INTRODUCTION:

Most parathyroid specimens seen by the surgical pathologist are obtained from patients with hyperparathyroidism; however, a small number are excised during neck exploration for other head and neck diseases. In the case of inadvertent removal, the cause may be due to variability's in the anatomic location of the gland or the misinterpretation of parathyroid tissue as thyroid or lymph node.
Embryology

Parathyroid glands are derived from third and fourth branchial pouches. There is more location variability in the lower glands. Abnormalities in the descent of the parathyroids from their origination to the final destination can cause the glands to reside anywhere along their embryologic pathway from the upper portions of the neck to upper thoracic inlet. Some parathyroid glands are located within other organs, such as thymus, thyroid, esophagus or larynx. (Most “intra-thyroidal” parathyroid glands are really located within indentations of the thyroid gland appearing surgically to be within the thyroid, but truly still found in the perithyroidal fat.)

Anatomy and Histology

A majority of normal individuals (>80%) have four parathyroid glands; however, in some cases one to twelve glands can be present.

Gross Anatomy

The parathyroid glands are oval to light yellow or brown in color and measure between 2 mm to 7 mm in length. Parathyroid glands can vary in weight but average around 35 to 55 mg. The average combined weight of the all parathyroids in normal adult males is approximately 120 mg and in females 145 mg.

Histology
A thin fibrous capsule envelops each parathyroid and extends into the parenchyma delineating it into multiple lobules. The parathyroid glands consist of parenchymal cells, fat cells and fibrovascular stroma (Fig 1). The parenchymal cells are usually arranged in nests and cords, nourished by a rich capillary network. The chief cell can develop cytoplasmic angles so that there may be oxyphils, clear cells and transitional cells among the chief cells. The number of oxyphil and transitional oxyphil cells increases with age.

**Pathology of the parathyroid**

Up to 90% or more of cases are hypercalcemia are due to primary hyperparathyroidism.

**Hyperparathyroidism**

Hyperparathyroidism can be divided into primary, secondary and tertiary types. Primary hyperparathyroidism is characterized by inappropriate secretion of the parathyroid hormone (PTH) from enlarged parathyroid glands in the absence of a known stimulus leading to hypercalcemia. Secondary hyperparathyroidism is an increase in parathyroid hormone most commonly in response to hypocalcemia or hyperphosphatemia associated with renal failure. Tertiary hyperparathyroidism refers to autonomous parathyroid hyperfunction in-patients with secondary hyperparathyroidism.

**Primary Hyperparathyroidism (PHP)**

PHP is a common disorder of the parathyroid gland and can occur in all age groups. In some patients, head and neck irradiation, and genetic abnormalities (mutations of MENIN gene in MENIN and germline mutations associated with the hypercalcemia, jaw tumor syndrome) may be responsible.

The pathologic lesions responsible for primary hyperparathyroidism include adenoma, atypical adenoma, double adenoma, multigland hyperplasia, and rarely, carcinoma.
Parathyroid Adenoma

Parathyroid adenoma is the single most common cause of primary hyperparathyroidism. The incidence of parathyroid adenoma is reported between 30 to 90 percent; this variation is due to lack of application of standardized diagnostic pathologic criteria: Adenomas are more common in females than males with a ratio of about 3 to 1.

Parathyroid adenoma is more common in the lower glands. About 10% of the adenomas are found at ectopic sites, including the mediastinum (often within the thymus), thyroid, esophagus and within the retroesophageal tissue.

Grossly, adenomas are oval or kidney-shaped, red brown in color and soft in consistency. Large adenomas (greater than 800 mg) may replace the entire parathyroid gland. In some cases the adenoma is multilobated, which may account for its incomplete excision. Some pathologists believe that the remaining normal parathyroid rim is a reliable criterion for the diagnosis of adenoma; however, it is seen in only 50 to 60 percent of cases and its absence does not preclude the diagnosis of “adenoma”. Parathyroid adenomas can markedly vary in size and weight; the size can range from less than 1 cm to over 3 cm; similarly the weight can range from 150 mg to several grams.

By light microscopy, adenomas are usually circumscribed, but not encapsulated. The tumor cells are usually arranged in nests and cords surrounded by a rich capillary network. Chief cells are the dominant cell types in the majority of parathyroid adenomas; oxyphil cells and transitional oxyphil cells can also be seen in varying proportions scattered within the collections of chief cells. Some adenomas are comprised exclusively of oxyphil cells, the so-called “oxyphil adenomas”.

The chief cells in adenomas can exhibit nuclear pleomorphism, multi-nucleation and giant cell formation. Mitotic figures are uncommon in adenomas
Parathyroid adenomas can show cystic degeneration; the fluid within the cyst contains parathyroid hormone. Other degenerative changes are more commonly seen in large tumors and include: fibrosis, hemorrhage, cholesterol clefts, hemosiderin and calcification. Increasingly, enlarged parathyroids are noted on ultrasound examination of the neck and may be interpreted as thyroid nodules. Fine-needle aspiration of these “thyroid” nodules may be performed and posttraumatic changes can occur in the parathyroid tumor (infarction, fibrosis, and distortion, cholesterol clefts, hemosiderin and mitotic figures as part of the healing).

Adenomas are virtually devoid of adipocytes.

Parathyroid adenoma is considered single gland disease; however, double adenomas have been reported. The proposed criteria for this diagnosis include presence of two enlarged hypercellular glands and the identification at least one other normal parathyroid. Long-term follow-up after excision of double adenomas must demonstrate lack of recurrence of hypercalcemia to accept this diagnosis. Unfortunately, some patients with double adenomas represent metasynchronous four gland disease, i.e. hyperplasia and the true nature of the cause of hyperparathyroidism in these cases may become apparent only after prolonged follow-up. In a recent study (Lewis, et. al., 2010 unpublished observations), of over 700 consecutive parathyroidectomies performed by one surgeon, the incidence of double adenoma was 3.2%. These operations were performed with intraoperative parathyroid hormone measurements and the patients were cured (eucalcemic) on follow-up.

Parathyroid Hyperplasia

Primary parathyroid hyperplasia is defined as proliferation of the parenchymal cells leading to increase in gland weight in multiple parathyroid glands in the absence of a known
stimulus for parathyroid hormone secretion. Two types of parathyroid hyperplasia are seen, the more common chief cell hyperplasia and the rare water cell or clear cell hyperplasia

Chief Cell Hyperplasia

It is estimated from the literature that approximately 15% of hyperparathyroidism are caused by parathyroid hyperplasia. Of the group of patients with hyperplasia, about 30% are familial (Familial hyperparathyroidism or multiple endocrine neoplasias (MEN) syndrome). It has been shown that hyperplasias and adenomas are monoclonal proliferations. Parathyroid hyperplasia associated with MEN I involves allelic deletions on chromosome 11. This suggests that the monoclonal proliferations may develop after a phase of polyclonal hyperplasia.

On gross examination, all four glands are enlarged and the combined weight is usually in the range of 1 g to 3 g. Chief cells form the dominant cell types, however, one may also observe intermixed oxyphil cells and transitional oxyphil cells. The cells are usually arranged in a solid, trabecular or nodular pattern. Nodule formation can also be seen leading to asymmetrical gland enlargement.

The cytoplasmic fat in chief cells is either reduced or absent. The nodular areas are usually devoid of fat, whereas, the ones between the nodules may contain fat. Nuclear pleomorphism and mitoses are rarely found in primary hyperplasia.

Water-Clear Cell Hyperplasia

This rare condition is characterized by proliferation of vacuolated water-clear cells in multiple parathyroid glands. It is more common in females and causes pronounced hypercalcemia and severe clinical disease.
**Parathyroid Carcinoma**

Parathyroid carcinoma is seen in 0.5 to 2 percent of cases of hyperparathyroidism. There appears to be an equal sex predilection. Patients with parathyroid carcinoma are younger than those with adenoma, and usually present with profound hypercalcemia, and/or its clinical consequences. The initial clinical presentation of parathyroid carcinoma may be that of palpable neck mass, which can be mistaken for a tumor originating in thyroid.

On gross examination parathyroid carcinomas are large tumors with adherence to and invasion of the surrounding neck structures such as soft tissues of neck, thyroid and periesophageal soft tissues. This infiltration into the neighboring neck structures serves as an important surgical finding. Parathyroid carcinoma involves only one gland, and rarely has been reported to arise in ectopic locations (eg. intrathyroidal).

By light microscopy the entire gland is traversed by broad fibrous bands, which seem to originate from the capsule and extend into the substance of tumor leading to a lobulated appearance. Parathyroid carcinomas are usually composed of chief cells, however, oxyphil cell and transitional cells can also be seen. In some cases the entire tumor is composed of oxyphil cells. The cells can exhibit bland cytology or show marked anaplasia. Mitotic figures are observed in most cases, and abnormal mitoses are often noted. Tumor necrosis and venous invasion (seen in 10% to 15% of parathyroid carcinomas) are also features of this tumor.

The only reliable indicators of malignancy in parathyroid carcinoma are invasion of the surrounding structures and metastases. Parathyroid carcinomas infiltrate into the surrounding neck structures and soft tissues in the form of “tongue-like” protrusions. The pathologist must be aware of the possibility of trapping and pseudoinvasion in adenomas which have been biopsied and should be cautious about making a diagnosis of carcinoma in light of such a history.
Histological clues include the presence of hemosiderin laden macrophages, granulation tissue and the finding of linear areas of scarring.

Non-functioning parathyroid carcinomas can occur. These lesions tend to be large and consist primarily of clear or oxyphil cells. These tumors can be confused with primary thyroid cancers, such as Hürthle cell lesions or medullary carcinoma. The parathyroid origin can be confirmed by positive immuno-histochemical staining for parathyroid hormone and chromogranin A, and negative reaction for thyroglobulin, calcitonin and TTF-1 (thyroid transcription factor 1).

Parathyroid carcinoma usually behaves in an indolent fashion. Metastases can be occur in up to one third of patients and are found in regional lymph nodes, bone, lung and liver. Multiple recurrences are common and can occur over a 15 to 20 year period. Fatal outcome in patients with parathyroid carcinoma is mainly due to the effects of excessive parathyroid hormone secretion and uncontrolled hypercalcemia rather than to tumor mass effect.

The hypercalcemia jaw tumor syndrome an unusual but important genetic syndrome has a high incidence of parathyroid carcinoma. This is associated with unusual cystic jaw lesions and elevation of serum calcium. The genetic mutation results in an inactivation of the protein parafibromin. This protein located within the nucleus in normal and benign parathyroid proliferations is lost in carcinomas. Thus immunostaining for parafibromin may be helpful in the diagnosis of parathyroid carcinoma. Originally it was reported that it was useful to distinguish adenoma from carcinoma in 96% of cases, more recent studied suggest that it is helpful in about
70%. Cystic adenomas, and hyperplastic glands in MEN I syndrome can show absence of nuclear staining for parafibromin. In addition, a few unequivocal parathyroid carcinomas will retain the protein staining.

**Atypical Adenoma**

This is a relatively new entity in parathyroid pathology. Some authors have suggested that if some features of malignancy including mitoses and fibrous bands are present without an infiltrative growth pattern or metastases, those cases should be designated as “atypical adenoma”. The few available follow-up studies have shown that these tumors will behave in a clinically benign fashion.

**Familial Hyperparathyroidism**

Primary hyperparathyroidism can present as a manifestation of MEN I and II or as a familial disease without involvement of other endocrine organs.

**Multiple Endocrine Neoplasia Syndromes (MEN)**

Parathyroid disease is found in about 90% of patients with Wermer syndrome (MEN I) and in about 10% to 20% of individuals with MEN II (Sipple Syndrome). Parathyroid involvement is identified as the earliest manifestation of the syndrome and is the pathologic changes in parathyroid are similar to those seen in nodular chief cell hyperplasia. Molecular analysis has shown that MEN I lesions represent monoclonal proliferations possibly originating in the background of polyclonal hyperplasia.
Primary hyperparathyroidism is seen in 10-20% of patients with MEN II. Usually all four parathyroid’s are involved but in some cases one gland is affected, suggesting an “adenoma”.

The degree of hypercalcemia in MEN II patients is usually less severe than in those with MEN I. Genetic studies have demonstrated the MEN II locus to be on chromosome 10q11.2, the region of ret proto-oncogene; specific mutations have been revealed in families with parathyroid involvement.

**UNUSUAL LESIONS OF THE PARATHYROID**

**Parathyromatosis:**

In primary and secondary hyperplasia of the parathyroid, small collections of parathyroid cells, mainly chief cells, rarely can be encountered embedded within the surrounding soft tissue of the neck and mediastinum outside the confines of parathyroid gland capsule. Normally these lesions are not detectable; however, in cases of diffuse hyperplasia of parathyroids, all functional tissue may become hyperplastic and appear as separate tissue fragments on histologic examination.

Parathyromatosis can occur in two situations; seeding of hypercellular parathyroid tissue during surgical excision of abnormal parathyroid tissue (usually hyperplasia), and overgrowth of embryologic parathyroid rests. Both forms of parathyromatosis can lead to recurrent hyperparathyroidism . These fragments can be confused with local invasion by parathyroid carcinoma. An examination of parathyroids along with clinical history will prove to be helpful in arriving at the correct diagnosis.

**INTRAOPERATIVE ASSESSMENT OF PARATHYROID (OLD and NEW)**

The intraoperative assessment of parathyroid gland during parathyroidectomy is usually limited to identification of the tissue. This procedure usually involves, correct labeling, gross
examination measurement and weighing the specimen. The representative sample is frozen and stained with hematoxylin and eosin stains. Usually the identification of parathyroid tissue is not difficult (accuracy rates of correct identification of tissue as parathyroid ranges up to 99%). However, in some cases it may difficult to distinguish from other neck tissues including lymph node, thyroid and ectopic thymus. Some authors have also advocated the use of intraoperative cytology preparations in conjunction with frozen section to increase the efficacy of identification of parathyroid tissue.

A frozen section error and failure to localize the abnormal parathyroid gland can lead to failed parathyroidectomy. A rapid parathyroid hormone assay in conjunction with frozen section can be helpful in indicating the successful excision of abnormal parathyroid gland(s). The samples for parathyroid hormone assay are obtained preoperatively from the thyroid veins. Follow-up samples are procured again after the removal of suspected abnormal parathyroid gland(s); a rapid fall in parathyroid hormone (by at least 50%) is indicative of successful removal of abnormal parathyroid.

In normal parathyroid glands, 80 percent of the cells are nonsecretory and contain intracytoplasmic fat, whereas, hyperfunctioning chief cells contain much less or are devoid of intracytoplasmic fat. Therefore, the pathologist can use fat stains (Sudan IV or oil Red O) or metachromatic stains (eg toluidine blue) to differentiate between adenoma and hyperplasia. However, fat stain is only helpful in 84 percent of cases and should be interpreted in conjunction with gross findings, gland weight, and size.

Cytology

A majority of parathyroid lesions are not palpable therefore; it is unlikely that a fine-needle aspiration (FNA) will be performed on a parathyroid tumor. However, image guided FNA is helpful in patients undergoing repeat surgical excisions for recurrent/persistent hypercalcemia where the anatomy is distorted. In addition, some parathyroid adenomas, especially the ones
located near or even within the capsule of thyroid can be mistaken for thyroid nodules and hence, will undergo FNA. The parathyroid FNA samples usually show a monotonous population of small round cells with even chromatin arranged in organoid or trabecular arrangement. Some cases may also show presence of vascular cores. Immunostain for parathyroid hormone may help in distinguishing these lesions from primary thyroid tumors.

**Genetics**

It has been shown that the over-expression of PRAD1 (for parathyroid adenoma/cyclin D1 induced by a DNA rearrangement of the parathyroid hormone (PTH) gene can be seen in parathyroid adenomas. This rearrangement is created by a break in the vicinity of the parathyroid gene on the short arm of chromosome 11 (band 11p 15), second break in the long arm (band 11q 13), rotation of the central fragment around the axis of the centromere, and rejoining. However, besides adenomas this gene has also been found to be over-expressed in nodular hyperplasia as compared to diffuse hyperplasia of parathyroid.

The retinoblastoma gene (Rb) is a tumor suppressor gene. Allelic deletion of the Rb gene on chromosome 13 has been reported in parathyroid tumors. It has been shown that a majority of parathyroid carcinomas show abnormal expression of Rb protein, a complete or predominant absence of nuclear staining for protein, whereas, parathyroid adenoma shows positive nuclear staining for Rb protein.

Parafibromin. This protein which is the product of the gene HPRT2. In the rare syndrome known as “hyperparathyroidism-jaw tumor” syndrome, there is a high frequency of parathyroid carcinoma (up to 15% of patients develop carcinoma). In the syndrome, there are germline mutations in this gene and the parafibromin product is lost. By immunostaining with antibodies to this protein, the nuclear positivity is lost. This is found in many but not all parathyroid carcinomas, but also is noted in “adenomas” that arise in the setting of MEN 1 and in cystic parathyroid adenomas. A few carcinomas retain the nuclear staining. Although originally
it was felt that, parafibromin immunostaining could distinguish adenomas from carcinomas, additional studies from other laboratories showed the utility of this marker was about 75%.
References


PARATHYROID PATHOLOGY
AN UPDATE
PARATHYROID PATHOLOGY

• PROBLEMS:
  – LOCATION, LOCATION, LOCATION
  – DISTINGUISHING ONE FROM MULTIGLAND DISEASE
PARATHYROID PATHOLOGY

- PRIMARY HYPERPARATHYROIDISM
  - Adenoma
  - Hyperplasia
  - Double Adenoma
  - Carcinoma
  - Atypical Adenoma
PARATHYROID

- LOCATION
  - *Because of embryological considerations, can be anywhere from upper portion of thyroid to mediastinum including medial mediastinum.*
  - *May be within other organs (thyroid, thymus, esophagus)*
PARATHYROID

- EMBRYOLOGY

- Upper glands descend farther than lower glands

- More variation in location for lower glands

- Association with thymus and other branchial remnants.
PARATHYROID PATHOLOGY

• Adenoma
  – 80% or more of primary hyperparathyroidism is caused by one gland abnormality
  – If identify one gland that is abnormal, cure the patient.
PARATHYROID PATHOLOGY

• **Hyperplasia**
  - Multigland disease
  - May be synchronous or metasynchronous
  - MEN patients
  - 15% of primary hyperparathyroidism
PARATHYROID PATHOLOGY

• **Carcinoma**

• Very rare –1% at most of primary hyperparathyroidism

• Need to show invasive growth especially into vessels or transcapsular

• Indolent malignancy

• Often die of metabolic consequences
PARATHYROID PATHOLOGY

• PARATHYROID CARCINOMA
• CAN IMMUNOSTAINS HELP?
  • Retinoblastoma
  • Parafibromin
PARATHYROID PATHOLOGY

• PARATHYROID CARCINOMA

• Parafibromin ("the new kid on the block"):  
  - Hyperparathyroidism-jaw tumor syndrome.
  - Product of gene HRPT2 and regulates cyclin D1 expression.
PARATHYROID PATHOLOGY

• PARAFIBROMIN (Gill et al AJSP Sept 2006)
  • Absent or focal weak nuclear staining in 11 of 12 carcinomas
  • Diffuse nuclear staining in 98 of 100 benign parathyroids (adenomas mostly)
PARAFIBROMIN STAINING

• Additional series indicate that
  a. Loss of nuclear staining in about 67% of unequivocal carcinomas of parathyroid
  b. Can see loss of staining in cystic adenomas, in parathyroid lesions in MEN1 which are not malignant either by pathology or clinical features.
  c. Some bona fide parathyroid carcinomas retain nuclear staining.
PARATHYROID PATHOLOGY

- **ATYPICAL ADENOMA**
  - Allow capsule invasion, not beyond
  - Allow mitoses and fibrous bands
  - Large size
  - Necrosis and vascular invasion probably cancer

- **FOLLOWUP SHORT.**
PARATHYROID PATHOLOGY

• **THE INFAMOUS DOUBLE ADENOMA**

  • Occurs but very rare
  • Most are asynchronous four gland disease
  • Need to identify two abnormal glands and wait 5 years.
PARATHYROID PATHOLOGY

- **Recurrent hyperparathyroidism:**
  - **CAUSES**
  - 1. Misinterpret multigand disease as solitary adenoma
  - 2. Underdiagnose parathyroid carcinoma
  - 3. PARATHYROMATOSIS
PARATHYROID PATHOLOGY

- **PARATHYROMATOSIS**
  - Primary—embryologic development of glands leads to fragments of them dispersed throughout neck (MEN)
  - Secondary---disruption of adenoma or hyperplastic gland during removal; the tissue “takes” in the vascular wound.
PARATHYROID PATHOLOGY

- PARATHYROMATOSIS

- Secondary—almost all are secondary to renal hyperparathyroidism.

- Can be impossible to control so clinically act like parathyroid carcinoma.
PARATHYROID PATHOLOGY

• **One final vinette:**
  - In the day of wide use of ultrasound and the possible confusion of thyroid nodules with parathyroid lesions, remember that the FNA needle can traumatize the parathyroid.
  - This can result in two possible events—
    - A) the patient’s Calcium and PTH may revert to normal
    - B) the adenoma can undergo infarction
PARATHYROID PATHOLOGY

• Intraoperative assessment:
  – Identification of abnormal gland
  – Biopsy or remove largest gland
  – Biopsy another gland
  – Frozen section on both
PARATHYROID PATHOLOGY

• Intraoperative evaluation
• Assess cellularity
• Assess extracellular fat
• Assess intracellular fat
PARATHYROID PATHOLOGY

- Fat stain
- Theory:
  - Normal and suppressed parathyroids have 80% or more of the parenchymal cells in the resting state and these contain intracytoplasmic fat. Hence a fat stain can tell if normal or suppressed gland.
PARATHYROID PATHOLOGY

- Fat stain
- Theory
- Hyperfunctioning gland has decreased or absent intracytoplasmic fat.
PARATHYROID PATHOLOGY

• Rapid assessment of intracellular fat:
  • Toluidine blue stain
  • 30 seconds
  • Can distinguish normal from abnormal gland.
PARATHYROID PATHOLOGY

• If decreased fat in both grossly abnormal and normal gland, consider that this is multigland disease.

• FAT STAIN IS ACCURATE IN 85% OF CASES
PARATHYROID PATHOLOGY

- **MODERN APPROACH**
  - Careful localization or at least lateralization by preop radiologic tests (Sestamibi scan)
  - Neck exploration and removal abnormal gland
  - Intraoperative rapid PTH hormone assay
  - If after gland removed, the PTH drops by 50% or more, that gland was the adenoma.
PARATHYROID PATHOLOGY

- MODERN APPROACH

- Most surgeons with experience with this technique require frozen section for identification of the tissue as parathyroid.

- Rarely thyroid nodules may mimic parathyroid anatomically; PTH may fall due to trauma to parathyroids yet adenoma still not removed.
PARATHYROID PATHOLOGY

• HOW GOOD ARE WE IN IDENTIFICATION OF PARATHYROID?

• 99.2% accurate (Westra et al AJSP 1999)

• Confusion with thyroid, lymph node

• Confusion if lesion is oncocyctic
PARATHYROID

• FOR MINIMALLY INVASIVE SURGERY
• MUST HAVE
• SUPERB RADIOLOGY
• EXPERIENCED SURGEON
• EXCELLENT LAB FOR RAPID PTH
PARATHYROID PATHOLOGY
AN UPDATE