Mediastinal Hyperfunctioning Parathyroid Tumors:

Review of 14 Cases

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DURING THE 43-year period from 1928 through 1970, approximately 1,000 patients with primary hyperparathyroidism were surgically treated at the Mayo Clinic. Not infrequently, hyperfunctioning parathyroid tissue was located in the superior mediastinum, often within the upper pole of the thymus gland, and was removed in the course of cervical exploration. Actual sternal splitting to expose the mediastinal structures was carried out much less frequently. In 14 cases, after one or more cervical explorations, the diagnosis of mediastinal hyperfunctioning parathyroid tumor was made after a sternal-splitting incision or at autopsy. The significant clinical, laboratory, and surgical findings in these 14 cases form the basis of this review.

Clinical Findings

The pertinent data on these 14 patients are summarized in the Table. The eight men and six women ranged in age from 27 to 57 years. The preoperative serum calcium values varied from 11.2 to 14.9 mg./100 ml. (normal, 8.9 to 10.1 mg./100 ml.). Renal calculi were present in 10 patients, roentgenographic bone disease of hyperparathyroidism was present in three patients, and no demonstrable osseous or renal complications were noted in four patients.

Surgical Procedures

The initial cervical exploration was carried out at the Mayo Clinic in nine of the 14 patients and elsewhere in five. Persistent hypercalcemia after the first cervical procedure resulted in a second cervical operation in five patients. In one patient (Case 9), the second cervical operation was performed as a third operation, that is, after removal of a large parathyroid tumor from the mediastinum.

Mediastinal surgery via a sternal-splitting approach was carried out at the Mayo Clinic in 11 patients, and elsewhere in 1 patient*; in the remaining two patients the mediastinal tumor was found at autopsy. The number of cervical parathyroid glands actually identified in previous cervical operations varied from 0 to 4. It is noteworthy that four glands were identified in the neck in five patients. Four patients had three glands identified, three patients had two, one patient had one, and in one other patient no gland was identified.

Pathologic Findings

A mediastinal tumor-like nodule, commonly called an "adenoma," was found in 14 patients. In five patients, an abnormality of one or more parathyroid glands was found on cervical exploration. We have not attempted to characterize these multiple gland enlargements as "chief cell hyperplasia," "mixed hyperplasia and adenoma," or "adenomatous chief cell hyperplasia."[5,9] In our opinion the present level of knowledge does not permit such an exact classification. Except for the carcinoma in Case 9, the mediastinal mass is referred to as a "tumor" (Table 1), whether or not one or more enlarged, apparently hyperplastic parathyroid glands also were removed from the cervical region.

The weight of tumor tissue removed from the mediastinum was recorded in 11 cases and varied from 500 mg. to 35 Gm. (average, 6 Gm.). The three tumors without

Submitted for publication July 3, 1972.

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TABLE 1 *Mediastinal Hyperfunctioning Parathyroid Tumors (14 Cases)*

Case & year	Sex & age, yr	Presternotomy blood values, mg/100 ml			Osseous* lesions	Renal calculi	Findings on cervical explorations	Mediastinotomy
		Ca	PO_4	Urea				
1 1942	F 54	12.7 13.7	1.9 2.2	16	+	+	Parathyroid adenoma, excision & diagnosis ew (Nov. 1941). Re-explored at M.C. (July 1942): no parathyroid tissue	Chief cell tumor—5 Gm. (Oct. 1942)
2 1946	M 51	12.1 11.9	2.1 1.4	36	−	+	Two normal inferior glands (April 1946)	Chief cell tumor—1.7 Gm. (May 1946)
3 1949	M 41	13.6† 12.5	2.7 2.5	48	−	+	R. inferior—hyperplasia—180 mg.; other three glands normal on biopsy (Nov. 1949). Reexplored (June 1951): R. superior gland—hyperplasia—70 mg.; L. superior & inferior—normal	Autopsy (Jan. 1952): chief cell tumor (3 × 2 × 2 cm.)
4 1955	F 56	14.9 14.7	2.1 2.3	26	−	−	Exploration ew (March 1955): negative. Re-explored at M.C. (Apr. 1955): no parathyroid tissue	Chief cell tumor within pericardium—780 mg. (May 1955)
5 1959	M 32	11.8 11.2	2.5 2.7	30	−	+	All four glands normal (Jan. 1959)	Chief & oxyphil tumor—520 mg. (Nov. 1959)
6 1960	F 37	11.8 11.4	2.1 1.9	24	−	+	Exploration ew (Oct. 1959): three normal glands, L. inferior not found. Re-explored at M.C. (June 1960): no abnormalities	Chief cell tumor within thymus—500 mg. (June 1960)
7 1960	F 34	11.3 12.2	11.2 2.7	14	−	−	L. superior & inferior glands normal; R. thyroid lobectomy; parathyroid within thyroid—20 mg. (July 1959)	Chief cell tumor removed ew (0.6 × 0.8 × 0.6 cm) (Dec. 1960)
8 1960	M 38	...	...	...	−	−	Exploration ew (Oct. 1960): four normal glands; 1 excised	Autopsy: parathyroid carcinoma—35 Gm. (Oct. 1960)
9 1961	M 50	11.2 11.5	2.8 2.8	31	−	+	L. superior gland—hyperplasia—950 mg.; R. superior & inferior grossly normal; L. inferior not seen (July 1961). Re-explored (July 1963): R. inferior—hyperplasia, 120 mg.; R. superior—hyperplasia	Parathyroid tumor—2.3 Gm. (Nov. 1961)
10 1964	M 46	11.9 11.4	1.7 1.9	30	−	+	Three normal glands seen (Oct. 1963)	Cystic chief cell tumor—3 Gm. (Jan. 1964)
11 1967	M 49	14.2 14.4	1.7 1.7	41	−	+	L. superior gland—hyperplasia, 160 mg.; three other glands grossly normal (Sept. 1966)	Chief cell tumor—15 Gm. (March 1967)
12 1968	F 27	11.3 11.5	2.5 2.1	83	+	+	R. superior gland; L. superior—excised, normal; L. inferior glands not seen (May 1967)	Chief cell tumor within thymus—2.1 Gm. (March 1968)
13 1970	F 57	12.3‡ 11.5 11.6	3.0 2.0 2.7	Creatinine 0.75	−	−	Exploration ew (Dec. 1969): Four normal glands biopsied	Chief cell tumor within thymus (2.5 × 1.5 × 1.0 cm) (Nov. 1970)
14 1971	M 49	12.3 11.7 *Postop. cervical exploration* 11.3§ 11.3	2.6 3.3 3.0	Creatinine 0.9 0.85	+	+	Chief cell "adenoma" of R. anterior mediastinum removed via neck incision; R. & L. superior—grossly normal; L. inferior not found (July 1970)	Chief cell tumor within thymus—920 mg. (Jan. 1971)

* Defined as bone cysts, subperiosteal resorption of phalanges, or granular demineralization of skull.
† Postoperative values after second neck exploration.
‡ Serum iPTH by radioimmunoassay—390 μl eq/ml. (normal, 45 μl eq/ml.).
§ Serum iPTH 195 μl eq/ml.

recorded weights measured 0.8 to 3.0 cm. in diameter. Microscopically, all cell types were represented from predominantly chief cells to predominantly oxyphil cells, with frequent mixtures of cell populations. A rim of normal parathyroid tissue was rarely noted. The tumor was situated within the thymus gland or showed thymic tissue immediately adjacent in the majority of cases. One tumor was considered to be a carcinoma based on size of the cells, presence of mitosis within the tumor, and definite microscopic evidence of invasion of surrounding tissue.

The combination of a tumor in the mediastinum and abnormalities in one or more parathyroid glands in the neck was observed in five patients (Cases 1, 3, 9, 11, and 14). The pathologic findings in these patients are summarized in the following paragraphs.

In two patients (Cases 1 and 14) removal of a mediastinal tumor was preceded by the removal of a so-called adenoma from the neck at a prior operation. In Case 1 the tissue was not available for review; in Case 14 the cervical adenoma consisted of a tumor-like nodule approximately 1 cm. in diameter composed of chief and oxyphil cells with no rim of normal parathyroid tissue and showing little persisting fat within its substance.

In one patient (Case 3) an enlarged hyperplastic gland weighing 180 mg was removed at the initial cervical operation in November 1949 (Fig. 1*A*). Nineteen months later the remaining three glands were removed. These weighed 70, 30, and 20 mg., respectively, and at least two showed microscopic hyperplasia. Hypercalcemia persisted and mediastinal operation was advised but the patient refused further surgical treatment. At autopsy, performed elsewhere, a mediastinal parathyroid tumor measuring 3 by 2 by 2 cm. was demonstrated within the thymus gland (Fig. 1*B* and *C*).

In another patient (Case 9) one greatly enlarged gland (950 mg.) was excised on initial cervical exploration. Microscopic findings were those of hyperplasia. Two other parathyroid glands were considered to be of normal size and were not biopsied. One gland was not found. Four months later, the mediastinum was explored and a tumor weighing 2.3 Gm. was found within the thymus gland. The lesion was well circumscribed but contained some cells undergoing mitosis. Subsequent cervical exploration was carried out because of persistent hypercalcemia and two hyperplastic appearing glands were removed, the larger of which weighed 120 mg. Hypocalcemia, which required treatment with vitamin D and an oral supplement of calcium, then developed.

Initial cervical exploration in the fifth patient (Case 11) revealed a single enlarged gland (160 mg.), which was resected. Microscopically, definite parathyroid hyperplasia was noted (Fig. 2*A*). The other three glands were identified grossly and appeared normal. Six months later a 15-Gm. encapsulated tumor was removed from the mediastinum (Fig. 2*B* and *C*).

The patient with parathyroid carcinoma died suddenly and unexpectedly shortly after transfer to a Rochester hospital. Five days earlier a cervical exploration had been performed by his home physician. Four grossly normal appearing parathyroid glands were identified and one normal gland was excised. The patient's preoperative serum calcium values were in the range of 18 mg./100 ml. Because of persistent hypercalcemia he was transferred to the Mayo Clinic for further studies but unfortunately he died suddenly before any blood tests or roentgenograms were obtained. At autopsy, a tumor weighing 35 Gm. was found in the mediastinum. Microscopically, the tumor was composed largely of

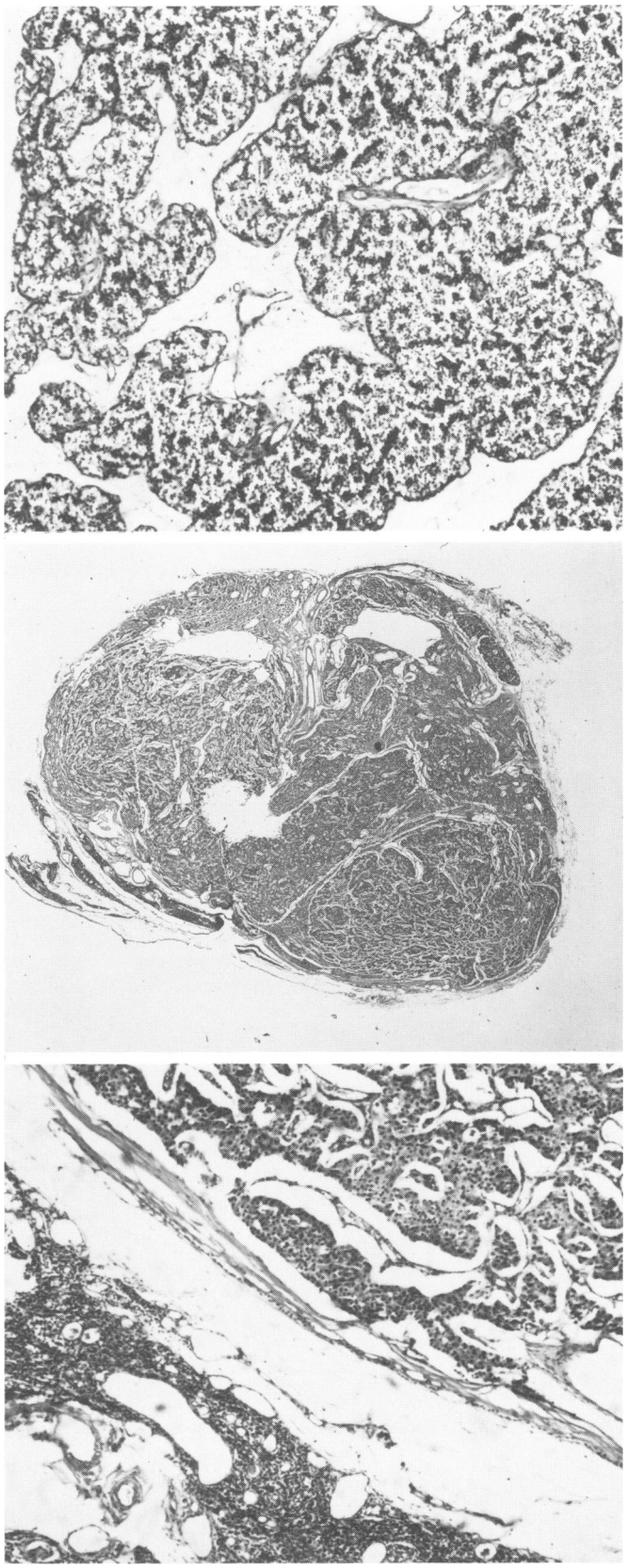

FIG. 1 (Case 3). *A*, Histologic section of large hyperplastic parathyroid gland (180 mg.) removed at cervical exploration. (H & E ×40.) *B*, Low-power section through mediastinal parathyroid tumor (3 cm. in diameter) found at autopsy in the same case. (H & E ×4.) *C*, Margin of tumor with rim of thymic tissue. (H & E ×40.)

Fig. 2 (Case 11). *A*, Histologic section of hyperplastic parathyroid gland (weight, 160 mg.) removed at cervical exploration. Note diminution of stromal fat. (H & E ×40.) B, External and cut surfaces of 15-Gm. encapsulated parathyroid tumor removed from mediastinum 6 months after initial operation. *C*, Histologic section through margin of tumor showing numerous oxyphil cells. (H & E ×40.)

chief cells with considerable mitotic activity and invasion beyond the capsule. The pathologic diagnosis was parathyroid carcinoma.

Discussion

The variability that may exist in the number and anatomic positions of the parathyroid glands poses a challenge to the surgeon endeavoring to identify and excise hyperfunctioning parathyroid tumors. Gilmour[7] was able to identify four glands in 87% of 428 autopsies, five glands in 6%, and three glands in 6.1%. In a review encompassing 281 excised parathyroid adenomas, Norris[13] assigned cervical aberrant positions to 30 (10.7%), with 19 (6.8%) being located in the mediastinum.

In 1952, Castleman[3] stated that almost 20% of functioning adenomas excised at the Massachusetts General Hospital were located in the mediastinum. More recently, Nathaniels *et al.*[12] reviewed the cumulative experience at the same institution and reported a mediastinal parathyroid tumor in 84 (21%) of 400 patients with hyperparathyroidism. Pachter and Lattes[15] reported 98 parathyroid adenomas including two parathyroid adenomas occupying a mediastinal position. Hellström and Ivemark,[8] in a review of 138 cases of primary hyperparathyroidism, reported excision of five adenomas and two hyperplastic parathyroid glands from the mediastinum with autopsy findings of a mediastinal adenoma in one case in which a prior negative mediastinal exploration was reported. Mathisen and associates[10] documented four adenomas in the mediastinum in 59 proved cases of primary hyperparathyroidism.

The large number of mediastinal parathyroid tumors reported by Castleman[3] and Nathaniels *et al.*[12] may be explained by the fact that they included all tumors that could be removed by blunt dissection from the anterior or posterior mediastinal compartments through a cervical incision, as well as a sternal-splitting procedure, while others only reported the tumors to be mediastinal in location when sternal splitting was necessary to perform adequate exploration. In the series of Nathaniels *et al.*,[12] 19 tumors were removed by mediastinotomy.

The thymus and inferior parathyroid glands normally arise from the third branchial pouch. Their migration together into the anterior mediastinum is the cited embryologic explanation for the frequent finding of a parathyroid tumor attached to or embedded in the thymus gland. Cope[4] and Walton[18] have theorized that as a cervical parathyroid is replaced by tumor, its weight and the act of deglutition accelerate a downward migration, abetted by the negative intrathoracic pressure. Most mediastinal tumors are located in the anterior mediastinum, with 35% occurring in the posterior mediastinal compartment. Most posterior mediastinal tumors have been found in a superior position.[15]

Black and Utley[2] and Hoehn and associates[9] have

stressed that the pathologic distinction between primary adenomatous chief cell hyperplasia and adenoma may be difficult. The spectrum of the gross and microscopic morphology of the parathyroid glands in such cases may be strikingly diverse. If all four glands are obviously hyperplastic (often to varying degrees), surgical removal of three glands and subtotal resection of the fourth gland usually restores the patient to a normocalcemic state, providing the remnant remains viable. Not infrequently, however, as in our cases, only one or two of the glands are enlarged at the time of initial exploration. The remaining glands appear grossly normal to the surgeon. When biopsy specimens from these "normal" appearing glands are examined under ordinary light microscopy, they often have been considered normal. Under these circumstances, it is not uncommon for hypercalcemia to persist, despite excision of the obviously hyperplastic tissue. However, even if the patient becomes normocalcemic after the initial operation, periodic reassessment is mandatory since hypercalcemia may recur. At a subsequent operation the remaining parathyroid tissue that initially appeared normal often shows evidence of hyperplastic changes as demonstrated in Case 3.

Preoperative studies to localize hyperfunctioning glands in the mediastinum, using selenomethionine (^{75}Se) as the radioisotope for scintiscanning[11] or selective arteriography,[6] were not performed in any of these patients. Selective cases in which isotope scanning has proved helpful in locating the site of the adenoma have been documented but, in general, the value of this technic has not been substantiated.[11] If a more specific agent for parathyroid gland tagging becomes available, this technic may be of more precise diagnostic help in tumor localization.

Beginning in April 1969, an immunoassay for serum immunoreactive parathyroid hormone (iPTH) became available for use in clinical study of patients with disorders of calcium metabolism.[1] Serum parathyroid hormone levels were available for the preoperative and postoperative assessment of our last two patients. The antiserum used in this assay often makes it possible to distinguish between iPTH present in the serum of patients with primary hyperparathyroidism and that of patients with hypercalcemia secondary to nonparathyroid malignancy.[17]

The finding of four normal parathyroid glands in the neck of one patient (Case 13) led to a suspicion of unrecognized malignancy. Extensive studies to exclude this possibility were conducted by the home physician with negative results. Significant elevation of the iPTH level was strong support for our recommendation for mediastinal exploration. In case 14 the persistence of hypercalcemia and a concomitant high level of serum iPTH after the removal of one cervical chief cell tumor, plus the identification of two normal cervical parathyroid glands, reinforced the probability that another functioning tumor was located in the mediastinum.

Efforts at localization of parathyroid tumors by selective venous catheterization with sampling of iPTH at various cervical and intrathoracic sites have been described by Reitz *et al.*[16] and O'Riordan *et al.*[14] Localization of tumors by this technic in a patient who has previously undergone a negative cervical exploration for hyperparathyroidism would be of great benefit to the surgeon.

Summary

The pertinent laboratory, roentgenographic, and surgical findings in 14 patients (eight men and six women) with mediastinal hyperfunctioning parathyroid tumors showed renal calculi in ten patients and roentgenographic evidence of bone disease of hyperparathyroidism in three; no osseous or renal complications were demonstrated in four patients. Twelve tumors were surgically excised through a sternal-splitting incision. Two tumors were ultimately found at autopsy but mediastinal exploration had not been performed in either patient. The combination of a tumor in the mediastinum and abnormalities in one or more parathyroid glands in the neck was observed in five patients.

A noteworthy finding is the fact that five of these 14 patients had five identified parathyroid glands, with four of the glands located in the cervical region.

Localization of hyperfunctioning parathyroid tissue by selective venous catheterization with sampling of iPTH at various cervical and intrathoracic levels would greatly assist the surgeon, especially in those patients who have had a negative cervical exploration or in whom a recurrence develops subsequently.

Addendum

Since this manuscript was submitted, hyperfunctioning mediastinal parathyroid tumors have been excised from three additional female patients. A 1.3 cm, calcified, cystic chief cell tumor was removed from one patient in whom four normal cervical parathyroid glands were identified. Three grossly normal cervical parathyroid glands were identified in the other two patients; a 6,000 mg. chief cell parathyroid tumor was removed from one and a 370 mg. chief cell parathyroid tumor was removed from the other. All three tumors were attached to thymic tissue.

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