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Primary Hyperparathyroidism: The Continuing Saga of Surgical Problems

Melvin A. Block, MD

Continuing problems in the management and surgical treatment of primary hyperparathyroidism include the localization of the elusive single tumor, the recognition and management of multiple gland involvement, prompt confirmation and operative treatment for hypercalcemic crisis, delineation of a liberal but selective policy relative to surgery for apparent uncomplicated hyperparathyroidism in the elderly, and recognition of the surgeon's responsibility to determine the extent of the operation on the basis of operative findings, realizing that histologic study may not confirm apparent gross abnormalities despite subsequent clinical recovery. When all four glands are involved in primary hyperparathyroidism, subtotal parathyroidectomy is recommended except for patients with multiple endocrine neoplasia, type I (MEN I), in which cases, with great enlargement of all glands, total parathyroidectomy and autotransplantation appear justified. Selective removal of parathyroid glands is indicated for multiple involvement affecting fewer than four glands. Recent experience emphasizes the importance of benign familial hypocalciuric hypercalcemia, the late appearance of primary hyperparathyroidism after radiation therapy to the neck, and the association of primary hyperparathyroidism with a number of other clinical entities.

This discussion of certain continuing and several newer problems of primary hyperparathyroidism is derived from over 25 years of experience with approximately 350 patients at Henry Ford Hospital and with 38 patients in the past two years at the Scripps Clinic.

**Continuing Problems**

The elusive single tumor

The single, enlarged parathyroid gland, which is responsible for primary hyperparathyroidism in approximately 85% of patients, is sometimes discovered in unusual locations. Knowledge of the normal anatomy of the neck and upper mediastinum along with awareness of the unusual locations of these glands is essential for the parathyroid surgeon (1). Missed enlarged parathyroid glands should be sought in several locations: deep in the sternoclavicular joint area, high in the neck (undescended), associated with the thymus in the anterior superior mediastinum (but accessible through a neck incision), deep in the neck associated with the fascia over the cervical vertebrae, or intimately associated with the thyroid gland, from which delineation is quite difficult.

While future refinement of non-invasive procedures, such as ultrasonography, may help to identify elusive parathyroid tumors, currently available instruments are not reliable in problem cases (2). Invasive studies, especially angiography, are valuable in locating parathyroid tumors but carry risks, especially neurologic complications. Moreover, the cost of angiography justifies its use for patients in whom initial exploration of the parathyroid glands was unsuccessful (3). The same difficulties characterize selective cervical venous sampling for parathyroid hormone assay as a method for localizing hyperfunctioning parathyroid tumors (4).
Although the mediastinal location of hyperfunctioning parathyroid glands is rare (less than 1%), the surgeon should be prepared to explore the mediastinum for a missed parathyroid tumor not identified by preoperative studies. At this time, computerized tomography can identify about 50% of parathyroid tumors lying deep in the mediastinum (5,6). Although this record justifies its use preoperatively, particularly in patients with increased risk for operation or reoperation, the CT scan is not entirely reliable. Arteriography is more accurate than other studies in detecting mediastinal parathyroid tumors (7), but associated risks require selectivity in its use.

Reoperation carries a substantial risk of inducing permanent hypoparathyroidism. The extent of the loss of parathyroid tissue consequent to the first operation may be unknown, and the need to dissect through scar tissue jeopardizes whatever normal parathyroid tissue remains (8). The decision to perform immediate autotransplantation of the parathyroid tissue or to freeze the tissue for possible later autotransplantation must be based on several factors of surgical judgment: whether or not the remaining parathyroid tissue is viable; whether or not the parathyroid tumor that produced hyperparathyroidism has been removed; whether or not the parathyroid tissue available for autotransplantation is normal. The elusive parathyroid tumor may be a supernumerary gland, and it may be found in an unusual location such as the mediastinum. Supernumerary glands reportedly are predisposed for location in the anterior superior mediastinum or in the more caudal mediastinum (9).

Recognition and management of multiple parathyroid gland involvement

Primary hyperparathyroidism with multiple parathyroid gland involvement can be categorized into two major entities (10): all parathyroid glands enlarged and hyperplastic; less than four glands enlarged and hyperplastic (11,12). In both categories, the degree of enlargement of the gland varies greatly, from slight enlargement of all involved glands, to great enlargement of some and slight enlargement of others in a single patient, to great enlargement of all involved glands.

The surgeon treating primary hyperparathyroidism with multiple parathyroid gland involvement encounters three major problems:

1. Failure to recognize the presence of multiple gland involvement. As a result, only one parathyroid gland is removed and hyperparathyroidism persists.

2. Failure to identify all involved parathyroid glands, so that the remaining hyperfunctioning glands cause persistent hyperparathyroidism. The remaining hyperfunctioning gland may be supernumerary.

3. Production of permanent hypoparathyroidism. Extensive dissection necessary to identify all parathyroid glands and the removal of more parathyroid tissue than needed (because of difficulty in judging at operation the number of involved glands) may cause permanent parathyroid deficiency.

Primary hyperparathyroidism with involvement of all glands has certain unique features. Among these is the association with multiple endocrine neoplasia (MEN) syndromes. Not all hyperparathyroid patients with involvement of all parathyroid glands have the MEN syndrome, but all patients with a MEN syndrome and primary hyperparathyroidism have all parathyroid glands involved. Primary hyperparathyroidism is characteristic of all patients with MEN I syndrome, of some patients with MEN IIa syndrome, but of no patients with MEN IIb (13,14).

Whenever multiple parathyroid gland involvement is recognized in primary hyperparathyroidism, family members should be screened for the disease. The extent of involvement in familial hyperparathyroidism can be predicted as follows: 1) in MEN II and MEN IIa syndrome patients, all parathyroid glands are involved; 2) in approximately 40% of patients with non-MEN familial primary hyperparathyroidism, all parathyroid glands are involved, and the same disorder occurs in all family members. The number of involved parathyroid glands varies in the other 60% of patients, but usually more than one gland is hyperfunctioning.

The best surgical management for primary hyperparathyroidism with all parathyroid glands involved remains controversial. Some advocate subtotal parathyroidectomy with preservation of 30-50 mg viable parathyroid tissue, while others recommend total parathyroidectomy and autotransplantation of parathyroid tissue (15-19). For patients who have fewer than four involved parathyroid glands, the objective must be to remove all involved tissue short of total parathyroidectomy (15,20). Results of this procedure are excellent. However, when all parathyroid glands are involved, no currently available operative procedures are successful in all cases. The expected results for surgical treatment (Table I) can be summarized in the following way.

Because the reported long-term recurrence rate after subtotal parathyroidectomy is approximately 50% in patients with MEN I syndrome (15,18), total parathyroid-
Primary Hyperparathyroidism

TABLE I
Primary Hyperparathyroidism Due to Multiple Gland Involvement:
Results of Operative Procedures

<table>
<thead>
<tr>
<th>Report</th>
<th>% Persistence or Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Subtotal parathyroidectomy</td>
<td>14</td>
</tr>
<tr>
<td>Edis, et al (16)</td>
<td>4</td>
</tr>
<tr>
<td>Wang, et al (17)</td>
<td>14±(50% MEN; 8% non-MEN)</td>
</tr>
<tr>
<td>Block, et al (15)</td>
<td>33 in MEN I</td>
</tr>
<tr>
<td>Prinz, et al (18)</td>
<td>3 (30% later hypercalcemic)</td>
</tr>
<tr>
<td>II. Total parathyroidectomy, autotransplantation</td>
<td>8</td>
</tr>
<tr>
<td>Wells, et al (19)</td>
<td>hypercalcemic</td>
</tr>
</tbody>
</table>

...
ings, the size of parathyroid tumor, and the clinical response to surgery is obscure.

It is well recognized, although not always respected, that pathologists find it difficult to differentiate between adenoma and hyperplasia and thereby to distinguish between single and multiple parathyroid gland involvement. The terms “single and multiple gland involvement” or “parathyroid tumor” are held to be more informative than “adenoma” or “hyperplasia” in characterizing the pathologic anatomy of primary hyperparathyroidism. In this regard, studies by Fialhow and colleagues indicate that primary hyperparathyroidism of all varieties has a multicellular rather than a single cellular origin (26).

Another discrepancy between pathologic and clinical findings relates to the significance of the fat content of parathyroid glands in determining abnormality. In four of our patients whose glands were enlarged by weight (59 to 95 mgm) and in whom hypercalcemia was corrected by removing the glands, the presence of considerable quantities of fat led to a pathologist’s report of normal parathyroid tissue. Thus, in the presence of fat cells, enlarged glands may be characterized as microscopically normal even though other evidence indicates abnormality. In our series, we removed parathyroid glands weighing 95, 90, 71, and 59 mgm from four different patients and permanently corrected the hypercalcemia, but the pathologist described the glands as normal. All had very high fat content. This problem tends to occur in elderly patients particularly. More detailed study can confirm the increased functioning tissue in these glands with variable fat content (27,28).

The hyperplasia found in patients with benign hypocalciuric hypercalcemia is another unclear issue of parathyroid pathology. In addition, fragments of parathyroid tissue are often found in adipose tissue surrounding a parathyroid gland, whether it is normal or enlarged and hyperfunctioning. These variables are not resolved by tests that depend on density or similar measurements to separate hyperfunctioning from normal parathyroid glands or other tissue (29). Measuring the weight and dimensions of a parathyroid gland is important gross evidence of pathologic significance (11,12).

New Experiences

Recognizing benign familial hypocalciuric hypercalcemia

In 1966, Jackson and colleagues (30) recognized the occurrence of familial hypercalcemia which failed to respond to standard treatment, and most large series of patients contained similar examples. Marx and colleagues (31,32) have defined benign familial hypocalciuric hypercalcemia as an entity of clinical significance. Essential clinical features include the presence of lifelong hypercalcemia at all ages, lack of relationship to MEN syndromes, a confusing elevation of serum parathyroid hormone levels, absence of clinical complications (except possibly pancreatitis in rare instances), and serious clinical manifestations in infants with hypotonia and skeletal undermineralization, which can justify total parathyroidectomy.

The parathyroid glands vary in size and, microscopically, are considered to be hyperplastic. Subtotal parathyroidectomy does not permanently correct the hypercalcemia.

Benign familial hypocalciuric hypercalcemia occurs often enough to justify its consideration whenever uncomplicated hypercalcemia is recognized. This entity has been recognized primarily as a result of the routine serum calcium determinations performed with increasing frequency in recent years. In patients with uncomplicated primary hyperparathyroidism who have no renal or skeletal complications, the diagnosis of benign familial hypocalciuric hypercalcemia may be confirmed by demonstration of urinary calcium levels of 100 mg or less per 24 hours, a calcium/creatinine clearance ratio of less than 0.010, and familial occurrence of the disorder (31). Serum parathyroid hormone levels are not of diagnostic significance.

Because in this entity complications of the hypercalcemia do not occur, other family members must be studied to identify the familial presence. As far as can now be ascertained, treatment is unnecessary for adults.

Confusing variations do occur in benign familial hypocalciuric hypercalcemia. We have encountered one family in whom subtotal parathyroidectomy reduced the serum calcium to normal levels at least for some months. Because some patients have enlarged parathyroid glands, the findings at surgery are not different from those of primary hyperparathyroidism. There is a reported 15% overlap in calcium/creatinine clearance ratios between patients with primary hyperparathyroidism and those with benign familial hypocalciuric hypercalcemia (32).

Late appearance of primary hyperparathyroidism after external radiation therapy

While I was at Henry Ford Hospital, I first suspected that an etiologic relationship exists between primary hyperparathyroidism and external radiation therapy to the head and neck. Our studies at the hospital confirmed the statistical significance of the relationship (33). Our original studies suggested that in these patients primary hyperparathyroidism usually occurs late, decades after
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radiation, and our experience in the past two years supports this observation.

In this time we have successfully operated on four patients for primary hyperparathyroidism 45, 34, 27, and 26 years after they had received external radiation therapy to the neck. Hyperparathyroidism had occurred in two of these patients 28 and 30 years after operation for thyroid neoplasms, and total thyroidectomy was necessary in one patient. In a fifth patient in whom we performed total thyroidectomy for a papillary thyroid carcinoma 25 years after he had received external radiation therapy to the neck, we encountered at operation an enlarged parathyroid gland weighing 66 mgm. Histologic study disclosed mild parathyroid hyperplasia. In this patient the preoperative serum calcium level of 10.1 mgm/dl (normal, 8.7-10.2) fell postoperatively to 7.0 mgm/dl before rapidly returning to normal (9.7 mgm/dl). We believe that hyperfunction was developing in this parathyroid gland and that hypercalcemia would eventually have occurred. Prinz and associates have reported a similar experience (34).

Another patient, 61 years old, developed evidence of primary hyperparathyroidism seven years after receiving high dose external radiation for therapy of carcinoma of the larynx. Two enlarged parathyroid glands weighing 1 gm and 95 mgm were removed, correcting the hypercalcemia.

Recently reported evidence implicates radioactive iodine therapy administered for treatment of hyperthyroidism as a factor in the late occurrence of primary hyperparathyroidism (35). Of 854 patients treated for primary hyperparathyroidism at the Cleveland Clinic, four had received radioactive iodine therapy, in three patients more than 20 years earlier and in one patient, six years earlier. The expected late incidence of primary hyperparathyroidism in patients receiving radioactive iodine therapy was estimated to be one in 800-900 patients. In addition, eight of 160 patients who were under 18 years of age when treated with radioactive iodine were found subsequently to have hypercalcemia, probably due to primary hyperparathyroidism.

Single gland enlargement is the usual finding in patients with primary hyperparathyroidism following external radiation therapy. However, these patients should be followed for possible recurrent primary hyperparathyroidism in the remaining glands. Moreover, it is recommended that patients receiving radiation therapy to the neck region be screened periodically for developing hypercalcemia. Certainly, surgeons should carefully evaluate the parathyroid glands when they operate for thyroid neoplasms, especially in patients who have received previous radiation therapy to the neck region. Removal of enlarged parathyroid glands seems justified.

Miscellaneous MEN syndromes

Combinations of primary hyperparathyroidism and other endocrine disease occur sporadically (36). In our patients with primary hyperparathyroidism, we have encountered coexisting non-functioning islet cell carcinoma, acromegaly, and unilateral aldosteronoma, all apparently non-hereditary. Primary hyperparathyroidism has been associated with pheochromocytomas, although these tumors can themselves be the cause of hypercalcemia (37,38). Occurrence of primary hyperparathyroidism with other endocrine tumors can be simultaneous, or either may precede the other. The question of which endocrine tissue is responsible for the hypercalcemia can be resolved by the demonstration of elevated parathyroid hormone levels in blood obtained selectively from neck veins. Parathyroid carcinoma, a rare lesion, occurs in families more than is to be expected for random distribution (39). This might be considered as MEN III.

Primary hyperparathyroidism may occur in association with other disease processes which by themselves can produce hypercalcemia. Examples are the simultaneous occurrence of primary hyperparathyroidism and malignancies such as breast and renal carcinoma, sarcoidosis, or multiple myeloma (40-43).

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>Primary Hyperparathyroidism: Reasons for Failed Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Erroneous diagnosis</td>
</tr>
<tr>
<td></td>
<td>Malignancy, other causes for hypercalcemia, medications</td>
</tr>
<tr>
<td></td>
<td>Benign familial hypocalciuric hypercalcemia</td>
</tr>
<tr>
<td>2.</td>
<td>Failure to identify elusive single tumor</td>
</tr>
<tr>
<td></td>
<td>Anterior superior mediastinum, under sternoclavicular junction</td>
</tr>
<tr>
<td></td>
<td>High in neck (undescended)</td>
</tr>
<tr>
<td></td>
<td>Intrathyroid</td>
</tr>
<tr>
<td></td>
<td>Mediastinum</td>
</tr>
<tr>
<td></td>
<td>Carotid sheath</td>
</tr>
<tr>
<td>3.</td>
<td>Failure to perform adequate operation for multiple gland involvement (removal of multiple but less than four enlarged glands, subtotal parathyroidectomy, total parathyroidectomy with autotransplantation)</td>
</tr>
<tr>
<td>4.</td>
<td>Supernumerary parathyroid tumor (usually located inferiorly)</td>
</tr>
<tr>
<td>5.</td>
<td>Continued stimulation of remaining parathyroid tissue after subtotal parathyroidectomy or total parathyroidectomy with autotransplantation</td>
</tr>
<tr>
<td>6.</td>
<td>Complications of hypoparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Preserved remnant not viable or inadequate</td>
</tr>
<tr>
<td></td>
<td>Excess removal of glands</td>
</tr>
<tr>
<td></td>
<td>Suppressed remaining parathyroid tissue incapable of adequate function</td>
</tr>
</tbody>
</table>

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Parathyroid cysts

Parathyroid cyst manifested as a palpable nodule in the anterior neck is a rare lesion recognized in recent years. These cysts are frequently thought to be thyroid nodules, particularly when a defect is produced in a thyroid scan. Needle aspiration biopsy and ultrasound studies which identify the cystic nature of this entity can identify parathyroid cysts without the need for operation. In our experience aspiration is curative.

Parathyroid cysts usually occur in young women. When aspiration of fluid, either clear and opalescent or thin and blood-tinged, results in complete disappearance of the nodule, the probable diagnosis is a simple parathyroid cyst. A high level of parathyroid hormone in the cyst fluid is confirmatory.

Simple parathyroid cysts should be distinguished from parathyroid tumors with cystic degeneration. Although simple cysts usually contain small fragments of parathyroid tissue in their wall, they probably are not formed by cystic degeneration of parathyroid tumors. Clinical hyperparathyroidism has not been reported in a patient with a single parathyroid cyst, although it certainly occurs in patients with cystic degenerating parathyroid tumors.

Overall Results of Operation for Primary Hyperparathyroidism

Although a number of factors can lead to a failed operation for primary hyperparathyroidism (Table II), results of surgical management are good. The overall success rate is 95-97% (Table III) with a very low incidence of complications (10,15,17,44).

TABLE III
Primary Hyperparathyroidism: Overall Results of Surgery

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Persistence or Late Recurrence</th>
<th>Permanent Hypoparathyroidism</th>
<th>Major Complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal—single gland involved (20,44)</td>
<td>1%</td>
<td>0.5%</td>
<td>±1%</td>
<td>0%</td>
</tr>
<tr>
<td>subtotal parathyroidectomy for multiple gland involvement (15,18)</td>
<td>MEN 1 ± 50% non-MEN 8%</td>
<td>3.4%</td>
<td>±1%</td>
<td>0%</td>
</tr>
</tbody>
</table>
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References


