Controversies and Advances in Primary Hyperparathyroidism

Primary hyperparathyroidism is a very common disease in the United States. It is increasingly being recognized because of the widespread availability of multiphasic screening for hypercalcemia and double-antibody immunoassays for intact parathyroid hormone. Approximately 100,000 new cases are diagnosed each year, and women are affected twice as often as men. Surgery is the major potentially curative form of treatment. Because of the common occurrence of this debilitating and life-threatening disease, general surgeons play an important role in the management of patients with primary hyperparathyroidism.

In this issue of the Annals of Surgery, Kaplan and Yashiro update the reader on important issues in the management of patients with primary hyperparathyroidism. Their review stresses the necessity of surgical “experience” for the successful management of these patients. Experience is essential for diagnosis, identification of parathyroid glands, and determination of the true extent and nature of the disease (hyperplasia versus adenoma versus carcinoma). The review provides numerous helpful hints and suggestions for improved management of these patients. From the standpoint of how to do it, it provides valuable information and is well worth careful consideration. There are additional current controversies and research in this fast-moving field that also should be considered, however. This editorial will attempt to highlight a few of the more important recent developments that will likely affect the management of patients with primary hyperparathyroidism.

Because of the use of multiphasic screening, many patients with the biochemical diagnosis of primary hyperparathyroidism are asymptomatic. These patients have minimally elevated serum levels of calcium and parathyroid hormone, but do not have symptoms or signs of bone, renal, gastrointestinal, or neuromuscular disease. A question arises about the proper management of these patients. Who can be safely followed without surgery and should they be? These questions were recently addressed by a consensus development conference at the National Institutes of Health. The group stated that there is a population of patients with primary hyperparathyroidism that can be safely managed medically and should be carefully followed. Patients with only mildly elevated serum levels of calcium, no prior episodes of severe hypercalcemia, and normal renal and bone status are eligible for nonsurgical management. This is a controversial point and one that deserves more debate. First, the ability of meticulous surgery to cure patients has been unequivocally demonstrated over and over again, and the success rate is probably greater than 95%. Second, the typical patient with no family history of endocrine or parathyroid disease who is diagnosed by screening most likely will have a parathyroid adenoma as a cause of the primary hyperparathyroidism and will be more readily cured by surgery than the more complex patients with familial hyperparathyroidism and hyperplasia. Third, as a parathyroid surgeon I have been impressed that patients with asymptomatic primary hyperparathyroidism are not really asymptomatic. For example, patients have subtle symptoms like memory loss, personality change, inability to concentrate, exercise fatigue, back pain, and others that are not uncommon in daily living, which may completely disappear with successful surgery. Finally, the surgery can be performed safely with very minimal complications (<1% recurrent laryngeal nerve injury rate), no transfusion requirement, and essentially no operative deaths. It is unclear whether careful follow-up with repetitive measurements of bone densitometry and chemistry determinations will be preferable over a simple surgical procedure that has a high likelihood of success, minimal complication rate, and the possibility of relieving subtle, but potentially significant, symptoms.

Another controversial point is the use of radiographic imaging studies to localize the abnormal parathyroid gland or glands in patients who are undergoing initial operations for primary hyperparathyroidism. Most experts agree that the use of imaging studies is not indicated and can be costly and misleading. However, many physicians commonly obtain these studies and use them to confirm the diagnosis of primary hyperparathyroidism and to determine whether or not to perform surgery. Imaging studies cannot reliably accomplish either task. Noninvasive studies have a 15% false-positive rate and only a 60% true-positive rate, which are clearly inferior to surgery that has a 95% success rate. The diagnosis is made solely by the
determination of abnormal serum levels of calcium and parathyroid hormone, and the decision to operate is based either on symptoms or unequivocal evidence of the disease. Radiographic imaging studies do not have a role in either.

Exciting new findings are providing insight into the cause and molecular pathology of primary hyperparathyroidism. In patients with multiple endocrine neoplasia type 1 (MEN-1), hyperparathyroidism is caused by hyperplasia of all four glands, and even patients whose remaining glands appear to be normal have a tendency toward recurrent enlargement, because there is a 50% recurrence rate with long-term follow-up. A parathyroid mitogenic factor had been described in the plasma of patients with MEN-1. This substance stimulates the proliferation of bovine parathyroid cells and resembles basic fibroblast growth factor. However, polyclonal hyperplasia secondary to a growth factor is not the only cause of enlargement of parathyroid glands in MEN-1 patients, because monoclonal enlargement has also been described. Allelic loss (loss of heterozygosity) from chromosome 11 was found in most abnormal parathyroid glands from patients with primary hyperparathyroidism in the setting of MEN-1. Ten of sixteen abnormal parathyroid glands from 14 different patients had losses of alleles from chromosome 11. Glands with losses were larger than those without, suggesting that a monoclonal growth may develop after a phase of polyclonal hyperplasia. Because the gene associated with MEN-1 is also located on chromosome 11 (11q13), it may normally inhibit tumor proliferation, and tumors could originate from inactivation of one or both alleles.

Similar genetic anomalies also have been described recently in sporadic parathyroid adenomas: a novel gene rearrangement involving the parathyroid hormone gene on chromosome 11q9 and allelic loss from at least two regions of chromosome 11. Allelic loss from chromosome 11 was found in a significant proportion of sporadic parathyroid adenomas. This frequency of allelic loss has several implications. First, it is consistent with the theory of a monoclonal origin for parathyroid tumors. Second, it is also consistent with the hypothesis that inactivation of a tumor suppressor gene contributes to the initiation or evolution of benign parathyroid tumors. Analogous loss of the normal homologue of a growth suppressor gene has been observed in acoustic neuroma, colon carcinoma, Wilms', and other tumors. Presumably the action of these genes is recessive at the cellular level. Another, less common (3%) mechanism of parathyroid adenoma initiation is DNA rearrangement involving the parathyroid hormone (PTH) gene. One of these DNA rearrangements has been shown to juxtapose the first intron of the PTH gene on the short arm of chromosome 11 to band q13 on the long arm and form an oncogene (PRAD-1). PRAD-1 has been cloned and encodes for a protein of 295 amino acids with sequence similarities to cyclins, which act as stage-specific regulators of progress across the cell cycle. PRAD-1 has been implicated in cancers, including breast and squamous cell carcinoma, but oncogenes have not previously been implicated in growth of benign tumors. Thus, the initiation of parathyroid tumor growth is heterogeneous, from deletion of a suppressor gene in a significant proportion of tumors, to induction of an oncogene in a minority of tumors.

Beside these most impressive advances in the molecular pathophysiology and initiation of parathyroid neoplasia, advances in the clinical and operative management of patients with parathyroid neoplasms also deserve attention and consideration. As mentioned, the diagnosis of primary hyperparathyroidism is dependent primarily on abnormally elevated circulating levels of PTH, and the current pathologic analysis of parathyroid glands (normal versus adenoma versus hyperplasia versus carcinoma) is, at best, an inexact science. Therefore, an intraoperative functional assay for the determination of surgical correction of hyperparathyroidism is valuable. These assays are especially helpful during tedious reoperations on patients with parathyroid hyperplasia who have a higher incidence of recurrent disease and who have had abnormal glands removed at multiple institutions by different surgeons. Intraoperative determination of urinary cyclic adenosine monophosphate levels or serum PTH levels have been shown to correlate with successful resection of all abnormal parathyroid tissue. These measurements provide the surgeon with functional confirmation of the outcome during the procedure.

Another technical advance is the use of high-resolution near-field real-time ultrasound during reoperations for primary hyperparathyroidism. Intraoperative ultrasound (IOUS) is able to image abnormal parathyroid tissue and direct the surgeon to the parathyroid tumor. It is especially adept at detecting tumors that are within or near the thyroid. It is valuable because it can take the place of extensive tedious dissection in scarred reoperative fields. We have found that approximately 20% of parathyroid adenomas removed during reoperation are within the thyroid and that IOUS will localize these tumors and allow resection without removing the entire thyroid lobe. Finally, another technical advance is the nonoperative management of mediastinal parathyroid adenomas by angiographic ablation. Angiographic ablation is the purposeful injection of extra contrast material into the feeding vessel of a parathyroid tumor selectively to destroy it. At the National Institutes of Health, where there is a large experience with parathyroid reoperations and localization, radiologists have treated 27 patients with mediastinal parathyroid adenomas by this method. Long-term control of primary hyperparathyroidism was achieved in 17 (63%) with no
complications and minimal pain. The remainder could have the gland removed easily by median sternotomy. These results suggest that angioablation may be the initial procedure of choice for patients with mediastinal parathyroid adenomas identified by angio- and that operation can be reserved for those who fail ablation.

The management of patients with primary hyperparathyroidism has rapidly evolved since the first patient was treated surgically in 1925. The future appears to be with the use of sensitive molecular biology techniques to determine the origin of the disease and to develop new diagnostic as well as localization techniques. As stated by Kaplan and Yashiro, an important criterion for successful surgical outcome is the experience of the operating surgeon. The challenge for teaching hospitals and professors of surgery is transferring that experience to surgical residents. Based on the high incidence of the disease, the fact that in most patients it is a progressive disease, and the potential curative outcome of surgery, the number of parathyroid explorations should continue to increase in the future. Young surgeons will not only need to know the principles of parathyroid surgery and technical options for more difficult cases, but they will need to understand the mechanisms of parathyroid tumorigenesis to continue to ensure excellence in the management of these patients.

REFERENCES

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