

Proliferative Lesions of Parathyroid Glands: An Update for Practicing Pathologists

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ABSTRACT

Pathological lesions of parathyroid glands encompass a wide range of lesions ranging from developmental anomalies to inflammatory disorders to neoplastic processes. Proliferative lesions of parathyroid glands represent the commonest causes of hyperparathyroidism in clinical practice. However, the parathyroid specimens represent only a tiny fraction of the workload received in a non-specialist histopathology laboratory. As a result, the familiarity of the pathologists with the spectrum of parathyroid lesions is generally limited. An accurate diagnosis of the parathyroid lesions is challenging and a daunting task for both the clinicians and the pathologists. The traditional morphological approaches have limitations. Ancillary techniques of immunohistochemistry and molecular biology are being increasingly employed to resolve the diagnostic dilemmas. This review briefly describes the proliferative pathological lesions affecting the parathyroid glands and provides some useful tips on accurately diagnosing these lesions.

Key Words: Adenoma. Carcinoma. Parathyroid glands. Parathyroid hyperplasia.

INTRODUCTION

Pathological lesions of parathyroid glands encompass a wide range of lesions ranging from developmental anomalies to inflammatory disorders to proliferative lesions. The proliferative lesions of parathyroid glands represent the commonest causes of hyperparathyroidism in clinical practice and one of the challenging fields, both diagnostically and therapeutically; and also both for the clinician as well as the pathologist. The histological assessment of parathyroid gland is indispensable in the evaluation of hyperparathyroidism but strangely enough, only rarely, it is encountered by the surgical pathologist in routine practice. Despite a few limitations, the role of the pathologist in the appraisal of parathyroid pathology is worth mentioning.¹ In this regard, the sound knowledge of normal histology of parathyroid glands and the spectrum of pathologic lesions, in adjunct to awareness of the recent trend of immunohistochemical and the molecular genetic studies, is crucial to arrive at the best possible diagnosis.² A variety of computer-based approaches have also been tried in various areas of surgical pathology and cytology to objectively assess the distinction between various lesions, but these have not yet found widespread use in clinical practice.³

Literature search strategy: The literature search was performed by using the database of PubMed. The

keywords used were pathology and parathyroid glands and the search was limited to English language articles on human species with no time bar. A total of 2401 articles including original articles, case reports, and review articles were scanned for their relevance to the current review and a final selection was made of 44 articles. Local literature on this topic was very scanty. These articles were then scrutinized in depth for updating existing information on this topic in this review.

The histology of normal parathyroid gland: There is reasonably sufficient data on the histology of normal parathyroid glands published in literature after the first accurate description of normal histology by Welsh in 1898.⁴ A brief account of the morphology of normal parathyroid glands is warranted in view of better understanding of morphologic features of pathologic conditions, which will be described later.

There are usually four parathyroid glands arranged in two pairs usually close to the upper and lower poles of thyroid gland, but may be found anywhere along pathways of descent of third and fourth branchial pouches.⁴ Macroscopically, each gland is yellowish brown to reddish brown in color and 25 - 40 mg in weight. Microscopic composition of normal parathyroid glands comprises of a combination of three types of cells and a variable amount of stromal fat, which is dependent upon age of the person. The whole gland is surrounded by thin, delicate fibrous capsule. The capsule sends thin, delicate and fibrous septae, which divide the gland into lobules of secretory cells. The pre-eminent cell population is of 'chief cells' or 'principal cells', which are 6 to 8 um in size, polygonal in shape, with rounded centrally placed nuclei, as shown in Figure 1.^{4,5} The cytoplasm is usually very scant and faintly acidophilic, often retracted towards the cell periphery giving an

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Received: April 16, 2015; Accepted: October 16, 2015.

impression of halo or vacuole surrounding the nucleus. This vacuole merely reflects an artifact of formalin fixation and dehydration. The cells with upto moderate degree of this vacuolar change are termed as transition wasserhelle cells. When the cytoplasm is almost completely absent and replaced with cytoplasmic vacuole, these cells are termed as water-clear cells.^{5,6} The water-clear cells are slightly larger than chief cells, 10 - 15 μm in diameter, with sharply distinct cell outlines and optically clear cytoplasm. The third type of cells is oxyphil cells; these are polyhedral cells with sharply demarcated cell membranes and are slightly larger than chief cells measuring 11 - 14 μm . Their nuclei are rounded and pyknotic and are almost equivalent in size to chief cells; however, as the name indicates, the cytoplasm is uniformly pink with fine granules. No vacuoles are seen in the cytoplasm.^{4,6}

The relative distribution of these cells varies with age. Until the age of puberty, the gland is almost entirely composed of chief or principal cells with very marginal tendency of cytoplasmic vacuolization. These cells contain glycogen but no fat, they later start to appear after puberty. Soon after puberty, the oxyphil cells gradually begin to appear and they increase in number with advancing age. First, they appear as individual cells, followed by large, sharply circumscribed but unencapsulated nests upto the age of 40 - 50 years.^{4,7} Subsequently, large fat cells appear in the stroma after puberty and continue to increase in number until the age of 40 years, as shown in Figure 1.⁸ Afterwards, their number remains fairly constant during the middle age.

The pathology of parathyroid glands: The majority of pathological lesions of parathyroid gland present clinically with symptoms of hyperparathyroidism. Primary hyperparathyroidism has now become the third most common endocrine disorder.⁹ The term primary hyperparathyroidism refers to an inappropriate over-production of parathyroid hormone (PTH) leading to abnormal calcium homeostasis and increased serum calcium levels with concomitant increase in PTH levels. Parathyroid hormone-related protein (PTHrP) levels remain normal. The primary hyperparathyroidism prevails in women with reported female to male ratio of 3 - 4:1. The average age of presentation in most series is 45 - 55 years. The clinical presentation is variable ranging from asymptomatic patients to nonspecific symptoms of weakness, nausea, constipation, severe bone and kidney disease; hence the Walter St. Goar's classic 1957 description of "stones, bones and abdominal groins".¹⁰ *Osteitis fibrosa cystica* is a markedly rare disease present in only 2 - 3% of cases with hyperparathyroidism. Genetic disorders such as familial hyperparathyroidism, Multiple Endocrine Neoplasia (MEN-1) and hyperparathyroidism jaw-tumor syndrome can lead to above mentioned disease, if left untreated.¹¹

Primary hyperparathyroidism results from parathyroid adenoma in the majority of cases (80 - 85%), followed by hyperplasia (10 - 15%), multiple adenomas (4%), atypical adenomas and parathyroid carcinomas in rare cases (< 1%).¹²

Chief cell hyperplasia: Chief cell hyperplasia is a proliferative lesion of parenchymal cells that results in an absolute increase in cell volume and weight. It typically involves all four glands; however, the involvement is usually not uniform.¹³ This disorder was first reported by Cope *et al.* in 1958.^{12,13} This condition can occur sporadically, but is more commonly seen in association with familial conditions like MEN syndrome, FIHP, neonatal severe hyperparathyroidism, familial hypocalciuric hypercalcemia and familial hypercalcemic hypercalciuria. Classically, 10 - 15% of cases of primary hyperparathyroidism are attributed to chief cell hyperplasia. However, the relative frequency rate is quite varying from 1.3 to 84%, possibly, due to lack of precise defining criteria.¹⁴

The MEN 1 syndrome is an autosomal dominant inherited disorder characterized by multiglandular parathyroid disease, pituitary adenomas, and neuroendocrine tumours of gastropancreatic regions. The responsible genetic mutation and the pattern of inheritance have been described earlier. MEN 2A syndrome is also an autosomal dominant disorder characterized by development of chief cell hyperplasia, C-cell hyperplasia of thyroid gland, medullary carcinoma, and pheochromocytoma. The gene responsible for this syndrome is RET oncogene which is mapped on chromosome 10q11.2. The detailed description of this mode of function of this oncogene is beyond the scope of this review article.²⁰

Gross morphology: Chief cell hyperplasia is characteristically a disease process involving all four glands, but the process is very slow and progressive resulting in discrepancy in size and weight of all glands. This phenomenon leads to marked enlargement of one or two glands making it difficult to distinguish it from adenoma, on gross inspection.¹² A few cases have been reported revealing symmetric hyperplasia of all four glands and majority of them were in the scenario of MEN syndrome.²⁰ Hyperplastic glands may appear grossly round to oval in shape and red brown in colour. The cut surface is usually homogenous and rarely slightly nodular.

Microscopic features: The hyperplastic gland is comprised of parenchymal cells with preponderance of chief cells, as the name indicates. However, oxyphil cells, transitional cells and even water clear cells may be found in variable numbers. Stromal fat component is markedly reduced in hyperplasia as compared to normal gland. This feature has remarkable variability; hence, its practical diagnostic value remains questionable.^{12,13}

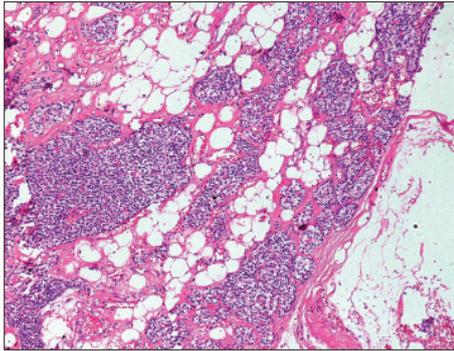


Figure 1: Normal parathyroid gland of a middle-aged man showing an admixture of parenchymal cells and stromal fat. The parenchymal cells are all chief cells. (H&E, x100).

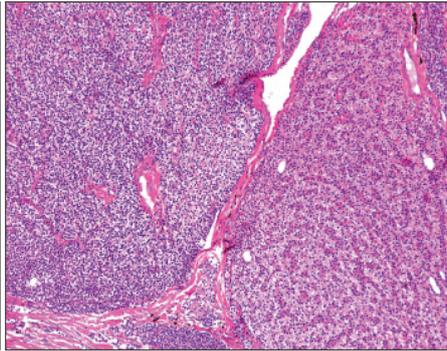


Figure 2: Photomicrograph of parathyroid hyperplasia. Note the nodular arrangement of tumour cells, separated by thin fibrous septae. (H&E, x200).



Figure 3: Gross photograph of parathyroid adenoma. Note complete encapsulation, oblong shape and area of hemorrhagic discoloration.

Microscopically, the involvement of gland may be diffuse or nodular, so called adenomatous or pseudo-adenomatous hyperplasia. Each nodule is composed of sheets, cords or acinar arrangement of parenchymal cells or admixture of all patterns. These nodules may be separated by fibrous connective tissue, mimicking fibrous capsule (Figure 2). The chief cells are hyperplastic with mild to marked nuclear pleomorphism with reduced stromal fat component. Secondary, degenerative changes such as cystic changes, hemosiderin pigment and fibrosis can be observed in markedly enlarged hyperplastic glands. When the hyperplastic parenchymal tissue lacks precise circumscription and it merges intimately with the surrounding tissue, this entity is coined as parathyromatosis.²⁸ Proliferative markers like proliferating cell nuclear antigen (PCNA) and MIB-1 may reveal significantly increased proliferative activity in nodular hyperplasia as compared to diffuse pattern.¹⁵

There are no unanimous criteria established for distinction among adenomas and hyperplasia, hence, it is a universal diagnostic dilemma for both surgeons and surgical pathologists. Similar situation also happens with regard to distinction between normal and abnormal glands.⁵ As we have described earlier, a multidisciplinary approach accompanied by intraoperative PTH assays and frozen section assessment may lead to best possible diagnosis. It has been claimed that ultra-structural examination by electron microscopy may aid in this diagnostic predicament; but it seems unlikely that hyperplasia, appreciable only on electron microscopic level, will lead to practical utility in the management of patients.^{23,13}

Water-clear (Wasserhelle) cell hyperplasia: First described in 1934, it is a rare entity and is usually observed as sporadic non-familial disorder. This kind of hyperplasia is generally associated with high serum calcium levels and approximately 90% of patients present with renal stones, even sometimes may lead to hypercalcemic crisis.

Gross morphology: In this variant of hyperplasia, glands are markedly enlarged. Upper ones are usually larger than the lower ones. All glands are enlarged but there is variability in size of individual glands. They are soft in consistency and chocolate brown to mahogany brown in color.¹⁶ Grossly, they cannot be confidently distinguished from chief cell hyperplasia.

Microscopic features: As the name indicates, the glands involved by water-clear cell hyperplasia exhibit sheets of large water-clear cells with exclusion of all other cells including fat cells. Other morphologic patterns including acinar, papillary, follicular, trabecular and nodular may be seen. The detailed morphology of these cells has been described earlier. This disorder reveals marked morphological mimicry to clear cell variant of renal cell carcinoma. Electron microscopy reveals that cytoplasm is packed with presumably Golgi complex derived membrane bound vacuoles, some of these vacuoles contain dense material, which may represent PTH.¹⁷

Parathyroid adenoma: There are no consistent morphologic criteria for the diagnosis of parathyroid adenomas. Although, by definition, an adenoma is a benign neoplastic lesion involving single gland in the majority of cases and perhaps rarely two or more glands may be involved, particularly in association of autosomal dominant endocrine disorders.^{11,18} Consequently, the diagnostic modalities including histopathological features and genetic studies are flawed by the lack of a gold standard test to distinguish this entity from other challenging differential diagnoses of hyperplasia and even carcinoma. Furthermore, the lesions of parathyroid gland show significant overlap and precise diagnostic criteria are not available. Hence, the role of multi-disciplinary team approach in making the diagnosis is crucial and remarkable.¹

The most universally acceptable criterion of adenoma is involvement of single gland but many pathologists presume that adenoma and hyperplasia cannot be distinguished histologically, if only one gland is

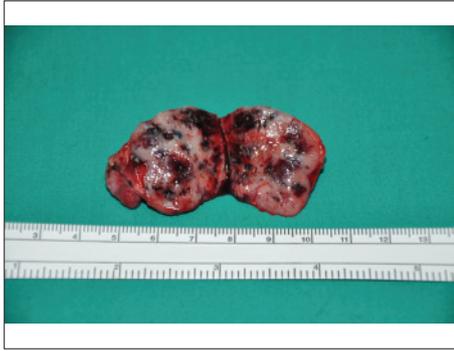


Figure 4: Cut section of parathyroid adenoma. Note large areas of hemorrhagic discoloration. A thin yellow rim of normal parathyroid tissue at the periphery.

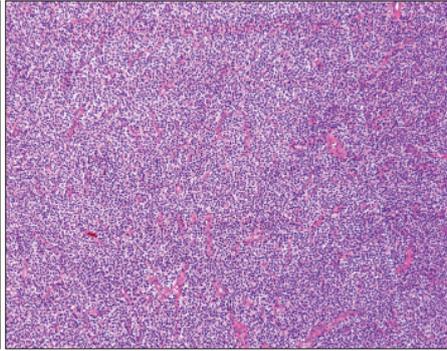


Figure 5: Photomicrograph of parathyroid adenoma. Note diffuse, sheet like arrangement of tumor cells with complete absence of fat. (H&E, x100).

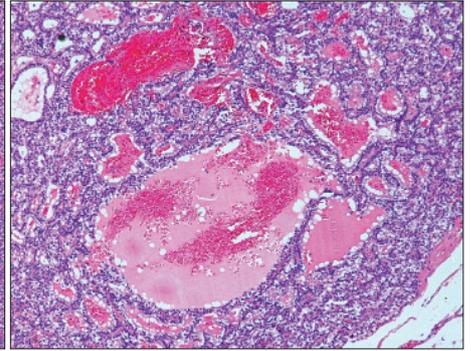


Figure 6: Sometimes, the tumour cells are arranged in follicular pattern, mimicking thyroid gland. (H&E, x400).

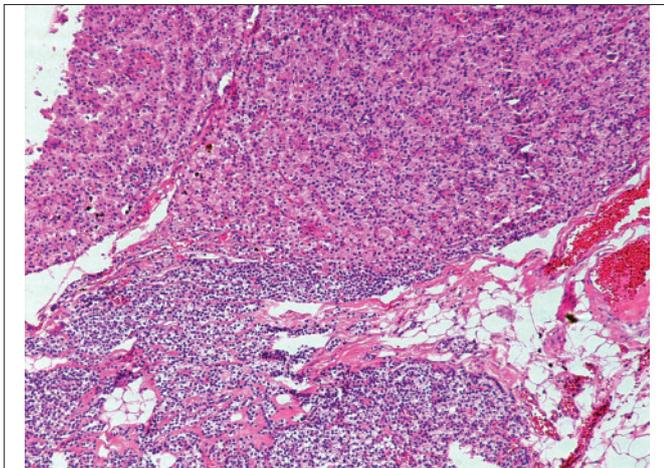


Figure 7: Photomicrograph of parathyroid adenoma. Note compressed normal parathyroid tissue at the periphery of adenoma in the lower part of the field. (H&E, x200).

submitted for histological assessment. Therefore, histological verification of at least one normal gland is mandatory to exclude the possibility of hyperplasia. However, some studies concluded that solitary parathyroid gland enlargement does not eliminate parathyroid hyperplasia, since 30 - 75% of patients with hyperplasia exhibit single gland enlargement.^{12,18} An additional controversy regarding parathyroid adenoma is the concurrent or sequential existence of double or multiple adenomas. However, in this regard the remote possibility of multi-glandular involvement by asymmetrical pseudoadenomatous hyperplasia or nodular hyperplasia should also be considered.

Gross pathology: Parathyroid adenomas arise in 90% of cases in superior and inferior parathyroid glands; they can also arise from any site where normal parathyroid tissue is described. The size and weight of adenoma is variable. The size may vary from 6 mm to approximately 10 mm and weight also varies from less than 100 mg to several grams. Grossly, adenomas are typically round or oval, sharply demarcated, nodular lesions with smooth edges. They are usually homogenous and soft in comparison with parathyroid carcinoma and other

tissues like lymph node or thyroid gland (Figure 3). Pathologists should do a careful and close examination of parathyroid gland, which may reveal an attached compressed yellow tan rim of normal parathyroid tissue, most often at the vascular pole. This finding is suggestive of an adenoma but diagnosis cannot entirely rely on it because compressed tissue is observed in only 50 - 60% of adenomas. The cut surface exhibits a completely circumscribed nodule with a well defined capsule and classically it is homogenous, but sometimes larger lesions reveal secondary degenerative changes including cystic changes, hemorrhage and calcification (Figure 4).^{12,18}

Microscopic features: Microscopically, the parathyroid adenoma is typically an encapsulated lesion composed predominantly of chief cells intermingled with oxyphil and transitional oxyphil cells. The arrangement of these component cells is also variable from arrangement in cords, nests to sheets and follicles, giving close mimicry to thyroid tissue (Figure 5). Some adenomas show predominant follicular arrangement with colloid like material within these follicles (Figure 6). This feature can readily be distinguished from normal or neoplastic thyroid tissue by the presence of birefringent calcium oxalate crystals that may be found in the latter.¹⁹ Immunohistochemical stain or thyroglobulin also helps differentiate these two tissues. Parathyroid adenomas also frequently possess palisaded arrangement of cells around delicate and florid capillary networks, giving rise to pseudo-rosette like appearance.

The nuclei are typically larger than adjacent non-neoplastic gland cells and are usually rounded. A few scattered cells, exhibiting enlarged, pleomorphic and hyperchromatic nuclei, the so-called endocrine atypia, are also not uncommon. This phenomenon is not indicative of malignancy *per se*, but, in fact presence of these features favours the diagnoses of adenoma as compared to hyperplasia or carcinoma.²⁰ Mitotic activity is observed in majority of adenomas, but the proliferative rate as assessed with proliferation markers is relatively low. Mitotic activity varies from scarce to 4 mitoses per

high power field (HPF). Although, sole mitotic activity is not considered a criterion for malignancy; rather its presence should heighten awareness of the possibility of malignancy and pathologists should scrutinize for other criteria.²¹

The peripheral rim of compressed tissue typically reveals smaller and more uniform cells admixed with abundant stromal fat (Figure 7). Fat stains are widely used to demonstrate more abundant cytoplasmic fat in compressed atrophic tissue rather than an adenoma itself. This technique is frequently applied during intraoperative assessment for frozen section.^{22,23}

Molecular studies and immunohistochemistry:

Adenomas are typically clonal proliferative lesions, which is similar in this context to significant number of cases of primary and secondary hyperparathyroidism. A few genes are suggested to play important role in the development of adenomas. One of the frequently observed is the rearrangement involving PTH locus on chromosome 11p15, with a locus on 11q13, which harbours Cyclin D1 gene, also called parathyroid adenomatosis 1 gene (CCND1/PRAD1). Overexpression of the latter gene results from pericentric inversion of Chromosome 11p, which renders CCND1 under control of PTH gene promoter sequences. A few series have reported this translocation in upto 8% of cases on FISH analysis.²⁴ However, over expression of Cyclin D1 is not only elucidated in adenomas, but also in hyperplasias as well as in carcinomas.

It is well known fact that parathyroid adenomas can develop in association with a few endocrine syndromes.¹¹ One of the most common syndromes is Multiple Endocrine Neoplasia (MEN) syndrome, which is affiliated with hyperparathyroidism. MEN syndromes are characterized by multigland involvement revealing either hyperplasia or neoplasia. In regard to parathyroid gland, there is predominantly hyperplasia followed by double or multiple adenomas. The latter phenomenon is susceptible to recurrences and persistence. The gene, which is mutated in this syndrome, is a tumour suppressor gene, MEN 1, which is located on chromosome 11q13 and encodes nuclear protein, menin, whose function is to suppress transforming growth factor β (TGF β) in collaboration with SMAD 3. Upto 40% of sporadic adenomas show loss of one allele of MEN 1 gene. Some authors have suggested that this abnormality is an early event in parathyroid tumorigenesis.²⁵ Majority of hyperparathyroidism cases are associated with MEN 1 syndrome, while 10% of the cases present with MEN 2A syndrome.

Hyperparathyroidism-jaw tumour syndrome is another familial hyperparathyroidism syndromic disorder characterized by adenoma or carcinoma of parathyroid gland, benign fibro-osseous lesions of jaw and renal tumours. The gene supposed to be responsible for this

syndrome is a tumour suppressor gene, HRPT2 gene, located on chromosome 1q25-q31 and encodes protein called parafibromin.¹² In familial cases, it is a germline mutation, while in sporadic cases it has been shown to be somatic mutation. Although it is an extremely rare syndrome, it should be kept in differentials among patients with hyperparathyroidism.

Familial Isolated Hyperparathyroidism (FIHP) is also a rare familial condition which is observed in only 1% of cases with hyperparathyroidism and it is distinguished from other familial conditions on the basis of absence of extra-parathyroidal disease.²⁶ Its putative responsible gene is not known. For the curiosity of readers, it should be mentioned that p53 gene mutation has not been observed in parathyroid adenomas.

Immunohistochemistry: The role of immunohistochemistry in confirmation of parathyroid tissue as well as an adjunctive diagnostic tool has been evaluated. The strong cytoplasmic staining of PTH in chief cells by using monoclonal antibody is straight forward and worth considering in definitive identification of parathyroid tissue. Monoclonal antibodies against putative calcium channel receptor reveal uniform and intense staining in normal parathyroid tissue and its staining intensity is markedly reduced in adenomas.²⁷ Immunohistochemical staining for retinoblastoma (Rb) protein may help distinguish between parathyroid carcinomas, which are thought to be Rb protein negative and adenomas which are Rb protein positive. In addition, positive immunohistochemical staining for p53 also favours the diagnosis of carcinoma rather than adenoma.

Immunohistochemically, positivity of low molecular weight cytokeratins (CK-8, 18 and 19) is also observed in adenomas. Chromogranin A is also found to be positive in most normal and neoplastic chief cells and it can readily be used to distinguish follicular lesions of thyroid and parathyroid gland. Immunohistochemistry for parafibromin, galectin-3 and some vasoactive amines have also been reported in literature.²⁷ However, the diagnostic utility of these markers in routine surgical pathology, especially in regard to distinction among adenoma and hyperplasia, is yet to be determined.

Electron microscopy has also been used to demonstrate the endocrine activity of chief cells in abnormally enlarged glands in aid to distinguish adenoma-hyperplasia diagnostic dilemma.²⁸

Variants of adenoma: Oncocytic adenoma: Oncocytic adenomas account for 4.4 - 8.4% of all adenomas. By definition, they are exclusively composed of oxyphils or they are predominantly (> 80 - 90%) composed of oxyphil cells. Initially, these adenomas were thought to be clinically non-functional, as they were assumed to be incapable to secrete PTH. However, some other studies have shown that pure oxyphil cell adenomas are capable of PTH synthesis and secretion.²⁹

Similar to classic adenomas, they are predominantly found in females in sixth to seventh decade and majority of the cases are asymptomatic. Grossly, the size and weight of these adenomas is variable ranging from 0.2 to 61 g. They are soft, ellipsoid or lobulated with variability in colour ranging from light tan to mahogany brown. The colour is usually not very distinctive from classic chief cell adenomas. Microscopically, sheets, anastomosing cords and acinar arrangement of polygonal cells with abundant granular, brightly eosinophilic cytoplasm and centrally placed rounded nuclei are seen. Transitional oxyphil cells are also seen in variable numbers. Mitoses are rare.

Ultrastructurally, these adenomas show cytoplasm which is densely packed with numerous mitochondria exhibiting numerous cristae and variable electron dense matrix. Immunohistochemical positivity for PTH has also been reported.²⁹

A. Lipoadenoma: Another variant, although remarkably rare, was described for the first time in 1958. Usually, they are found in neck but can present as an anterior or posterior mediastinal masses. They are composed of nests and cords of chief cells with a few oxyphil cells intimately admixed with variable amount of mature adipose tissue and fibrous stroma, hence they were earlier considered as hamartomas. They vary in weight from 0.5 to 420 g and typically they are rimmed by delicate fibrous capsule. Lipothymoadenoma is another rare variant described along the same theme.³⁰ Lipoadenomas may be non-functional or they may rarely present with primary hyperparathyroidism.

B. Large clear cell (light chief cell) adenoma: This is another scarcely reported variant of adenoma, which occasionally may be associated with primary hyperparathyroidism. They are comprised of polygonal cells with abundant cytoplasmic vacuoles filled with glycogen. This could be appreciated with special stain, Periodic Acid-Schiff (PAS) with or without diastase digestion. Although this variant can be seen in patients with MEN syndrome but information regarding its clinical significance is scarce in the literature.¹²

C. Water-clear cell adenoma: Parathyroid adenomas of water-clear type are exceptionally rare; only a few cases are reported in the literature. These adenomas exhibit nests and acini with clear cells containing abundant foamy, granular cytoplasm. Mild nuclear pleomorphism is also reported. Some authors believe that they likely represent large clear cell adenomas with glycogen accumulation rather than true water-clear cells with membrane bound vesicles.^{31,32}

D. Atypical adenoma: This variant is debatable and yet a controversial variant.³³ Categorically, this is a variant of adenoma with alarming and bothersome features but not fulfilling the criteria of malignancy. Seethala *et al.* have suggested some morphological features, of which

presence of two or more attributes would lead to diagnosis of carcinoma.³⁴ They are incomplete capsular invasion, prominent trabecular growth pattern, broad fibrous bands, entrapment of lesional cells in fibrous bands, adherence to surrounding structures, tumour necrosis, and conspicuous mitotic activity.³³ One should be very careful to search other suggestive features for malignancy, if any abnormal mitosis is encountered. A few studies have described that serum calcium levels in patients with atypical adenomas are intermediate between those of adenoma and carcinomas. Some authors have suggested that molecular phenotype of atypical adenoma is also intermediate between adenoma and carcinoma. Several studies have been published and observed that atypical adenomas generally pursue benign course.^{33,34}

Parathyroid carcinoma: Parathyroid carcinoma is one of the rarest pathologies involving the parathyroid glands and in regard to primary hyperparathyroidism it accounts for only 1 - 2% of cases.^{12,35} Nevertheless, its frequency varies in different studies reflecting the racial and geographic differences. Another possibility behind it might be the lack of uniform diagnostic criteria for carcinoma. Parathyroid carcinomas may rarely arise in the background of pre-existing parathyroid hyperplasia, even in adenomas, sometimes in familial settings.^{16,28} The diagnostic difficulties among hyperplasia, adenoma in recurrent cases, render this assessment more complicated. Furthermore, the possibility of hyperplasia-carcinoma sequence has been questioned and is far from clear as yet. A few cases have been reported of the occurrence of parathyroid carcinoma in the setting of previous neck irradiation exposure.^{35,36}

In contrast to the female preponderance in parathyroid adenoma, carcinoma occurs with almost equal male to female ratio. Moreover, it tends to occur roughly one decade earlier in comparison with adenoma. Some of the clinical features, which might help in distinguishing carcinoma from adenoma, are relatively high serum calcium and PTH levels in carcinoma. In addition, patients with parathyroid carcinoma have remarkable tendency to present with palpable cervical masses in 15 - 75% of cases with concurrent bone and kidney disease. Rarely, they may present as a non-functional mass.³⁵

Gross morphology: They are characteristically large tumours with variable size and weight. These tumours measure from 1.5 to 6 cm in diameter with weight ranging from 0.6 to 110 g. Any of the all four glands may be involved; rarely, carcinoma may arise in ectopic locations. They are grossly firm to hard with grayish white appearance in contrast to soft consistency of adenoma. The adherence of mass with the surrounding structures may be an indication to the surgeon for the possibility of malignant lesion; however, previous

surgery or previous hemorrhage in pre-existing adenoma renders its significance unreliable.³⁷ Metastatic disease at the time of presentation is the *sine qua non* for malignancy, which is rarely found at that time.³⁸

The pathologic diagnosis of parathyroid carcinoma is challenging for both surgeons and pathologists. It poses great difficulty to the pathologist due to interobserver variability in histological features. Despite the fact that no single histologic feature in isolation is pathognomonic criterion for malignancy as per WHO recommendation. The proposed histologic criteria by Shantz and Castleman in 1973 include: presence of lobular architecture with broad fibrous bands, cytologic atypia, presence of atypical mitoses, capsular invasion with extension into surrounding tissues, vascular invasion in capsule or adjacent tissues and/or the presence of metastasis.³⁹

Microscopic features: The difficulties faced by the pathologists in diagnosing parathyroid carcinoma have been mentioned above. Generally, these lesions are large masses composed of solid sheets of cohesive cells. The cellularity varies widely among these lesions, Moreover, the composition of cells also shows substantial variation. Majority of the tumours are comprised of predominantly chief cells, while others may exhibit oncocyctic cells dominance or even exhibit mixed cellular pattern.^{38,39} The nuclear morphology may be bland or moderate nuclear pleomorphism with macronucleoli may be appreciated. Areas of necrosis and significant mitotic activity with more than 5 mitoses per 10 high power fields are also observed. Bondeson *et al.* have reported, foci of coagulative necrosis in approximately one-third of the cases and substantial proportion of them had markedly high mitotic activity, which was correlated to aggressive behavior of the tumours.³⁷ The value of mitotic activity is still debatable in cases of carcinomas; however, presence of atypical mitoses is worth considering in this context.

The presence of thick irregular fibrous bands should raise the suspicion of malignancy. These traverse the parenchyma and also encircle the lesion. Invasive pattern is another indication of malignancy in the form of tongue-like protrusions into the encapsulating fibrous tissue and even extension through the capsule to the surrounding structures including the thyroid gland, strap muscles, and soft tissues, etc. One should be aware of pseudocapsular invasion and should search for definite features of true invasion.³⁹ The criteria for vascular invasion to be fulfilled are at least partial attachment of tumour cells with the vessel wall or tumour cells associated with thrombus formation. Some authors suggest that it should be documented outside the vicinity of neoplasm, to be considered as positive vascular invasion.⁴⁰ Perineural invasion, though rarely seen in parathyroid carcinomas; but whenever observed, it is another indication of malignancy.

Several studies have shown loss of heterozygosity (LOH) on chromosome 13q, a region which harbours both retinoblastoma (Rb) and BRCA2 genes in parathyroid carcinomas. However, their contribution in the development of carcinoma is controversial.¹⁹ The HPRT2 gene, located on chromosome 1q25-q32, was first acknowledged in the development of sporadic carcinomas in 2003. These mutations were thought to be responsible for inactivation of parafibromin. Furthermore, several studies later showed that patients with this sporadic mutation also had germline mutation of the same gene and might develop hyperparathyroidism-jaw tumour syndrome. In this respect, carcinoma patients should be screened for kidney and jaw lesions. Moreover, family genetic screening should always be considered.⁴¹

Ancillary techniques may also be helpful diagnostically as well as prognostically. Proliferative markers like Ki-67, MIB-1 and PCNA can be added to conventional mitotic count to further validate the diagnosis of carcinoma. Tan *et al.* have reported loss of parafibromin as a marker of parathyroid carcinoma; however, the results observed in several other studies are conflicting.⁴² Despite these conflicts, lack of parafibromin staining has shown promising diagnostic utility. Other markers purported to be useful are galectin-3, PGP9.5 and loss of APC, but their diagnostic applicability is still under consideration.^{43,44}

Parathyroid carcinomas usually pursue an indolent course with prolonged survival, multiple local recurrences, and development of metastasis late in the course of disease.^{36,40} Frequent and early recurrences are indicators of poor prognosis. The morbidity and mortality rate is attributable to hypercalcemic crisis rather than parathyroid carcinoma itself.

CONCLUSION

An accurate diagnosis of the lesions of parathyroid gland has significant impact on the management of patients. The histological features should always be correlated with clinical, biochemical, radiological, cytogenetic and immunohistochemical findings to achieve best possible categorization of the lesions.

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