Review Article

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The Parathyroid Adenoma

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Abstract

Parathyroid adenomas are benign neoplasms with a predilection for the inferior parathyroid glands. Genetic mutations identified as contributing to development of parathyroid adenomas include MEN 1 and cyclin D1. Predisposing factors include female gender and radiation exposure. The natural history of parathyroid adenomas, including malignant potential, is poorly understood. Specific indications for surgical removal in addition to surgical and non surgical therapeutic modalities are discussed in this review.

Key words: *Parathyroid glands, adenoma, parathyroid neoplasm*

Introduction

Normal parathyroid glands are mainly composed of chief cells which are the secretory, granule-rich cells responsible for Parathyroid Hormone (PTH) release. This hormone is responsible for regulating serum calcium levels and bone metabolism [1]. Other cell types in the parathyroid gland include the oncocytic (or oxyphilic) and transitional oncocytic cells. These cell types are larger than chief cells, have an acidophilic cytoplasm, and are devoid of secretory granules. The fat composition of parathyroid glands increases with age, reaching a maximum of 30% of the gland [2].

Parathyroid Adenomas

Parathyroid adenomas are benign neoplasms composed usually of chief cells but may also be rarely derived from oncocytic or transitional oncocytic cells. Parathyroid adenomas have now been largely proven to be monoclonal or oligoclonal proliferations [3] rather than polyclonal ones. On pathological examination, parathyroid adenomas usually appear as well-circumscribed lesions with hypercellularity and decreased lipid in both the stroma and cytoplasm. Minimal nuclear pleomorphism and mitotic activity are present. A rim of normal compressed parathyroid tissue at the periphery

of the lesion is one of the main histological hallmarks of this entity. Parathyroid adenomas have a predilection for the inferior parathyroid glands which tend to be more variable in location compared to the superior parathyroid glands [4].

Differential Diagnosis

Parathyroid adenomas are usually discovered during the course of investigating the etiology of proven or suspected primary hyperparathyroidism. Primary hyperparathyroidism is defined by inappropriately elevated PTH production, by overactive parathyroid tissue, leading to hypercalcemia. The differential diagnosis of primary hyperparathyroidism includes single parathyroid adenoma, parathyroid gland hyperplasia, double gland adenomas, and parathyroid carcinoma. The commonest of these is single gland parathyroid adenoma, accounting for about 85% of all cases of primary hyperparathyroidism [5]. A rare condition which mimics primary hyperparathyroidism is benign familial hypocalciuric hypercalcemia (BFHH). This familial condition results from genetic abnormalities in the calcium receptors in the kidneys and cannot be corrected by parathyroidectomy [5].

Genetics

Several genetic mutations have been identified in conjunction with parathyroid adenoma development. However, the mutations identified to date account for only a minority of the parathyroid adenomas observed in clinical practice. The Multiple Endocrine Neoplasia (MEN) type 1 gene is a tumor suppressor gene that has been found to harbor somatic mutations in both copies in about 20% of parathyroid adenomas [6]. Mutations in the cyclin D1 oncogene have been identified in only 5% of parathyroid adenomas [7].

No mutations in the parathyroid calcium sensing receptor (CaSR) gene have been identified. This receptor, located on the surface of chief cells, is responsible for regulation of PTH secretion based on serum calcium concentrations [8]; it has been implicated in the pathogenesis of benign familial hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism [9]. Likewise, no mutations in the chief cell vitamin D receptor gene have yet been identified.

Risk Factors

Female gender is known to impart a higher risk for the development of parathyroid adenomas and hyperparathyroidism; in fact, the prevalence in women has been found to be twice that found in men [5]. Exposure to ionizing radiation of the head and neck is also correlated with increased risk of parathyroid adenoma development. Studies suggest that the higher the dose of radiation received and the younger the age of exposure, the higher the risk [10,11]. However, the percentage of patients that develop symptomatic parathyroid disease or cancer as a result of radiation exposure is not known. Also, the time interval from radiation exposure to diagnosis has been found to be around +20 years [12], although the time to development of softer neuropsychiatric symptoms is unknown.

Malignancy Potential

The natural history of parathyroid adenomas is poorly understood. This is because parathyroid adenomas have historically been detected only after causing symptoms, an event which was usually followed by surgical resection. Because of this, there is a lack of reliable long-term follow-up data on the natural history of histologically proven parathyroid adenomas. Only asymptomatic adenomas that do not meet criteria for surgical resection lend themselves to long-term observation. Few longitudinal studies have been performed, with none of these having reported cancer development. This is not surprising given the rarity of parathyroid carcinomas in general. In addition, it is not known whether parathyroid adenomas that behave in such a benign manner on longitudinal follow-up carry an inherently lower or different malignancy potential than other adenomas. Therefore, the exact malignancy potential of any given parathyroid adenoma is unknown.

To date, no consistent anatomic, histologic, metabolic, or genetic features have been linked to subsequent malignancy in parathyroid adenomas. Several other practical issues have likely deterred the identification of markers of malignant potential (if any actually exist). One such factor is the lack of specific pathological markers differentiating parathyroid adenomas from carcinomas. The distinction between the two entities is based solely on the clinical confirmation of locoregional invasion or metastasis. Currently, the diagnosis of parathyroid carcinoma is restricted to those lesions showing overt locoregional invasion on surgery, cap-

sular invasion, neurovascular invasion, and/or distant metastasis [13]. In fact, unanimous histological criteria for the diagnosis of parathyroid adenomas themselves are lacking, thus making the pathological differentiation among adenoma, hyperplasia, and carcinoma difficult.

Clinical Features

Epidemiology

The exact incidence and prevalence of parathyroid adenomas are not known. However, parathyroid adenomas are known to account for greater than 80% of cases of primary hyperparathyroidism. Primary hyperparathyroidism has been estimated to affect one in every 500 women and one in every 2,000 men over the age of 40 years [14]. It is thought that the vast majority of parathyroid adenomas are functional.

Presentation

By far, the commonest presentation of a parathyroid adenoma is hyperparathyroidism resulting from inappropriate PTH secretion relative to the serum calcium level. Currently, the commonest presentation of a parathyroid adenoma is asymptomatic primary hyperparathyroidism detected incidentally on biochemical serum screening tests [15].

Surgical Therapy

Indications for Surgical Resection

Hyperparathyroidism is the commonest indication for surgical resection of a parathyroid adenoma. It is well agreed that any patient presenting with symptomatic hyperparathyroidism should undergo surgical resection. Such symptoms include renal stones, fractures resulting from osteoporotic bone disease, myopathies, hypercalcemia-induced pancreatitis or peptic ulcer disease, or marked neuropsychiatric disturbances. Patients with asymptomatic hyperparathyroidism, detected serendipitously by biochemical serum testing, should also be treated surgically if they meet one of the following criteria set out by the National Institute of Health (NIH): age less than 50 years, serum calcium level 1 mg/dl above the upper limit of being normal, 24-hour urine calcium excretion greater than 400 mg, 30% reduction in creatinine clearance, and osteoporosis as defined by a T score below -2.5 at any one of three sites (lumbar spine, hip, distal third of radius).

The main area of controversy is the dilemma in managing supposedly asymptomatic patients who do not meet any of the NIH criteria but who present with mild neuropsychiatric disturbances. The difficulty in managing these patients stems from the fact that such symptoms are difficult to define and difficult to attribute to any one specific cause. Many studies have asserted that most patients labeled as having asymptomatic hyperparathyroidism suffer from vague neuropsychiatric symptoms and, therefore, are not truly asymptomatic [16–18]. Adding to the difficulty is that the exact risk of progression to symptomatic disease in patients who present with asymptomatic hyperparathyroidism is unknown [19]. A large population-based study has demonstrated that while mild asymptomatic hyperparathyroidism did not confer an increased mortality risk, the risk of death was higher in those patients with calcium levels in the highest quartile [20]. Retrospective studies have demonstrated, however, that patients who were operated on for mild "asymptomatic" hyperparathyroidism that did not meet any of the NIH criteria usually report significant postoperative improvement in overall well-being and mental status [21,22].

Clinical suspicion of malignancy should also warrant surgical resection. Patients presenting with clinically palpable lesions, vocal cord paralysis, lymphadenopathy, serum calcium levels greater than 3 mmol/l, and serum PTH levels greater than four times the upper limit of being normal have been associated with a higher risk of diagnosis of parathyroid cancer [23].

Preoperative Localization

Preoperative imaging localization of parathyroid adenomas has traditionally been considered unnecessary in the context of bilateral neck exploration. The success rates attributed to bilateral exploration and direct four gland inspection, in fact, supercede any of the imaging modalities available today. A saying attributed to Doppman in 1986 states that the only preoperative localization effort necessary in parathyroid surgery is "to localize an experienced parathyroid surgeon" [24]. Preoperative localizing imaging is mandatory, however, if unilateral neck exploration or minimally invasive methods are being planned. In fact, failure to successfully and unequivocally localize a parathyroid adenoma preoperatively by imaging is a major contraindication to unilateral or minimally invasive surgery.

In contrast to initial surgical attempts, the need for preoperative imaging for second operations being planned after failed initial explorations is uncontested. This is because the initial operation likely failed due to the presence of an ectopically located culprit gland that could not be identified on the initial operation. In addition, any reoperation presents a more challenging field due to scarring, thus making intraoperative identification even more difficult and leading to a higher risk of complications.

99mTc-sestamibi scanning, especially with single photon emission CT, has been shown to be the most specific imaging modality for the detection of parathyroid adenomas [25]. In addition, ultrasound has been found to be complementary to sestamibi scanning in parathyroid adenoma localization [26,27]. MRI and CT scans are generally used as second-line imaging tests and are more useful in the localization of ectopically located adenomas. Selective venous sampling for intraoperative PTH measurement is generally reserved as a last resort in parathyroid adenoma identification. Studies concerning the utility of FDG-PET scans in the evaluation of parathyroid adenomas have yielded conflicting results [28,29]. PET scans have been found to be more sensitive but less specific than sestamibi scans in identifying abnormally functioning ectopic parathyroid tissue [29].

Surgery

The mainstay of therapy for parathyroid adenomatous disease is surgical removal. Four gland bilateral neck exploration is still technically considered the gold-standard surgical treatment for primary hyperparathyroidism [30]. The approach relies on identification and visual inspection of all four parathyroid glands. The diagnosis of parathyroid adenoma or hyperplasia is determined by the gross morphology of the glands on exploration, with the extent of surgery being determined accordingly. This approach has been shown to be effective in curing hyperparathyroidism in greater than 95% of cases [31]. Nevertheless, most centers have now shifted toward more focused surgical procedures with the improvements in preoperative imaging and the advent of rapid intraoperative PTH assays.

A unilateral neck exploration can be performed if the preoperative imaging is successful in localizing a solitary adenoma to one side of the neck. The other normal gland is usually identified in order to visually rule out another adenoma or more commonly multigland hyperplasia for which preoperative imaging is less accurate. It should be noted that both ultrasound and sestamibi scanning are much less reliable in detecting multigland hyperplasia and double adenomas compared to solitary adenomas (up to 70% sensitivity for hyperplastic glands and 45% sensitivity for double adenomas) [32–35]. In addition, multigland hyperplasia cannot be reliably distinguished from an adenoma on pathological examination without examination of tissue from at least two different glands. A rapid intraoperative PTH assay is used by some in this situation; however, it is not necessary as it would only be advantageous in the uncommon circumstance in which a second adenoma, either in the contralateral side or in a supernumerary ectopic gland, was present that was not detected by preoperative imaging. Patients in whom unilateral neck exploration is successful endure less operative time and a lower risk of postoperative hypercalcemia [36].

A third option is selective radioguided parathyroidectomy; with this approach, a small incision guided by a gamma probe is used to extract a solitary adenoma detected on preoperative imaging. This approach should be accompanied by rapid intraoperative PTH assay measurement after the culprit gland is removed, since none of the remaining glands are inspected or biopsied. While such an approach may significantly decrease operative time, thus presenting an attractive option for poor operative risk patients, the rates of efficacy have not yet been demonstrated to match more traditional surgical procedures [37,38]. Lastly, video-assisted and endoscopic techniques have been advocated by some authors. These hinge on the same criteria as open selective parathyroidectomy, enjoying the same advantages and success rates [39].

Non-Surgical Therapy

The calcimimetic drug cinacalcet increases the parathyroid glands' sensitivity to serum calcium levels by increasing the CaSR's affinity for extracellular calcium [40,41]. While this agent has been shown to be efficacious in long-term lowering of serum calcium levels, no information is available on its effect on bone density or fracture incidence [42,43]. Likewise, no evidence is available on the long-term effects of this agent on any

of the other manifestations of primary hyperparathyroidism. This drug may prove especially helpful, however, in treating patients for recurrent disease not amenable to a surgical cure or in poor surgical candidates with short life expectancies.

The use of estrogen replacement or raloxifene in postmenopausal women with primary hyperparathyroidism has demonstrated only small favourable effects on serum calcium levels and bone density [44,45]. However, effects on other outcomes associated with hyperparathyroidism have not been documented with these treatments. In addition, bisphosphonates have been shown to significantly increase bone mineral density without much change in either serum calcium or PTH levels [46]. In general, no convincing evidence for the efficacy of medical treatments in asymptomatic hyperparathyroidism exists, with surgery remaining the mainstay of therapy.

Areas of Uncertainty

The significance of enlarged parathyroid glands discovered incidentally during operations performed for other purposes, such as thyroid resections, is unknown. It is not known whether such glands will ever go on to cause significant disease. In addition, the significance of incidental parathyroid adenomas detected on imaging studies for other purposes is also not known. Such findings should trigger serum calcium and PTH testing.

It has been shown that bilateral neck exploration results in a greater rate of diagnosis of double adenomas compared to selective parathyroidectomy [47,48]. This raises the likelihood that direct inspection and histological sampling may, in fact, overcall parathyroid gland disease. The percentage of double adenomas that are actually clinically significant is not known.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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