Chapter 32

Non-Neoplastic Lesions of the Parathyroid Glands

CLASSIFICATION OF NON-NEOPLASTIC LESIONS OF THE PARATHYROID GLANDS

(Box 32-1)

BOX 32-1 Non-Neoplastic Lesions of the Parathyroid Glands

- Parathyroid hyperplasia
  - Primary chief cell hyperplasia
  - Water-clear cell hyperplasia
- Parathyroiditis
- Parathyroid cyst

PRIMARY CHIEF CELL HYPERPLASIA (Figs. 32-1 through 32-5, Table 32-1)

Definition: Non-neoplastic increase in parenchymal cell mass of multiple parathyroid glands in the absence of a known clinical stimulus for increased secretion of parathyroid hormone.

Clinical

- Responsible for approximately 13% of cases of hyperparathyroidism
- An autopsy incidence of 7% has been reported.

- Affects females more often than males (F:M = 3:1); incidence increases with age
- Occurrence:
  - Sporadic cases represent 80% of patients with primary chief cell hyperplasia.
  - 20% have familial disease, usually associated with one of the multiple endocrine neoplasia syndromes, although familial parathyroid hyperplasia without other endocrine abnormalities also occurs.
- See under hyperparathyroidism for signs, symptoms, and laboratory findings (see Chapter 31).
- Approximately 20% of patients with primary chief cell hyperplasia have one of the multiple endocrine neoplasia syndromes (MEN):
  - Association is most frequent in MEN type 1 (MEN-1, Wermer syndrome).
  - Parathyroid proliferative disease is seen in 30% to 40% of patients with MEN-2A (Sipple syndrome), but is rare in MEN-2B (Gorlin syndrome).
- MEN-1 (Wermer syndrome) includes:
  - Autosomal-dominant transmission with variable penetrance:
    - Germline mutation on chromosome 11q13

Fig. 32-1. Parathyroid hyperplasia.
This gland was one of three enlarged glands in a patient with primary hyperparathyroidism. The gland has a variegated nodular appearance.

Fig. 32-2. Parathyroid hyperplasia.
The multinodular appearance of this gland is the result of proliferation of groups of cells with different cytologic features; the entire gland is affected by the proliferative process; no rim of normal parathyroid tissue is seen.
Fig. 32-3. Parathyroid hyperplasia.

A, The nodules within the gland are composed of those with clear cells and another with oncocytic cells.
B, Different areas of the same hyperplastic gland may contain predominantly chief cells (left) or oncocytic cells (right).

Fig. 32-4. Parathyroid hyperplasia.
The hyperplastic features may be unevenly distributed among the four glands or even within a single gland. Left, Nodules and areas of solid growth with high cellularity. Right, Area showing a higher percentage of lipocytes admixed with diffuse cellular areas of chief cells and scattered small oncocytic nodules.

Fig. 32-5. Recurrent parathyroid hyperplasia.
Recurrent parathyroid hyperplasia in parathyroid autografted into the forearm. This patient had a history of chronic renal failure with secondary hyperparathyroidism. His hypercalcemia recurred several months after subtotal parathyroidectomy with autoimplantation of portions of parathyroid gland into the soft tissue of the forearm. The irregular islands of cellular parathyroid tissue may appear to be infiltrating skeletal muscle. This pattern, and even the presence of mitotic figures in the parathyroid tissue, do not indicate malignancy.

- MEN-2A (Sipple syndrome):
  * Characterized by development of bilateral C-cell hyperplasia, thyroid medullary carcinoma, pheochromocytoma, and parathyroid hyperplasia

- MEN-2B (Gorlin syndrome): characterized by development of bilateral C-cell hyperplasia,
### TABLE 32-1 Comparative Features of Parathyroid Proliferative Diseases

<table>
<thead>
<tr>
<th></th>
<th>Hyperplasia</th>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender; age</strong></td>
<td>Slight female predilection; most common in 5th-6th decades</td>
<td>More common in women; most common in 4th decade</td>
<td>Equal gender predilection; wide age range</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Asymptomatic or complaints of lethargy, weakness, polyuria, polydipsia, arthralgia, constipation, and depression</td>
<td>Similar to hyperplasia</td>
<td>Similar to hyperparathyroidism of benign etiology but more severe due to the higher serum calcium levels; higher proportion of renal disease (nephrolithiasis) and bone disease; peptic ulcer disease; palpable neck mass more common than in adenoma</td>
</tr>
<tr>
<td><strong>Serum calcium</strong></td>
<td>11.7 mg/dl (average)</td>
<td>12.5 to 13.5 mg/dl</td>
<td>Often &gt;14 mg/dl</td>
</tr>
<tr>
<td><strong>Intraoperative findings</strong></td>
<td>2 or more glands enlarged, easily dissected; enlargement may be asymmetric</td>
<td>1 gland enlarged; easily dissected; more frequent in lower glands or ectopic sites</td>
<td>1 gland enlarged; often adherent to surrounding tissues</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Total gland weight usually &lt;1 g, but may be up to 5 g</td>
<td>0.3 to 1.0 g commonly, but may weigh several grams in patients with bone disease</td>
<td>&gt;1.5 g (often much larger)</td>
</tr>
<tr>
<td><strong>Capsule</strong></td>
<td>Circumscribed by capsule of parathyroid gland, may be incomplete No compressed rim of atrophic or normal parathyroid tissue</td>
<td>Thin tumor capsule, often surrounded by rim of uninvolved parathyroid, which may appear atrophic</td>
<td>Thickened capsule; rim of normal parathyroid rarely seen</td>
</tr>
<tr>
<td><strong>Gross appearance</strong></td>
<td>Gray-brown, soft Cut surface may be homogeneous or nodular Lacks fibrous bands</td>
<td>Red-brown, firm Usually homogeneous, lacks fibrous bands but may appear nodular</td>
<td>Gray-white, firm, often lobulated or irregular Fibrous bands often produce coarse nodularity</td>
</tr>
<tr>
<td><strong>Histologic pattern</strong></td>
<td>Diffuse or nodular, sometimes follicular or acinar</td>
<td>Diffuse or nodular, frequently follicular or acinar</td>
<td>Predominantly solid or diffuse; may include trabecular, organoid, spindle, or follicular</td>
</tr>
<tr>
<td><strong>Cytologic features</strong></td>
<td>Chief cells predominate; transitional and oncocytic cells often present</td>
<td>Chief cells predominate, but mixture of chief, transitional, and oncocytic cells may be seen; rarely, purely oncocytic</td>
<td>Cells usually resemble chief cells, but variable cytoplasmic oncocytic change may be seen; cell borders often indistinct</td>
</tr>
<tr>
<td><strong>Intracytoplasmic lipid</strong></td>
<td>Decreased</td>
<td>Decreased in tumor; abundant in atrophic rim of parathyroid</td>
<td>Usually absent</td>
</tr>
<tr>
<td><strong>Stromal fat cells</strong></td>
<td>Scanty to absent</td>
<td>Usually absent in tumor; present in rim of atrophic parathyroid</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Nuclear morphology</strong></td>
<td>Normal to slightly increased N-to-C ratio; usually without nuclear pleomorphism</td>
<td>Nuclei enlarged, with variability in size; scattered groups of large pleomorphic, hyperchromatic nuclei, or multinucleated cells</td>
<td>Increased N-to-C ratio; enlarged atypical nuclei; often with very monotonous (bland appearing) nuclei</td>
</tr>
<tr>
<td><strong>Nucleoli</strong></td>
<td>Inconspicuous to small Inconspicuous to small</td>
<td>Frequently prominent and enlarged</td>
<td></td>
</tr>
<tr>
<td><strong>Mitoses</strong></td>
<td>Common (60% of cases; most with &lt;1 mitotic figure/10 HPF)</td>
<td>Common (70% of cases; most with &lt;1 mitotic figure/10 HPF)</td>
<td>Common (80% of cases), may include atypical mitoses</td>
</tr>
<tr>
<td><strong>Capsular and vascular invasion</strong></td>
<td>Absent</td>
<td>Absent; entrapment of tumor cells may occur in capsule if degenerative changes present</td>
<td>Capsular invasion present in two thirds; may involve only capsule or extend into adjacent tissues Vascular invasion present in up to 15%; usually in capsular vessels</td>
</tr>
</tbody>
</table>
TABLE 32-1 Comparative Features of Parathyroid Proliferative Diseases—cont’d

<table>
<thead>
<tr>
<th></th>
<th>Hyperplasia</th>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remainder of gland</td>
<td>Entire gland is abnormal</td>
<td>Normal or atrophic</td>
<td>Normal</td>
</tr>
<tr>
<td>Degenerative changes</td>
<td>May be seen in very large glands; includes hemorrhage, areas of fibrosis, and cystic change</td>
<td>Common, especially in larger adenomas; includes hemorrhage, fibrosis, and cystic change, sometimes calcification</td>
<td>Tumor cell necrosis; calcification and cystic changes may be present</td>
</tr>
<tr>
<td>Treatment</td>
<td>Subtotal parathyroidectomy with surgical removal of three glands leaving a remnant of the fourth or total parathyroidectomy* with autotransplantation of parathyroid tissue in forearm</td>
<td>Surgical removal of the enlarged gland</td>
<td>En bloc resection, including ipsilateral thyroid lobe and adjacent soft tissues</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Up to 50% of patients are cured by en bloc resection; considered an indolent malignancy even in presence of recurrence or metastasis with long survival even after recognition of tumor recurrence; morbidity and mortality correlate to complications of severe hypercalcemia</td>
</tr>
<tr>
<td>Recurrence and metastasis</td>
<td>Recurrence in approximately 16% of cases due to inadequate neck exploration and may not be evident for years</td>
<td>Absent</td>
<td>Recurrence in two thirds of patients usually within 3 years of the first surgery; metastasis is 35%, is a late event usually preceded by local recurrence; most commonly to lung, cervical lymph nodes, and liver</td>
</tr>
<tr>
<td>Familial and/or MEN association</td>
<td>Yes, in approximately 20% of cases</td>
<td>Uncommon</td>
<td>Rare</td>
</tr>
</tbody>
</table>

*Particularly in cases of familial hyperparathyroidism.

Radiography

- Radiographic imaging techniques applied to localization of hyperfunctioning parathyroid glands include retrograde phlebotomy with serum parathormone assays, CT scanning, ultrasonography, magnetic resonance imaging (MRI), thallium subtraction scanning, and technetium-99m sestamibi imaging.

- Imaging procedures have been significantly less effective in localizing glands in cases of hyperplasia as compared with parathyroid adenomas or carcinomas.

- Technetium-99m sestamibi has been effective in localizing up to 60% of hyperplastic glands; it has been more widely used in the evaluation of patients with recurrent hyperparathyroidism after parathyroid resection.

Pathology

- Cytologic findings in aspirate smears of parathyroid adenomas and parathyroid adenoma are indistinguishable and allow only documentation of “parathyroid proliferative disease.”

Gross

- Although all four glands may be enlarged, it is not uncommon for hyperplasia to be somewhat asymmetric, with two or three glands being much larger than the others.

- In some cases one gland is so much larger than the others that the gross appearance suggests an adenoma, emphasizing the importance of sampling.
SECTION 9 Parathyroid Glands

Grossly “normal” glands to facilitate accurate discrimination between hyperplasia and adenoma, because increased cellularity of the smaller glands may be the key to recognizing the multiglandular nature of the proliferation.

- Glands may be diffusely enlarged or may be nodular, particularly with increasing size.
- Cystic change may be present but is not common.
- Total gland weight in primary chief cell hyperplasia is variable, and has been reported as:
  - <1 g in 54% of patients
  - 1 to 5 g in 28% of patients
  - 5 to 10 g in 18% of patients
- Glands are usually soft and tan-brown
- Distinction between hyperplastic and adenomatous glands generally cannot be made by gross examination.

**Histology**

- Primary chief cell hyperplasia results from an increase in parenchymal cell mass, predominantly involving chief cell proliferation; however, oncocytic cells may be present as well.
- Chief cell hyperplasia may be diffuse or nodular;
- Chief cells may be arranged in solid sheets, cords, acinar-like, or follicular structures or commonly mixed patterns are identified.
- Variable nodularity
- Nodules may be small (micronodular), solitary, or pleomorphic
- Small follicular structures may contain PAX8-positive material resembling dense colloid; this material is thyroglobulin negative.
- Stromal fat cells are absent or markedly decreased in number in most areas, although foci of stromal fat cells may mimic normal gland:
- Variations in distribution of fat cells and variability in the density of the chief cells, particularly in a nodular hyperplasia, may yield a confusing histologic picture.
- Areas with residual fat may mimic a rim of “normal” gland, particularly when they are adjacent to large nodules, which generally lack fat cells, may suggest a diagnosis of adenoma, again emphasizing the importance of microscopic examination of multiple glands and the need for processing multiple sections of larger glands.

- Although circumscribed by the delicate fibrous capsule of the gland, hyperplasia may also involve nests of parathyroid tissue in the soft tissue of the neck (“parathyromatosis”).
- This phenomenon may be the cause of recurrent disease after an apparently complete resection of the grossly evident hyperplastic glands.
- Should not be mistaken for “invasion” as one would see in carcinoma; the lack of a fibroblastic reaction or infiltrative contour, absence of an intravascular location of these nests, and lack of other histologic features of carcinoma should help exclude malignancy.

- Hyperplastic cells usually contain less intracytoplasmic fat than normal or atrophic parathyroid tissue when demonstrated by oil red O or Sudan black stains; however, some hyperplastic parathyroid tissue may contain abundant intracytoplasmic fat:
  - Intracytoplasmic fat may be more abundant in the chief cells between hyperplastic nodules, whereas it is usually absent in cells within the nodules.
  - The term lipohyperplasia has been used in cases of hyperplastic glands with abundant fat:
    - Presence of fat in this setting makes the diagnosis of hyperplasia challenging.
    - Biopsies may contain only fat or be predomi-
    - nantly of fat with limited parenchymal cells.
    - The clinical setting and enlargement of multi-
    - ple glands is important in the diagnosis of lipohyperplasia.

- Although mitotic figures may be seen, they usually number less than 1 per 10 high-power fields; some cases demonstrate mitotic rates of 1 to 5 per 10 high-power fields; however, atypical mitoses are not present.

- Immunohistochemistry:
  - Chief cells are positive for parathyroid hormone, chromogranin A; staining for PTH and chromogranin A is less intense as compared with normal (nonhyperplastic) chief cells.
  - Calcitonin and synaptophysin typically negative but in small percentage of cases may be focally positive
  - PAX8 (nuclear) reactivity present in approxi-
  - mately 40% of hyperplasia and adenomas
  - Negative for thyroglobulin and TTF-1

- Electron microscopy:
  - Cells contain abundant mitochondria, endoplas-
  - mic reticulum, and large Golgi areas, as well as characteristic secretory granules.

- Cytogenetics and molecular genetics:
  - Chief cell hyperplasia associated with MEN: see previously

**Differential Diagnosis**

- Parathyroid proliferative disease, especially adenoma
- Lithium therapy for psychiatric disorders has been associated with a form of hyperparathyroidism similar to primary hyperparathyroidism with hypercalcemia and elevated serum parathormone levels.

ISBN: 978-1-4557-3382-8; PII: B978-1-4557-3382-8.00033-5; Author: Wenig; 00033
chief cell hyperplasia and “adenomas” have been described in these patients:

- Hyperparathyroidism resolves after discontinuing lithium therapy.
- Patients requiring lithium may be treated successfully with subtotal parathyroidectomy.

Humoral hypercalcemia of malignancy (HHM) is an important clinical differential diagnostic consideration in patients suspected of having primary hyperparathyroidism.

- HHM is independent of the extent of metastatic disease involving bone and is characterized by hypercalcemia, hypophosphatemia, and elevated urinary cyclic AMP levels.
- Unlike hyperparathyroidism, serum parathormone, and 1,25-dihydroxyvitamin D are suppressed.
- Mechanism for hypercalcemia appears to be increased bone resorption due to a humoral factor known as parathyroid hormone-related protein.
- This form of hypercalcemia was most frequent in patients with squamous cell carcinoma (lung, upper aerodigestive tract, and female genital tract), renal cell carcinoma, and transitional cell carcinoma.

A second mechanism of hypercalcemia associated with malignancy is related directly to the osteolytic effect of bone metastases; this form of hypercalcemia is more common in patients with breast carcinoma and hematologic malignancies; these patients have suppressed levels of parathormone, but urinary cyclic AMP is not elevated and parathyroid hormone-related protein has not been implicated.

Familial benign hypercalcemia or familial hypocalciuric hypercalcemia:

- Autosomal-dominant condition
- Caused by inactivating mutations in the calcium sensing receptor (CASR) gene, leading to a general calcium-hyposensitivity, compensatory hypercalcemia, and hypocalciuria
- Should be suspected in young patients with presumptive diagnosis of hyperparathyroidism and family history
- Hypercalcemia often starts in childhood.
- Persistent hypercalcemia following subtotal parathyroidectomy for presumed primary hyperparathyroidism
- Many patients are asymptomatic or have vague symptoms.
- Signs and symptoms of hypercalcemia are rare.
- Calcium:creatinine clearance ratio is traditional test to diagnose this disorder.
- Patients have low urinary calcium excretion relative to serum calcium levels, elevated serum magnesium levels, parathyroid hormone levels are usually elevated but lower than in primary hyperparathyroidism
- Histologically, parathyroid glands are normal or show mild chief cell hyperplasia.

Treatment and Prognosis

- Subtotal parathyroidectomy with complete removal of three glands, leaving a remnant of the fourth, is the most widely accepted therapy.
- Total parathyroidectomy with autotransplantation of remnants of parathyroid tissue in the forearm is also a common surgical therapy.
- Recurrence rate of hyperparathyroidism following subtotal parathyroidectomy is approximately 16%:
  - Recurrences may not be evident for several years.
  - Recurrences may be due to inadequate neck exploration, which may result from diagnosis of “adenoma” in cases of asymmetric hyperplasia.
  - Less frequent causes include failure to recognize supernumerary or ectopic glands, parathyromatosis, or surgical implantation of hyperplastic tissue in the soft tissue of the neck.

**WATER-CLEAR CELL HYPERPLASIA** (Figs. 32-6 and 32-7)

**Definition:** Non-neoplastic increase in parenchymal cell mass of multiple parathyroid glands by proliferation of large cells with clear, vacuolated cytoplasm, in the absence of a known clinical stimulus for increased secretion of parathyroid hormone.

**Synonym:** Wasserhelle cell hyperplasia

In water-clear cell hyperplasia the glands are usually markedly enlarged and are replaced by a diffuse proliferation of clear cells with no stromal fat, although in other examples, limited intraparenchymal fat may be present.
Clinical

- Slightly more common in men than in women (M:F = 1.4:1); most common in fifth decade
- Very rare cause of hyperparathyroidism:
  - Reason for the virtual disappearance of water-clear cell hyperplasia in the population is not known; some suggest that it represents an advanced form of primary chief cell hyperplasia.
- Decreasing incidence and severity of chief cell hyperplasia as a result of routine biochemical screening of patients lends some support to this theory.
- Electron microscopic appearance of water-clear cell hyperplasia sufficiently distinctive from primary chief cell hyperplasia to doubt that it develops from pre-existing chief cell hyperplasia.

Pathology

- Hypercalcemia and symptoms are usually more severe than in chief cell hyperplasia.
- Mean serum calcium, 13.2 mg/dl, compared with 11.7 mg/dl in cases of chief cell hyperplasia.
- Nephrolithiasis occurs in 90% of patients, in contrast to a rate of 53% of patients with chief cell hyperplasia during the same period.
- Overall incidence of bone disease similar to chief cell hyperplasia, with occasional patients presenting with osteitis fibrosa cystica.
- No documented association with multiple endocrine neoplasia or other familial syndromes.

Pathology

Gross

- Usually all four glands are enlarged, although asymmetry is common, and the upper glands are often larger than the lower glands.

- Mean total gland weight >10 g in 47% of cases; combined weight under 1 g not reported.
- Involved glands are dark brown and may exhibit cystic change, areas of fibrosis, or hemorrhage; nodularity within the glands is uncommon, but the gland contour is often irregular.

Histology

- Glands are usually diffusely replaced by large clear cells, with little or no remaining stromal adipose tissue.
- Cells are from 10 to 40 µ in diameter, with distinct borders arranged in sheets, cords, or sometimes in acinar groups.
- Cytoplasm appears clear with distinct cell membranes but may contain many small vacuoles, which give a finely reticulated pattern in hematoxylin-eosin stained sections:
  - Vacuoles are more readily apparent in plastic-embedded thin sections.
  - Glycogen is demonstrable in the cytoplasm with periodic acid Schiff.
  - Neutral fat stains are negative.
- Nuclei are small, round to ovoid, rather hyperchromatic, and are basally oriented in the polyhedral to slightly columnar cells.
- Scattered multinucleated cells and occasional large hyperchromatic nuclei may be observed.
- Immunohistochemistry:
  - Parathyroid hormone (PTH), parafibromin:
    - Staining for PTH and chromogranin A less intense as compared with normal (nonhyperplastic) chief cells.
    - Calcitonin staining may focally be present.
  - Cyclin D1 expression present in majority of cases (approximately 61%).
  - Negative for thyroglobulin and TTF-1.
- Electron microscopy:
  - Clear cells contain numerous membrane-bound vacuoles, many of which appear “empty”;
  - however, some contain electron-dense material similar to the smaller typical parathyroid secretory granules, which are also scattered through the cytoplasm.

Differential Diagnosis

- Primary chief cell hyperplasia.
- Parathyroid adenoma (particularly if only one gland has been sampled or if the hyperplasia is very asymmetric).
- Metastatic renal cell carcinoma with differentiation based on the presence in parathyroid hyperplasia of:
  - Biochemical findings of hyperparathyroidism.
  - Positive immunohistochemistry for PTH, parafibromin, and chromogranin.
CHAPTER 32 Non-Neoplastic Lesions of the Parathyroid Glands

SECONDARY HYPERPARATHYROIDISM

Definition: An increase in parathyroid parenchymal cell mass of multiple glands in response to a known clinical stimulus for increased secretion of parathyroid hormone; usually characterized by hypocalcemia and hyperphosphatemia.

Clinical

Causes of secondary hyperparathyroidism include chronic renal failure (most common), dietary vitamin D deficiency or abnormalities of vitamin D metabolism, malabsorption, and pseudohypoparathyroidism.

Occurs over broad age range, reflecting the incidence of chronic renal failure, the most common cause of secondary hyperparathyroidism.

Symptoms of secondary hyperparathyroidism are related primarily to parathyroid hormone-mediated bone resorption, which results in osteomalacia and osteitis fibrosa cystica.

Abnormal calcium deposits may be seen, including:

In the soft tissues, particularly in a periarticular distribution

Cutaneous calciphylaxis:

Uncommon

Mainly seen in renal failure-associated hyperparathyroidism

Progressive cutaneous vascular calcification

Potentially lethal

Laboratory studies reveal elevation of parathyroid hormone levels with hypocalcemia and hyperphosphatemia.

Pathology

Gross

Not significantly different from that of primary chief cell hyperplasia; there may be uniform enlargement of all glands or the enlargement may be asymmetric.

Glands are yellow-brown to gray, with weights ranging from 0.12 to 6 g.

Histology

Proliferation includes chief cells, oncocytic cells, and transitional cells.

Increased parenchymal cell mass varies depending on the duration of disease, as does the number of residual stromal fat cells:

In advanced disease the fat cells are absent.

Parenchymal cells may grow in sheets, cords, or acinar structures.

Nodular aggregates of chief cells or oncocytic cells are common in very enlarged glands; areas of fibrosis, cystic change, and calcification may be present.

Oncocytic cells seem to be a more common component than in primary chief cell hyperplasia.

Differential Diagnosis

Primary chief cell hyperplasia

Parathyroid adenoma

Treatment and Prognosis

Subtotal parathyroidectomy is the preferred treatment:

Remnant of parathyroid gland may be left in situ or transplanted to the soft tissue of the forearm.

Auto-transplantation of parathyroid tissue into the forearm musculature following total parathyroidectomy may be associated with graft failure and hypoparathyroidism, or with recurrent hyperparathyroidism due to hyperplasia of the transplanted remnant of parathyroid.

Recurrence of hyperparathyroidism is a common problem in patients with chronic renal failure, since the stimulus for hypersecretion of parathyroid hormone is frequently not correctable.

Recurrent hyperplasia may be associated with a multifocal proliferation of islands of parathyroid tissue in the adipose tissue and skeletal muscle, sometimes rather widely separated from the original site of transplantation:

Hyperplastic cells may be somewhat more pleomorphic than the original parathyroid proliferation and may even be mitotically active.

These changes should not be interpreted as evidence of malignancy.

TERTIARY HYPERPARATHYROIDISM

Definition: An absolute increase in parathyroid parenchymal cell mass associated with autonomous hyperfunction and resultant hypercalcemia in a patient with previously known secondary hyperparathyroidism following implementation of dialysis or renal transplantation.

ISBN: 978-1-4557-3382-8; PII: B978-1-4557-3382-8.00033-5; Author: Wenig; 00033
Clinical

Tertiary hyperparathyroidism occurs over a broad age range, reflecting the incidence of chronic renal failure.

Hypercalcaemia usually develops several years after the diagnosis of renal disease.

Hypercalcaemia due to tertiary hyperparathyroidism represents a serious threat to renal grafts and requires prompt surgical therapy.

Laboratory findings are similar to those of primary hyperparathyroidism.

Increase in parathyroid parenchymal cell mass of multiple glands in response to a known clinical stimulus for increased secretion of parathyroid hormone. These conditions are usually characterized by hypocalcaemia and hyperphosphatemia.

The cause of autonomous hyperfunction of the parathyroids in patients with treated renal failure is not known; an elevation of the “set point” for serum calcium has been postulated; this would result in stimulation of parathyroid tissue in spite of normal serum calcium levels.

There is also evidence that the sheer mass of parathyroid tissue in patients with tertiary hyperparathyroidism may cause autonomous function.

Removal of the bulk of the hyperplastic tissue results in a readily suppressible remnant.

Differential Diagnosis

- Parathyroid adenoma:
  - The rare parathyroid adenomas responsible for tertiary hyperparathyroidism are indistinguishable from parathyroid adenomas associated with primary hyperparathyroidism.

Treatment and Prognosis

- Subtotal parathyroidectomy is the preferred therapy.
- Recurrent hyperparathyroidism has been seen in approximately 8% of patients after surgery.

PARATHYROID CYST (Figs. 32-8 through 32-10)

Definition: Cystic lesion associated with a parathyroid parenchymal cell lining or associated parathyroid tissue in the cyst wall; these lesions may represent either hyperplasia or adenomas with cystic degeneration or developmental cysts (if nonhyperfunctioning).

Clinical

- Rare lesion
- More common in women than in men; occur in adults
- Symptoms may be due to the presence of an asymptomatic neck mass that preoperatively may be mistaken for a thyroid lesion, thyroglossal duct cyst, or branchial cleft cyst; may be incidentally discovered during surgery or by radiographs (especially in the case of mediastinal parathyroid cysts) or, rarely, to hypercalcemia (as in other cases of primary hyperparathyroidism); pressure symptoms may result in symptoms including dyspnea and stridor due to tracheal compression or hoarseness and vocal cord palsy due to compression of the recurrent laryngeal nerve.
- May be nonfunctional or functional with elevated levels of parathyroid hormone
- Patients may be either normocalcemic or hypercalcemic:
  - Hypercalcemia is associated with the usual biochemical pattern of primary hyperparathyroidism.
- Most are located in the neck arising from any of the parathyroid glands although more commonly arise in association with the lower parathyroid glands; mediastinal parathyroid cysts have been reported.
- Rarely reported in association with MEN-1
- Radiology:
  - On imaging parathyroid cysts are large and unilocular with varying MR imaging and CT findings, depending on their protein content.
**Fig. 32-8. Parathyroid cysts.**

A, Unenhanced axial T1-weighted MR image shows a unilocular 3-cm cyst (arrows) in the right paratracheal region, just below the inferior pole of the right thyroid lobe. B, Corresponding axial T2-weighted MR image shows the hyperintense cyst. Note the small hemorrhage level (arrows) in the dependent portion of the cyst, which was confirmed at pathology. C and D, Axial contrast-enhanced CT scans show a cystic mass adjacent to the posterior right thyroid lobe. The cyst has nodules within it (arrows). This was a functioning parathyroid cyst. E, Axial T2-weighted MR image shows a cystic mass behind the left thyroid lobe with a nodule within it (arrow). This is a functioning parathyroid cyst. *(From Som PM, Curtin HD: Head and neck imaging, ed 5, Philadelphia, 2011, Elsevier, Fig. 41-111, p 2675.)*
SECTION 9 Parathyroid Glands

Fig. 32-9. Parathyroid cyst.
Gross appearance of a (unilocular) parathyroid cyst.

Fig. 32-10. Parathyroid cyst.
A. Intraparathyroid unilocular cyst surrounded by islands of normal parathyroid parenchyma. B. At higher magnification the cyst is lined by a single flattened layer of chief cells (arrow) histologically similar to the chief cells in the surrounding parathyroid gland.

- The cyst fluid is thin and colorless to yellow, although sometimes it may be bloody; the cyst fluid may be rich in parathyroid hormone.

Histology
- The cyst may be lined by flattened epithelium or by recognizable chief cells.
- Islands of parathyroid tissue are present within or adjacent to the cyst wall; this parathyroid tissue may appear normal or may represent a parathyroid adenoma or a hyperplastic parathyroid gland.

Differential Diagnosis
- Cystic thyroid neoplasm or adenomatoid nodule
- Lymphangioma
- Thymic cyst

Origin for parathyroid cysts is unknown; considerations include developmental and degenerative:
- Developmental due to cystic change in remnants of a branchial pouch or from gland-like structures (called canals of Kürsteiner) in the fetal parathyroid glands
- Degenerative due to cystic change in a pre-existing lesion (e.g., adenoma, hyperplasia)

Fine-needle aspiration has been useful in identification of some parathyroid cysts preoperatively, particularly palpable cervical lesions.

Aspirated cyst fluid may contain clusters of cells in microacinar or papillary-like groups with the coarse chromatin and finely granular cytoplasm with poorly defined cell borders.

The cellular component may be difficult to distinguish from follicular thyroid epithelium; immunohistochemistry for thyroglobulin and chromogranin may be helpful if adequate tissue is present.

Assay of the cyst fluid for parathormone can be used to establish the diagnosis of a parathyroid cyst.

Most parathyroid cysts are unilocular with a well-defined capsule and a cyst wall that may be thin and translucent with a gray-white appearance; in some cases the wall has a tan-yellow appearance due to the presence of a rim of parathyroid tissue.

Cysts vary in size; although many smaller cysts obviously represent cystic change in a parathyroid adenoma, some as large as 10 cm have been described.
CHAPTER 32 Non-Neoplastic Lesions of the Parathyroid Glands

• Bronchogenic, neurenteric, or esophageal foregut cysts
• Pericardial or pleural cysts

Treatment and Prognosis

Preferred treatment is surgical removal.

If hypercalcemia is present the approach should include investigation of the status of other parathyroid glands intraoperatively if the cyst is cervical or postoperatively if the lesion is intrathoracic.

CHRONIC PARATHYROIDITIS

(Fig. 32-11)

Definition: Infiltration of the parathyroid gland by mature lymphocytes (mixed B- and T-cells) and plasma cells with glandular atrophy and fibrosis.

Synonyms: Autoimmune parathyroiditis; hyperplastic parathyroiditis

Clinical

Focal lymphocytic infiltrate of the parathyroid glands has been found at autopsy in approximately 10% of patients who were euparathyroid.

Uncommon finding that may be seen in patients with hypoparathyroidism, or even more rarely in primary chief cell hyperplasia

Possible autoimmune cause postulated:

Histologic changes equivalent to those seen in association with chronic lymphocytic (Hashimoto) thyroiditis, an autoimmune disease

In some patients with chronic parathyroiditis there are autoimmune diseases of other organs.

Experimental model in rabbits has shown induction of autoimmune parathyroiditis following ozone inhalation.

Pathology

Gross

May be seen in grossly normal glands, as an incidental finding, or in enlarged glands with hyperplasia

Histology

Scattered aggregates of lymphocytes and plasma cells are present in the gland.

Parathyroid parenchyma appears nodular separated by fibrous tissue with associated lymphocytes and plasma cells.

The inflammatory cell infiltrate may vary from scattered aggregates to diffuse infiltrate.

References may be accessed online at ExpertConsult.

FURTHER READING
CHAPTER 32 Non-Neoplastic Lesions of the Parathyroid Glands

FURTHER READING

Primary Chief Cell Hyperplasia


Water-Clear Cell Hyperplasia


ISBN: 978-1-4557-3382-8; PII: B978-1-4557-3382-8.00033-5; Author: Wenig; 00033
Secondary Hyperparathyroidism


Tertiary Hyperparathyroidism


Parathyroid Cyst


Chronic Parathyroiditis


