Chapter 6
Parathyroidectomy Outcomes and Pathology in Primary Hyperparathyroidism

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Case Presentation

A 59 year-old female was referred for evaluation of primary hyperparathyroidism (PHPT). She had enjoyed excellent health her entire life, but during a routine health screen was found to have a serum calcium of 10.7 mg/dL (nl, 8.9–10.1). A repeat calcium once again was elevated at 10.6 mg/dL with a PTH that was 2 ½-fold times the upper limit of normal. Subsequent review of her prior laboratory work revealed that her calcium was slightly elevated 9 years prior and was high normal after that measurement. She denied symptoms related to hypercalcemia such as involuntary weight loss, abdominal pain, polyuria,

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fatigue, or depression and did not have a history of nephrolithiasis or fragility fractures. Her past medical history was significant for hypertension that was well controlled with an ACE inhibitor, thiazide diuretic, and a beta-blocker. She was on estrogen replacement therapy after a hysterectomy for benign disease. She also had primary hypothyroidism and was on stable levothyroxine therapy. Her family history was unremarkable for familial hypercalcemia. Her physical examination was unremarkable.

Assessment and Diagnosis

The patient's lab work is consistent with PHPT. Although she is on a thiazide diuretic which has been associated with hypercalcemia, most patients with thiazide-associated hypercalcemia have underlying PHPT, and her higher PTH level would be consistent with PHPT in this context [1]. After a diagnosis of PHPT, clinical assessment for related complications may include dual-energy X-ray absorptiometry bone mineral density of the spine, hip, and nondominant wrist and imaging for nephrolithiasis by computed tomography (CT) of the abdomen and pelvis without contrast, renal ultrasound, or kidney-ureter-bladder (KUB) plain film radiographs with tomography. This patient had a KUB with tomography that revealed small opaque renal calculi in both kidneys. Hence, she was referred to endocrine surgery for consideration of parathyroidectomy. A 24-h urine calcium and creatinine is often assessed if surgery is a consideration due to the possibility of familial hypocalciuric hypercalcemia (FHH). However, her negative family history for PHPT or hypercalcemia combined with normal serum calcium levels on prior measurements essentially rules out FHH as the cause of her hypercalcemia. Patients with FHH are also usually devoid of PHPT complications (e.g., nephrolithiasis), and PTH levels are elevated in only 5–25 % of FHH subjects [2, 3].

Localization of the parathyroid pathology is often considered once a decision is made to proceed with surgery. Although there are several modalities utilized for parathyroid localization [4], the decision regarding which test to use is often determined by the test which has the highest sensitivity and specificity at the institution performing the study. This patient underwent a parathyroid scan with I-123 and 99mTc sestamibi which revealed a right inferior parathyroid adenoma.

Management

The patient underwent uncomplicated cervical exploration where in the right inferior position in the thyrothymic tongue a 350 mg parathyroid adenoma was identified and excised.

Outcome

Her postoperative calcium dropped to 9.4 mg/dL. Pathology revealed a 370 mg, $1.1 \times 0.8 \times 0.6$ cm parathyroid lipoadenoma (Fig. 6.1). Complications related to parathyroid surgery are rare but most commonly include recurrent laryngeal nerve injury (0.5–1 %), hematoma formation (0.2 %), and hypocalcemia (0.1 %) [5]. Disease cure depends on the parathyroidectomy surgical volume, but in highly experience centers, >95 % of patients are normocalcemic postoperatively [5]. PTH on the other hand remains elevated in 8–40 % of patients with normocalcemia after parathyroidectomy for unclear reasons [6]. However, most of these patients do not get recurrent hypercalcemia (i.e., recurrent PHPT) [7]. Persistent PHPT is defined by failure of biochemical cure with the initial parathyroid surgery. Recurrent PHPT is defined by an initial biochemical cure

(normocalcemia), followed by recurrent disease >6 months after the initial surgery.

Parathyroid glands typically weigh 20–40 mg, while those weighing more than 50–60 mg are usually abnormal [8]. Normal parathyroid glands consist of chief cells – the main source of PTH, transitional cells, oxyphil cells, and adipose tissue. Adipose tissue is the primary component of the parathyroid stroma and occupies approximately 20–30 % of an adult parathyroid gland. Also parathyroid cellularity can be highly variable within a single gland, among glands in the same patient, and between patients. It also varies by age, sex, and body habitus, among others.

PHPT is due to a single parathyroid adenoma in 80–85 % or more of patients [9]. Chief cell parathyroid adenomas are the most common pathologic variant in PHPT [10]. Oxyphil cells typically comprise less than 5 % of parathyroid volume [11], but oxyphil parathyroid adenomas can be seen in PHPT and have been associated with larger adenomas [12–14]. However, a recent case-matched study found no significant difference in weight between oxyphil and chief cell adenomas [15].

PHPT due to parathyroid lipoadenomas are rare but, clinically, present in a similar fashion to those associated with common parathyroid pathologic variants [16]. Parathyroid lipoadenomas are defined by extensive stromal adipose tissue, myxoid change, and fibrosis [17]. Clear cell parathyroid adenomas are composed of cells with finely vacuolated cytoplasm in a solid or acinar pattern [18]. Atypical parathyroid adenomas have atypical features such as mitoses and fibrous bands but lack definitive invasion or metastases. They generally behave in a benign fashion [19].

A definitive histopathological diagnosis of parathyroid carcinoma is difficult and often presents as severe PHPT where it is suspected or as PHPT recurrence 2–3 years after the initial parathyroid surgery. Classical pathologic criteria include uniform sheets of cells arranged in a lobular pattern separated by dense fibrous trabeculae, mitotic figures in tumors cells, and capsular

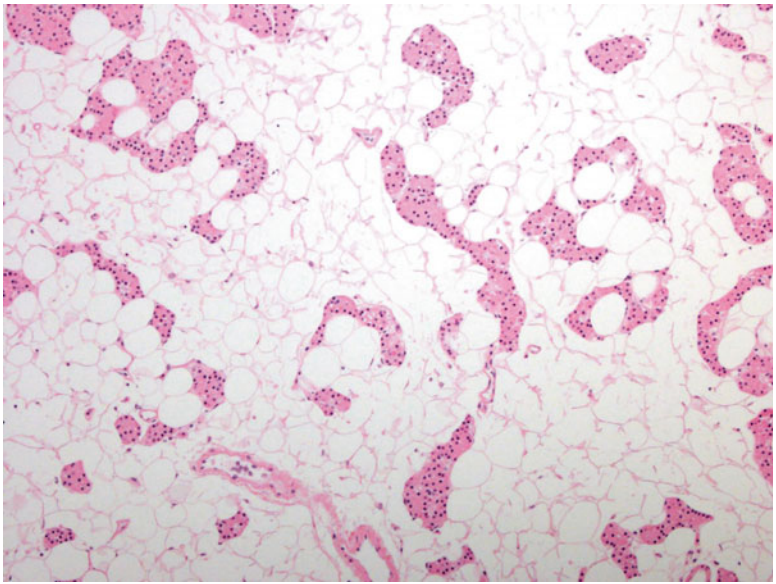

Fig. 6.1 Parathyroid lipoadenoma with proliferation of parenchymal parathyroid tissue and stromal elements with adipose tissue comprising greater than 50 % of the adenoma. The parenchymal tissue is comprised of oxyphilic cells and small numbers of chief cells organized in small groups and thin, branching cords. Hematoxylin and Eosin stain: medium power

and vascular invasion [20, 21]. Invasive growth is required for a diagnosis of parathyroid carcinoma. Only 3–30 % of patients have evidence of regional lymph node involvement or distant metastases at the initial surgery (see Chap. 10) [22]. Parathyromatosis is a rare pathologic variant in PHPT that is characterized by small nodules of hyperplastic parathyroid tissue composed primarily of chief cells that are scattered throughout the soft tissues of the neck and upper mediastinum [19, 23]. Clinically, this condition is characterized by recurrent or persistent PHPT. On occasion, parathyroid glands removed in patients with prior thyroidectomy or re-explorative parathyroid surgery may present challenges to the surgeon and pathologist due to fibrosis (see Chap. 11).

PHPT due to parathyroid hyperplasia, which accounts for approximately 15 % of PHPT, is defined as multiple parathyroid glands with proliferation of parenchymal cells leading to parathyroid gland enlargement independent of secondary factors that stimulate PTH production. Preoperative imaging studies and intraoperative PTH monitoring aid in differentiating single from multiple gland disease. Chief cell hyperplasia is the most common form of parathyroid hyperplasia, but rarely clear cell hyperplasia and lipohyperplasia are seen. Asymmetric hyperplasia is a challenging issue as only around 50 % of PHPT has symmetric enlargement of all four glands. Approximately one-third of PHPT hyperplasia is due to familial parathyroid disorders (e.g., MEN, MEN2A, MEN4, hyperparathyroidism-jaw tumor syndrome, familial isolated PHPT).

Clinical Pearls/Pitfalls

- After the diagnosis of PHPT is confirmed, evaluate for related complications.
- Parathyroidectomy has a high rate of cure and complications are rare.

- Review the outcome of parathyroid surgery, utilizing serum calcium rather than PTH for surveillance postoperatively.
- Parathyroid adenomas are the cause of PHPT in ≥80 % of patients and pathologically are usually due to chief cell adenomas, but oxyphil adenomas, lipoadenomas, clear cell adenomas, and atypical parathyroid adenomas are additional pathologic variants.
- Parathyroid carcinoma often presents with severe PHPT or is identified with disease recurrence 2–3 years after the initial parathyroid surgery.
- Parathyroid hyperplasia is the cause of PHPT in approximately 15 % of patients and is seen in familial parathyroid disorders such as MEN1, MEN2A, MEN4, hyperparathyroidism-jaw tumor syndrome, and familial isolated PHPT.

Conflict of Interest All authors state that they have no conflicts of interest.

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