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Primary Hyperparathyroidism and Associated Neoplasms

Angelos A. Kambouris, MD,* Mohammed R. Ansari, MD,* and Gary B. Talpos, MD*

Frequent use of automated multichannel analyzers has contributed to the diagnosis of hypercalcemia in large numbers of patients, many of them completely asymptomatic. While primary hyperparathyroidism has been diagnosed in 0.1% to 0.3% of these patients, malignant neoplasms continue to be the most frequent cause of hypercalcemia (1,2). This is particularly true in patients with known and previously treated cancers, where hypercalcemia is attributed to bone metastases or to humoral factors secreted by the neoplasms, downplaying the role of primary hyperparathyroidism as the underlying cause. Such assumptions may lead to inappropriate workup, to delay in diagnosis, and occasionally to treatment delay in patients with previously treated cancers that are known to have a poor prognosis. The repetitive encounter of patients with hypercalcemia, either en masse attributed to malignancy or whose parathyroid disease was left untreated because of previously treated cancers, prompted a review of our experience with parathyroidectomy over a four-year period and formulates the basis for this report.

Materials and Methods

The records of 111 patients who underwent parathyroidectomy between January 1, 1980, and December 31, 1983, were retrospectively reviewed. The series included 85 women (76.5%) and 26 men ranging in age from 25 to 91 years, with a median age of 57 years. Of the 111 patients, 84 were white and 27 were black.

Operative reports, histopathological reports, and discharge summaries were carefully reviewed to ascertain primary diagnosis, associated tumors or tumorous conditions found at operation, and extent of operative procedures performed. In all instances, information regarding existing or previously treated neoplasms was carefully sought, and the status of such malignancies was recorded. In addition, information regarding previous operations in the head and neck area, and exposure to neck irradiation, was carefully extracted. Postoperative calcium levels were also reviewed to assess the effectiveness of parathyroidectomy in controlling hypercalcemia.

Results

Ten (9%) of the 111 patients underwent treatment for 13 various invasive cancers prior to parathyroidectomy. Table 1 details histologic types and time of definitive treatment of those carcinomas as well as parathyroid histology on the excised glands. Significantly, one patient had undergone successful treatment of sequential bilateral breast cancers and colon cancer, the last one 16 years prior to parathyroidectomy; and another patient had undergone surgical treatment of cancer of the larynx and of the lung, the latter one three years prior to parathyroidectomy. In all instances, carcinoma had been successfully treated, and detailed investigation failed to reveal metastases. Benign thyroid nodules were found and excised in two of these patients at parathyroidectomy. Hypercalcemia was corrected in all ten patients by removal of a single adenoma in seven patients and two or more hyperplastic glands in the remaining three patients.

Nine patients (8.1%) were found to have concurrent malignant neoplasms at parathyroidectomy (Table 2). One of these patients (case 1, Table 2), a 68-year-old white woman, had squamous cell carcinoma of the tongue with neck metastases. Primary hyperparathyroidism was diagnosed through orderly workup of her hypercalcemia. Removal of two hyperplastic parathyroids at the time of radical neck dissection corrected her hypercalcemia. Of the remaining eight patients, five had occult papillary thyroid carcinomas found and excised at parathyroidectomy. Four of these (cases 3-6, Table 2) were incidental findings in the histological examination of excised thyroid nodules. The fifth patient (case 2, Table 2) was found to have an 11 mm papillary thyroid cancer in a totally atrophic thyroid gland during removal of three parathyroid glands, only one of which was hyperplastic. Hypercalcemia persisted, and the patient was reoperated on two months later. Reexploration of the neck and mediastinal exploration failed to locate the missing parathyroid. The patient was hypercalcemic two years later. Another patient (case 9, Table 2), the only one with irradiation to the neck for hypertrophic tonsils 24 years previously, underwent total thyroidectomy and subtotal parathyroidectomy for concurrent papillary thyroid cancer and parathyroid hyperplasia. Hypercalcemia persisted but was corrected when additional hyperplastic parathyroid tissue was excised five months later. The remaining two patients (cases 7 and 8, Table 2) had...
### Table 1
Previously Treated Carcinomas in Patients Undergoing Parathyroidectomy

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Previously Treated Carcinoma</th>
<th>Treatment Year</th>
<th>Parathyroid Diagnosis</th>
<th>Treatment Year</th>
<th>Additional Findings and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71/F</td>
<td>Carcinoma left breast</td>
<td>1962</td>
<td>Adenoma</td>
<td>1982</td>
<td>Hysterectomy 1962</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoma right breast</td>
<td>1966</td>
<td></td>
<td></td>
<td>Parotidectomy 1971</td>
</tr>
<tr>
<td>2</td>
<td>55/F</td>
<td>Carcinoma right breast</td>
<td>1979</td>
<td>Adenoma</td>
<td>1982</td>
<td>Multinodular goiter</td>
</tr>
<tr>
<td>3</td>
<td>67/F</td>
<td>Carcinoma of colon</td>
<td>?</td>
<td>Adenoma</td>
<td>1983</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>66/M</td>
<td>Carcinoma of bladder (cystectomy, ileal loop)</td>
<td>1967</td>
<td>Hyperplasia, 2 glands</td>
<td>1980</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>57/F</td>
<td>Papillary thyroid carcinoma</td>
<td>1979</td>
<td>Adenoma</td>
<td>1980</td>
<td>Hashimoto's thyroiditis</td>
</tr>
<tr>
<td>6</td>
<td>76/F</td>
<td>Carcinoma of rectosigmoid colon (low resection)</td>
<td>1967</td>
<td>Adenoma</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>58/M</td>
<td>Carcinoma of stomach</td>
<td>1978</td>
<td>Adenoma</td>
<td>1981</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>8</td>
<td>58/F</td>
<td>Carcinoma of colon</td>
<td>1983</td>
<td>Adenoma</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>67/F</td>
<td>Carcinoma of larynx (laryngectomy); carcinoma of lung, resected</td>
<td>1975</td>
<td>Nodular hyperplasia, 2 glands</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>43/F</td>
<td>Renal adenocarcinoma (nephrectomy)</td>
<td>1977</td>
<td>Hyperplasia, 3 ½ glands</td>
<td>1980</td>
<td></td>
</tr>
</tbody>
</table>

Clinically recognized and appropriately treated papillary cancers at parathyroidectomy. Excluding the patient with oral cancer, associated nonmalignant thyroid nodules were excised in five of these eight patients and in fact led to the diagnosis of all thyroid cancers.

Eight patients (7.2%) had nonneoplastic thyroid nodules of significance at parathyroidectomy (cases 1 and 2, Table 1, and cases 1-6, Table 2). Seven of the excised nodules were of the colloid variety, and one represented Hashimoto's thyroiditis. Parathyroidectomy was successful in seven patients, but misinterpretation of a colloid nodule at surgery accounted for the failure to identify parathyroid pathology in one patient. She was subsequently reoperated on elsewhere, and her hypercalcemia was corrected. Thus, nonneoplastic thyroid nodules alone (eight instances in patients (two cases in each patient) in this series (Table 2).

Three patients had papillary nodules; the remaining nodules were of follicular adenoma. Parathyroidectomy for hyperparathyroidism was successful in three patients. The nodules included a follicular adenoma, a colloid nodule, and Hashimoto's thyroiditis.
instances), with concurrent thyroid cancers (five instances), or in patients treated for carcinomas prior to parathyroidectomy (two cases) were present in 15 (13.5%) of the 111 patients in this series (Table 3).

Three patients had benign thyroid neoplasms resected at parathyroidectomy. Two of these were benign follicular adenomas; the third was a benign Hurthle cell tumor. Hashimoto's thyroiditis was also present in this last patient. In addition, a follicular adenoma had been resected seven years before parathyroidectomy in one patient. Thus, concurrent or previously treated benign thyroid neoplasms were found in four patients in this series.

In summary, 38 (34.2%) of 111 patients had various tumors or tumorous conditions either previously treated or concurrently managed at the time of parathyroid resection. Ten (9%) had been successfully treated for invasive cancers. Nine (8.1%) had concurrent cancers, eight of them involving the thyroid gland, four had neoplasms related to MEN syndromes, and four had benign thyroid neoplasms. Nonneoplastic nodules, either alone or in conjunction with concurrent or previously treated cancers, were found in 15 (13.5%) of the patients. These findings and the details of the types of the previously treated carcinomas are summarized in Table 3.

Discussion

The association of primary hyperparathyroidism with nodular thyroid disease and also with nonmedullary thyroid carcinoma has been extensively reported in the past 30 years. Comprehensive reports by Prinz et al (3), Nishiyama et al (4), Linos et al (5), Granberg et al (6), and Hedman and Tisell (7) summarize available information.

These reports emphasize that 1) nodular thyroid disease is found in 20% to 50% of patients undergoing parathyroidectomy; 2) nonmedullary thyroid carcinoma of the occult as well as of the clinically significant variety occurs in 1.5% to 24.5% of the patients; 3) this association is more obvious in patients with prior exposure to neck irradiation, especially for papillary thyroid cancers; and 4) many patients with primary hyperparathyroidism, when carefully questioned, will confirm irradiation exposure at some remote point in the past.

In our series, 15 patients (13.5%) had thyroid nodules of nonneoplastic nature excised at parathyroidectomy, and another ten patients (9%), excluding the four MEN-related cancers, had nonmedullary thyroid cancers excised. Two additional patients had been previously treated for nonmedullary thyroid cancers, and one had a follicular adenoma resected seven years before parathyroidectomy. Thus, 25% of the patients in this series had nodular thyroid disease, the majority resected at parathyroidectomy. This association may in fact be lower than its actual occurrence, since only significant thyroid nodules are likely to be removed, while small or insignificant nodular disease or thyroiditis may not be biopsied or resected. While the frequency of nodular thyroid disease in our patients falls in the range of that reported in the literature, only one patient in the entire group had been exposed to neck irradiation 24 years before undergoing total thyroidectomy for papillary thyroid cancer and parathyroidectomy for hyperplasia. Irradiation to the neck cannot be considered a causative factor in the development of nodular thyroid disease, nonmedullary thyroid cancers, or primary hyperparathyroidism in this series. Since Rao et al (8) reported in 1980 a 17% incidence of childhood irradiation among 130 patients with hyperparathyroidism from our institution and a 5% prevalence of hyperparathyroidism in irradiated patients (30 times that found in the general population), the issue of irradiation exposure needs to be further investigated. Failure of our patients to recall such information, or failure to obtain and record such information, may account for the difference.

The association of nonthyroid cancers and hyperparathyroidism was emphasized by Katz et al (9) in a 1970 report of six patients with primary hyperparathyroidism and breast cancer. Subsequent to that report, Kaplan et al (10) reported on an autopsy study of 200 cases; 42% of patients with parathyroid adenomas found at autopsy and 16% of those with surgically confirmed adenomas had malignancies of other organs. In 1973 Farr et al (11) reported that 34 of 100 patients undergoing treatment for primary hyperparathyroidism at Memorial Hospital, NY, had other cancers, antecedent, concurrent, or subsequent to parathyroidectomy. In 1974 Samaan et al (12) reemphasized this association in reporting on 23 patients who underwent preoperative localization and surgical treatment of hyperparathyroidism. Ten of these 23 patients (43.4%) had other tumors, nine of them carcinomas. Two of the nine carcinomas were in the thyroid, but seven were in other organs, including two intestinal carcinoids and one islet cell tumor of the pancreas. In our series ten patients (9%) had been treated for 13 different carcinomas prior to parathyroidectomy (Tables 1 and 3). All cancers were inactive at the time of workup of the hypercalcemia, and primary hyperparathyroidism was confirmed in all instances. Breast, colon, and urinary tract cancers were the
most frequent types, but the numbers are too small to be significant. Diagnosis of primary hyperparathyroidism in these patients was established through an orderly process of ruling out active cancers or bone metastases by multiple documentations or elevated serum calcium levels, elevated immunoreactive parathormone and nephrogenous cyclic AMP, and other appropriate studies. Such a diagnostic process, as emphasized by Purnell et al (2), Skrabanek et al (13), and Drezner and Lebovitz (14), facilitates the diagnosis of primary hyperparathyroidism and its differentiation from pseudohyperparathyroidism or from hypercalcemia of skeletal metastases. Despite the definitive exclusion of active cancers, parathyroidectomy was occasionally delayed for reasons difficult to pinpoint. Eventually, however, primary hyperparathyroidism was surgically corrected in all ten patients with a history of previously treated cancer. This experience underscores the importance of appropriate workup of hypercalcemia in patients with a history of or concurrent invasive carcinomas and de-emphasizes the theoretical fear of metastases in that particular subgroup of hypercalcemic patients.

Conclusions

In our review of 111 patients undergoing parathyroidectomy over a four-year period, 38 patients (34.2%) had associated or previously treated tumors and tumorous conditions of the thyroid or of other organs. Significantly, nine patients had concurrent carcinomas, eight of them of the thyroid gland, and ten patients had undergone successful treatment for 13 various carcinomas before parathyroidectomy.

The frequent concurrence of thyroid nodules and primary hyperparathyroidism mandates extremely careful assessment and appropriate management of all thyroid masses at parathyroidectomy. Hypercalcemia in patients with previously treated cancers should be independently evaluated, and primary hyperparathyroidism should be excluded. In absence of bone metastases, hypercalcemia due to parathormone-like activity is rare. Therefore, biochemical evaluation of such patients should include multiple calcium and phosphorus determinations, parathormone determinations, and nephrogenous cyclic AMP measurements to facilitate diagnosis. If the diagnosis of primary hyperparathyroidism is established, timely parathyroidectomy should be considered depending on risk factors and other clinical parameters.

References