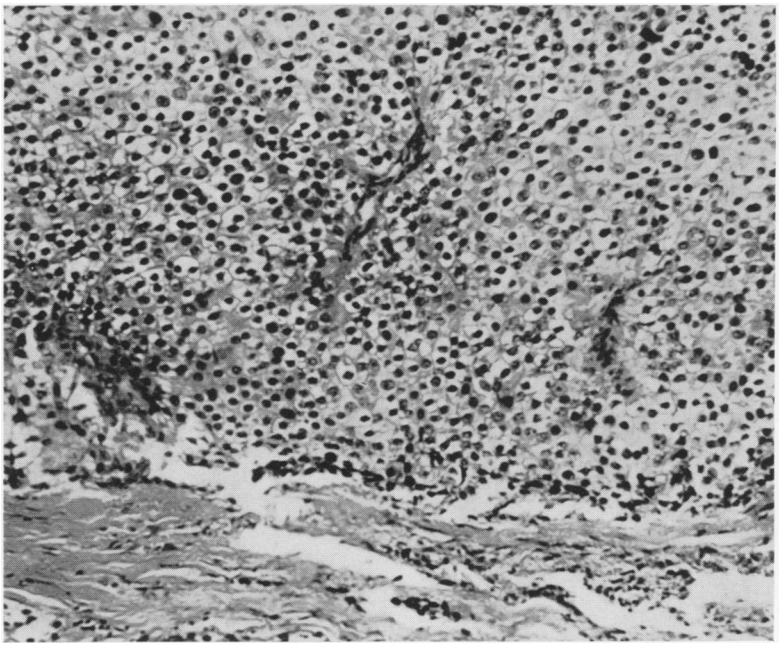

FIG. 1. Microscopic section of parathyroid carcinoma.

gressively decreased to 12.0 mg.% 2 hours after operation and to 11.0 mg.% within 4 hours. By the fourth postoperative day serum calcium levels were normal, and the patient was asymptomatic for about 8 months when weight loss, anorexia, moderately severe diarrhea, polyuria and fatigue ensued. Serum calcium at this time was 13.6 mg.%. No evidence of metastatic disease was found other than some small nodules in the left anterior cervical chain of lymph nodes. A radical neck dissection was performed and a cluster of 6 lymph nodes contained metastatic tumor. The remainder of the lymph nodes were normal. In the postoperative period the patient received 3,600 rads of x-ray delivered to the left side of the neck. He remained symptom free with no evidence of metastases until January 1964, when a chest x-ray film showed a single metastasis in the left upper lung field. No additional lesions appeared during the next 6 months and in July 1964, wedge resection of this solitary tumor was performed. Pathologic examination of the tissues again showed metastatic adenocarcinoma of the parathyroid. In April 1965, chest x-ray films showed further metastatic disease in the right lung field and shortly thereafter the patient experienced easy fatigability, apathy, weakness, diarrhea, mild nausea and polyuria. A pain in the lower left side of the chest was unrelated to respiratory activity or the ingestion of food.

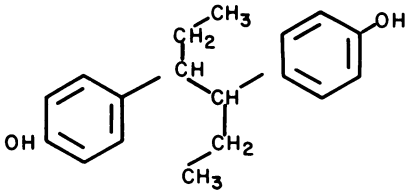

FIG. 2. Molecular diagram of Hexestrol. Phenol,4,4'-(1,2-diethyl-ethylene) di-.

The patient was referred to the UCLA Center for the Health Sciences for further therapy. Initial laboratory tests showed: serum calcium 7.19 mEq./L., serum phosphorus 1.1 mEq./L., alkaline phosphatase 4.9 KA units, blood urea nitrogen 11.5 mg.% and serum creatinine 1.0 mg.%. X-ray films showed at least two distinct metastases in the right lung field (Fig. 3A), no osteoporosis or bone resorption in the skull and bones, and no abnormal calcifications in the abdomen. The patient was instructed to continue his low calcium diet and Hexestrol (phenol,4,4',-(1,2-diethyl ethylene) di- (Fig. 2), a synthetic estrogenic compound was administered. This drug has been in Phase 2 study trial as part of the Central-Western Region of the Clinical Drug Evaluation Program. A daily dose of 25 mg./Kg. body weight for a total of 2.0 Gm. taken in 2 doses were given. After 3 weeks (Table 1), serum calcium decreased but the symptoms remained the same as prior to hormonal therapy. During the fourth week, however, marked subjective improvement

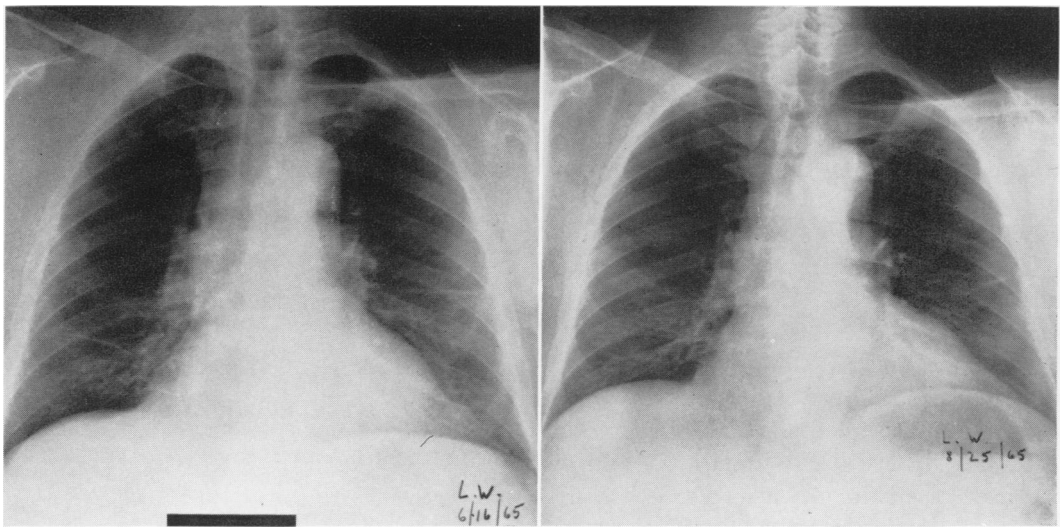

FIG. 3A, B. Chest roentgenograms prior to and at eleventh week of treatment.

accompanied a continued decrease in serum calcium. Serum phosphorus and alkaline phosphatase did not change significantly. By the end of the seventh week of therapy, in addition to continued decrease in serum calcium toward normal, a measurable decrease in size of the metastatic lesions was seen on chest x-ray. By the tenth week, serum phosphorus increased toward normal and urinary calcium excretion was normal. Chest x-ray films at this time showed a striking improvement over pretreatment x-rays (Fig. 3A, B).

Discussion

Morphologic criteria for the diagnosis of adenocarcinoma of the parathyroid have been discussed.[1, 4, 7, 11, 13] Functional metastases in either regional lymph nodes or distant areas is the established feature of adenocarcinoma. Benign adenomas are three times more frequent in females than in males, while adenocarcinoma is slightly more common in males.[1, 11, 15] Ellis[6] re-

TABLE 1. *Clinical Course*

	Week of Therapy							
	0	1	3	5	7	9	11	13
Dose Hexestrol		2,000 mg. daily p.o.	2,000	2,000	2,000	2,000	2,000	2,000
Serum calcium (N = 4.5–5.5 mEq./L)	7.19	6.7	6.4	6.1	5.9	5.95	5.62	5.62
Serum phosphorus (N = 1.6–2.7 mEq./L.)	1.1	1.0	1.2	1.0	1.0	1.2	1.6	1.5
Serum alk. phos. (K.A. Units)	4.9	7.1	6.8	6.4	6.8	6.3	6.3	5.2
BUN (8–20 mg.%)	11.5	15	15.5	11.4	13.5			15.5
Creatinine (0.6–1.3 mg.%)	1.0						1.0	
Weight (Kg.)	83	84.5	84	85.5	84	81.5	82	83
Blood pressure (mm. Hg)	160/120	170/100	170/120	170/120	170/120	170/110	160/110	154/110

ported a patient who received estrogens for about 6 weeks prior to death and in whom hypercalcemia was reduced and there was temporary subjective improvement. Caley [3] reported a woman who developed menstrual abnormalities during the primary phase and these symptoms recurred with metastases some years later.

In the patient here reported there was not only a decrease in hypercalcemia to normal but also evidence of regression of the tumor. The patient's performance status was improved from an estimated 60 per cent before therapy to 90 per cent after the sixth week of treatment, and at the time of writing he has returned to his usual occupation. The synthetic estrogen, Hexestrol produced no toxic side effects in the dose administered. There have been reports of difficulties in patients with hypertension or peptic ulcer,[5] but such effects did not appear to be progressive and responded to conservative treatment.

Although this patient was hypertensive prior to therapy, he was not affected. Fluid retention or other complications related to mineralocortocoid activity of the steroid did not occur. The only complication was gynecomastia which appeared after 4 months of therapy.

Summary

A case of a 48-year-old man with metastatic adenocarcinoma of the parathyroid gland is reported. The patient was treated with Hexestrol and has had both subjective and objective remission of his disease. This remission continues 5 months after initiation of therapy.

Addendum

The patient remained in remission from his disease process for 10 months at which time symptoms of hypercalcemia again developed along with elevation in serum calcium to 6.2 mEq./L. He has now been started on therapy with another hormonal agent.

References

1. Black, B. K.: Carcinoma of the Parathyroid. Ann. Surg., **139**:355, 1954.
2. Blixenkrone-Moller, N.: Carcinoma of the Parathyroid. Acta Chir. Scand., **Suppl. 283**: 282, 1961.
3. Caley, J. P., Jones, E. E. and Collins, D. H.: Fatal Recurrence of Parathyroid Carcinoma after 7 Years. J. Clin. Path., **15**:438, 1962.
4. Castleman, B.: Tumors of the Parathyroid Glands; Atlas of Tumor Pathology, Section IV Fascicle 15. Washington, D. C., Armed Forces Institute of Pathology, 1952.
5. Clinical Drug Evaluation Program; Specific Protocol for Hexestrol. Cancer Research Hospital, University of Wisconsin, 1963.
6. Ellis, J. T.: Metastatic Carcinoma of the Parathyroid and Hyperfunction. Amer. J. Path., **27**:383, 1951.
7. Florer, R. E.: Carcinoma of the Parathyroid. Amer. Surg., **30**:834, 1964.
8. Greep, R. O. and Talmage, R. V. (eds.): The Parathyroids. Springfield, Ill., Charles C Thomas, Publisher, 1961.
9. Henly, R.: Management of the Parathyroid Crisis. Amer. J. Surg., **108**:183, 1964.
10. Hellner, H.: Hyperparathyroidismus. Chirurg., **36**:103, 1965.
11. Justin-Besancon, L. J., Lamotte-Barrillon, S., Lamotte, M., Grivaux, M., Segrestaa, J. M. and Bene, P.: Epithelioma parathyroidien hypersecretant mortelle. Sem. hôp. Paris, **38**:984, 1962.
12. Kerr, W. H., Currie, D. J. and Welsh, K.: Surgical Aspects of Primary Hyperparathyroidism, A Review. Canad. J. Surg., **5**:422, 1962.
13. Lazar, A. W., Landau, R. L. and Kappas, A.: Metastatic Parathyroid Carcinoma and Persistent Hyperparathyroidism. Arch. Path., **72**:484, 1961.
14. Leman, J. and Donatelli, A. A.: Ca Intoxication Due to Primary Hyperparathyroidism. Ann. Intern. Med., **60**:447, 1964.
15. Pollack, S., Goldin, R. and Cohen, M.: Parathyroid Carcinoma, Case Report and Review of the Literature. Arch. Intern. Med., **108**:583, 1961.
16. Selye, H.: Participation of Ovarian Hormones in the Development of Nephrocalcinosis. Gynecologia, **145**:161, 1958.
17. Sunderman, F. W. and Sunderman, F. W., Jr. (eds.): Evaluation of Thyroid and Parathyroid Functions. Philadelphia, J. B. Lippincott Co., 1963.
18. Wilson, R. E., Bernhard, W. F., Polet, H. and Moore, F. D.: Hyperparathyroidism, Problem of Acute Intoxication. Ann. Surg., **159**:79, 1964.